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Faculty of Sciences of the Matter

Department of Chemistry

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Doctoral degree

Presented by :

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Theme :

Synthesis of novel phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines and their corresponding Diazepines; HPLC Resolution of their structural Isomers

Specialty : Organic Chemical

Supported ….. /….. / 20….

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Abstract :

A combination of fluorinated and diphenylphosphinoyl groups in azo-compounds and thier corresponding diazepines compounds will hopefully make them very interesting biological active compunds. It was therefore decided to investigation the synthesis of this type of the compounds. New compound of phosphorus fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines and their corresponding diazepines have been synthesized in high yields via adding n-buLi in hexane to a stirred solution of methyldiphenylphosphine oxide in dry THF at 0°C, then cooled to around -78°C, treated with (2,4,6 trimethylphenylazopyridines and then allowed to warm at room temperature over 2 hours. The isomers of(E)-((5-chloro-3,6-difuoro-4-(mesityldiazenyl)pyridin-2-yl)methyl)diphenyl phosphine oxide (4b) and (E)-((3,6-difuoro-4-(mesityldiazenyl)5-methoxypyridin-2-yl)methyl)diphenyl phosphine oxide (4c) was separated on analytical HPLC: Chiralcel OD-H column, hexane:2-PrOH, (9:1, v:v) mobile phase, flow-rate, 1.0 mL/min, 25°C, λ = 254 nm and polarimetric detection, 20μL injection volume. The resolution of this isomers were 2.12, 1.84,respectively.

ملخص :

ومن خلال الجمع بين الجماعات المفلورة وديفنيل فوسفين في الآزو المركبات و ديازبين المقابلة لها, هذه المركبات التي نأمل لدورها المثيرة جدا للاهتمام على النشطة البيولوجية. لذلك تقرر التحقيق تركيب هذا النوع من المركبات. مركبات جديدة من الفوسفور المفلورة 2، 4، 6- ثلاثي فينيل أزو بردين وديازبين المقابلة لها تم تصنيعه بنسب عالية عبر أضافت ن- بيوتيل اللثيوم في الهكسان الى أكسيد مثيل فنيل فوسفين في THF الجاف في صفر درجة مئوية، ثم يبرد إلى حوالي -78 درجة مئوية، وتعامل مع (2،4،6 ثريمثيل فنيل أزو بيردين ثم يسخن في درجة حرارة الغرفة أكثر من 2 ساعة . إيزومرات - (E)-5كلورو-6،3- ديفلورو -4-مسثيل ديازنيل (بيردين-2-يل) الميثيل) ثنائي الفوسفين أكسيد (4b) و - (E)-6،3- ديفلورو -4-مسثيل ديازنيل (بيردين-2-يل) الميثيل)-5- مثكسي بردين ثنائي الفوسفين (4c) أكسيد يمكن فصلها بواسطة HPLC التحليلية: Chiralcel OD-H العمود، الطور المتحرك مشكل من الهكسان: 2-بروبانول بنسبة (1 :9) ، (ح: ح) ، بمعدل التدفق، 1.0 مل / دقيقة، 25 ° C، 254 = λ نانومتر، والاستقطابي كشف، 20μL حجم الحقن. وكان مقدرية فصل هذه أيزومرات 2.12، 1.84 على التوالي.

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Introduction

Introduction

In this introduction we have paid attention in the biochemistry and medical applications of compounds containing the carbon-fluorine bond, which has increased substantially during the past seventy years. The biochemical aspects have developed rapidly since the pioneering studies (begun in the late 1940s) of Sir Rudolf Peters, Goldman and Milne, Witkopes group, Weissman and Koe and Charles Heidelberger, Ernest Kun. These and other historical highlights are covered some reviews of the biochemistry of carbon-fluorine compounds. So in the medicinal field, there has been an enormous upsurge in the use of fluorine-containing compounds; many new fluorine containing compounds have been prepared, clinically evaluated, and, in many cases, marketed as drugs with enhanced effectiveness, often coupled with diminished side effects. Significant among the medicinal compounds are antimetabolites, non-steroidal anti-inflammatory drugs and analgesics, antibiotics, antifungal agents, and central nervous system agents. An increasing number of reports dealing with the assessment of the use of various diazepines are frequently available. The fluorinated and organic phosphorus compounds are also a heterogeneous class of products widely used for the treatment of a number of cardiovascular diseases, including congestive heart failure and coronary heart disease.

A combination of fluorinated and diphenylphosphinoyl groups in azo-compounds will hopefully make them very interesting biological active compounds. Since phosphorus substituents regulate important biological functions and fluorine containing compounds play important role in organic synthesis and in medicinal chemistry.

Since the literature contains little or no information on phosphorus fluorinated azo-compounds and their corresponding diazepine, It was therefore decide to investigate:

- The synthesis of this type of the novel phosphorus fluorinated 2,4,6-trimethylphenylazopyridines and their corresponding diazepines, HPLC will be used to separate the structural isomers.
- The study of their biological antimicrobial activities against several Gram-positive and Gram-negative bacterial strains in vitro, due to the appearance of new strains of the bacteria and the weakness of chemotherapeutics and antibiotic resistance exhibited by pathogens.

So the project is divided into two parts:

The first part contains three chapters:

- Chapter one in which we gave general information about the compounds.
- Chapter two presents the results obtained and their interpretation.

- Chapter three, we introduced the tools, equipments used and the general methods employed in this project.

The second part contains three chapters:

- Chapter four includes the theoretical chapter which includes some properties of the alkyl and aromatic compounds.
- Chapter V contains the results and discussion.
- Chapter VI contains the experimental section.

The research is concluded with a conclusion

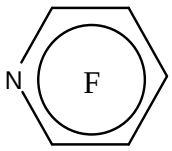
Part I

Summary
Part I

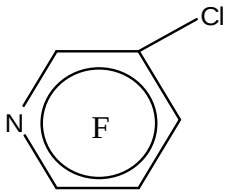
4- amino- 2,3,5,6- tetrafluoropyridine (VIII) was synthesised from Pentafluoropyridine (I) and aqueous ammonia in 81% yield. 3- chlorotetrafluoropyridine (II) and aqueous ammonia were heated under reflux for ca. 23 hour in THF to give, 4-Amino- 3- chloro- 2,5,6- trifluoropyridine (IX). 4- Amino- 2,3,5,6- tetrafluoropyridine was oxidised to 4- nitrotetrafluoropyridine (VII) with trifluoroactic anhydride and 85% hydrogen peroxide in methylene chloride.

4- nitrotetrafluoropyridine was treated with methanolic Sodium methoxide at O C° gave 3-methoxy-2,5,6-trifluoronitropyridine (III)(51%), 2-methoxy-3,5,6-trifluoronitropyridin (IV)(15%),3,5-dimethoxy-2,6-difluoronitropyridine(V)(21%) and 2,5-dimethoxy-3,6-difluoronitropyridine (VI)(17%). After removal of the solvent at reduced pressure the mixture was purified by flash column chromatographic on silica gel using methylene chloride and petrolehter (1:1) as eluant.

The reduction of 3-methoxy-2,5,6-trifluoronitropyridine with $Fe/H_2O/HCl$ gave 3-Amino - 2,5,6 – trifluoromethoxpyridine(X) and 4-amino-3- hydroxy trifluoropyridine respectively 98% and 2%.



I



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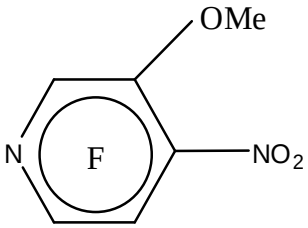

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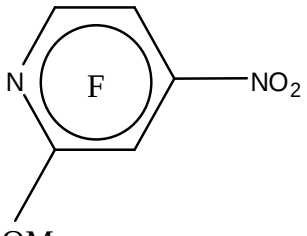

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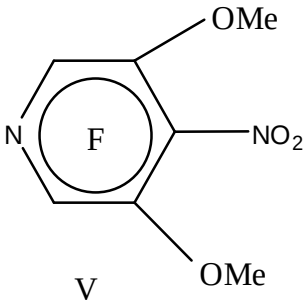

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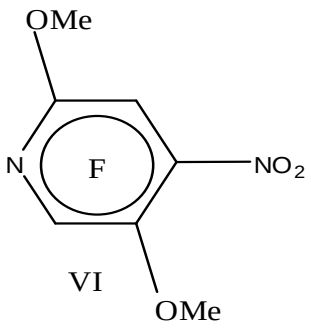

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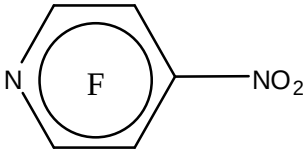

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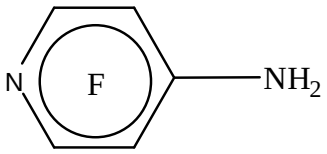

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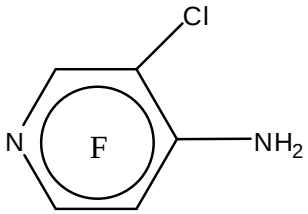

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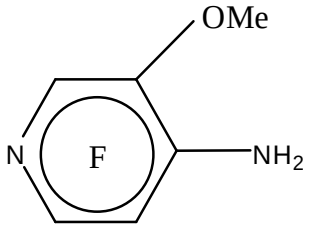
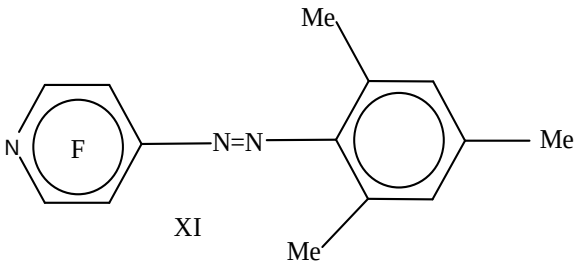
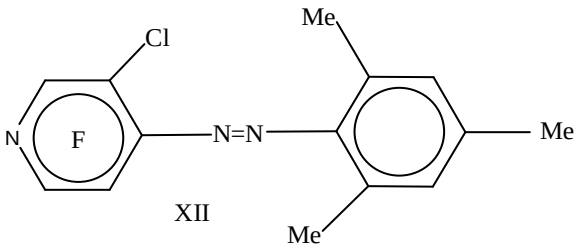


X

4-Amino- 2,3,5,6- tetrafluoropyridine, 4- Amino- 3- chlorotrifluoropyridine and 3-Amino - 2,5,6 – trifluoromethoxpyridine have been successfully diazotised with dry powdered Sodium nitrite in an acid medium based on 98% Sulphuric acid (H_2SO_4). The resulting diazonium ions were coupled to mesitylene, giving the azo – compound 2,3,5,6- tetrafluoro -4 – (2,4,6 trimethyl phenylazo) pyridine (XI) (82 %), 3- Chloro- 2,5,6- trifluoro -4 – (2,4,6 trimethyl phenylazo) pyridine (XII) (86 %) and 3- methoxy - 2,5,6- trifluoro -4 – (2,4,6 trimethyl phenylazo) pyridine (XIII) (77 %). Methyldiphenyl phosphine oxide was lithiated by n- BuLi at - 78 °C then treated with (XI), (XII) and (XIII) respectively to afford mixture isomers of phosphorus fluorinated azo compounds respectively (E)- diphenyl((3,5,6- trifluoro-4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide (XIV), (E)- ((5- chloro-3,6- difluoro-4-(mesityl diazenyl) pyridin -2- yl) methyl) diphenyl phosphine oxide (XV) and (E)- ((3, 6- difluoro-4-(mesityl diazenyl)-5- methoxypyridin -2- yl) methyl) diphenyl phosphine oxide (XVI). In our previous studies, were separeted these mixture using HPLC.



XI



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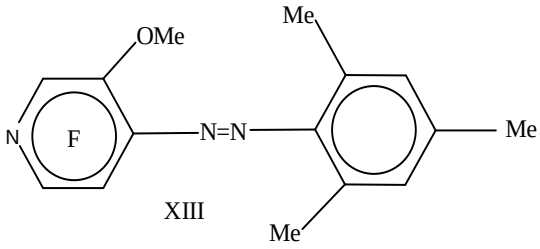

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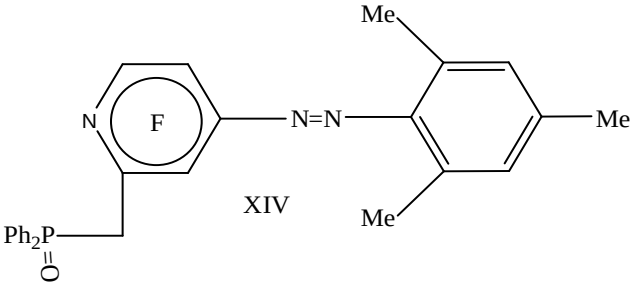

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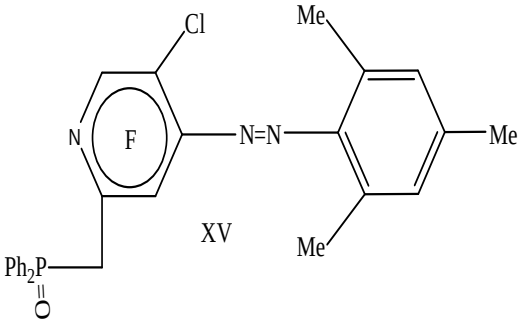

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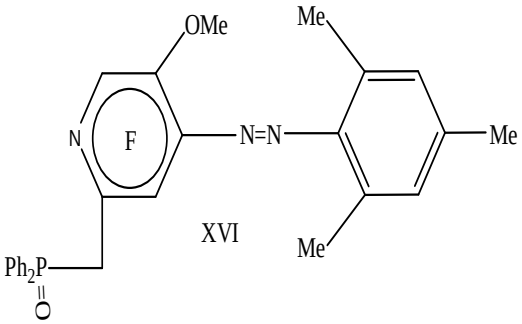
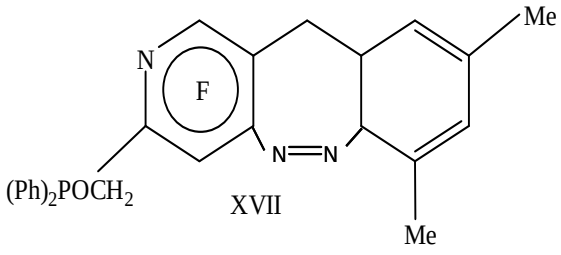
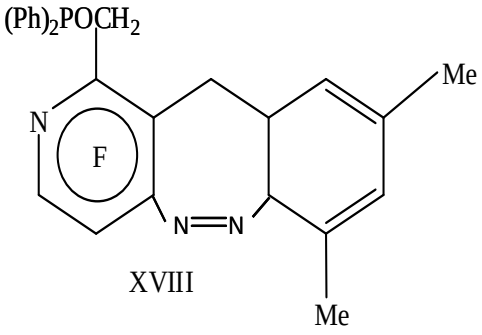


XVI

The resulting phosphorus fluoroinated azo-compounds (XIV, XV and XVI) resulted from precedent step thermolysed in mesitylene for 6- 12 hours to give the structural isomers of corresponding diazepines. Finally, HPLC has been to separate the structural isomers. According to the most relevant bibliography.The diazepines were isolated as yellow solids which were recrystallised from pet-ether to give orang needles of (XVII) and (XVIII) .



XVII



XVIII

The theoretical side
Part I

Introduction:

Organic synthesis including mechanistic studies of biologically relevant molecules is the main objectives of the research at the division of organic chemistry. The asymmetric heterocyclic compounds play an important role for high stereoselectivity. They are one of the most versatile and widely utilized class of materials used today, this products are of interest because of its application to stereochemistry in inorganic chemistry, organic chemistry, physical chemistry, biochemistry, and supramolecular chemistry.

I-1- History:

Isomerism was first noticed in 1825, when Friedrich Woehler's prepared cyanic acid and noted that although its elemental composition was identical to fulminic acid (prepared by Justus von Liebig the previous year), its properties were quite different. This finding challenged the prevailing chemical understanding of the time, which held that different compounds were different because they had different elemental compositions. After additional discoveries of the same sort were made, such as Woehler's 1828 discovery that urea had the same composition as, yet was not, ammonium cyanate, Berzelius introduced the term isomerism to describe the phenomenon [1].

Isomers are molecules that have the same molecular formula, but have a different arrangement of the atoms in space. That excludes any different arrangements which are simply due to the molecule rotating as a whole, or rotating about particular bonds.

Where the atoms making up the various isomers are joined up in a different order, this is known as structural isomerism [1].

Many isomers share similar if not identical properties in most chemical contexts.

I-2- Different forms of isomerism:

There are two main forms of isomerism: structural isomerism and stereoisomerism.

In structural isomers, the atoms and functional groups are joined together in different ways, as in the example of propyl alcohol above. This group includes chain isomerism whereby hydrocarbon chains have variable amounts of branching; position isomerism which deals with the position of a functional group on a chain; and functional group isomerism in which one functional group is split up into different ones. In stereoisomers the bond structure is the same, but the geometrical positioning of atoms and functional groups in space differs. This class includes optical isomerism where different isomers are mirror-images of each other, and geometric isomerism where functional groups at the end of a chain can be twisted in different ways. While structural isomers typically have different chemical properties, stereoisomers behave identically in most chemical reactions. Enzymes however can distinguish between different stereoisomers of a compound, and organisms often prefer one stereoisomer over the other. Some stereoisomers also differ in the way they rotate polarized light. There also exist topological isomers called topoisomers. Molecules with topoisomers include catenanes and DNA. Topoisomerase enzymes can knot DNA and thus change its topology [1].

I-3- fluorinated in organic chemsitry:

Nearly forty years have passed since syntheses of organofluorine compounds were first collected together in encyclopedic form in the Houben- Weyl series (volume 5/3), in 1962, still together with organochlorine compounds. In the years that followed, developments in the field occurred at a breathtaking pace, especially after it became recognized that fluorine substituents in organic compounds could alter the properties in unique ways, or even result in completely new and unexpected properties, effects that are now sought after in almost every area of commerce and the life sciences. The range of substances includes, for example, the chemically inert perfluorocarbons (now being developed in the lom molecular mass domain as blood substitutes, or forming the basis for important polymeric materials), polyfluorinated surface- active agents, and partially fluorinated compounds with special biological properties of importance for pharmaceutical or agrochemical applications.Meanwhile, fluorinated heterocyclic compounds have received increasing attention due to their potential biological and industrial applications [2].In the past few

decades, considerable efforts have been paid to the exploitation of new and convenient synthetic routes to these compounds[3].

Comparing with direct fluorination and haloexchange reactions, the application of fluorine-containing building blocks in organic synthesis has become a more and more important strategy for the construction of fluorinated heterocycles due to its higher selectivity and milder conditions.

I-3-1Back ground:

Compounds containing C-F bonds are rarely found in nature, in contrast to the abundant fluoride anions [4,5]. The fluoride ion is extensively hydrated and therefore relatively unreactive as a nucleophile, inhibiting C-F bond formation in nature. However, fluorinated organic compounds play an important role and are widely used in the synthesis of pharmaceuticals and agrochemicals due to their favourable chemical and biological properties.

In general, the introduction of a fluorine atom in a molecule does not result in a considerable

change in the size or the shape of the compound. Due to the minimal conformational effects, the fluorinated molecule generally also fits in the active site of the receptor and the fluorine atom is thus a suitable isosteric substitution of hydrogen. The incorporation of fluorine into organic molecules may change the solubility properties and enhance the lipophilicity and thus increase the rate of cell penetration and transport of a drug to an active site. The higher electronegativity of fluorine may also alter the physical and chemical properties of a molecule, and the higher polarizability due to the new C-F bond may give new possibilities for binding to the receptor.

original C-H bond and fluorinated compounds are more resistant to metabolic degradation. On this background, the development of new and efficient methods for the preparation of fluoroorganic compounds has got increased attention in recent years.

As a general fact, aromatic substrates are very unreactive towards nucleophilic substitution. However, substitution is accelerated by the presence of electron-withdrawing groups o- or p- to the leaving group. A hetero-P atom in the ring is also activating. Surprisingly, the phosphor group, which is not generally lost in aliphatic systems, is a particularly good leaving group in nucleophilic aromatic substitutions [6-8].

I-3-2- Selective Synthesis of Fluorinated Compounds:

Process Development and Preparation of Fluorinated Compounds on a Kilolab Scale Our expertise in fluorine chemistry and the synthesis of small molecules allows Solvias to develop sophisticated synthesis processes for complex organo-fluorine compounds. We not only have the necessary infrastructure but also a broad portfolio of selective fluorination methods designed for this special substance class. These capabilities have permitted us to synthesize more than 1,000 organo-fluorine compounds over the years.

fluorinated compounds are often used in pharma and crop protection research laboratories.

This is to the fact that fluorine atoms have a positive influence on the properties of biologically active compounds. Today, research and development chemists can purchase many commercially available fluorinated molecules as building blocks. However, if certain fluorinated molecules are unavailable or if a novel process needs to be developed for a specific fluoro compound, Solvias is able to provide the necessary assistance. We have all the equipment and expertise required to contribute successfully to challenging projects in the area of fluorine chemistry. We synthesize the target molecules on a gram to kilogram scale and develop efficient processes for large-scale manufacturing. Our technology platform consists of a broad range of fluorination methods. Solvias offers several synthetically useful fluo-rination methods for the selective formation of carbon-fluorine [9].

I-3-3- bonds in organic molecules, including:

• Schiemann- Reaction

• Chlorine-Fluorine exchange

• Fluorination using SF4

• Electrophilic fluorination using F+-reagents

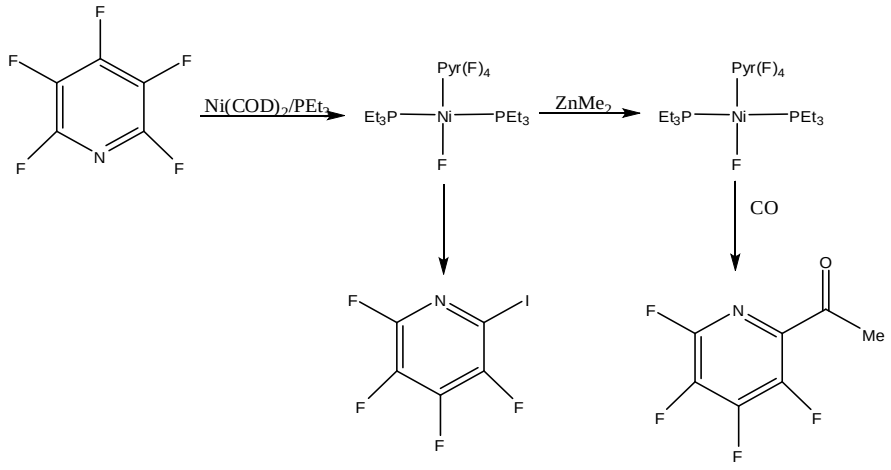
• Direct fluorination using F2.

For more than 30 years, Solvias has successfully used these methods to prepare over 1,000 fluorinated compounds on a preparative scale for our customers. Below is a brief overview of the most frequently used fluorination methods at Solvias [10].

Nickel has also been used to synthesize fluorinated heterocyclic aromatic compounds [11].

These fluorinated aromatics, specifically pyrimidines and pyridines, have found application as liquiq crystals, herbicides, antibiotics, and anti-cancer agents. Braun and Perutz observed that the nickel catalyst Ni(COD)2 in the presence of triethylphosphine

oxidatively added the C-F bond of these heterocyclic aromatic molecules and reductively eliminated a substituted product [11].



Scheme 1

I-4- Chemistry of organophosphorus compounds:

I-4-1-Historical introduction:

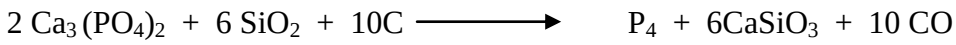
Organic compounds of phosphonis have been in existence at least since the beginning of the life of this planet. Such substances were probably prepared artificially for the first time in the Middle Ages. For example, Robert Boyle [12] observed the oxidation of phosphonis in the presence of turpentine in 1681. However, the scientificallly planned research of these compounds was not accomplished until the early nineteenth century when Lassalgne [13] studied

the esterification of dehydrated phosphoric acids with alcohols in 1820. Some two decades later, phosphine derivates were prepared by Thenard [14], and in the succeeding years of that century the chemistry of organophosphorus compounds developed at a rather rapid pace. The development continued through the opening of this century as may be witnessed by the enormous literature on the subject in its various aspects.

I-4-2- Organophosphorus compounds :

The definition of organophosphorus compounds is variable, which can lead to confusion. In industrial and environmental chemistry, an organophosphorus compound need only contain an organic substituent, but need not have a direct P-C bond. Thus most herbicides, e.g. are often included in this class of compounds.

Most organophosphorus compounds are manufactured from elemental phosphorus, obtained by electrothermal reduction of calcium phosphate with coke in the presence of silca.

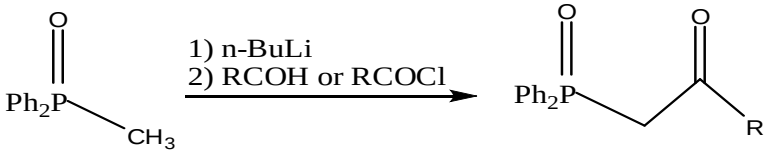


Scheme 2

This phosphorus is then converted to phosphorus trichloride by direct reaction with excess of chlorine or phosphoryl chloride, $POCl_3$, formed by exposure of the trichloride to air. Phosphorus trichloride (PCl_3) and phosphoryl chloride ($POCl_3$) are then used as the starting materials for the preparation of most organophosphorus compounds .

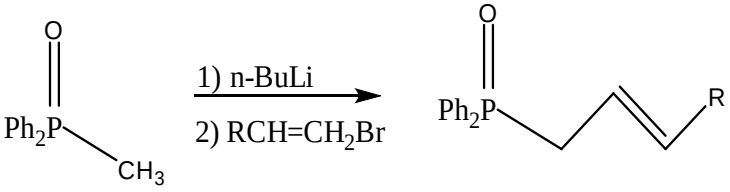
I-4-3- Nucleophiles characterization of methyldiphenylphosphine oxide:

Compounds of phosphorus are frequently excellent nucleophiles and we might expect the element itself to attack electrophiles such as carbonyl compounds, olefins and alkyl halides.



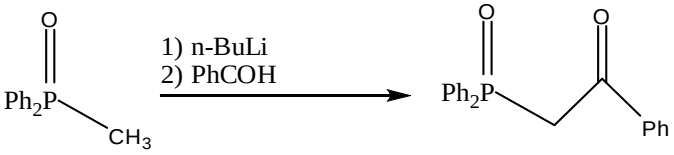
Scheme 3

The phosphine oxide 3 with n-BuLi at – 78°C and then treated substituted allylbroide (scheme 4)



Scheme 4

The rate of this nucleophilie attack is dependent on many factors, including electronic , sterie, and solvent effects [15].



Scheme 5

Work- up of the reaction product gave diphenylphosphinoyl-1-phenyl ethan -1-one over 2 hours, this product was prepared over 3 hours when we used benzoylchloride

I-4-5- Uses of Organophosphorus compounds:

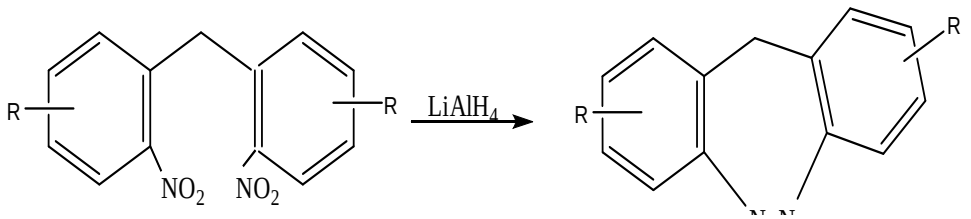
The study of the organophosphonis chemistry became more systematical only after Michaelis synthesized a great number of organophosphorus compounds, which laid the foundation for the study of the formation of P-C, P-S, P-Se and P-N bonds.

Phosphorus compounds have found many important commerciel applications including fertilizer in the form of CaHPO4.alng with detergents animal feed fire retardants. and even in the pharmaceutical industry. Trivalent phosphorus compounds hzve also been utilized as antioxidants and stabilizers in rubbers and plastics[15-18].

I-5- The corresponding diazepines:

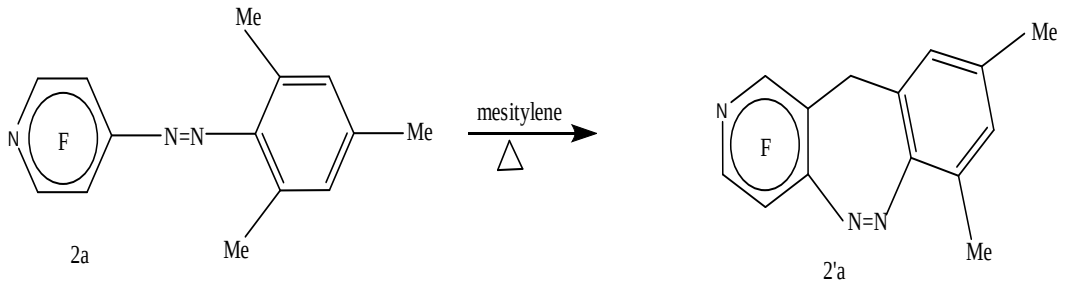
The name 1,2 diazepine reveals, according to IUPAC rules [19], that the compound under consideration contains unsaturated 7- membered ring containing 2 adjacent nitrogens.

However, the literature conceming 1,2- diazepine chemistry contains little,or no, information on construction of the 11-H-dibenzo[c,f] [1,2] diazepine ring system [20,21] and apparently none on the above type, wherevone (or both) of the annelating moieties is (are) heterocyclic in nature. However, information does exist on the 11-H-dibenzo[c,f] [1,2] diazepine ring system where the aromatic annelating moieties present are carbocyclic in nature. Reduction of 2,2- dinitrodiphenylmethanes provides general route to such systems (scheme 6) [22- 26]



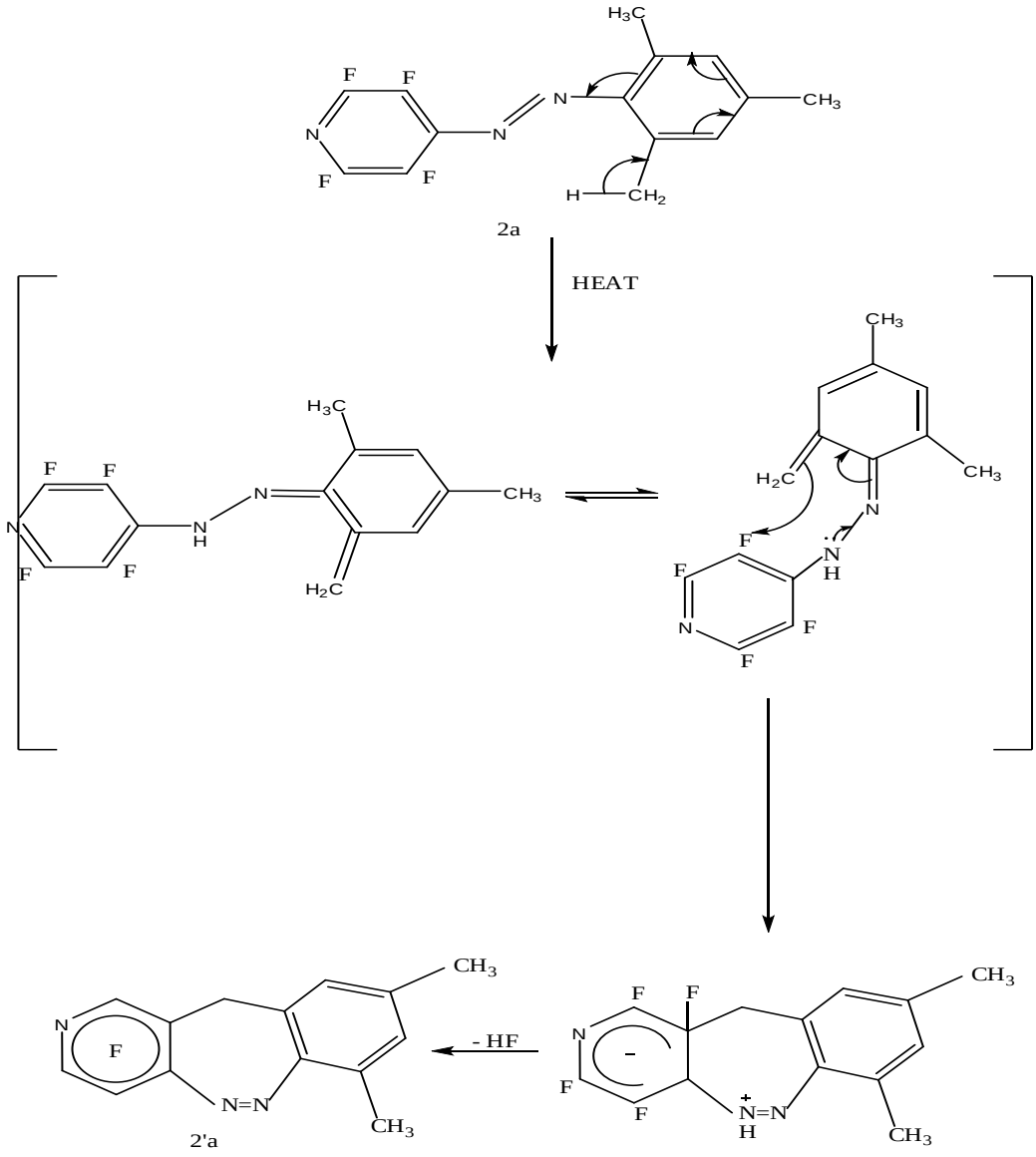
Scheme 6

In 1984, Banks and al. [27] reported a simple method for converting aminated monocyclic fluoroaromatic compounds into 11-H-dibenzo[c,f] [1,2] diazepine. A much better technique was found to involve heating the azo- compound 2a in boiling mesitylene, complete conversion of starting material into the 1,2- diazepine 2'a occured during 24 hours and the latter was isolated in at least 81% yield by dry- column flash chromatography (DCFC) (scheme 7)



Scheme 7

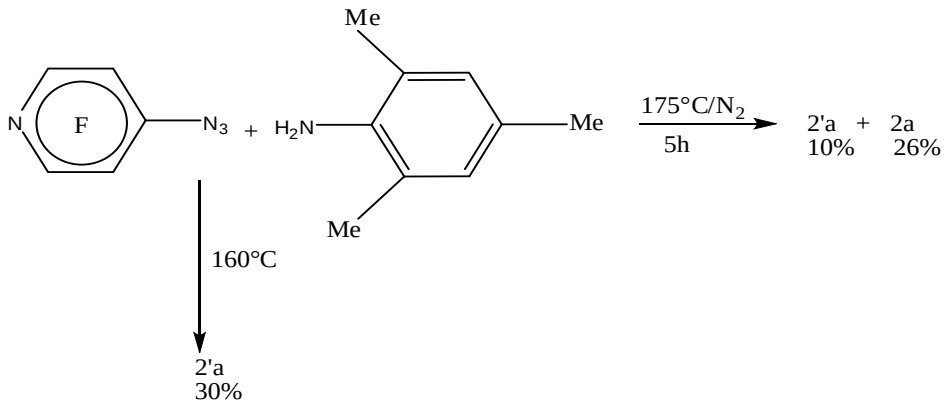
The mechanisms of diazepine formation shown in Scheme 8



Scheme 8

I-5-1- Preparation of diazepine (2'a) by 4- azidotetrafluoropyridine:

In 1985, Banks and Madany [28] disclosed a further method of synthesis of the 1,2-diazepine (2'a). They found that DCFC work up of the crude product formed when 4-azidotetrafluoropyridine and freshly distilled mesidine were heated together at 175°C under an atmosphere of nitrogen for 5 hours provided tetrafluoro-4- (2,4,6-trimethylphenylazo) pyridine (2a) in 26% yield plus 1,3,4-trifluoro-7,9-dimethyl-11 H-pyrido-[4,3-c]benso[1.2]diazepine (2'a) (10% yield). When the reaction was repeated at 160°C for 14 hours, the complex reaction product was found to contain no tetrafluoro-4-(2,4,6-trimethylphenylazo) pyridine (2a) and the yield of the diazepine (2'a) isolated was 30%. Since the limit of this one-pot azide to the novel diazepine (2'a) was 30%, the method is not as efficient as Alty's method [27].

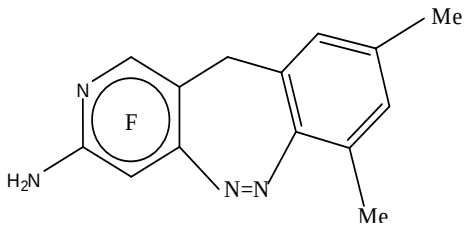


Scheme 9

I-5-2- Some reactions of diazepine (2'a):

I-5-2-1- Nucleophile substitution reactions

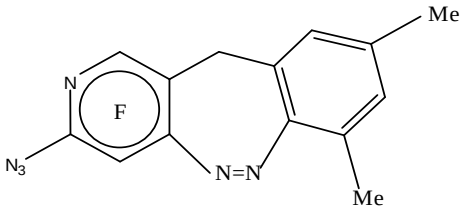
1) With ammonia



3

Tsiliopoulos [29] used a 2molar excess of gaseous ammonia at ca. 70°C to attack compound 2'a dissolved in toluene. This gave 3-amio-1,4-difluoro-7,9-dimethyl-11 H-pyrido[4,3-c]benso[1.2]diazepine() in 13% yield.

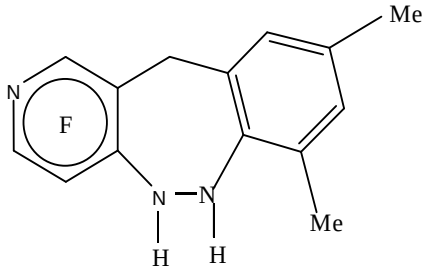
2) With sodium azide



4

A mixture of the diazepine [29] 2'a in acetonitrile and sodium azide was stirred under reflux for 6 days. The new azide (4) was isolated by DCFC in 28% yield .

I-5-2-2- Reduction of diazepine (2'a):

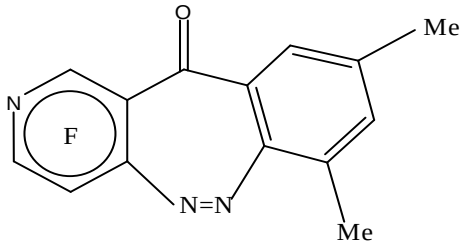


5

Tsiliopoulos [29] was interested in the effect of a fairly large nucleophile on the substitution pattern in 1,3,4-trifluoro-7,9-dimethyl-11 H-pyrido-[4,3-c]benso[1.2]diazepine. Surprisingly, however, when he refluxed the parent diazepine(2'a) with a large excess of aniline for 2 hours, he isolated only a product believed to be 1,3,4-trifluoro-5,6-dihydro-7,9-dimethyl -11 H-pyrido [1.2]diazepine() in 22% yield. To identify Tsiliopoulos compound without doubt, Djebli [30] sought a conventional synthesid of the same compounds. Thus, reduction of 1,3,4-trifluoro-7,9-dimethyl-11 H-pyrido-[4,3-c]benso[1.2]diazepine with glacial acetic acid and zinc dus twas undertaken. 1,3,4-trifluoro-5,6-dihydro-7,9-dimethyl -11 H-pyrido [1.2]diazepine (5) in 60% yield.

I-5-2-3- Oxidation reactions

1) With chromic anhydride



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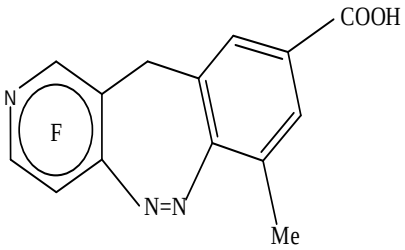

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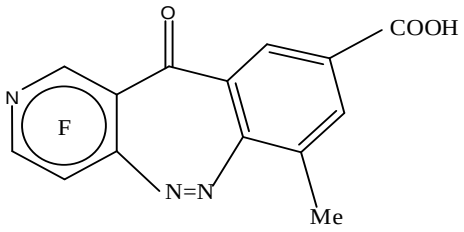


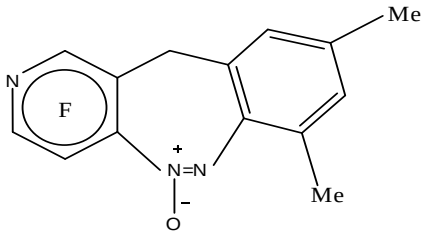
8

Tsiliopoulos [29] prepared 1,3,4-trifluoro-7,9-dimethylpyrido-[4,3-c]benso[1.2]diazepine-11-one (6) in 17% yield, following Catala's procedure[25] via the oxidation of the methylene group of 1,3,4-trifluoro-7,9-dimethyl-11 H-pyrido-[4,3-c]benso[1.2]diazepine with chromic anhydride in glacial acetic acid.

Djebli[30] repeated Tsiliopoulos' reaction to prepare the starting material for further work on the diaezpine, so she followed Tsiliopoulos' procedure, which involved the use of an excess of chromic anhydride with diazepine (2'a) in glacial acetic acid. Three products were isolated, 1,3,4-trifluoro-7,9-dimethylpyrido-[4,3-c]benso[1.2]diazepine-11-one (6) (23%), 1,3,4-trifluoro-7-methylpyrido-11 H-[4,3-c]benso[1.2]diazepin-9-carboxylic acid (7) (56%) and 1,3,4-trifluoro-7-methylpyrido [4,3-c]benso[1.2]diazepine-11-one-9-carboxylic acid (8) (22%).

I-5-2-3- With peroxytrifluoroaetic acid

Tsiliopoulos [29] oxidised the parent diazepine (2'a) with CF_3CO_3H in CH_2Cl_2.Wor up of the reaction product gave two materials, the first of which was believed to be 1,3,4-trifluoro-7,9-dimethyl-11 H-pyrido-[4,3-c]benso[1.2]diazepin-6-oxide (9) (35%). The second was not identified conclusively.



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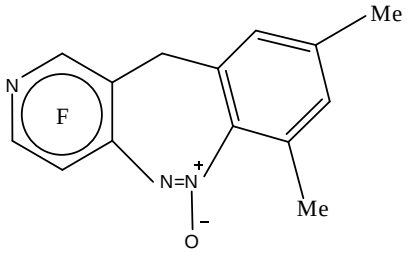

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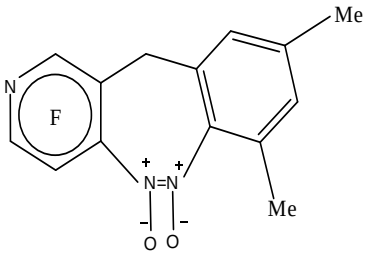

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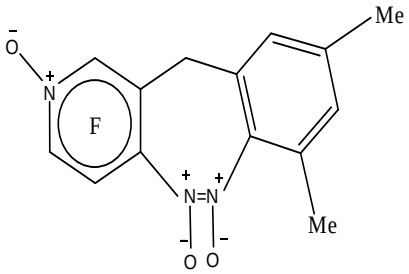


12

Subsequently Djebli [30] reacted diazepine (2'a) with glacial acetic acid and 30% H_2O_2 to give a mixture of 2 mono-oxides 1,3,4-trifluoro-7,9-dimethyl-11 H-pyrido-[4,3-c]benso[1.2]diazepin-6-oxide (9) (39%) and the corresponding 5-oxide(10) (20%). The structure of isomer (9) was established absolutely by X- ray crystal analyses and this enabled "rules" regarding ^{19}F n.m.r. parameters to be established.

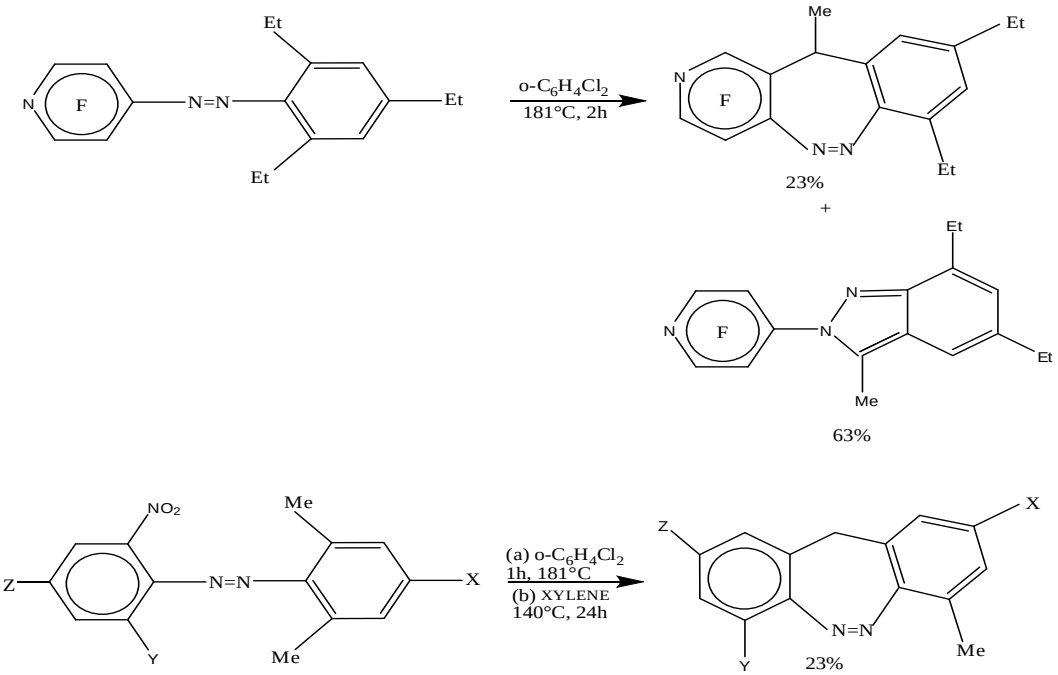
When Djebli [30] used CF_3CO_3H to oxidise the diazepine (2'a), the 6-oxide was accompanied higher oxidic material, shown to be 1,3,4-trifluoro-7,9-dimethyl-11 H-pyrido-[4,3-c]benso[1.2]diazepin-5,6-dioxide(11). That the dioxide had structure (11) and did not, therefore, involve oxidation of the nitrogen of the pyridine ring was established by an X-ray analysis carried out by Dr R.G. Pritchard.

Finally; two attempts were made by Djebli [30] to prepare tri-oxide (12) .

The first attempt was by the use of H_2O_2 with a mixture of 1,3,4-trifluoro-7,9-dimethyl-11 H-pyrido-[4,3-c]benso[1.2]diazepin-5-oxide(10) and the corresponding 6-oxide (9) inglacial acetic acid; this gave only starting materials in quantitative yield.

I- 6- Other [1.2]diazepine:

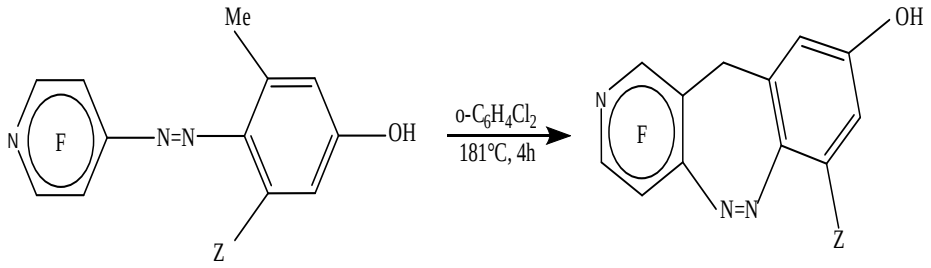
The number of [1.2]diazepine were prepared using other method (scheme 10- 12)



(1) X= Me, Y= Br, Z= NO_2

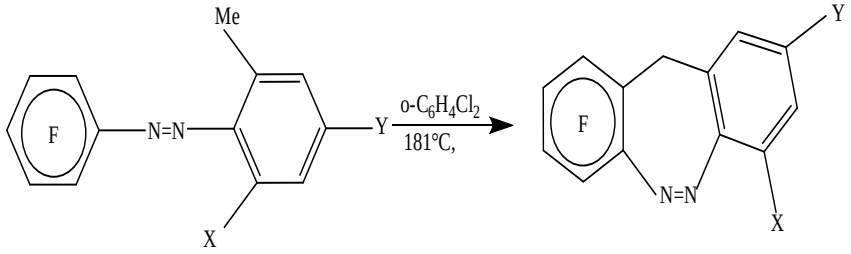
(2) X= Oet, Y= NO_2, Z= H

Scheme 10



Z = H
Z = Me

Scheme 11



(1) X= Y= H
(2) X= H, Y= Me
(3) X= Me, Y= H

Scheme 12

I-7-High Performance Liquid Chromatography (HPLC):

Chromatography is a way to:

*separate mixtures of compounds

*identify unknown compounds

*establish the purity or concentration of compounds

*monitor product formation

All chromatography involves transporting a sample along a mobile phase, which can be a liquid (liquid chromatography) or a gas (gas chromatography). High Performance Liquid Chromatography (HPLC) was developed along the principles of Thin Layer Chromatography (TLC) but is fully automated and more quantitative [31- 33].

I-7-1-General HPLC Column Care:

The stationary phase comprises a column which is usually stainless steel and packed with silica particles bonded with alkyl chains. The length of the chain will depend on the type of molecule being analysed. The length of the chain will depend on the type of molecule being analysed. For example, for large protein molecules a C4 column could be used but for smaller molecules C8 or even C18 may be more appropriate [31- 33].

Figure 1: HPLC column

I-7-2-Silica based columns :

Stationary phases based on silica are mechanically very stable. Silica based stationary phases are compatible with all organic solvents in the above mentioned pH range. In general, HPLC columns are stable within a pH range of 2 to 8. If you are measuring a pH value, the measurement must be done in the aqueous media before mixing the eluent with organic solvents. The use of non pure solvents in HPLC causes irreversible adsorption of impurities on the column head. These impurities block adsorption sites, change the selectivity of the column and lead to peak splitting in the chromatogram. In gradient elution, impurities cause so called "Ghost Peaks".

For long term storage, silica based columns should be stored in an aprotic solvent. The water content should not be higher than 50%. The best storing solvent is Acetonitrile.

The equilibration time of a column depends on the column dimensions. In general, a column is equilibrated after flushing with 20 column volumes. The equilibration time for the most important column dimensions is summarized in the following table[31- 33].

Table 1: The equilibration time for the most important column dimensions

Column dimension	Column volume [ml]*	Flow rate [ml/min]	Equilibration time [min
250 x 4.6 mm	2,91	1,00	58
150 x 4.6 mm	1,74	1,00	35
100 x 4.6 mm	1,16	1,00	23
50 x 4.6 mm	0,58	1,00	12
250 x 4.0 mm	2,20	1,00	44
125 x 4.0 mm	1,10	1,00	22
250 x 2.0 mm	0,55	0,25	44
150 x 2.0 mm	0,33	0,25	26
50 x 2.0 mm	0,11	0,25	9

*_T = 0,7

20 column volumes are necessary to ensure a 100% equilibration.

I-7-3-Regeneration of a column:

Irreversible adsorption of impurities stemming from the matrix on the column head can cause changes in selectivity or peak splitting. Often those "dirty columns" can be regenerated by applying the following protocols.

I-7-4-Regeneration of RP packings:

RP- packings are C18, C8, C4, C1, C30, CN or Phenyl stationary phases.

• Flush the column with 20 column volumes Water
• Flush the column with 20 column volumes Acetonitrile
• Flush the column with 5 column volumes Isopropanol
• Flush the column with 20 column volumes Heptane
• Flush the column with 5 column volumes Isopropanol
• Flush the column with 20 column volumes Acetonitrile

I-7-5-Regeneration of NP (Normal Phase) packings:

NP-packings are Silica, Diol, Nitro and Amino stationary phases.

• Flush the column with 20 column volumes Heptane
• Flush the column with 5 column volumes Isopropanol
• Flush the column with 20 column volumes Acetonitrile
• Flush the column with 20 column volumes Water
• Flush the column with 20 column volumes Acetonitrile
• Flush the column with 5 column volumes Isopropanol
• Flush the column with 20 column volumes Heptane

I-7-6-Regeneration of Ion Exchange Packings:

Ion exchange packings are Anion or Cation exchangers (WCX, SCX, WAX and SAX)

• Flush the column with 20 column volumes of the same eluent, but double the buffer concentration
• Follow the regeneration protocol for RP packings (see above)
• Flush with 20 column volumes of Water
• Equilibrate the column now to the original conditions [31- 33].

I-7-7-Polymer based columns:

Polymer based stationary phases show higher pH stability but lower mechanical stability, compared to silica based columns. Also, polymer based packings are not compatible with all organic solvents. They swell or shrink in some organic solvents. Unfortunately, the pressure stability and solvent compatibility are different for the different nature of polymers and from manufacturer to manufacturer. Therefore, no general rules for the

column care of polymer based materials can be given. Always read the instructions for the use of those columns. In case of doubt please contact the corresponding manufacturer.

I-7-8-Sample detection:

After the sample passes through the column, it is detected by ultraviolet absorption. For many compounds this is usually at 254nm. The sample and the mobile phase are collected as waste and the absorption spectrum is outputted as a chromatogram. This process is fully automated and controlled by a PC. The time taken for a sample to pass through the system is recorded as its retention time and is one of the characteristics used to identify a compound. Retention times can vary from a few minutes to an hour. The area under a peak is used for calculating the concentration of a sample [31- 33].

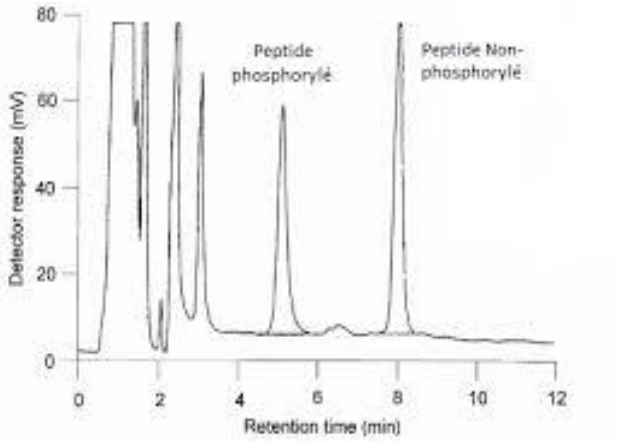


Figure 2: HPLC chromatogramme

I-7-9-Uses of HPLC:

In the pharmaceutical industry the purity of drugs can be calculated by first running a series of standards at known concentrations. A curve is then plotted of the concentration of the standards (x axis) versus their peak area (y axis). The drug samples to be tested are injected and from the chromatogram peak areas, it is possible to calculate the concentration of the drug sample [31- 33].

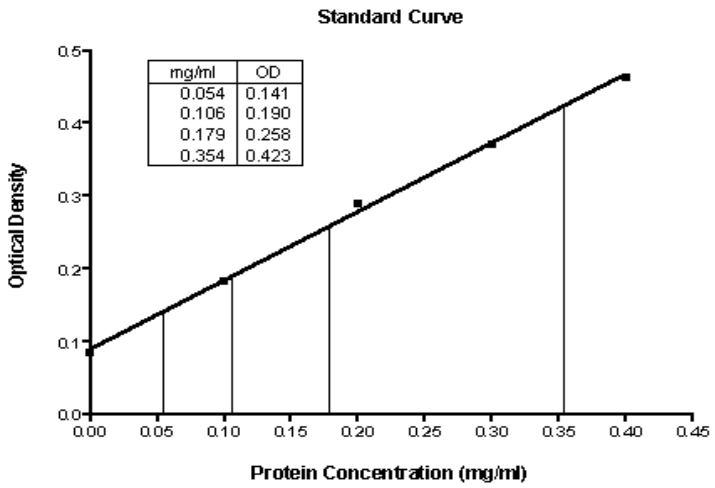


Figure 3: Standard curve used to calculate concentrations

HPLC can also be used to separate enantiomers. Enantiomers are molecules that contain the same number of atoms but the different groups have different spatial arrangements so that they are non superimposable mirror images.

Both forms often exhibit very different characteristics in biological systems. The most famous case being that of thalidomide, which was manufactured as a racemic mixture (50:50) of two enantiomers. One enantiomer was effective in treating morning sickness but the other caused side effects. Identifying and separating enantiomers is key when developing drugs that have a chiral centre. HPLC allows chemists to confirm which enantiomer is present and calculate the ratios where both are present. HPLC is also used to monitor product formation in chemical reactions [31- 33].

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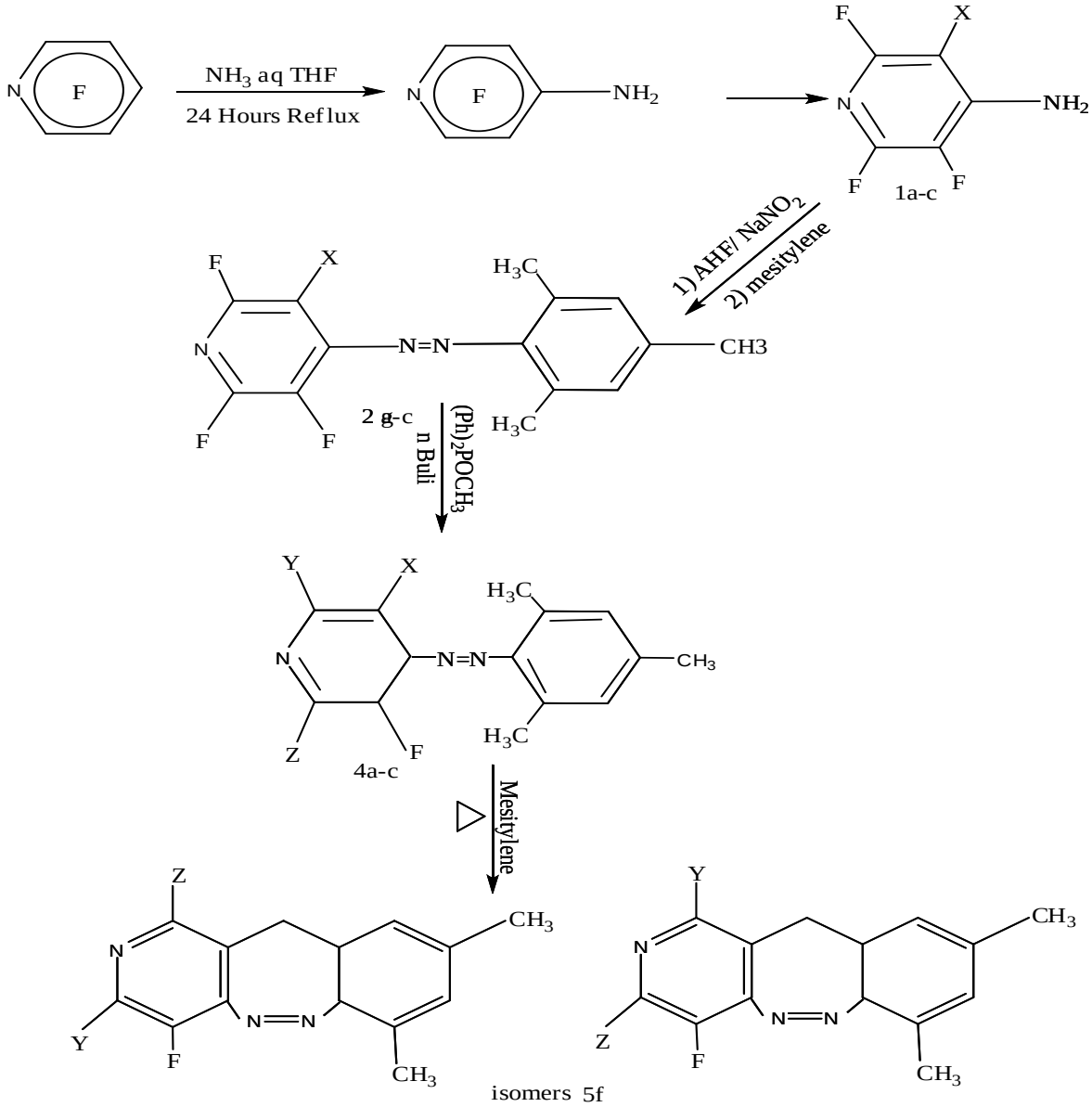
II-1 Preamble



Scheme 13

1a : X= F

1b : X= Cl

1c : X= OMe

2a : X= F

2b : X= Cl

2C: X= OMe

4a : X= F, Y= F, Z= $(Ph)_2POCH_2$

$4b_1$:X= Cl, Y= F, Z= $(Ph)_2POCH_2$

$4b_2$: X= Cl, Y= $(Ph)_2POCH_2$, Z= F

$4c_1$: :X= OMe, Y= F, Z= $(Ph)_2POCH_2$

$4c_2$: X= OMe, Y= $(Ph)_2POCH_2$, Z= F

$5f_1$: Z= F, Y= $(Ph)_2POCH_2$

$5f_2$: Z= $(Ph)_2POCH_2$, Y= F

Results and Discussion

Part I

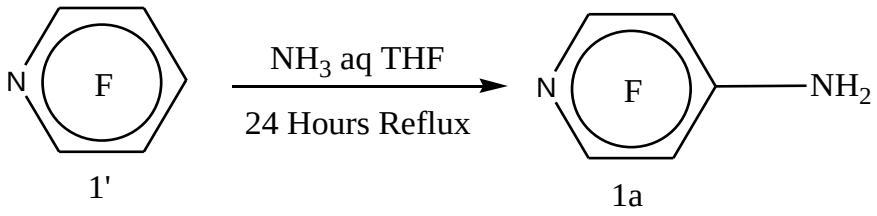
The first aim of the project was to attempt a synthesis fluorinated azo and diazopine compounds of phosphorus of type **4a -c** and **5f,** in order to support the development synthesis of biological active.

II-2- Synthesis of the derivatives (2,4,6-trimethyl phenylazo) pyridines:

background

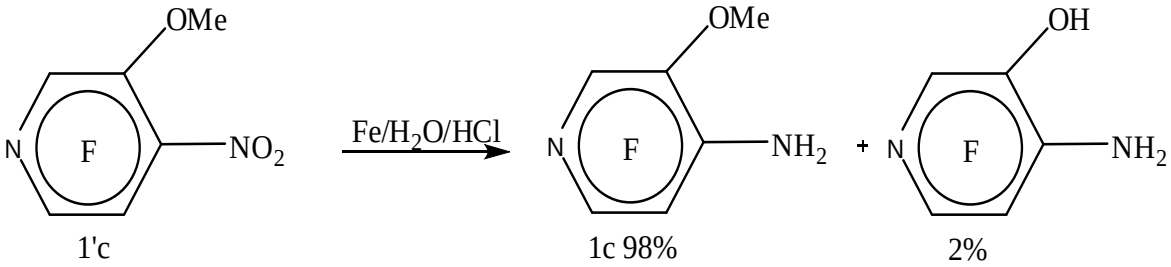
The purpose of using mixture of 98% H_2SO_4 CH_3CH_2COOH was found to be give better yield of these azo compound **4a-c**.

4-amino tetra fluoropyridine was prepared from penta fluoropyridine and aqueous ammonia (scheme14)



Scheme 14

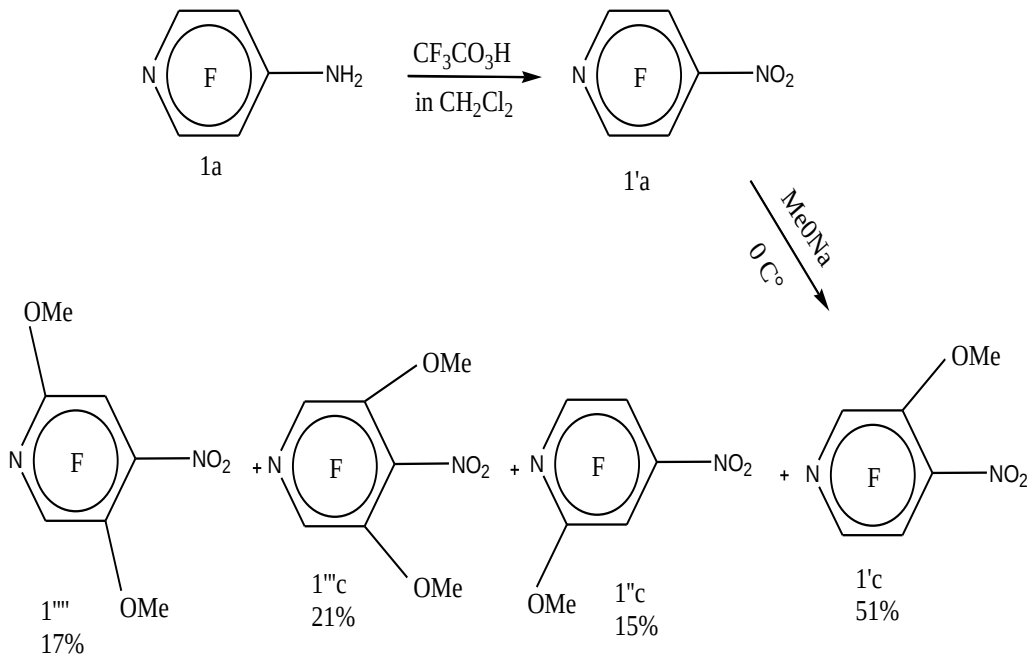
This preparation was repeated several times in order to produce large quantities of starting material of 4-amino -3- chlorotrifluoropyridine was commercially available 4-Amino -2,5,6 – trifluoro- 3-methoxpyridine prepared form 3-Nitro -2,5,6 - trifluoromethoxpyridine and (Fe/H_2O/HCl) (scheme 15).



Scheme 15

The reduction is preferred since the saving of one step it has been the subject of comsiderable effort due to their importance in synthesis.

3-methoxy-2,5,6- trifluoro – 4 – nitropyridine 1’c prepared form 4 – amino tetrafluoropyridine and methanolic sodium methoxide (scheme 16)



Scheme 16

II-2-1- Preparation of starting Aminopyridine:

4 – Amino – 2,3,5,6-tetrafluoropyridine **1a** was first prepared in the early 1960's by Banks et Al [1] and by Chambers and his co-workers [2] via nucleophilic attack of aqueous ammonia on pentafluoropyridine. Alty used a modification of those procedures, employing THF as solvent and obtained **1a**.

4 – Amino – 2,3,5,6-tetrafluoropyridine m.p 84 - 86 C°, a compound was prepared in 81% % yield by using the procedures described earlier by Alty (scheme 16).It was identified by IR. Spectroscopy [primary amine NH st in the region 3500 – 3100 cm^{-1}], the spectrum showed a strong band at 1360 cm^{-1} corresponding to C-F group. In the mass spectrum the base peak at 165 m/e (100%) [M+ H^+] and [M-NH_2] at 150 m/e (42%), the ^{19}F spectrum comprised three doublet of doublets of equal intensity at (- 15.1, 2F, s) and (- 85.1, 2F, s)

Tetrafluoro -4- nitropyridine 1'a was prepared by Chambers and his co-workers [3- 8] as shown in scheme 16, and the author also prepared this compound for futher work on azo-compound by using Chambers' procedure (for more details, see the experimental section).

As shown by Chambers et Al [3- 8] , Tetrafluoro -4- nitropyridine undergoes nucleophilic substitution by Nu (charged nucleophile in case of Tetrafluoro -4- nitropyridine at the 4-position, whereas ortho attack is preferred [3- 8],Chambers et Al showed that Tetrafluoro –

4- nitropyridine reacted simply with ammonia on bubbling the gas through its ether solution at 0C° for 4 hours. The solution wad filtered and ether was distilled off in vacui to leave an orange solide4-Amino -2,5,6 – trifluoro- 3-methoxpyridine m.p (92-94°C) a compound was prepared in 98% yield by the author (scheme 15) using the procedure used to obtain the corresponding tetrafluoro- compound. It was identified by elemental analysis and ^{1}H an ^{19}F n,m,r. In order to prepare 1'c, the first step involved the preparation of 1a' from 1a and trifluoroacetic anhydride in metylene choride. The seconde step was to attempt the synthesis of 1c' with the use of methanolic sodium méthoxide which are sumnarised in (scheme 16) The sepration was carriect out HPLC analysis, Chromatographic fractionation of the dinoflagellate or fish components in the crude extract was accomplished using [Daicel Co – 250 mm x 46 mm chiracel OD column, 15% i- ProH in Hexane 1mol/min]. The eluant was collected in 1 minute fractions using a Gilson Model FC-80K Fractionator (Gilson Medical Electronics, Middletown,Wis.). As evident from their typical chromatographic profile good separation and a distinctive elution pattern were obtained (Figure 4) , the eluation was eluted between 4 and 16(Table 2).

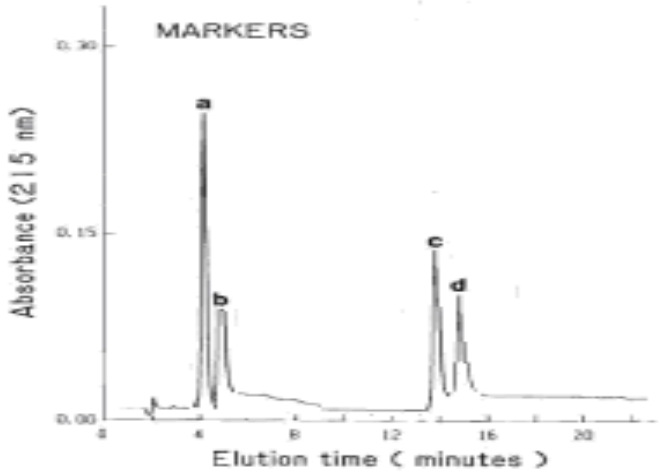
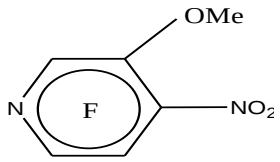
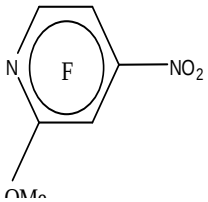
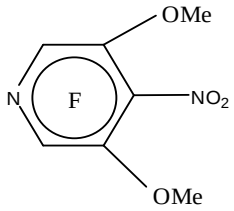
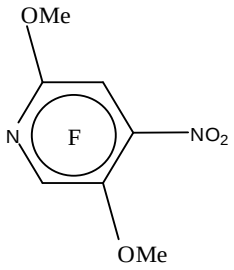


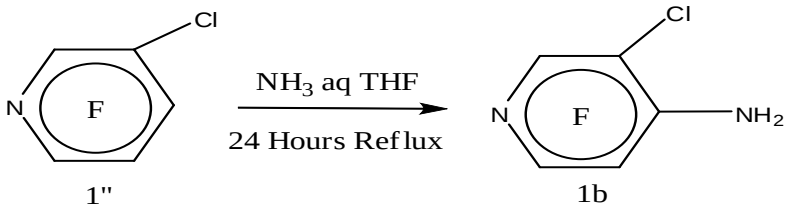
Figure 4: chromotographic profiles of mixter, Daicel Co – 250 mm x 46 mm chiracel OD column, 15% i- ProH in Hexane 1mol/min

Table 02: performance data for the proposed HPLC method

Compound	N	Yield%	Retention time(min)
	a	51	4.77
	b	15	5.08
	C	21	13.9
	d	17	15.21

Products 1a' and 1'c were identified by elemental analysis and spectroscopic data the ^{19}F spectrum of compound 1'c showed tree peaks at – 3.1, - 27.5 and – 80.3 IR spectra of compound 1a' and 1'c were very similar absorptions revealed the presence of the NO_2 group at 1550.7 cm^{-1}.

The reaction of 1'c with (Fe/ H_2O/ HCl) has be found to be a convenient synthsis of **1c** (scheme 15). The purity of this compound was confirmed by elemental analysis and their structures was firmly established spectroscopially. **1b** was prepared from 3-chlorotetrafluoropyridine (scheme 17)

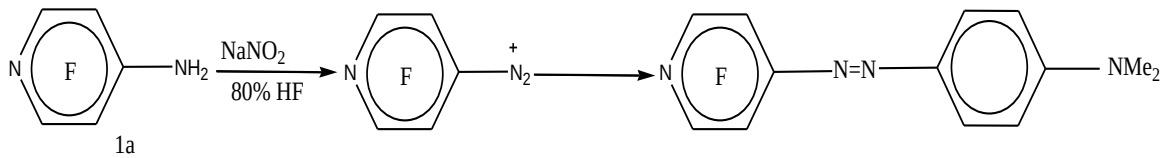


Scheme 17

II-2-2- Preparation of fluorinated azo compounds:

Diazotization of negatively- substituted aromatic amines usually requires special conditions, but diazotization of 4 – Amino tetrafluoropyridine **1a** was further complicated by the possibility of loss of fluoride ion from the diazonium salt, a difficulty which has been encountered by using fluoride- rich diazotization media [9, 10].

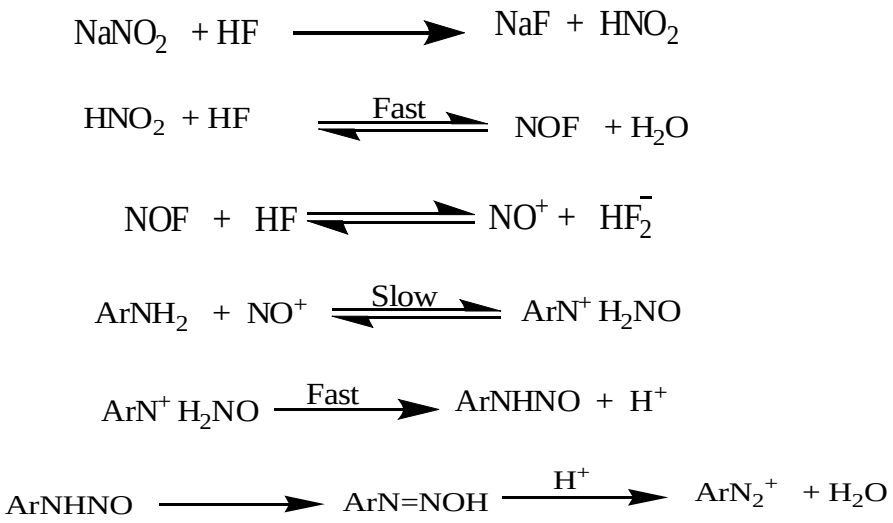
4- aminotetrafluoropyridine **1a** was diasotised to **2a** proceeds via two steps, first synthesis of starting aminopyridines, in the seconde step the studies on the thermal comversion of the previous fluorinated azo pyridines .Chambers and his co-workers successfully performed the diazotization of **1a** with sodium nitrite in a medium of hydrofluoric acid (80% HF). At -20°C this provides tetrafluoropyridine-4- diazonium fluoride, which couples with NN-dimethyl aniline to give 4- NN- dimethylaminophenylazopyridine



Scheme 18

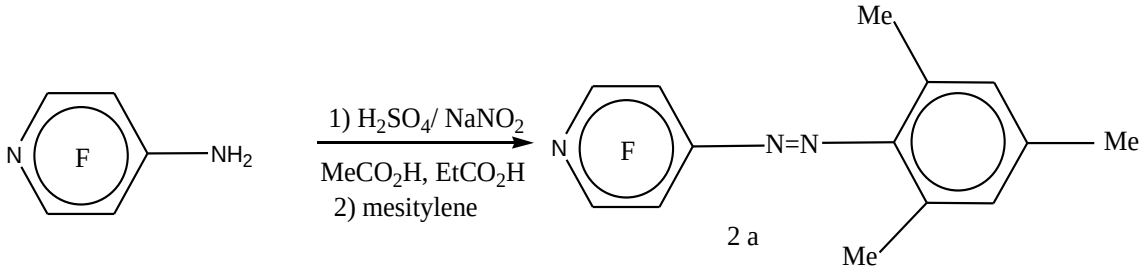
Banks et al [11] successfully performed the diazotization of hydrofluoric acid (80% HF) to – 50 C° before adding the mesitylene they obtained the derivatives 2,4,6-trimethyl phenylazo) pyridines in 15%- 20% yield subsequently, Alty et al [12] found that a much better yield of this azo-compound could be achieved using anhydrous HF as the diazotization medium.

The mechanism of diazotization of fluorinated amines in AHF



Scheme 19

In contrast to the previous methods, Alty [13] also showed that the diazotization could be achieved by adding the 4- aminotetrafluoropyridine to a solution of sodium nitrite in a mixture of 98% H_2SO_4, CH_3COOH and CH_3CH_2COOH subsequent coupling with mesitylene at room temperature gave the azo-compound **2a** in 82% yield (scheme 20).



Scheme 20

The mechanism of diazotization of fluorinated amines in 98% H_2SO_4

$$NaNO_2 + H_2SO_4 \longrightarrow NaHSO_4 + HNO_2$$

$$HNO_2 + H_2SO_4 \overset{\text{Fast}}{\rightleftharpoons} NO^+ HSO_4^- + H_2O$$

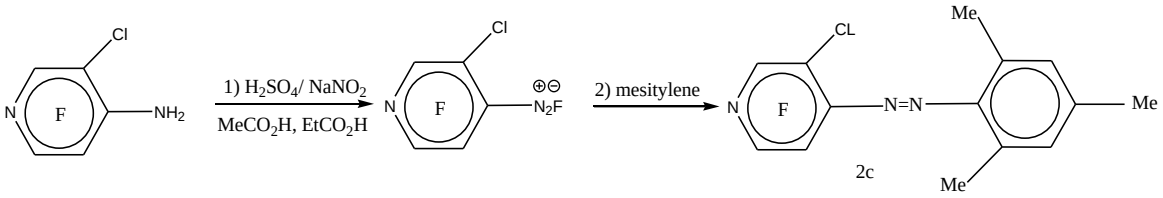
$$ArNH_2 + NO^+ \overset{\text{Slow}}{\rightleftharpoons} ArN^+ H_2NO$$

$$ArN^+ H_2NO \xrightarrow{\text{Fast}} ArNHNO + H^+$$

$$ArNHNO \xrightarrow{\text{Fast}} ArN_2^+ + OH$$

Scheme 21

3- chloro -2,5,6 – trifluoro - 4- (2,4,6 –trimethylphenylazo)pyridine **2b** m.p 150-151°C a compound not studeid by alty was prepared in 82% by the author using the procedure used to obtain the corresponding tetrafluorocompound (scheme 22)



Scheme 22

The novels fluorinated azo compounds were identified by a satisfactory elemental analysis and through spectroscopie methods. The IR spectrum showed strong absorptions peak at 1600.8, 1558.4 and 1581.5 cm^{-1} due to N=N.

The mass spectrum showed the$[M+H]^+$ peak at m/z 119 which was also the base peak.

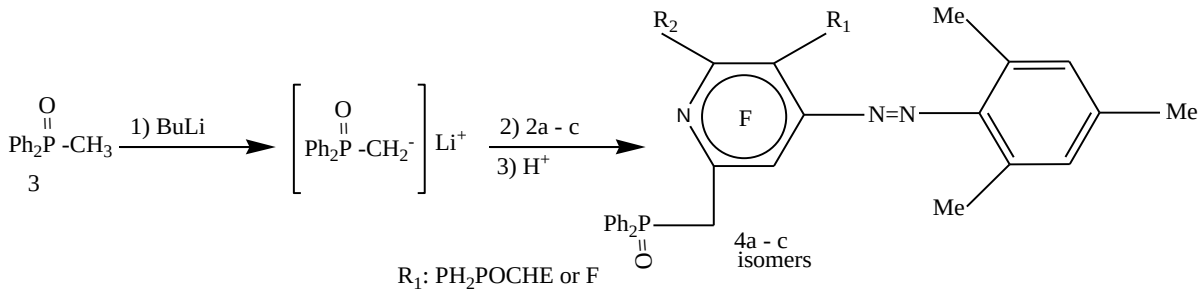
The ^{19}Fn,m,r spectrum of 2,3,5,6- tetrafluoro - 4 –(2,4,6- trimethylphenylazo)pyridine **2a** m.p 143°C, isolated in 82% showed two absorption bands of intensity 1:1 at – 75.5, - 11.2 ppm, fluorinated azo compounds (2c) 77% yield showed only three ^{19}Fn,m,r absorptions of intensity at – 15.8, - 75.8 and – 98.7 ppm.

We also examined aqueous ammonia to pentafluoropyridine because it is much easier, cheaper and less dangerous to use than ammonia gaz.

II-2-3- Synthesis of phosphorus fluorinated 2,4,6 – trimethyl phenyl azo pyridine:

Back ground:

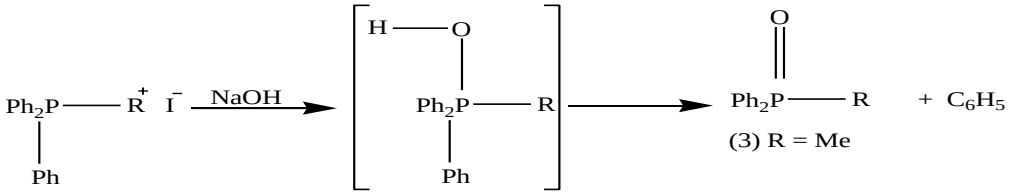
The phosphorus fluorinated was prepared by our reported procedure which involed dropwise addition of an equimolar quantity of a solution of n-buLi in hexane to a stirred solution of methyldiphenylphosphine oxide in dry THF at 0°C, then cooled to around -78°C, treated with (2,4,6 trimethylphenylazopyridines and then allowed to warm at room temperature over 2 hours [8-12]. Work up of the reaction product gave the corresponding phosphorus fluorinated azo compounds (scheme 23).



Scheme 23

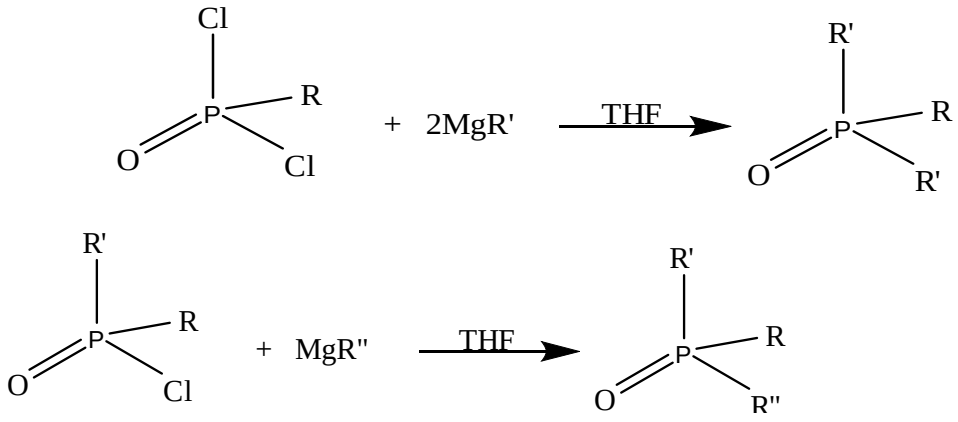
II-2-4- Preparation of methyldiphenylphosphine oxide:

Phosphine oxides may be synthesized using a variety of techniques , the thermal decomposition of alkyl triphenylphosphinium hydroxides represents one of the easiest ways to make phosphine oxides from readily available materials. This involves simply heting the corresponding alkyl triphenylphosphinium halide with 20 – 40% sodium hydroxide solution.This procedure is suitable for the synthesis of phosphine oxide when the carbanion of the displacement follows the order alkyl> benzyl> phenyl> 2-phenylethyl> ethyl> higher alkyl. This benzyl and alkyl phosphine oxides must be made by other methods.



Scheme 24

Grignard reation can also be applied to the synthesis of phosphine oxides; for example , Kormachev et al.[14] showed that dialkylaryl and alkylaryl phosphine oxides could be synthesized using alkyl Grignard reagents, as illustrated by the equations below



Scheme 25

Methyldiphenylphosphine oxide was either commercially or can be prepared by the procedure described in the experimental.

II-2-5- Preparation of phosphorus and fluorinated azo compounds:

The aim was to prepare the compounds **4a-c**.The preparation started with R_1= F and the product was easily isolated as a solid. The crude product obtained by concentration on the rotatory evaporator ,was further dried on the high vacuum line and purified by recrystallisation. The product was identified by elemental analysis and spectral data

The last product is new and was identified by IR spectroscopy P=O st in the region (1040-1180 cm^{-1}). Phosphorus fluorinated 2,4,6-trimethylphenylazopyridines **4a-c** were synthesized according to the procedures reported in Scheme 22.The general procedure involves drop wise addition of an equimolar quantity of a solution of *n*-BuLi in hexane to a stirred solution of methyldiphenylphosphine oxide in dry THF at 0°C, then cooled to around -78°C. Fresh solutionazo-pyridines(**2a-c**) [15] was added in one portion. After the addition was complete, the red color of the anion had disappeared. The resulting pale yellow solution was stirred for 15 min at -78°C, then allowed to warm to room temperature over 2 h. Work-up of the reaction product gave the corresponding phosphorus fluorinated compound **4a-c** in high yields ranging from 76 to 89% after purification by column chromatography.

The obtained products were identified by elemental analysis and spectral data. The IR spectrum of the compounds showed characteristic P=O stretching at frequency in the region (1040-1180 cm^{-1}). The proton coupled ^{1}H NMR of compound **4b** and **4c** showed a singly centered at δ 3.33 and 3.32 ppm corresponding to the CH_2 group. The mass spectrum of compound **4a**, **4b** and**4c** showed the base peaks at *m/z*493, 474 and 490, respectively, and clearly showed the presence of $(Ph)_2P=O$ and C_9H_{11} in the chemical structure. Crystallization of compound **4a** from ethylacetate gave crystals in 81% yield. Thus, attack by nucleophilic at the position 2 (or 6) has a faster rate than that at the 3- (or 5-) position. The preferential substitution at the 2- or 6-position because the result was by attained the essence compound. The substitution in these positions was preferred comparison with the 3- or 5-position because they offered a stable position the X-ray single crystal diffraction analysis showed the conformation of this bond ,the crystal data are listed in Table3.We have succeeded in achieving the nucleophilic aromatic substitution of the fluoro group in compound **2b** with $(Ph)_2$-$POCH_2$- anion at 2- and 6-position, thus obtaining compound **4b** isomers. The substitution at the 2- or 6-positionin exchange for the 5-position because they are crowd in this position.

Compound **4b** and **4c** were resolved into the corresponding isomers (Scheme 13) by chiral chromatography using a ChiralcelOD column in a high degree of optical purity. These separations were amenable to semi-preparative scale.

Table 3: Crystal data of compound **4b** and **4c**.

Parameters	**4b**	**4c**
Chemical formula	$C_{27}H_{23}ON_3F_2ClP$	$C_{28}H_{26}O_2N_3F_2P$
Crystal system	Orthorhombic	Orthorhombic
Cell dimension, Å	*a* = 9.940(2)	*a* = 12.773(2)
	b = 25.077(7)	*b* = 6.694(3)
	c = 7.654(2)	*c* = 11.890(2)
Cell volume, $Å^3$	1907.7(3)	1006.1(5)
Space group	*P*2/*c* (no. 13)	*P*21/*c* (no. 14)
Z	4	4
ρ(calc.), g/cm^{-3}	1.13	1.11
μ, cm^{-1}	2.0	1.7

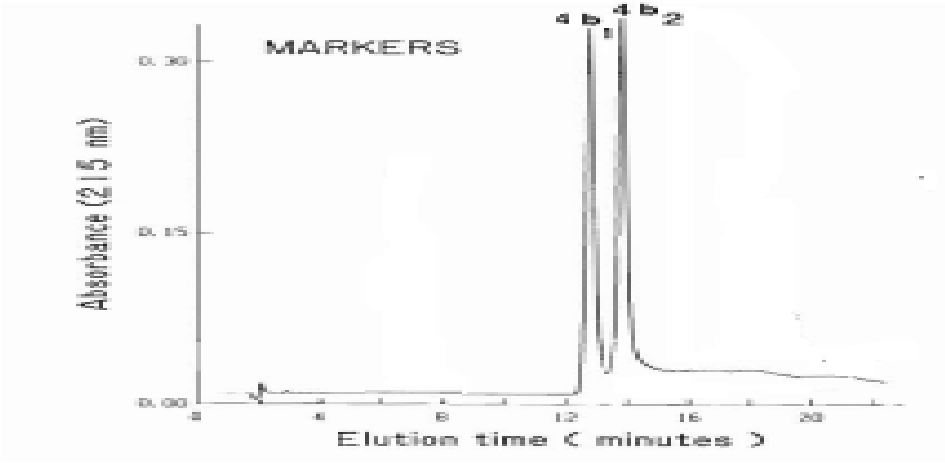


Figure 5: chromotographic profiles of 4b, Chiralcel OD-H column, hexane:2- PrOH, (9:1, *v*:*v*) mobile phase, flow-rate, 1.0 mL/min

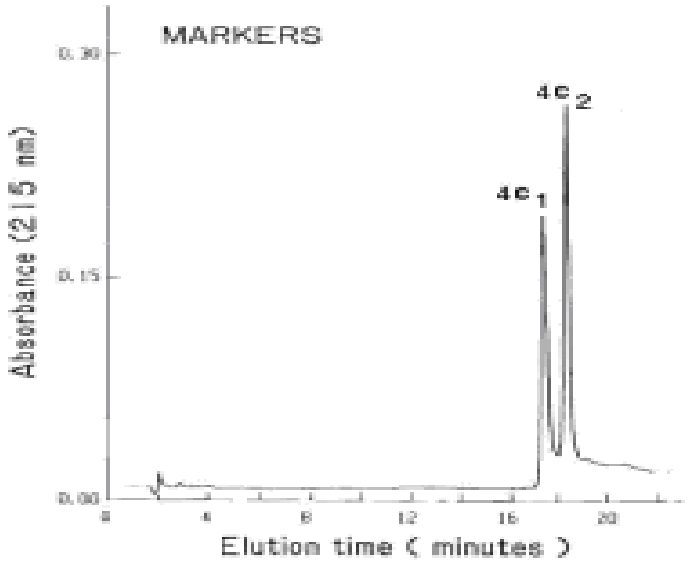


Figure 6: chromotographic profiles of 4b, Chiralcel OD-H column, hexane:2- PrOH, (9:1, *v*:*v*) mobile phase, flow-rate, 1.0 mL/min

The phosphorus and fluorinated azo compounds **4b$_1$**(M.p.: 194-196°C) was identified by elemental analysis and spectroscopic methods.The ^{1}H NMR spectrum showed four absorptions. The ^{19}F NMR spectrum showed two doublet absorption bands of equal intensity at δ -14.5(F2) and -84.3(F5) ppm which suggests tha tthe $(Ph)_2$-$POCH_2$- group lies in position 6 not 2. the bond distances and bond angles are given in

Table 4and5.The mass spectrum of compound **4b$_1$**showed a molecular ion at *m/z*119 and 201 clearly showed the presence of C_9H_{11} and $(Ph)_2$-P=O in the chemical structure and a base peak at *m/z*474.

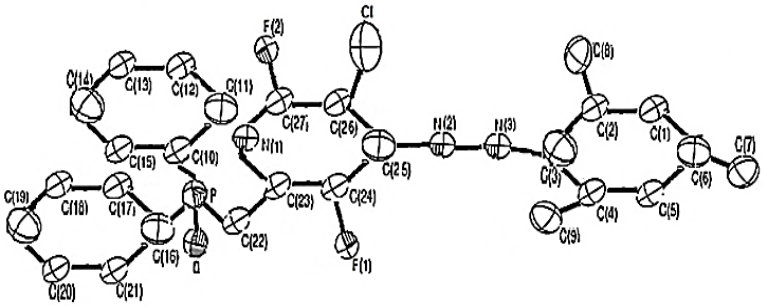


Figure 7. Molecular structure of **4b$_1$**, showing the atoms labelling (hydrogen atoms are omitted for clarity).

.

The other novel isomer compound **4b$_2$**(M.p.: 190-192°C) was also identified by elemental analysis and spectroscopically. The IR, ^{1}H NMR and the mass spectrum were very similar to that of compound **4b$_1$**. It's^{19}F NMR spectrum showed two doublets absorptions of equal intensity at δ -9.4 and -79.0ppm, which suggests that the $(Ph)_2$-$POCH_2$ group lies in position 2 not 6,the new structure ofcompound **4b$_2$** present in Figure 8 was elucidated by single crystal X-ray diffraction analysis. The bond distances and bond angles are listed in Table 3and 4.

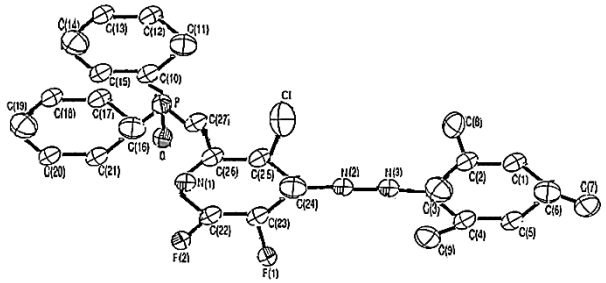


Figure 8. Molecular structure of compound **4b$_2$**, showing the atoms labelling (hydrogen atoms are omitted for clarity).

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Isomers **4c** was separated by on analytical HPLC to give compound **4c$_1$** and **4c$_2$** (Scheme 13). The structure of compound **4c$_1$** and **4c$_2$**presented in Figure 9 and 10 was elucidated by single crystal X-ray diffraction analysis and reveals new carbon atom bonded together, C(25)-C(26) for compound **4c$_1$**, new carbon atom C(22)-C(23) for compound **4c$_2$** for compoundand the distance between them (Table4).

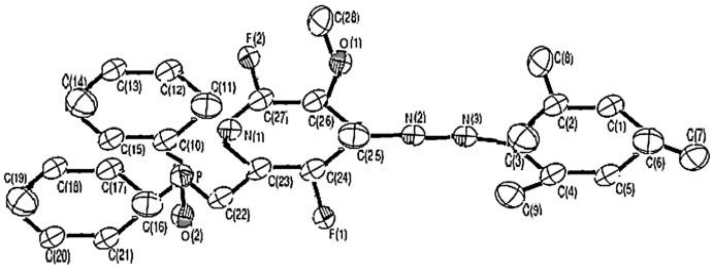


Figure 9. Molecular structure of **4c$_1$**, showing the atoms labelling (hydrogen atoms are omitted for clarity).

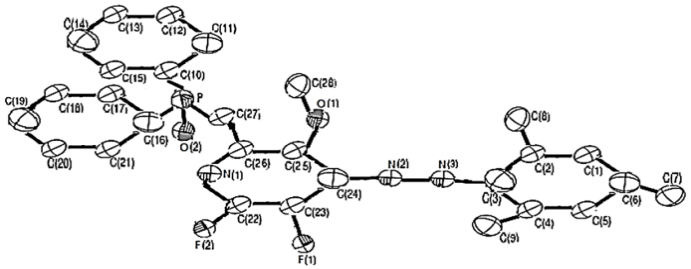


Figure 10. Molecular structure of **4c$_2$**, showing the atoms labelling (hydrogen atoms are omitted for clarity).

Table 4. Selected bond lengths (Å).

Compound 4b$_1$					
C(26)-C(27)	1.3401(6)	C(22)-C(23)	1.5090(16)	P-C(10)	1.8560(17)
C(24)-C(25)	1.3340(8)	C(23)-N(1)	1.2600(10)	P-C(16)	1.8560(17)
C(2)-C(8)	1.4970(24)	C(27)-N(1)	1. 2600(7)	P-C(22)	1.8560(15)
C(4)-C(9)	1.4970(23)	C(24)-F(1)	1.3920(2)	C(3)-N(3)	1.3430(4)
C(6)-C(7)	1.4970(23)	C(27)-F(2)	1.3920(9)	C(25)-N(2)	1.3430(3)
Compound4b$_2$					
C(26)-C(27)	1.5090(28)	C(22)-C(23)	1.3340(30)	P-C(10)	1.8560(25)
C(24)-C(25)	1.3340(32)	C(22)-N(1)	1.2600(36)	P-C(16)	1.8560(17)
C(2)-C(8)	1.4970(21)	C(26)-N(1)	1.2600(36)	P-C(27)	1.8560(19)
C(4)-C(9)	1.4970(21)	C(22)-F(2)	1.3920(30)	C(3)-N(3)	1.2600(36)
C(6)-C(7)	1.4970(22)	C(23)-F(1)	1.3920(33)	C(24)-N(2)	1.2600(29)
Compound4c$_1$					
C(26)-C(27)	1.4170(36)	C(22)-C(23)	1.5090(25)	P-C(10)	1.8560(24)
C(24)-C(25)	1.4170(36)	O(1)-C(28)	1.5090(36)	P-C(16)	1.8560(16)
C(2)-C(8)	1.4970(24)	C(26)-O(1)	1.4912(33)	P-C(22)	1.8560(15)
C(4)-C(9)	1.4970(23)	C(24)-F(1)	1.3920(17)	C(3)-N(3)	1.4170(33)
C(6)-C(7)	1.4970(23)	C(27)-F(2)	1.3920(19)	C(25)-N(2)	1.4170(28)
Compound 4c$_2$					
C(22)-C(23)	1.4200(15)	C(25)-C(26)	1.4200(13)	P-C(10)	1.8560(11)
C(26)-C(27)	1.4200(16)	O(1)-C(28)	1.3960(19)	P-C(16)	1.8560(16)
C(2)-C(8)	1.4970(14)	C(25)-O(1)	1.3550(21)	P-C(27)	1.8560(13)
C(4)-C(9)	1.4970(14)	C(22)-F(2)	1.3920(17)	C(3)-N(3)	1.4560(10)
C(6)-C(7)	1.4970(14)	C(23)-F(1)	1.3920(19)	C(24)-N(2)	1.4560(13)

Table 5: Selected bond angles (°).

Compound $4b_1$			
C(10)-P-C(16)	109.5200(11)	C(8)-C(2)-C(3)	121.4000(12)
P-C(22)-C(23)	109.4618(11)	C(9)-C(4)-C(3)	121.4000(12)
F(1)-C(24)-(23)	120.0000(16)	C(24)-C(25)-C(26)	114.5118(14)
F(1)-C(24)-(25)	120.0000(16)	Cl-C(26)-C(27)	122.7441(18)
F(2)-C(27)-N(1)	117.2559(16)	Cl-C(26)-C(25)	122.7441(18)
Compound$4b_2$			
C(10)-P-C(16)	109.5200(10)	C(8)-C(2)-C(3)	121.4000(12)
P-C(27)- C(26)	109.4618(10)	C(9)-C(4)-C(3)	121.4000(12)
F(1)-C(23)-C(22)	115.0000(10)	C(24)-C(25)-C(26)	117.2559(12)
F(1)-C(23)-C(24)	120.0000(16)	Cl-C(25)-C(26)	122.7441(18)
F(2)-C(22)-N(1)	116.5000(11)	Cl--C(25)-C(24)	122.7441(18)
Compound$4c_1$			
C(10)-P-C(16)	109.4618(10)	C(8)-C(2)-C(3)	121.4000(12)
C(10)-P-C(22)	109.5200(17)	C(9)-C(4)-C(3)	121.4000(12)
F(1)-C(24)-C(23)	120.0000(16)	C(24)-C(25)-C(26)	120.0000(11)
F(1)-C(24)-C(25)	120.0000(14)	C(24)-C(25)-N(2)	117.2559(10)
F(2)-C(27)-N(1)	120.0000(14)	C(26)-C(27)-N(1)	125.4882(17)
Compound $4c_2$			
C(10)-P-C(16)	109.5200(10)	C(8)-C(2)-C(3)	121.4000(12)
C(10)-P-C(27)	109.5000(10)	C(9)-C(4)-C(3)	121.4000(12)
F(1)-C(23)-C(24)	120.0000(16)	C(25)-C(26)-C(27)	121.4000(12)
F(1)-C(23)-C(22)	115.0000(10)	C(23)-C(22)-N(1)	120.0000(12)
F(2)-C(22)-N(1)	116.5000(11)	C(27)-C(26)-N(1)	125.4882(20)

The novel phosphorus and fluorinated azo compounds **$4c_1$**(m.p. 202-204 °C) possessed satisfactory elemental composition. It's ^{1}H NMR spectrum showed four absorption bands The ^{19}F NMR spectrum showed two doublets absorptions bands of intensity -11.2 and -82.5 ppm which clearly the position of $(Ph)_2$-$POCH_2$ group the mass spectrum showed a molecular ion at 260, 201, 119 and base peak at 490 *m/z*.The isomer **$4c_2$** (M.p.: 201-203 °C) was identified by comparison of its IR and ^{19}F-, ^{1}HNMR spectra.The ^{19}F NMR of compound **$4c_2$**exhibits showed two doublets absorptions bands of intensity -8.1 and -72.2 ppm, the mass spectrum were very similar to that of compound **$4c_1$**.

II-2-6- Synthesis of their corresponding diazepines:

Back ground:

Amuch better technique was found to involve heating the phosphorus and fluorinated azo - compound **4a** in boilling mestiylene complete conversion of starting material into the

corresponging 1,2 diazepine **5f** occured during 24 hours and the latter was isolated in at least 81 -90% yield by dry-column flash chromatography (DCFC) (scheme 13)

Diazepine **5f** (via elimination of HF, HCl and MeOH) on the ring closure of phosphorus fluorinated 2,4,6 trimethylphenylazopyridine **4a-c**.

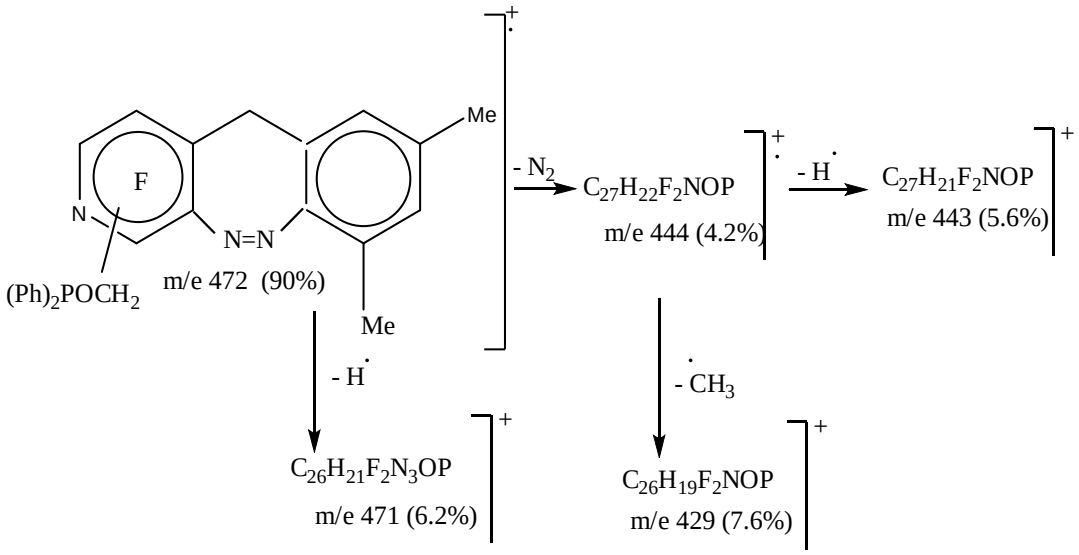
II-2-6-1- Preparation of diazpines:

The method used to prepare the diazepines was adapted from the procedure which was dexised by A.C Aly All the resulting phosphorus and fluorinated azo compounds resulted step 2 thermolyzed in mesitylene to give similar structural isomers of corresponding diazepine **5f** (via elimination HF, HCl, MeOH respectively).

The solution was refluxed and the progress of the reaction was followed by thin layre chromatograp to give unreacted azo compound (3%, 97% conversion) and a yellow – orange compound **5f** (3.88g, 8.32 mmol, 81%) mixture of two isomeris diazepines there were separted by HPLC a C8 silica –based reserse phase 150 mm x 4.6 mm, 5µm ; mobile phase 5% water 95% methanol; flow rate 1.0 ml/minute ; column temperature 30 °C ; detection:UV .

.The new product **5f**contain two isomers these were separated by HPLC, the first was coloeur solid formd to be **$5f_1$** (2.21g, 4.68 mmol, 57 %) mp 212 – 214°C, the second isomer eluted by HPLC was a shiny (coleur) solid shower to be **$5f_2$** (1.67g, 43%) mp 202-210°C. The product **$5f_1$** was identified by ^{1}H,nm,r which 8 absorption of intensity 3, 3, 2, 1,1, 1,1, 10 at 2.3, 2.52, 3.4, 6.85, 7.12, 2.76, 3.00, and 7.03-7.85 ppm respectively.The mass spectrum showed a molecular ion 258 m/e (80%) and a base peak at 272 m/e ($C_{14}H_{12}F_2N_3CH_2^+$, 100), the ^{19}F,n,m,r chemical shift data of compound **$5f_1$** showed the expectes effect of $(Ph)_2$-P=O on F1 F4, the absorptions for which were shifted to – 14.2 (F1) -80.9 (F4) ppm .the mass spectrum of **$5f_2$** showed a molecular ion at 272 m/e which was also the base peak and the compound possessed a satisfactory elemental analysis.

The other novel isomer **$5f_2$** was demonstrated spectroscopically and elemental analysis, the 1H,n,m,r , mass was very similar at that of **$5f_1$,** the ^{19}F,n,m,r spectrum showed two doublet absorption bands of equal intensity at – 9.4 and 76.5 ppm (TEA ext) which suggests that the $(Ph)_2$-P=O group lies in position 1 not 3. The mass spectrum showed a molecular ion at m/e 258 and base peak at 272 m/e (scheme 26)



Scheme 26

The results of separation the isomers **5f** gave **$5f_1$** and **$5f_2$** (Figure 11).

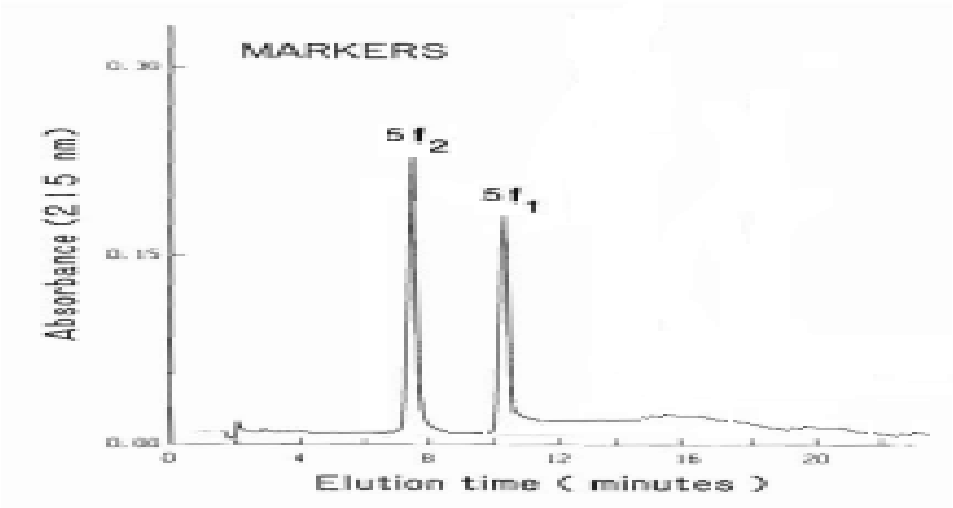


Figure 11 : chromotographic profiles of 5f, C8 silica –based reserse phase 150 mm x 4.6 mm, 5µm ; mobile phase 5% water 95% methanol; flow rate 1.0 ml/minute ; column temperature 30 °C ; detection:UV

The good quality resolution along with the excellent quantitation without response factor ability of the HPLC,gave excellent quantitation for each isomers of **5f** because the sepration by C8 columns is achieved by reverse phase partitioning between the stationary hydrophobic actasilane phase bonded to the silica gel matrix and the moving hydrophilic solvent.The results presented in (table 1) show isomer of $\mathbf{5f_1}$ with retention time of 10.21and $\mathbf{5f_2}$ with retention time of 07.89.

Chosen of mobile phase consisting of water-methanol achieved optimal separation high sensitivity and good peak shape . The detection wavelength at 215 nm Halpe that $\mathbf{5f_1}$, $\mathbf{5f_2}$ have better absorption and sensitivity at this wavelength.

II-2-7-Results and discussion of biological testing:

The diameters of inhibition around the discs were measured using a ruler the diameter of the zone of inhibition as determined by the different concentrations of the different extracts around the discs. It should be noted that a strain whose sensitivity to antibiotics is evaluated and may be declared "sensitive, intermediate or resistant"

II-2-7-1- antibiotic resistance:

Antibiotic resistance is the ability of a microorganism to withstand the effects of antibiotics. [16]

1). Sensitive (S): The categorized S strains are those for which the probability of therapeutic success is strong in the case of systemic treatment.

2). Resistant (R): The categorized R strains are those for which there is a high probability of treatment failure regardless of the type of treatment and dose of antibiotic used.

3). Intermediate (I): I categorized the strains are those for which therapeutic success is unpredictable. These strains are a heterogeneous set for which the in vitro results are not predictive of therapeutic success.

II-2-7-2- bacteriological tested:

II-2-7-2-1 Escherichia coli:

The results presented in the following figures (12-15) show that the antibacterial effect fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines compounds E- diphenyl((3,5,6-trifluoro-4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide **4a** and (E)-((3, 6-difluoro-4-(mesityl diazenyl)-5- methoxypyridin -2- yl) methyl) diphenyl phosphine oxide $\mathbf{4c_1}$ with the Escherichia coli:

Figure12 : Escherichia coli (25-50) ppm

Figure13 : Escherichia coli (100-200- 400) ppm

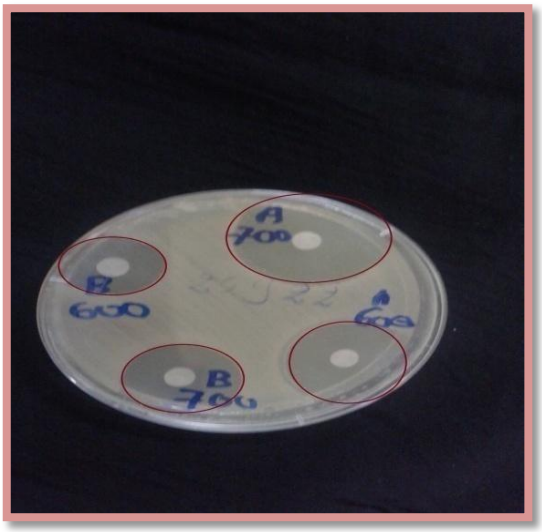


Figure14 : Escherichia coli (600-700) ppm

Figure15 : Escherichia coli (500-800-1000) ppm

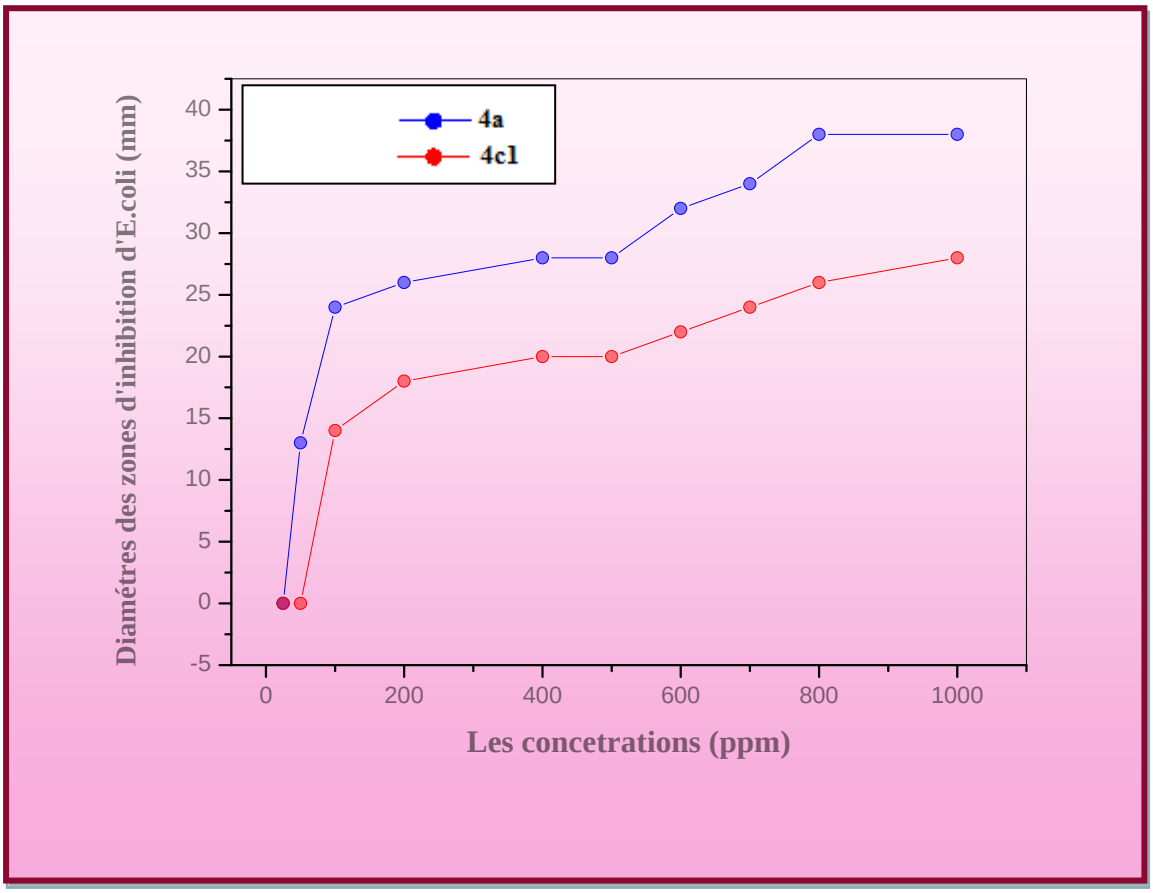


Figure 16: Changes in the diameters of the inhibition zones E. Coli versus concentrations for each 4a and $4c_1$.

Figure 16 represents changes of the diameters of the inhibition areas E. Coli versus concentrations for each fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines compounds **4a** and **$4c_1$**, when the focus 25ppm; **4a** and **$4c_1$** do not give any result (0mm). The point 50 ppm, the fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines compounds **4a** shows the diameter (13 mm) but there is no result for the **$4c_1$** direct correlation relationship. Whenever the concentration decreased from 25ppm to 1000ppm, we see an increase in the diameter but the increase in diameter for **4a** and larger than the fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines compounds **$4c_1$.**

II-2-7-2-2 staphylococcal:

The results presented in the following figures (17- 21) show that the antibacterial effect **4a** and **$4c_1$.** with staphylococcal strain:

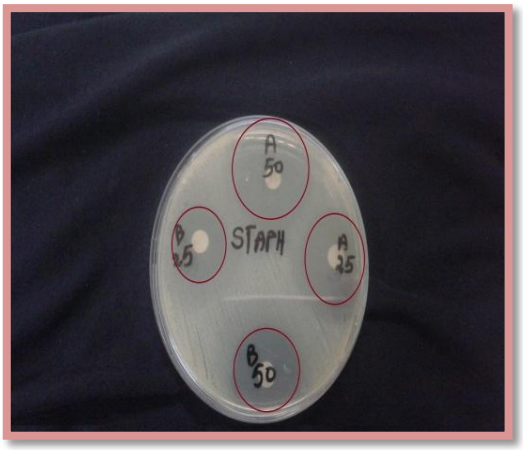


Figure 17 : Staphylococciques (25-50) ppm

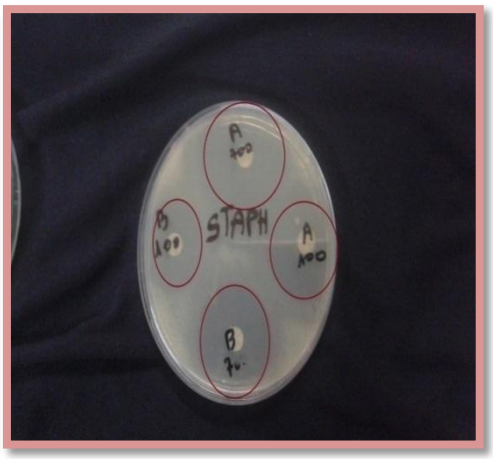


Figure 18 : Staphylococciques (100-700) ppm

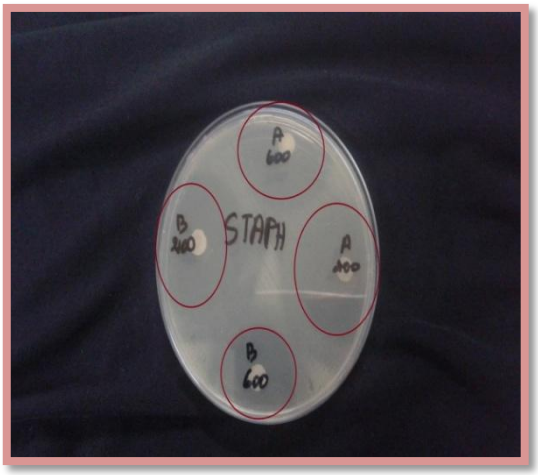


Figure 19 : Staphylococciques (200-600) ppm

Figure 20 : Staphylococciques (400) ppm

Figure 21 : Staphylococciques (500-800-1000) ppm

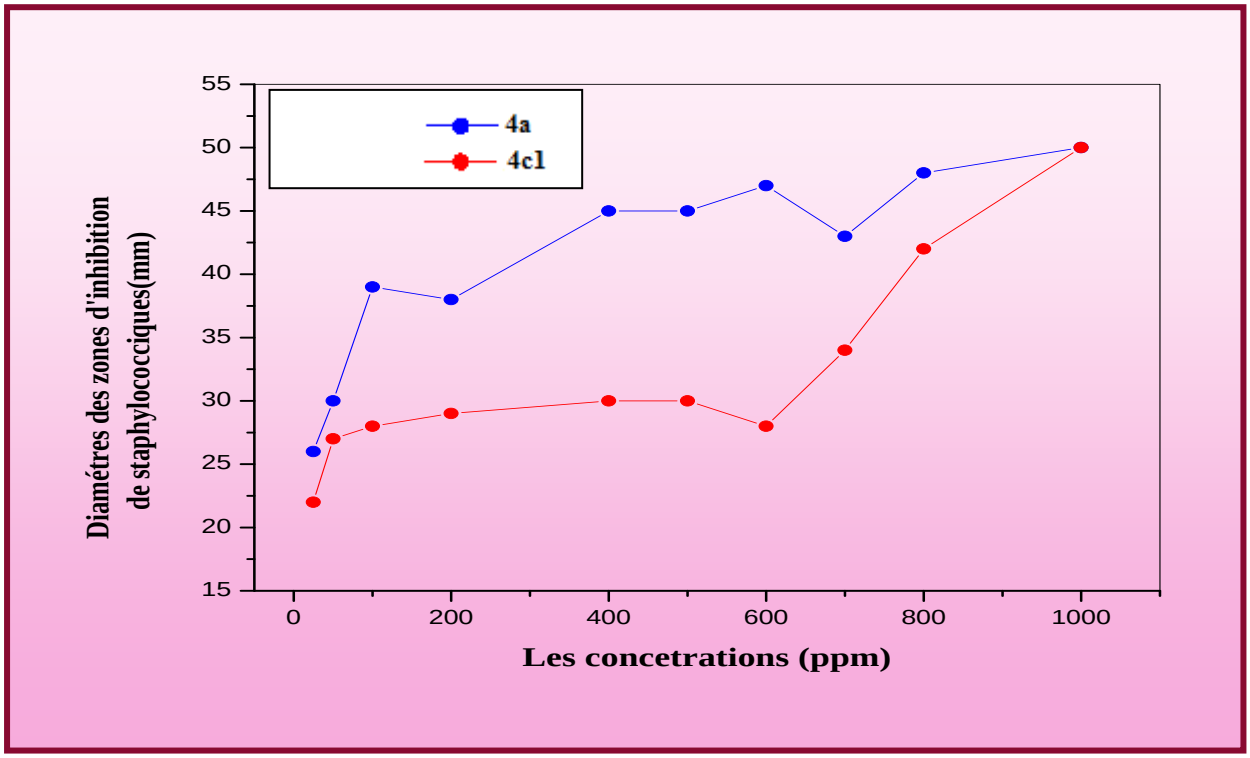


Figure 22: Changes of the diameters of staphylococcal inhibition areas versus concentrations for each 4a and $4c_1$.

Figure 22 shows the changes of the diameters of staphylococcal inhibition zones depending on the concentrations for each **4a** and **$4c_1$** when the focus 25ppm; 4a gives the diameter 26 mm and **$4c_1$** gives the diameter 22 mm and then note the increase in diameter remarkably and very large especially for **4a**.

direct correlation relationship. Whenever the concentration decreased from 25ppm to 1000 ppm, we see an increase in the diameter **4a** and **$4c_1$** but the rate of increase in the diameter **$4c_1$** is lower than **4a.**

II-2-7-2-3-PseudomonasAeruginosa:

The results presented in the following figures (23-25) show that the antibacterial effect **4a** and **$4c_1$** with the strain PseudomonasAeruginosa:

Figure 23 : Pseudomonas Aeruginosa (100-200-400) ppm

Figure 24 : Pseudomonas Aeruginosa (600-700) ppm

Figure 25 : Pseudomonas Aeruginosa (500-800-1000) ppm

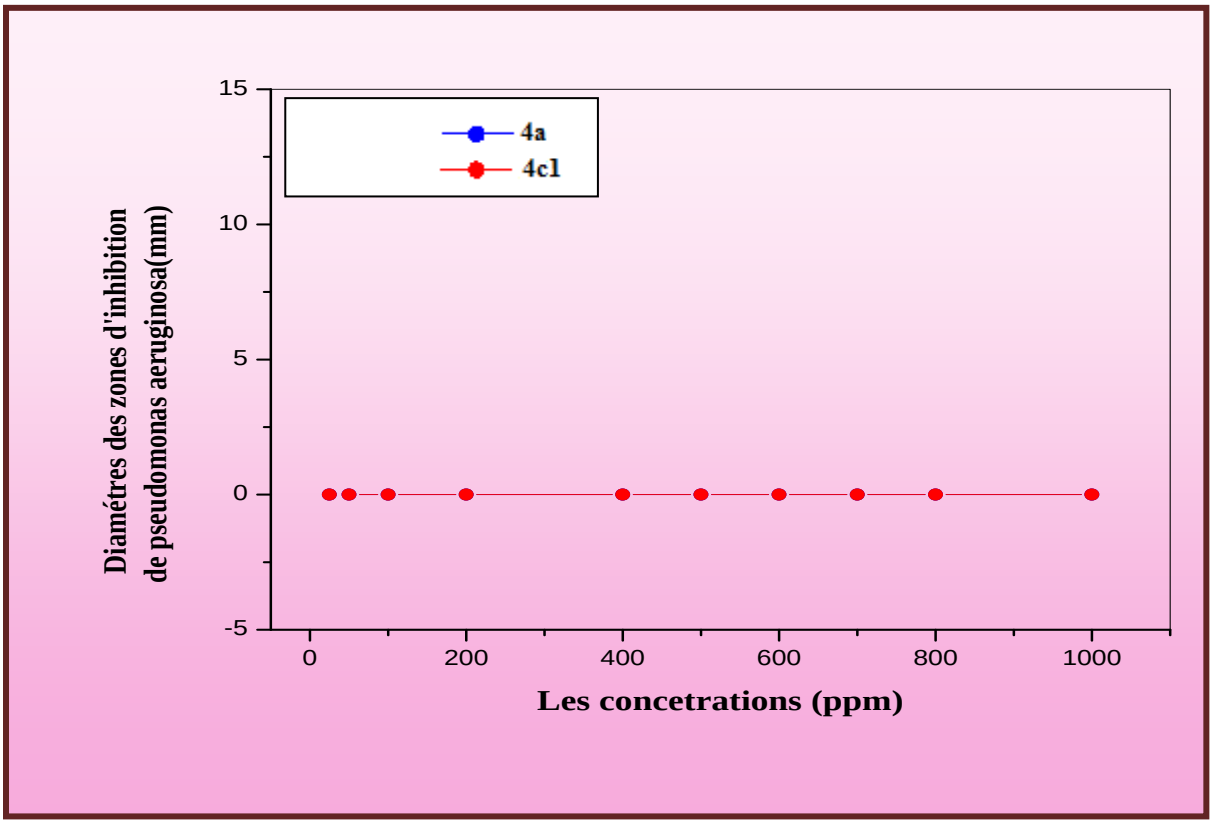


Figure 26: Changes of the diameters of Pseudomonas aeruginosa of zones of inhibition against concentration for each 4a and $4c_1$.

Figure 26 shows the changes of the diameters of inhibition zones Pseudomonas aeruginosa according to the concentrations for each **4a** and **$4c_1$** any results you do not notice with all concentrations of 25 ppm to 1000 ppm or with the **4a** or **$4c_1$**.

II-2-7-3-The results of the categories of each bacterial strain:

Table 6: The categories of each strain with the Bactrian **4a** and **$4c_1$**.

<table>
<tr><td></td><td colspan="2">Escherichia coli</td><td>Staphylococciques</td><td>Pseudomonas Aeruginosa</td></tr>
<tr><td rowspan="4">4a</td><td>Concentrations</td><td>Categorie of bacterial strain</td><td rowspan="4">Categorie of bacterial strain :
≥ 25 ppm : S</td><td rowspan="4">Categorie of bacterial strain :
≥ 25 ppm : R</td></tr>
<tr><td>25 ppm</td><td>R</td></tr>
<tr><td>50 ppm</td><td>I</td></tr>
<tr><td>≥ 50ppm</td><td>S</td></tr>
<tr><td rowspan="4">$4c_1$</td><td>Concentrations</td><td>Categorie of bacterial strain</td><td rowspan="4">Categorie of bacterial strain :
≥ 25 ppm : S</td><td rowspan="4">Categorie of bacterial strain :
≥ 25 ppm : R</td></tr>
<tr><td>≤ 50 ppm</td><td>R</td></tr>
<tr><td>≤ 500 ppm</td><td>I</td></tr>
<tr><td>≥ 600ppm</td><td>S</td></tr>
</table>

Table 5 represent categories of each strain with Bactrian **4a** and **$4c_1$** which are classified based on the document "Algerian Surveillance Network of the resistance of bacteria to antibiotics". [17]

We notice a difference categories for each bacterial strain with either **4a** or **$4c_1$** depending on the concentrations; firstly E. coli; for **4a** sensitivity becomes clear from 100 ppm. The fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines compounds **$4c_1$**; S Class starts 600ppm. The staphylococcal S is more sensitive to all concentrations with either **4a** or **$4c_1$** .Unlike Pseudomonas aeruginosa is more resistance.

The compound **4a** and **$4c_1$** give a biological effectiveness against bacterial strain (E. coli, staphylococcus) because of their chemical structures containing the group F, Cl, $(Ph)_2POCH_2$ these have chemically active atoms and which due to the existence of free electrons which are capable of forming connections on the wall of the thing bacterial cells which hampers the movement of the latter.

The compound **4a** gave the best results with E. coli compared of **$4c_1$** to cause the fluorine is more electronegative than chlorine thus the fluorine has the ability to form bonds of easy faction as chlorine.

Results for Pseudomonas aeruginosa strain were negative because the latter has a cell-resistant wall.

Experimental section

Part I

III-1- General Experimental:

Melting points were determined on Gallenchamp melting point apparatus and were uncorrected. IR spectra were obtained with a Perkin- Elmer 983 G spectrometer on KBr disks. All 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra were run on a bruker AC 300 spectrometer, 200 MHz NMR spectra were run on a bruker AC 200 spectrometer. ^{13}C NMR spectra were recorded using Distortionless Enhancement by polarisation transfer. NMR ^{1}H and ^{13}C spectra were recorded using $CHCl_3$ as internal standard.

Fast atom Bombardement (FAB) were recorded with a Kratos MS50 with a metanitrobenzylalcohol matrix. Accurate mass determinations were carried out on a Kratos Concept IS spectrometer. Elemental analysis were performed using a Carlo-Erba 1106 elemental analyzer Column chromatography was conducted using silica gel 60 230-400 mesh (Merck & Co) silica thin layer chromatography T.L.C was conducted on precoated aluminium sheets (60 F 254) with a 0.2 mm thickness (aldrich Chemical Co.).

III-1-2 Dyring of solvent:

Tetrahydrofuran was distilled from sodium metal in the presence of benzophenone immediately prior to use.

Petroleum ether and diethyl ether were dried over sodium wire. Methanol or ethanol were dried using magnesium turnings and iodine under reflux conditions, then distilled and collected over 4A molecular sieves.

III-2-Synthesis of the derivatives (2,4,6-trimethyl phenylazo) fluoropyridines 2_{a-c}:

III-2-1- Synthesis of 4- amino – 2,3,5,6 – tetrafluoropyridine 1a:

Pentafluoropyridine (50g, 0.296mol) was dissolved in THF (350 ml) in a round- bottomed flask equipped with a reflux condenser to give a cleae solution. On addition of aqueous ammonia (sp. gr. 0.88, 250 ml) a cloudy solution was produced and an exothermic reaction ensued. The mixture was then refluxed for 24hr. The clear solution produced was poured into water (1000 ml) and the whole mixture was extracted with ether (4 x 150 ml). The extract was dried ($MgSO_4$), evaporated using a rotary evaporator, and the residue freed from the last traces of solvent in vacuo, to give a pale cream solid. Recrystallisation of this crude material from light petroleum (b.p. 80 – 100 °C) gave long white needles of 4- amino – 2,3,5,6 – tetrafluoropyridine (40g, 0.241mol, 81%), m.p. 84- 86 °C .

The product was identified by comparing its IR and ^1H spectra with those of an authentic sample. This preparation was repeated several times in order to produce large quantities of starting material for conversion into :

1. Tetrafluoro- 4- nitropyridine
2. Tetrafluoro- 4- nitrosopyridine (part 2)
3. 4- amino – 2,3,5, – tetrafluoro- 6 – methoxypyridine
4. 2,3,5,6 – Tetrafluoro – 4- (2,4,6 – trimethylphenylazo)pyridine.

ν max (KBr Disc, cm^{-1}) : 1360 (C-F), 1099.3 (C-N) and 3500-3100 (NH)

δF (54.6 MHz ; $CDCl_3$) : -85.1(2F, s), -15.1(2F,s).

m/z (FAB) 165(M^+-1,100), 150 (M^+-NH2,42), 147(17)

Anal. Calcd for $C_5H_2N_2F_4$: Requires C, 36.2% ; H, 1.2% ; N, 16.9% ; F, 45.7%.

Found C, 36.3% ; H, 1.2% ; N, 16.8% ; F, 45.8%.

III-2-2- Synthesis of tetrafluoro- 4- nitropyridine 1a':

A mixture of methylene chloride (214 ml), trifluoroacetic anhydride (54 ml) and24ml hydrogen peroxide (85%) was refluxed and stirred for 15 min.

A solution of 4- amino – 2,3,5,6 – tetrafluoropyridine (20g, 0.119mol) in methylene chloride (110 ml) was then added to the refluxing solution and the mixture immediately became yellow and changed to bright green in a few minutes. Hydrogen peroxide (12 ml) was added after a futher 20 min, followed 3 hr later by more hydrogen peroxide (12 ml) and trifluoroacetic anhydride (12 ml). After 6 – 7 hr, the solution had become yellow. When the solution had been heated for a total of 22 hr, water (200 ml) was added, the methylene chloride layer was separated, washed three times with, dried ($MgSO_4$), and the solvent was distilled off through a short vigreux column. Distillation of the residual liquid (from P_2O_5) affored pale yellow tetrafluoro- 4- nitropyridine (15.11g, 91mmol, 80%) b.p. 152- 154 °C . The produc twas identified by comparison of its IR (see p.) and ^1H n,m,r spectra with those of an authentic sample.

ν max (KBr Disc, cm^{-1}) : 1550.7 (NO2) and 1209.3-1325.0 (C-F)

δF (54.6 MHz ; $CDCl_3$) : -67.9(2F, m), -4.9(2F,m).

m/z (FAB) 180(6), 177(M^+-F,100), 150 (40.8) .

Anal. Calcd for $C_5O_2N_2F_4$: Requires C, 30.6% ; N, 14.3% ; F, 38.8% .

Found C, 30.4% ; N, 14.2% ; F, 39.0% .

III-2-3- Synthesis of 3- methoxy- 2,5,6- trifluoro -4- nitropyridine 1'c:

To a cold (0 °C) stirred solution of tetrafluoro- 4- nitropyridine (2.1g, 10.7 mmol) in methanol (15 ml) was added (during 15 min) a solution of methanolic sodium methoxide (30 % W/V 1.26g, 23 mmol) in methanol (30 ml). The mixture was then stirred for 20 minutes. Water was added and the mixture was extracted with ether. The ether layer was dried ($MgSO_4$), and evaporated (rotary evaporated) to leave a red brown solide.Which was separated by H.P.L.C analysis [Daicel Co – 215mm x 46 mm chiracel OD column, 15% i- ProH in Hexane 1mol/min].

Band 1 : A red compound which was recrystallised from methanol to give bright red needies of 3- methoxy- 2,5,6- trifluoro -4- nitropyridine 1'c (1.071g, 5.14 mmol, 51%) which was shown by IR, ^1H n,m,r spectra with those of an authentic sample.

Band 2 : A red 2-methoxy-3,5,6- trifluoro-4-nitropyridine (1c'') (0.315g, 1.51 mmol, 15%).

Band 3 : Pale brown of 3,5-dimethoxy-2,6- difluoro-4-nitropyridine (1c''')(2%) and

Band 4 : The pure pale brown compound of 2,5-dimethoxy-3,6- difluoro-4-nitropyridine 1''''c (17%).

ν max (KBr Disc, cm^{-1}) : 1139.9-1209.3 (C-O), 1550.7 (N=O) and 1253.6 (C-F)

δF (54.6 MHz ; $CDCl_3$) : -8O.3(1F, dd, J=29.6,21.6Hz,F-), -27.5(1F, dd, J=21.6,12.7Hz,F-), -3.1(1F, dd, J=29.6,12.7Hz,F-).

m/z (FAB) 207 (M^+-1,35), 193 (M^+-Me,41), 179(6.8), 177(M^+-OMe,100), 162(80)

Anal. Calcd for $C_6H_3O_3N_2F_3$: Requires C, 34.6% ; H, 1.5% ; N, 13.5% ; F, 27.4% .

Found C, 34.6% ; H, 1.4% ; N, 13.7% ; F, 27.4% .

III-2-4-Synthesis of 4- amino -2,5,6- trifluoro -3- methoxy pyridine 1c:

40g of powder iron was added to wather (60ml) and concentrated chloric acid (6ml) in a 250 ml round bottomed 2- necked flask equipped with a reflux condenser and a magntic stirrer bar. The mixture was heated for 10 min then, (1g, 4.8 mmol) of 3- methoxy- 2,5,6- trifluoro -4- nitropyridine 1'c was added . The reaction was continued until the mixture was incolourless then 3g of Na_2CO_3 was added,the mixture was satured with NaCl. The combined organic was extracted with etherdietylique (3X 50 ml) and dried over KOH, filtration and evaporation in vacuo furnished crude product.

ν max (KBr Disc, cm^{-1}) : 1199.6 (C-O), 1550.7 (N=O), 3035.7-3700.1(NH2) and 1245.9 (C-F).

δF (54.6 MHz ; $CDCl_3$) : -98.3(1F, dd, J=28.8,23.4Hz,F-), -73.8(1F, dd, J=23.4,13.2Hz,F-), -15.8(1F, dd, J=28.8,13.2Hz,F-).

m/z (FAB) 177 (M^+-1,62), 162(40), 159(13.8), 147 (M^+-Me,100) .

Anal. Calcd for $C_6H_5ON_2F_3$: Requires C, 40.4% ; H, 2.8% ; N, 15.8% ; F, 32.02%. Found C, 40.3% ; H, 2.7% ; N, 15.8% ; F, 32.0%.

III-3- Synthesis of 2,4,6- trimethyl phenylazofluoropyridins 2a-c:

III-3-1-Synthesis of 2,3,5,6 – Tetrafluoro – 4- (2,4,6 – trimethylphenylazo)pyridine 2a:

An 86 ;14 V/V mixture of glacial acetic acid (51.6 ml) and propionic acid (8.4 ml) was added dropwise to a mechanically stirred solution of dry, powdered sodium nitrite (2.1g, 30 mmol) in 98% sulphuric acid (60 ml). The acetic acid/ propionic acid mixture is added as a solubiliser.This proportion does not freeze at 0 °C whereas glacial acetic acid freezes at 16 °C. This mixture was maintained at 30 °C in order to avoid the decomposition of nitrosyl sulphuric acid (revealed by the evolution of brown fumes of NO_2). The temperature of the nitrosating medium was then lowered to 0 °C by means of an ice- salt bath, and 4- amino – 2,3,5,6 – tetrafluoropyridine (5g, 30 mmol) was added slowly. Stirring was continued for 1 .30 hrs. AT this stage diazotisation was shown to be complete, when addition of a small drop of the reaction mixture to N- N,N- diethyltoluidine gave an intense red colouration. Mesitylene (4.17 cm3, 3.6g, sp. gr. 0.864g cm-3, 30 mmol) was then adeed over a 15 minute period, so that any temperature rise caused by the coupling reaction would not be too drastic, and also to ensure complete reaction.

Addition of the mesitylene resulted in the formation of a red slurry. For a 30 mintues period after addition had been completed, the temperature was kept below 0 °C to prevent the immediate destruction of any remaining diazonium ion. Stirring was then continued for 1 hr at room temperature, and then the solution was added to water (1000 ml). The red precipitate was filtered off and dried in an air oven at 80 °C. Recrystallisation of the crude material from ethanol gave dark pinkish- red needles of . 2,3,5,6 – Tetrafluoro – 4- (2,4,6 – trimethylphenylazo)pyridine (7.38g, 24.84 mmol, 82%), m.p. 143 °C which was identified by comparison of its IR and ^1H n,m,r spectra with those of an authentic sample.

This preparation was repeated several times to give enough material for further conversion into (a) 1,2,4- trifluoro- 7,9- dimetyl- 11H- pyrido[4, 3- c]- benzo [1,2] diazepine ; (b) 2,3,5- trifluoro-6- methoxy -4- (2,4,6 – trimethylphenylazo)pyridine, and thence to the corresponding diazepines ; and (c) 2,6- dimethoxy – 3,5 difluoro -4- (2,4,6 – trimethylphenylazo)pyridine, and thence to their corresponding diazepine.

ν max (KBr Disc, cm^{-1}) : 1685.7 (C=N), 1600.8 (N=N) and 1190-1480 (Ar-F)

δF (54.6 MHz ; $CDCl_3$) : -75.5(2F, d, F-), -11.2(1F, d, F-).

δH (300 MHz ;$CDCl_3$) : 2.35(3H, s, 4-CH_3) , 2.5(6H, s, 2,6-CH_3), 7.05(2H, s, Ha)

m/z (FAB) 297 (M^+,78.5), 277($C_{14}H_{10}N_3F_4^+$,13.3), 178($C_5N_3F_4^+$,9.0), 147 (24.8), 134(6.6), 119(100), 91(16.6) .

Anal. Calcd for $C_{14}H_{11}N_3F_4$: Requires C, 56.9% ; H, 3.8% ; N, 14.1% ; F, 25.6% .

Found C, 56.9% ; H, 3.6% ; N, 14.2% ; F, 25.7% .

III-3-2-Synthesis of 3- chloro-2,5,6- trifluoro -4- (2,4,6- trimetyl- phenylazo)pyridine 2b:

Using a medium of 98% sulphuric acid, glacial acetic acid and propionic acid.

An 86 ;14 V/V mixture (30 ml) of glacial acetic acid and propionic acid (6.4 ml) was added dropwise to a stirred solution of dry, powdered sodium nitrite (0.95g, 13.77 mmol) in 98% sulphuric acid (30 ml) [made by heating sulphuric acid to ca. 70 °C to completely dissolve the sodium nitrite]. The resulting nitrosating medium was cooled at 0 °C then treated with 4- amino-3- chloro-2,5,6- trifluoropyridine (2.5g, 13.70 mmol) ; stirring was continued for 2 hrs. Addition of mesitylene (1.66g, 13.83 mmol) gave a red precipitate which was isolated by addition of the mixture to water (1000 ml) after it had been stirred for 3 hrs at room temperature. After being dried (oven, 70 °C), the resulting red solid was recrystallised from pet- ether (b.p. 80- 100 °C) to give orange red needles of 3- chloro-2,5,6- trifluoro -4- (2,4,6- trimetyl- phenylazo)pyridine (3.68g, 11.37 mmol, 86%), m.p. 150- 151 °C.

ν max (KBr Disc, cm^{-1}) : 1733.9 (C-Cl), 1558.4 (N=N) and 1182.3-1458.1 (Ar-F)

δH (300 MHz ;$CDCl_3$) : 2.40(3H, s, 4-CH_3) , 2.55(6H, s, 2,6-CH_3), 7.05(2H, s, Ha)

m/z (FAB) 313 (M^+,33.8), 293($C_{14}H_{10}N_3F_3Cl^+$,6.6), 278($C_{14}H_{11}N_3F_3^+$,20.4), 147 (12.3), 134(78.7), 119(100), 91(48.3), 77(18.1) .

U.V.λmax(ε) hexane : 460(561.87) ; λmax(ε) : 408(327.76).

Anal. Calcd for $C_{14}H_{12}N_3F_3Cl$: Requires C, 53.6% ; H, 3.2% ; N, 13.4% ; F, 18.2% ; Cl , 11.1% . Found C, 53.3% ; H, 3.5% ; N, 13.2% ; F, 18.4% ; Cl , 11.1% .

III-3-3- Synthesis of 2,5,6- trifluoro-3- methoxy-4-(2,4,6- trimetyl- phenylazo)pyridine 2c:

An 86 ;14 V/V mixture of glacial acetic acid (7.94 ml) and propionic acid (1.3 ml) was added dropwise to a mechanically stirred solution of dry, powdered sodium nitrite (0.294g, 4.26 mmol) in 98% sulphric acid (15 ml). The acetic acid/ propionic acid mixture is added as a solubiliser.This proportion does not freeze at 0 °C whereas glacial acetic acid freezes at 16 °C. This mixture was maintained at 30 °C in order to avoid the decomposition of nitrosyl sulphuric acid (revealed by the evolution of brown fumes of NO_2). The temperature of the nitrosating medium was then lowered to 0 °C by means of an ice- salt bath, and 4- amino – 2,3, 6 – trifluoro -5- methoxy pyridine (0.7g, 4.14 mmol) was added slowly. Stirring was continued for 1 .30 hrs. AT this stage diazotisation was shown to be complete, when addition of a small drop of the reaction mixture to N- N,N- diethyltoluidine gave an intense red colouration. Mesitylene (0.46g, 4.14 mmol) was then adeed over a 15 minute period, so that any temperature rise caused by the coupling reaction would not be too drastic, and also to ensure complete reaction.

Addition of the mesitylene resulted in the formation of a red slurry. For a 30 mintues period after addition had been completed, the temperature was kept below 0 °C to prevent the immediate destruction of any remaining diazonium ion. Stirring was then continued for 1 hr at room temperature, and then the solution was added to water (300 ml). The red precipitate was filtered off and dried in an air oven at 80 °C. Recrystallisation of the crude material from ethanol gave dark pinkish- red needles of 2,5,6- trifluoro -3- methoxy -4- (2,4,6- trimetyl- phenylazo)pyridine 2c (0.539g, 1.74 mmol, 77%), m.p. 143 °C which was identified by comparison of its IR and ^{1}H n,m,r r spectra with those of an authentic sample.

ν max (KBr Disc, cm^{-1}) : 1564.2-1581-5 (N=N), 1190-1480 (Ar-F)

1250(C-O asym.stretch) and 1049.2(C-O sym.stretch).

δF (54.6 MHz ; $CDCl_3$) : -98.7(1F, dd, J=28.8,21.6Hz,F-5), -75.8(1F, dd, J=21.6,12.3Hz,F-3), -15.8(1F, dd, J=28.8,12.3Hz,F-2).

δH (300 MHz ;$CDCl_3$) : 2.32(3H, s, 4-CH_3) , 2.46(6H, s, 2,6-CH_3), 4.02(-OCH_3) 7.05(2H, s, Ha)

m/z (FAB) 309 (M^+,24.6), 285($C_{15}H_9N_3F_2O^+$,5.9), 147 (4.0), 119(100), 91(20.4), 77(10.3) .

Anal. Calcd for $C_{15}H_{17}ON_3F_3$: Requires C, 58.3% ; H, 5.5% ; N, 13.6% ; F, 18.4% .

Found C, 58.2% ; H, 5.5% ; N, 13.5% ; F, 18.5% .

III-4-Synthesis of phosphours fluorinated 2,4,6-trimethylphenylazopyridine 4a-c:

We report the general route for the synthesis of phosphours fluorinated 2,4,6-trimethylphenylazopyridine 4a-c as an alternative for the method reported by kagan [9].We have found that, the reaction of methyldiphenylphosphine oxide 3 with (2,4,6-trimethylphenylazo) fluoropyridines 2a-c is a convenient synthesis of azo fluorinated phosphours of type 4. The general procedure involves dropwise addition of an equimolar quantity of a solution of n-buli in hexane to a stirred solution of methyldiphenylphosphine oxide in dry THF at 0 °C , then cooled to around – 78 °C.

Freshly solution 2,4,6- trimethyl phenylazofluoropyridins 2a-c was added in one portion. After the addition was complete, the red colour of the anion had disappeared. The resulting pale yellow solution was stirred for 15 min – 78 °C, then allowed to warm to ambient temperature over 2 hrs. Work-up of the reaction product gave the corresponding phosphours fluorinated 4a-c in high yields ranging from 76 to 89% (scheme 10)

III-4-1-Preparation of E- diphenyl((3,5,6- trifluoro-4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide 4a:

A dry, 500 ml flask equipped with a magnetic stirring bar was charged with (6.0g, 27.6mmol) of methyldiphenylphosphine oxide, capped with a rubber septum, and flushed with nitrigen. Anhydrous tetrahydrofuan (175 ml) was then added to the flask via cannula, and the resulting solution cooled in an ice bath to 0 °C. A solution (11.04 ml, 27.6 mmol, 2.5 M butyllithium in hexane) was added dropwise via a syringe over a 5 min period. The solution turned deep red. The resulting red solution was stirred for 30 min at 0 °C, then cooled to around – 78 °C in an acetone-solide carbone dioxide- cooling bath. Freshly solution 2a (8.2g, 27.6 mmol) was added in one portion by syringe. After the addition was complete, the red colour of the anion had disappeared. The resulting pale yellow solution was stirred for 15 min – 78 °C, then allowed to warm to ambient temperature over 2 hrs. Water (40 ml) was added and the bulk of the tetrahydrofuran and hexane removed on a rotary evaporator (bath temp. Ca. 25- 30 °C). Brine and dilute hydrochloric acid (200 ml) was added to the aqueous residue and extracted with dichloromethane (3x 100 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure on a rotavapor, and the residue, light yellow oil, was placed in a refrigerator overnight to crystallise. The resulting solid was recrystallised from ethylacetate to give 3,5,6- trifluoro-2- diphenyl phophinomethyl-4-

(trimethylphenylazo)pyridine 4a (6.642g, 13.89 mmol, 81%). As white crystalline solid, m.p. 167°C.

ν max (KBr Disc, cm^{-1}) : 1650-1565 (N=N), 1260-1454.2 (Ar-F)
and 1049.2(P=O).

δH (300 MHz ;$CDCl_3$) : 2.52(3H, s, 4-CH_3) , 2.32(6H, s, 2,6-CH_3), 3.33(2H, s, CH_2PO), 6.89(2H, s, Ha) 7.05(10H, m, Ha)

m/z (FAB) 493 (M^++1,100), 374($C_{18}H_{12}F_3PON_3^+$, 40), 292(80.1),278(10.2), 215(6.2), 201 (20), 119(60) .

Anal. Calcd for $C_{27}H_{23}$ ON_3F_3P : Requires C, 65.8% ; H, 4.6% ; N, 8.5% ; F, 11.5% ; P, 6.00%. Found C, 65.8% ; H, 4.8% ; N, 8.5% ; F, 11.6% ; P, 6.1%.

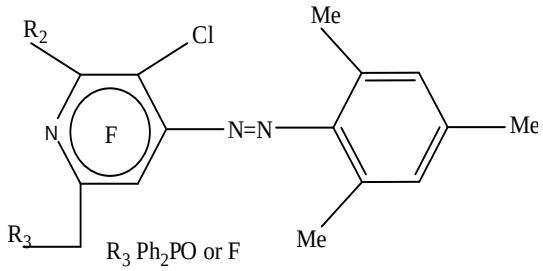
III-4-2-Synthesis of 5- chloro-3,6- difluoro-4-(mesityl diazenyl) pyridin -2- yl) methyl) diphenyl phosphine oxide 4b isomers:

4b was prepared from methyldiphenylphosphine oxide (6.0g, 27.6mmol), and 2b (8.65g, 27.6 mmol) in a similar way to 4a .Work –up of the reaction product gave a white crystalline solid of 4b isomers (6.574g, 13.3 mmol, 76%) after recrystallisation from ethyl acetate.They were separated by HPLC.

III-4-2-1-HPLC of 5- chloro-3,6- difluoro-4-(mesityl diazenyl) pyridin -2- yl) methyl) diphenyl phosphine oxide 4b isomers:

In this paper a simple, rapid HPLC method with UV detection was developed and validated for the determination of 4b using C8 silica – based reverse phase column with dimensions of 4.6 mm by 250mm and flow rate of 1.0 ml/minute . The mobile phase was methanol- water (50:50) and protected with an appropriate guard column (5 j.l particle size; Altech Assoc. 1, Deerfield, Ill.) . Dupont Instruments 8800-series Gradient Controller, Gradient Pump. The detection of these markers was monitored by absorption at 215 nm absorbance recorded on a Shimadzu C-R3A Integrating Recorder (Shimadzu Corp. ,Kyoto, Japan). $4b_1$and $4b_2$ can be separated on analytical HPLC: Chiralcel OD-H column, hexane:2- PrOH, (9:1, *v*:*v*) mobile phase, flow-rate, 1.0 mL/min, 25 °C, λ = 254 nm and polarimetric detection, 20 μL injection volume. The retentions times are listed in table 6.

Table 7: Retention time of $4b_1$ and $4b_2$



R_2	Compound	Elution time (min)[t]
F	$4b_1$	12.95 ± 0.35
Ph_2POCH_2	$4b_2$	14.01 ± 0.41

III-4-2-1-1-Spectral Data for $4b_1$:

ν_{max} (KBr Disc, cm^{-1}) : 1600 (N=N), 1436.9 (Ar-F), 1250-1070 (Ar-Cl) and 1182.3(P=O).

δF (54.6 MHz ; $CDCl_3$) : -84.3(1F, d, J=25.6.6Hz,F-5), -14.5(1F, d, J=25.6Hz,F-2)

δH (300 MHz ;$CDCl_3$) : 2.3(6H, s, 2,6-CH_3), 2.55 (3H, s, 4-CH_3) , 3.38(2H, s, CH_2PO), 6.9(2H, s, Ha) 7.14(10H, m, Ha)

m/z (FAB) 474 (M^+-Cl,100), 215(6.0), 201 (22), 147(18)119(63) .

Anal. Calcd for $C_{27}H_{23}ON_3F_2ClP$: Requires C, 63.7% ; H, 4.5% ; N, 8.2% ; F, 7.4% ; P, 5.8% ; Cl , 6.9. Found C, 63.7% ; H, 4.5% ; N, 8.2% ; F, 7.5% ; P, 5.7% ; Cl , 7.0.

III-4-2-1-2-Spectral Data for $4b_2$:

ν_{max} (KBr Disc, cm^{-1}) : 1600-1565 (N=N), 1436.9 (Ar-F), 1250-1070 (Ar-Cl) and 1181.1(P=O).

δF (54.6 MHz ; $CDCl_3$) : -79.0(1F, d, J=21.1Hz,F-5), -9.4(1F, d, J=21.1Hz,F-6)

δH (300 MHz ;$CDCl_3$) : 2.35(6H, s, 2,6-CH_3), 2.7(3H, s, 4-CH_3) , 3.36(2H, s, CH_2PO), 6.9(2H, s, Ha) 7.14(10H, m, Ha)

m/z (FAB) 474 (M^+-Cl,100), 215(6.0), 201 (20), 147(17)119(60) .

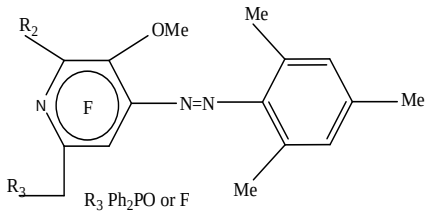
III-4-3- Synthesis of 3, 6- difluoro-4-(mesityl diazenyl)-5- methoxypyridin -2- yl) methyl) diphenyl phosphine oxide 4c isomers:

4c was prepared from methyldiphenylphosphine oxide (1.0g, 4.6mmol), and 2c (0.5g, 1.61 mmol) in a similar way to 4a . The white solid resulted was recrystallised from acetate to give a solid do 4c isomers (0.445g, 0.908 mmol, 89%) . THE composition were determined by HPLC.

III-4-3-1-HPLC of 3, 6- difluoro-4-(mesityl diazenyl)-5- methoxypyridin -2- yl) methyl) diphenyl phosphine oxide 4c isomers:

Figure shows the separation of isomers **4c** was obtained using the same HPLC condition of the separation 4b isomers . The retentions times are presented in table 7

Table 8: Retention time of $4c_1$ and $4c_2$



R_2	Compound	Elution time $(min)^t$
F	$4c_1$	17.65 ± 0.33
Ph_2POCH_2	$4c_2$	18.51 ± 0.27

III-4-3-1-1-Spectral Data for $4c_1$:

ν_{max} (KBr Disc, cm^{-1}) : 1600 (N=N), 1436.9 (Ar-F),1172.6(P=O), 1203.5-1276.8(C-O asym.stretch) and 1041.5(C-O sym.stretch).

.δF (54.6 MHz ; $CDCl_3$) : -82.5(1F, d, J=25.3Hz,F-5), -11.2(1F, d, J=25.3Hz,F-2)

δH (300 MHz ;$CDCl_3$) : 2.3(6H, s, 2,6-CH_3), 2.45 (3H, s, 4-CH_3) , 3.32(2H, s, CH_2PO), 3.95 (3H, s, O-CH_3), 6.85(2H, s, Ha) 7.02(10H, m, Ha)

m/z (FAB) 490 (M^++1-Me,100), 304(78.5), 290(18.5) 215(6.0), 201 (22), 147(18)119(63) .

Anal. Calcd for $C_{28}H_{26}$ $O_2N_3F_2P$: Requires C, 66.6% ; H, 5.1% ; N, 8.3% ; F, 7.5% ; P, 5.9%. Found C, 66.7% ; H, 5.1% ; N, 8.3% ; F, 7.5% ; P, 6.0%.

(0.36g, 0.76mmol, 9.7%conversion),

III-4-3-1-2- Spectral Data for $4c_2$:

ν_{max} (KBr Disc, cm^{-1}) : 1600-1565 (N=N), 1436.9 (Ar-F),1174.6(P=O), 1203.5-1276.8(C-O asym.stretch) and 1041.5(C-O sym.stretch).

δF (54.6 MHz ; $CDCl_3$) : -72.2(1F, d, J=21.0Hz,F-5), -8.1(1F, d, J=21.0Hz,F-2).

δH (300 MHz ;$CDCl_3$) : 2.3(6H, s, 2,6-CH_3), 2.45 (3H, s, 4-CH_3) , 3.35(2H, s, CH_2PO), 4.05 (3H, s, O-CH_3), 6.9(2H, s, Ha) 7.1(10H, m, Ha)

m/z (FAB) 490 (M^++1-Me,100), 304(76), 290(15.5) 215(6.0), 201 (22), 147(17)119(60) .

III-5- Single crystal structure determination

In order to establish the absolute configuration of the newly created isomers, the structure of the major product of compound **4b** and **4c** were elucidated by X-ray single crystal diffraction analysis (Figure 7-10).

The crystals used for the X-ray single crystal diffraction study were grown by routine recrystallization from acetonitrile and ethyl acetatefor compound **4b** and **4c**,respectively. The unit cell dimensions were determined by least-squares using 25 for compound **4b** and 15 forcompound **4c**centered reflections using graphite monochromated Cu-Kα radiation. Data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.53319×10^{-5} for **4b**, 0.878954×10^{-5} for compound **4c**). The structures for compound **4b** and **4c** were solved by direct methods. The non-hydrogen atoms (for compound **4b** and **4c**) were refined anisotropically. All other hydrogens were located on difference Fourier maps and were refined isotropically. The molecule of compound **4c** crystallizes with the solvent ethyl acetate in the proportion 2:1. The ethyl acetate molecule is disordered over two orientations about the two-fold axis. Each orientation corresponds to 50% occupancy. No atoms are on the axis but the methylene and carbonyl carbons are close. The carbonyl carbon was refined isotropically because of its proximity to the two-fold axis. Hydrogen atoms in the solvent molecule were not included in the model.

III-6- Synthesis of their corresponding diazepines:

corresponding diazepines prepared from phosphours fluorinated 2,4,6-trimethylphenylazopyridine 4a-c and mesitylene

III-6-1- Reaction of 4a with mesitylene:

4a (5g, 10.46 mmol) was dissolved in mesitylene (50 ml) in a round- bottomed flask (100 ml) equipped with a reflux condenser. The solution was refluxed and the progress of the reaction was followed by thin – layer chromatography Eventually the solution turned brown of ther 8 hrs relfluxing , t.l.c. analysis showed that most of the red starting material had been converted to a yellow product, so the solvent was removed by distillation (rotary evaporator, 80 °C, 1 mmHg). The dark brown residue was subjected to dry_ column flask chromatography [silica (40x 50 mm) light petroleum (b.p. 40- 60 °C) - dichloromethane] to give :

1) Unreacted azo compound (0.45g, 0.95mmol, 9.4% conversion), identified by comparing its t.l.c. Rf value, IR spectrum and m.p. with those of an authentic sample.

2) A yellow component which was recrystallised from aqueous ethanol to give yellow needles of 5f

3) A brown tar 40mg which was discarded.

III-6-2-Reaction of 4b with mesitylene:

In a typical experiment, 3- chloro- 2,5,6- trifluoro- 4- (2,4,6- trimethylphenylazo)pyridine (4.10g, 8.3 mmol) was refluxed in mesitylene (60 ml) for 7 hrs. Removal of mesitylene by distillation (rotary evaporator, 80 °C, 1 mmHg)revealed a yellow- brown oil which was purified by dry_ column flask chromatography [silica (40x 50 mm) light petroleum (b.p. 40- 60 °C) - dichloromethane] to give :

1) Unreacted azo compound (0.36g, 0.76mmol, 9.7%conversion), identified by comparing its t.l.c. Rf value, IR value with that of an authentic sample.

2) A yellow orange component which was recrystallised form pet- ether (80- 100 °C) to give yellow needles of 5f Analysis HPLC.

III-6-3-Reaction of 4c with mesitylene:

4c (0.40g, 0.80mmol) was dissolved in mesitylene (10 ml) in a round- bottomed flask equipped with a reflux condenser. The solution turned brown. After 12 hr relfluxing , t.l.c. analysis showed that most of the red starting material had been converted to a yellow product, so the solvent was removed by distillation (rotary evaporator, 80 °C, 1 mmHg).

The dark brown residue was subjected to dry_ column flask chromatography [silica (40x 50 mm) light petroleum (b.p. 40- 60 °C) - dichloromethane] to give :

1) Unreacted azo compound (0.033g, 0.21mmol, 9.1%conversion), identified by comparing its t.l.c. Rf value, IR value with that of an authentic sample.

2) A yellow component which was form pet- ether (80-100 °C) to give yellow needles of 5f.

3) A brown tar 30mg, not analysed further.

III-6-4- HPLC method and conditions:

Chromatographic of isomers 5f was accomplished using a C8 silica –based reserse phase 150 mm x 4.6 mm, 5µm ; mobile phase 5% water 95% methanol; flow rate 1.0 ml/minute ; column temperature 30 °C ; detection:UV absorbance at 254 nm. Figure11 shows the separation of 5f. The separation illustrated in figure was obtained using the same phase mobile and column at flow rate of 1.é ml/minute. Table 9 present the times retentions

Table 9: Retention time of **$5f_1$** and **$5f_2$**

Compound	Elution time (min)^t
$5f_1$	10.21
$5f_2$	07.89

III-6-4-1- Spectral Data for $5f_1$:

mp : 212-214°C

ν_{max} (KBr Disc, cm^{-1}) : 2968.2(CH_2 asym.stretch and 2850-2860 CH_2 sym.stretch). 1600 (N=N), 1434.9 (Ar-F),1174.6(P=O).

δF (54.6 MHz ; $CDCl_3$) : -80.9(1F, d, J=23.7Hz,F-4), -14.2(1F, d, J=23.7Hz,F-1)

δH (300 MHz ;$CDCl_3$) : 2.3(3H, s, 7-CH_3), 2.52 (3H, s, 9-CH_3) , 2.76 (1H, dd, J= 13.7Hz HCHPO), 3.0 (1H, ddd, J= 13,62 HCHPO), 3.4 (2H, s, H-CH_2), 6.85(1H, s, 8-H), 7.12(1H, s, 10-H), 7.03-7.85((10H, m, Ha)

m/z (FAB) 473 (M^++1,72.7), 396(41), 272($C_{14}H_{12}F_2N_3$ CH_2,$^+$100), 258(80), 215(25), 201 (12), 147(18)119(63) .

Anal. Calcd for $C_{27}H_{22}$ N_3F_2OP : Requires C, 68.6% ; H, 4.6% ; N, 8.8% ; F, 8.0% ; P, 6.3%. Found C, 68.6% ; H, 4.7% ; N, 8.6% ; F, 8.1% ; P, 6.3%.

III-6-4-2- Spectral Data for $5f_2$:

ν_{max} (KBr Disc, cm^{-1}) : 1600 (N=N), 1434.9 (Ar-F),1174.6(P=O).

δF (54.6 MHz ; $CDCl_3$) : -76.5(1F, d, J=21.2Hz,F-4), -9.4(1F, d, J=21.2Hz,F-1)

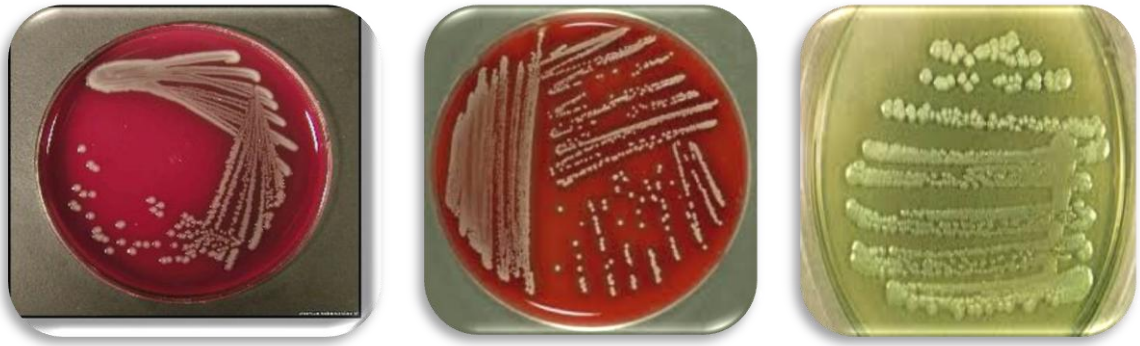
δH (300 MHz ;$CDCl_3$) : 2.3(3H, s, 7-CH_3), 2.52 (3H, s, 9-CH_3) , 2.76 (1H, HCHPO), 3.0 (1H, HCHPO), 3.4 (2H, s, H-CH2), 7.1(1H, s, 8-H), 7.12(1H, s, 10-H), 7.02-7.85((10H, m, Ha).

m/z (FAB) 473 (M^++1,72.7), 396(41), 272($C_{14}H_{12}F_2N_3$ CH_2,$^+$100), 258(80), 215(25), 201 (12), 147(18)119(63) .

III-7- biological testing:

III-7-1 Bacterial strains:

We tested the antibacterial activity of fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines with three bacterial strains in the laboratory of bacteriology of the hospital Mohamed Boudiaf Ouargla:



Escherichia coli ATCC 25922 | **Staphylocoques aureus ATCC 25923** | **Pseudomonas Aeruginosa ATCC 27853**

Figure 27: Bacterial strains

fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines may be important in organic synthesis and the preparation of biologically active compounds of interest in medicinal chemistry. [18, 19].

III-7-2- Methodology:

III-7-2-1 Préparation solutions:

We have two fluorinated 2, 4, 6- Trimethyl Phenyl azo Pyridines compounds E-diphenyl((3,5,6- trifluoro-4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide **4a** and (E)-((3, 6- difluoro-4-(mesityl diazenyl)-5- methoxypyridin -2- yl) methyl) diphenyl phosphine oxide **$4c_1$**.

*For the compound **4a**:

We take a quantity (0.1 g) of a compound **4a** and put into a beaker, add distilled water to (100 ml) with heating to 50 ° C and mix well the solution. Finally, we obtain the concentration of the solution equal to (1000) ppm. For other concentrations, we dilute the stock concentration (1000 ppm) with distilled water.

*To compound **$4c_1$**:

We take a quantity (0.1 g) of a compound**$4c_1$** and put into a beaker, add distilled water to (100 ml) with heating to 50 ° C and mix well the solution. Finally, we obtain the concentration of the solution equal to (1000) ppm. For other concentrations, we dilute the stock concentration (1000 ppm) with distilled water.

III-7-3- Procedure:

III-7-3-1-Preparation of agar:

The molten Mueller-Hinton agar autoclave was poured in Petri dishes respecting a thickness of about 4 mm [20]. Figure (28,29).

Figure 28 : La gélose M-H

Figure 29 : Autoclave

was poured in a Petri dish

III-7-3-2-Suspensions strains:

A sample is taken from a strain, it is put into a test tube containing a sufficient amount of physiological saline (10 ml), stirred until homogenize the solution.

III-7-3-2-1-seeding:

Note that all manipulations are done in the sterile area of the Bunsen burner, it dipped a swab into the suspension and was spread the entire surface of the agar (Agar Mueller Hinton) three times, turning the box around 60 ° after each application which aims to have an even distribution of the inoculum, Finally, it was swabbed all around the edge of the agar surface. Finally we left dry Petri dishes for a few minute [21]. (Figure 30).

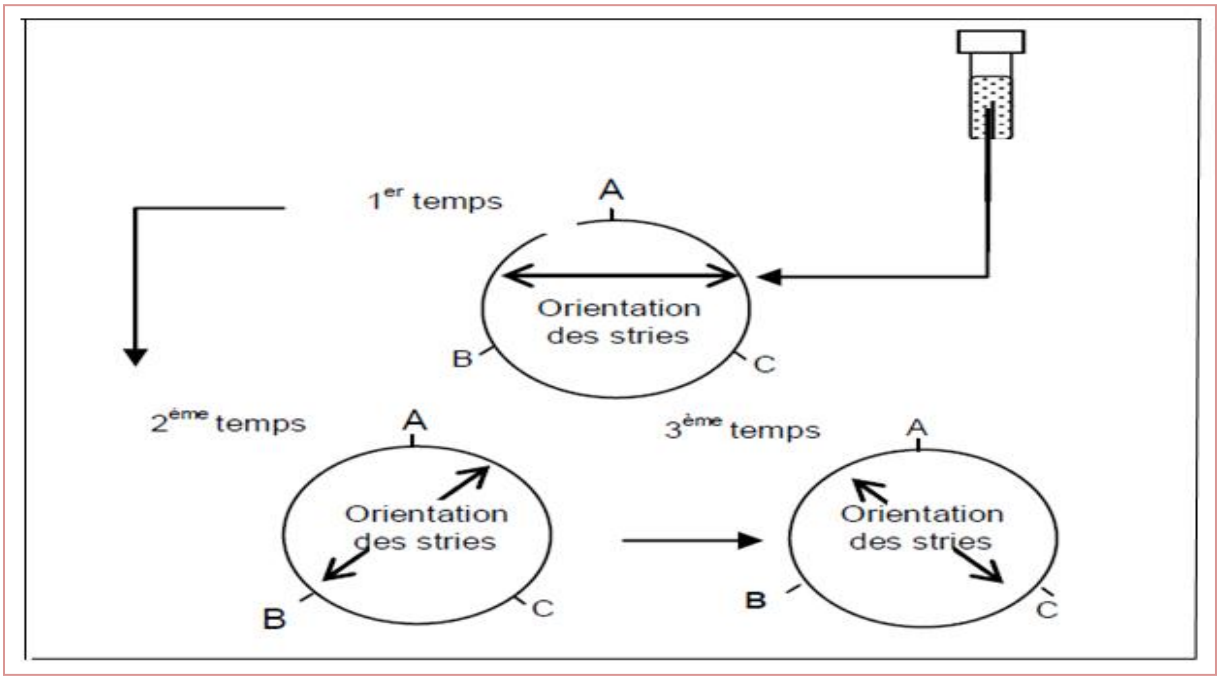


Figure 30: Diagram of steps seeding in a Petri box [22].

III-7-3-3-Preparation of Discs:

Using the paper Wattman # 1 was used to prepare discs 5 mm in diameter, they are deposited in a test tube for sterilization in an oven .with the pipette past the flame is removed a small amount (10 .mu.l) was loaded discs with various test solutions, lets a little time and then puts them in the Petri dishes, leave spaces between the discs; gently pressing on each drive to ensure uniform contact with the medium (M-H) [21] (Figure 31).

Figure 31: Prepare discs.

III-7-3-3-1-incubation:

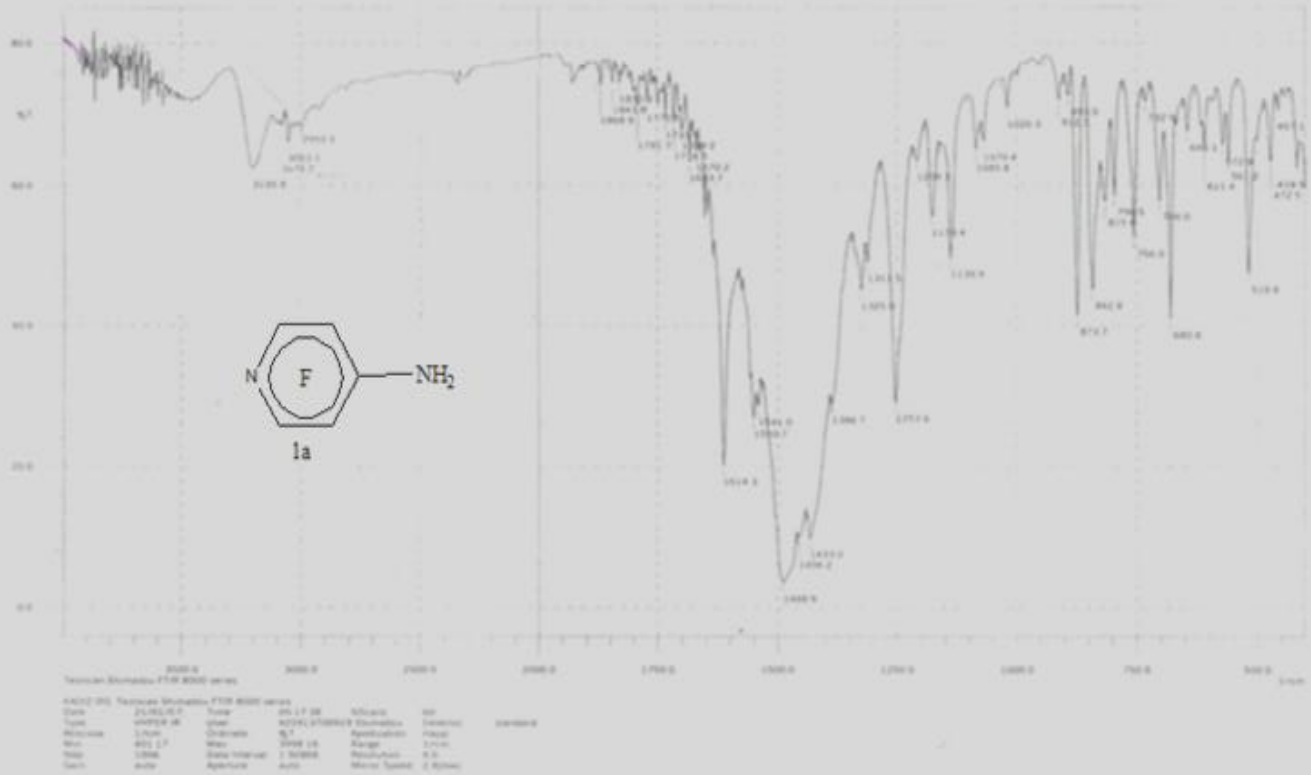
The Petri dishes are placed upside down in the oven at 37 ° C for 24 hours.

Appendices

Part I

Appendix I

Infrared spectra



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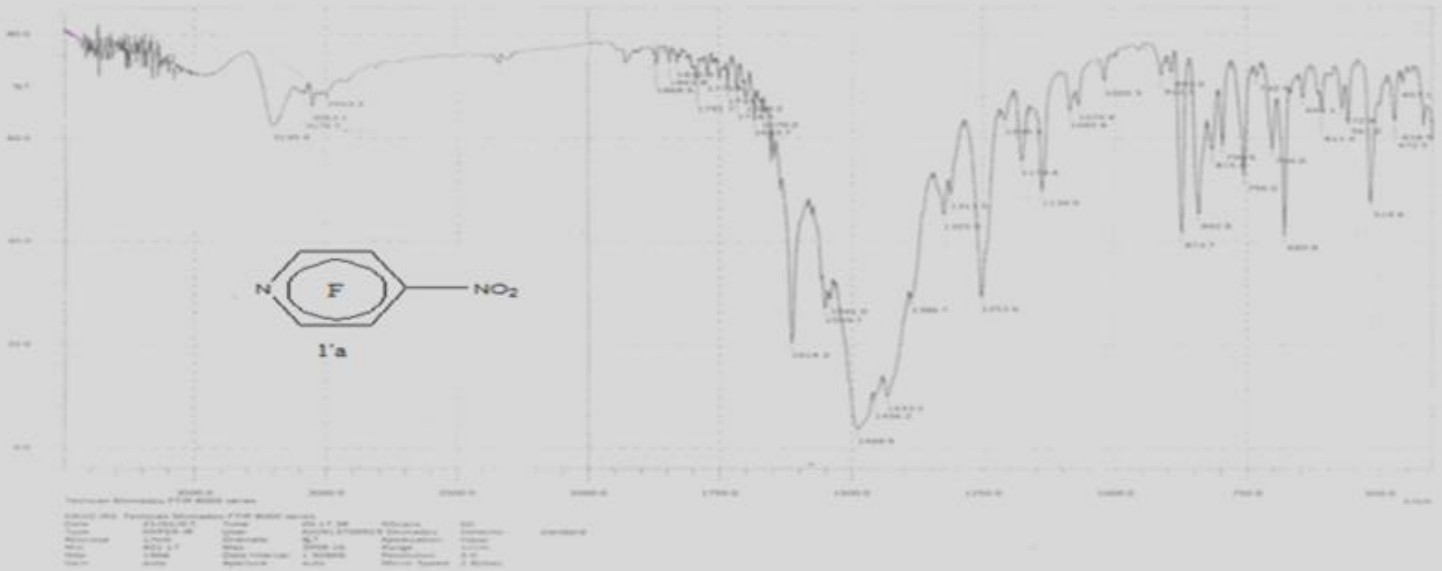

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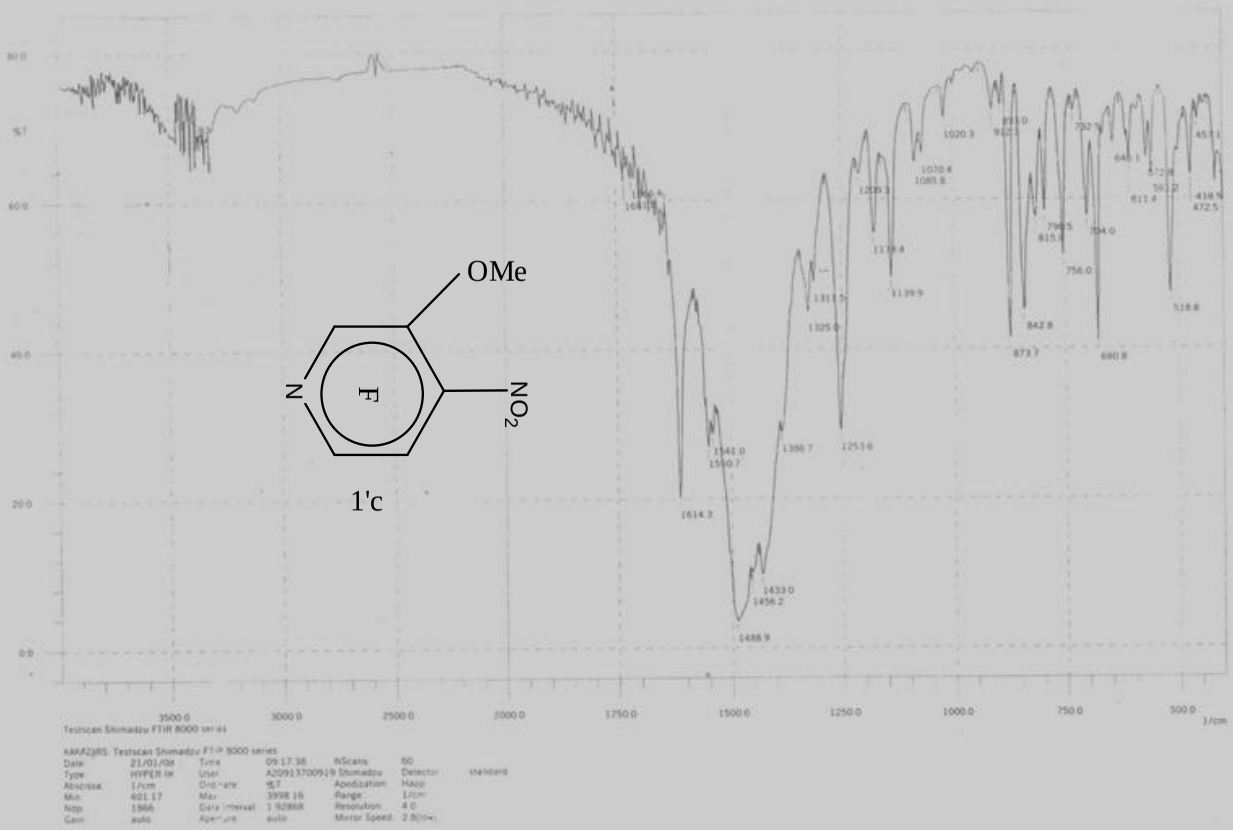
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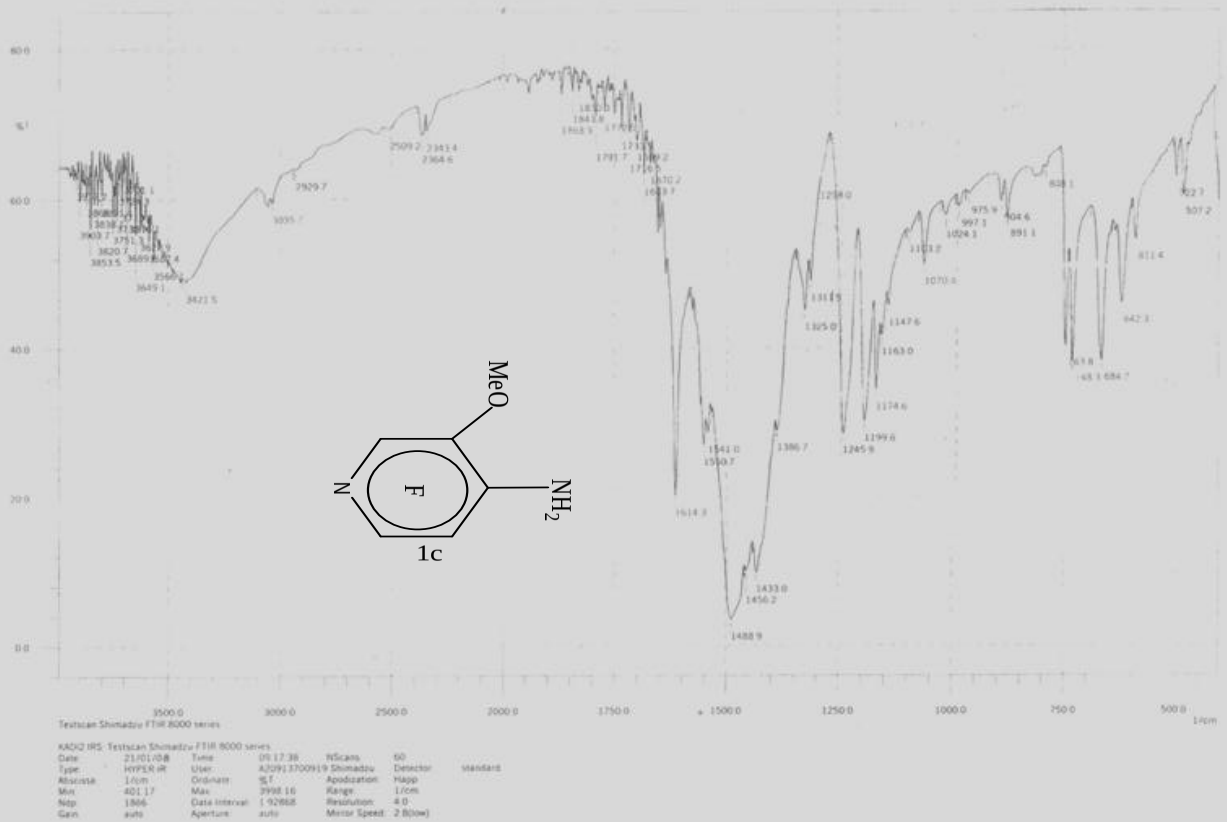
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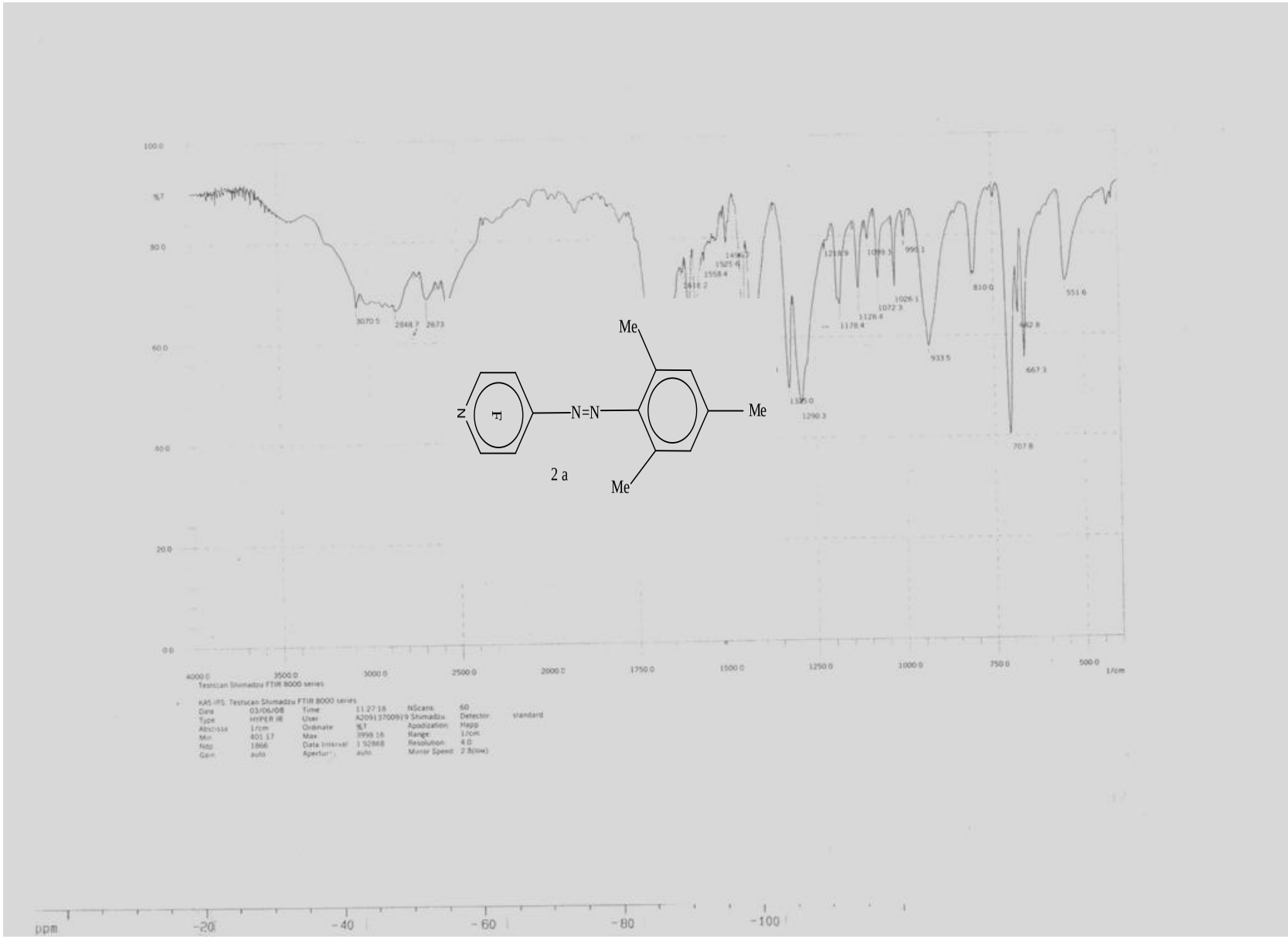
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-60
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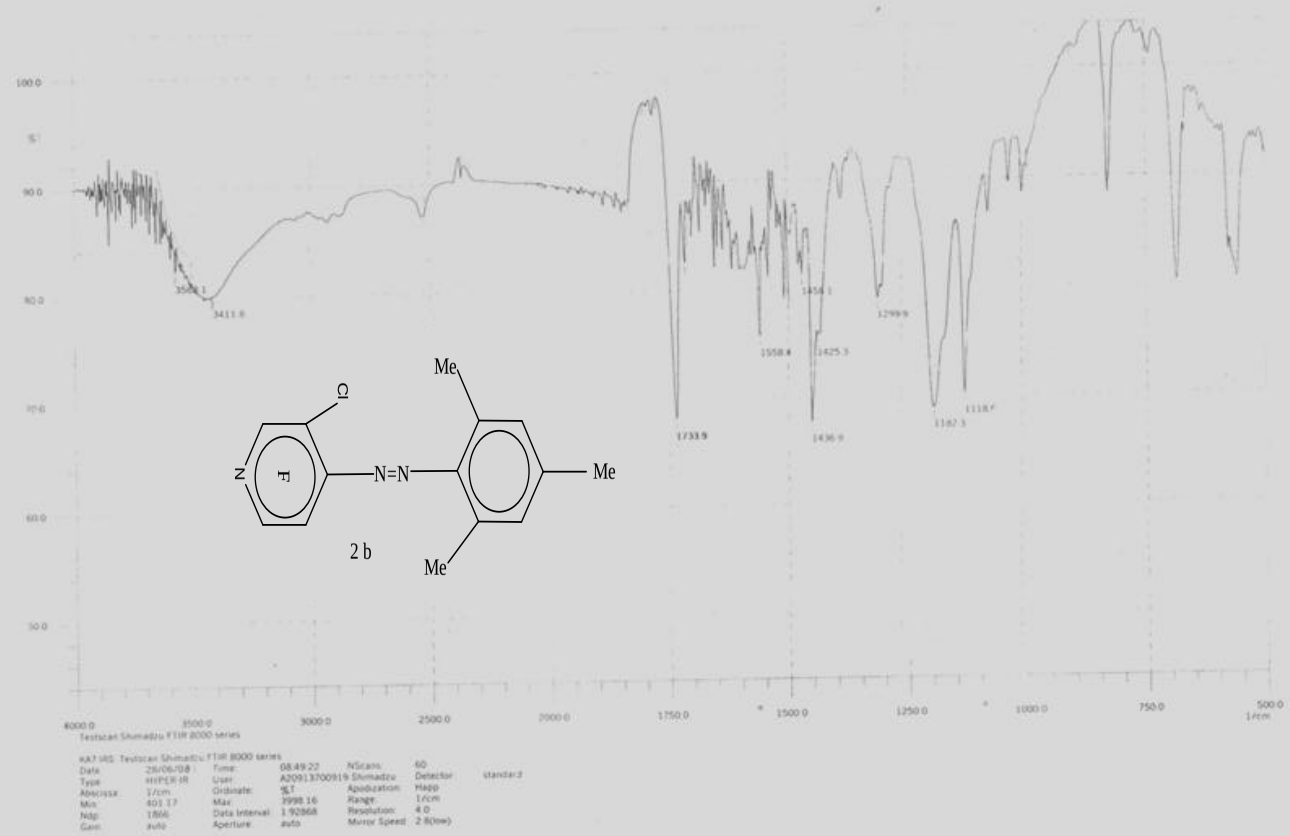
-100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Testscan Shimadzu FTIR 8000 series
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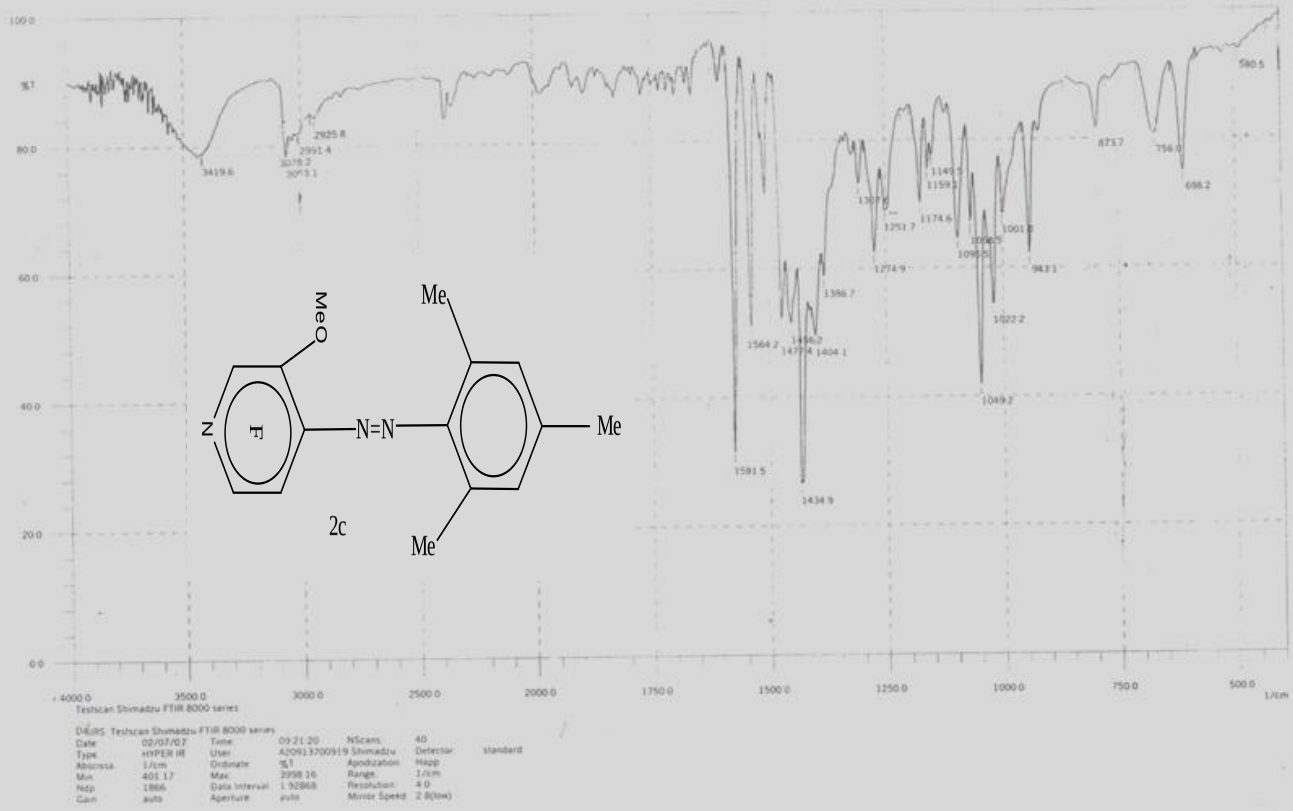
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Date 02/07/07
Time 09:21:20
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Type HYPER IR
User A2091370091$ Shimadzu
Detector standard
Abscissa 1/cm
Ordinate %T
Apodization Happ
Min 401.17
Max 3998.16
Range 1/cm
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Mirror Speed 2.8(low)

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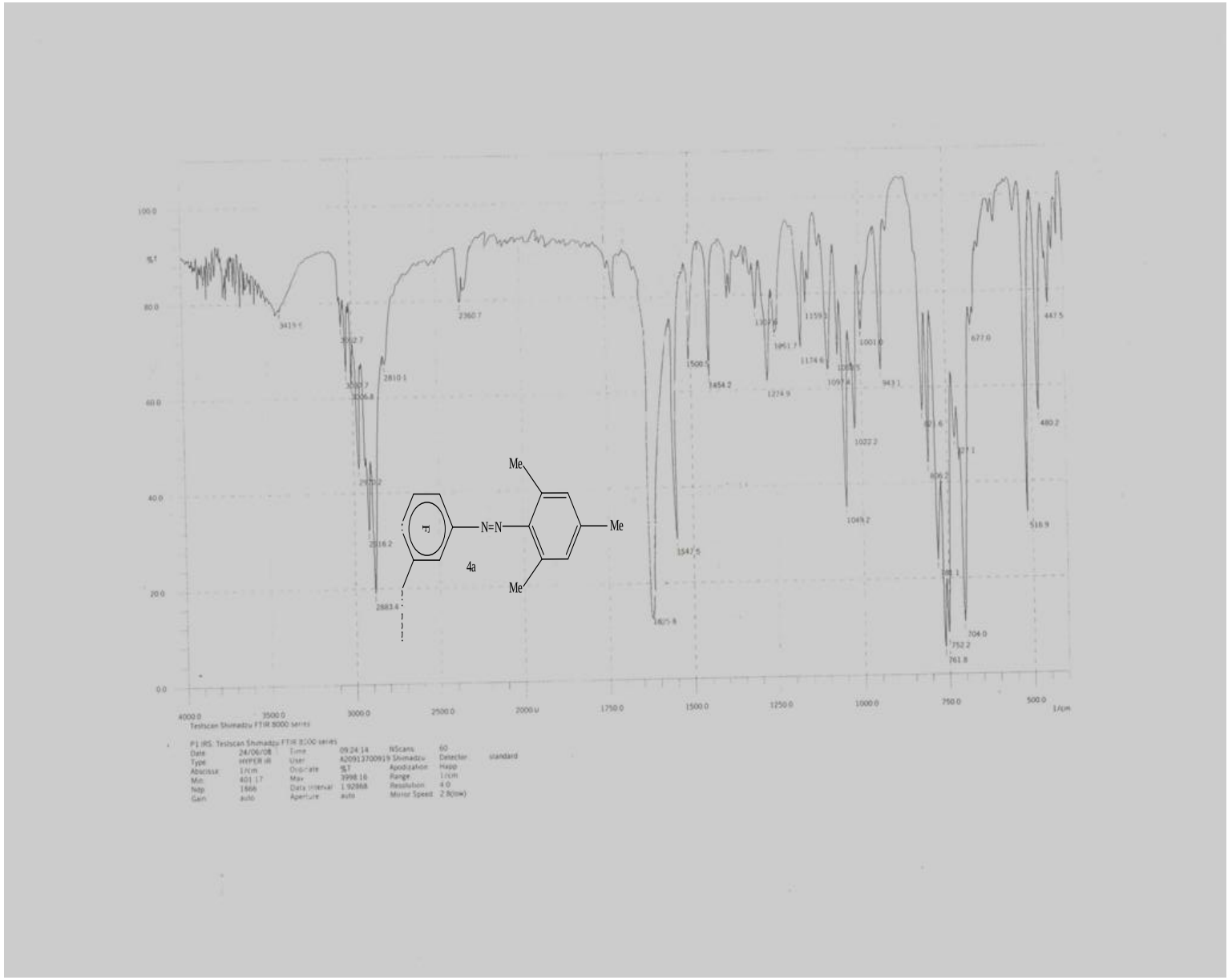
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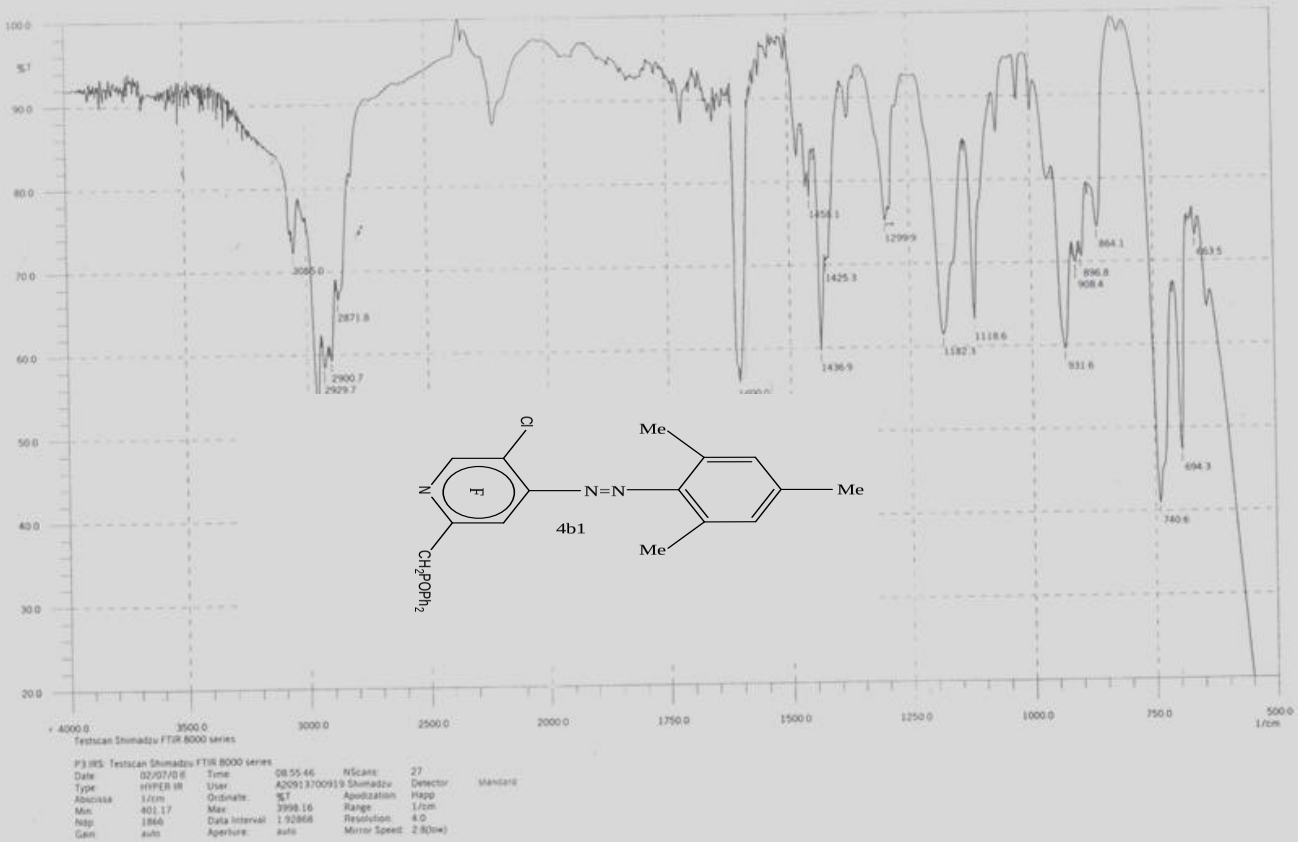
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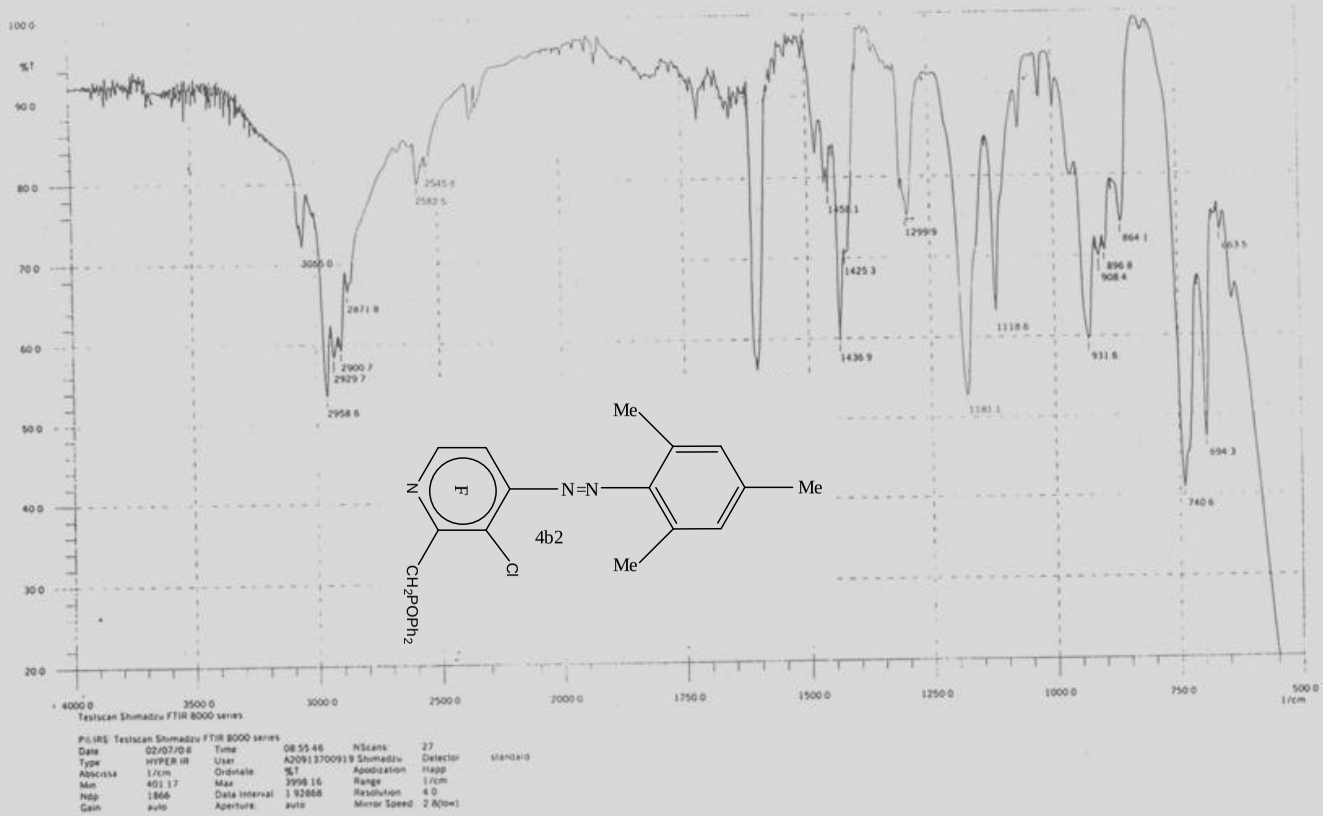
1118.6
931.6
896.8
908.4
864.1
740.6
694.3
663.5
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Testscan Shimadzu FTIR 8000 series
P3.IRS: Testscan Shimadzu FTIR 8000 series
Date 02/07/08
Time 08.55.46
NScans 27
Type HYPER IR
User A20913700919 Shimadzu
Detector
Standard
Abscissa 1/cm
Ordinate %T
Apodization Happ
Min 401.17
Max 3998.16
Range 1/cm
Nop 1866
Data Interval 1.92868
Resolution 4.0
Gain auto
Aperture auto
Mirror Speed 2.8(low)
Cl
N
F
N=N
Me
Me
Me
CH2POPh2
4b1


%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
4000.0
3500.0
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2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
3055.0
2871.9
2900.7
2929.7
2958.6
2545.0
2582.5
1456.1
1425.3
1436.9
1299.9
1181.1
1118.6
931.6
896.8
908.4
864.1
740.6
694.3
Me
N=N
Me
Me
F
N
Cl
CH2POPh2
4b2
Testscan Shimadzu FTIR 8000 series
P:\IRS\ Testscan Shimadzu FTIR 8000 series
Date 02/07/06
Time 08:55:46
NScans 27
Type HYPER IR
User A2091370091 9 Shimadzu
Detector standard
Abscissa 1/cm
Ordinate %T
Apodization Happ
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Max 3998.16
Range 1/cm
Nbp 1866
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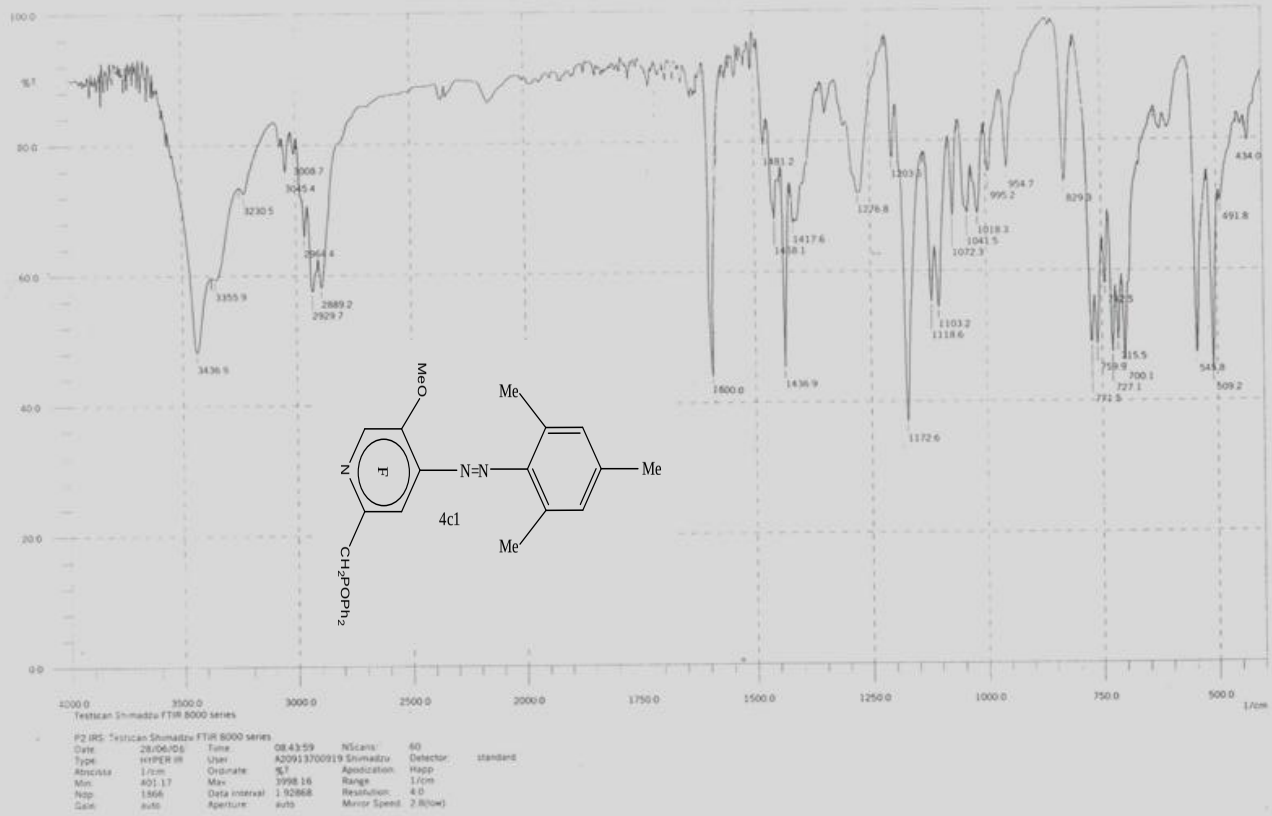
Resolution 4.0
Gain auto
Aperture auto
Mirror Speed 2.8(low)


%T
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80.0
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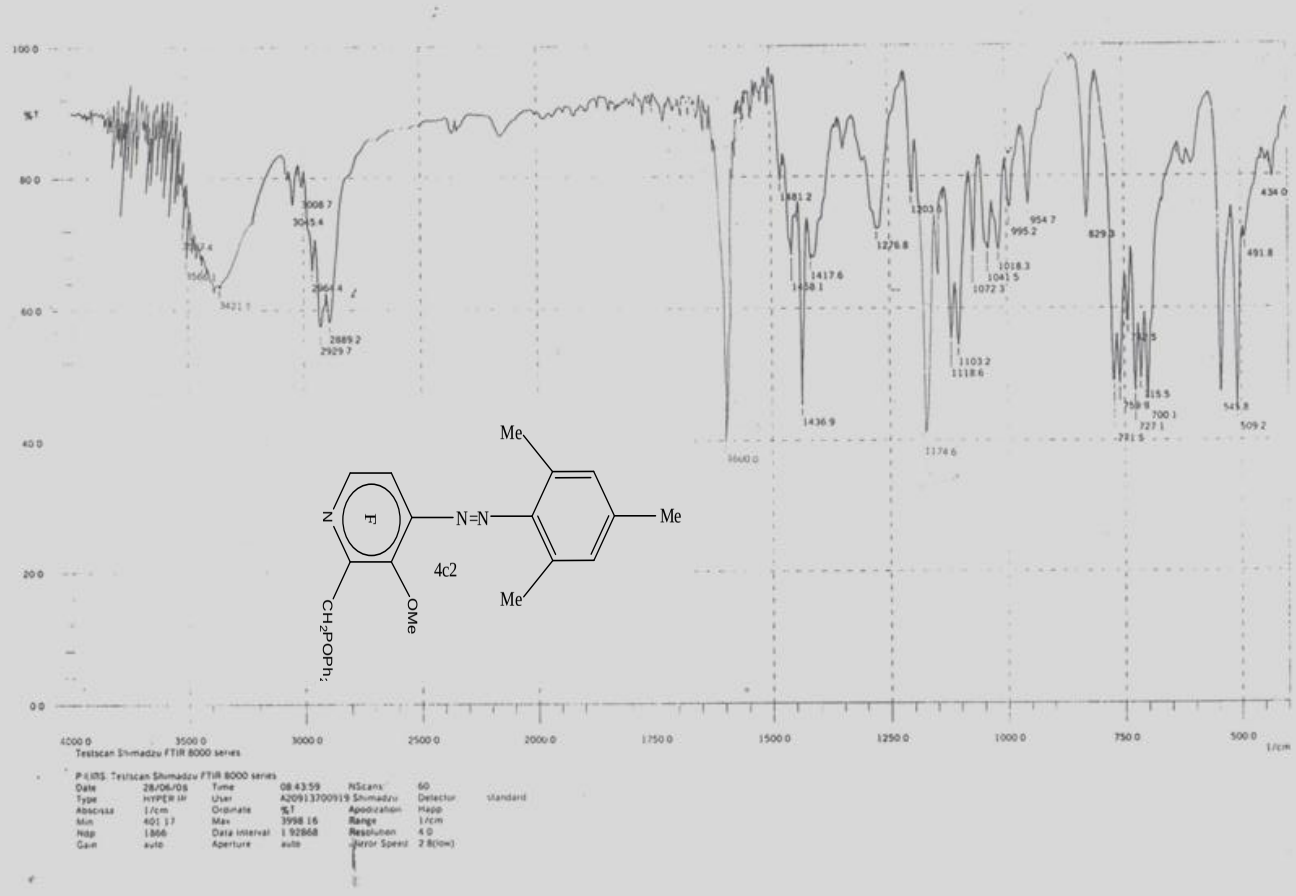
20.0
0.0
3436.9
3355.9
3230.5
3068.7
3045.4
2964.4
2929.7
2889.2
1600.0
1436.9
1417.6
1458.1
1276.8
1203.2
1172.6
1103.2
1118.6
1072.3
1041.5
1018.3
995.2
954.7
829.3
759.9
727.1
700.1
715.5
791.5
545.8
509.2
491.8
434.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Testscan Shimadzu FTIR 8000 series
P2 IRS: Testscan Shimadzu FTIR 8000 series
Date 28/06/16
Time 08:43:59
NScans 60
Type HYPER IR
User A20913700919 Shimadzu
Detector standard
Abscissa 1/cm
Ordinate %T
Apodization Happ
Min 401.17
Max 3998.16
Range 1/cm
Nop 1866
Data interval 1.92868
Resolution 4.0
Gain auto
Aperture auto
Mirror Speed 2.8(low)

MeO
Me
N
F
N=N
Me
Me
CH2POPh2

4c1


100.0
%T
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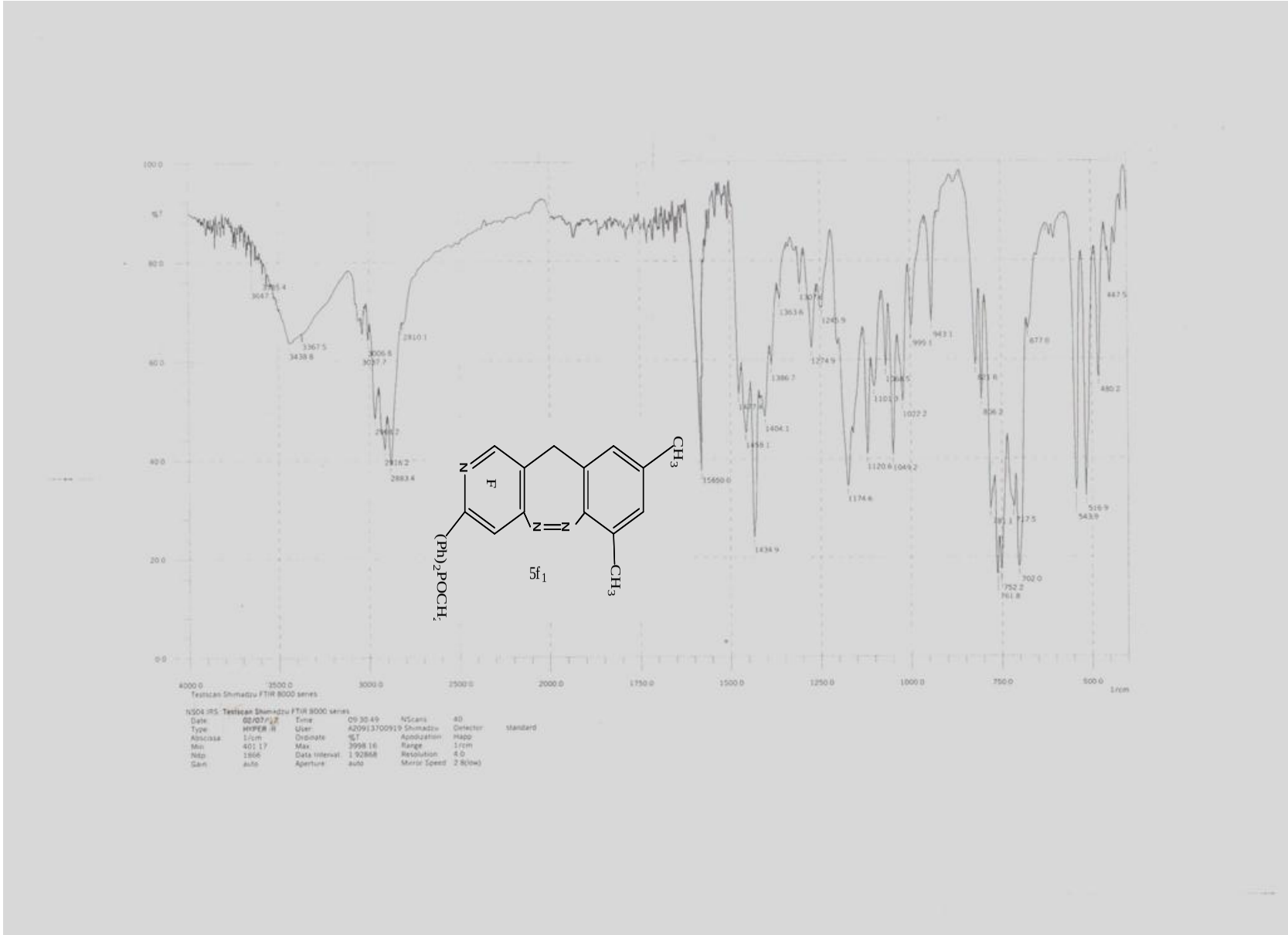
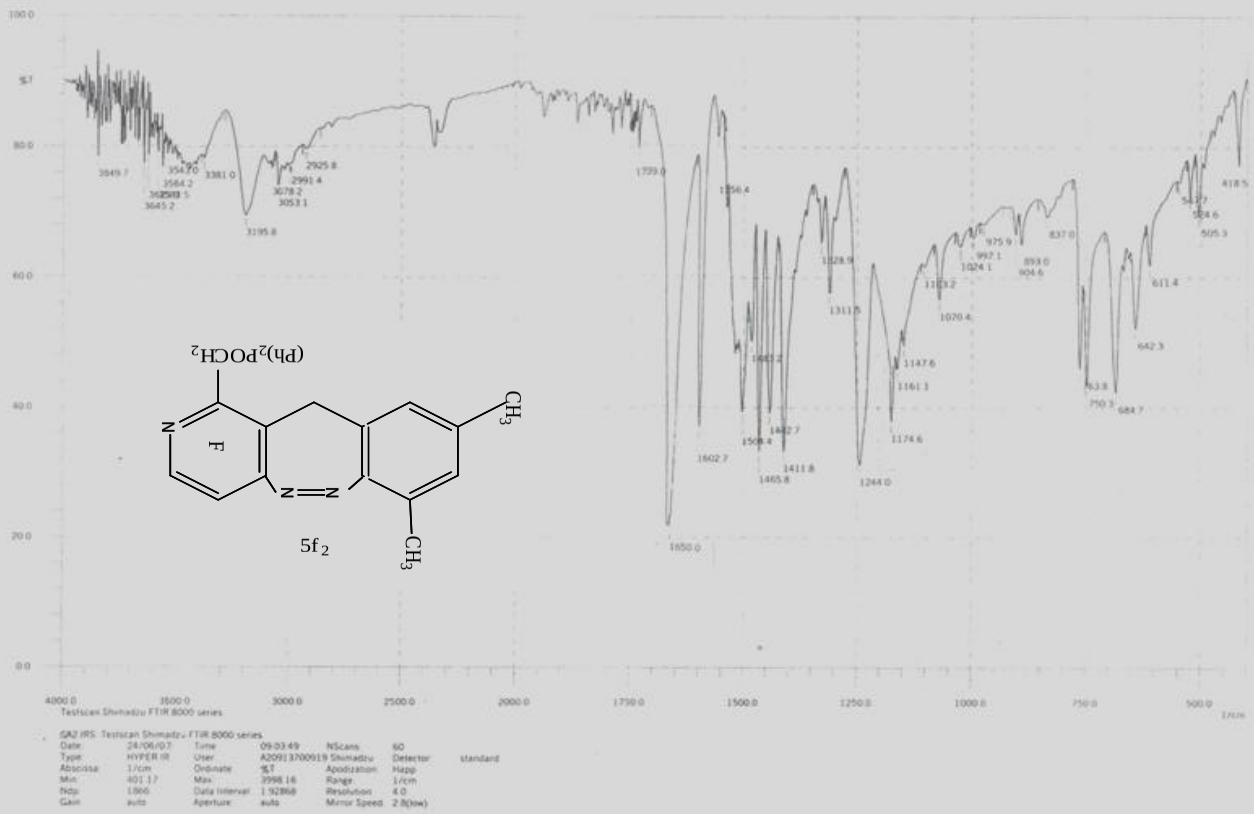
60.0
40.0
20.0
0.0
3008.7
3045.4
2889.2
2929.7
1481.2
1417.6
1458.1
1436.9
1276.8
1203.6
1103.2
1118.6
1174.6
1072.3
1041.5
1018.3
995.2
954.7
829.3
759.9
727.1
700.1
509.2
491.8
434.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Me
Me
Me
N=N
F
N
OMe
CH2POPh2
4c2
Testscan Shimadzu FTIR 8000 series
P:\IRS\ Testscan Shimadzu FTIR 8000 series
Date 28/06/08
Time 08:43:59
NScans 60
Type HYPER IR
User A20913700919 Shimadzu
Detector standard
Abscissa 1/cm
Ordinate %T
Apodization Happ
Min 401.17
Max 3998.16
Range 1/cm
Nap 1866
Data interval 1.92868
Resolution 4.0
Gain auto
Aperture auto
Zerofr Speed 2.8(low)


100.0
%T
80.0
60.0
40.0
20.0
0.0
3438.8
3367.5
3006.8
3037.7
2810.1
2883.4
1650.0
1434.9
1404.1
1363.6
1274.9
1240.9
1174.6
1120.6
1049.2
1022.2
999.1
943.1
856.2
752.2
702.0
677.0
543.9
516.9
480.2
447.5
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Testscan Shimadzu FTIR 8000 series
N
F
Z
Z
CH3
CH3
(Ph)2POCH2

$5f_1$



$(Ph)_2POCH_2$

CH_3

F

N

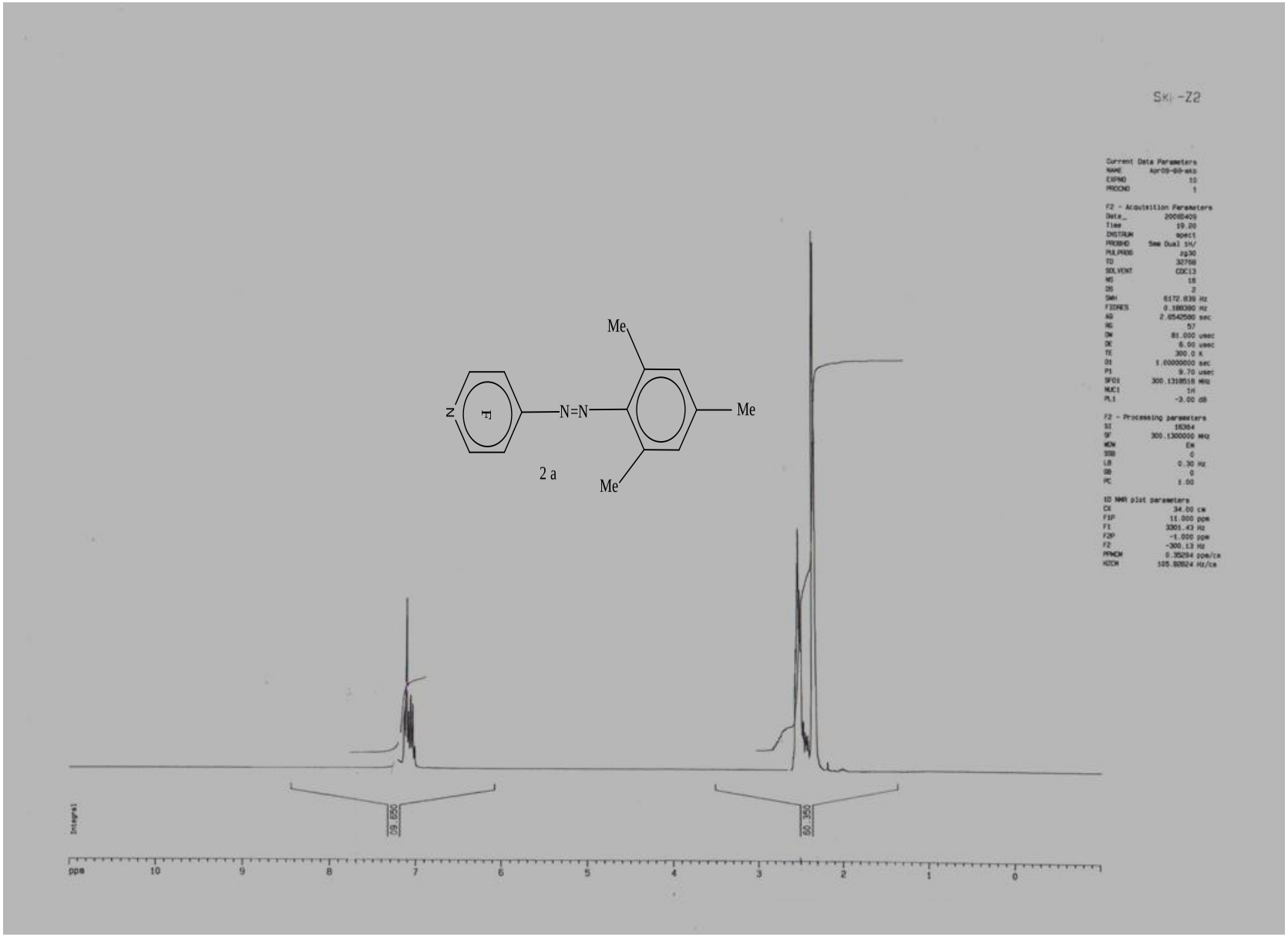
N=N

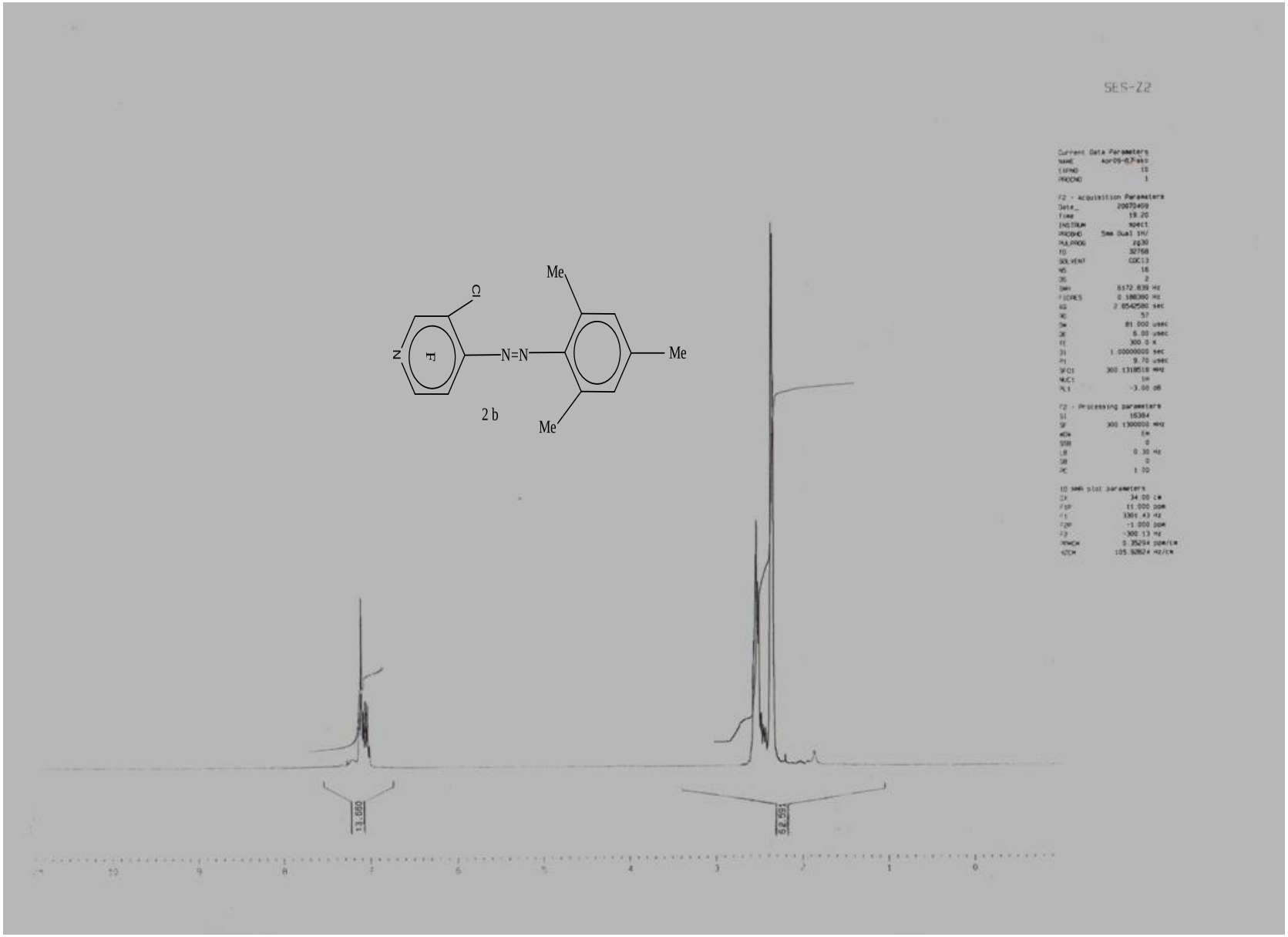
CH_3

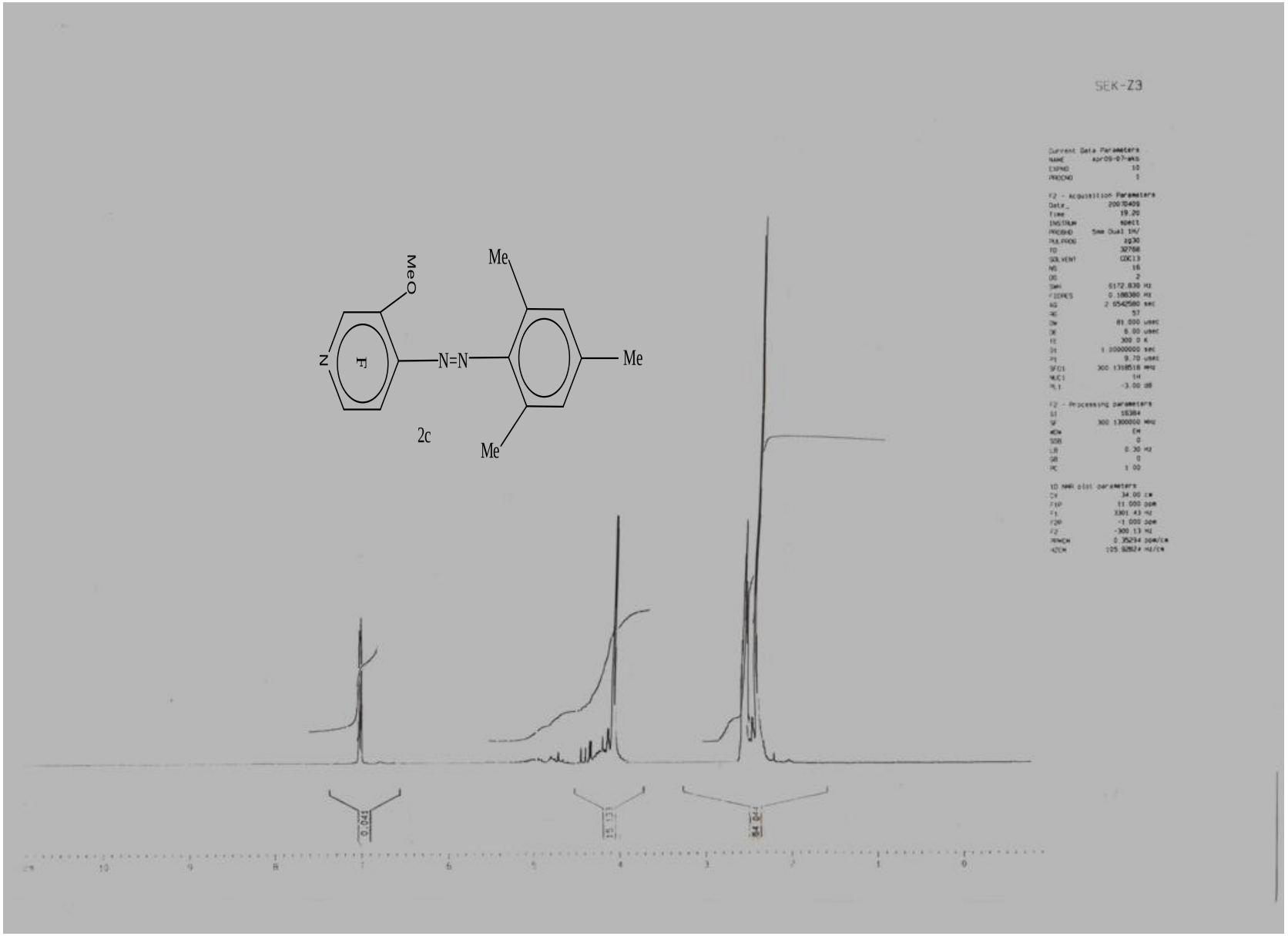
$5f_2$

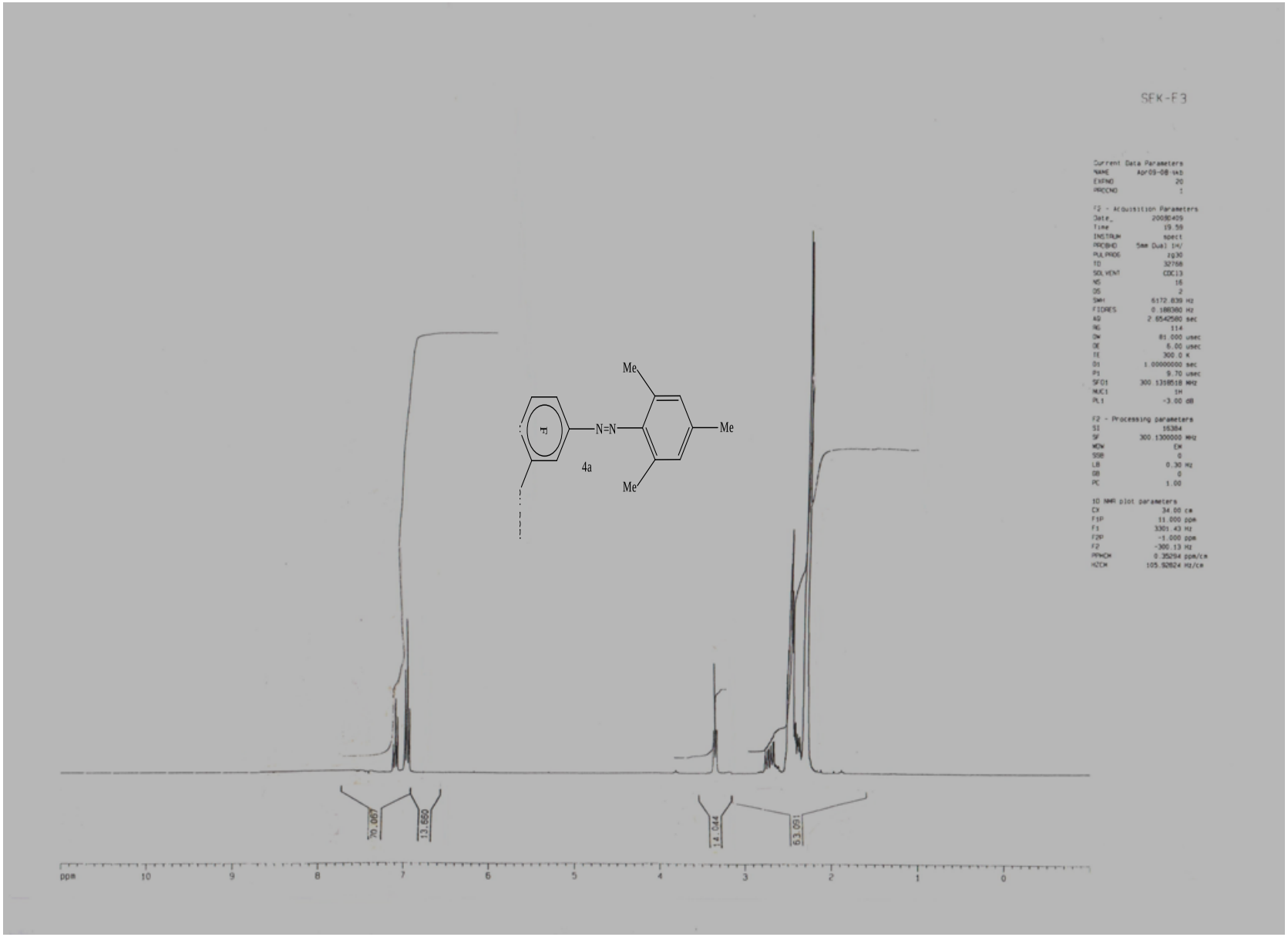
Appendix II
Nuclear Magnetic Resonance spectra

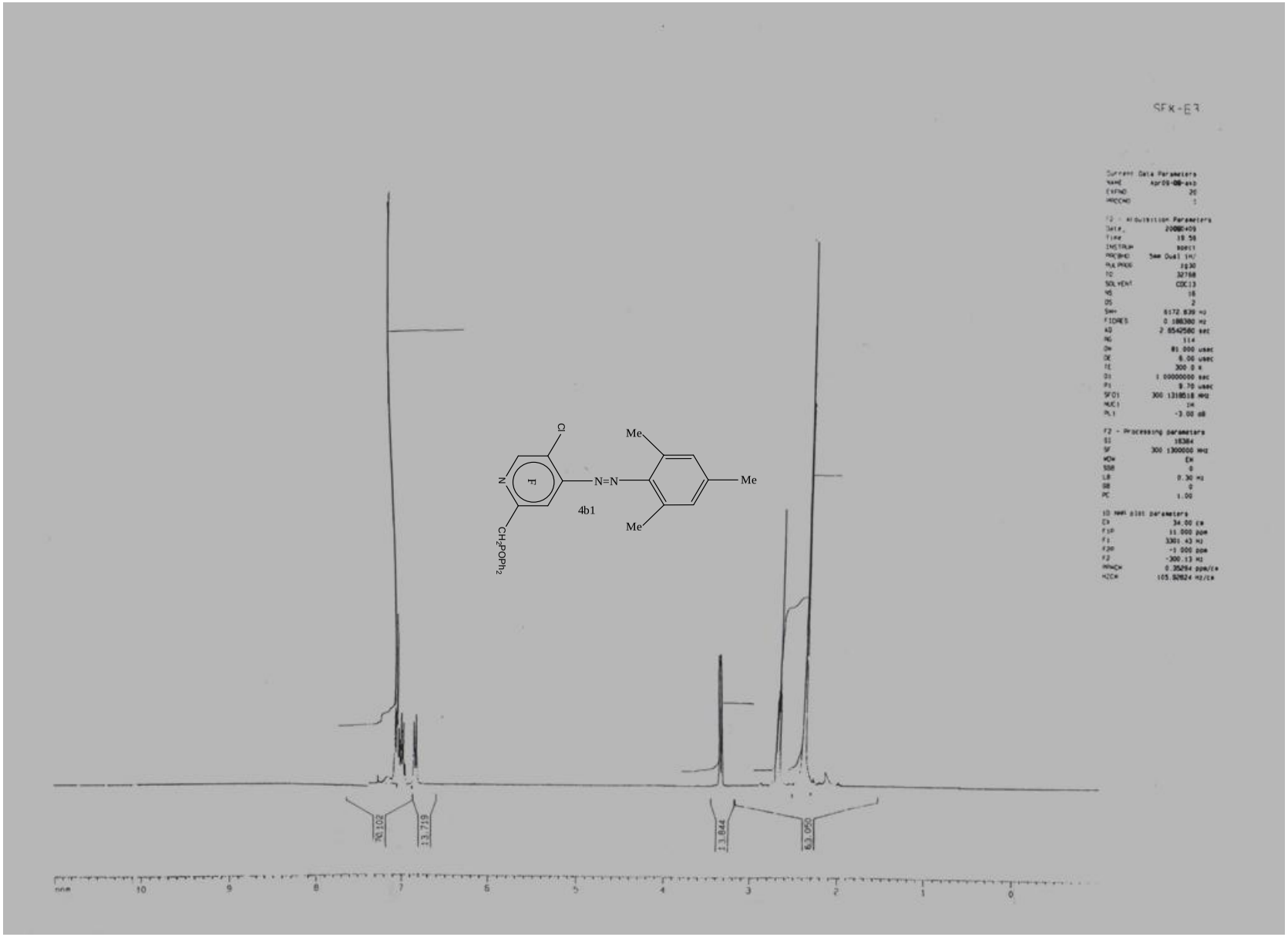
^{1}H spectrum

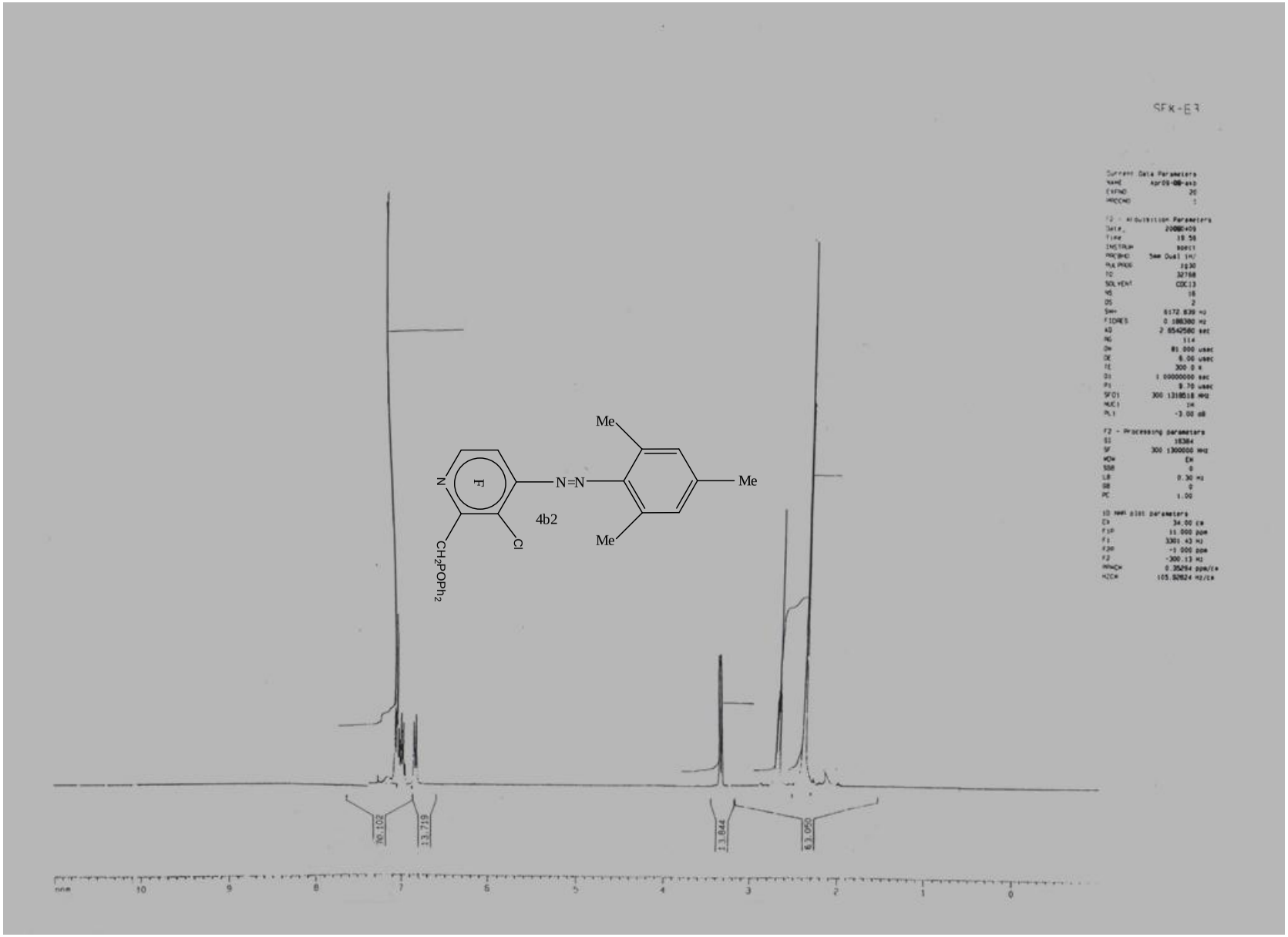

SKI-Z2
Me
N=N
Me
F
N
2 a
Me
Current Data Parameters
NAME Apr09-09-eks
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090409
Time 19.20
INSTRUM spect
PROBHD 5mm Dual 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188390 Hz
AQ 2.6542590 sec
RG 57
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.70 usec
SFO1 300.1318516 MHz
NUC1 1H
PL1 -3.00 dB
F2 - Processing parameters
SI 16384
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 34.00 cm
F1P 11.000 ppm
F1 3301.43 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.35294 ppm/cm
HZCM 105.92924 Hz/cm
Integral
09.650
00.350
ppm
10
9
8
7
6
5
4
3
2
1
0

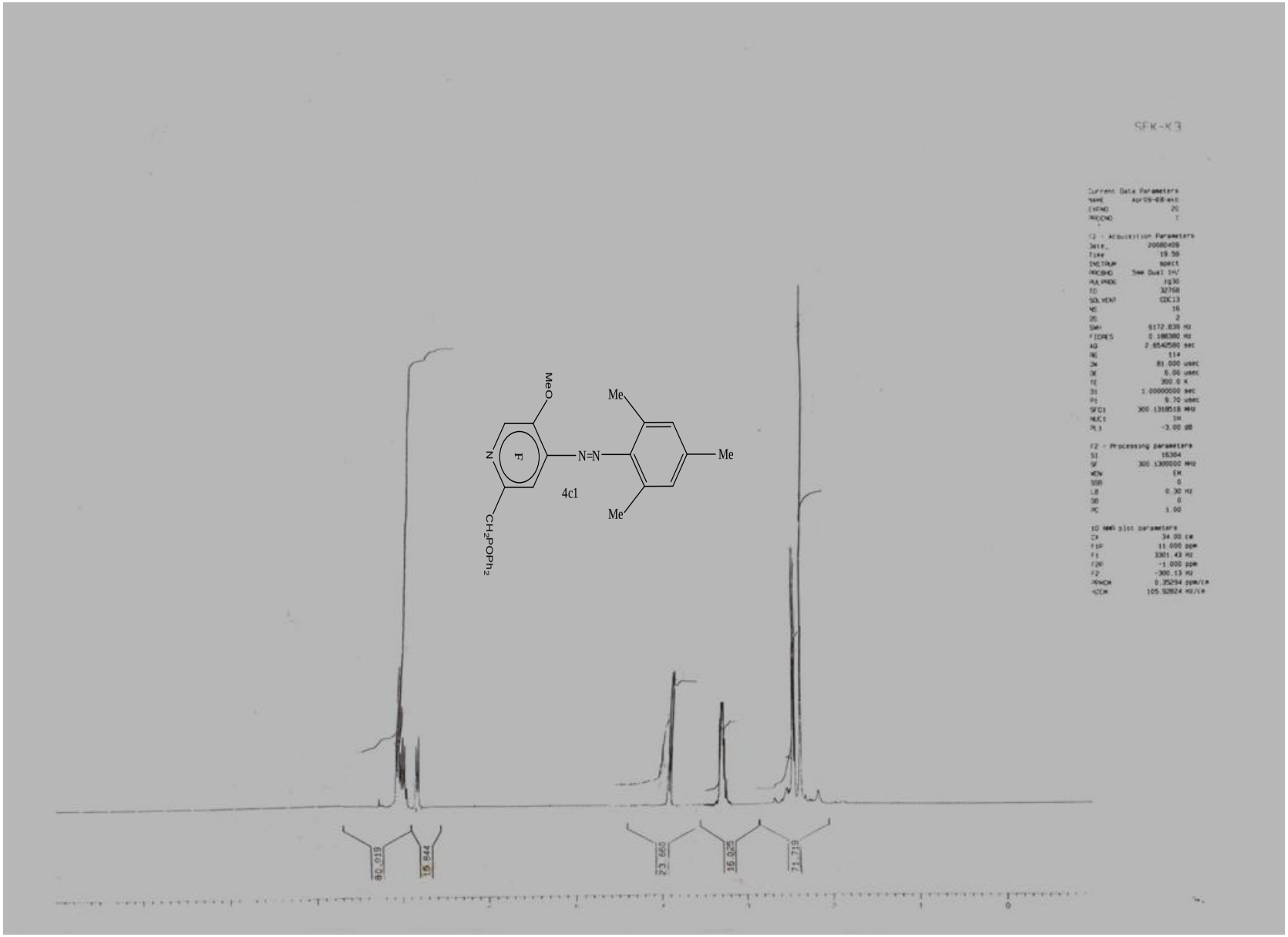

SES-Z2
Me
Cl
N
F
N=N
Me
2 b
Me
13.680
52.591

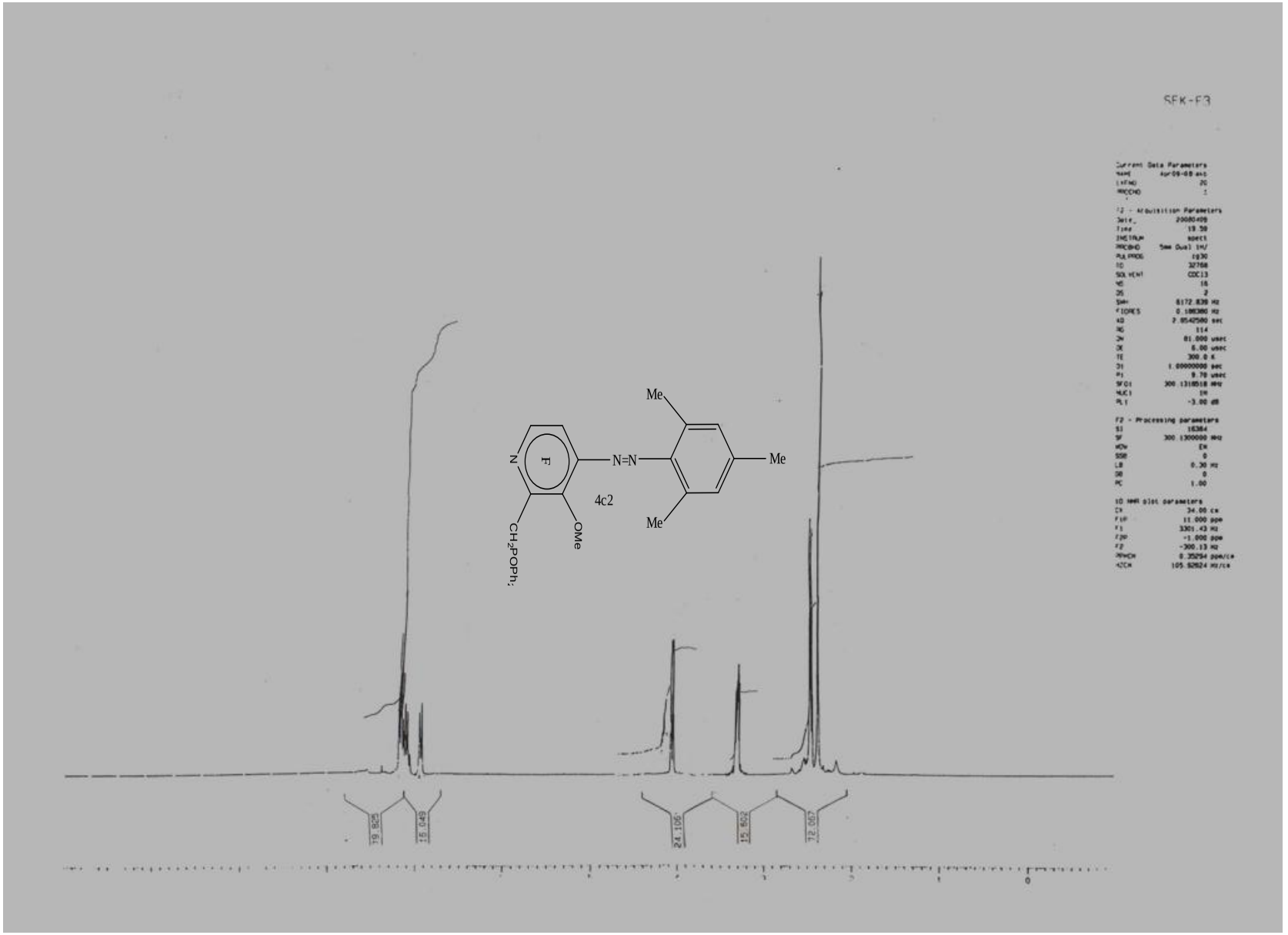

SEK-Z3
MeO
Me
N=N
Me
Me
N
2c
Current Data Parameters
NAME apr09-07-wks
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070409
Time 19.20
INSTRUM spect
PROBHD 5mm Dual 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.838 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 57
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.70 usec
SFO1 300.1318518 MHz
NUC1 1H
PL1 -3.00 dB
F2 - Processing parameters
SI 16384
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 34.00 cm
F1P 11.000 ppm
F1 3301.43 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.35294 ppm/cm
HZCM 105.92824 Hz/cm
3.041
15.131
14.424
10
9
8
7
6
5
4
3
2
1
0

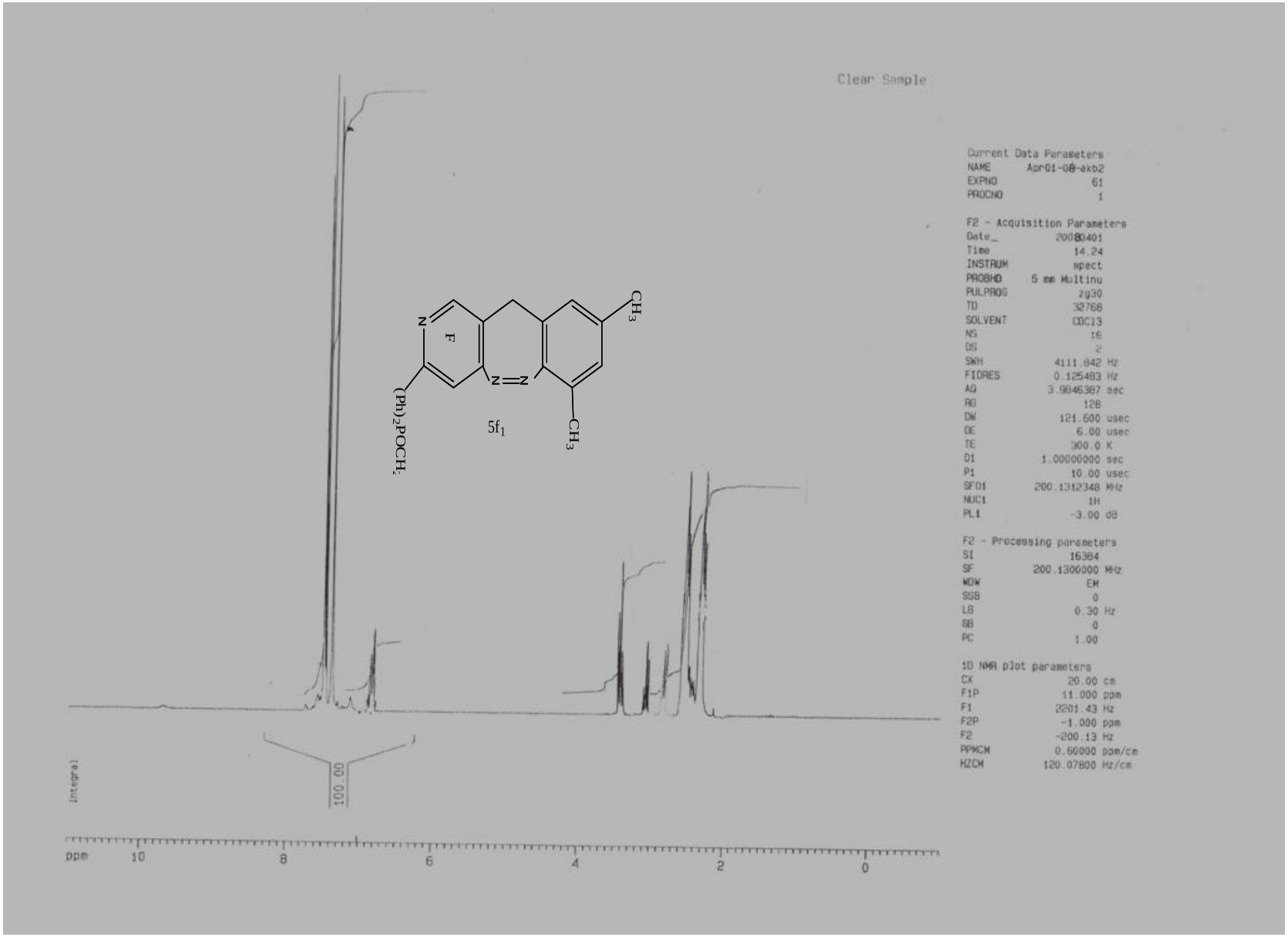

SFK-F3
Current Data Parameters
NAME Apr09-08-sab
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080409
Time 19.59
INSTRUM spect
PROBHD 5mm Dual 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 114
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.70 usec
SFO1 300.1318518 MHz
NUC1 1H
PL1 -3.00 dB
F2 - Processing parameters
SI 16384
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 34.00 cm
F1P 11.000 ppm
F1 3301.43 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.35294 ppm/cm
HZCM 105.92624 Hz/cm
Me
N=N
Me
Me
4a
70.067
13.660
14.044
63.091
ppm
10
9
8
7
6
5
4
3
2
1
0


SFK-E7
Cl
Me
N=N
Me
Me
N
F
CH2POPh2
4b1
2.102
3.419
3.844
3.000
ppm

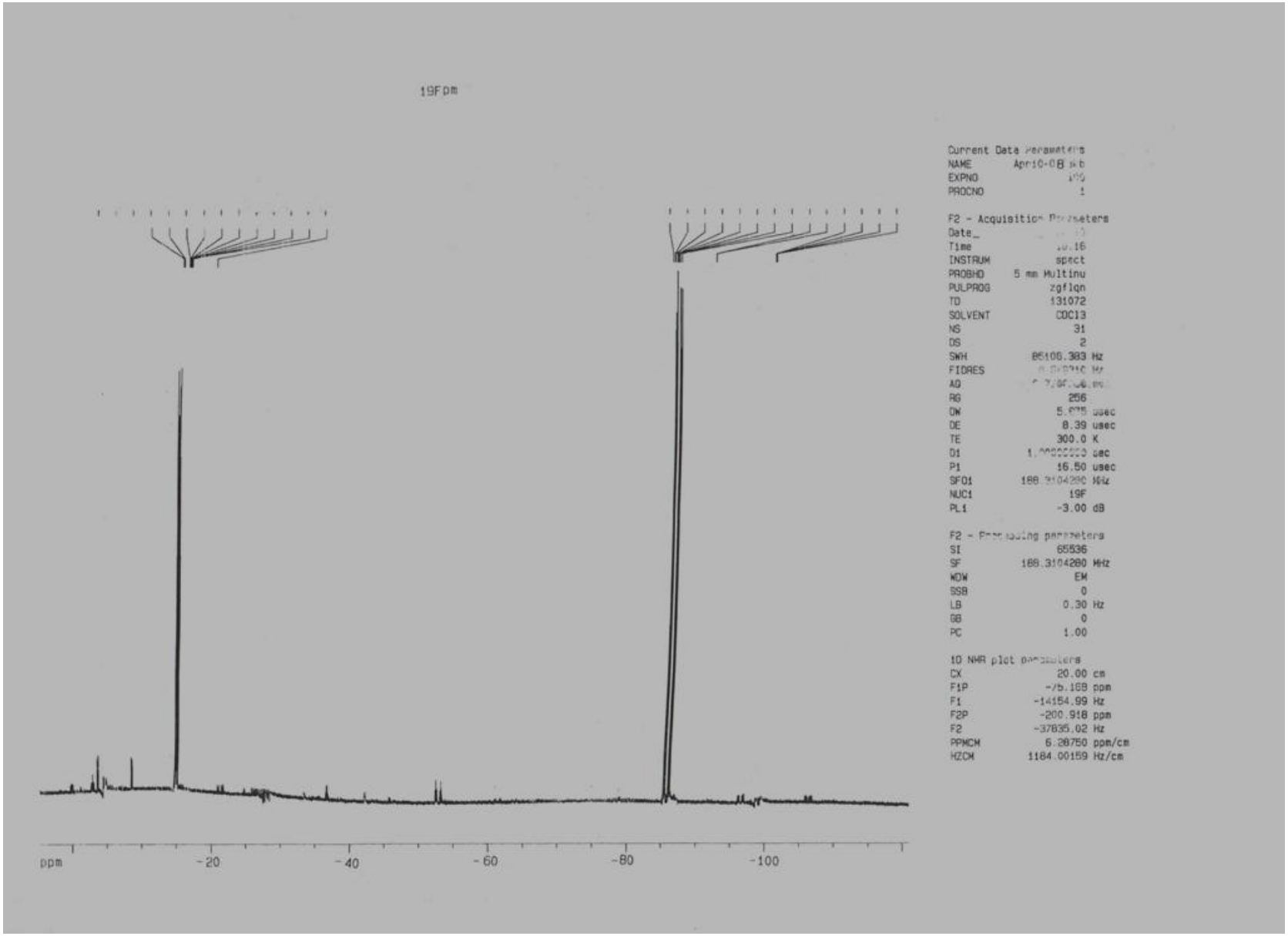

SFK-E7
Me
N=N
Me
N
F
Cl
Me
CH2POPh2
4b2
201.102
13.678
13.844
63.090
ppm
10
9
8
7
6
5
4
3
2
1
0


MeO
Me
N
F
N=N
Me
Me
4c1
CH2POPh2
85.019
15.844
23.660
16.025
71.719


SFK-F3
Me
N=N
Me
N
F
Me
4c2
OMe
CH2POPh2
19.825
15.049
24.106
15.853
7.267
0


Clear Sample
Current Data Parameters
NAME Apr01-08-akb2
EXPNO 61
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080401
Time 14.24
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 4111.842 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 128
DW 121.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 10.00 usec
SFO1 200.1312348 MHz
NUC1 1H
PL1 -3.00 dB
F2 - Processing parameters
SI 16384
SF 200.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 2201.43 Hz
F2P -1.000 ppm
F2 -200.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 120.07800 Hz/cm
CH3
F
N
Z=N
(Ph)2POCH2
CH3
5f1
Integral
100.00
ppm
10
8
6
4
2
0

^{19}F spectrum

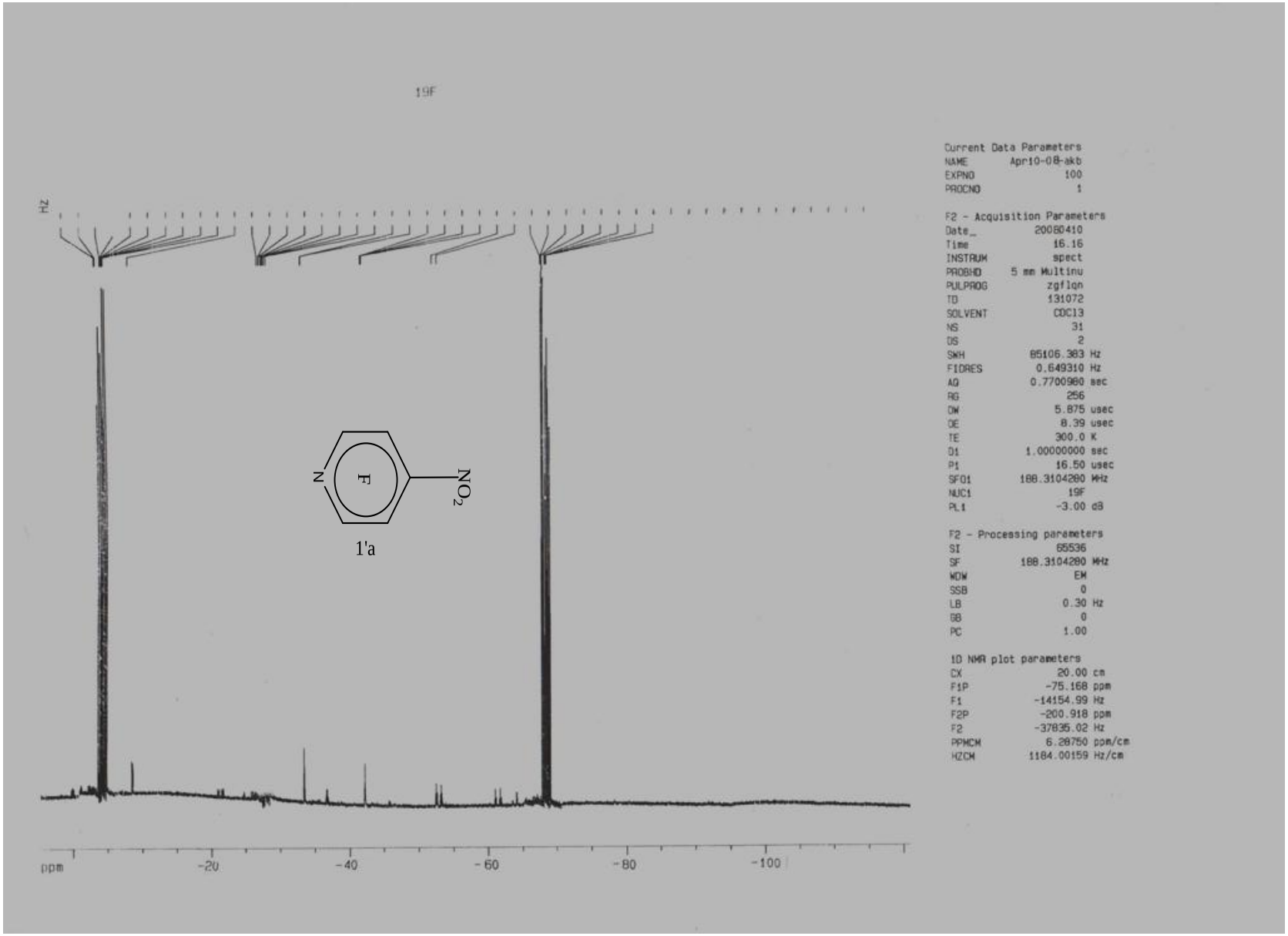


Current Data Parameters
NAME Apr10-08 a b
EXPNO 109
PROCNO 1

F2 - Acquisition Parameters
Date_
Time 10.16
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 31
DS 2
SWH 85106.383 Hz
FIDRES
AQ
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.3104280 MHz
NUC1 19F
PL1 -3.00 dB

F2 - Processing parameters
SI 65536
SF 188.3104280 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P -75.168 ppm
F1 -14154.99 Hz
F2P -200.918 ppm
F2 -37835.02 Hz
PPMCM 6.28750 ppm/cm
HZCM 1184.00159 Hz/cm

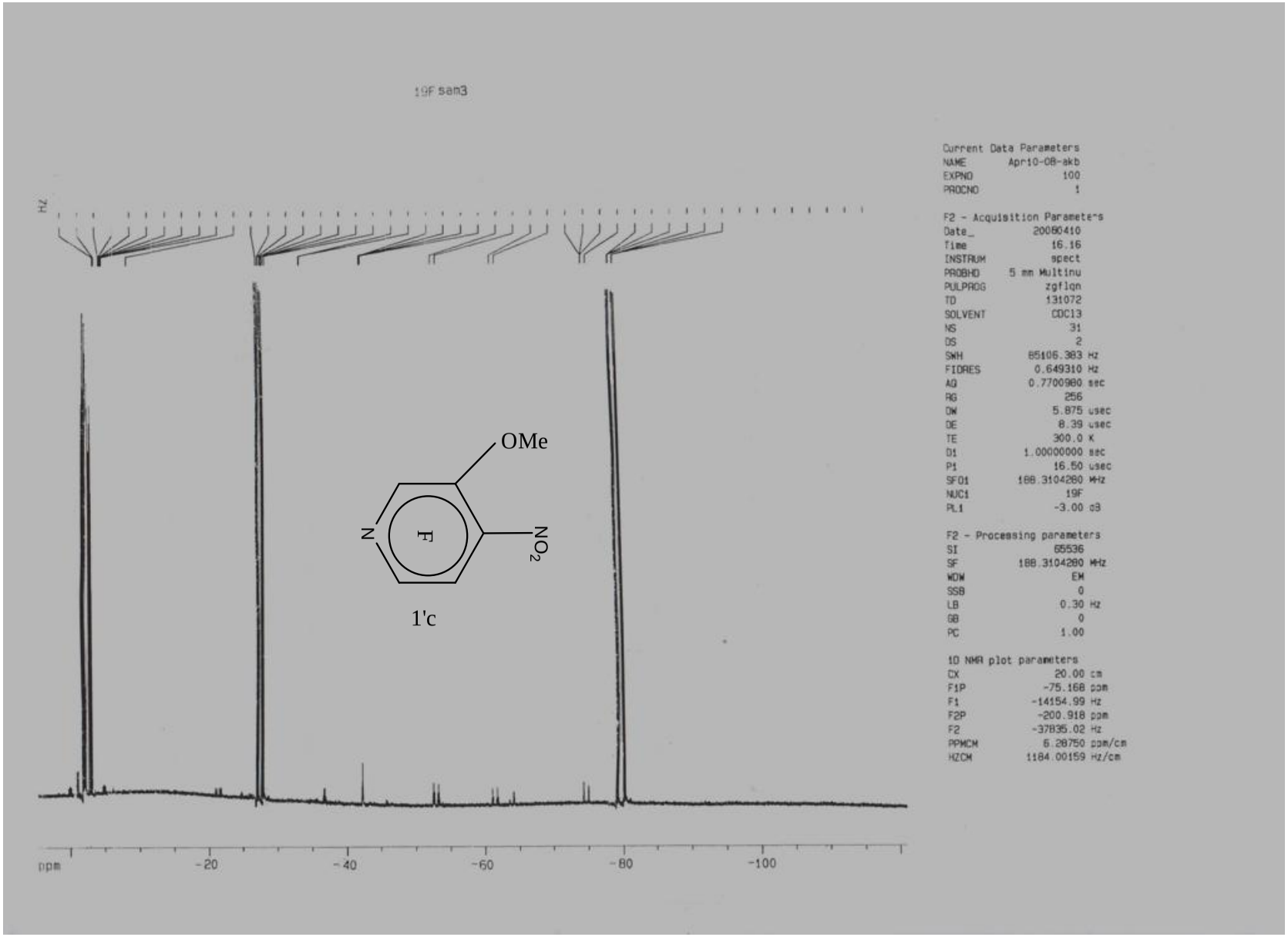


Current Data Parameters
NAME Apr10-08-akb
EXPNO 100
PROCNO 1

F2 - Acquisition Parameters
Date_ 20080410
Time 16.16
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 31
DS 2
SWH 85106.383 Hz
FIDRES 0.649310 Hz
AQ 0.7700980 sec
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.3104200 MHz
NUC1 19F
PL1 -3.00 dB

F2 - Processing parameters
SI 65536
SF 188.3104200 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P -75.168 ppm
F1 -14154.99 Hz
F2P -200.918 ppm
F2 -37835.02 Hz
PPMCM 6.28750 ppm/cm
HZCM 1184.00159 Hz/cm

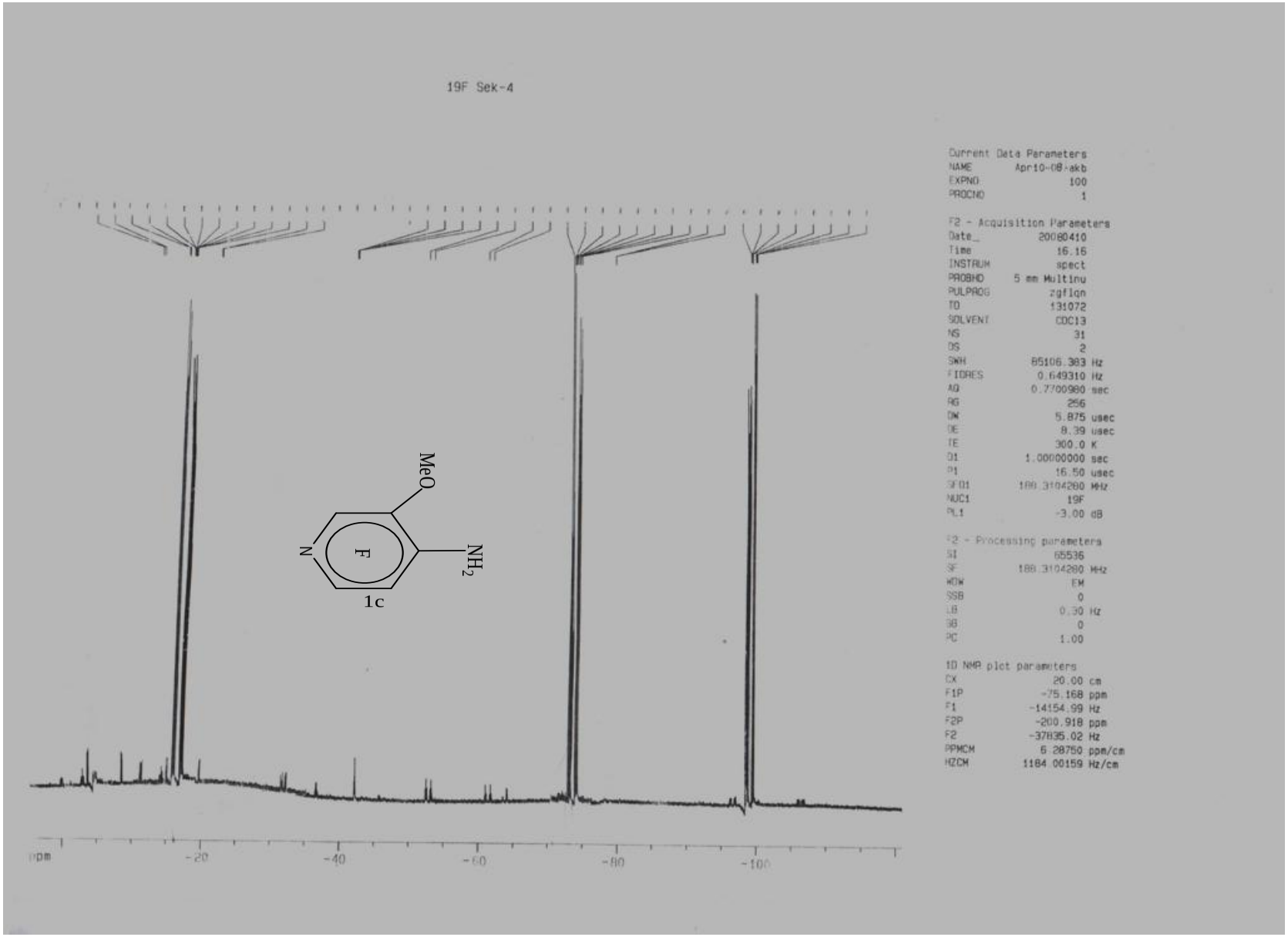


Current Data Parameters
NAME Apr10-08-akb
EXPNO 100
PROCNO 1

F2 - Acquisition Parameters
Date_ 20080410
Time 16.16
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 31
DS 2
SWH 65105.383 Hz
FIDRES 0.649310 Hz
AQ 0.7700980 sec
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.3104280 MHz
NUC1 19F
PL1 -3.00 dB

F2 - Processing parameters
SI 65536
SF 188.3104280 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P -75.168 ppm
F1 -14154.99 Hz
F2P -200.918 ppm
F2 -37835.02 Hz
PPMCM 6.28750 ppm/cm
HZCM 1184.00159 Hz/cm



Current Data Parameters

NAME	Apr10-08-akb
EXPNO	100
PROCNO	1

F2 - Acquisition Parameters

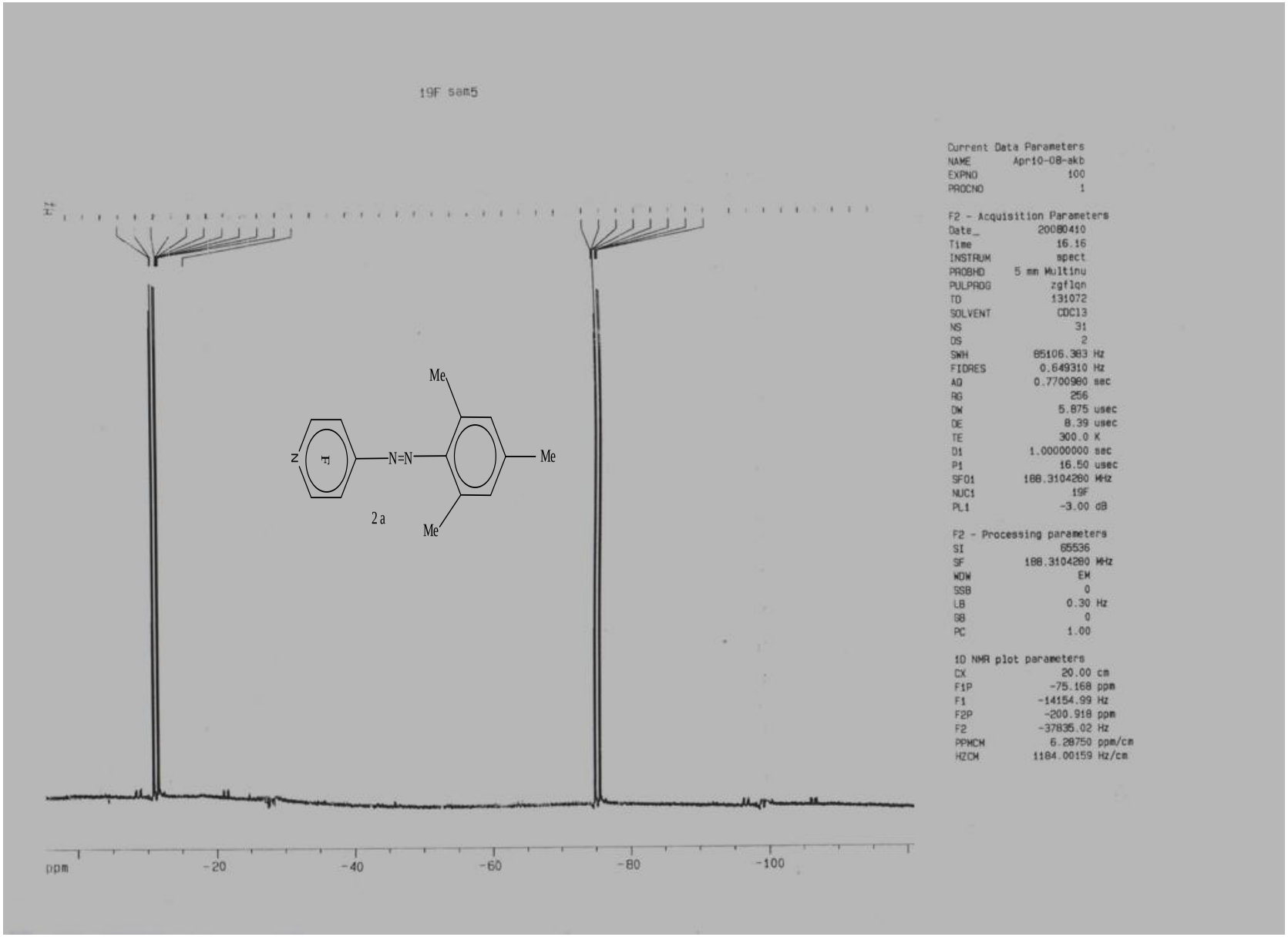
Date_	20080410
Time	16.16
INSTRUM	spect
PROBHD	5 mm Multinu
PULPROG	zgflqn
TD	131072
SOLVENT	CDCl3
NS	31
DS	2
SWH	85106.383 Hz
FIDRES	0.649310 Hz
AQ	0.7700980 sec
RG	256
DW	5.875 usec
DE	8.39 usec
TE	300.0 K
D1	1.00000000 sec
P1	16.50 usec
SFO1	188.3104280 MHz
NUC1	19F
PL1	-3.00 dB

F2 - Processing parameters

SI	65536
SF	188.3104280 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	-75.168 ppm
F1	-14154.99 Hz
F2P	-200.918 ppm
F2	-37835.02 Hz
PPMCM	6.28750 ppm/cm
HZCM	1184.00159 Hz/cm



Current Data Parameters

NAME	Apr10-08-akb
EXPNO	100
PROCNO	1

F2 - Acquisition Parameters

Date_	20080410
Time	16.16
INSTRUM	spect
PROBHD	5 mm Multinu
PULPROG	zgflqn
TD	131072
SOLVENT	CDCl3
NS	31
DS	2
SWH	85106.383 Hz
FIDRES	0.649310 Hz
AQ	0.7700980 sec
RG	256
DW	5.875 usec
DE	8.39 usec
TE	300.0 K
D1	1.00000000 sec
P1	16.50 usec
SFO1	188.3104280 MHz
NUC1	19F
PL1	-3.00 dB

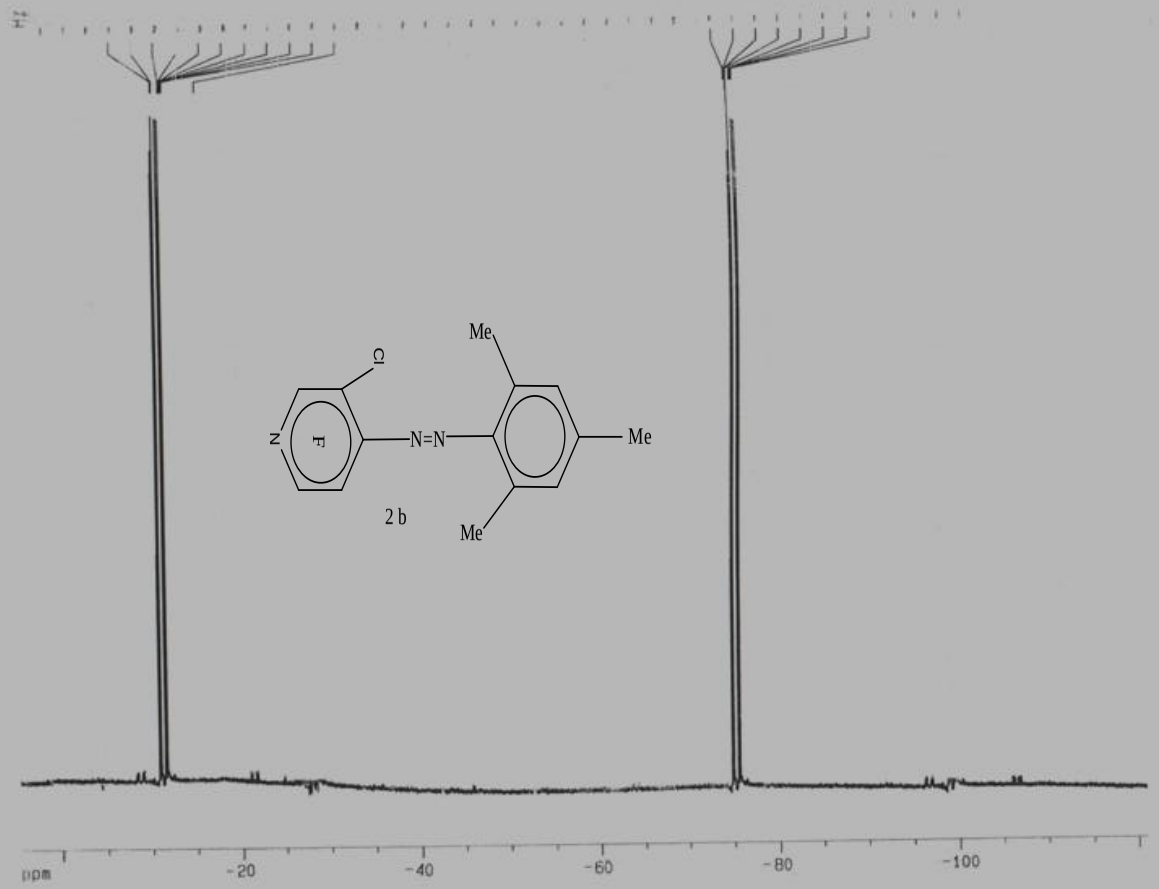
F2 - Processing parameters

SI	65536
SF	188.3104280 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	-75.168 ppm
F1	-14154.99 Hz
F2P	-200.918 ppm
F2	-37835.02 Hz
PPMCM	6.28750 ppm/cm
HZCM	1184.00159 Hz/cm

19F sam1



2 b

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NAME          Apr10-08-akb
EXPNO                  100
PROCNO                   1

F2 - Acquisition Parameters
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Time                 16.16
INSTRUM              spect
PROBHD     5 mm Multinu
PULPROG            zgflqn
TD                 131072
SOLVENT              CDCl3
NS                      31
DS                       2
SWH              85106.383 Hz
FIDRES           0.649310 Hz
AQ               0.7700980 sec
RG                     256
DW                 5.875 usec
DE                 8.39 usec
TE                 300.0 K
D1              1.00000000 sec
P1                 16.50 usec
SFO1           188.3104280 MHz
NUC1                   19F
PL1                -3.00 dB

F2 - Processing parameters
SI                     65536
SF             188.3104280 MHz
WDW                       EM
SSB                        0
LB                  0.30 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                  20.00 cm
F1P                -75.168 ppm
F1              -14154.99 Hz
F2P                -200.918 ppm
F2              -37835.02 Hz
PPMCM            6.28750 ppm/cm
HZCM           1184.00159 Hz/cm
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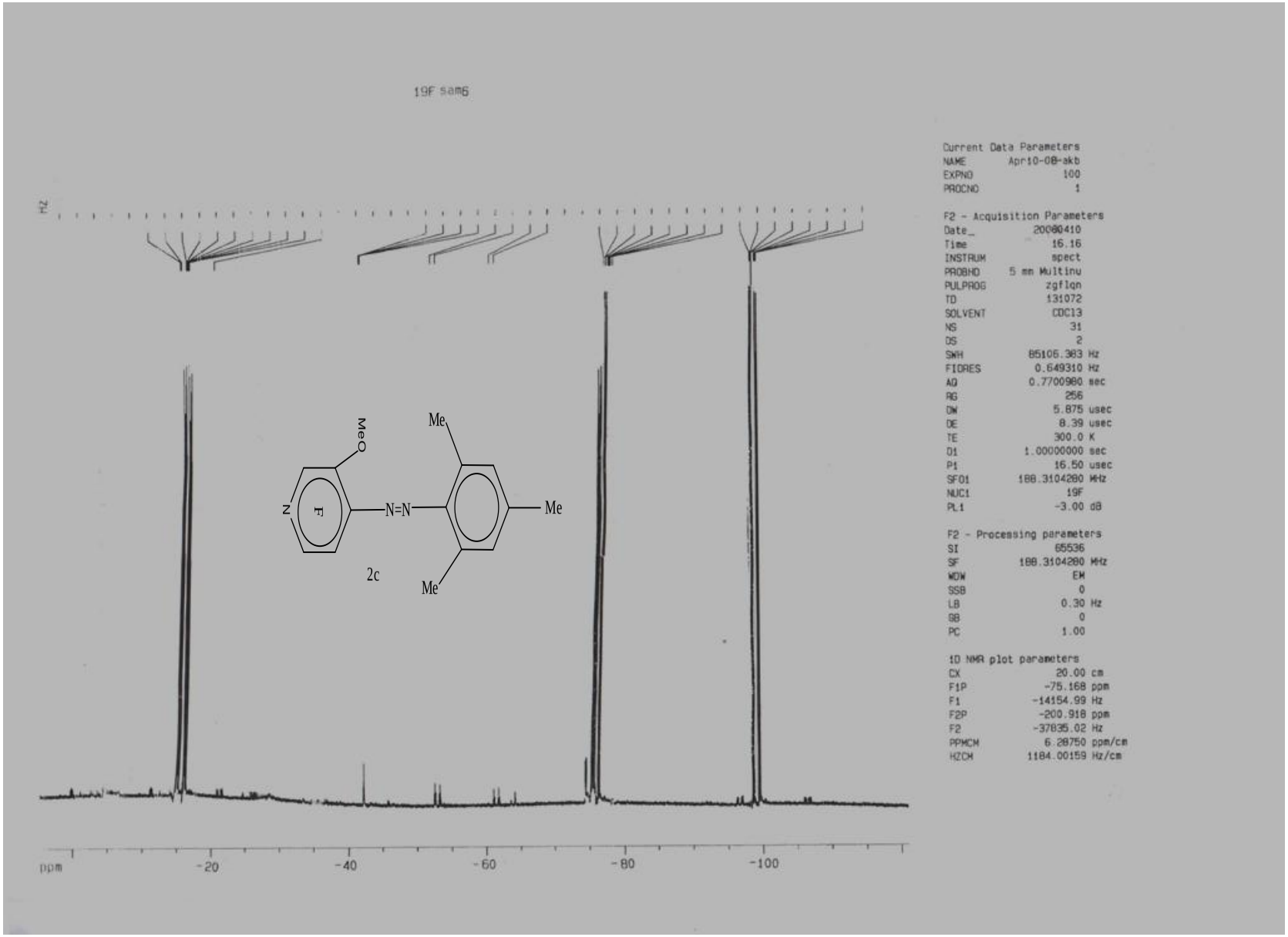

Current Data Parameters
NAME Apr10-08-akb
EXPNO 100
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F2 - Acquisition Parameters
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INSTRUM spect
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PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 31
DS 2
SWH 85106.383 Hz
FIDRES 0.649310 Hz
AQ 0.7700980 sec
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.3104280 MHz
NUC1 19F
PL1 -3.00 dB

F2 - Processing parameters
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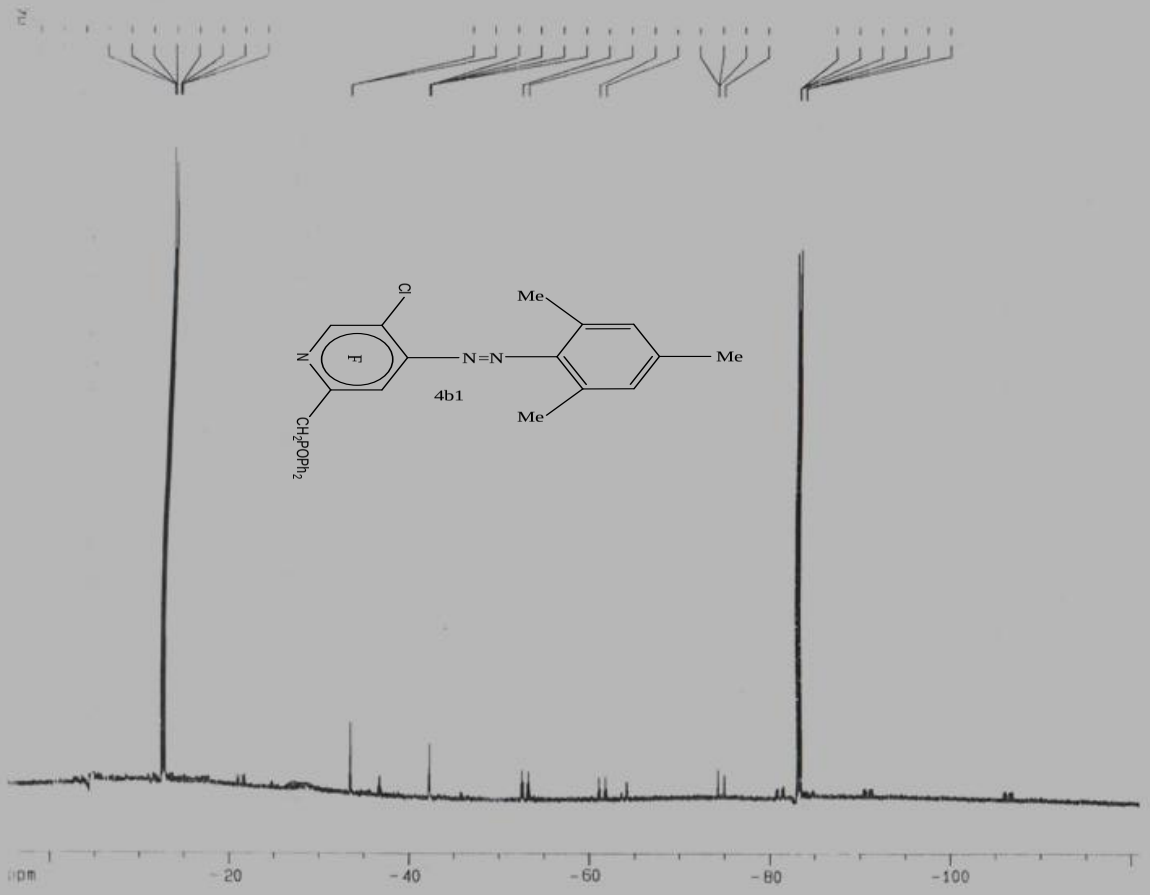
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P -75.168 ppm
F1 -14154.99 Hz
F2P -200.918 ppm
F2 -37835.02 Hz
PPMCM 6.28750 ppm/cm
HZCM 1184.00159 Hz/cm

19F sam6



Current Data Parameters
NAME Apr10-08-akb
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PROCNO 1

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TD 131072
SOLVENT CDCl3
NS 31
DS 2
SWH 85106.383 Hz
FIDRES 0.649310 Hz
AQ 0.7700980 sec
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
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NUC1 19F
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1D NMR plot parameters
CX 20.00 cm
F1P -75.168 ppm
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F2 -37835.02 Hz
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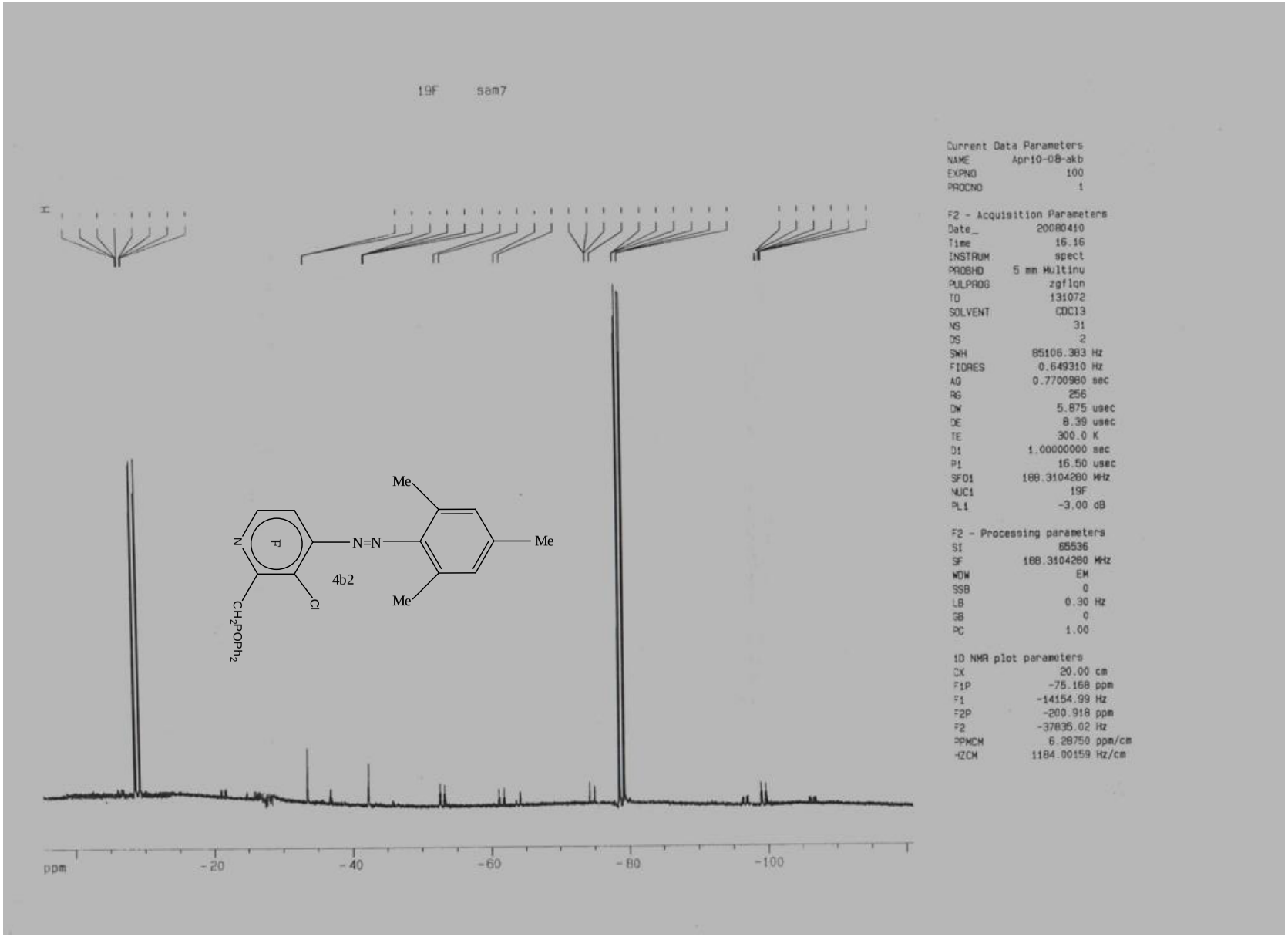
HZCM 1184.00159 Hz/cm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PROCNO 1
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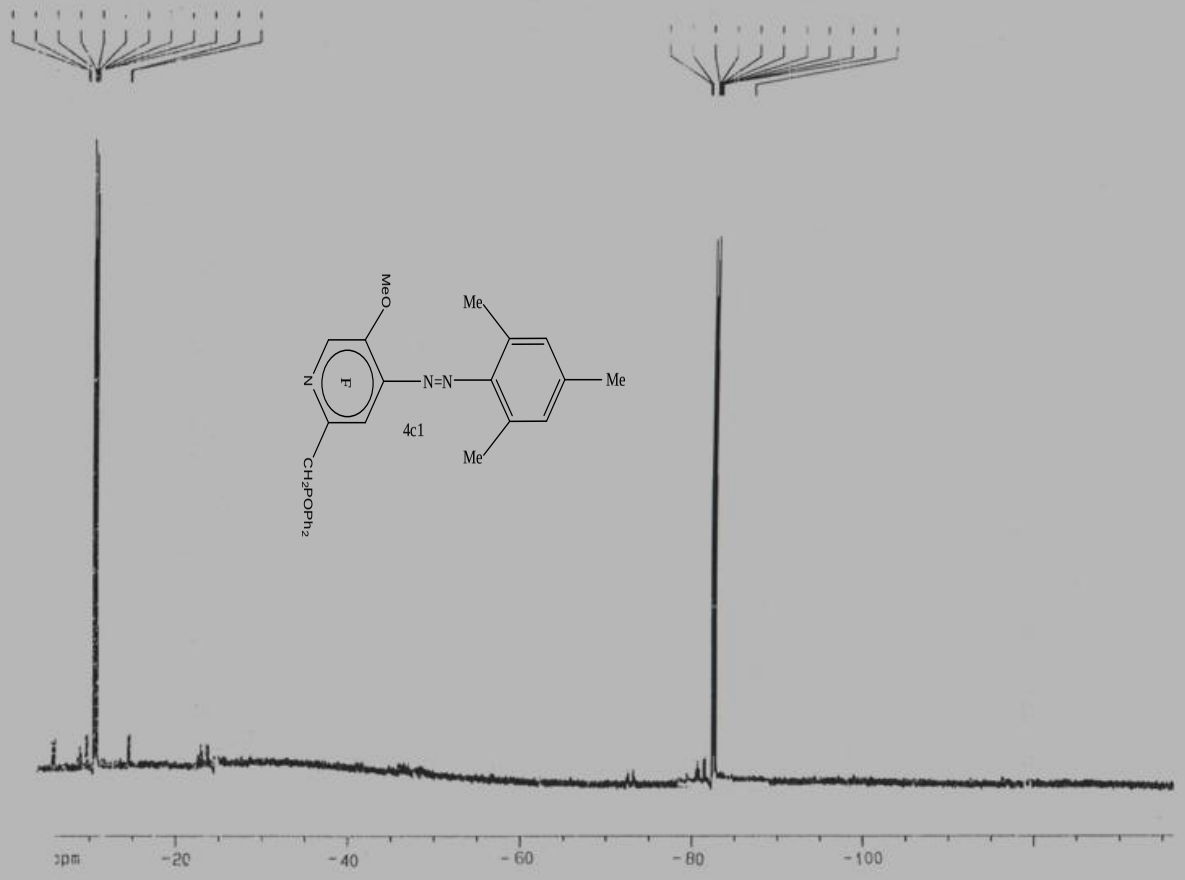
PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 31
DS 2
SWH 85106.383 Hz
FIDRES 0.649310 Hz
AQ 0.7700980 sec
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.3104280 MHz
NUC1 19F
PL1 -3.00 dB
F2 - Processing parameters
SI 65536
SF 188.3104280 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P -75.168 ppm
F1 -14154.99 Hz
F2P -200.918 ppm
F2 -37835.02 Hz
PPMCM 6.28750 ppm/cm
HZCM 1184.00159 Hz/cm
Me
N=N
Me
Me
N
F
Cl
CH2POPh2
4b2
ppm
-20
-40
-60
-80
-100

19F Sem-4



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EXPNO	90
PROCNO	1

F2 - Acquisition Parameters

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INSTRUM	spect
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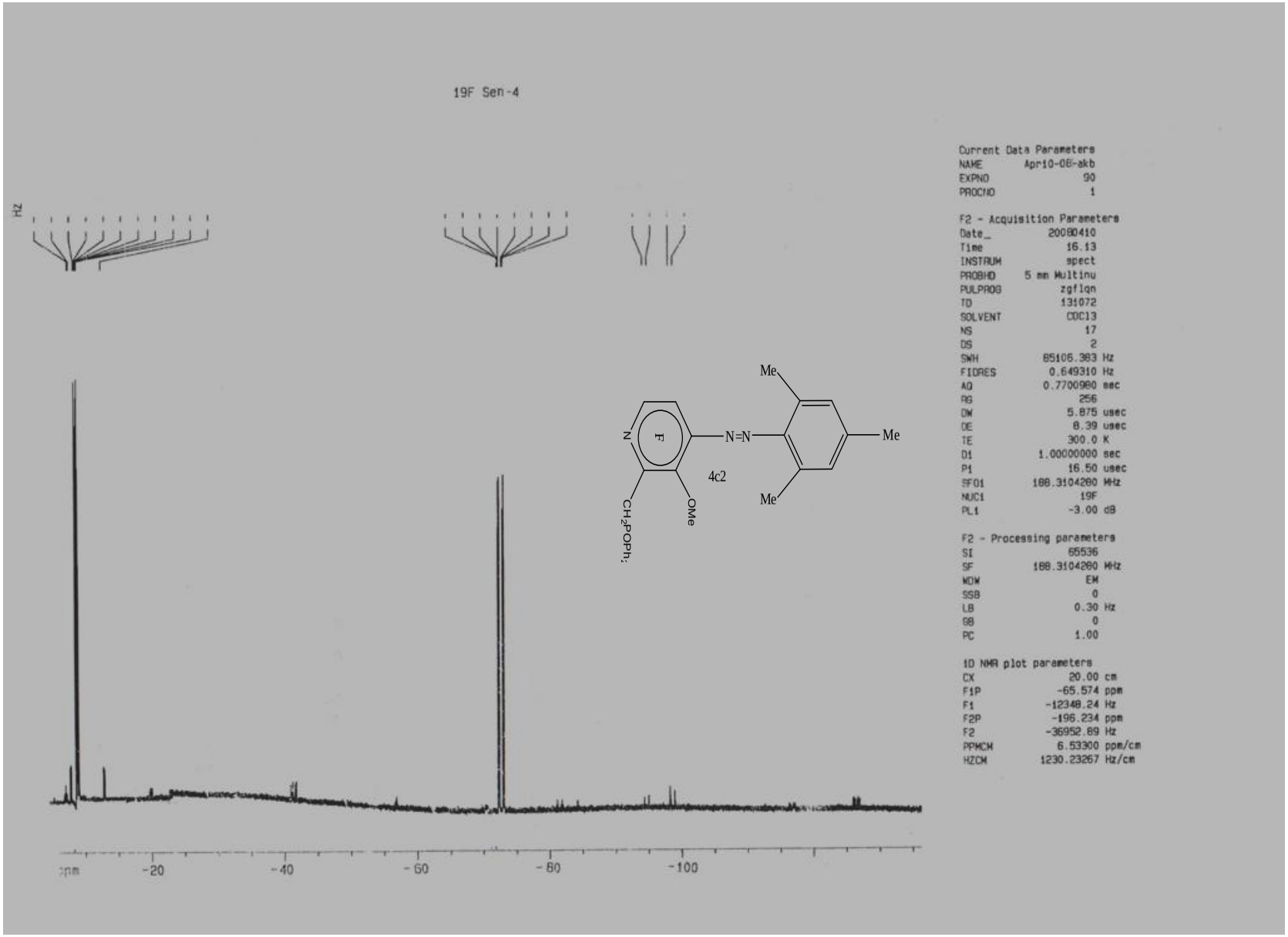
PULPROG	zgflqn
TD	131072
SOLVENT	CDCl3
NS	17
DS	2
SWH	85106.383 Hz
FIDRES	0.649310 Hz
AQ	0.7700980 sec
RG	256
DW	5.875 usec
DE	6.39 usec
TE	300.0 K
D1	1.00000000 sec
P1	16.50 usec
SFO1	188.3104280 MHz
NUC1	19F
PL1	-3.00 dB

F2 - Processing parameters

SI	65536
SF	188.3104280 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	-65.574 ppm
F1	-12348.24 Hz
F2P	-196.234 ppm
F2	-36952.89 Hz
PPMCM	6.53300 ppm/cm
HZCM	1230.23267 Hz/cm



Current Data Parameters
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EXPNO 90
PROCNO 1

F2 - Acquisition Parameters
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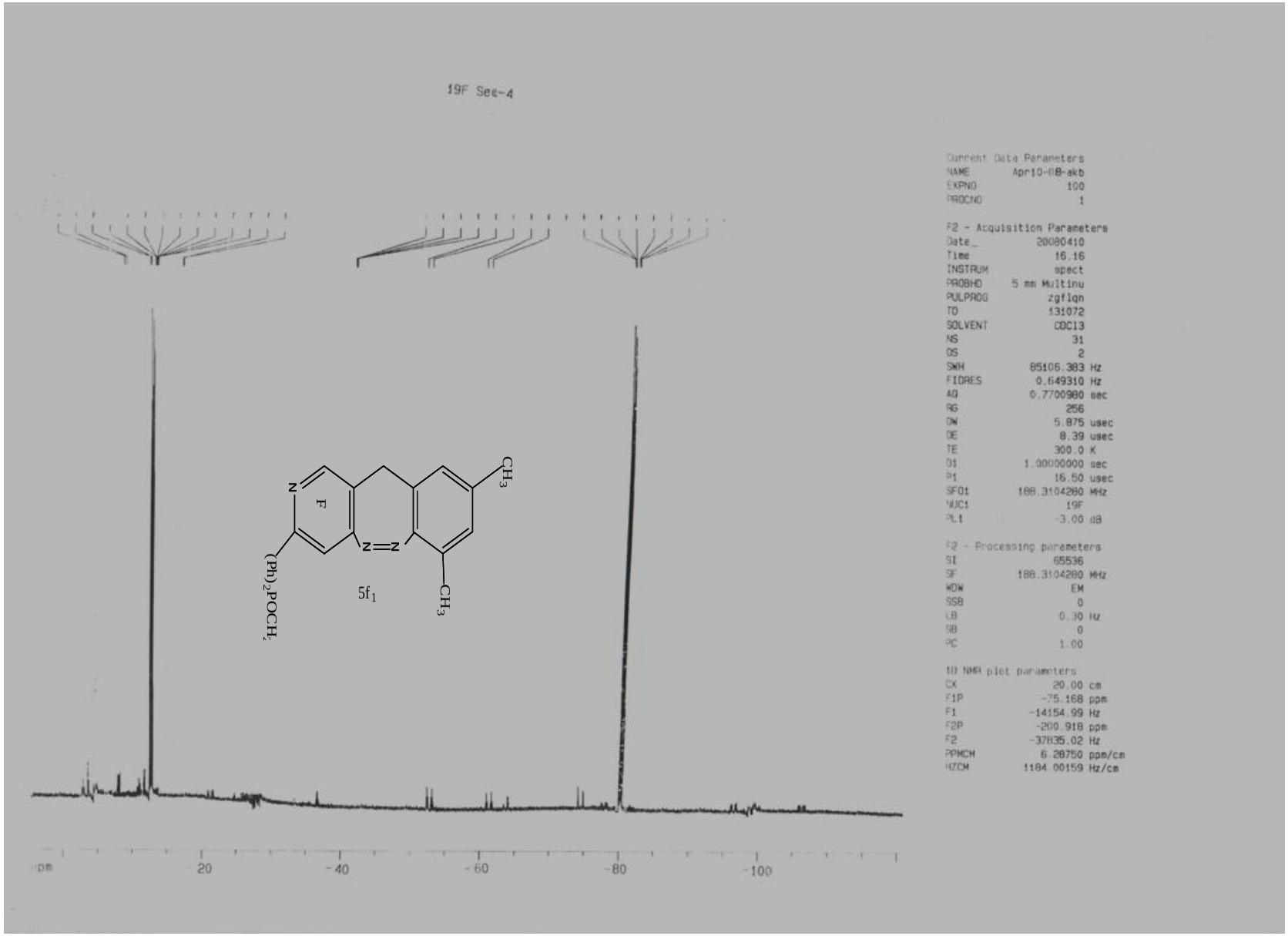
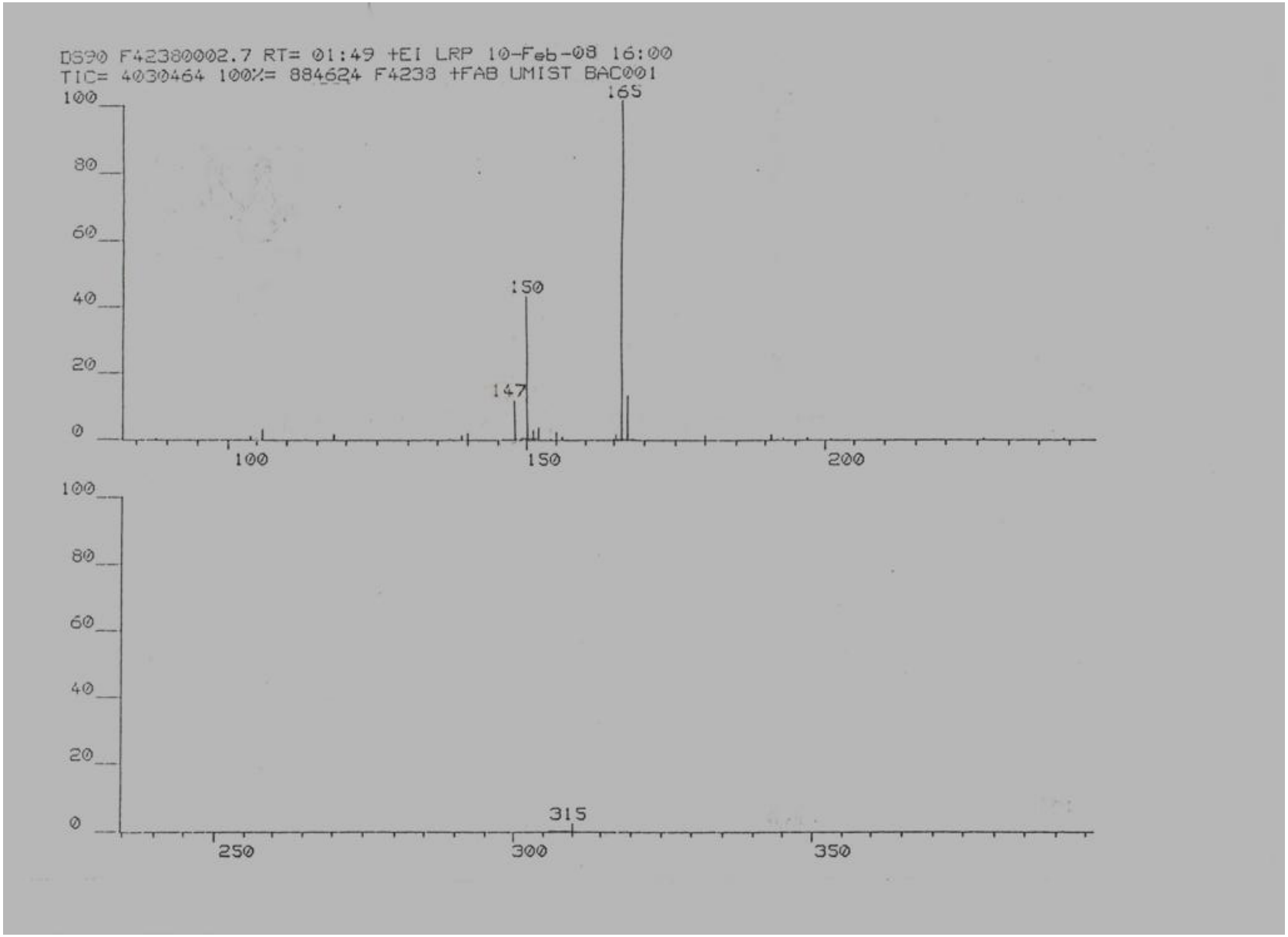
Time 16.13
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 17
DS 2
SWH 85106.383 Hz
FIDRES 0.649310 Hz
AQ 0.7700980 sec
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.3104200 MHz
NUC1 19F
PL1 -3.00 dB

F2 - Processing parameters
SI 65536
SF 188.3104200 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P -65.574 ppm
F1 -12348.24 Hz
F2P -196.234 ppm
F2 -36952.89 Hz
PPMCM 6.53300 ppm/cm
HZCM 1230.23267 Hz/cm


19F See-4
Current Data Parameters
NAME Apr10-08-akb
EXPNO 100
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080410
Time 16.16
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 31
DS 2
SWH 85106.383 Hz
FIDRES 0.649310 Hz
AQ 0.7700980 sec
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.3104280 MHz
NUC1 19F
PL1 -3.00 dB
F2 - Processing parameters
SI 65536
SF 188.3104200 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P -75.168 ppm
F1 -14154.99 Hz
F2P -200.918 ppm
F2 -37835.02 Hz
PPMCM 6.28750 ppm/cm
HZCM 1184.00159 Hz/cm
N
F
N=N
CH3
CH3
(Ph)2POCH2
5f1
ppm
-20
-40
-60
-80
-100

Appendix III
Mass spectra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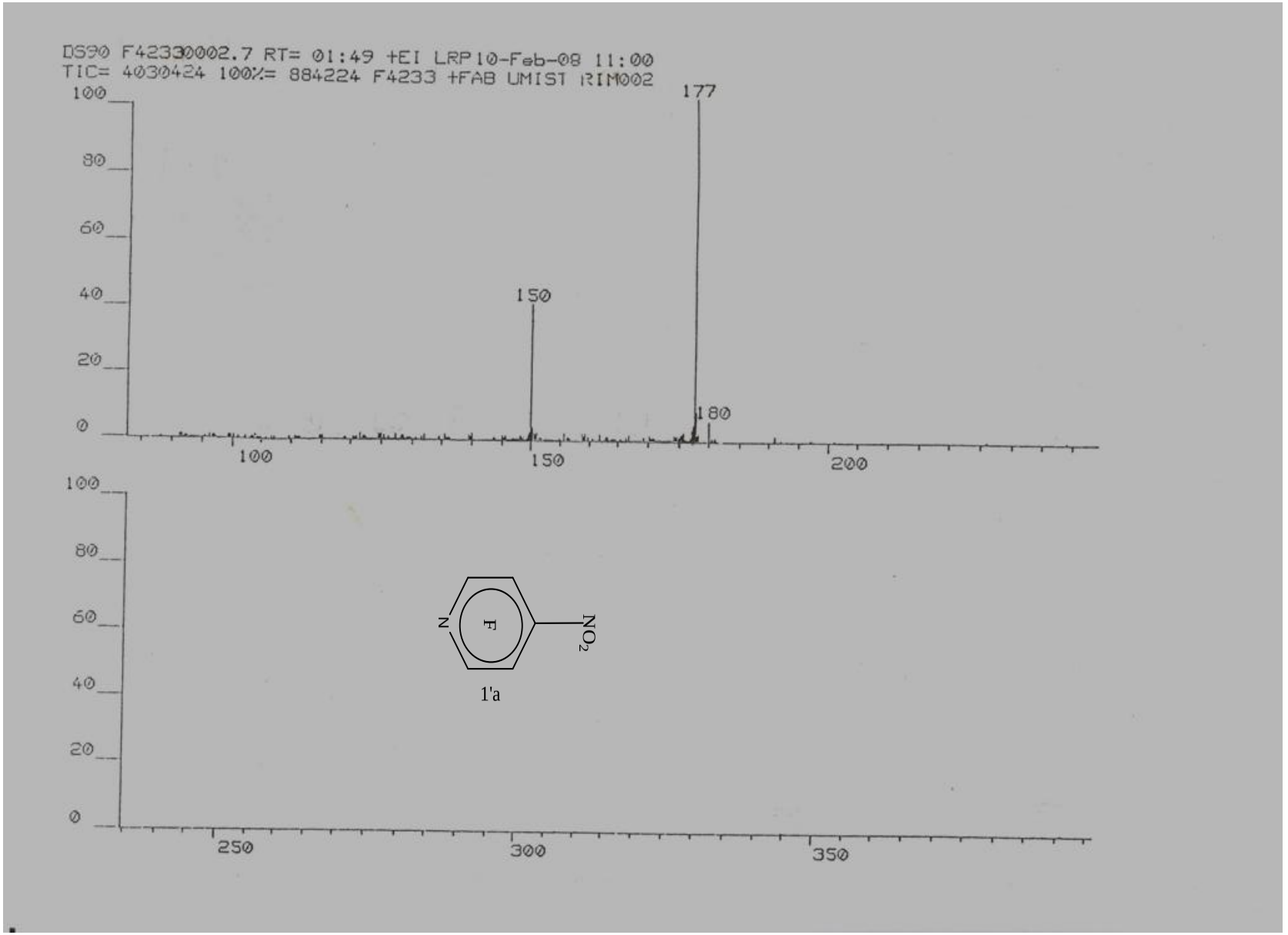
150
147
100
80
60
40
20
0
100
150
200
315
250
300
350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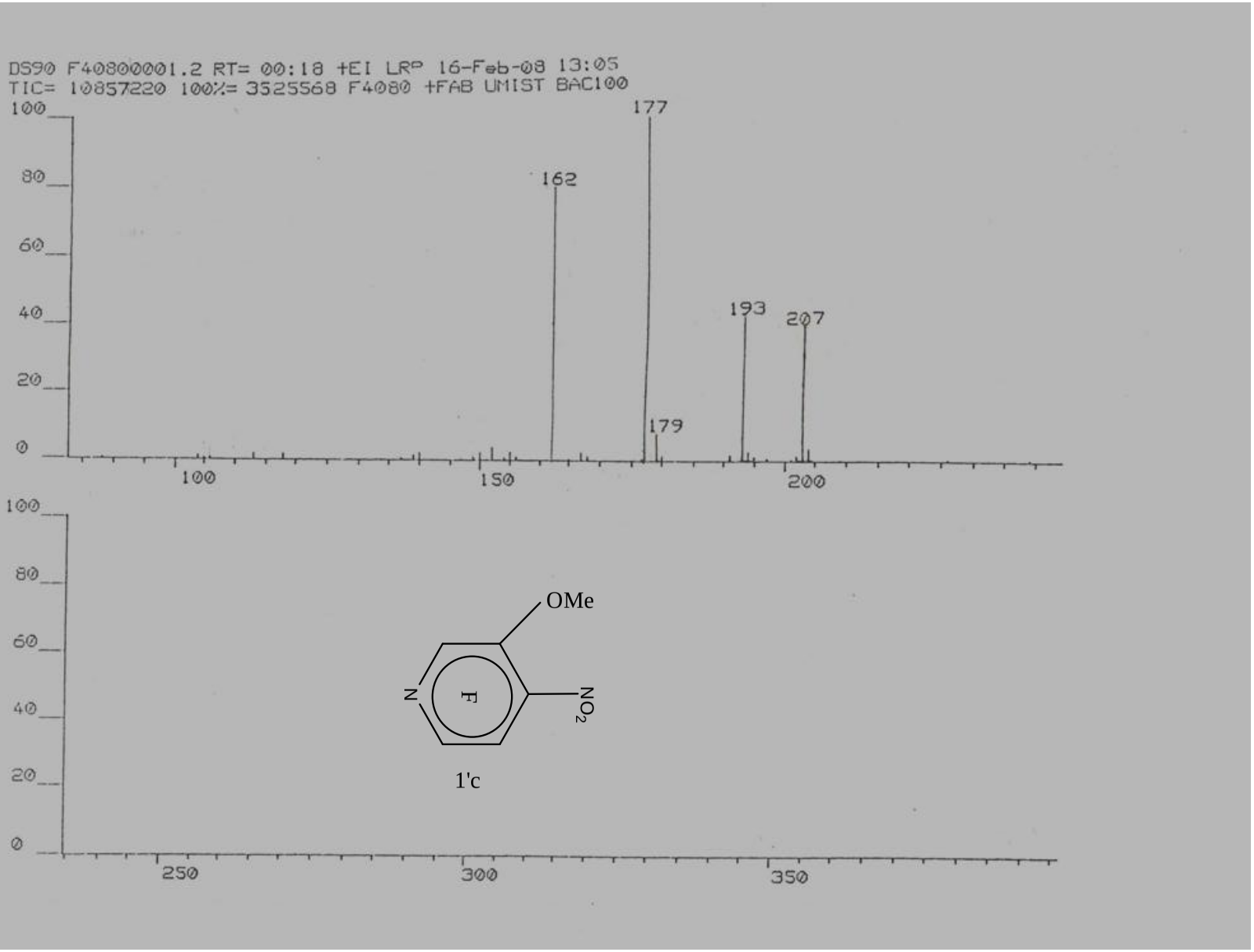
TIC= 4030424 100%= 884224 F4233 +FAB UMIST RIM002
177
150
180
100
80
60
40
20
0
100
150
200
250
300
350
N
F
NO2

1'a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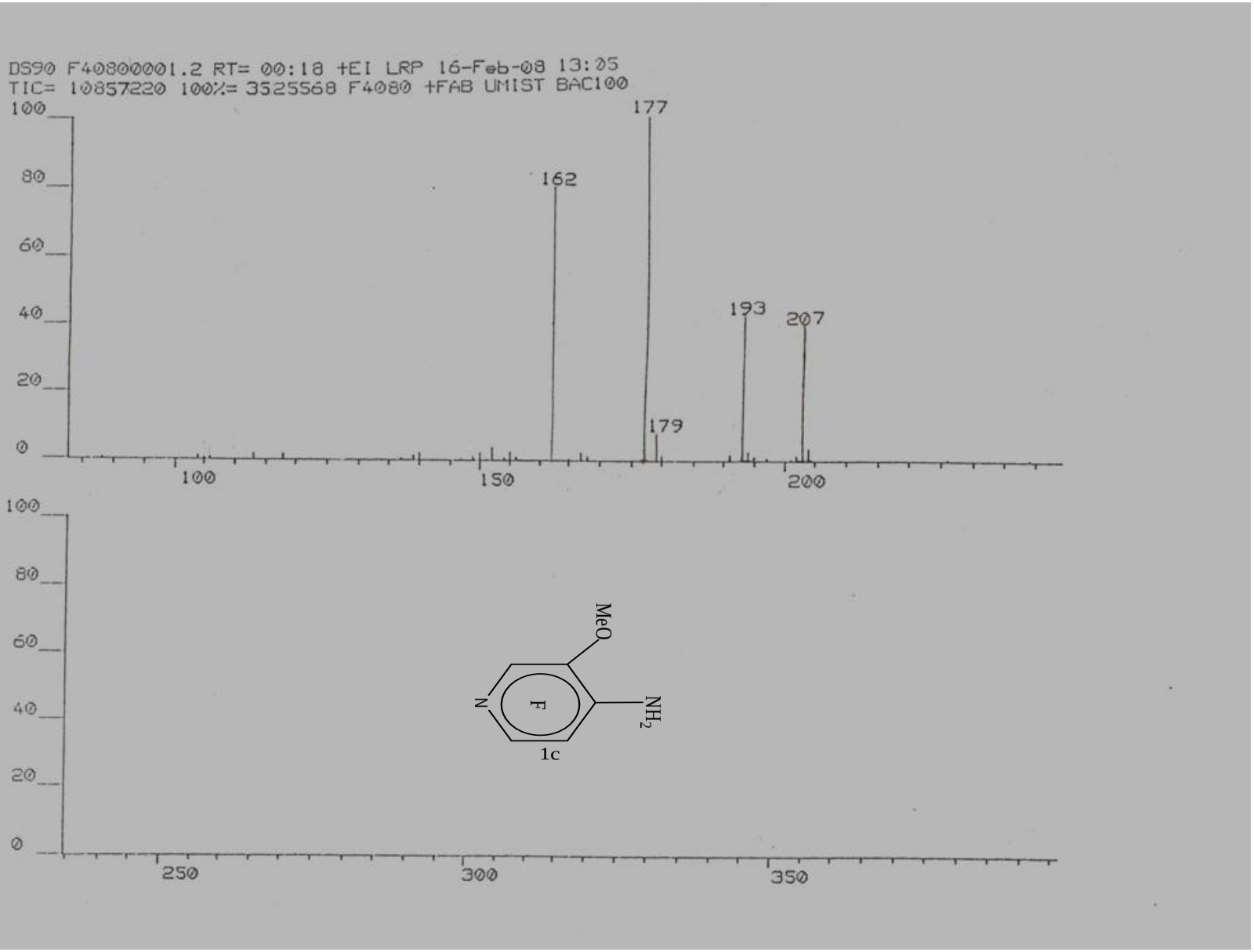
TIC= 10857220 100%= 3525568 F4080 +FAB UMIST BAC100
100
80
60
40
20
0
177
162
193
207
179
100
150
200
250
300
350
OMe
N
F
NO2

1'c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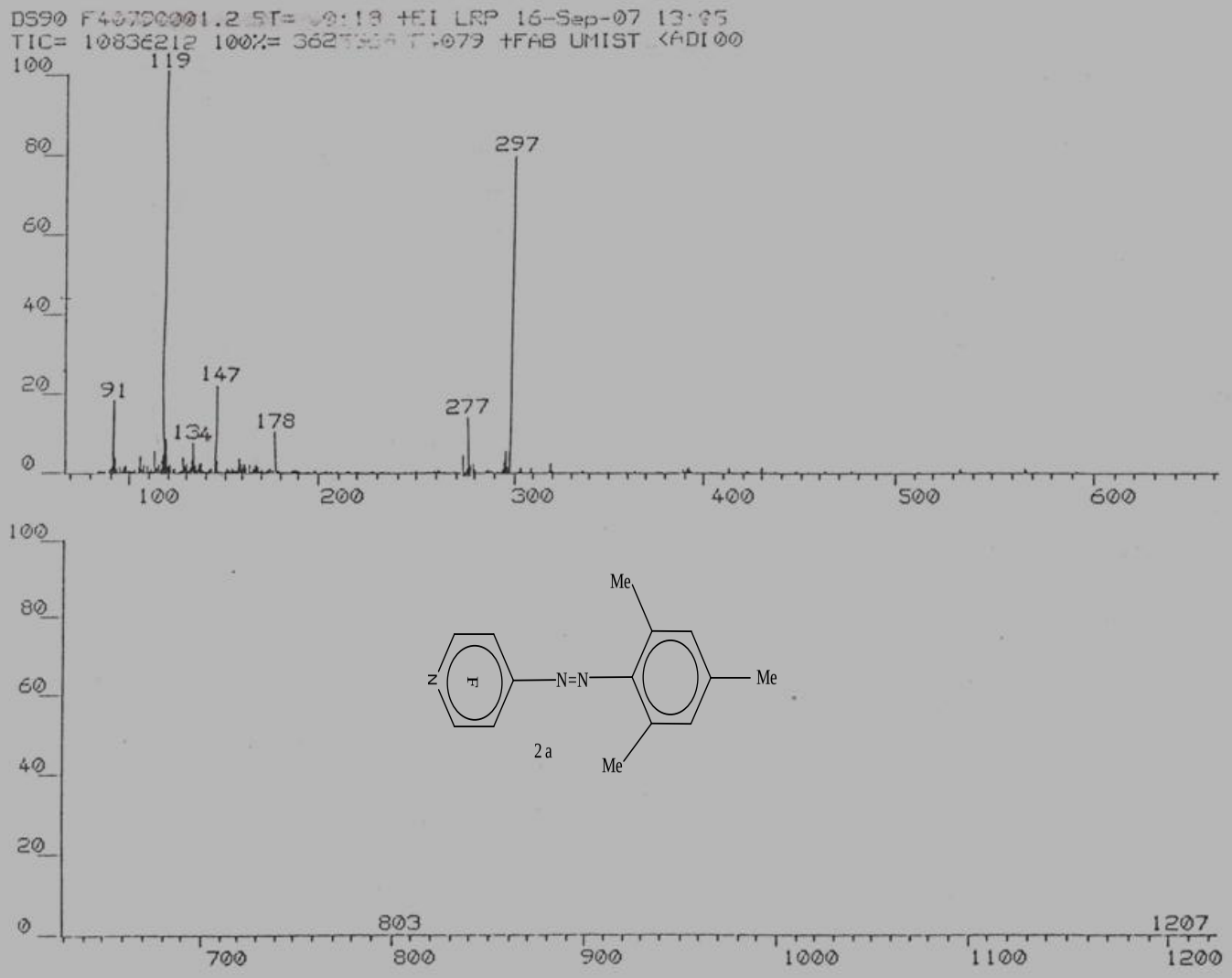
TIC= 10857220 100%= 3525568 F4080 +FAB UMIST BAC100
100
80
60
40
20
0
177
162
193
207
179
100
150
200
250
300
350
MeO
N
F
NH2
1c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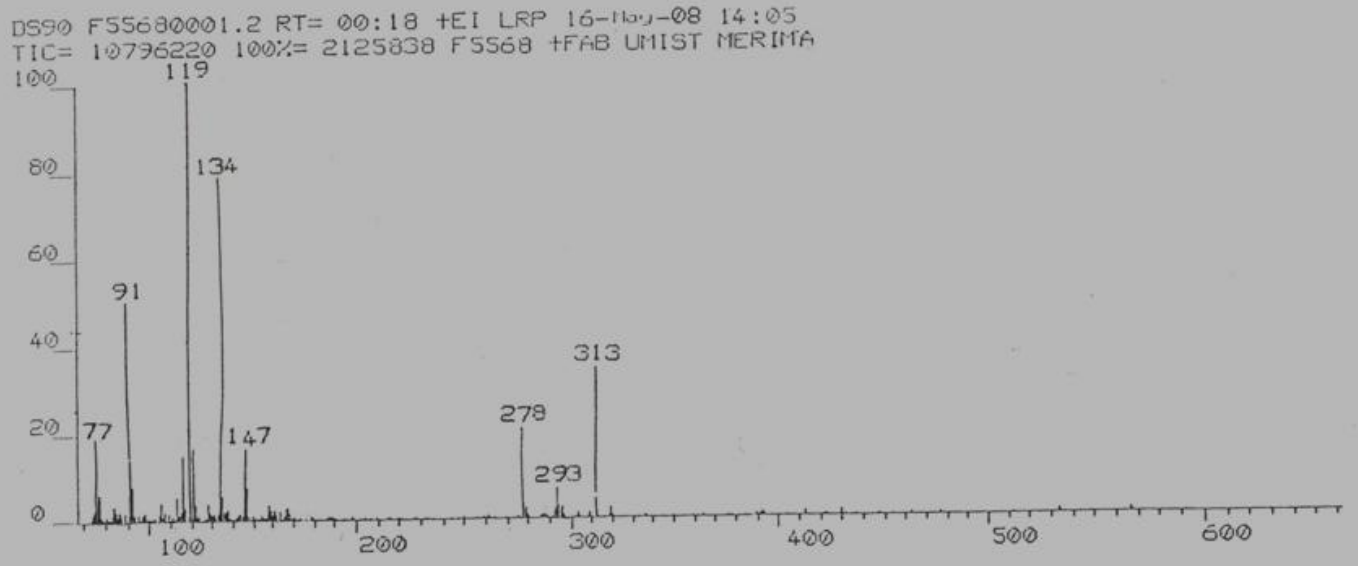
100
80
60
40
20
0
119
297
91
147
178
134
277
100
200
300
400
500
600
Me
N=N
Me
Me
2 a
803
1207
700
800
900
1000
1100
1200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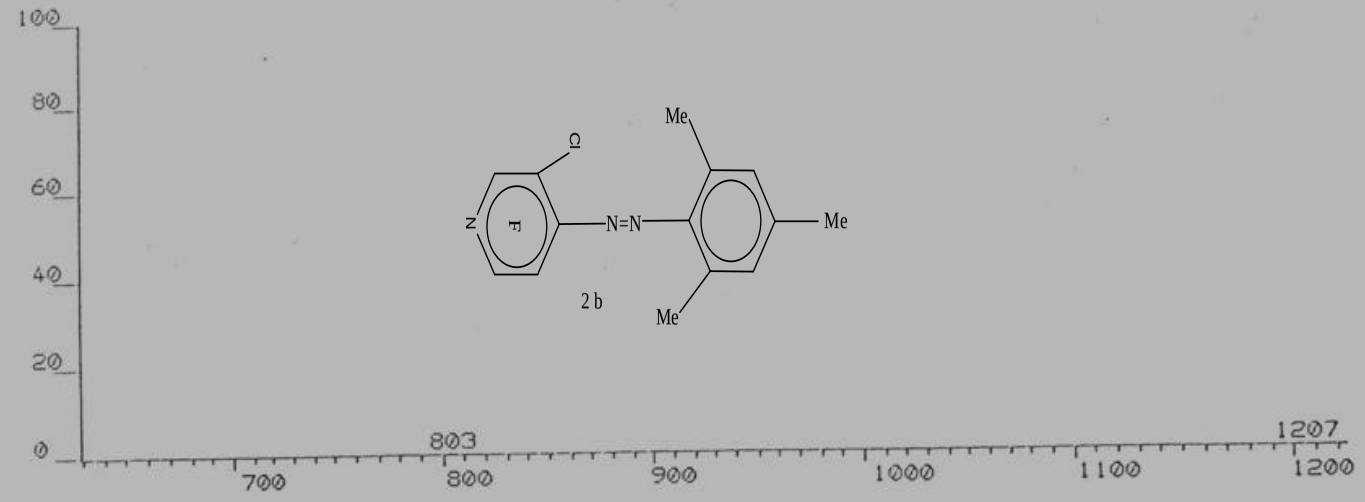
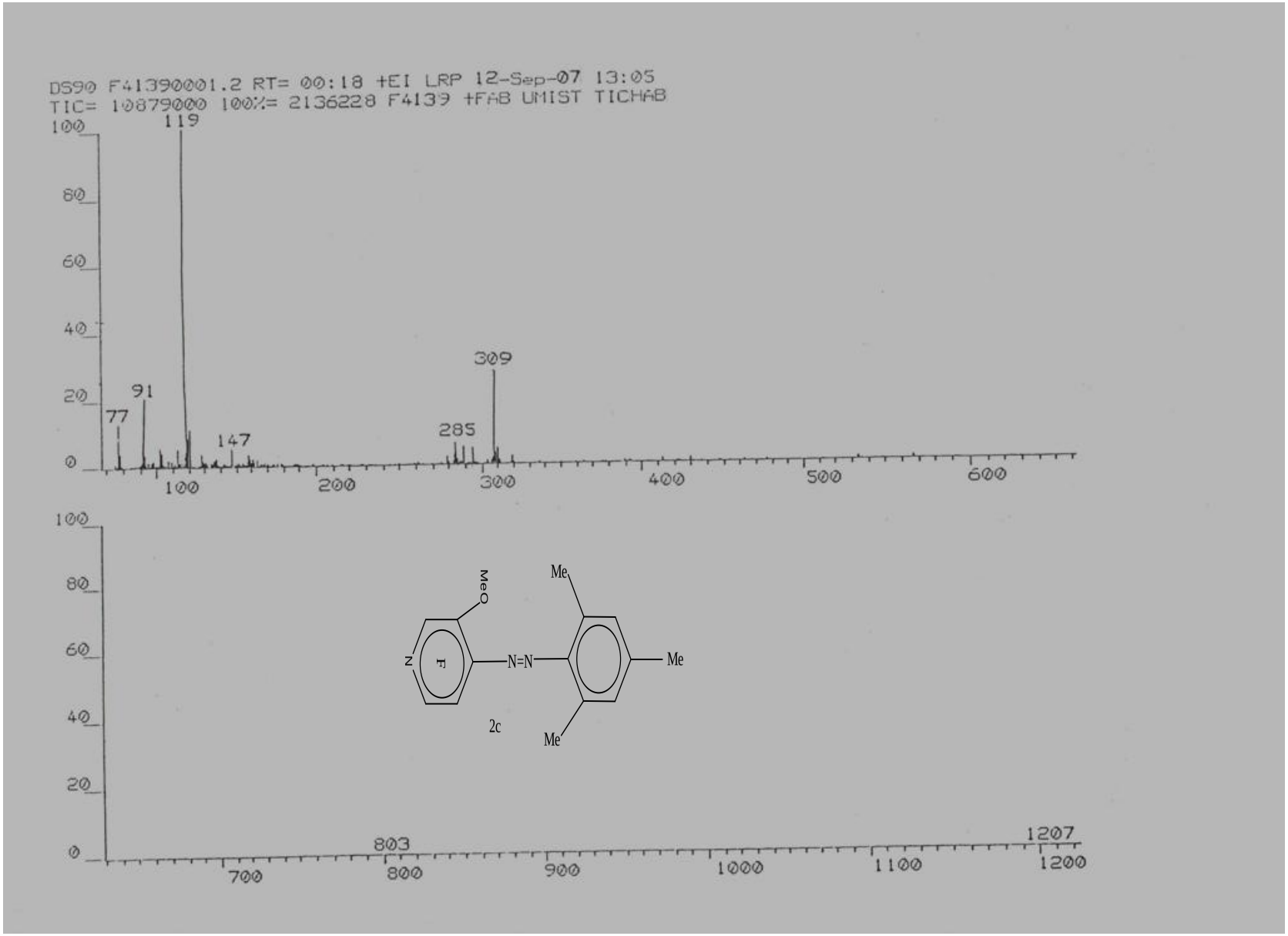
80
60
40
20
0
119
134
91
313
278
77
147
293
100
200
300
400
500
600


100
80
60
40
20
0
803
1207
700
800
900
1000
1100
1200

Me
O
N=N
Me
Me
2 b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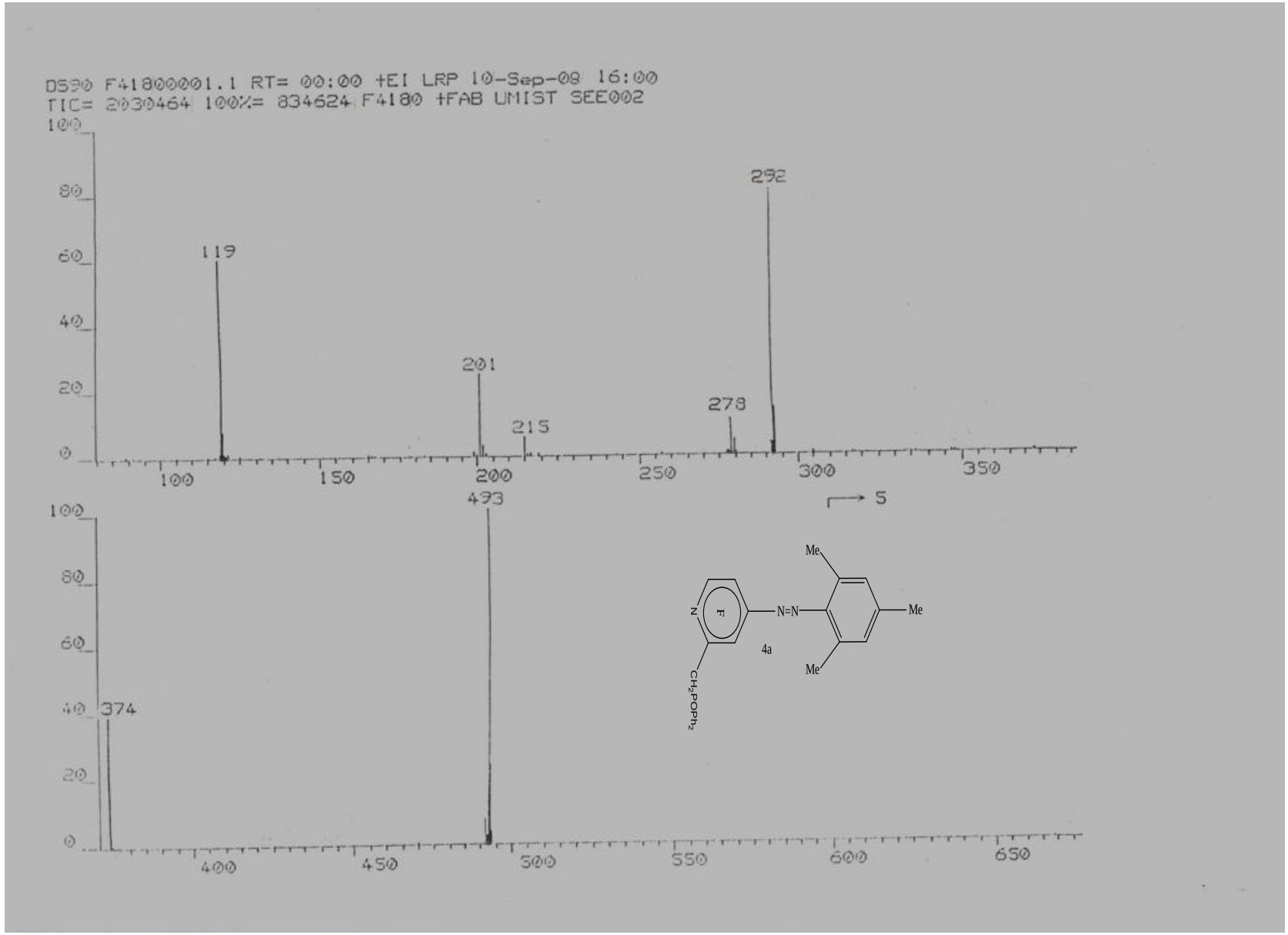
80
60
40
20
0
119
91
77
147
285
309
100
200
300
400
500
600
MeO
Me
Me
Me
N=N
F
2c
803
1207
700
800
900
1000
1100
1200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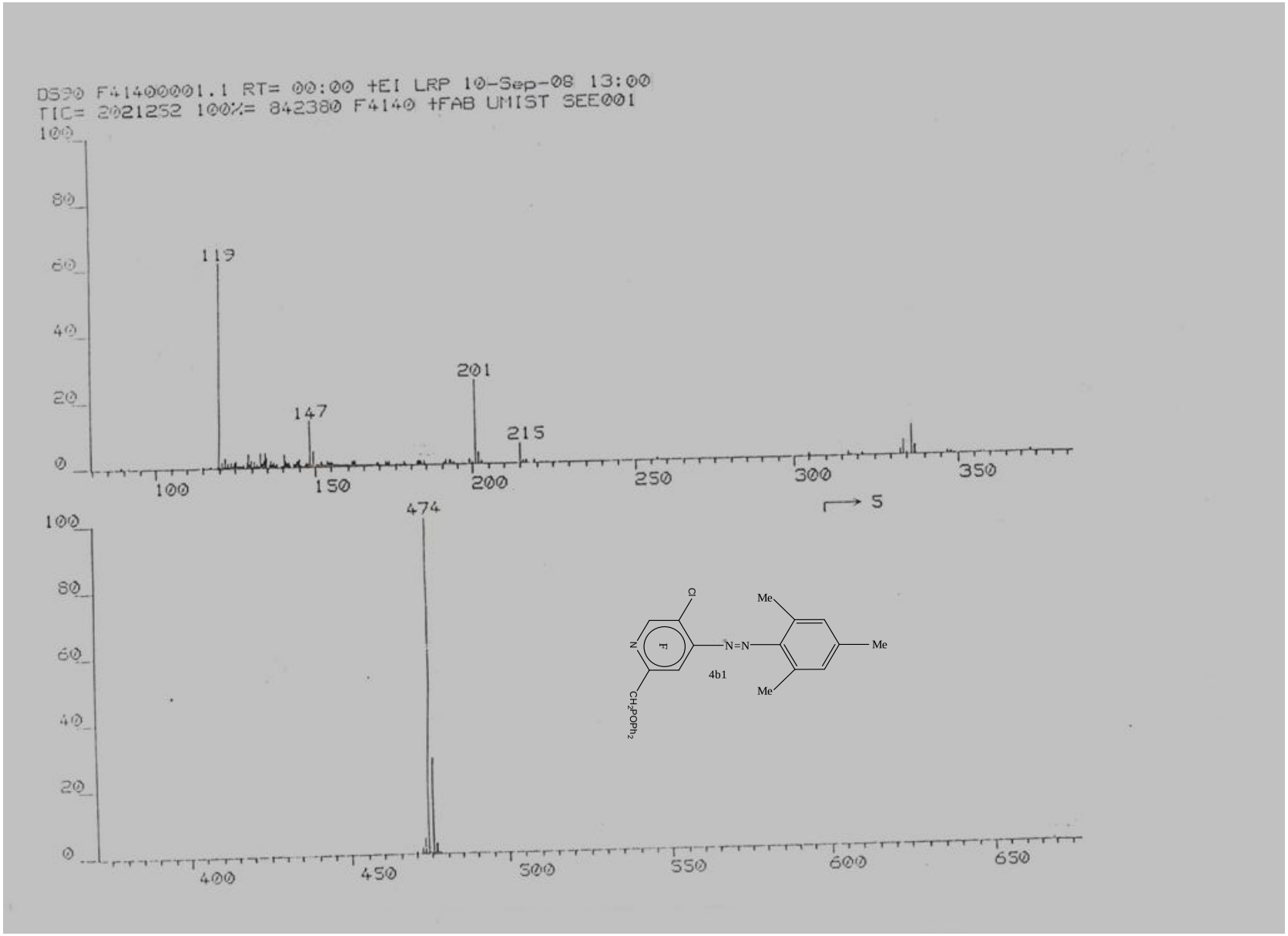
80
60
40
20
0
119
201
215
278
292
100
150
200
250
300
350
5
100
80
60
40
20
0
374
493
400
450
500
550
600
650
Me
N
F
N=N
Me
Me
4a
CH2POPh2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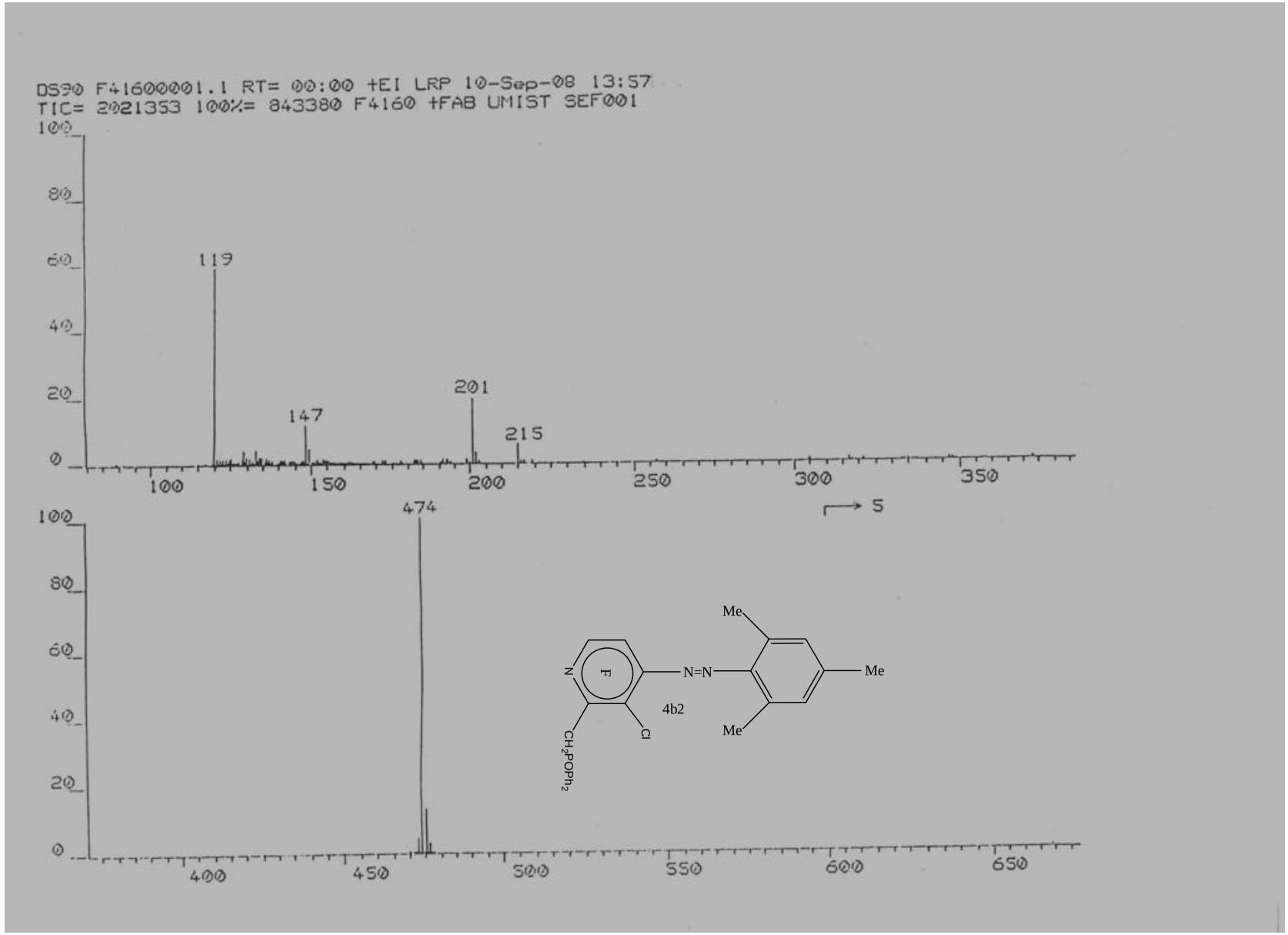
60
40
20
0
119
147
201
215
100
150
200
250
300
350
5
100
80
60
40
20
0
474
400
450
500
550
600
650
Cl
Me
N
F
N=N
Me
Me
4b1
CH2POPh2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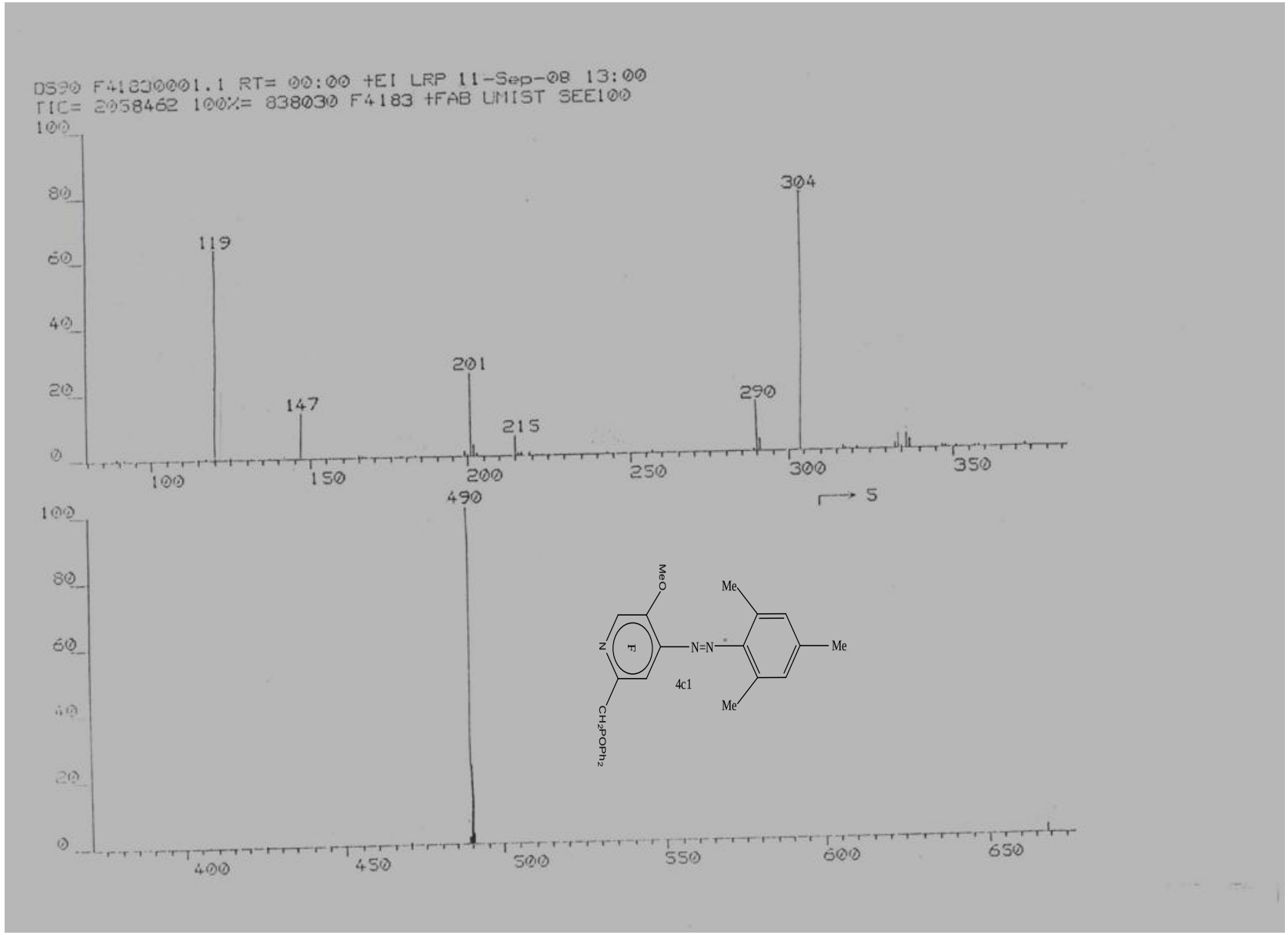
60
40
20
0
119
147
201
215
100
150
200
250
300
350
5
474
400
450
500
550
600
650
Me
N=N
Me
Me
N
F
Cl
CH2POPh2
4b2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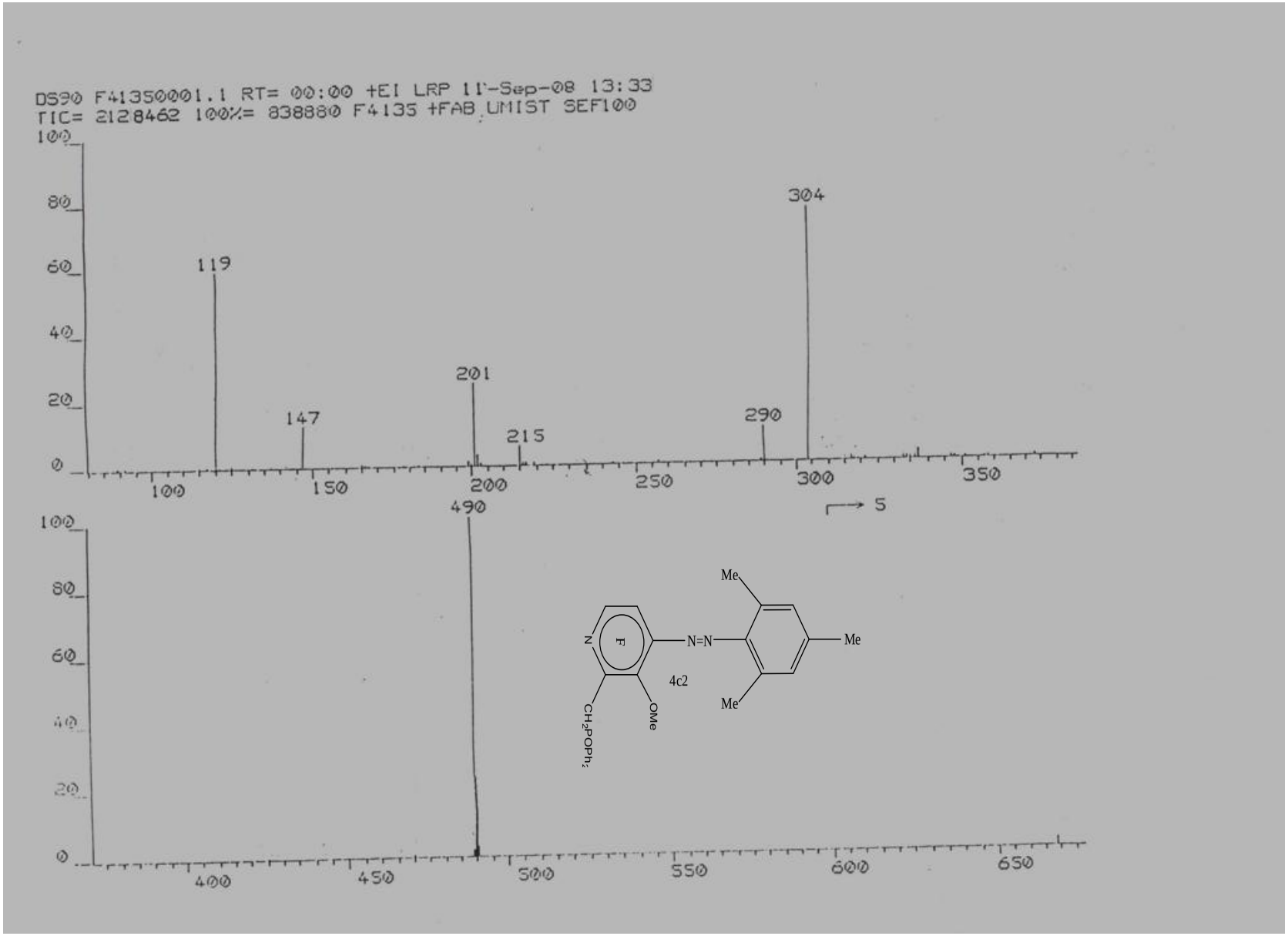
TIC= 2058462 100%= 838030 F4183 +FAB UNIST SEE100
304
119
201
147
290
215
490
MeO
Me
Me
Me
N
F
N=N
CH2POPh2
4c1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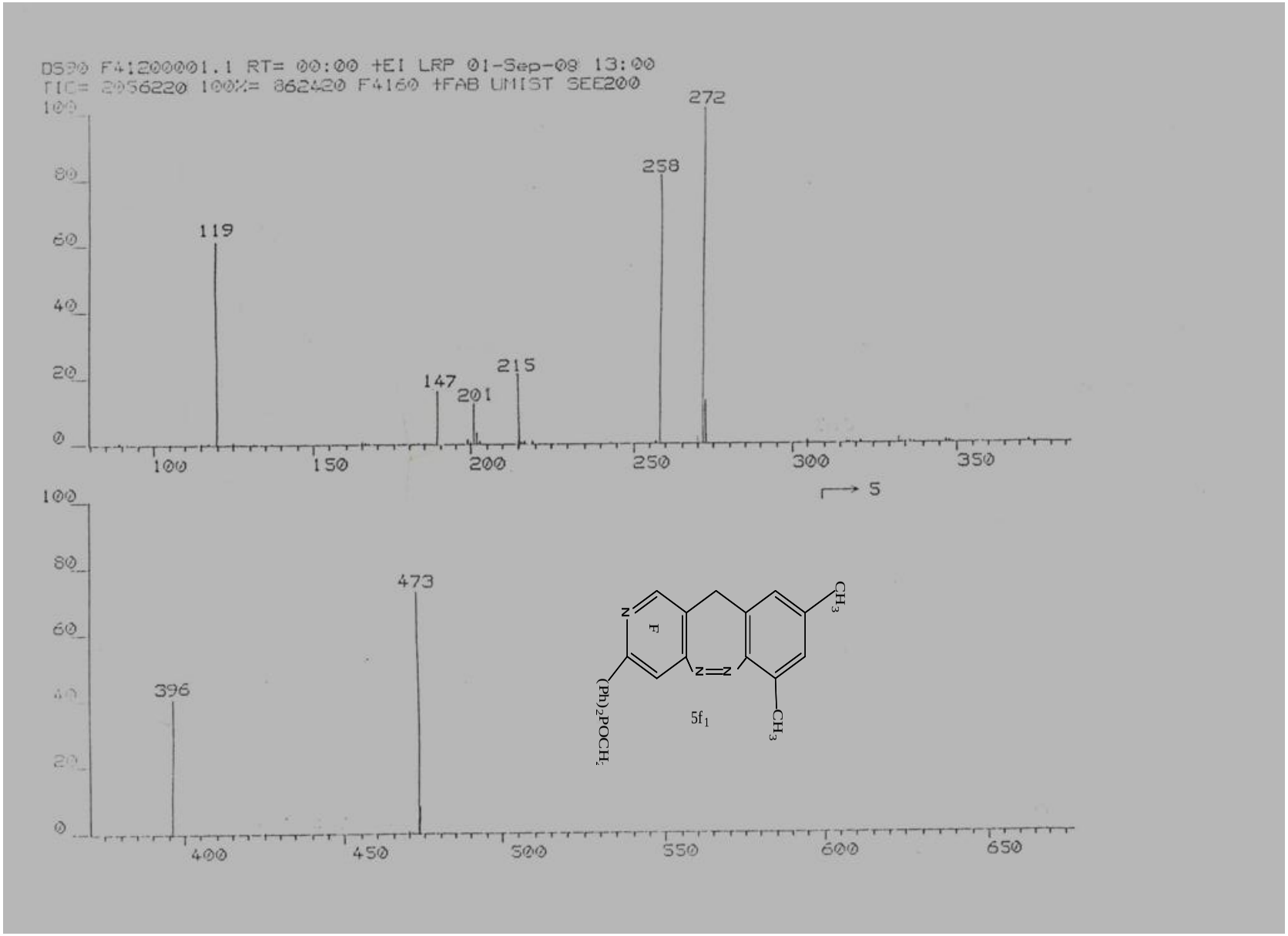
60
40
20
0
119
147
201
215
290
304
100
150
200
250
300
350
5
490
400
450
500
550
600
650
Me
N
F
N=N
Me
4c2
OMe
Me
CH2POPh2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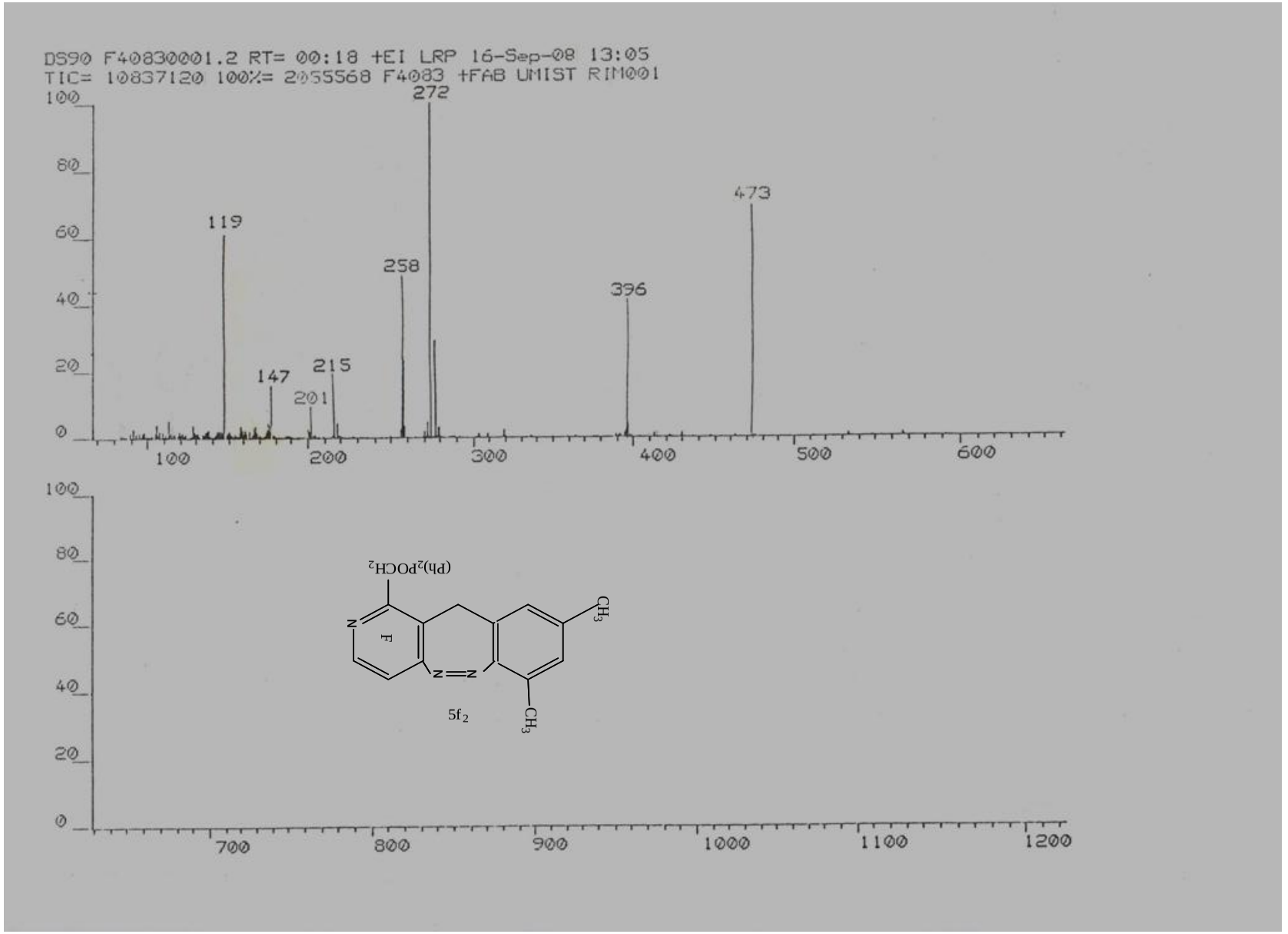
TIC= 2056220 100%= 862420 F4160 +FAB UMIST SEE200
272
258
119
215
147
201
100
150
200
250
300
350
5
473
396
400
450
500
550
600
650
N
F
N=N
CH3
CH3
(Ph)2POCH2
5f1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272
473
119
258
396
147
215
201
100
80
60
40
20
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
(Ph)2POCH2
N
F
N=N
CH3
CH3
5f2

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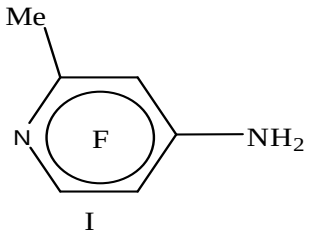
Part II

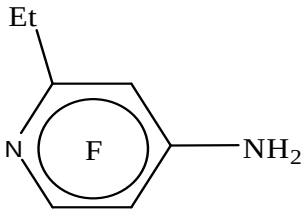
Summary
Part II

4- Amino- 3- methyltrifluoropyridine was synthesised from 4-Amino- 2,3,5,6- tetrafluoropyridin and methyl iodide in the presence of the nickel catalyst Ni(COD)2 and triethyl phosphine. Similarly, ethyl iodide, propyl iodide, isopropyl iodide, butyl iodide, iodide and iodide were heated for Ca – 1- 4 hours to give, respectively 4- Amino- 2,3,5- trifluor -6- methylpyridine **I** (80%) 4- Amino- 2,3,5- trifluor -6- ethylpyridine **II** (71%),4- Amino- 2,3,5- trifluor -6- propylpyridine **III** (62%),4- Amino- 2,3,5- trifluor -6- isopropylpyridine **IV** (67%),4- Amino- 2,3,5- trifluor -6- butylpyridine **V** (68%),4- Amino- - 6- benzyl- 2,3,5- trifluor pyridine **VI** (82%),and 4- Amino- 2,3,5- trifluor -6- diphenylmethanylpyridine **VII** (75%).

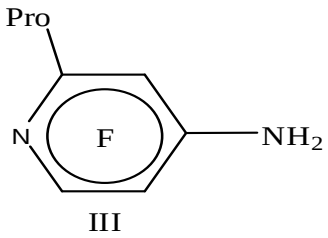
The reaction of **I**, **II**, **III**, **IV**, **V**, **VI** and **VII** with dry powdered sodium nitrite in acid (H2SO4 98%) gave the diazonium ions which were coupled to mesitylene, giving the azo- compounds 4- (2,4,6- trimethyl phenylazo) -6- methyl pyridine **VIII** (57%),4- (2,4,6- trimethyl phenylazo) -6- ethyl pyridine **IX** (54%),4- (2,4,6- trimethyl phenylazo) -6- propyl pyridine **X** (51%),4- (2,4,6- trimethyl phenylazo) -6- isopropyl pyridine **XII** (53%),4- (2,4,6- trimethyl phenylazo) -6- butyl pyridine **XI** (48%), 6- benzyl 4- (2,4,6- trimethyl phenylazo pyridine **XIII** (47%) and 4- (2,4,6- trimethyl phenylazo) -6- diphenylmethanylpyridine **XIV**(41%) .



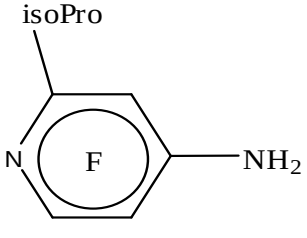
I



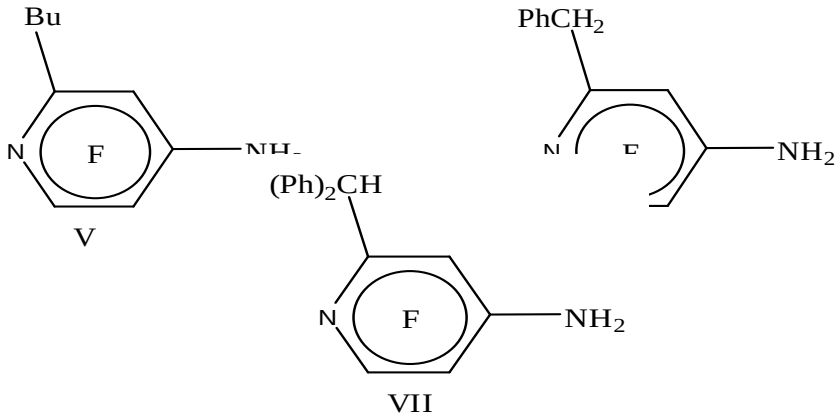
II

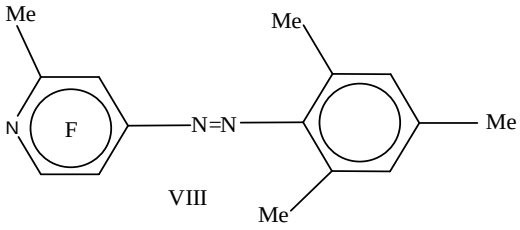


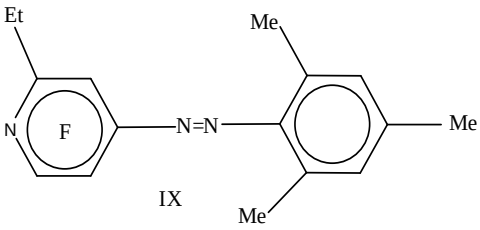
III

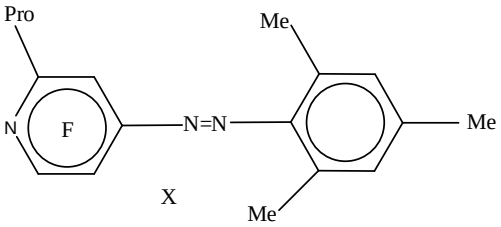


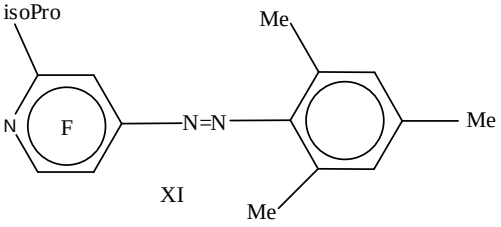
IV

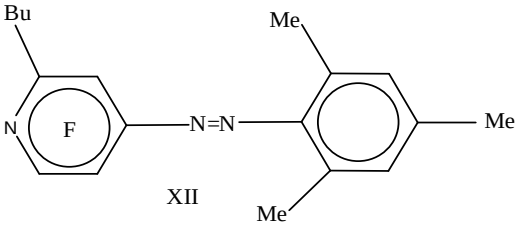

Bu
N
F
NH2
V
PhCH2
NH2
(Ph)2CH
N
F
NH2
VII

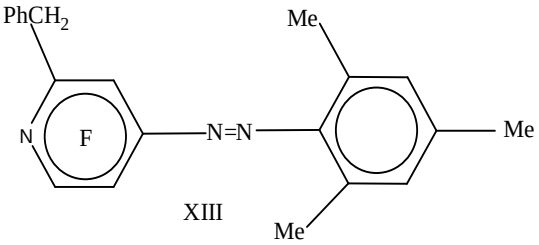

Me
N
F
N=N
Me
Me
Me
VIII

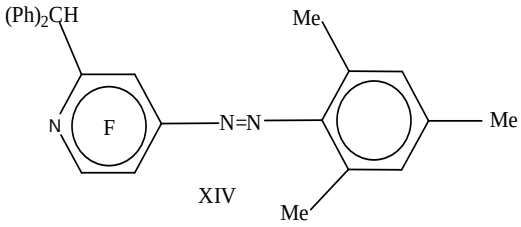

Et
N
F
N=N
Me
Me
Me
IX


Pro
N
F
N=N
Me
Me
Me
X


isoPro
N
F
N=N
Me
Me
Me
XI


Bu
N
F
N=N
Me
Me
Me
XII

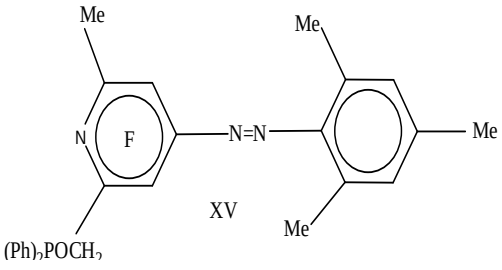

PhCH2
N
F
N=N
Me
Me
Me
XIII



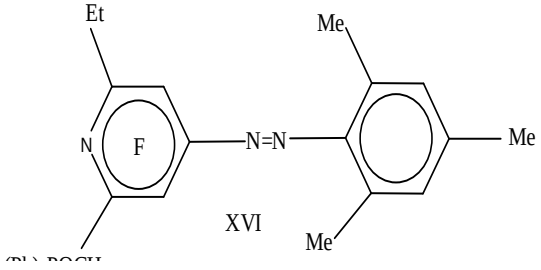
XIV

Reaction of methyl diphenyl phosphine oxide using n- Buli and then treated with **VIII**, **IX**, **X**, **XI**, **XII**, **XII** and **XIV** yielded the following Alkyl (Aryl) fluoroniated phosphorus azo-compounds: diphenyl((3,5,- difluoro- 6 methyl-4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide **XV** (75%), diphenyl((3,5,- difluoro- 6 ethyl-4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide **XVI** (91%), diphenyl((3,5,- difluoro -4 -(mesityl diazenyl- 6 propyl) pyridin -2- yl) methyl) phosphine oxide **XVII** (87%), diphenyl((3,5,- difluoro -4-(mesit yl diazenyl- 6 isopropyl) pyridin -2- yl) methyl) phosphine oxide **XVIII** (76%), diphenyl((- 6 butyl- 3,5,- difluoro -4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide **XIX** (65%), diphenyl((- 6 benzyl- 3,5,- difluoro -4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide **XX** (78%) and diphenyl((3,5,- difluoro -4-(mesit yl diazenyl-6-diphenylmethanyl) pyridin -2- yl) methyl) phosphine oxide **XXI** (67%).

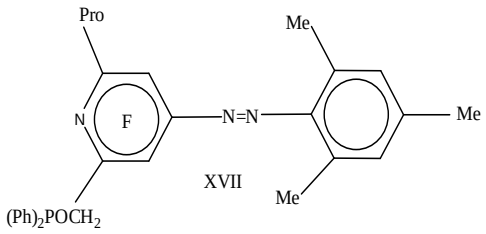
The isomers diazepines were produced in (57%-79%) yield, when the appropriate azo – compounds were heated in boilling mesitylene for 6- 12 hours.



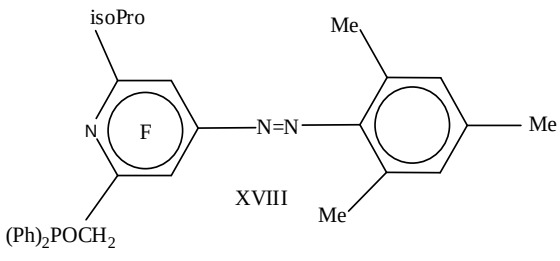
XV



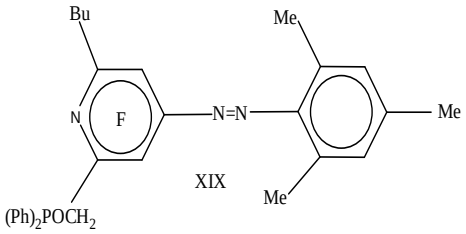
XVI



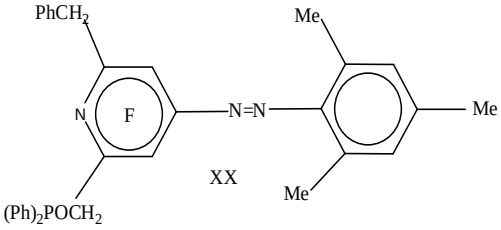
XVII



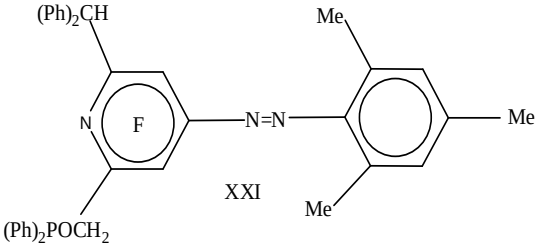
XVIII


Bu
Me
N
F
N=N
Me
Me
(Ph)2POCH2

XIX


PhCH2
Me
N
F
N=N
Me
Me
(Ph)2POCH2

XX


(Ph)2CH
Me
N
F
N=N
Me
Me
(Ph)2POCH2

XXI

The theoretical side
Part I

IV-1- Alkylation chemistry:

The alkylation reaction combines light C3-C5 olefins with isobutane in the presence of a strong acid catalyst. Although alkylation can take place at high temperature without catalyst, the only processes of commercial importance involve low to moderate temperatures using either sulfuric or hydrofluoric acid [1-5].

Alkylation reactions are complex and consequently the product has a wide boiling range. From 75 to over 150 different isoparaffin isomers are normally produced by alkylation. With careful attention to operating conditions, the product will fall into the gasoline boiling range with motor octane numbers from 88-95 and research octane numbers from 90-98. For the purposes of this paper only sulfuric acid catalyzed alkylation will be considered.

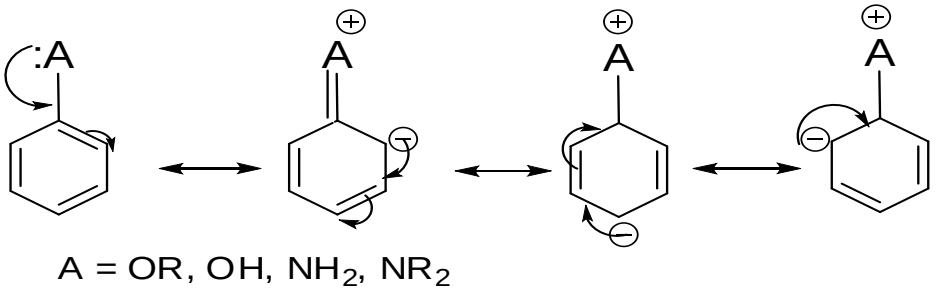
The STRATCO® Contactor™ reactor, along with DuPont's STRATCO® Effluent Refrigerated alkylation process, are designed to promote reactions that favor the production of gasoline boiling range products and minimize competing reactions. Some of these unfavorable reactions can result in poor product quality with respect to octane and end point, or greater than necessary acid consumption [6,7].

IV-2- Substituent Effects

Most of what I've talked about so-far has involved the addition of a compound to an *unsubstituted* benzene ring. What about additions to a *substituted* ring? I will summarize:

IV-2-1- Activating/de-activating groups

Because the benzene ring's electrons are acting as the nucleophile in all of the above reactions, rings substituted with strong electron-donating groups (particularly π-electron donating) are considered "activated" - they will often even react without a catalyst! Some examples of activating groups are: OH, OR, NH2, NR2, Alkyl [1-7].

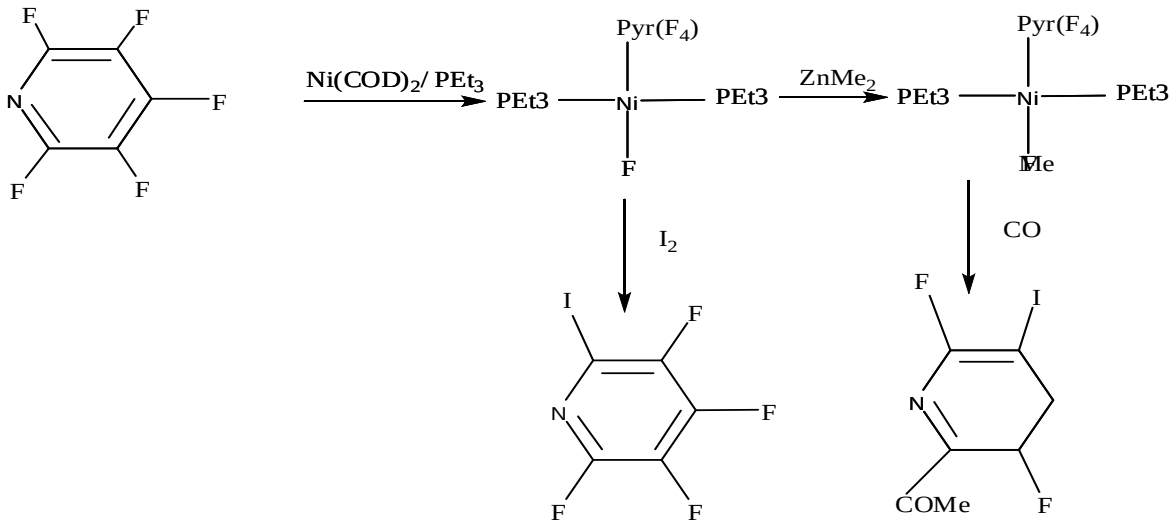


Scheme 27

The oxygen and nitrogen-based activating groups increase reactivity by a resonance effect: As you can see, the very nature of the activation requires *ortho-para* direction!
Alkyl groups work somewhat differently. They are not as strong at activating the ring, and their main function is stabilizing the positive charge formed after the attack on the electrophile [1-7].

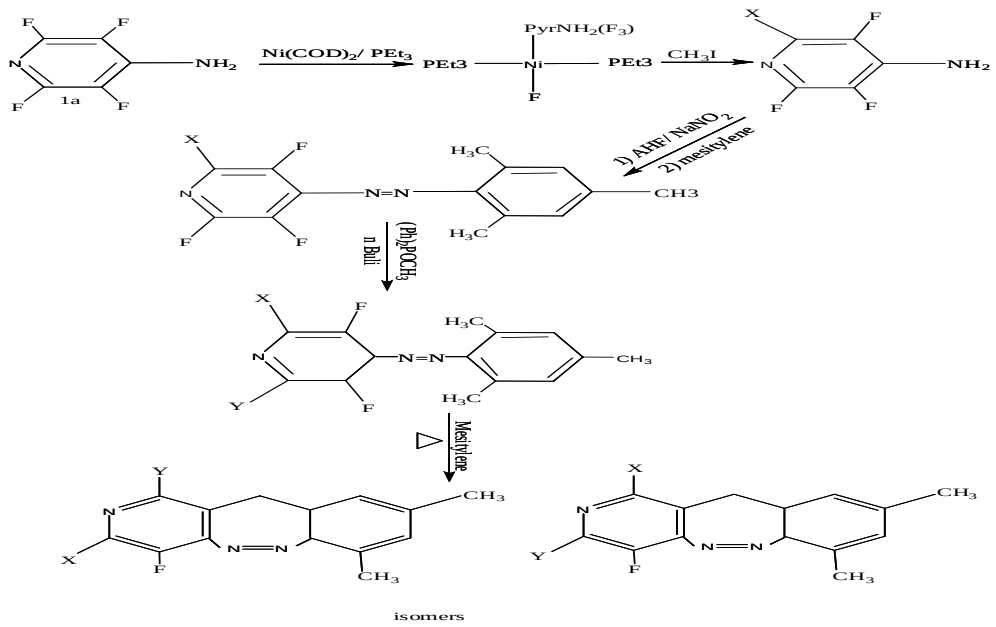
IV-3- C-F Activatin by late transition metals :

Nickle has also been used to synthsize fluorinated heterocyclic aromatic [5-7].
Thes fluorinated aromatic, specifically pyrimidines and pyridines, have application as liquid crystals, herbicides, antibiotics, and anti-cancer agents. Braun and Perutz observed that the nickel catalyst Ni(COD)2 in the presence of triethylphosphine oxidatively added the C-F bond of these heterocyclic aromatic molecules and reductively eleiminated a substituted produt.



Scheme 28

V-1- Preamble



Scheme 29

1g : X= Me

1h : X= Et

1i : X= Pro

1j: X= isoPro

1k : X= Bu

1l : X= $PhCH_2$

1m: X= $(Ph)_2CH$

2g : X= Me

2h : X= Et

2i : X=Pro

2j: X= isoPro

2k : X= Bu

2l: X= Ph CH_2

2m: X= $(Ph)_2CH$

4g : X= Me, Y= $(Ph)_2PO$

4h : X= Et, Y= $(Ph)_2POC$

4i : X= Pro, Y= $(Ph)_2POCH_2$

4j: X= isoPro, Y= $(Ph)_2POC$

4k : X= Bu, Y= $(Ph)_2POC$

4l : X= $PhCH_2$, Y= $(Ph)_2POCH_2$

$5g_1$: X= Me, Y= $(Ph)_2POCH_2$

$5h_1$: X= Et, Y= $(Ph)_2POCH_2$

$5i_1$: X=Pro, Y= $(Ph)_2POCH_2$

$5j_1$: X= isoPro, Y= $(Ph)_2POCH_2$

$5k_1$: X= Bu, Y= $(Ph)_2POCH_2$

$5l_1$: X= Ph CH_2, Y= $(Ph)_2POCH_2$

V-1- Preamble

34m: Y= $(Ph)_2CH$, X= $(Ph)_2POCH_2$

$5g_2$: Y= Me, X= $(Ph)_2POCH$

$5h_2$: Y= Et, X= $(Ph)_2POCH_2$

$5k_2$: Y= Bu, X= $(Ph)_2POCH_2$

$5m_2$: Y= $(Ph)_2CH$, X= $(Ph)_2POCH_2$

$5m_1$: X= $(Ph)_2CH$, Y= $(Ph)_2POCH_2$

$5i_2$: Y=Pro, X= $(Ph)_2POCH_2$

$5j_2$: Y= isoPro, X= $(Ph)_2POCH_2$

$5l_2$: Y= Ph CH_2, X= $(Ph)_2POCH_2$

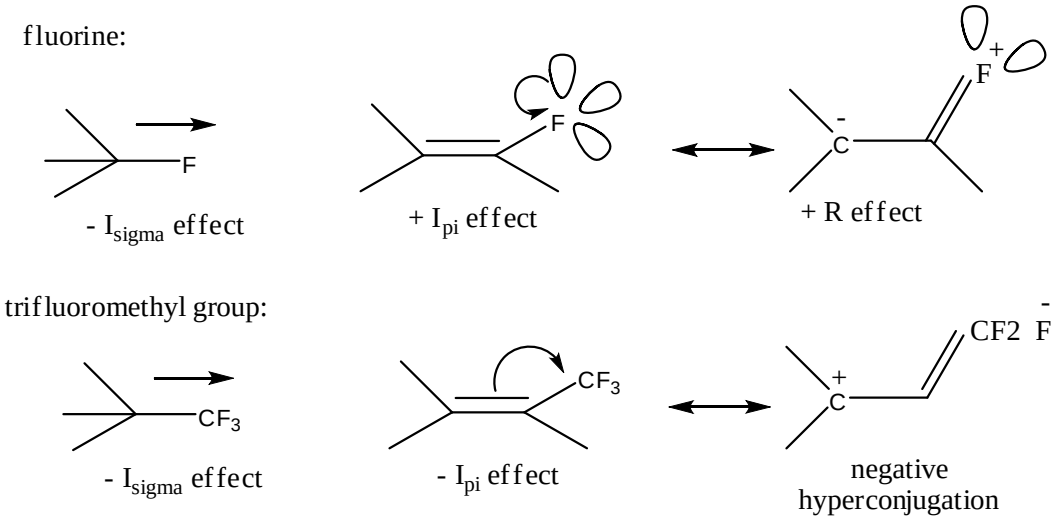
Results and Discussion

Part II

V-2- Discussion:

Besides the lighter noble gases fluorine is the most electronegative of the elements.its ionization potential is also the largest with the exception of helium and neon.The C-F bond is longer than the C-H bond by approximately 0.22 A° and is 27 kcal higher in energy. Due to fluorine's electronegativity, the carbon in the C-F bond is polarized to δ^+ in contrast to the almost neutral C-H bond, and the fluorine and hydrogen atomic radii only differ by 0.15 A° [8,9].

Replacing hydrogen with fluorine in organic molecules allows for polarization of the bond without a large distortion in geometry. This effect can be explained in terms of resonance and inductive effets (scheme 30)



Scheme 30

Because of its large electronegativity, fluorine induces a negative I_ effect to reduce the electron density at the carbon of a C-F bond. However, unshared electron pairs on the fluorine atom interact with the π-electrons of a neighboring carbon- carbon double bond in a repulsive manner to create a δ^- charge on a beta carbon. These lone pairs can also resonate with the double bond creating a positive I_π and R effect.

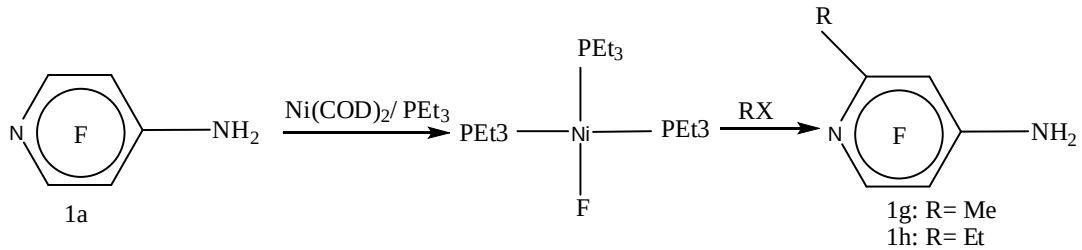
The bulk of the literature concerning C-F activation involves oxidative addition with an electron rich metal center. Oxidative addition, which can be an intramolecular or intermolecular process, is a common reaction in organometallic chemistry but for activation og fluorocarbons the mechanism is not well understood. There are four

basic mechanism that have been proposed for oxidative addition of alkyl and aryl halides to transition metals [5,6]. The first is a free-radical chain mechanism involving a stepwise transfer of two electrons. Two of the mechanism, SN2 and frontside displacement, involve a concerted transfer of two electrons and direct insertion of the metal into the carbon-halogen bond. The fourth is an electron transfer process which may be partially, or totally concerted.

An example of C-F activation by a late transition-metal that has found utilization in synthesis is the cross coupling of secondary alkyl Grignard reagents with Ni(0) compounds.In an ether solution isopropyl magnesium chloride was reacted withfluorobenzene and $Ni(Me_2PCH_2CH_2PMe_2)Cl_2$ which yielded the alkyl products propyl and isopropyl benzene, as well as unsubstituted benzene. The point of importance is the oxidative addition of the C-F bond in the fluorobenzene to the Ni(0) center before the cross coupling step and isomerization. It is also worth pointing out that both the chlorobenzene, and bromobenzene display comparable reactivities[5-27].

V-3- Synthesis of amino Alkyl (Aryl)fluorinated pyridine:

Ni(COD)2 in the presence of triethylphosphine is a powerful catalyst and has been used for the alkylation (arylation) of 4- amino -2,3,5,6- tetrafluoropyridine. Using Ni(COD)2 in the presence of triethylphosphine as the alkylation (arylation) agent, we successfully synthesized 4- amino -2,3,5- trifluoro -6- Alkyl (Aryl) pyridine (scheme31)



1a

1g: R= Me
1h: R= Et
1i: R= nPr
1j: R= iPr
1k: R= Bu
1l: R= $PhCH_2$
1m: R= $(Ph)_2CH$

Scheme 31

The remarkable characteristic of this proposed oxidative addition is concerted, although nucleophilic attack cannot be ruled out. For the oxidative additin, the authors count as evidence the preferential substitution at the 2-position or 6-position of 4-amino -2,3,5,6- tetrafluoropyridine. An electron transfer pathway would lead to preferential substitution at the other position. Nucleophilic attak would give some substitution at the 2-position or 6-position, but would probably substitute at other position also.

Work–up of the reaction product gave colourless crystals of 4- amino -2,3,5- trifluoro -6- Methyl pyridine **1g** m.p 77-79 C° is olated in 80 % yield. The purity of this compound was confirmed by elemental analysis (C,H,N,F)

The i.r. spectrum showed an absorption peak at 3100-3500 characteristic of NH and peaks at 1350, 1375 which could be assigned to the groups $-CH_3$, C-F respectively.The ^{19}Fn.m.r, spectrum (see p) exhibited three absorptions at -18.1 (dd, F2), -81.0 (dd, F3) and -94.3 (dd, F5) ppm which revealed mono-replacement of an alpha- fluorine (F6). The mass spectrum showed a molecular ion peak at m/z 162 which was also the base peak. The prominent peaks at m/z 163 (9.4%) and 147 (70%).

The author also used the method described earlier (see p) to prepar 4- amino -2,3,5-trifluoro -6- Ethyl pyridine **1h** in 71% yield from 4- amino -2,3,5,6-tetrafluoropyridine an Ethyl Iodide, the i.r spectrum revealed the presence of NH, C-F and $-CH_3$, $-CH_2CH_3$ groups, a revealing replacement of both fluorine (F6) which was revealed by 19Fn.m.r,spectroscopy which proved a three –absorption spectrum -17.5 (dd, F2), -86.7 (dd, F3) and -92.5 (dd, F5). The mass spectrum (see p) complied with a normal fragmentation mechanism for 4- amino -2,3,5- trifluoro -6- Ethyl pyridine **1h**. Novel products 4- amino -2,3,5- trifluoro -6- propyl pyridine **1i,** 4- amino -2,3,5-trifluoro -6- isopropyl pyridine **1j** and 4- amino -2,3,5- trifluoro -6- butyl pyridine **1k** were identified by elemental analysis (C,H,N,F)) and spectroscopie data. The ^{1}H n.m.r spectrum of compound **1i** showed the absorptions at .The ^{13}C n.m.r, spectrum revealed the presence of C-F and ethyl groups. The mass spectrum showed a molecular ion at 191 (30.4%) prominent peak at m/z 147 (M+ -Pr) and a base peak at 190. the i.r, ^{13}C n.m.r, and MS spectra of compound **1j** and **1k** were very similar to that of compound **1i** for more details see experimental section.

The preparation started with R = $PhCH_2$,$(Ph)_2CH$ and the products were easily isolated as a solid . the crude product **1l** obtained byusing Benzyl chloride and purified by chromatography. Chromatography was carried out by the dry column

‘’flash’’ method, becouse this technique combines the avantages of ‘’flash’’ chromatography (good separation), speed and simplicity of apparatus and operation. The product was identified by elemental analysis and spectral data .

The ^{1}Hn.m.r spectrum showed the peaks at3.93, 7.5 ppm and broad NH_2 at 5.0 ppm, the mass spectrum of compound **1l** clearly showed the presence of group C_6H_5 in the chemical structure (for more details see experimental section). The IR. spectra and mass spectrum of compound **1m** were similar to that compound **1l**.

V-4- Conversion of Alkyl (Aryl)-4- (2,4,6- trimethyl phenylazo) fluorinated pyridine:

Alty was also able to successfully diazotize 4-amino Alkyl (Aryl) pyridines at room temperature using dry powdered sodium nitrite in a medium of anhydrous hydrogen fluoride (AHF), and the resulting 2,3,5- trifluoro -6- Alkyl (Aryl) pyridyl -4- diazonium ion was coupled, in situ, to a variety of aromatic agents, including mesitylene. This method of diazotization has two advantages over thr method described by chambers and his co- workers [16-50], and by Bank and co- workers [16-50] using 80 % HFaq.

1) The diazotization- coupling reaction was effected at ambient temperature compared with – 20 to – 50 °C, hence the use of coolants, e.g. cardice/meths was avoided.

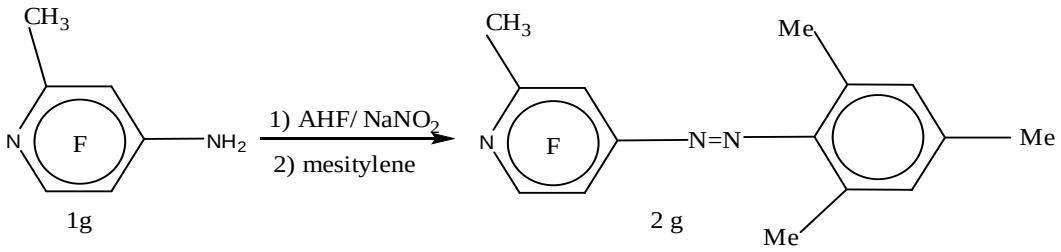
2) The work- up procedure was simplified because the AHF was simply allowed to evaporate slowly in a spcial fume cupboard(cf. addition of the 80% HF solution to water followed by neutralisation to remove the HF). Thus, 4-amino Alkyl (Aryl) pyridines was diazotised as above and coupled to mesitylene, giving the expected azo compound **2g** in 57% yield.

Alty [16-27] suggested that the mechanism of diazotization of the fluorinated amines in AHF proceeds as follows(scheme 32)

This method used to prepare the corresponding 2,4,6 trimethyl phenylazo) Alkyl (Aryl) pyridines

V-4-1- Conversion of 4- amino – 2,3,5 – trifluoro – 6- methyl (ethyl, propyl, isopropyl and butyl) pyridine to the corresponding 4 – (2,4,6 – trimethyl phenylazo) – Alkyl pyridines 2g,2h,2i,2j and 2k

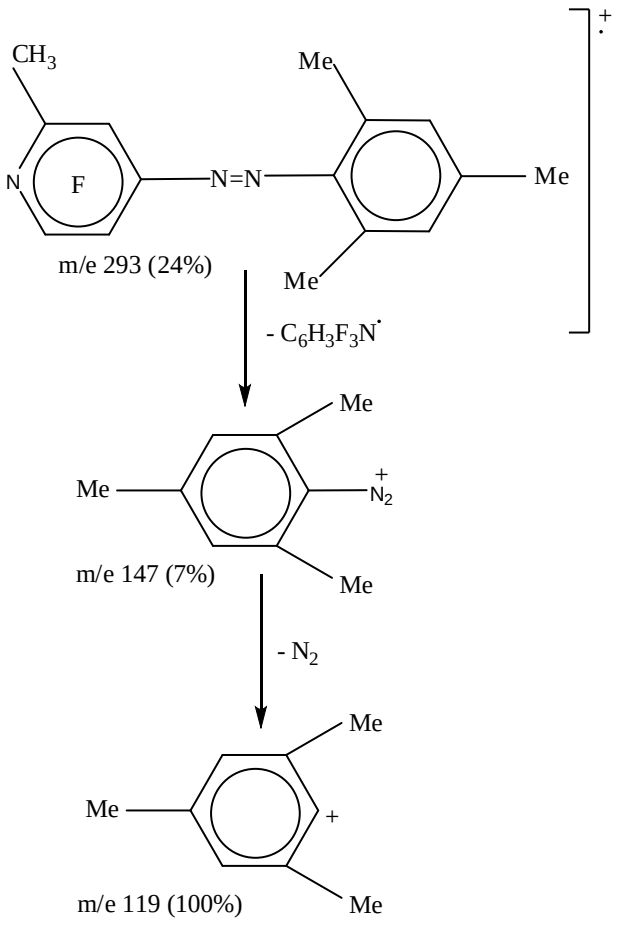
Diazotisation of negatively – substituted aromatic amines usually requires special conditions, diazotisation of 4- amino – 2,3,5 – trifluoro – 6- Methyl pyridine with sodium nitrite in AHF subsequent coupling with mesitylene at room temperature gave the azo compound **2g** in 57% yield (scheme 32)



Scheme 32

2g was identified by elemental analysis and ^{1}H and ^{19}F n.m.r.(p)

^{1}H n.m.r. spectrum showed the peaks at 2.32, 2.46, 2.52 and 7.05 ppm , the mass spectrum showed a molecular ion at m/z 147 and base peak at m/z 119.



Scheme 33

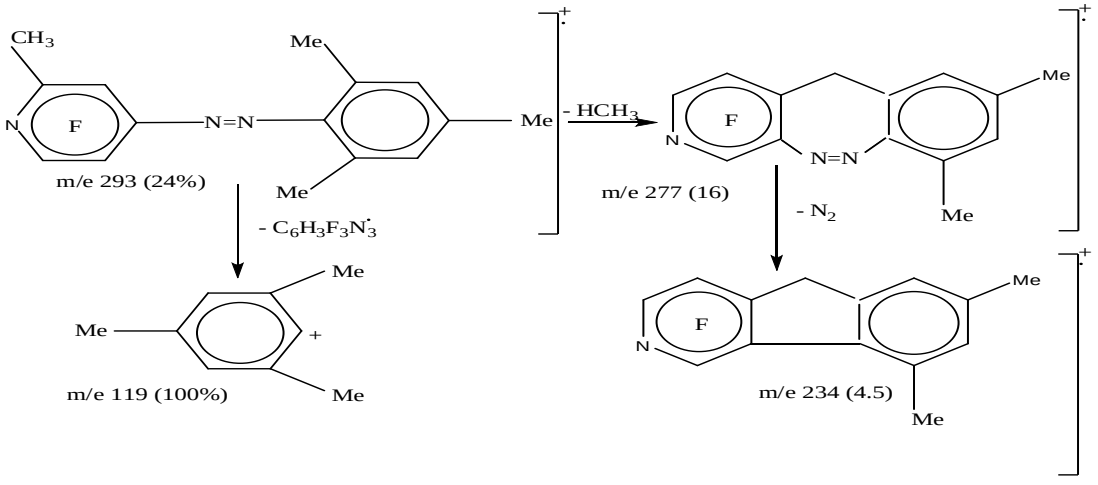
The author repeated the same reaction in order to prepare the starting material for further wark on the synthesis of azo-compounds (**2h**,**2i**,**2j**,**2k**).As described in the

earlier procedure. The purity and identity of this novels compound were demorstrated spectroscopically [i.r, n.m.r(^{1}H, ^{19}F),mass]

V-4-2-Conversion of 4- amino – 2,3,5 – trifluoro – 6- Benzyl (diphenylmethyl) pyridine to the corresponding 4 – (2,4,6 – trimethyl phenylazo) – Aryl pyridines

The author followed the method described earlier by Alty to prepare **2l** and **2m**.This involved adding dry powder sodium; nitrite (56 mmol) over a 5 minute period to a stirred solution of **1l** in AHF contained in polythene beaker. After stirring had been continued for 2 hours at room temperature, an excess of mesitylene was added. This caused an immediate deep-red colour to be formed. Stirring was continued at room temperature until all the AHF had evaporated; then the residual red soli was subjected to dry-column flask chromatography to give the known **2l**, m.p 136-137°C in 47% yield. The new azo compound was identified spectroscopically.Its ^{1}Hn.m.r. spectrum (see p) showed 5 absorptions of intensity 3:6:2:2:5 at 2.34 (4-CH_3), 2.48 (2,6 CH_3), 3.8 ($PhCH_2$), 7.1 (H aromatic) and 7.2-7.5 (phenyl protons). The ^{19}Fn.m.r. spectrum exhibited three absorptions at -10.8 (dd, F2), -71.8 (dd, F3) and -80.5 (dd, F5) p.p.m.nThe mass spectrum of this compound is analysed on page .

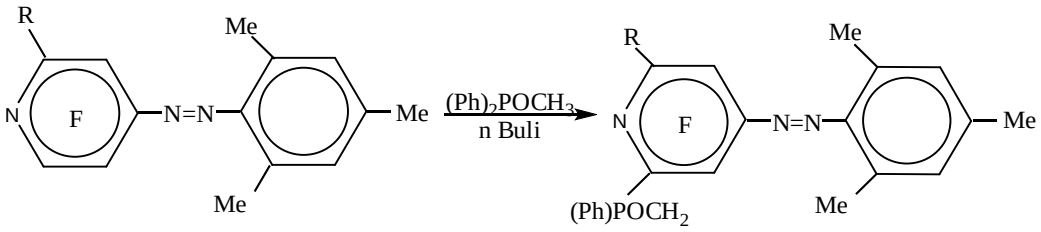
Also isolated was a pale brown solid of **2m** in 41% yield, m.p 131-133 °C. Its ^{1}Hn.m.r. spectrum was very similar to those of azo compound **2l**. The mass spectrum showed a molecular ion at m/z and base peak at m/z 119 (scheme 33) and it is analysed more fully on page.



Scheme 34

V-5-Synthesis of corresponding Alkyl (Aryl) phosphours fluorinated pyridines:

We have succeeded in achieving the nucleophilic aromatic substitution of the fluoride group in the corresponding 4-(2,4,6- trimethyl phenylazo) – Alkyl (Aryl) pyridine with group $(Ph)_2P\text{-}CH_2$, thus obtaining the corresponding fluorinated Alkyl (Aryl) phosphours pyridines **4g- 4m** in 65-91% yield



2g: R=Me. 2h: R=E. 2i: R= nPr
2j: R=iPr. 2k: R=Bu
2l: $PhCH_2$. 2m:$(Ph)_2Ch$

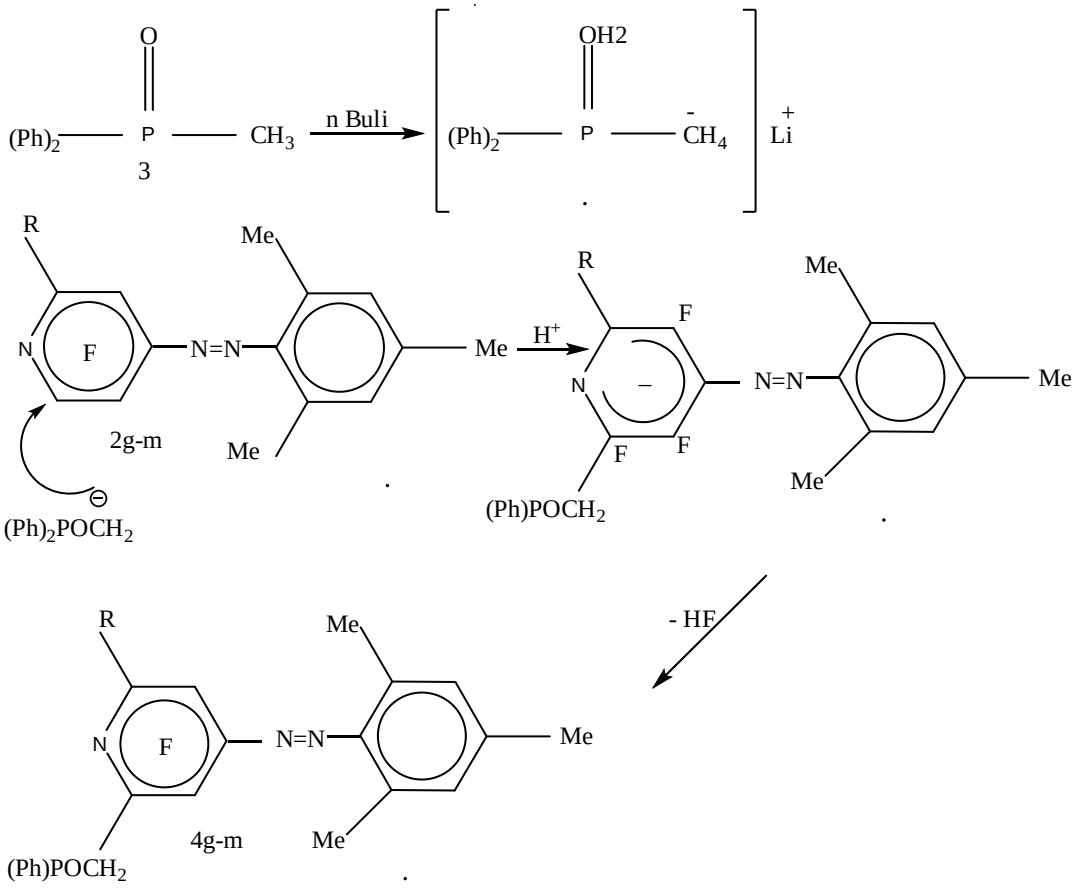
4g-m .

Scheme 35

Based on our experience with the good leaving group ability of the Alkyl (Aryl) group in 4-(2,4,6- trimethyl phenylazo) – Alkyl (Aryl) pyridine, we have now investigated it as a pontential substrate for the preparation of the corresponding fluorinated Alkyl (Aryl) phosphours pyridinesm substitution at the 2-position has a faster rate than that at the orther position because this position was very active.

The reported procedure involved dropwise addition of an equimolar quantity of a solution of n-BuLi in hexane to a stirred solution of Methyl diphenyl phosphine Oxide in dry THF at 0°C then cooled to -78 °C treated with an azo compounds and then allowed to warm to ambient temperature over 2.5 hours.

Among the components, after characterization by ^{1}Hn.m.r., ^{19}Cn.m.r. and mass spectroscopy was found to be the corresponding fluorinated Alkyl (Aryl) phosphours pyridines **4g- 4m** shown in (scheme), proceeds as follows



Scheme 36

The product **4g** was identified by elemental analysis an spectral data.The i.r. spectrum confirmed that the P=O group was still present in this compound. The mass spectrum showed the peak at which was also the base peak and the absence of the fluorine atom.The i.r. spectra of compound **4h – 4k** were similar to that of compound **4g**. The mass spectrum of compound **4h – 4k** clearly showed the presence of a group P=O in the chemical structure .

In the present work, the compound **4l** and **4m** were prepared in 78% and 67% yields respectively by adding to a solution of Methyl diphenyl phosphine Oxide in ButylLithium.The mixture was cooled at -78 °C and The progress of the reaction being followed by adding of azo compounds.

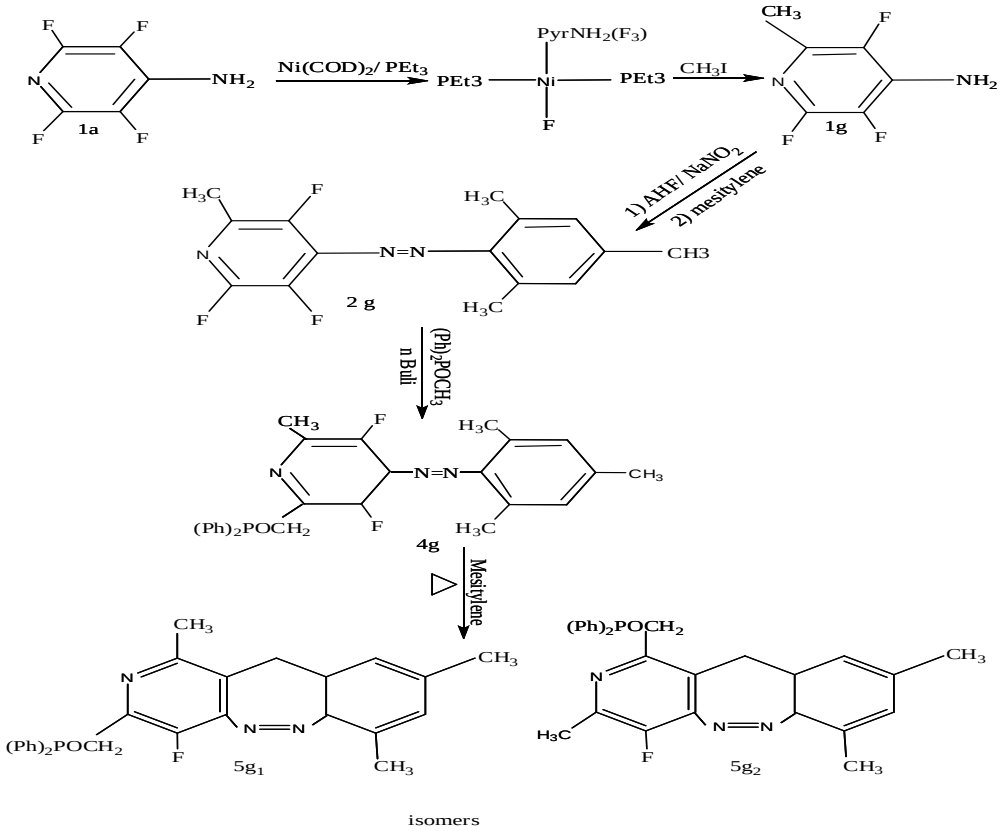
The product **4l** possessed a correct elemental analysis and fully consistent spectroscopic parameters.bThe i.r. spectrum showed the presence an absorption due to P=O group in this compound, the i.r. spectrum also shows an absorption peak at characteristic of N=N. the ^{1}Hn.m.r. spectrum showed the peaks.

V-6- Synthesis of diasepines:

The strategy we have adopted for the synthesis consists of the following steps: i) synthesis of starting amino Alkyl (Aryl)fluorinated pyridine 1g, 1h, 1i, 1j, 1k, 1l, and 1m which was converted to the corresponding **Alkyl (Aryl) fluorinated- 4- (2,4,6-trimethyl phenylazo) pyridine** 2g, 2h, 2i, 2j, 2k, 2l and 2m .

ii) red the anion resulted from Lithiating of methyl dipheny phosphine oxide, was added to the previous fluorinated azo compound.

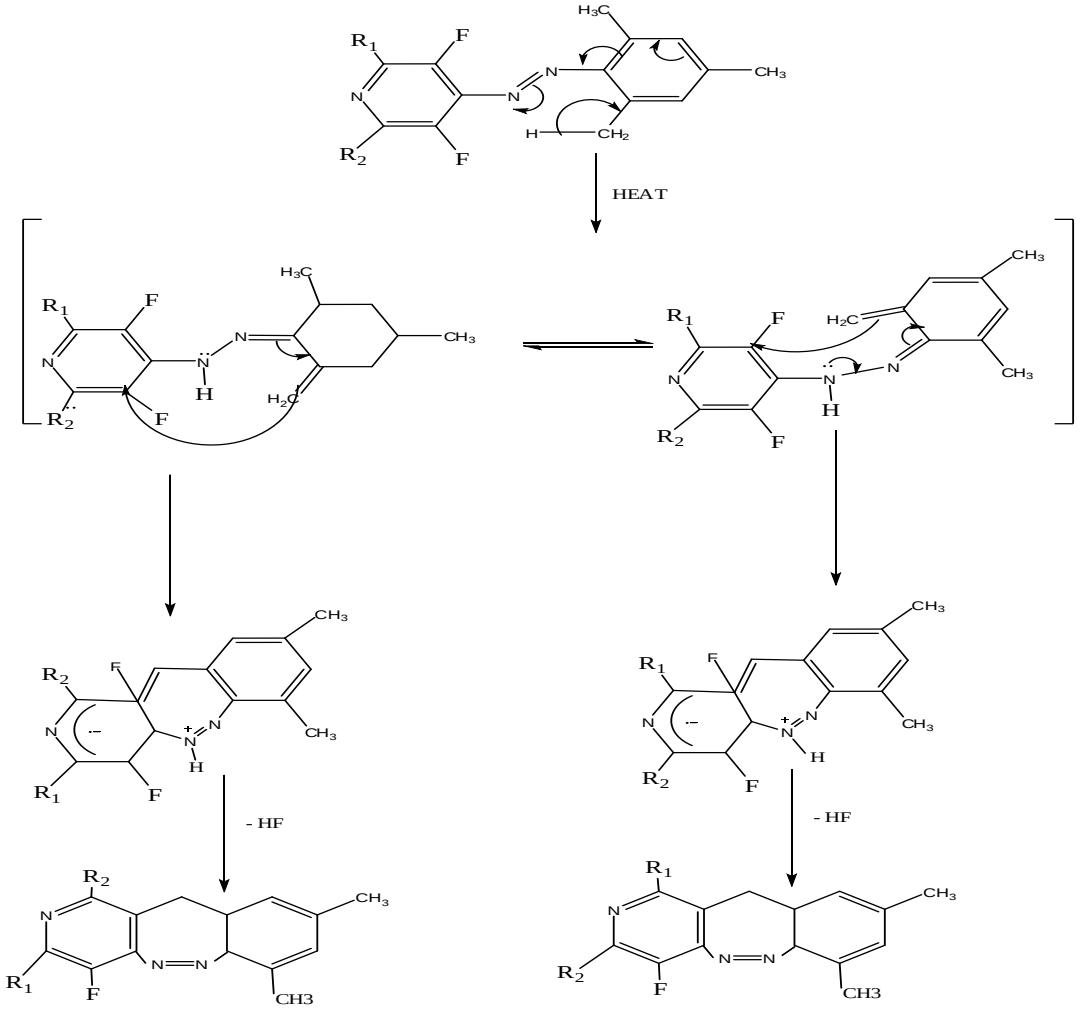
iii) the resulting phosphorus and fluorinated azo compound resulted from step two thermolyzed in mesitylene to give the structural isomers of corresponding diazepine. Finally, HPLC will be used to separate the structural isomers (scheme 37)



Scheme37

The nickel catalyst Ni(COD)2 in the presence of triethylphosphine is a powerful catalyst and has been used for the alkylation of 4- amino -2,3,5,6- tetrafluoropyridine gave 4- amino -2,3,5- trifluoro -2- methyl pyridine. Nucleophilic attack would give a substitution at the 2-position of 4- amino -2,3,5,6- tetrafluoropyridine. Clearly, the azo compound 4g may give the corresponding diazepine $5g_1$-g_2 (via elimination of HF), the mechanism of this reaction may be assumed as following (scheme38). The

elimination of 3 or 5 –fluorine does not cause severe steric effects because these two atom have similar diameters ;how ever the fluorine is very electronegative. The $(Ph)_2PO$ and methyl can stabilize the structure and in crease significantly the energy of steromutation. The method used to prepare the corresponding diazepine was adapted from the procedure which was devised by A.C. Alty [27]; this involves heating the fluorinated phosphorus azo compound in boiling mesitylene. The corresponding diazepine was resolved into the corresponding isomers (Scheme 38) by HPLC as a mobile phase added on a Chiralcel OD-H column, hexane/2-PrOH, 9/1 v/v mobile phase, flow-rate 1.0 ml/min, 25°C, λ = 254 nm and polarimetric detection, 20µL injection volume.

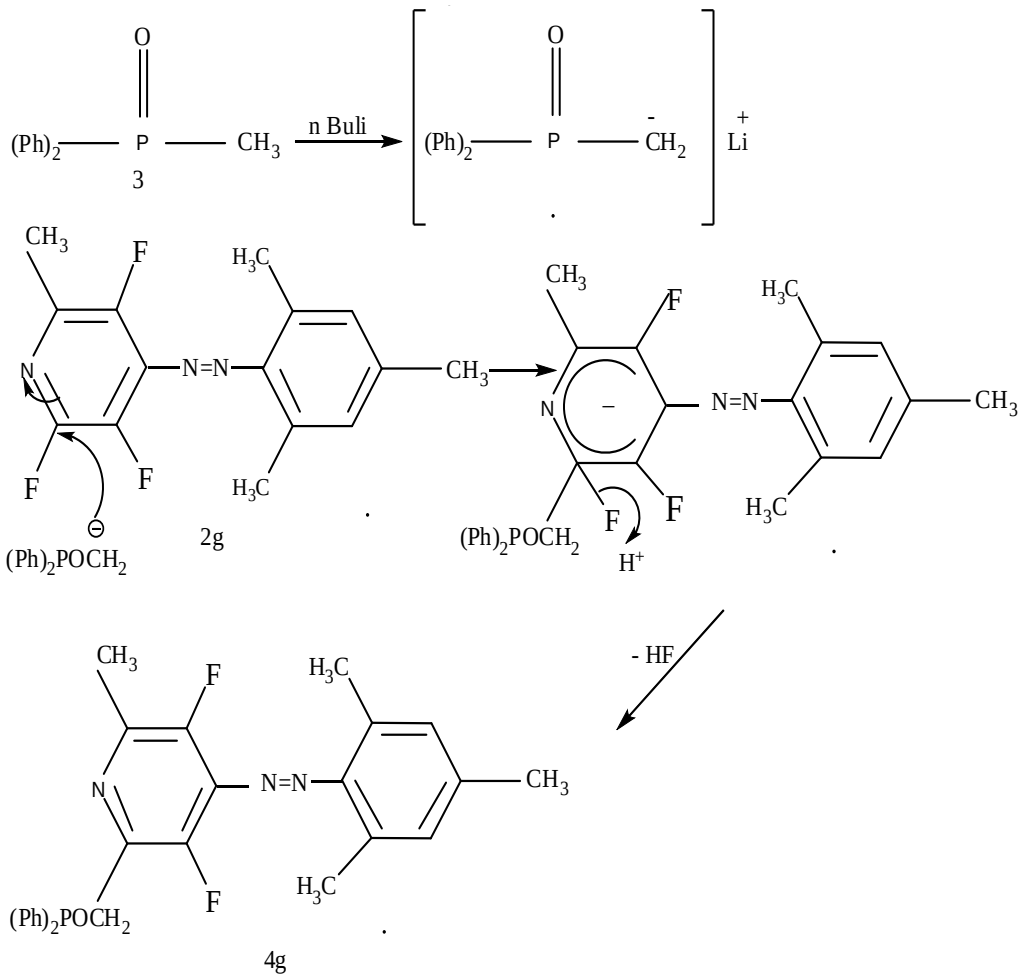


R_1: CH_3 and R_2: $(Ph)_2POCH_2$

Scheme38

Alty was also able to successfully diazotize 4-amino Alkyl pyridines at room temperature using dry powdered sodium nitrite in a medium of anhydrous hydrogen

fluoride (AHF), and the resulting 3,5,6- trifluoro -2- Alkyl pyridyl -4- diazonium ion was coupled, in situ, to a variety of aromatic agents, including mesitylene. We have succeeded in achieving the nucleophilic aromatic substitution of the fluoride group in the corresponding 3,5,6- trifluoro- 2-methyl -4-(2,4,6- trimetyl- phenylazo)pyridine with group $(Ph)_2POCH_2$-, thus obtaining the corresponding fluorinated Alkyl phosphours pyridines 4g (scheme 39).



Scheme 39

These separations were amenable to semi-preparative scale. Special care was taken during all the semi preparative experiments and the isolated isomers were kept covered by the solvent of elution during the concentration step to minimize the

explosive hazard. However, as the Alcohols (2-PrOH) decreased, the resolution (*Rs*) was all steadily increased, suggesting that the polar interaction (mainly hydrogen-bonding interaction) between solute and stationary phase was not only the primary factor for solute retention but also playing some roles in isomeric recognition.

The isomer of diazepine was separated by normal phase chromatographic technique, by using High performance liquid chromatography as a mobile phase added on a Chiralcel OD-H column (Figure 32- 38). The isolated compound was characterized by using IR,^{1}H ,^{19}F RMN, and MS spectroscopic technique. The synthesis of diazepine was also discussed in brief.

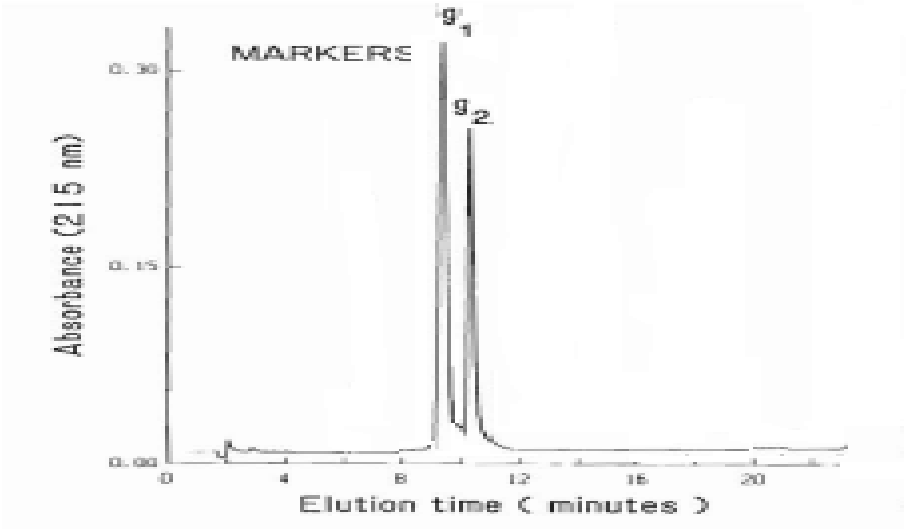


Figure 32: chromatographic profiles of 5g Chiralcel OD-H column, hexane/2-PrOH, 9/1 v/v mobile phase, flow-rate 1.0 ml/min, 25°C

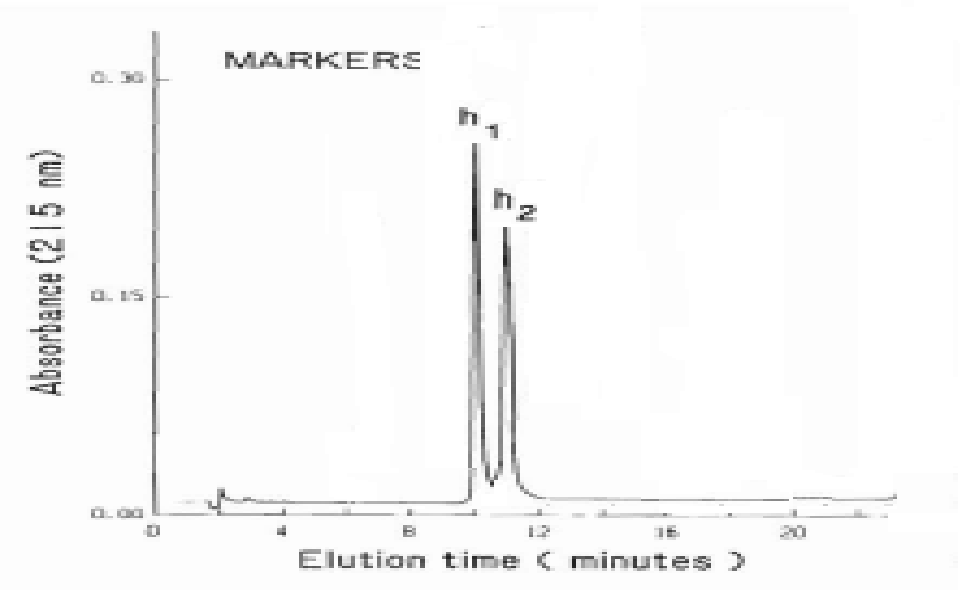


Figure 33: chromatographic profiles of 5h Chiralcel OD-H column, hexane/2-PrOH, 9/1 v/v mobile phase, flow-rate 1.0 ml/min, 25°C

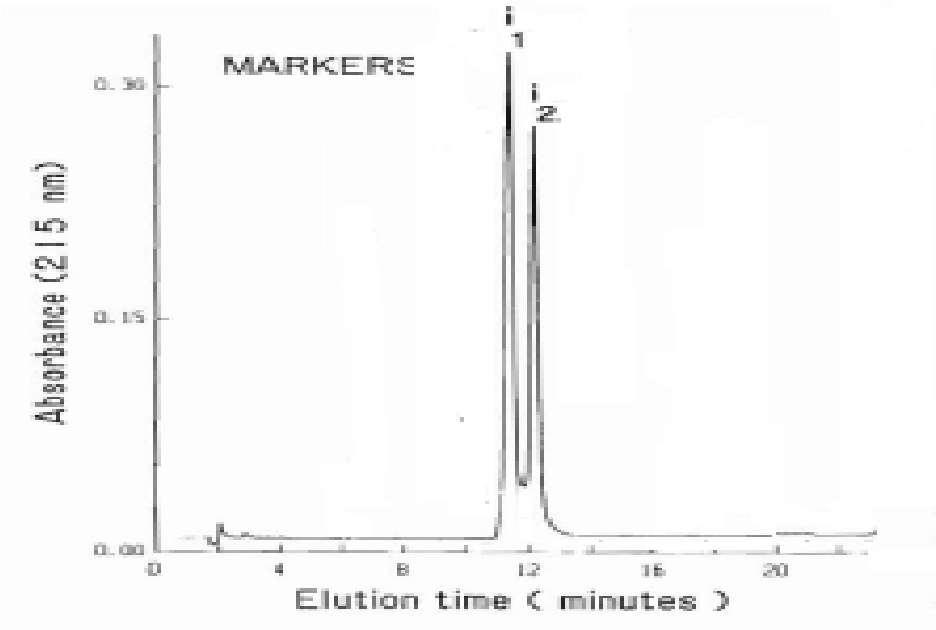


Figure 34: chromatographic profiles of 5i Chiralcel OD-H column, hexane/2-PrOH, 9/1 v/v mobile phase, flow-rate 1.0 ml/min, 25°C

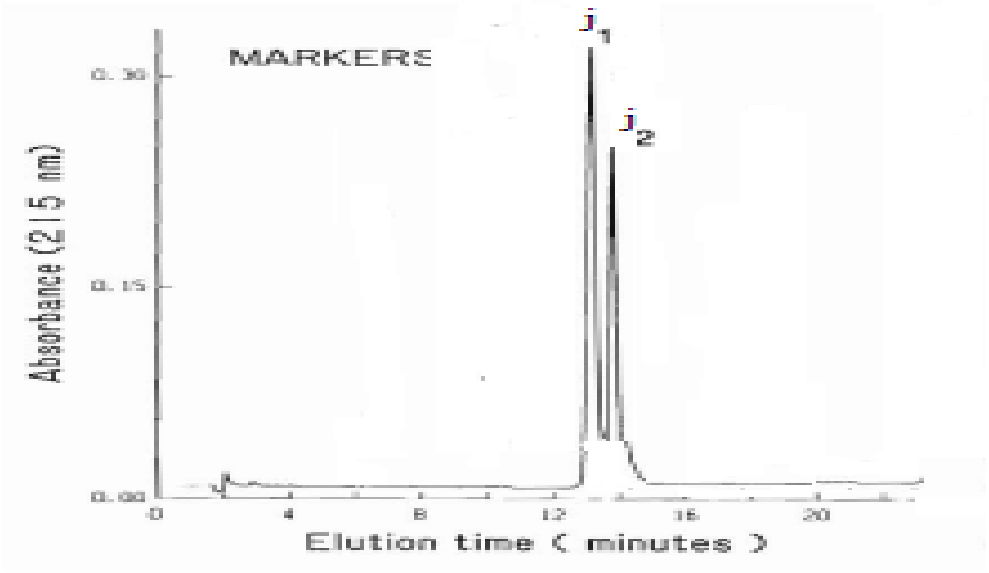


Figure 35: chromatographic profiles of 5j Chiralcel OD-H column, hexane/2-PrOH, 9/1 v/v mobile phase, flow-rate 1.0 ml/min, 25°C

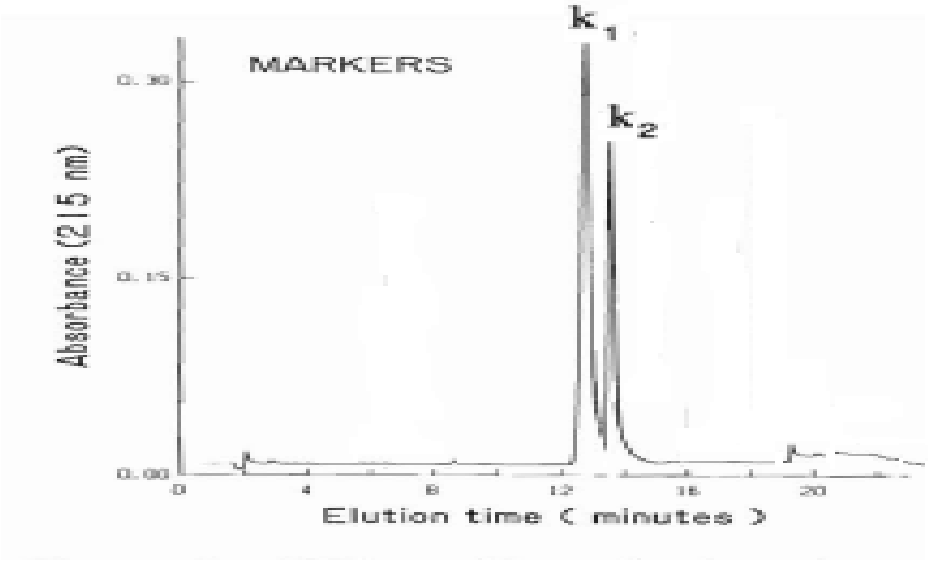


Figure 36: chromatographic profiles of 5k Chiralcel OD-H column, hexane/2-PrOH, 9/1 v/v mobile phase, flow-rate 1.0 ml/min, 25°C

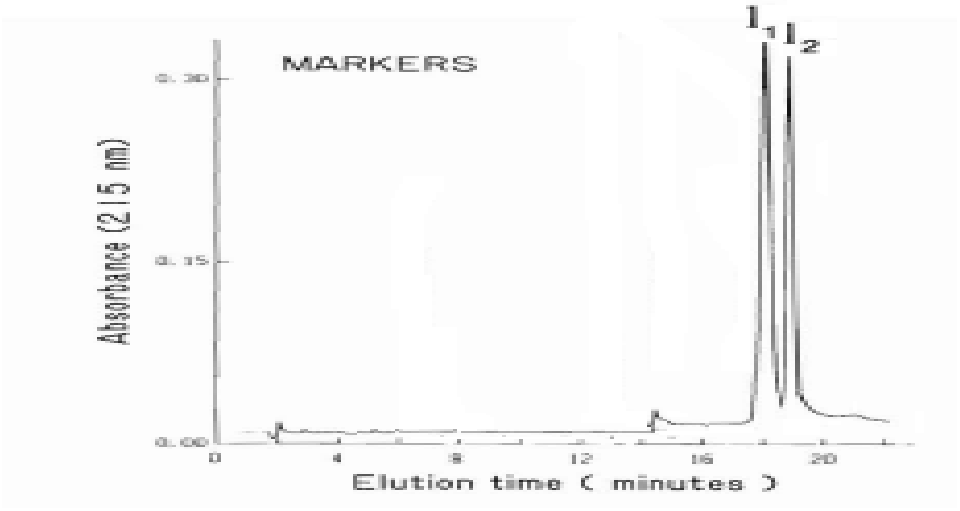


Figure 37: chromatographic profiles of 5l Chiralcel OD-H column, hexane/2-PrOH, 9/1 v/v mobile phase, flow-rate 1.0 ml/min, 25°C

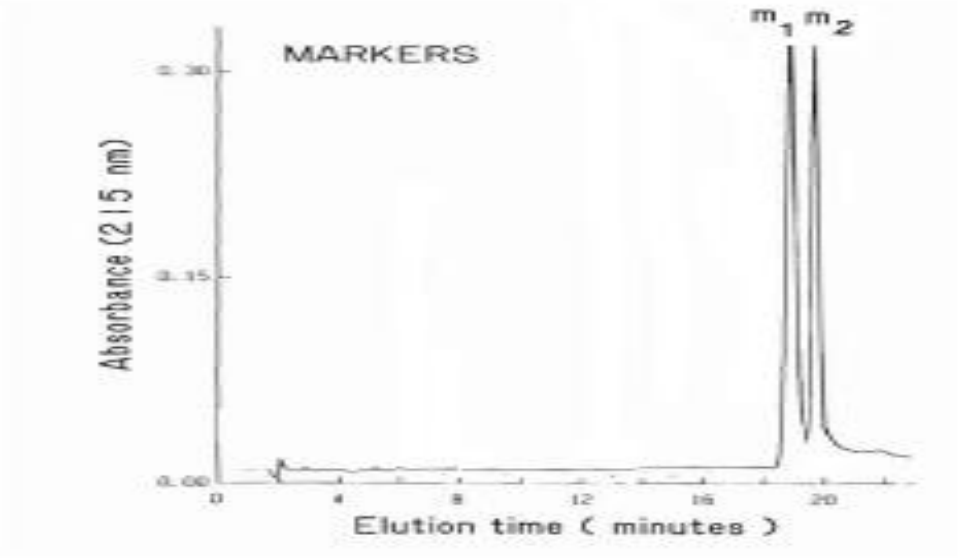


Figure 38: chromatographic profiles of 5m Chiralcel OD-H column, hexane/2-PrOH, 9/1 v/v mobile phase, flow-rate 1.0 ml/min, 25°C

Experimental section

Part II

VI-1- Synthesis of amino Alkyl (Aryl)fluorinated pyridine:

VI-1-1- Synthesis of 4- amino -2,3,5- trifluoro -6- methyl pyridine 1g:

In a 200 ml three-neck flask equipped with a dropping funnel, a magnetic stirring bar and condenser, was added 5.23 g of nickel catalyst $Ni(CODD)_2$ in the presence of triethylphosphine and 16 ml of dichloromethane under argon atmosphere.The temperature was raised to 50 °C, and 13 g 4- amino – 2,3,5,6 – tetrafluoropyridine was added in slowly via dropping funnel over 30 (60 mmol) minutes period. Then the temperature was raised to 70 °C and 8.52 g Methyl Iodide was dropped in slowly, and the reaction mixture was kept stirring at 70 ~ 100 °C for another 1 hour.the mixture was cooled and stirred overnight at room temperature. The volatile material (~ 25 g) was distilled into a liquid nitrogen trap under high vacuum, followed by washing with cold 10% NaOH aqueous solution, brine and water respectively. After drying over anhydrous sodium sulfate, the crude product was purified by flash chromatography (4:1 EtDAc/ pentane) yielding 10.14 g (80%) of an oily m.p 77-79C°. The product has the following spectroscopic properties:

ν_{max} (KBr Disc, cm^{-1}) : 1350 ($N\text{-}CH_3$), 1375 (C-F), 2850-3000 (CH Aliphatic), 3120 (CH Aromatic), 3100-3500 (NH).

δF (54.6 MHz ; $CDCl_3$) : - 18.1(1F, dd, j= 3.2 Hz, F-2), -81.0(1F, dd, j= 22.7 Hz, F-3), -94.3(1F, dd, j= 29.5 Hz, F-5).

m/z (FAB) 162(M^+,100), 164 (M^++ 2,0.5), 163 (M^++ 1,9.4), 147 (M^+- CH_3, 70), 120(49.3), 93(19.3), 75(21), 44(7.0), 42(59.2), 41(38.3)

Anal. Calcd for $C_6H_5N_2F_3$: Requires C, 44.4% ; H, 3.08% ; N, 17.28% ; F, 35.18%

Found C, 44.6% ; H, 3.00% ; N, 17.20% ; F, 35.20%

VI-1-2-Synthesis of 4- amino -2,3,5- trifluoro -6- ethyl pyridine 1h:

In a 200 ml three-neck flask equipped with a condenser, a stirring bar and two rubber septa, was added 5.41 g of nickel catalyst $Ni(CODD)_2$ in the presence of triethylphosphine and 16 ml of dichloromethane under argon atmosphere.At 50 °C, and 13 g 4- amino – 2,3,5,6 – tetrafluoropyridine was added in slowly via a syringe. After 30 °C minutes at 50 °C, the temperature was raised to 70°C slowly, followed by slow addition of 9.36 g Ethyl Iodide (60 mmol). The reaction mixture was stirred at 70°C for 1hour, then at 100°C for another 1hour. The reaction mixture was cooled, and stirred overnight at room temperature. The reaction mixture was mixed. The

volatile material (~ 25 g) was distilled into a liquid nitrogen trap under high vacuum, followed by washing with cold 10% NaOH aqueous solution, brine and water respectively. After drying over anhydrous sodium sulfate, the crude product was purified by flash chromatography and 9.78 g (71%) of 2 was isolated, m.p 82- 84

ν_{max} (KBr Disc, cm^{-1}) : 1310 (N-C), 1367.4 (C-F), 1447.5-1480.7 (-CH2-), 2900 (CH Aliphatic), 3100 (CH Aromatic).

δF (54.6 MHz ; $CDCl_3$) : - 17.5(1F, dd, j= 4.64 Hz, F-2), -86.7(1F, dd, j= 21.2 Hz, F-3), -92.5(1F, dd, j= 25.4 Hz, F-5).

δc (75 MHz, CDCl3) : 137.1(C), 134.2(C), 132.8(C), 131.0(C), 130.6(CH), 44.1(CH2), 15.2(CH3).

m/z (FAB) 176(M^+,100), 178 (M^++ 2,0.7), 177 (M^++ 1,8.3), 147 (M^+- Et, 61), 161(23), 120(52.7), 97(9.3), 75(20.3), 44(8.2), 42(47.1), 41(33.3)

Anal. Calcd for $C_7H_7N_2F_3$: Requires C, 47.72% ; H, 3.97% ; N, 15.90% ; F, 32.38%

Found C, 47.50% ; H, 3.90% ; N, 15.90% ; F, 32.70%

VI-1-3-Synthesis of 4- amino -2,3,5- trifluoro -6- propyl pyridine 1i:

In a 200 ml three-neck flask equipped with a stirring bar, a condenser and two rubber septa, was added 5.0 g of nickel catalyst $Ni(CODD)_2$ in the presence of triethylphosphine and 16 ml of dichloromethane under argon atmosphere.At 50 °C, 13 g 4- amino – 2,3,5,6 – tetrafluoropyridine was added in reaction mixture slowly via a syringe. After 30 °C minutes at 50 °C, the temperature was raised up 70°C slowly, followed by the slow addition of 10.2 g Propyl Iodide (60 mmol). The reaction mixture was stirred at 70°C for 1hour, then at 100°C for another 1hour.After distillation, the reaction mixture was washed with cold 10% NaOH aqueous solution, brine and water respectively. After drying over anhydrous sodium sulfate, the crude product was purified and 9.22 g of 3 (62%) was isolated, m.p 95- 97C°.

ν_{max} (KBr Disc, cm^{-1}) : 1244 (N-C), 1311.5-1328.9 (C-F), 1350-1450 (-CH3-), 3053.1 (CH Aromatic), 3078.2-3436.9 (NH).

δH (300 MHz ;CDCl3) : 0.94(3H, t J=7.2Hz, CH2-C<u>H</u>3) , 2.3(1H, dq, J=7.8, 12.5Hz C<u>H</u>2-CH3), 2.31(1H, s, NH), 2.43(1H, dq, J=7.8, 12.5Hz C<u>H</u>2-CH3), 5.3(2H, s, NH2).

δc (75 MHz, CDCl3) : 172.7(C), 132.1(C), 131.9(C), 131.5(C), 130.9(C), 47.6(CH2), 24.1(CH2), 18.2(CH3).

m/z (FAB) 190(M^+,100), 192 (M^++ 2,1.3), 191 (M^++ 1,30.4), 147 (M^+- nPr, 72.5), 175(13.6), 161(17.3), 120(40.1), 97(9.4), 75(19.7), 44(6.2), 42(43.5), 41(31.7).

Anal. Calcd for $C_8H_9N_2F_3$: Requires C, 50.52% ; H, 4.73% ; N, 14.73% ; F, 30.0%

Found C, 50.52% ; H, 4.70% ; N, 14.74% ; F, 30.04%

VI-1-4-Synthesis of 4- amino -2,3,5- trifluoro -6- isopropyl pyridine 1j:

4 was prepared in a similar as 3. 4- amino – 2,3,5,6 – tetrafluoropyridine (13 g) reacts with Isopropyl Iodide (10.2 g, 60 mmol) at 50- 100 °C for 1h, and the product was purified to give 9.96 g (67%) 4,

ν_{max} (KBr Disc, cm^{-1}) : 1244 (N-C), 1311.5-1328.9 (C-F), 1350-1450 (-CH3-), 3053.1 (CH Aromatic), 3078.2-3436.9 (NH).

δH (300 MHz ;CDCl3) : 0.73(3H, t J=6.6Hz, CH-C<u>H</u>3) , 0.76(3H, t J=6.6Hz, CH-C<u>H</u>3), 2.37(1H, C<u>H</u>-CH3), 5.5(2H, s, NH2).

δF (54.6 MHz ; $CDCl_3$) : - 15.2(1F, dd, j= 3.94 Hz, F-2), -84.0(1F, dd, j= 20.2 Hz, F-3), -96.7(1F, dd, j= 25.4 Hz, F-5).

m/z (FAB) 190(M^+,100), 192 (M^++ 2,1.3), 191 (M^++ 1,30.4), 147 (M^+- iPr, 72.5), 175(13.6), 161(17.3), 120(40.1), 97(9.4), 75(19.7), 44(6.2), 42(43.5), 41(31.7).

Anal. Calcd for $C_8H_9N_2F_3$: Requires C, 50.52% ; H, 4.73% ; N, 14.73% ; F, 30.0%

Found C, 50.52% ; H, 4.70% ; N, 14.74% ; F, 30.04%

VI-1-5-Synthesis of 4- amino -2,3,5- trifluoro -6- butyl pyridine 1k:

In a 200 ml three-neck flask equipped with a dry ice condenser, a stirring bar and two rubber septa, was added 4.0 g of nickel catalyst $Ni(CODD)_2$ in the presence of triethylphosphine and 16 ml of dichloromethane under argon atmosphere.At 50 °C, 13 g 4- amino – 2,3,5,6 – tetrafluoropyridine was added into the mixture slowly via a syringe. After 30 °C minutes at 50 °C, the temperature was raised to 70°C slowly, followed by slow addition of 11.4 g Butyl Iodide (60 mmol). Reaction mixture was kept at 70 °C for 1 hour and then cooled down to room temperature, followed by stirring overnight. 10 ml of 10% NaOH aqueous solution, was added into the reaction mixture. After drying over anhydrous sodium sulfate, the product was purified. Totally 10.86 g (m.p 115-117C°, 68%) 1k was isolated

ν_{max} (KBr Disc, cm^{-1}) : 1345.9 (Ar-F), 1450 and 1375(-CH3), 1465(-CH2), 1650 (C=N), 3100-3500(NH).

δF (54.6 MHz ; $CDCl_3$) : - 15.1(1F, dd, j= 3.75 Hz, F-2), -81.9(1F, dd, j= 23.4 Hz, F-3), -92.7(1F, dd, j= 28.4 Hz, F-5).

m/z (FAB) 204(M^+,100), 206 (M^++ 2,3.4), 205 (M^++ 1,19.3), 147 (M^+- Bu, 75.6), 189(23.4),175(15.6), 161(19.2), 120(30.4), 97(15.7), 75(11.5), 44(10.0), 42(8.2), 41(26.7).

Anal. Calcd for $C_9H_{11}N_2F_3$: Requires C, 52.94% ; H, 5.39% ; N, 13.72% ; F, 29.94%

Found C, 52.00% ; H, 5.20% ; N, 13.65% ; F, 29.15%

VI-1-6-Synthesis of 4- Amino- -6- benzyl- 2,3,5- trifluor pyridine 1l:

In a 200 ml three-neck flask equipped with a stirring bar, a condenser and two rubber septa, was added 6.22 g of nickel catalyst $Ni(CODD)_2$ in the presence of triethylphosphine and 20 ml of dichloromethane under argon atmosphere.At 50 °C, 12 g 4- amino – 2,3,5,6 – tetrafluoropyridine was added into the mixture slowly via a syringe. After 30 °C minutes at 50 °C, the temperature was raised to 70°C slowly, followed by slow addition of 8.64 g Phenyl Iodide (40 mmol). The reaction mixture was stirred at 70 °C for 1 hour , then at 100 °C. The reaction mixture was cooled , and stirred overnight at room temperature. The reaction mixture was added in 20 ml of ether and washed with cold 10% NaOH aqueous solution for 3 times. The ether layer was washed with brine and water 3 times, respectively. The ether phase was dried over magnesium sulfate and the product was further purified by silica gel column chromatography (hexanes as eluent) to afford 14.10 g (m.p 152- 155, 82%) of 1l

ν_{max} (KBr Disc, cm^{-1}) : 1350 (Ar-F), 1475-1600(C=Caromatic), 1650.9 (C=N), 3050-3150(CH Aromatic), 3100-3500(NH).

δH (300 MHz ;CDCl3) : 3.93(2H, s, C<u>H</u>2) , 7.5(5H, d, Ha), 5.0(2H, s, NH2).

m/z (FAB) 238(M^+,100), 240 (M^++ 2,0.8), 239 (M^++ 1,15.5), 147 (37.4), 161(76.5), 97(9.7), 93(23.3), 77(43), 75(20), 44(5.9), 42(59.3), 40(10.7), 39(27).

Anal. Calcd for $C_{12}H_9N_2F_3$: Requires C, 60.50% ; H, 3.78% ; N, 11.76% ; F, 23.94%

Found C, 60.50% ; H, 3.76% ; N, 11.76% ; F, 23.98%

VI-1-7-Synthesis of 4- Amino- 2,3,5- trifluor -6- diphenylmethanylpyridine 1m:

In a 200 ml three-neck flask equipped with a dropping funnel stirring bar a condenser was added 8.6 g of nickel catalyst $Ni(CODD)_2$ in the presence of triethylphosphine and 20 ml of dichloromethane under argon atmosphere.The temperature was raised to 50 °C, and 12 g 4- amino – 2,3,5,6 – tetrafluoropyridine was added in slowly via a syringe. Then the temperature was raised to 70 °C and 11.76 g Diphenyl Iodide (60 mmol) was dropped in slowly, and the reaction was kept stirred at 70 ~ 100 °C for another 1 hour. The reaction mixture was cooled , and stirred overnight at room temperature. The reaction mixture was mixed with 20 ml of ether and washed with 10% NaOH aqueous solution trice, and the organic phase was washed with brine and water, respectively. The organic phase was dried over magnesium sulfate and the solvent was evaporated off. After column chromatography using hexanes as eluent 17.01 g (m.p 151- 153C°, 75%) of 1m was isolated.

ν_{max} (KBr Disc, cm^{-1}) : 1311.5-1328.9 (Ar-F), 1650.9 (C=N), 3050-3150(CH Aromatic).

δH (300 MHz ;CDCl3) : 3.03(1H, s, C<u>H</u>) , 7.1- 7.92(10H, m, Ha), 5.7(2H, s, NH2).

m/z (FAB) 314(M^+,100), 316 (M^++ 2,0.7), 315 (M^++ 1,25.8), 237(85.4), 97(9.3), 93(14.5), 77(46), 75(20.1), 44(4.3), 42(59.7), 40(11), 39(23).

Anal. Calcd for $C_{18}H_{13}N_2F_3$: Requires C, 68.78% ; H, 4.14% ; N, 8.91% ; F, 18.15%

Found C, 68.75% ; H, 4.12% ; N, 8.94% ; F, 18.19%

VI-2- Synthesis of Alkyl (Aryl) fluorinated- 4- (2,4,6- trimethyl phenylazo) pyridine:

VI-2-1- Synthesis of 2,3,5- trifluoro 4- (2,4,6- trimethyl phenylazo) -6- methyl pyridine 2g:

In a typical experiment, dry powdered sodium nitrite (3.32g, 48mmol) was added over a period of 5 minutes to a stirred solution of a mixture of 1 (7.78g, 48mmol), in AHF (400 ml) contained in polythene beaker. After stirring had been continued for 2 hours at room temperature, mesitylene (5.78 g, 48 mmol) was added, which caused an immediate deep- red colour to be formed. Stirring was continued at room temperature until all the AHF evaporated, then the red precipitate was isolated following addition of the mixture to water (1100 ml). After being dried (oven, 70 °C), the product was

subjected to dry- column flash chromatography [silica (70 x 55 mm) light petroleum (b.p 40- 60 / dichloromethanel] to give**2g** m.p 111- 113C° (8.02 g, 27 mmol, 57%)

ν_{max} (KBr Disc, cm^{-1}) : 1176.5-1271.0 (Ar-F), 1558.4 (N=N), 810(CH Aromatic).

δH (300 MHz ;CDCl3) : 2.32(3H, s, 4-CH3) , 2.46(6H, s, 2,6-CH3), 2.52(3H, s, 6-CH3), 7.05(2H, s, Ha).

δF (54.6 MHz ; $CDCl_3$) : - 14.3(1F, dd, j= 3.1 Hz, F-2), -75.4(1F, dd, j= 21.7 Hz, F-3), -84.17(1F, dd, j= 27.0 Hz, F-5).

m/z (FAB) 293(M^+,24), 295 (M^++ 2,0.3), 294 (M^++ 1,4), 292(40), 147 ($C_9H_{11}N_2^+$, 7), 119($C_9H_{11,}$100), 120(10), 77(11), 41(13), 39(6.4).

Anal. Calcd for $C_{15}H_{14}N_3F_3$: Requires C, 61.43% ; H, 4.77% ; N, 14.33% ; F, 19.45%. Found C, 61.33% ; H, 4.77% ; N, 14.33% ; F, 19.57%

VI-2-2- Synthesis of 2,3,5,- trifluoro -4- (2,4,6- trimethyl phenylazo) -6- ethyl pyridine 2h:

9 was prepared in a similar manner as 8. the following amounts were taken; (3.32 g, 48 mmol) of sodium nitrite, (8.45 g, 48 mmol) 2 and (5.78 g, 48 mmol) the mesitylene to give a pure solid (7.95 g, 25 mmol, 54%) of 2h m.p 129C°, after purification by flash column chromatography on silica gel and recrystallistion from ethyl acetate. The product was identified

ν_{max} (KBr Disc, cm^{-1}) : 1174.6-1270 (Ar-F), 1602.7 (N=N), 3050-3150(CH Aromatic).

δF (54.6 MHz ; $CDCl_3$) : - 14.8(1F, dd, j= 3.4 Hz, F-2), -75.3(1F, dd, j= 20.0Hz, F-3), -83.9(1F, dd, j= 25.6 Hz, F-5).

m/z (FAB) 307(M^+,20), 309 (M^++ 2,0.9), 308 (M^++ 1,7), 306(53), 292(62), 147 ($C_9H_{11}N_2^+$, 11), 119($C_9H_{11,}$100), 120(13), 77(15), 41(9), 39(5).

Anal. Calcd for $C_{16}H_{16}N_3F_3$: Requires C, 62.54% ; H, 5.21% ; N, 13.68% ; F, 18.56%.Found C, 62.56% ; H, 5.19% ; N, 13.69% ; F, 18.56%

VI-2-3- Synthesis of 3,5,6- trifluoro - 4- (2,4,6- trimethyl phenylazo) -6- propyl pyridine 2i:

10 was prepared in a similar manner as 8 .The following amounts were taken; (3.32 g, 48 mmol) of sodium nitrite, (9.12 g, 48 mmol) 3 and (5.78 g, 48 mmol) the

mesitylene to afford (7.85 g, 24 mmol, 51%) of 2i m.p 132- 134C°, after purification by flash column chromatography on silica gel and recrystallistion from ethyl acetate.

ν_{max} (KBr Disc, cm^{-1}) : 1174.6-1298 (Ar-F), 1602.7 (N=N), 650-904.6(CH Aromatic).

δF (54.6 MHz ; $CDCl_3$) : - 14.7(1F, dd, j= 3.2 Hz, F-2), -74.9(1F, dd, j= 19.0Hz, F-3), -83.5(1F, dd, j= 25.2 Hz, F-5).

m/z (FAB) 321(M^+,23), 323 (M^++ 2,3), 322 (M^++ 1,8), 320(50), 306(40), 292(73), 147 ($C_9H_{11}N_2^+$, 10), 119($C_9H_{11,}$100), 120(11), 77(13), 43(17), 41(5), 39(5), 29(3).

Anal. Calcd for $C_{17}H_{18}N_3F_3$: Requires C, 63.55% ; H, 5.6% ; N, 13.08% ; F, 17.75%

Found C, 63.54% ; H, 5.4% ; N, 13.08% ; F, 17.98%

VI-2-4- Synthesis of 2,3,5- trifluoro -4- (2,4,6- trimethyl phenylazo) -6- isopropyl pyridine 2j:

11 was prepared in a similar manner as 8 .The following amounts were taken; (3.32 g, 48 mmol) of sodium nitrite, (9.12 g, 48 mmol) 4 and (5.78 g, 48 mmol) the mesitylene, affording a crude product which was recrystalliused from ethyl acetate to give a pure crystals (8.16 g, 25 mmol, 53%) of 2j m.p 134- 135C°

δF (54.6 MHz ; $CDCl_3$) : - 14.2(1F, dd, j= 3.0 Hz, F-2), -75.0(1F, dd, j= 21.0Hz, F-3), -84.07(1F, dd, j= 26.9 Hz, F-5).

m/z (FAB) 321(M^+,23), 323 (M^++ 2,3), 322 (M^++ 1,8), 306(53), 320(50), 306(40), 292(73), 147 ($C_9H_{11}N_2^+$, 10), 119($C_9H_{11,}$100), 120(11), 77(13), 43(17), 41(5), 39(5), 29(3).

Anal. Calcd for $C_{17}H_{18}N_3F_3$: Requires C, 63.55% ; H, 5.6% ; N, 13.08% ; F, 17.75%

Found C, 63.54% ; H, 5.4% ; N, 13.08% ; F, 17.98%

VI-2-5- Synthesis of 2,3,5- trifluoro -4- (2,4,6- trimethyl phenylazo) -6- butyl pyridine 2k:

12 was prepared in a similar manner as 8 .The following amounts were taken; (3.32 g, 48 mmol) of sodium nitrite, (9.79 g, 48 mmol) 5 and (5.78 g, 48 mmol) the mesitylene, affording a crude product which was recrystalliused from ethyl acetate to give a pure crystals (7.71 g, 23 mmol, 48%) of 2k m.p 143-146C°

ν_{max} (KBr Disc, cm^{-1}) : 1178.4-1253.6 (Ar-F), 1614.7 (N=N), 650-893(CH Aromatic).

δF (54.6 MHz ; $CDCl_3$) : - 15.1(1F, dd, j= 3.6 Hz, F-2), -75.8(1F, dd, j= 23.0Hz, F-3), -81.3(1F, dd, j= 27.6 Hz, F-5).

m/z (FAB) 335(M^+,20), 338 (M^++ 2,2), 336 (M^++ 1,9), 334(36), 320(450), 306(33), 292(80), 147 ($C_9H_{11}N_2^+$, 9), 119($C_9H_{11,}$100), 120(13), 77(16), 57(12), 43(67), 41(9), 39(3), 29(6).

Anal. Calcd for $C_{18}H_{20}N_3F_3$: Requires C, 64.47% ; H, 5.97% ; N, 12.53% ; F, 17.01%. Found C, 64.47% ; H, 5.94% ; N, 12.51% ; F, 17.08%

VI-2-6- Synthesis of 6- benzyl- 2,3,5- trifluoro -4- (2,4,6- trimethyl phenylazo pyridine 2l:

A solution (3.86 g, 56 mmol) of sodium nitrite was added dropwise into an ice-cooled stirred solution of 6 (13.32 g, 56 mmol) in 450 ml of AHF over a period of 5 minutes. The mixture was stirred at room temperature for 2 hours, then mesitylene (6.73 g, 56 mmol) was added, which caused an immediate deep- red colour to be formed. Stirring was continued at room temperature until all the AHF evaporated, then 1500 ml of water was added to the red precipitate. After being dried (oven, 70 °C), the residue was purified by flash column chromatography on silica gel using ethyl acetate and petroleum (1: 1) as eluent to give 2l m.p 136- 137C° (9.7 g, 26 mmol, 47%).

ν_{max} (KBr Disc, cm^{-1}) : 1180.4-1263.3 (Ar-F), 1598.9-1650 (N=N), 650-906.5(CH Aromatic).

δH (300 MHz ;CDCl3) : 2.34(3H, s, 4-C<u>H</u>3) , 2.48(6H, s, 2,6-C<u>H</u>3), 3.8(2H, s, PhCH2), 7.1(2H, s, Ha), 7.2- 7.5(5H, s, Ha).

δF (54.6 MHz ; $CDCl_3$) : - 10.8(1F, dd, j= 12.7 Hz, F-2), -71.8(1F, dd, j= 21.6 Hz, F-3), -80.5 (1F, dd, j= 29.6 Hz, F-5).

m/z (FAB) 369(M^+,25), 371 (M^++ 2,0.9), 370 (M^++ 1,6), 349(16), 325(4.5), 321(5) 292(69), 278(15), 235(16.5), 147 ($C_9H_{11}N_2^+$, 18), 119($C_9H_{11,}$100), 120(9), 91(40), 77(12), 41(6), 39(3).

Anal. Calcd for $C_{27}H_{22}N_3F_3$: Requires C, 68.29% ; H, 4.87% ; N, 11.38% ; F, 15.44%. Found C, 68.27% ; H, 4.89% ; N, 11.38% ; F, 15.44%

VI-2-7- Synthesis of 2,3,5- trifluoro - 4- (2,4,6- trimethyl phenylazo) -6- diphenylmethanylpyridine 2m:

Attempted of preparation of 14 from 7 (15.07 g, 48 mmol), sodium nitrite (3.32 g, 48mmol) and mesitylene (5.78 g, 48 mmol), by the same procedure to 13. The resulting solid was recrystallised from ethyl acetate to yield 2m m.p 131- 133C° (8.75 g, 19 mmol, 41%).

ν_{max} (KBr Disc, cm^{-1}) : 1191.9-1286.4 (Ar-F), 1587.3-1654.8 (N=N), 651.9-900(CH Aromatic).

δH (300 MHz ;CDCl3) : 2.2(3H, s, 4-CH3) , 2.46(6H, s, 2,6-CH3), 4.43(2H, s, PhCH2), 6.9(2H, s, Ha), 7.5- 7.75(10H, s, Ha).

m/z (FAB) 445(M^+,20), 447 (M^++ 2,0.59), 446 (M^++ 1,5), 425(13), 397(4), 368(45) 278(13), 167(40), 147 ($C_9H_{11}N_2^+$, 16), 119($C_9H_{11,}$100), 120(8), 77(14), 41(4), 39(4).

Anal. Calcd for $C_{27}H_{22}N_3F_3$: Requires C, 72.80% ; H, 4.94% ; N, 9.43% ; F, 12.8%

Found C, 72.81% ; H, 4.94% ; N, 9.43% ; F, 12.82%

VI-3-Synthesis of Alkyl (Aryl)phosphours fluorinated 2,4,6-trimethylphenylazopyridine:

VI-3-1- Synthesis of diphenyl((3,5,- difluoro- 6 methyl-4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide 4g:

Methyldiphenylphosphine oxide (4.7 g, 21.76 mmol) was dissoleved in anhydrous THF (130 ml) in a 500 ml round bottomed flash equipped with a stirrer bar and capped with a rubber septum connected, via a needle, to a position pressure of dry nitrogen. The solution was cooled in ice bath to 0 °C n- Butyl lithium (8.7 ml of 2.5 M solution in hexane, 21.76 ml) was added dropwise via a syring and the mixture was stirred for 15 min, then the mixture was cooled to – 78 °C. 8 (6.37 g, 21.76 mmol) in dry THF (20 ml) was added and warmed to room temperature over 2.5 hours by removing the cooling bath and insulating the flash with cotton. 50 ml of water was added and THF was removed under reduced pressure on rotavapor. The mixture wa extracted with CH2Cl2 (3x 50 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure on a rotavapor to give a deep foam which was subjected to column chromatography on silica gel (ethyl acetate as eluent) to give a crystalline solid (7.95 g, 16.3 mmol, 75%) of 4g m.p 169-171C°

ν_{max} (KBr Disc, cm^{-1}) : 1178.4-1218.9 (Ar-F), 1290.3 (P=O), 1558.4-1685.7 (N=N).

δH (300 MHz ;CDCl3) : 2.34(3H, s, 4-CH3) , 2.51(6H, s, 2,6-CH3), 3.8(2H,d, J=15Hz CH2PO), 4.05(3H, s, CH3), 6.9(2H, s, Ha), 7.05(2H, s, 3,5-CH3) 7.2- 7. 5(10H, m, Ha).

m/z (FAB) 488(M^+,30.9), 489 (M^++ 1,5.2), 472 $C_{27}H_{22}ON_3F_2P^+$, 5), 444(97), 273($C_{15}H_{13}N_3F_2$+, 22.5), 147(36.7), 119(100), 117(C_9H_9+, 2.5), 104(C_8H_8+, 1.6), 103(C_8H_7+, 1.5), 91(C_7H_7+, 39.3), 79(6), 41(14.5).

Anal. Calcd for $C_{28}H_{26}ON_3F_2P$: Requires C, 68.85% ; H, 5.32% ; N, 8.60% ; F, 7.78% ; P, 6.14%. Found C, 68.85% ; H, 5.33% ; N, 8.60% ; F, 7.77% ; P, 6.15%.

VI-3-2- Synthesis of diphenyl((3,5,- difluoro- 6 ethyl-4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide 4h:

4h was preparted by procedure is identical to the previous procedure prepartion of 4g. The following amounts were taken; Methyldiphenylphosphine oxide (4.7 g, 21.76 mmol) a solution of (8.7 ml, 21.76 mmol) of 2.5 M Butyl lithium in hexane and 2h (6.68 g, 21.76 mmol). The usual wash up provided only 4h m.p 172- 174C° (9.93 g, 19.78 mmol, 91%). The product has the following spectroscopic properties:

ν_{max} (KBr Disc, cm^{-1}) : 1174.6-1251.7 (Ar-F), 1049.2 (P=O), 1404.1-1477.4 (N=N).

δH (300 MHz ;CDCl3) : 0.96(3H,t, J= 7.1Hz CH2CH3), 2.31(3H, s, 4-CH3) , 2.47(1H,dq, J= 7.1,11.2Hz CH2CH3),2.53(6H, s, 2,6-CH3), 2.58(1H,dq, J= 7.1,11.2Hz CH2CH3), 4.02(2H,d, J=15Hz CH2PO), 7.05(2H, s, 3,5-H) 7.2- 7. 5(10H, m, Ha).

m/z (FAB) 502(M^+,33.8), 505 (M^++ 1,3.3), 472 ($C_{27}H_{22}ON_3F_2P^+$, 5), 444(97.1), 287($C_{16}H_{15}N_3F_2$+, 29.5), 147(35.4), 119(100), 117(C_9H_9+, 2.1), 104(C_8H_8+, 1.6), 91(C_7H_7+, 31.6), 79(4.2), 41(26.7), 30(6.4), 29(1.9).

Anal. Calcd for $C_{29}H_{28}ON_3F_2P$: Requires C, 69.32% ; H, 5.57% ; N, 8.36% ; F, 7.56% ; P, 5.97%. Found C, 69.34% ; H, 5.57% ; N, 8.35% ; F, 7.55% ; P, 5.98%.

VI-3-3-Synthesis of diphenyl((3,5,- difluoro -4 -(mesityl diazenyl- 6 propyl) pyridin -2- yl) methyl) phosphine oxide 4i:

4i was prepared from Methyldiphenylphosphine oxide (4.7 g, 21.76 mmol) a solution of (8.7 ml, 21.76 mmol) of 2.5 M Butyl lithium in hexane and 2i (7.0 g, 21.76 mmol) in a smilar way to 4g.The product 4i (9.78 g, 19.0 mmol, 87%) was obtained as solid m.p 184-186C° after recrystallisation from ethyl acetate

ν_{max} (KBr Disc, cm^{-1}) : 1174.6-1274.9 (Ar-F), 1049.2 (P=O), 1404.1-1477.4 (N=N).

δH (300 MHz ;CDCl3) : 0.78(3H,t, J= 7.1Hz CH2CH3), 2.33(3H, s, 4-CH3) , 2.39(1H,ddd, J= 6.6,7.8,11.2Hz CH2CH2), 2.51(1H,ddd, J= 6.6,7.8,11.2Hz CH2CH2),2.56(6H, s, 2,6-CH3), 3.8(2H,d, J=15Hz CH2PO), 7.1(2H, s, 3,5-H) 7.7-7. 9(10H, m, Ha).

m/z (FAB) 516(M^+,29.3), 517 (M^++ 1,4.1), 500(6.3), 486(16.7), 472 ($C_{27}H_{22}ON_3F_2P^+$, 5.2), 301($C_{17}H_{17}N_3F_2$+, 27.5),444(86), 147(45.2), 119(100), 117(1.2), 104(3), 91(51.4), 79(6), 44(36.7), 41(26.7), 30(17), 29(6.3).

Anal. Calcd for $C_{30}H_{30}ON_3F_2P$: Requires C, 69.76% ; H, 5.81% ; N, 8.13% ; F, 7.36% ; P, 5.81%. Found C, 69.77% ; H, 5.81% ; N, 8.15% ; F, 7.38% ; P, 5.82%.

VI-3-4- Synthesis of diphenyl((3,5,- difluoro -4-(mesit yl diazenyl- 6 isopropyl) pyridin -2- yl) methyl) phosphine oxide 4j:

4j was prepared from Methyldiphenylphosphine oxide (4.7 g, 21.76 mmol) a solution of (8.7 ml, 21.76 mmol) of 2.5 M Butyl lithium in hexane and 2j (7.0 g, 21.76 mmol), by the same procedure described earlier. 4j (8.55 g, 16.56 mmol, 76%)was obtained as a solid m.p 196-198C° after recrystallisation from ethyl acetate. The product has the following spectroscopic properties:

Anal. Calcd for $C_{30}H_{30}ON_3F_2P$: Requires C, 69.76% ; H, 5.81% ; N, 8.13% ; F, 7.36% ; P, 5.81%. Found C, 69.77% ; H, 5.81% ; N, 8.15% ; F, 7.38% ; P, 5.82%.

VI-3-5- Synthesis of diphenyl((- 6 butyl- 3,5,- difluoro -4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide 4k:

2k (7.29 g, 21.76 mmol) was transformed to 4k in similar way to 4g. 4k (7.49 g, 14.13 mmol, 65%) was otained as solid m.p 191-192C°. The product has the following spectroscopic properties:

ν_{max} (KBr Disc, cm^{-1}) : 1174.6-1274.9 (Ar-F), 1049.2 (P=O), 1404.1-1477.4 (N=N).

δc (75 MHz, CDCl3) : 147.5(Ar-F), 146.5(Ar-F), 145.7(CAr(Ph)2), 143.7.4(CAr), 137.4(CAr), 136.1(CAr), 133.0(CHAr(Ph)2), 132.9(CAr), 132.3(CHAr(Ph)2), 131.6(CAr), 131.4(CHAr(Ph)2), 130.9(CHAr(Ph)2), 129.4 (CHAr(Ph)2), 125.7(CHAr), 33.3(CH2PO), 31.2(CH2CH2), 30.8(CH2CH2), 26.7(CH2-Ar), 18.3(CH3), 17.2(CH3), 15.1(CH3).

m/z (FAB) 530(M^+,10.7), 531 (M^++ 1,1.9), 514(8.6),500(14.4), 486(47.5), 472 ($C_{27}H_{22}ON_3F_2P^+$, 5.2), 444(72), 315($C_{18}H_{19}N_3F_2$+, 59.4), 147(44), 119(100), 117(1.4), 104(4.3), 91(51.4), 79(6), 58(14.7), 44(31.5), 41(23.4), 30(15), 29(8.6).

Anal. Calcd for $C_{31}H_{32}ON_3F_2P$: Requires C, 70.18% ; H, 6.03% ; N, 7.92% ; F, 7.16% ; P, 5.66%. Found C, 70.18% ; H, 6.04% ; N, 7.94% ; F, 7.16% ; P, 5.65%.

VI-3-6- Synthesis of diphenyl((- 6 benzyl- 3,5,- difluoro -4-(mesityl diazenyl) pyridin -2- yl) methyl) phosphine oxide 4l:

Methyldiphenylphosphine oxide (5.0 g, 23.0 mmol) in dry THF (140 ml) was placed in a 500 ml round bottomed flash equipped with a stirrer bar, the remaining neck was sealed with a septum and a nitrogen line attached, and the solution was cooled to 0 °C in an ice bath. n- Buty lithium (9.2 ml, 23 mmol) 2.5 M in hexane was added and the mixture stirred at 0 °C for 21 min, then the mixture was cooled to – 78 °C 2l (8.48 g, 23mmol) in dry THF (25 ml) was added and the mixture warmed to room temperature over 1.5 hours by removing the cooling bath and insulating the fkash with cotton. In the step two water (75 ml) was added and the THF removed under reduced pressure on a rotavapor. The residue was extracted with dichloromethane. The combined organic were dried over (magnesium sulfate), filtered, and the solvent removed under reduced pressure on rotavapor to yield a deep which was separated by column chromatography on silica gel (ethyl acetate/ dichloromethane as eluent) to give 4l m.p 200-202C° (10.10 g, 17.9 mmol, 78%). The product was identified by spectroscopic properties

ν_{max} (KBr Disc, cm^{-1}) : 1118.6-1299.9 (Ar-F), 1182.3 (P=O), 1436.9 (N=N), 600-908.4(CH Aromatic).

δc (75 MHz, CDCl3) : 145.6(Ar-F), 145.6(Ar-F),143.7(CAr(Ph)2), 137.7(CAr),136.1(CAr), 135.4(CAr), 134.5(CHAr(Ph)2), 133.4(CAr), 132.6(CAr),132.1(CHAr(Ph)2), 132.O(CHAr(Ph)2), 131.9(CHAr(Ph)2), 131.6(CAr), 131.5(CHAr(Ph)2), 131.3 (CAr), 130.8(CHAr), 130.2(CHAr(Ph)2), 129.4(CHAr), 124.8(CHAr), 124.4(CHAr),35.4(CH2PO), 28.3(CH2-Ar), 17.2(CH3), 17.2(CH3), 17.2(CH3).

m/z (FAB) 564(M^+,11.8), 565 (M^++ 1,1.6), 486(86.1), 472 ($C_{27}H_{22}ON_3F_2P^+$, 5.4), 444(78.7), 119(100), 117(1.2), 92(48.6), 91(1.6), 79(6.5).

Anal. Calcd for $C_{34}H_{30}ON_3F_2P$: Requires C, 72.34% ; H, 5.31% ; N, 7.44% ; F, 6.73% ; P, 5.31% . Found C, 72.33% ; H, 5.31% ; N, 7.45% ; F, 6.75% ; P, 5.31%.

VI-3-7-Synthesis of diphenyl((3,5,- difluoro -4-(mesit yl diazenyl-6-diphenylmethanyl) pyridin -2- yl) methyl) phosphine oxide 4m:

Into a dry, 500 ml flash equipped with a magnetic stirring bar was introduced Methyldiphenylphosphine oxide (3.9 g, 17.94 mmol) in dry THF (110 ml). the flash was sealed with a rubber septum and swept with nitrogen. A thermometer was inserted through the rubber septum, and the contents of the flash were cooled to 0 °C. n- Buty lithium (7.18 ml, 17.94 mmol) 2.5 M in hexane was introduced via a syringe for 21 min, then the mixture was cooled to – 78 °C. The solid 2m (7.98 g, 17.94 mmol) was dissolved in THF (15 ml) was added to the mixture. The next step is in a similar manner as step two of preparation the 4l to afforded 4m m.p 197-199C° (7.68 g, 12 mmol, 67%)

ν_{max} (KBr Disc, cm^{-1}) : 1118.6-1276.8 (Ar-F), 1172.6 (P=O), 1436.9 (N=N) 600-900(CH Aromatic).

δH (300 MHz ;CDCl3) : 2.24(3H, s, 4-CH3) , 2.32(6H, s,2,6-CH3), 4.1(2H,d, J=15Hz CH2PO), 6.6(2H, s, 3,5-H), 7.1- 7. 8(10H, m, Ha), 8.2- 8.85(10H, m, Ha).

Anal. Calcd for $C_{40}H_{34}ON_3F_2P$: Requires C, 75.00% ; H, 5.31% ; N, 6.56% ; F, 5.93% ; P, 4.68%. Found C, 75.00% ; H, 5.32% ; N, 6.54% ; F, 5.94% ; P, 4.68%.

VI-4- Synthesis of the diazepines:

VI-4-1 Synthesis of diazepine 5g:

4g (6.96 g, 14.28 mmol) was dissolved in mesitylene (60 ml) in a round bottomed flask (250 ml) equipped with a reflux condenser. The solution was refluxed and the proqress of thr reaction was followed by thin- layer chromatography. Eventually the solution turned brown. After 9 hours refluxing, t.l.c analysis showed that most of the red starting material had been converted yellow product, so the solvent mesitylene was removed at oil pump pressure using a rotary evaporator The dark brown residue was subjected to dry column flash chromatography, the polarity of eluent being increased gradually. A red band came first off the column, in light petroleum (40- 60 °C) dichloro;ethqne mixture, a yellow band was removed from the column; evaporation of the solvent gave an isomers orange solid 5g (3.8 g, 8.11 mmol, 57%), which was separted by HPLC [Chiralpak AD-H, length 250 mm x i.d. 20 mm; flow

rate 6 ml/min; detection: UV (254 nm)] using n- hexane – isoPrOh (15:1) to give $5g_1$ retention times and $5g_2$

VI-4-1-1- Spectral Data for $5g_1$

δH (300 MHz ;CDCl3) : 2.20(3H, s, 7-CH3) , 2.38(3H, s, CH3), 2.46(3H, s, 9-CH3), 3.33(2H, s, 11-CH2), 3.93(2H, s, 3-POCH2), 6.89(1H, s, 8-H), 7.5(1H, s, 10-H), 7.75(10H, s, Ha).

δF (54.6 MHz ; $CDCl_3$) : - 84.3(1F, d, F-4)

m/z (FAB) 468(M^+,100), 470 (M^++ 2,2.4), 469 (M^++ 1,19.5), 467(M^+-H, 27.2), 439(11.5) ,432(79.5), 426(11.2), 425(37.2), 391(40), 268(69).

Anal. Calcd for $C_{28}H_{25}ON_3FP$: Requires C, 71.79% ; H, 5.34% ; N, 8.97% ; F, 4.05%; P, 6.41%.Found C, 71.79% ; H, 5.33% ; N, 8.98% ; F, 4.07%; P, 6.40%.

VI-4-1-2 Spectral Data for 5g2

Anal. Calcd for $C_{28}H_{25}ON_3FP$: Requires C, 71.79% ; H, 5.34% ; N, 8.97% ; F, 4.05%; P, 6.41%. Found C, 71.79% ; H, 5.33% ; N, 8.98% ; F, 4.07%; P, 6.40%.

VI-4-2- Synthesis of diazepine 5h:

5h (4.05 g, 8.4 mmol, 77%) was synthesized procedures as described above to give $5h_1$ and $5h_2$ after separted by HPLC

VI-4-2-1 Spectral Data for $5h_1$

δH (300 MHz ;CDCl3) : 0.96(3H,tj= 7.1Hz CH2-CH3), 2.1(3H, s, 7-CH3) , 2.43(1H,CH2), 2.45(3H, s, 9-CH3), 2.54(1H,CH2), 3.30(2H, s, 11-CH2), 3.94(2H, s, 3-POCH2), 6.9(1H, s, 8-H), 7.7(1H, s, 10-H), 7.9(10H, s, Ha).

δF (54.6 MHz ; $CDCl_3$) : - 79.6(1F, d, F-4)

m/z (FAB) 482(M^+,100), 484 (M^++ 2,2.1), 483 (M^++ 1,19.9), 440(13.7), 439(15.3) , 411(3.2),377(60), 363(19.4), 240(80).

Anal. Calcd for $C_{29}H_{27}ON_3FP$: Requires C, 72.19% ; H, 5.60% ; N, 8.71% ; F, 3.94%; P, 6.22%.Found C, 72.19% ; H, 5.60% ; N, 8.70% ; F, 3.94%; P, 6.24% .

VI-4-2-1 Spectral Data for $5h_2$

Anal. Calcd for $C_{29}H_{27}ON_3FP$: Requires C, 72.19% ; H, 5.60% ; N, 8.71% ; F, 3.94%; P, 6.22%. Found C, 72.19% ; H, 5.60% ; N, 8.70% ; F, 3.94%; P, 6.24%.

VI-4-3- Synthesis of diazepine 5i:

5i was prepared in a similar manner as 5g .The following amounts were taken; (5.2 g, 10.08 mmol) of 4i and mesitylene (52 ml) affording an isomers solid 5i (3.99 g, 8.04 mmol, 80%) . The orange solid which resulted was separted by HPLC [Chiralpak AD-H, length 250 mm x i.d. 20 mm; flow rate 6 ml/min; detection: UV (254 nm)] using n-hexane – isoPrOh (15:1) to give $5i_1$ retention times and $5i_2$

VI-4-3-1- Spectral Data for $5i_1$

δH (300 MHz ;CDCl3) : δH (300 MHz ;CDCl3) : 0.79(3H, tlJ=7.3Hz, CH2-C<u>H</u>3) , 2.2(3H, s, 7-C<u>H</u>3), 2.32(1H, ddd, J=6.6, 7.8, 11.2Hz C<u>H</u>2-CH2), 2.43(3H, s, 9-C<u>H</u>3)2.47(1H, ddd, J=6.6, 7.8, 11.2Hz C<u>H</u>2-CH2), 3.32(2H, s, 11-CH2), 3.90(2H, s, 3-POCH2), 6.85(1H, s, 8-H), 7.1(1H, s, 10-H), 7.4(10H, s, Ha).

m/z (FAB) 496(M^+,100), 498 (M^++ 2,12.3), 497 (M^++ 1,16.8), 495(M^+- H, 2.3), 481(13.5) , 467(40),454(23.7), 419(30.5), 296(72.3).

Anal. Calcd for $C_{30}H_{29}ON_3FP$: Requires C, 72.58% ; H, 5.84% ; N, 8.46% ; F, 3.83%; P, 6.04%. Found C, 72.58% ; H, 5.84% ; N, 8.47% ; F, 3.83%; P, 6.03%.

VI-4-3-2-Spectral Data for $5i_2$:

Anal. Calcd for $C_{30}H_{29}ON_3FP$: Requires C, 72.58% ; H, 5.84% ; N, 8.46% ; F, 3.83%; P, 6.04%. Found C, 72.58% ; H, 5.84% ; N, 8.47% ; F, 3.83%; P, 6.03%

VI-4-4- Synthesis of diazepine 5j:

5j(3.94 g, 7.94 mmol, 79%) was synthesized procedures as described above to give $5j_1$ and $5j_2$ after separted by HPLC

VI-4-4-1- Spectral Data for $5j_1$:

δH (300 MHz ;CDCl3) : δH (300 MHz ;CDCl3) : 0.84(3H, tlJ=6.1Hz, CH-C<u>H</u>3) , 0.94(3H, d, J=6.1Hz CH-C<u>H</u>3),2.39(3H, s, 7-C<u>H</u>3), 2.51(3H, s, 9-C<u>H</u>3), 3.34(2H, s, 11-CH2), 3.89(2H, s, 3-POCH2), 6.60(1H, s, 8-H),7.1(1H, s, 10-H), 7.75(10H, s, Ha).

m/z (FAB) 496(M^+,100), 498 (M^++ 2,12.3), 497 (M^++ 1,16.8), 495(M^+- H, 2.3), 481(13.5) , 467(40),454(23.7), 419(30.5), 296(72.3).

Anal. Calcd for $C_{30}H_{29}ON_3FP$: Requires C, 72.58% ; H, 5.84% ; N, 8.46% ; F, 3.83%; P, 6.04%. Found C, 72.58% ; H, 5.84% ; N, 8.47% ; F, 3.83%; P, 6.03%

VI-4-4-2- Spectral Data for $5j_2$

Anal. Calcd for $C_{30}H_{29}ON_3FP$: Requires C, 72.58% ; H, 5.84% ; N, 8.46% ; F, 3.83%; P, 6.04%. Found C, 72.58% ; H, 5.84% ; N, 8.47% ; F, 3.83%; P, 6.03%.

VI-4-5- Synthesis of diazepine 5k:

5k was prepared from 5.34g (10.08 mmol) of 19 and 52 ml of mesitylene, by the same procedure described earlier. The crude material was purified by silica gel column chromatography using light- petroleum, dichloromethane (1: 1) to give the isomers $5k_1$ and $5k_2$ these were separated by HPLC

The products have the following spectroscopic properties

VI-4-5-1-Spectral Data for $5k_1$

δH (300 MHz ;CDCl3) : δH (300 MHz ;CDCl3) : 0.78(3H, tlJ=7.3Hz, CH2-C<u>H</u>3) ,2.24(3H, s, 7-C<u>H</u>3), 2.59(3H, s, 9-C<u>H</u>3), 3.38(2H, s, 11-CH2), 3.91(2H, s, 3-POCH2), 6.87(1H, s, 8-H),7.1(1H, s, 10-H), 7.8(10H, s, Ha).

m/z (FAB) 510(M^+,100), 512 (M^++ 2,2.7), 511 (M^++ 1,23.4), 509(3.3), 495(20.1) , 481(12),468(8.2), 467(5.2), 447(36.7), 433(40), 328(20.4), 310(76.4).

Anal. Calcd for $C_{31}H_{31}ON_3FP$: Requires C, 72.94% ; H, 6.07% ; N, 8.23% ; F, 3.72%; P, 5.88%. Found C, 72.94% ; H, 6.07% ; N, 8.23% ; F, 3.72%; P, 5.89%.

VI-4-5-2-Spectral Data for $5k_2$

Anal. Calcd for $C_{31}H_{31}ON_3FP$: Requires C, 72.94% ; H, 6.07% ; N, 8.23% ; F, 3.72%; P, 5.88%. Found C, 72.94% ; H, 6.07% ; N, 8.23% ; F, 3.72%; P, 5.89%.

VI-4-6- Synthesis of diazepine 5l:

In a typical experiment, 4l (9.10 g, 16.13 mmol) was refluxed in mesitylene (60 ml) for 6hours. Removal of mesitylene by distillation (rotary evaporator, 80 °C, 1 mmHg) gave an isomers orange solid 5l (3.8 g, 8.11 mmol, 57%), after purificatin by silica gel column chromatography , which was separted by HPLC [Chiralpak AD-H, length 250 mm x i.d. 20 mm; flow rate 6 ml/min; detection: UV (254 nm)] using n- hexane – isoPrOh (15:1) to give $5l_1$ retention times and $5l_2$

VI-4-6-1-Spectral Data for $5l_1$

2.26(3H,s, 7-C<u>H</u>3), 2.47(3H, s, 9-C<u>H</u>3), 3.32(2H, s, 11-CH2), 3.95(2H, s, 3-POCH2) 7.39(1H, s, 8-H), 5.24(2H,s,CH2), 7.4(1H,s,10-H), 7.65(5HAromatic), 8.15(10H).

m/z (FAB) 544(M^+,100), 546 (M^++ 2,2.7), 545 (M^++ 1,69), 543(4.3), 515(79.9) 502(13.4) , 501(15.8),467(20), 453(23), 439(21), 344(77).

Anal. Calcd for $C_{34}H_{29}ON_3FP$: Requires C, 75.00% ; H, 5.33% ; N, 7.72% ; F, 3.49%; P, 5.51%. Found C, 75.00% ; H, 5.33% ; N, 7.72% ; F, 3.49%; P, 5.51% .

VI-4-6-2- Spectral Data for $5l_2$

Anal. Calcd for $C_{34}H_{29}ON_3FP$: Requires C, 75.00% ; H, 5.33% ; N, 7.72% ; F, 3.49%; P, 5.51%. Found C, 75.00% ; H, 5.33% ; N, 7.72% ; F, 3.49%; P, 5.51%

VI-4-7- Synthesis of diazepine 5m:

4m (6.4 g, 10 mmol) was dissolved in mesitylene (60ml) in a round- bottomed flask equipped with a reflux condenser. The solution was refluxed and the progress of the reaction was followed by thin- layer chromatography.

After 6 hours refluxing, t.l.c analysis showed that most of the red starting material had been converted yellow product, so the solvent mesitylene was removed at oil pump pressure using a rotary evaporator The dark brown residue was subjected to dry column flash chromatography, the polarity of eluent being increased gradually. A red band came first off the column, in light petroleum (40- 60 °C) dichloro;ethqne mixture, a yellow band was removed from the column; evaporation of the solvent gave an isomers orange solid 5m (4.83 g, 7.79 mmol, 78%), which was separted by HPLC [Chiralpak AD-H, length 250 mm x i.d. 20 mm; flow rate 6 ml/min; detection: UV (254 nm)] using n- hexane – isoPrOh (15:1) to give $5m_1$ retention times and $5m_2$

VI-4-7-1- Spectral Data for $5m_1$

2.3(3H,s,7-CH3), 2,51(3H,s,9-CH3), 3.34(2H, s, 11-CH2), 3.7(2H, s, 3-POCH2) 6.84(1H, s, 8-H), 5.24(2H,s,CH2), 7.17(1H,s,10-H), 7.9(10H Aromatic), 8.21(10H Aromatic).

δF (54.6 MHz ; $CDCl_3$) : - 73.6(1F, d, F-4)

m/z (FAB) 620(M^+,100), 622 (M^++ 2,11.4), 621 (M^++ 1,2.3), 619(27), 591(10.7) , 578(5.5),576(11.4), 543(80), 453(12.6), 420(76).

Anal. Calcd for $C_{40}H_{33}ON_3FP$: Requires C, 77.41% ; H, 5.32% ; N, 6.77% ; F, 3.06%; P, 4.83%. Found: C, 77.42% ; H, 5.31% ; N, 6.77% ; F, 3.07%; P, 4.84%

VI-4-7-2- Spectral Data for $5m_2$

m/z (FAB) 620(M^+,100), 622 (M^++ 2,11.4), 621 (M^++ 1,2.3), 619(27), 591(10.7) , 578(5.5),576(11.4), 543(80), 453(12.6), 420(76).

Anal. Calcd for $C_{40}H_{33}ON_3FP$: Requires C, 77.41% ; H, 5.32% ; N, 6.77% ; F, 3.06%; P, 4.83%. Found: C, 77.42% ; H, 5.31% ; N, 6.77% ; F, 3.07%; P, 4.84%.

Conclusion

Conclusion

In conclusion the preparation of phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines are easily achieved by the condensation of 2, 4, 6-trimethylphenylazopyridines with methyldiphenylphosphineoxide. The success and yields of the reaction are affected by the following factors:the stability and nucleophilicity of the group substitution, then we have developed a new method for the synthesis of phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines. The identity of the isomers was then confirmed with the established HPLC method, the resolution of their structural isomers was superior. The methods have potential applications in the determination of this isomer. Furthermore, since ChiraSphe column is characterized by its high stability and high loading capacity, this column can be used for semi-preparative separation of phosphorus fluorinated azo compounds isomers and therefore this method could be useful for further pharmacological investigation of the individual isomer of phosphorus fluorinated azo compounds.

As a future work we recommend;

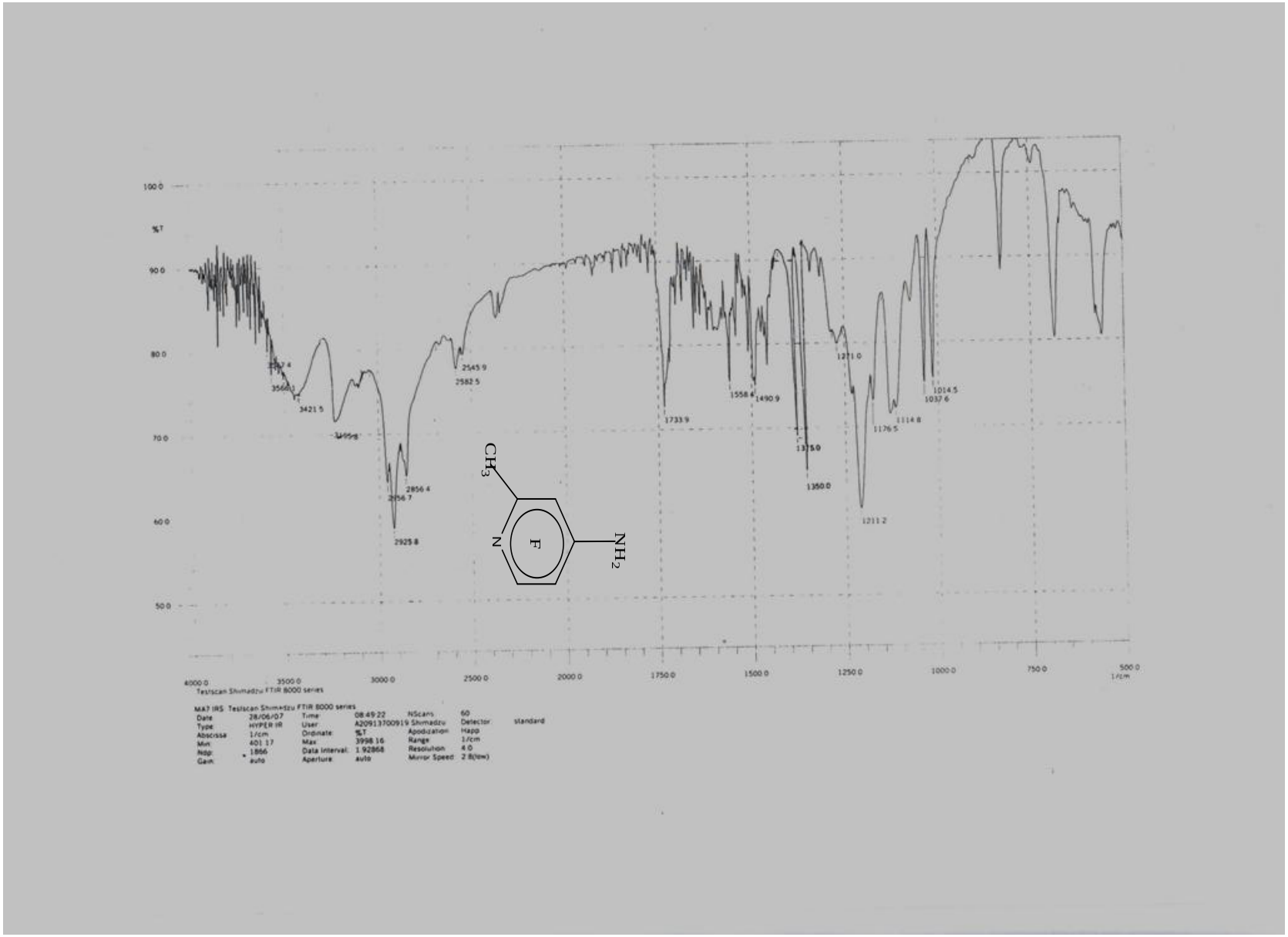
- Preparation of new derivatives of compounds by adding new groups.
- The test biological efficacy of the same compounds prepared in this study with other types of bacteria and virus in different concentrations and compared with antibiotics.
- Study the antioxidant efficacy of these compounds.

Appendices

Part II

Appendix IV

Infrared spectra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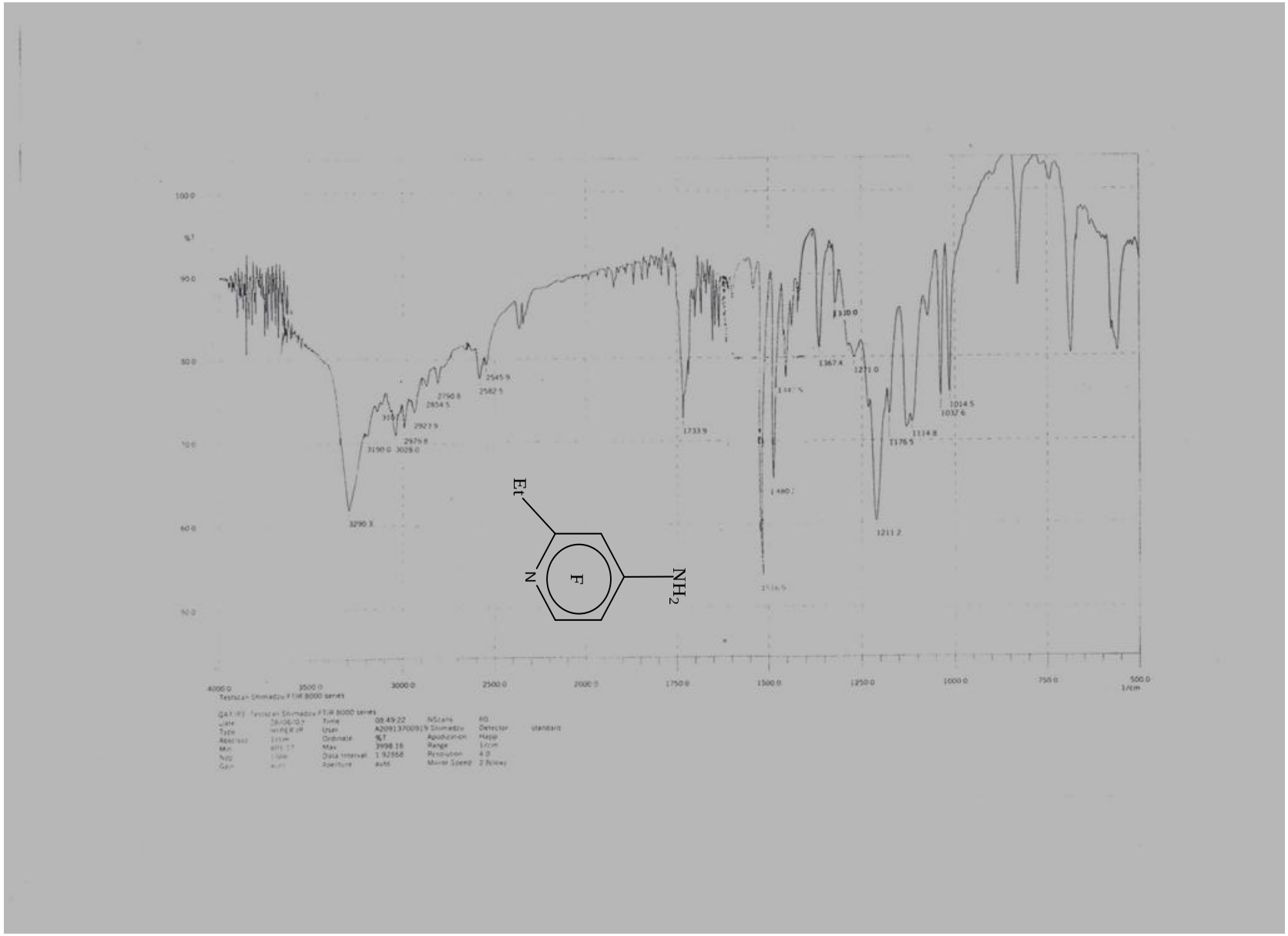
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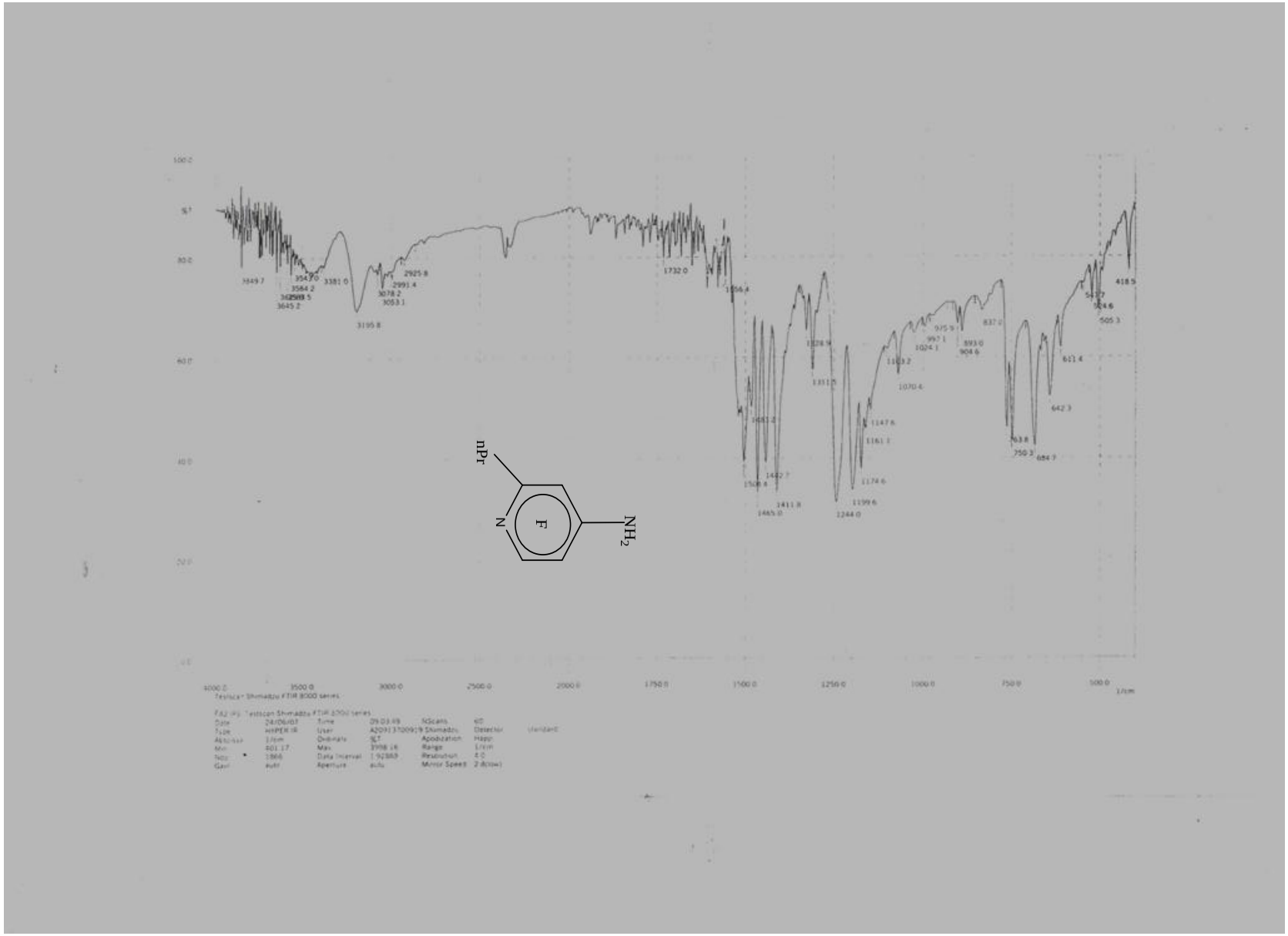
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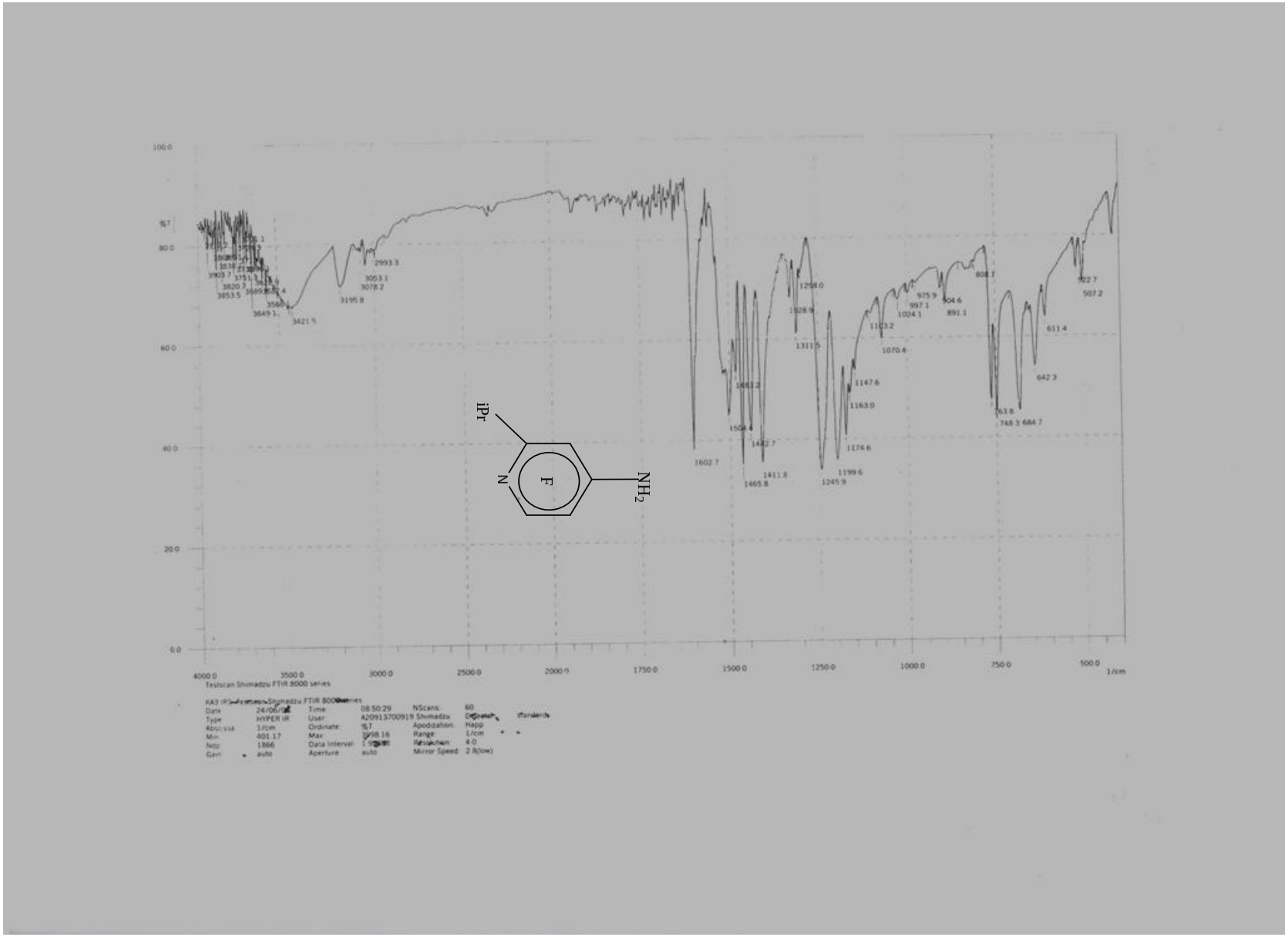
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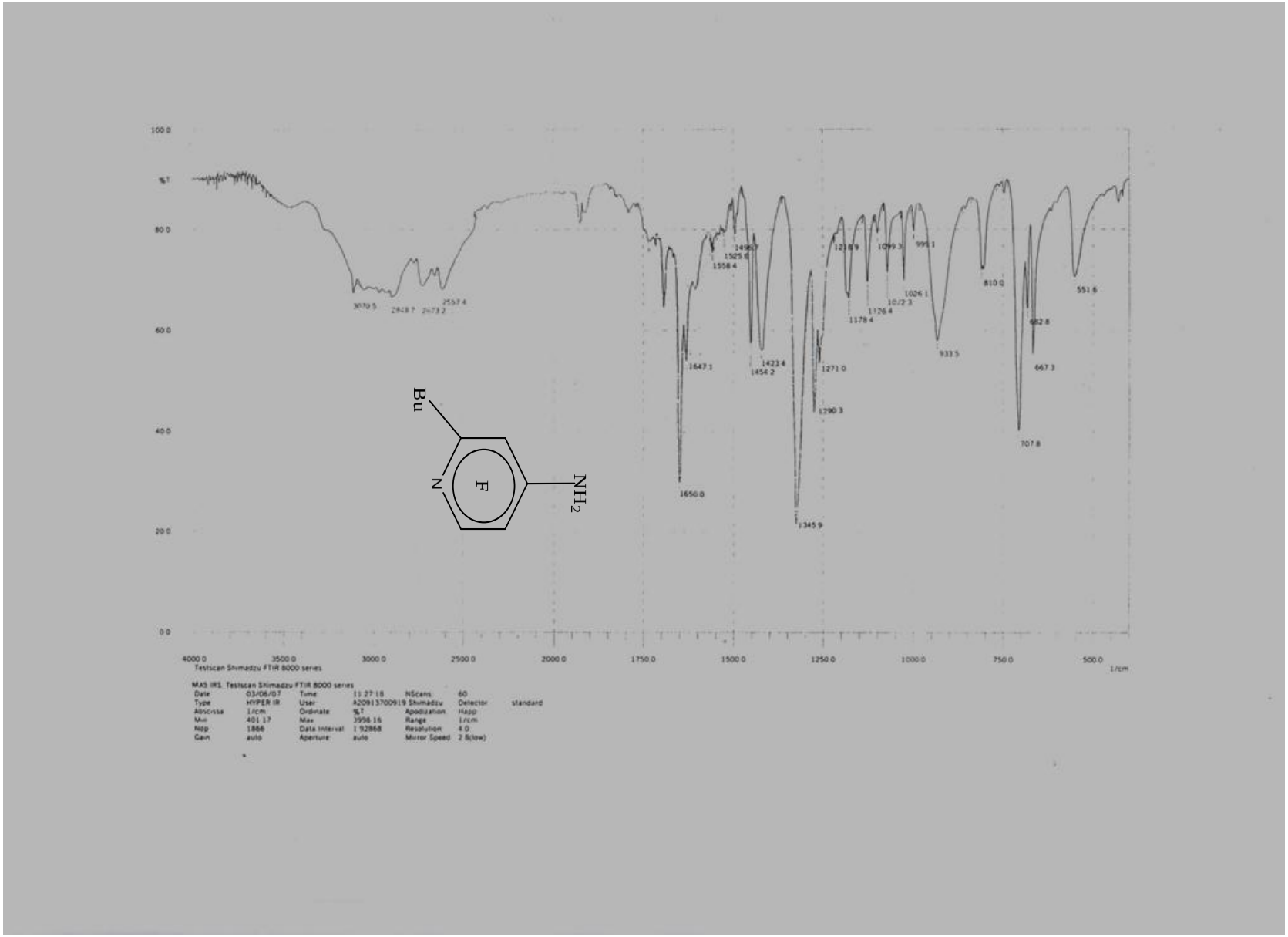
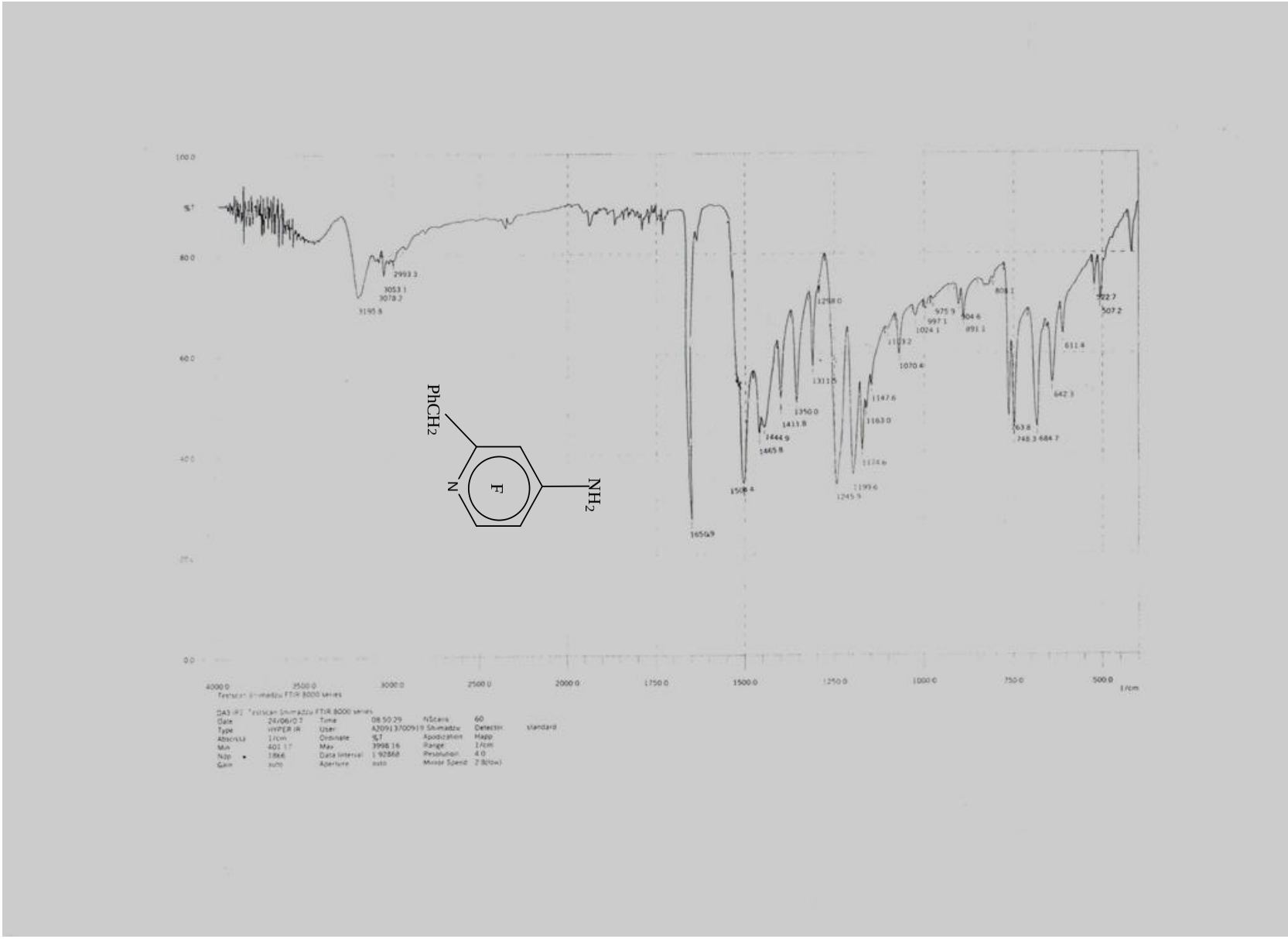
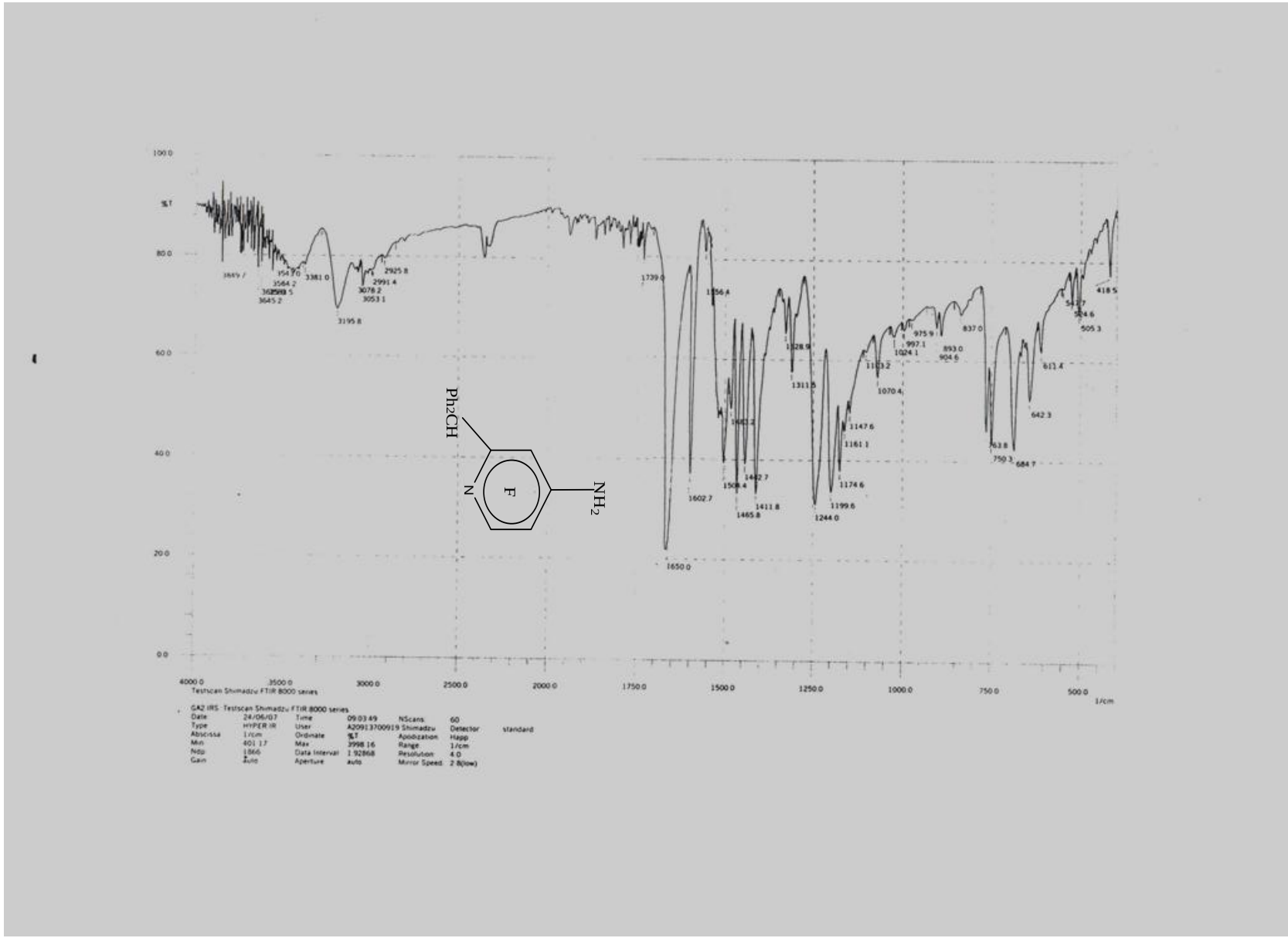
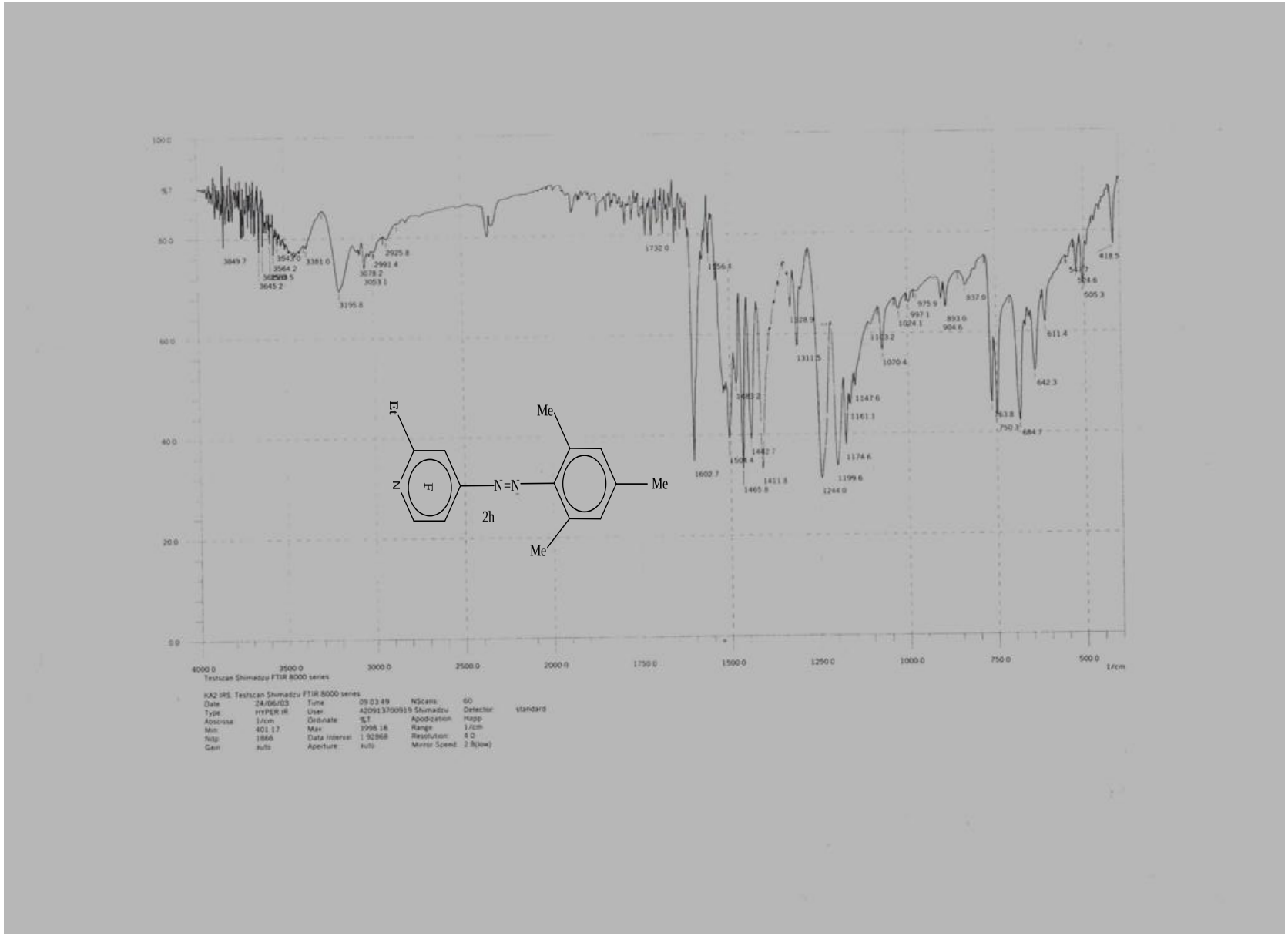
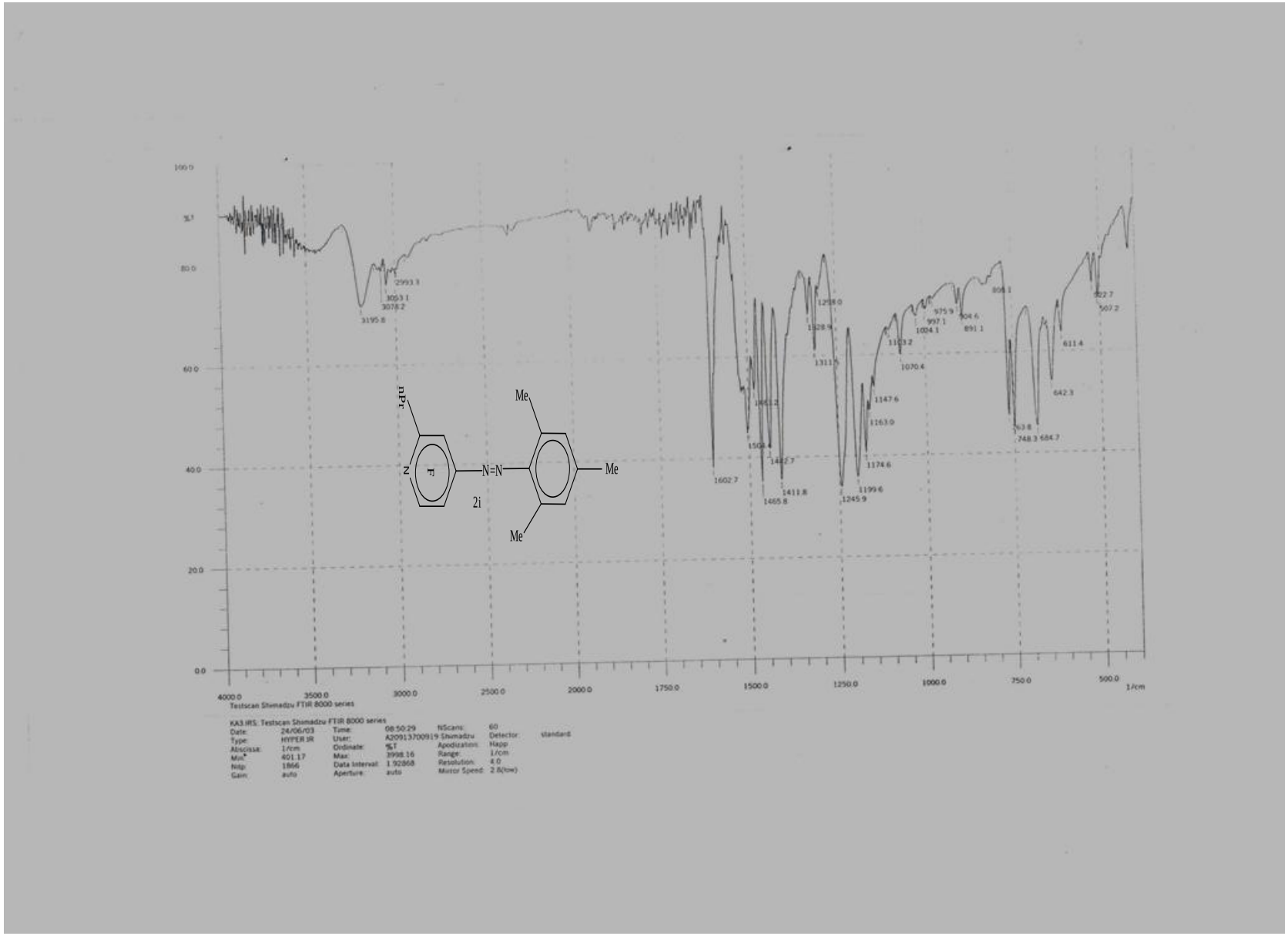
Data Interval
Aperture auto
NScans 60
Shimadzu
Apodization Happ
Range 1/cm
Mirror Speed 2.8(low)

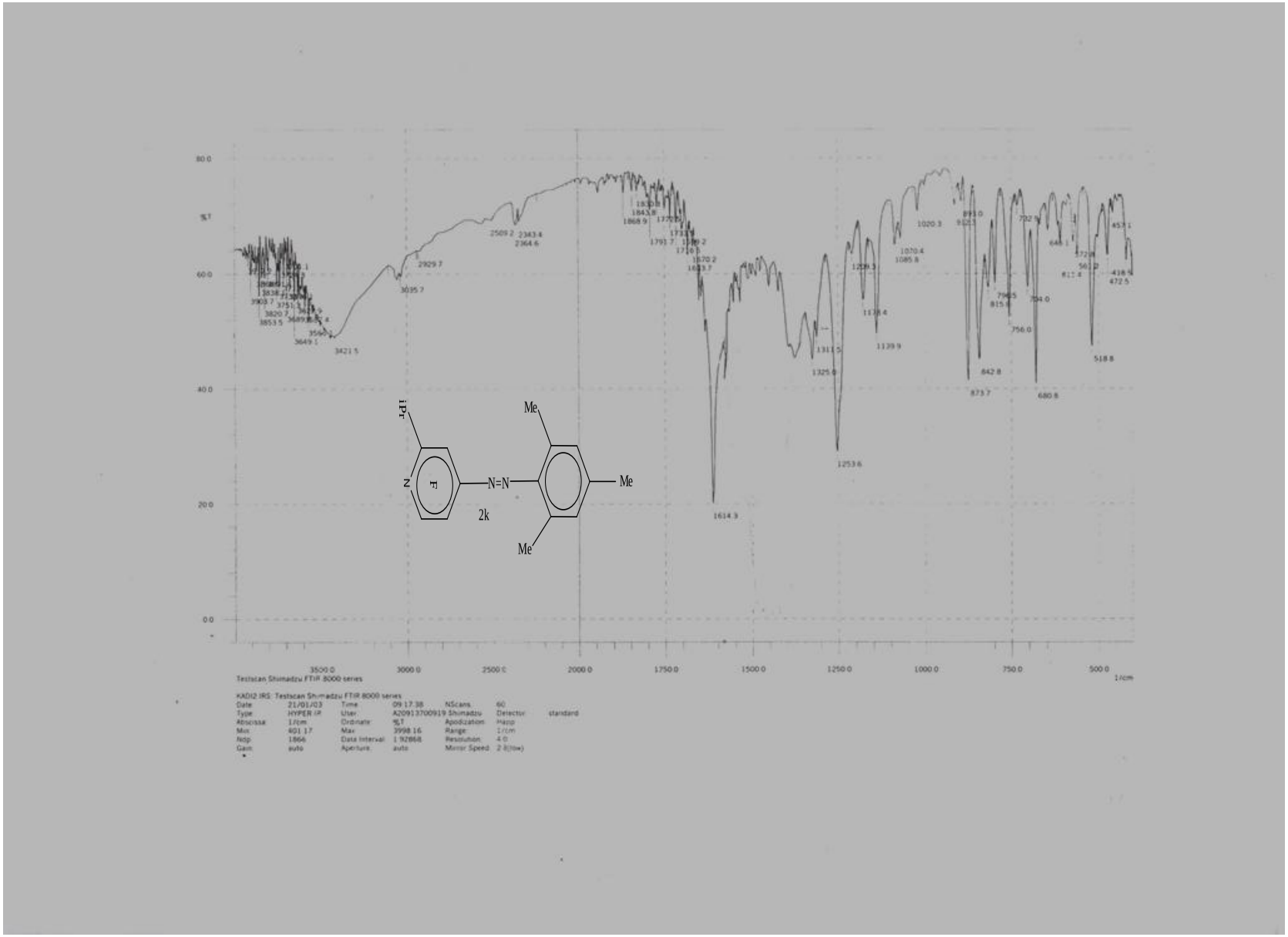

100.0
%T
80.0
60.0
40.0
20.0
0.0
3670.5
2918.7
2673.2
2557.4
1647.1
1650.0
1558.4
1525.6
1454.2
1423.4
1345.9
1271.0
1290.3
1218.9
1178.4
1126.4
1072.3
1026.1
999.1
933.5
810.0
707.8
682.8
667.3
551.6
Bu
N
F
NH2
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Testscan Shimadzu FTIR 8000 series
MAS IRS. Testscan Shimadzu FTIR 8000 series
Date 03/06/07 Time 11:27:18 NScans 60
Type HYPER IR User A20913700919 Shimadzu Detector standard
Abscissa 1/cm Ordinate %T Apodization Happ
Min 401.17 Max 3998.16 Range 1/cm
Npp 1866 Data Interval 1.92868 Resolution 4.0
Gain auto Aperture auto Mirror Speed 2.8(low)

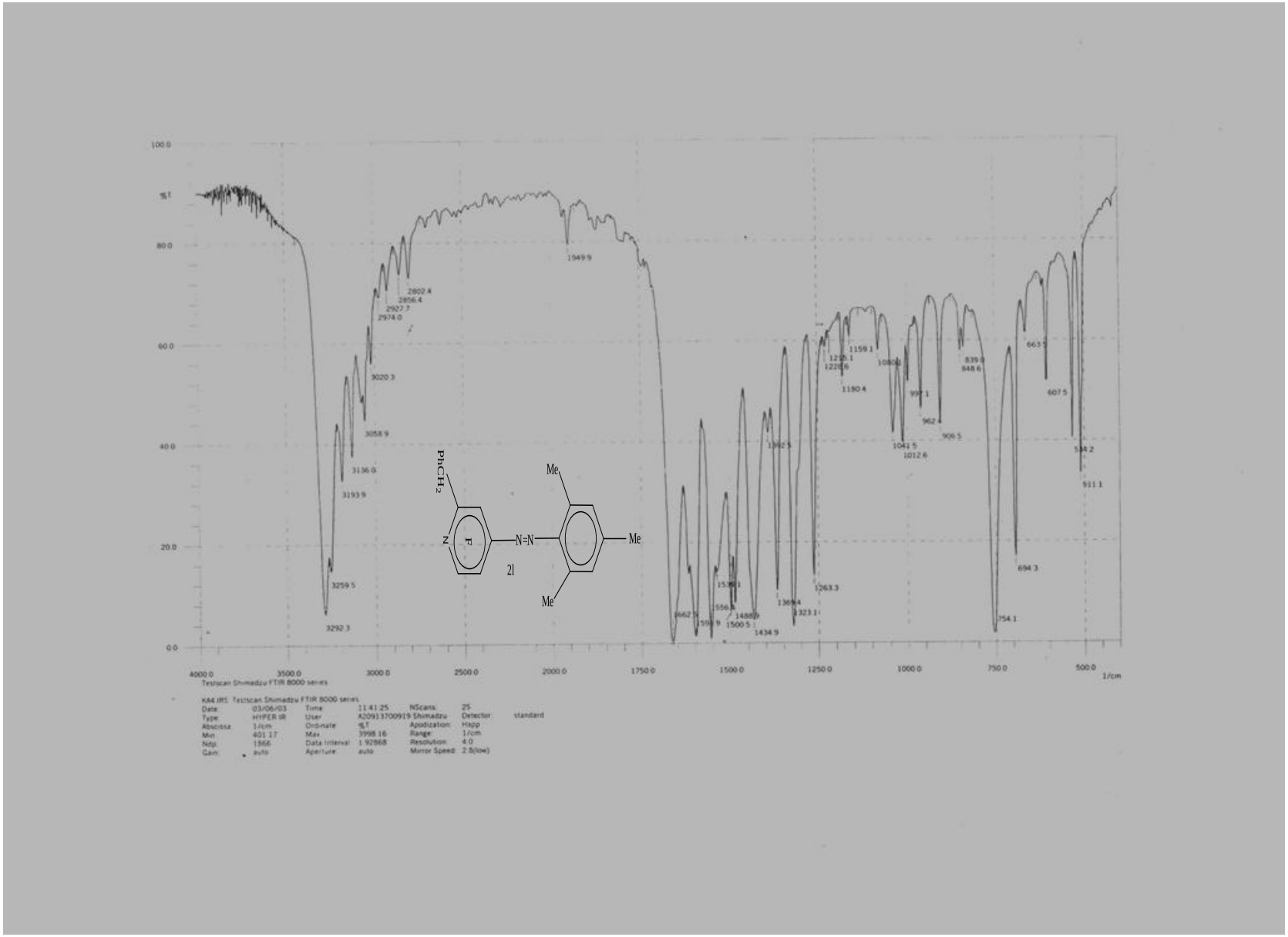

100.0
%T
80.0
60.0
40.0
20.0
0.0
3195.8
2993.3
3053.1
3078.2
1650.9
1508.4
1465.8
1444.9
1411.8
1350.0
1313.5
1298.0
1245.9
1199.6
1163.0
1147.6
1070.4
1024.1
997.1
975.9
904.6
891.1
808.1
748.3
693.8
684.7
642.3
611.4
522.7
507.2
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
PhCH2
N
F
NH2

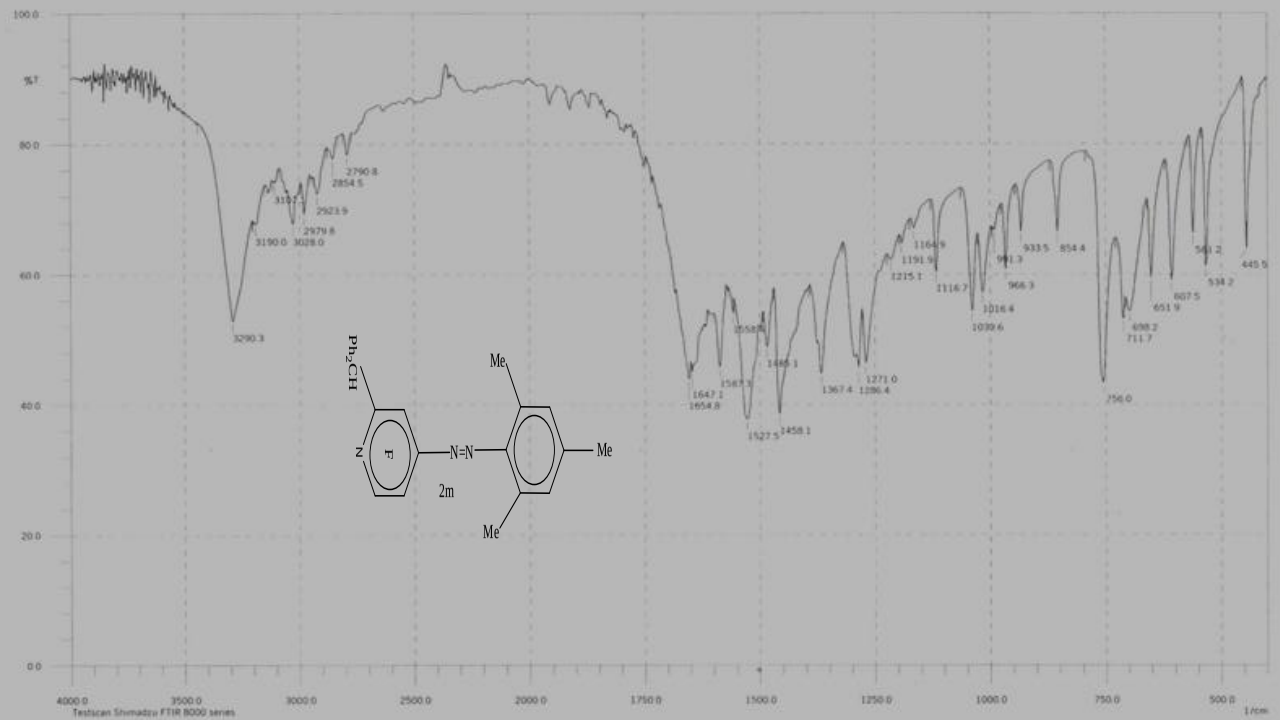

100.0
%T
80.0
60.0
40.0
20.0
0.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
3649.7
3564.2
3381.0
3195.8
2925.8
2991.4
3078.2
3053.1
1739.0
1650.0
1602.7
1508.4
1465.8
1442.7
1411.8
1356.4
1328.9
1311.5
1244.0
1199.6
1174.6
1161.1
1147.6
1123.2
1070.4
1024.1
997.1
975.9
904.6
893.0
837.0
811.4
763.3
684.7
642.3
638.8
505.3
418.5
Ph2CH
N
F
NH2
Testscan Shimadzu FTIR 8000 series
GA2 IRS Testscan Shimadzu FTIR 8000 series
Date 24/06/07
Time 09:03:49
NScans 60
Type HYPER IR
User A20913700919 Shimadzu
Detector standard
Abscissa 1/cm
Ordinate %T
Apodization Happ
Min 401.17
Max 3998.16
Range 1/cm
Ndp 1866
Data Interval 1.92868
Resolution 4.0
Gain Auto
Aperture Auto
Mirror Speed 2.8(low)

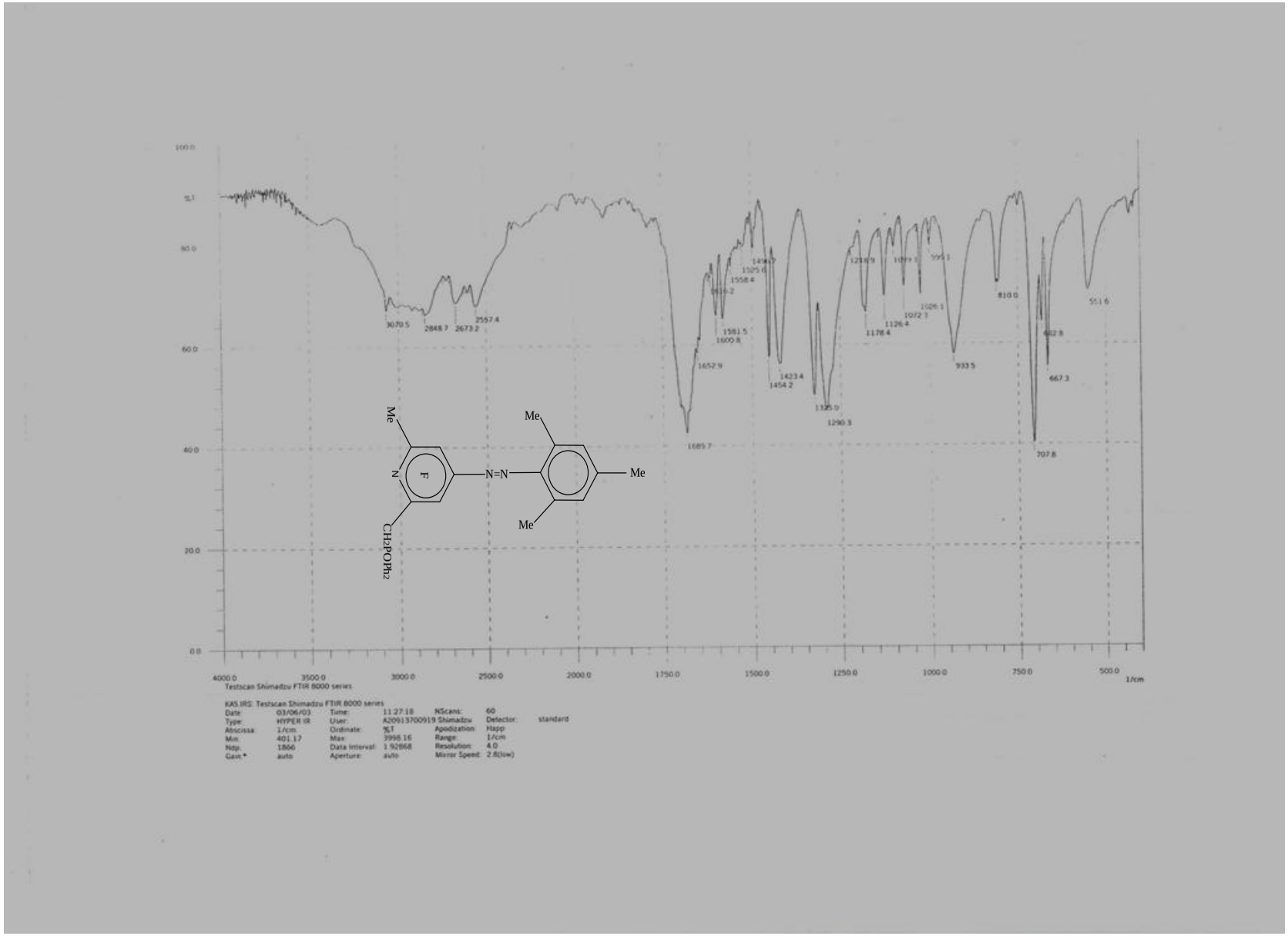

100.0
%T
50.0
60.0
40.0
20.0
0.0
3849.7
3645.2
3564.2
3381.0
3195.8
3078.2
3053.1
2991.4
2925.8
1732.0
1602.7
1508.4
1465.8
1442.7
1411.8
1356.4
1328.9
1311.5
1244.0
1199.6
1174.6
1161.1
1147.6
1103.2
1070.4
1024.1
997.1
975.9
904.6
893.0
837.0
750.3
684.7
642.3
611.4
505.3
418.5
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Et
N
F
N=N
Me
Me
Me
2h
Testscan Shimadzu FTIR 8000 series
KA2 IRS Testscan Shimadzu FTIR 8000 series
Date 24/06/03
Time 09:03:49
NScans 60
Type HYPER IR
User A20913700919 Shimadzu
Detector standard
Abscissa 1/cm
Ordinate %T
Apodization Happ
Min 401.17
Max 3998.16
Range 1/cm
Ndp 1866
Data Interval 1.92868
Resolution 4.0
Gain auto
Aperture auto
Mirror Speed 2.8(low)

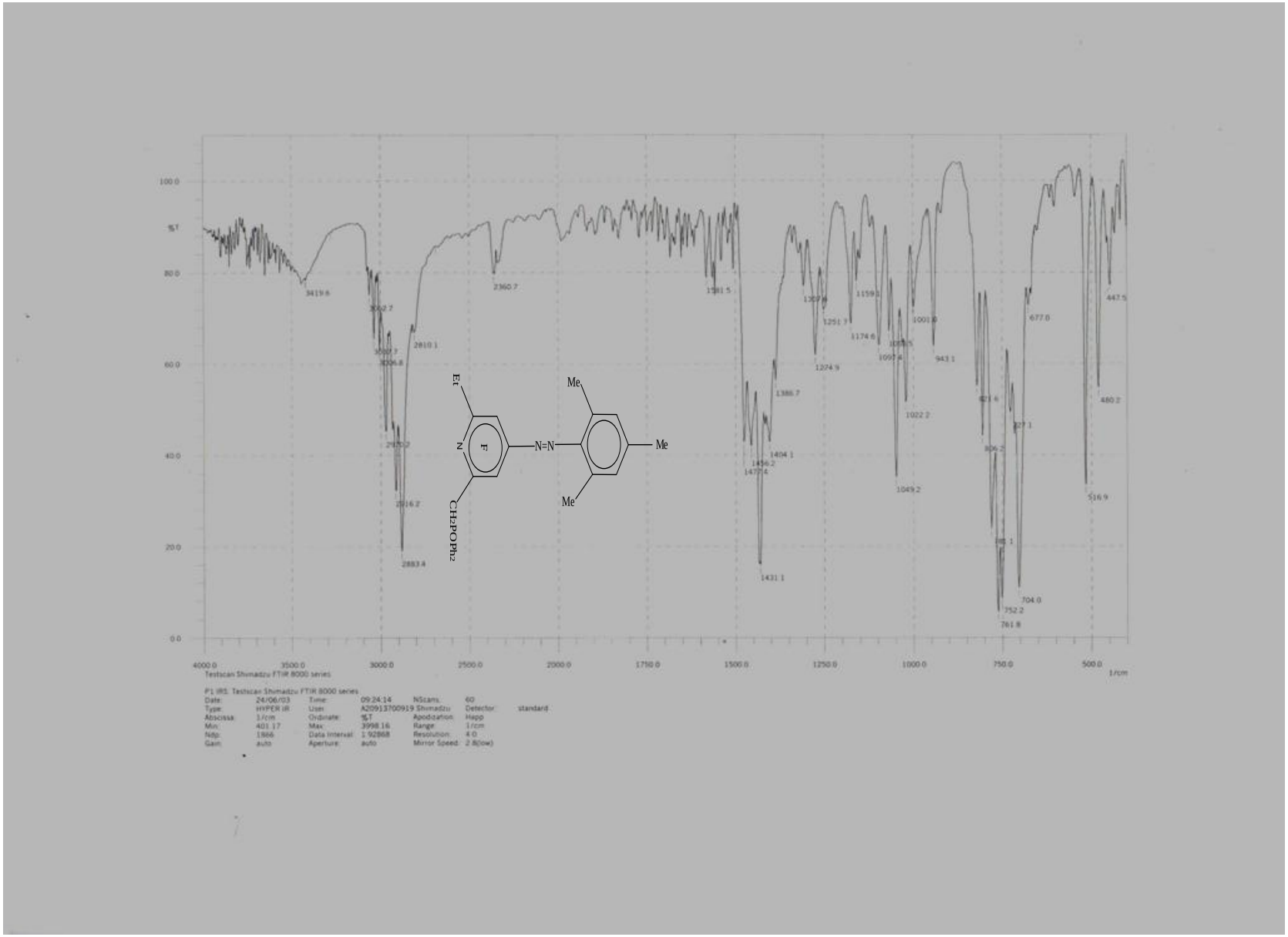

100.0
%T
80.0
60.0
40.0
20.0
0.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
3195.8
3053.1
3078.2
2993.1
1602.7
1568.4
1482.7
1465.8
1411.8
1328.9
1298.0
1311.5
1245.9
1199.6
1174.6
1163.0
1147.6
1123.2
1070.4
1004.1
997.1
975.9
904.6
891.1
806.1
748.3
684.7
642.3
611.4
522.7
507.2
nPr
Me
Me
Me
N=N
2i
Testscan Shimadzu FTIR 8000 series
KA3.IRS, Testscan Shimadzu FTIR 8000 series
Date: 24/06/03
Type: HYPER IR
Abscissa: 1/cm
Min*: 401.17
Nrip: 1866
Gain: auto
Time: 08:50:29
User: A20913700919
Ordinate: %T
Max: 3998.16
Data Interval: 1.92868
Aperture: auto
NScans: 60
Shimadzu
Detector: standard
Apodization: Happ
Range: 1/cm
Resolution: 4.0
Mirror Speed: 2.8(low)

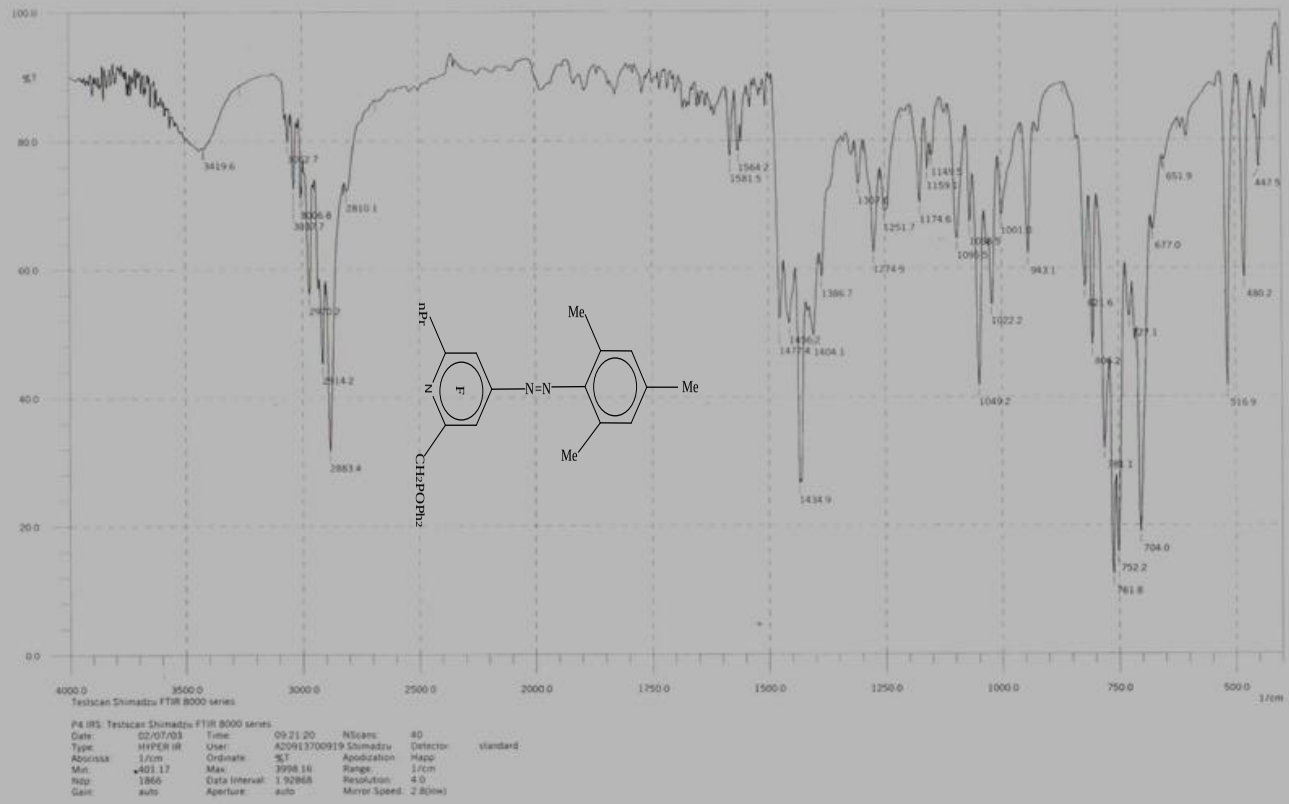

80.0
%T
60.0
40.0
20.0
0.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
2929.7
3035.7
2509.2
2343.4
2364.6
3649.1
3421.5
1614.3
1253.6
1325.9
1311.5
1139.9
1138.4
1070.4
1085.8
1020.3
873.7
842.8
815.6
756.0
704.0
680.8
518.8
Me
Me
Me
N=N
N
2k
Testscan Shimadzu FTIR 8000 series
KADI2 IRS: Testscan Shimadzu FTIR 8000 series
Date 21/01/03 Time 09:17:38 NScans 60
Type HYPER IP User A20913700919 Shimadzu Detector standard
Abscissa 1/cm Ordinate %T Apodization Happ
Max 401.17 Max 3998.16 Range 1/cm
Nop 1866 Data Interval 1.92868 Resolution 4.0
Gain auto Aperture auto Mirror Speed 2.8(low)

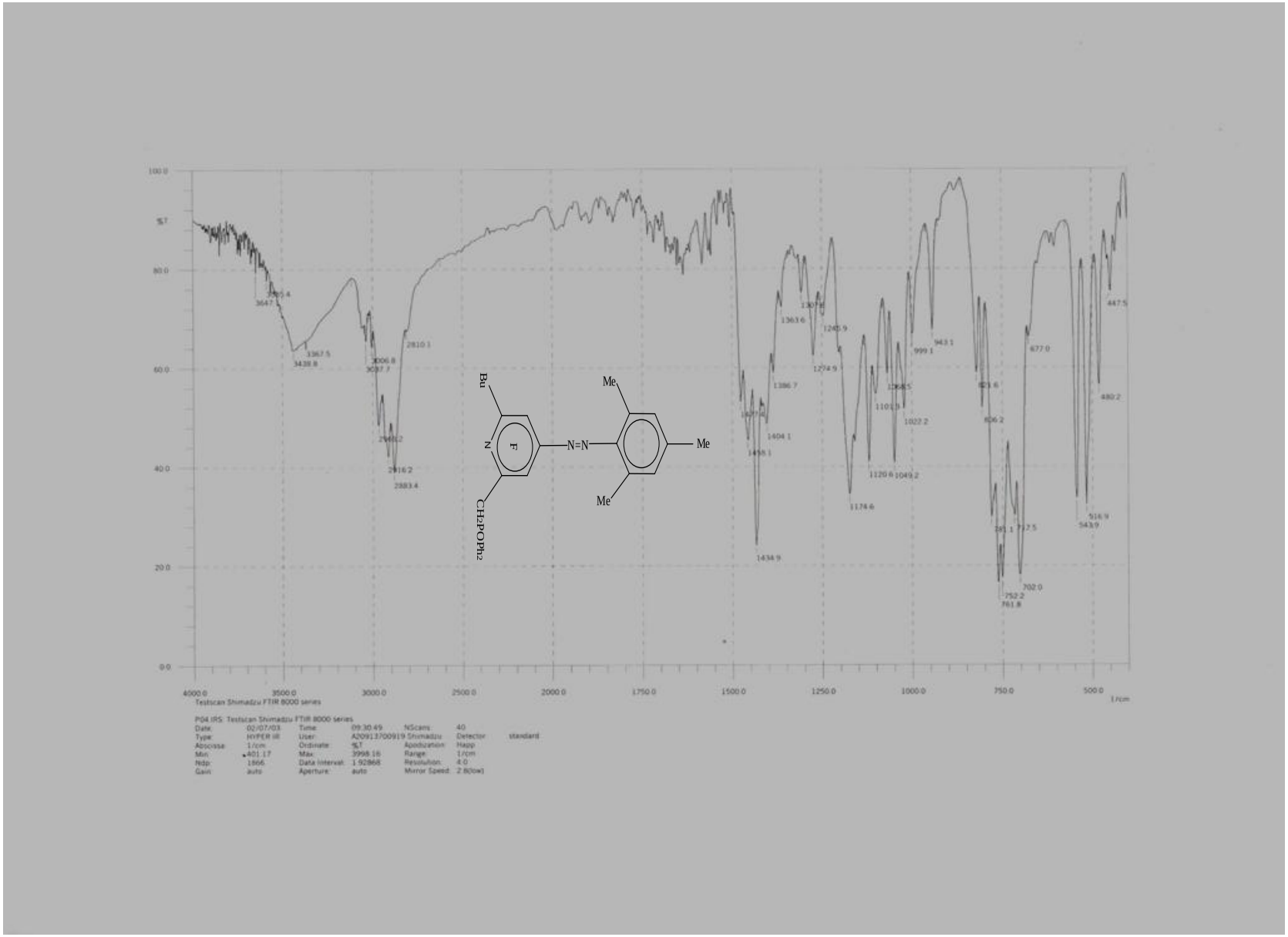

100.0
%T
80.0
60.0
40.0
20.0
0.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
3292.3
3259.5
3193.9
3136.0
3058.9
3020.3
2974.0
2927.7
2856.4
2802.4
1949.9
1180.4
1159.1
1041.5
1012.6
962.4
839.0
848.6
754.1
694.3
663.5
607.5
534.2
511.1
1434.9
1323.1
1263.3
1369.4
1392.5
1500.5
1488.9
1556.8
1593.9
1662.2
PhCH2
N
P
N=N
Me
Me
Me
2l
Testscan Shimadzu FTIR 8000 series
KBr IRS Testscan Shimadzu FTIR 8000 series
Date 03/06/03
Time 11:41:25
NScans 25
Type HYPER IR
User A20913700919 Shimadzu
Detector standard
Abscissa 1/cm
Ord-nate %T
Apodization Happ
Min 401.17
Max 3998.16
Range 1/cm
Ndp 1866
Data Interval 1.92868
Resolution 4.0
Gain auto
Aperture auto
Mirror Speed 2.8(low)

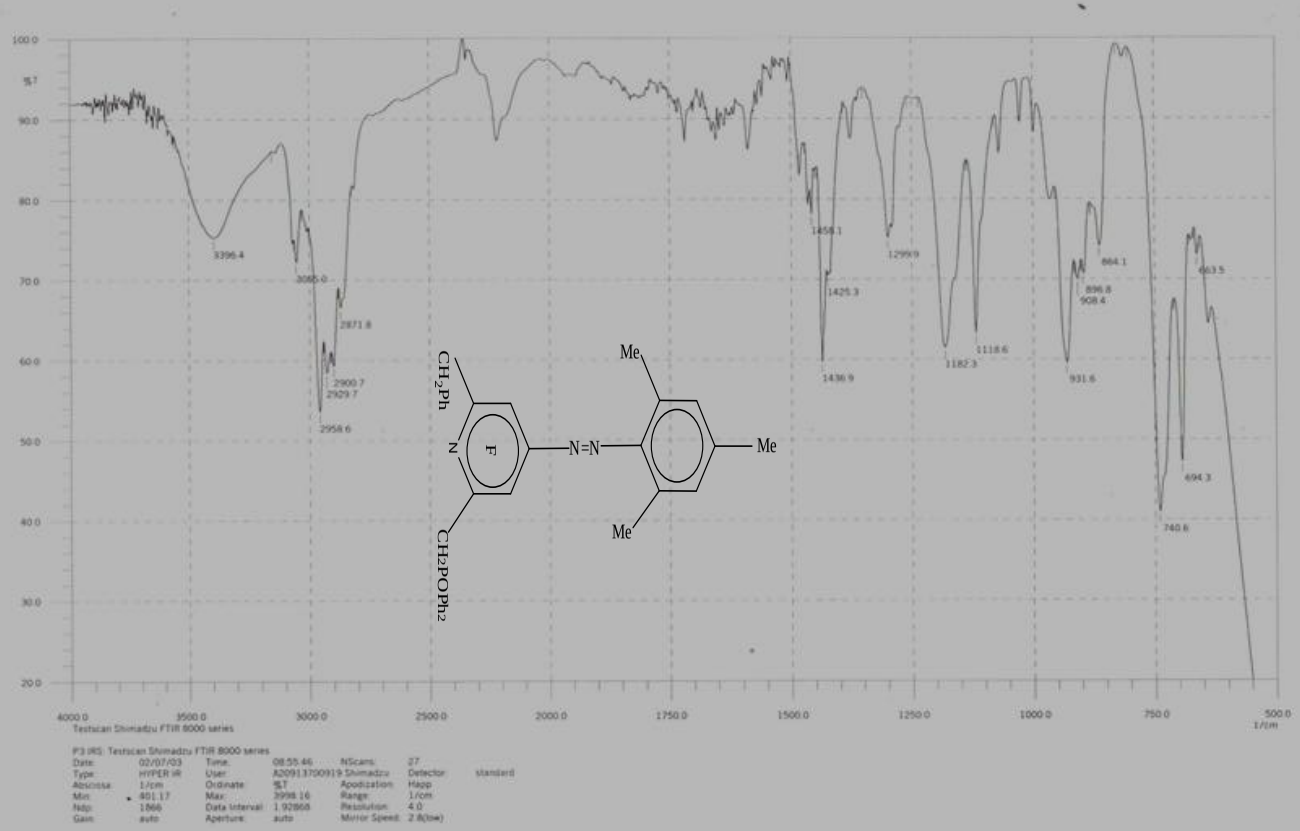

100.0
%T
80.0
60.0
40.0
20.0
0.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
3290.3
3190.0
3028.0
2979.8
2923.9
2854.5
2790.8
1654.8
1647.1
1527.5
1458.1
1367.4
1271.0
1215.1
1191.9
1164.9
1116.7
1039.6
1016.4
991.3
966.3
933.5
854.4
756.0
711.7
698.2
651.9
607.5
561.2
538.2
445.5
Ph2CH
N
F
N=N
Me
Me
Me
2m
Testscan Shimadzu FTIR 8000 series
KAI.IRS: Testscan Shimadzu FTIR 8000 series
Date: 03/06/03
Time: 10:41:51
NScans: 60
Type: HYPER IR
User: A20913700919 Shimadzu
Detector: standard
Abscissa: 1/cm
Ordinate: %T
Apodization: Happ
Min: 401.17
Max: 3998.16
Range: 1/cm
Ndp: 1866
Data Interval: 1.92868
Resolution: 4.0
Gain: auto
Aperture: auto
Mirror Speed: 2.8(low)

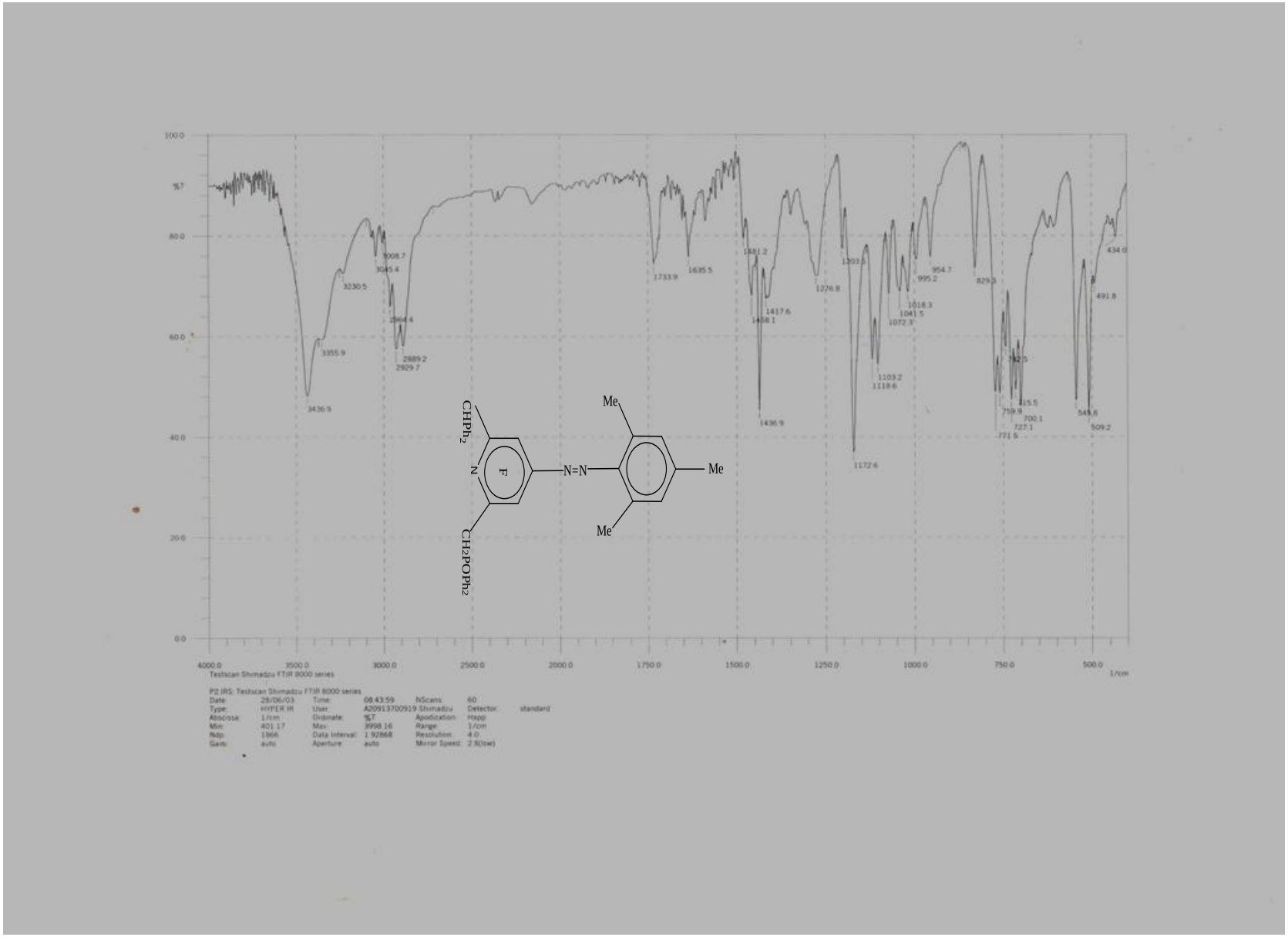

100.0
%T
80.0
60.0
40.0
20.0
0.0
3070.5
2848.7
2673.2
2557.4
1685.7
1652.9
1600.8
1581.5
1558.4
1525.6
1454.2
1423.4
1335.9
1290.3
1178.4
1126.4
1072.3
1026.1
933.5
810.0
707.8
667.3
602.8
551.6
Me
Me
N
F
N=N
Me
Me
CH2POPh2
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Testscan Shimadzu FTIR 8000 series
KAS.IRS: Testscan Shimadzu FTIR 8000 series
Date: 03/06/03 Time: 11:27:18 NScans: 60
Type: HYPER IR User: A209137000919 Shimadzu Detector: standard
Abscissa: 1/cm Ordinate: %T Apodization: Happ
Min: 401.17 Max: 3998.16 Range: 1/cm
Ndp: 1866 Data Interval: 1.92868 Resolution: 4.0
Gain:* auto Aperture: auto Mirror Speed: 2.8(low)


100.0
%T
80.0
60.0
40.0
20.0
0.0
3419.6
2883.4
2360.7
1581.5
1431.1
1404.1
1386.7
1274.9
1049.2
1022.2
943.1
761.8
752.2
704.0
677.0
516.9
447.5
480.2
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Et
N
F
N=N
Me
Me
Me
CH2POPh2
Testscan Shimadzu FTIR 8000 series
P1 IR1. Testscan Shimadzu FTIR 8000 series
Date: 24/06/03
Type: HYPER IR
Abscissa: 1/cm
Min: 401.17
Ndp: 1866
Gain: auto
Time: 09:24:14
User: A20913700919 Shimadzu
Ordinate: %T
Max: 3998.16
Data Interval: 1.92868
Aperture: auto
NScans: 60
Apodization: Happ
Range: 1/cm
Resolution: 4.0
Mirror Speed: 2.8(low)
Detector: standard


100.0
%T
80.0
60.0
40.0
20.0
0.0
3419.6
2810.1
2914.2
2883.4
1564.2
1581.5
1434.9
1386.7
1274.9
1251.7
1174.6
1049.2
1022.2
943.1
752.2
761.8
704.0
677.0
651.9
516.9
480.2
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
nPr
N
F
N=N
Me
Me
Me
CH2POPh2
Testscan Shimadzu FTIR 8000 series
P4 IRS: Testscan Shimadzu FTIR 8000 series
Date: 02/07/03
Time: 09:21:20
NScans: 40
Type: HYPER IR
User: A20913700919 Shimadzu
Detector: standard
Abscissa: 1/cm
Ordinate: %T
Apodization: Happ
Min: 401.17
Max: 3998.16
Range: 1/cm
Ndp: 1866
Data Interval: 1.92868
Resolution: 4.0
Gain: auto
Aperture: auto
Mirror Speed: 2.8(low)

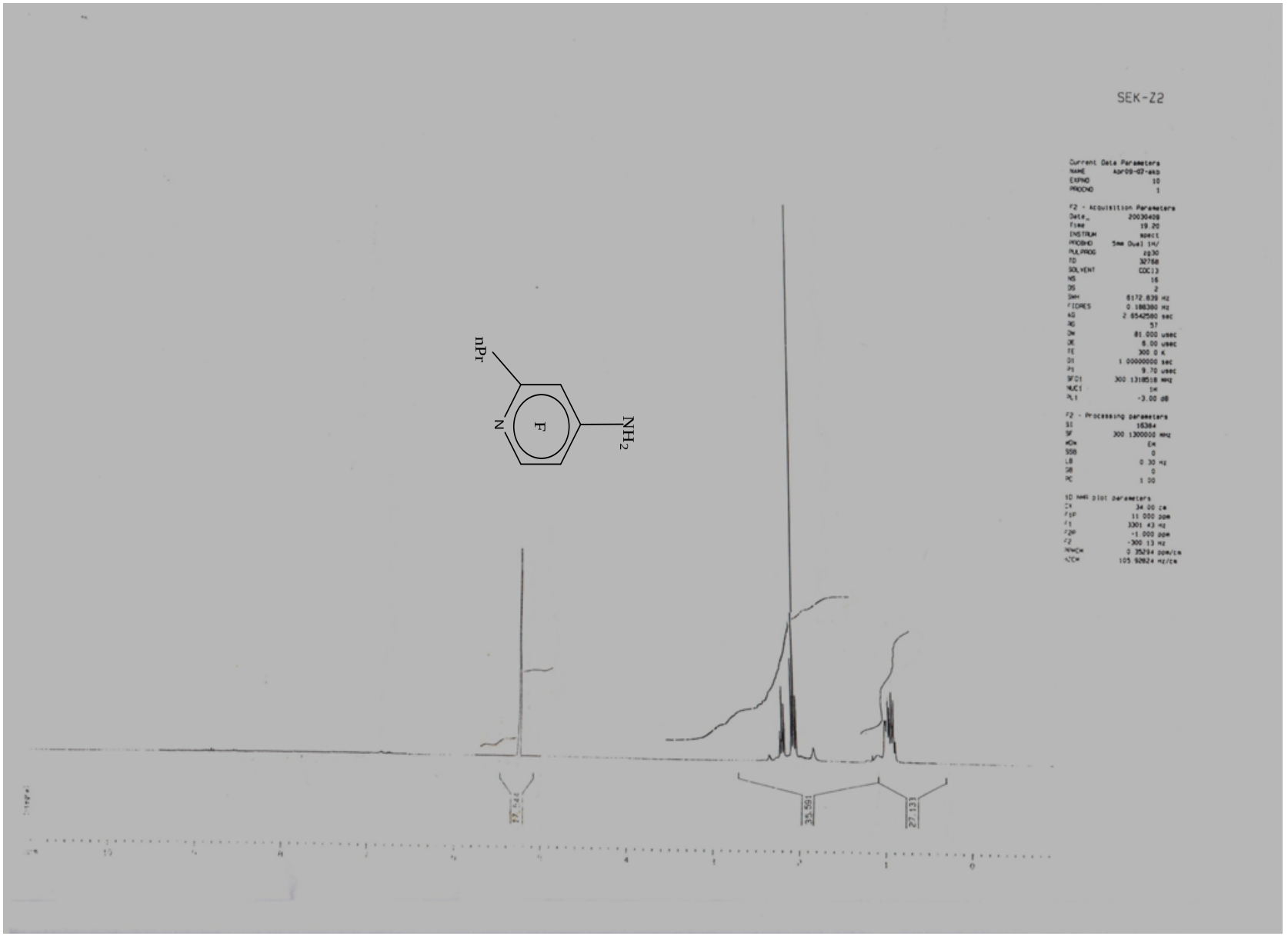

100.0
%T
80.0
60.0
40.0
20.0
0.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
3647.1
3438.8
3367.5
3006.8
2957.7
2916.2
2883.4
2810.1
1434.9
1404.1
1386.7
1363.6
1274.9
1240.9
1174.6
1120.6
1049.2
1022.2
999.1
943.1
806.2
761.8
752.2
702.0
677.0
543.9
516.9
480.2
447.5
Bu
F
N
N=N
Me
Me
Me
CH2POPh2
Testscan Shimadzu FTIR 8000 series
P04.IRS: Testscan Shimadzu FTIR 8000 series
Date: 02/07/03
Time: 09:30:49
NScans: 40
Type: HYPER IR
User: A2091370091 9 Shimadzu
Detector: standard
Abscissa: 1/cm
Ordinate: %T
Apodization: Happ
Min: 401.17
Max: 3998.16
Range: 1/cm
Ndp: 1866
Data Interval: 1.92868
Resolution: 4.0
Gain: auto
Aperture: auto
Mirror Speed: 2.80kw

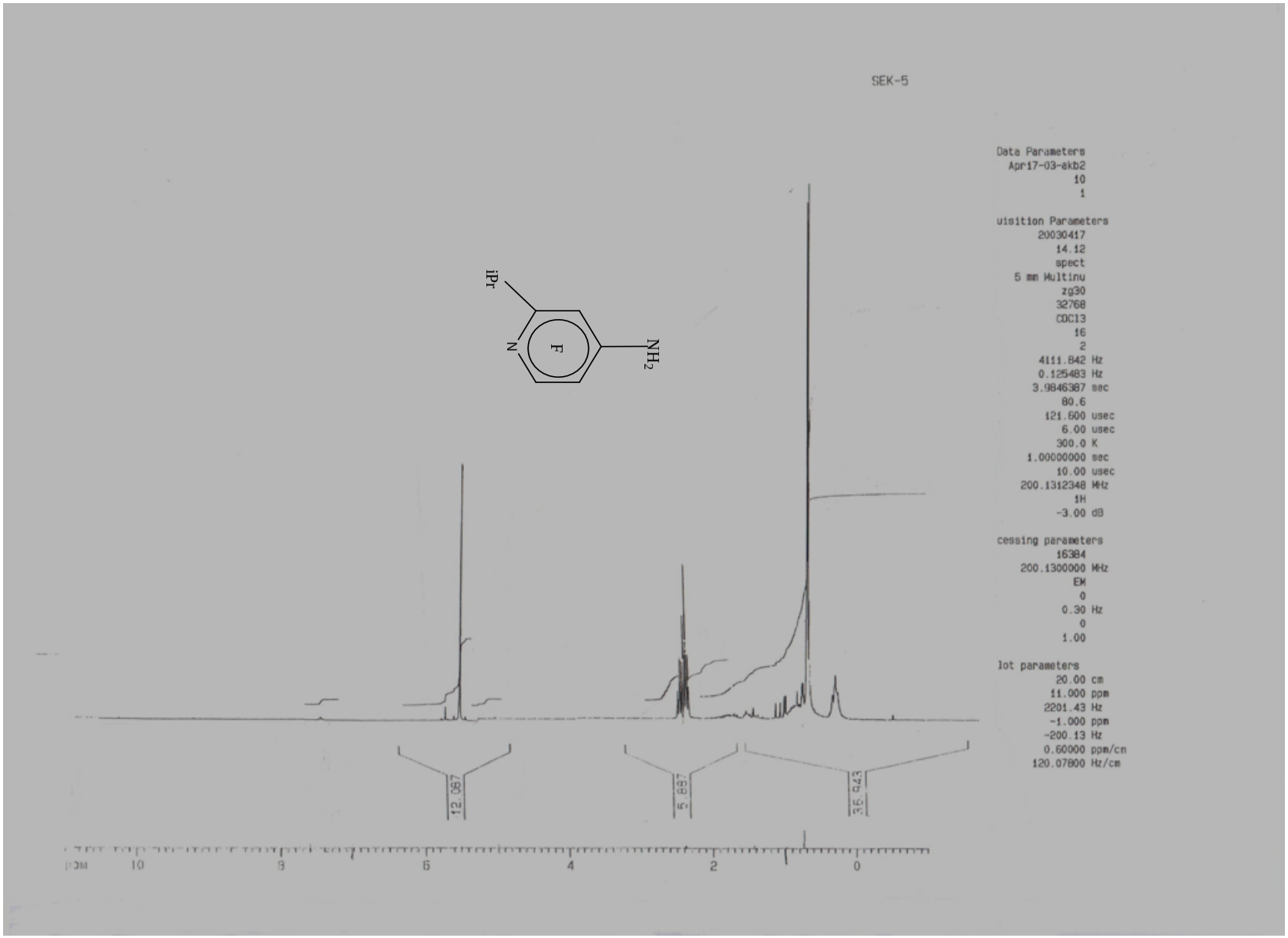

%T
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
3396.4
3065.0
2871.8
2900.7
2929.7
2958.6
1458.1
1425.3
1436.9
1299.9
1182.3
1118.6
931.6
908.4
896.8
864.1
740.6
694.3
463.5
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Testscan Shimadzu FTIR 8000 series
P3 (IR): Testscan Shimadzu FTIR 8000 series
Date: 02/07/03
Time: 08:55:46
NScans: 27
Type: HYPER IR
User: A20913700919 Shimadzu
Detector: standard
Abscissa: 1/cm
Ordinate: %T
Apodization: Happ
Min: 401.17
Max: 3998.16
Range: 1/cm
Ndp: 1866
Data Interval: 1.92868
Resolution: 4.0
Gain: auto
Aperture: auto
Mirror Speed: 2.8(low)
CH2Ph
N
F
N=N
Me
Me
Me
CH2POPh2

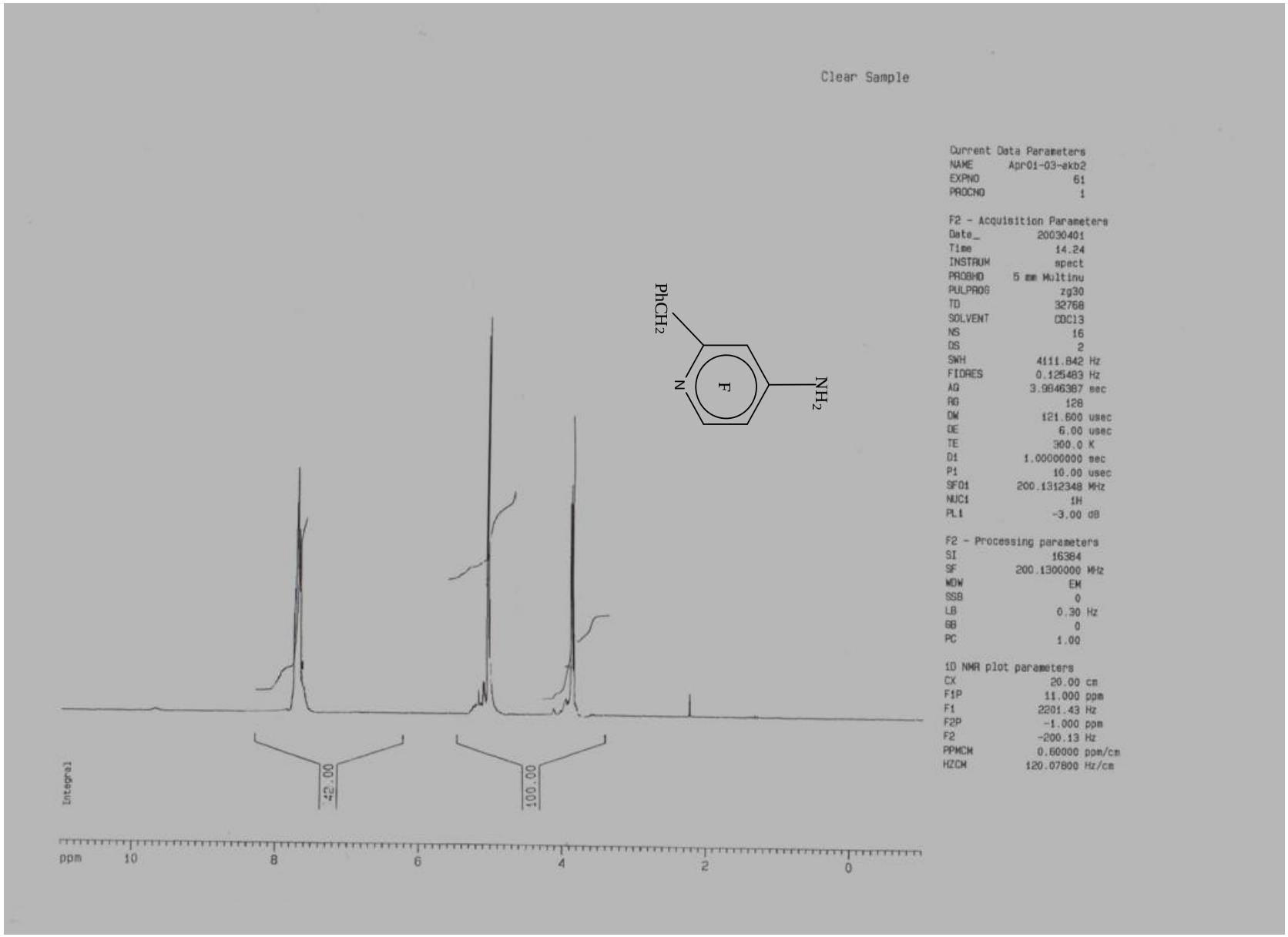

100.0
%T
80.0
60.0
40.0
20.0
0.0
3436.9
3355.9
3230.5
3008.7
3045.4
2964.4
2889.2
2929.7
1733.9
1635.5
1481.2
1458.1
1417.6
1436.9
1276.8
1203.3
1172.6
1103.2
1118.6
1072.3
1041.5
1018.3
995.2
954.7
829.3
759.9
727.1
771.5
700.1
615.5
545.8
509.2
491.8
434.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
Testscan Shimadzu FTIR 8000 series
P2.IRS: Testscan Shimadzu FTIR 8000 series
Date: 28/06/03
Time: 08:43:59
nScans: 60
Type: HYPER IR
User: A20913700919 Shimadzu
Detector: standard
Abscisse: 1/cm
Ordinate: %T
Apodization: Happ
Min: 401.17
Max: 3998.16
Range: 1/cm
Ndp: 1866
Data Interval: 1.92868
Resolution: 4.0
Gain: auto
Aperture: auto
Mirror Speed: 2.8(low)
CHPh2
N
F
N=N
Me
Me
Me
CH2POPh2

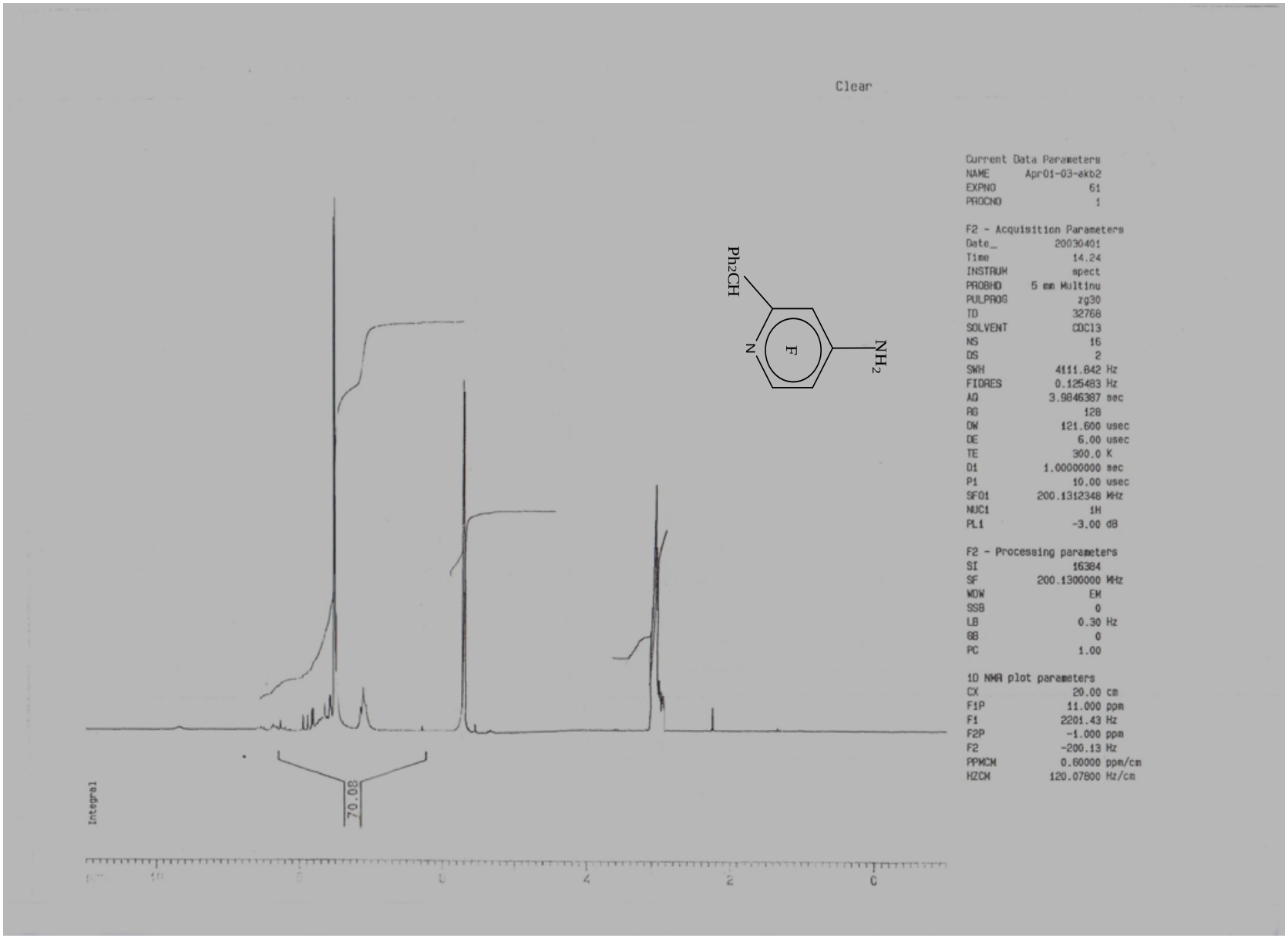
Appendix II
Nuclear Magnetic Resonance spectra

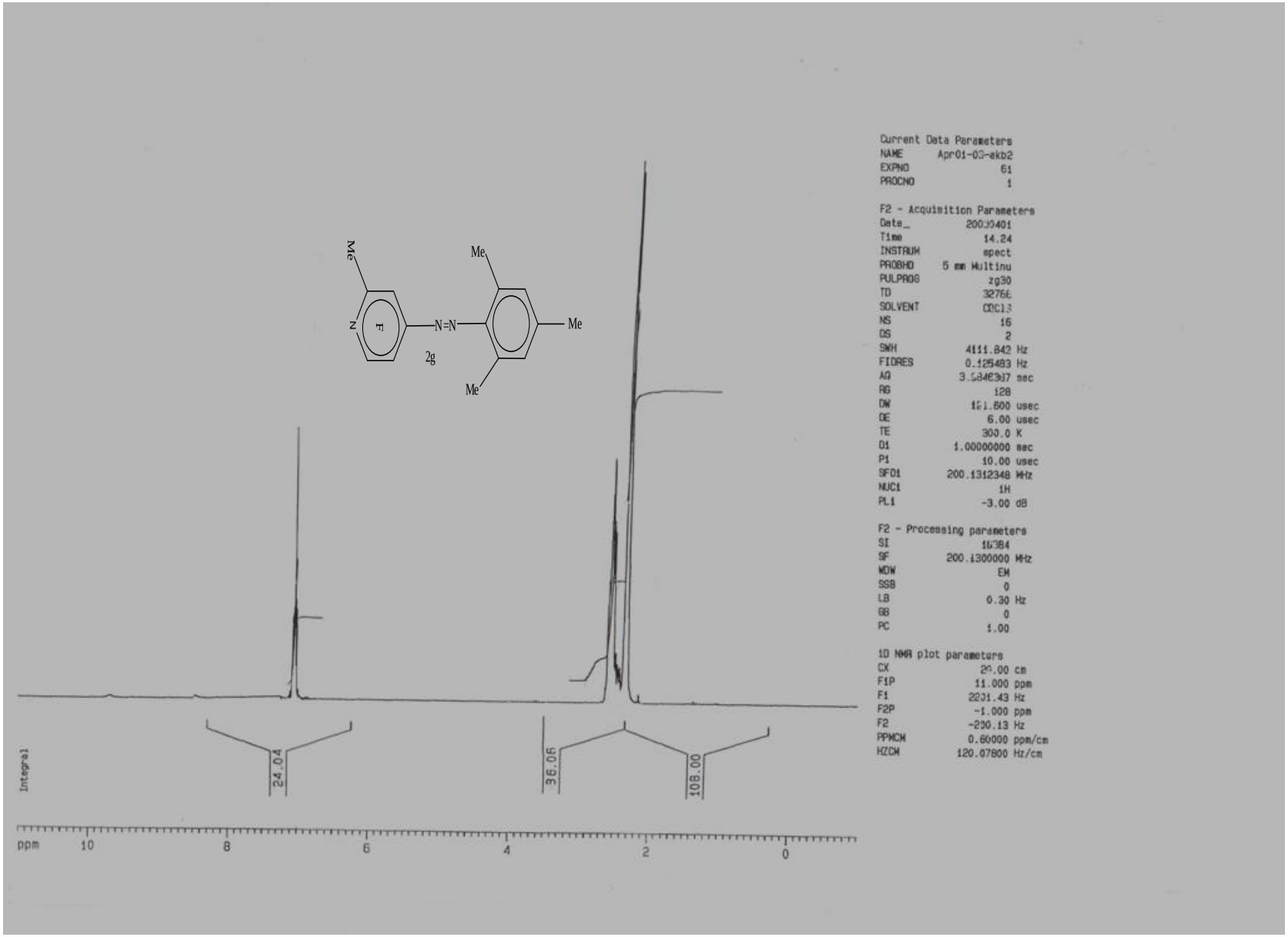
^{1}H spectrum


SEK-Z2
nPr
N
F
NH2
27.146
35.591
27.133


SEK-5
iPr
N
F
NH2
12.087
5.887
36.943
ppm
10
8
6
4
2
0
Data Parameters
Apr17-03-akb2
10
1
uisition Parameters
20030417
14.12
spect
5 mm Multinu
zg30
32768
CDCl3
16
2
4111.842 Hz
0.125483 Hz
3.9846387 sec
80.6
121.600 usec
6.00 usec
300.0 K
1.00000000 sec
10.00 usec
200.1312348 MHz
1H
-3.00 dB
cessing parameters
16384
200.1300000 MHz
EM
0
0.30 Hz
0
1.00
lot parameters
20.00 cm
11.000 ppm
2201.43 Hz
-1.000 ppm
-200.13 Hz
0.60000 ppm/cn
120.07800 Hz/cm


Clear Sample
Current Data Parameters
NAME Apr01-03-ekb2
EXPNO 61
PROCNO 1
F2 - Acquisition Parameters
Date_ 20030401
Time 14.24
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 4111.842 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 128
DW 121.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 10.00 usec
SFO1 200.1312348 MHz
NUC1 1H
PL1 -3.00 dB
F2 - Processing parameters
SI 16384
SF 200.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 2201.43 Hz
F2P -1.000 ppm
F2 -200.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 120.07800 Hz/cm
PhCH2
N
F
NH2
Integral
42.00
100.00
ppm
10
8
6
4
2
0


Clear
Ph2CH
N
F
NH2
Integral
70.08
10
8
6
4
2
0
Current Data Parameters
NAME Apr01-03-ekb2
EXPNO 61
PROCNO 1
F2 - Acquisition Parameters
Date_ 20030401
Time 14.24
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 4111.842 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 128
DW 121.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 10.00 usec
SFO1 200.1312348 MHz
NUC1 1H
PL1 -3.00 dB
F2 - Processing parameters
SI 16384
SF 200.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 2201.43 Hz
F2P -1.000 ppm
F2 -200.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 120.07800 Hz/cm

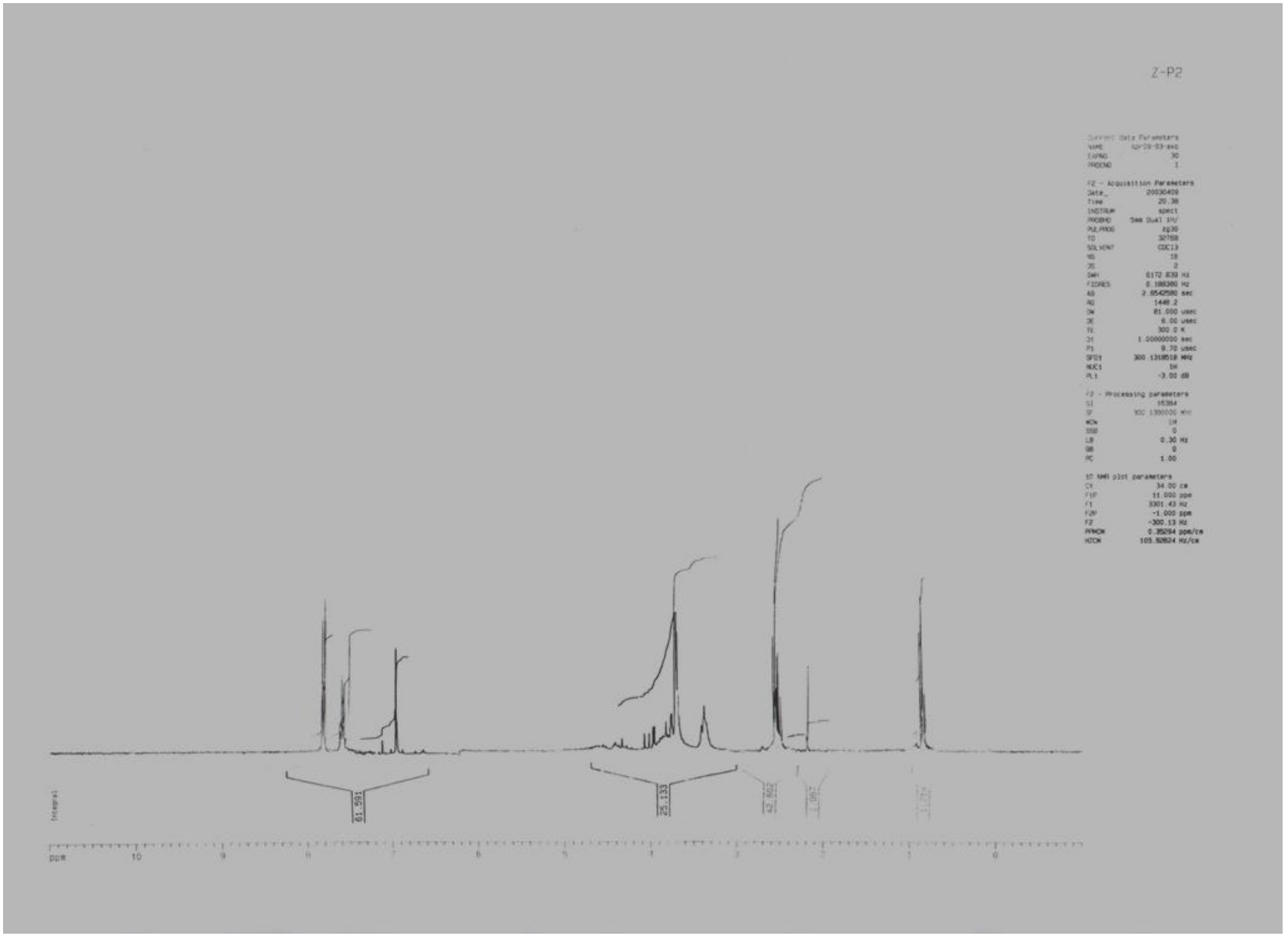


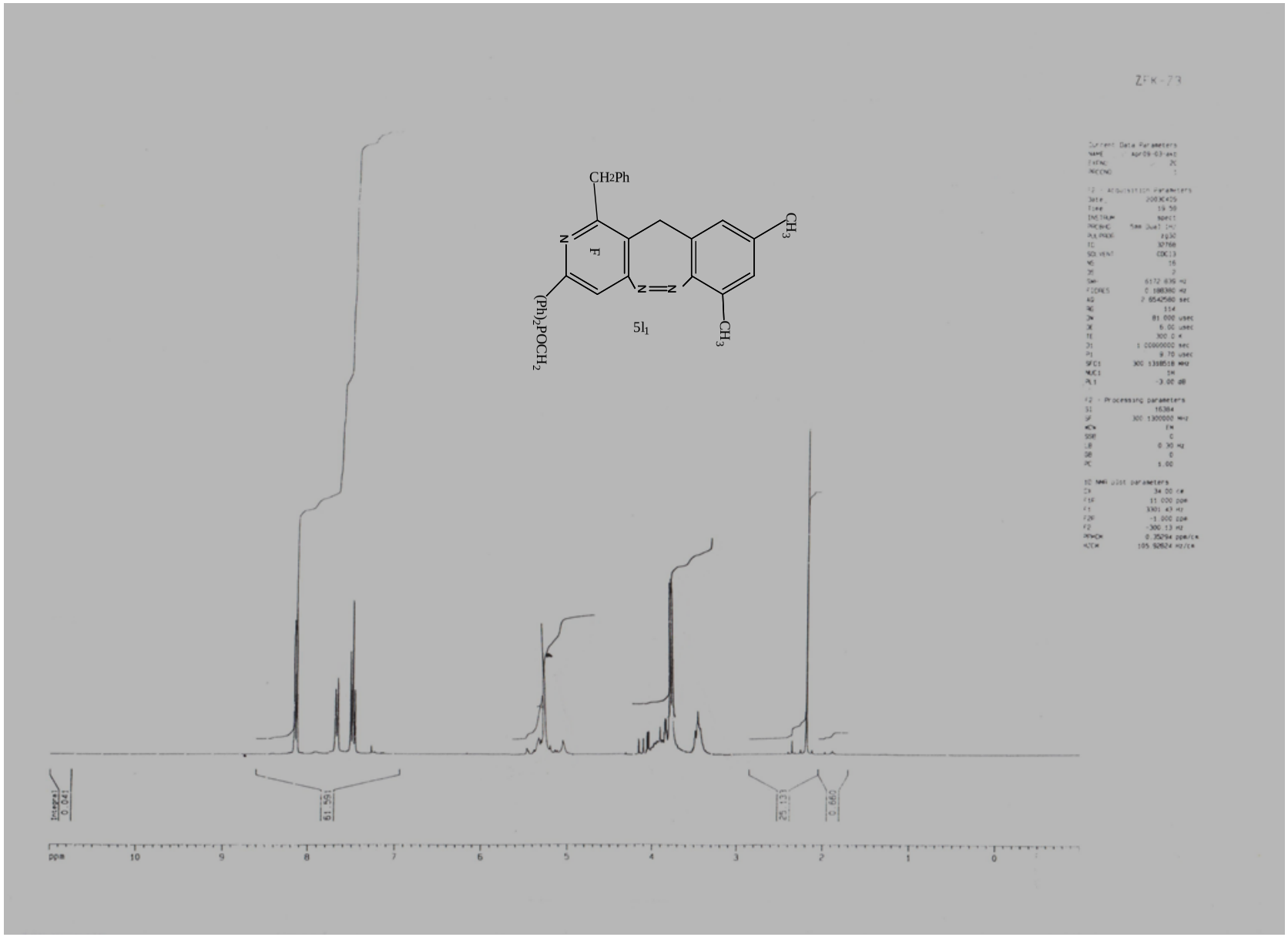
Current Data Parameters
NAME Apr01-03-akb2
EXPNO 61
PROCNO 1

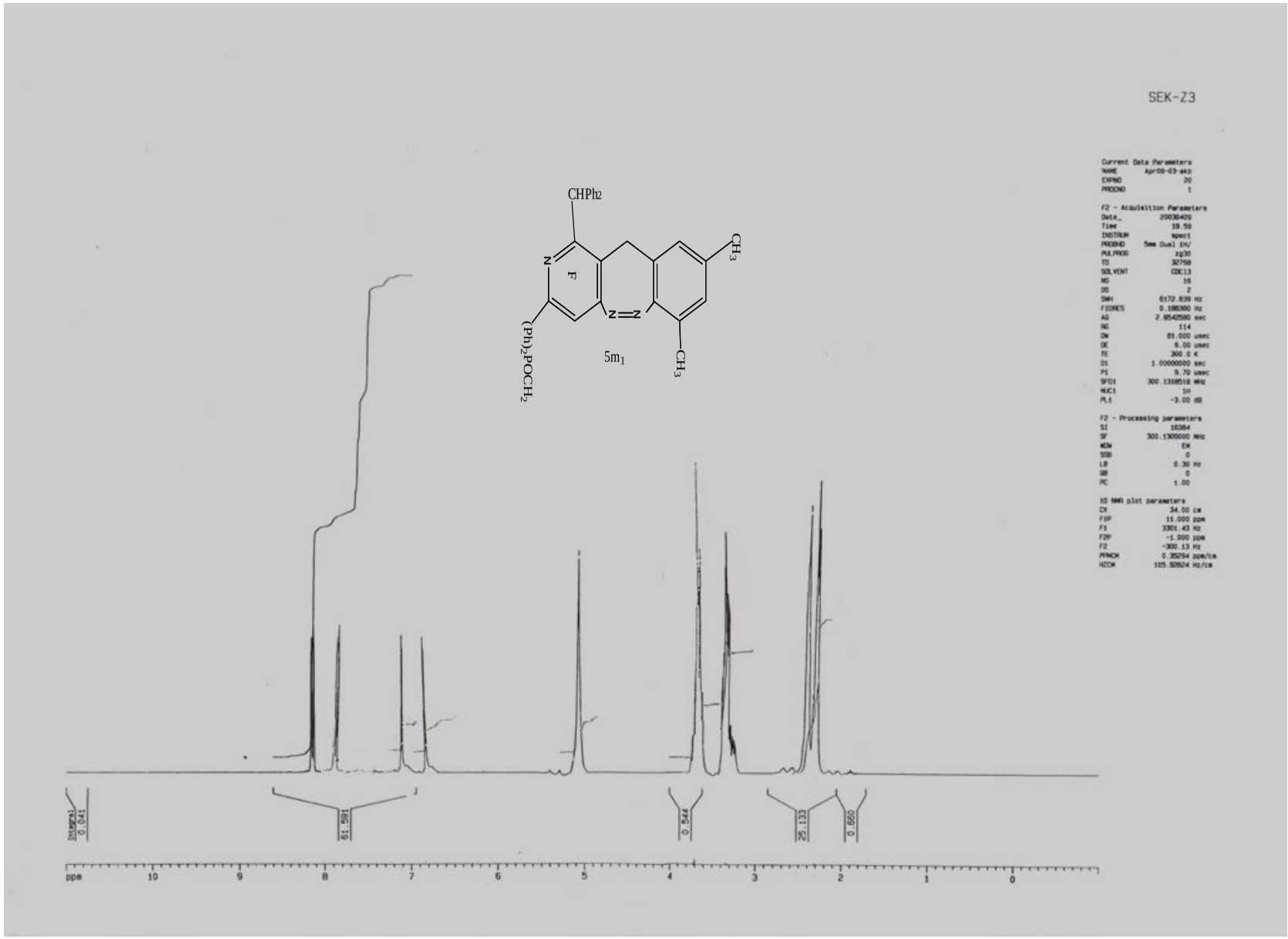
F2 - Acquisition Parameters
Date_ 20030401
Time 14.24
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zg30
TD 32766
SOLVENT CDCl3
NS 16
DS 2
SWH 4111.842 Hz
FIDRES 0.125483 Hz
AQ 3.984e3d7 sec
RG 128
DW 121.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 10.00 usec
SFO1 200.1312348 MHz
NUC1 1H
PL1 -3.00 dB

F2 - Processing parameters
SI 16384
SF 200.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

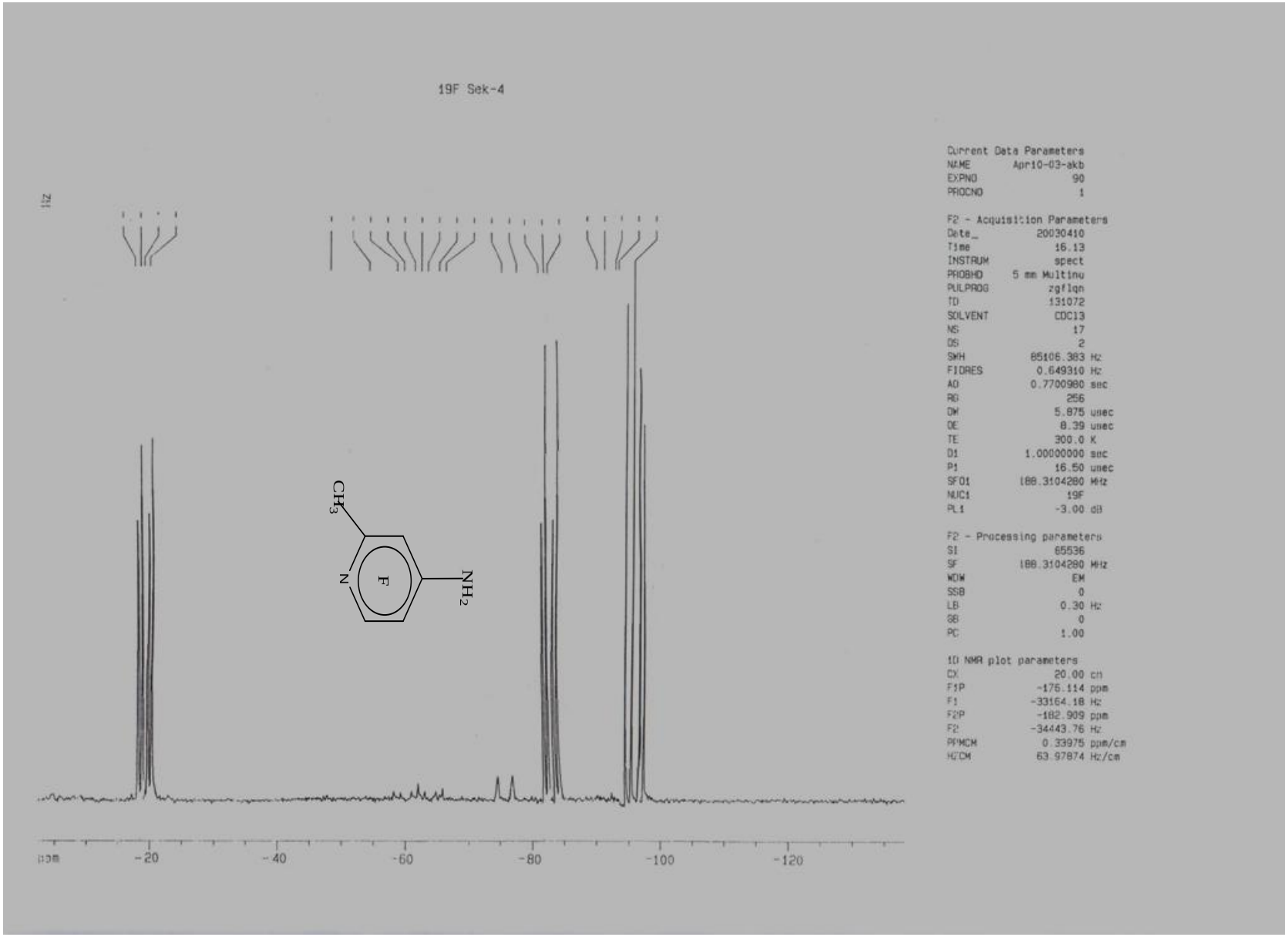
1D NMR plot parameters
CX 20.00 cm
F1P 11.000 ppm
F1 2201.43 Hz
F2P -1.000 ppm
F2 -200.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 120.07800 Hz/cm


Z-P2
Current Data Parameters
NAME sp09-03-exo
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20030409
Time 20.38
INSTRUM spect
PROBHD 5mm Dual 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8172.830 Hz
FIDRES 0.186380 Hz
AQ 2.0542580 sec
RG 1448.2
DW 61.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.70 usec
SFO1 300.1318518 MHz
NUC1 1H
PL1 -3.00 dB
F2 - Processing parameters
SI 16384
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 34.00 cm
F1P 11.000 ppm
F1 3301.43 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.35294 ppm/cm
HZCM 105.92824 Hz/cm
Integral
61.991
25.133
43.862
1.067
3.137
ppm
10
9
8
7
6
5
4
3
2
1
0


ZFK-73
CH2Ph
CH3
N
F
N=N
CH3
(Ph)2POCH2
5l1
Integral
0.041
61.591
25.133
2.660
ppm
10
9
8
7
6
5
4
3
2
1
0


SEK-Z3
CHPh2
CH3
N
F
N=N
(Ph)2POCH2
5m1
CH3
Current Data Parameters
NAME Apr09-03-ekb
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20030409
Time 19.58
INSTRUM spect
PROBHD 5mm Dual 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 114
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.70 usec
SFO1 300.1318518 MHz
NUC1 1H
PL1 -3.00 dB
F2 - Processing parameters
SI 16384
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 34.00 cm
F1P 11.000 ppm
F1 3301.43 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.35294 ppm/cm
HZCM 105.92624 Hz/cm
Integral
0.041
61.591
0.544
25.133
0.660
ppm
10
9
8
7
6
5
4
3
2
1
0

^{19}F spectrum



Current Data Parameters

NAME	Apr10-03-akb
EXPNO	90
PROCNO	1

F2 - Acquisition Parameters

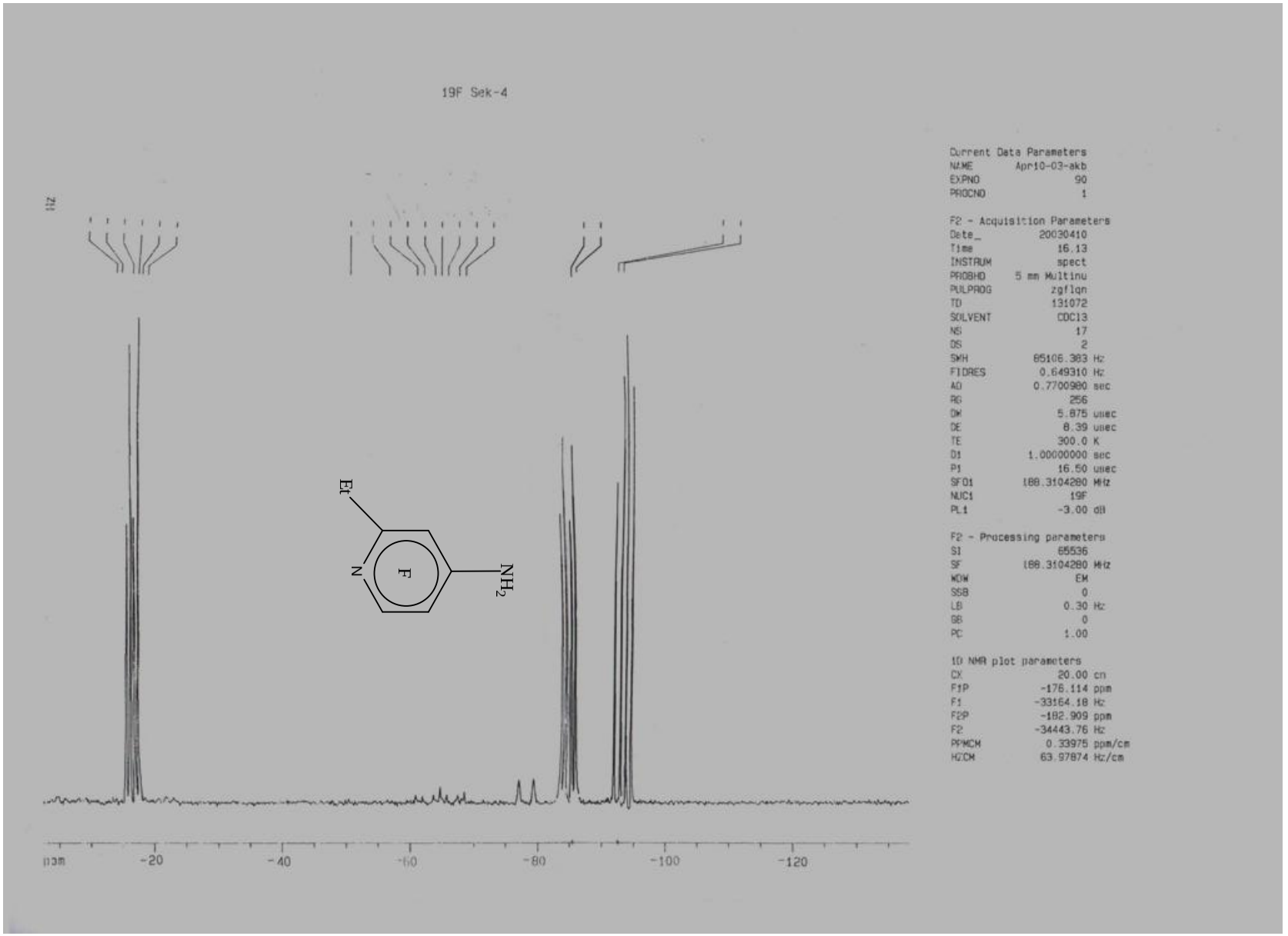
Date_	20030410
Time	16.13
INSTRUM	spect
PROBHD	5 mm Multinu
PULPROG	zgflqn
TD	131072
SOLVENT	CDCl3
NS	17
DS	2
SWH	85106.383 Hz
FIDRES	0.649310 Hz
AQ	0.7700980 sec
RG	256
DW	5.875 usec
DE	8.39 usec
TE	300.0 K
D1	1.00000000 sec
P1	16.50 usec
SFO1	188.3104280 MHz
NUC1	19F
PL1	-3.00 dB

F2 - Processing parameters

SI	65536
SF	188.3104280 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	-176.114 ppm
F1	-33164.18 Hz
F2P	-182.909 ppm
F2	-34443.76 Hz
PPMCM	0.33975 ppm/cm
HZCM	63.97874 Hz/cm



Current Data Parameters

NAME	Apr10-03-akb
EXPNO	90
PROCNO	1

F2 - Acquisition Parameters

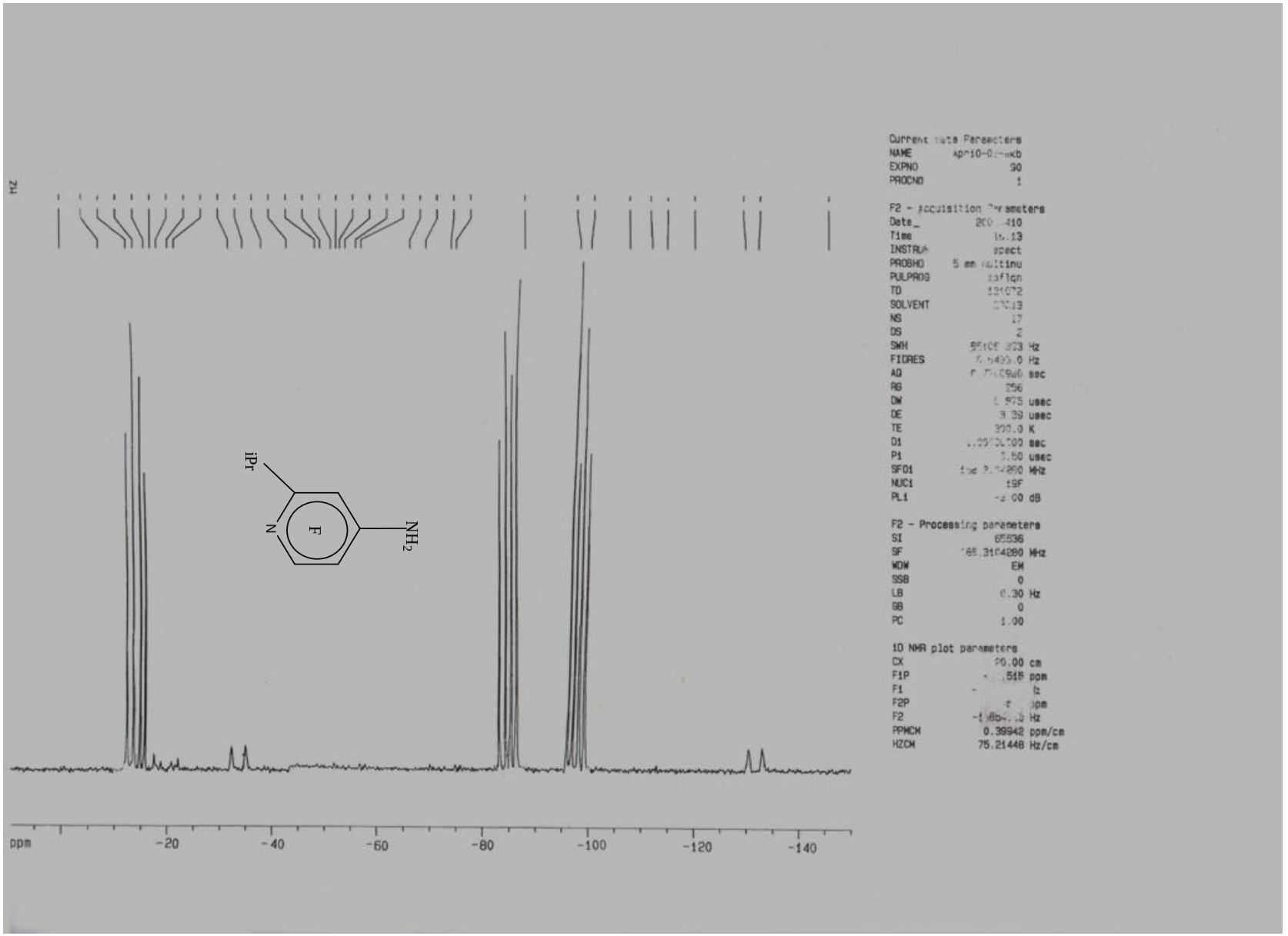
Date_	20030410
Time	16.13
INSTRUM	spect
PROBHD	5 mm Multinu
PULPROG	zgflqn
TD	131072
SOLVENT	CDCl3
NS	17
DS	2
SWH	65106.383 Hz
FIDRES	0.649310 Hz
AQ	0.7700980 sec
RG	256
DW	5.875 usec
DE	8.39 usec
TE	300.0 K
D1	1.00000000 sec
P1	16.50 usec
SFO1	188.3104280 MHz
NUC1	19F
PL1	-3.00 dB

F2 - Processing parameters

SI	65536
SF	188.3104280 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	-176.114 ppm
F1	-33164.18 Hz
F2P	-182.909 ppm
F2	-34443.76 Hz
PPMCM	0.33975 ppm/cm
HZCM	63.97874 Hz/cm

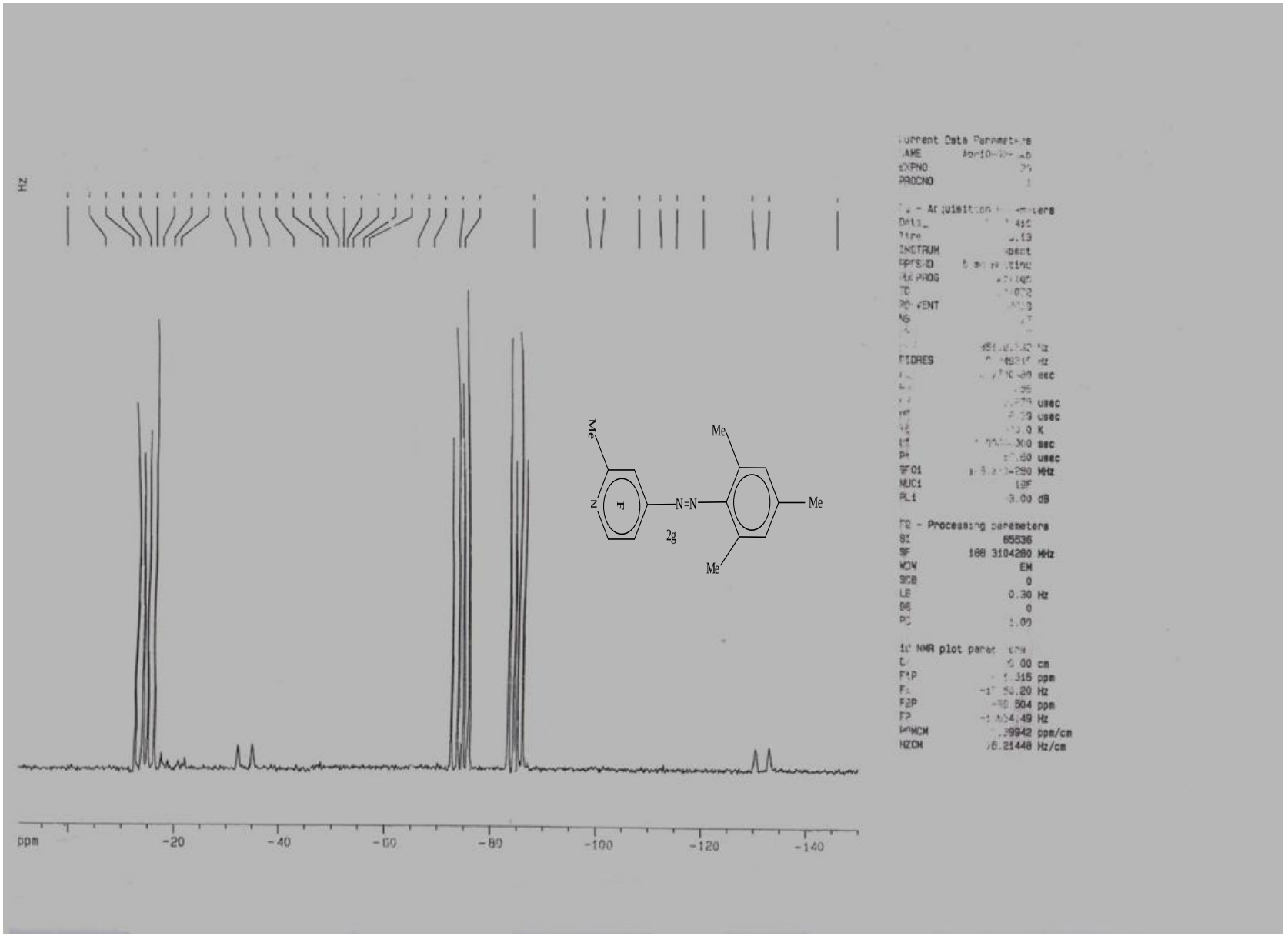


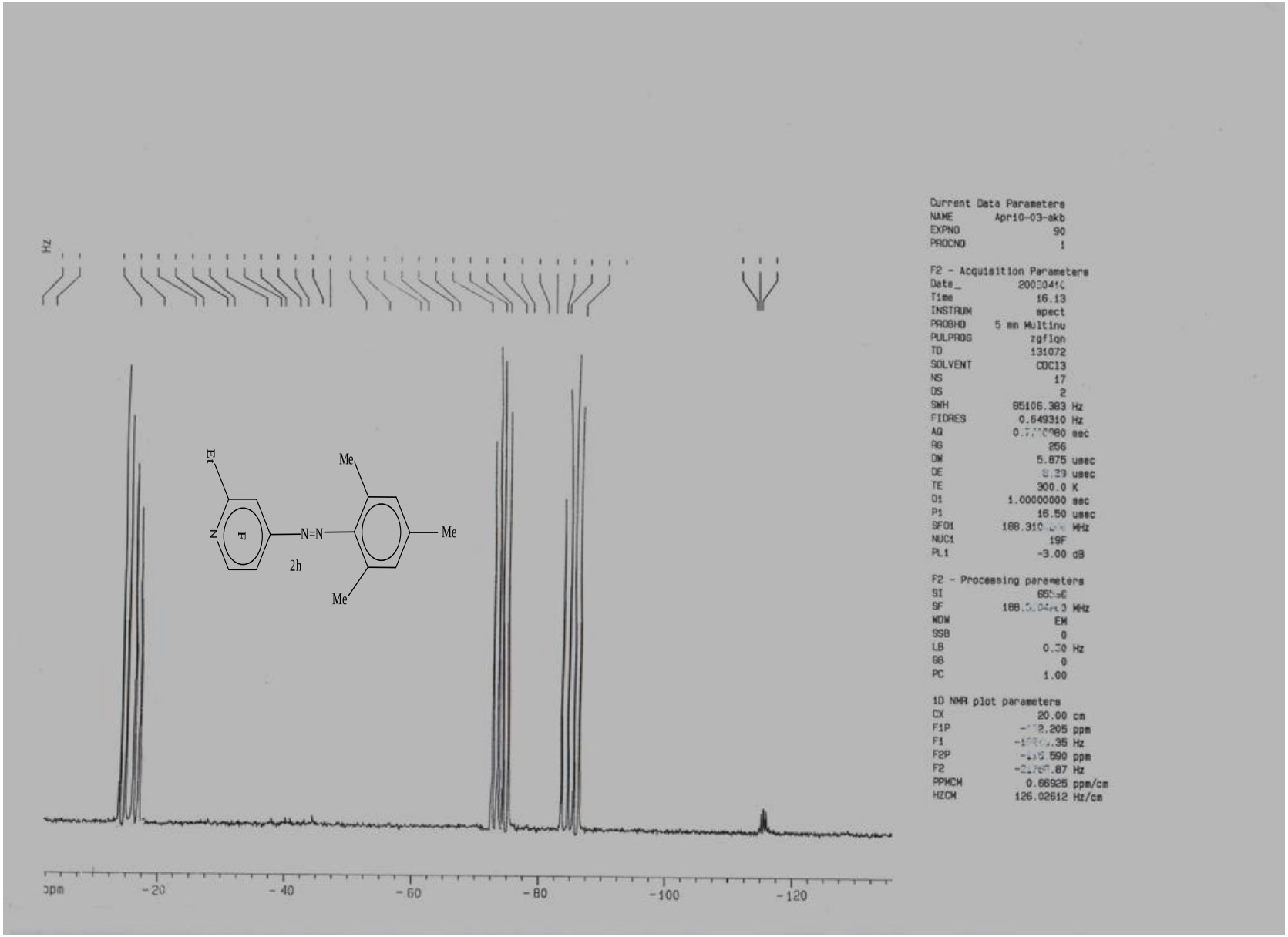
Current data Parameters
NAME
EXPNO 90
PROCNO 1

F2 - Acquisition Parameters
Date_
Time
INSTRUM
PROBHD 5 mm Multinu
PULPROG
TD
SOLVENT
NS
DS
SWH Hz
FIDRES Hz
AQ sec
RG
DW usec
DE usec
TE K
D1 sec
P1 usec
SFO1 MHz
NUC1 19F
PL1 dB

F2 - Processing parameters
SI 65536
SF MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX cm
F1P ppm
F1 Hz
F2P ppm
F2 Hz
PPMCM 0.39942 ppm/cm
HZCM 75.21448 Hz/cm


Hz
ppm
-20
-40
-60
-80
-100
-120
-140
Me
Me
N
F
N=N
Me
Me
2g

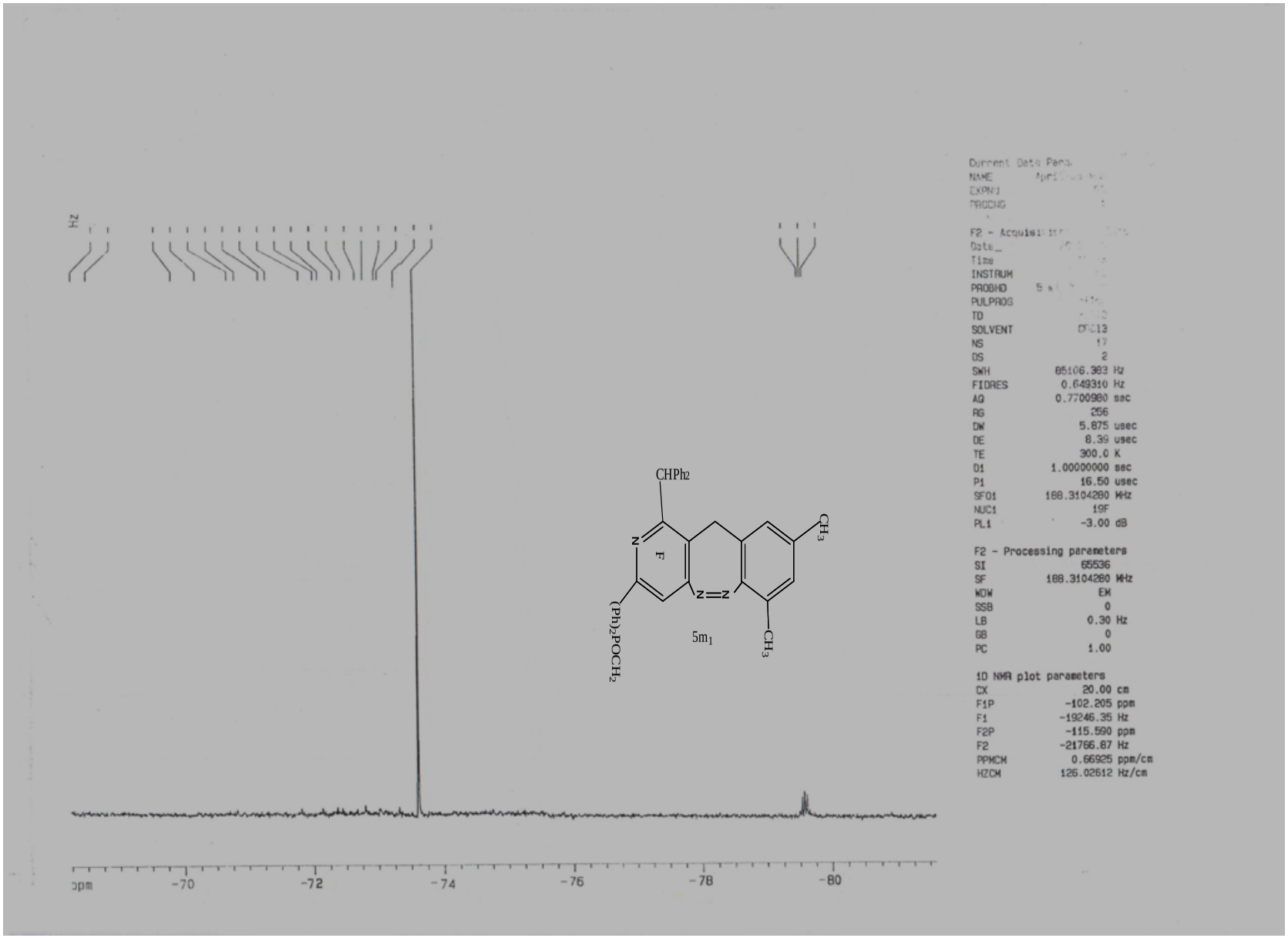


Current Data Parameters
NAME Apr10-03-akb
EXPNO 90
PROCNO 1

F2 - Acquisition Parameters
Date_ 2003041[illegible]
Time 16.13
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG zgflqn
TD 131072
SOLVENT CDCl3
NS 17
DS 2
SWH 65106.383 Hz
FIDRES 0.649310 Hz
AQ 0.[illegible] sec
RG 256
DW 5.875 usec
DE [illegible].29 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.310[illegible] MHz
NUC1 19F
PL1 -3.00 dB

F2 - Processing parameters
SI 65[illegible]6
SF 188.[illegible]3 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P -[illegible]2.205 ppm
F1 -[illegible].35 Hz
F2P -[illegible]5.590 ppm
F2 -[illegible].87 Hz
PPMCM 0.66925 ppm/cm
HZCM 126.02612 Hz/cm



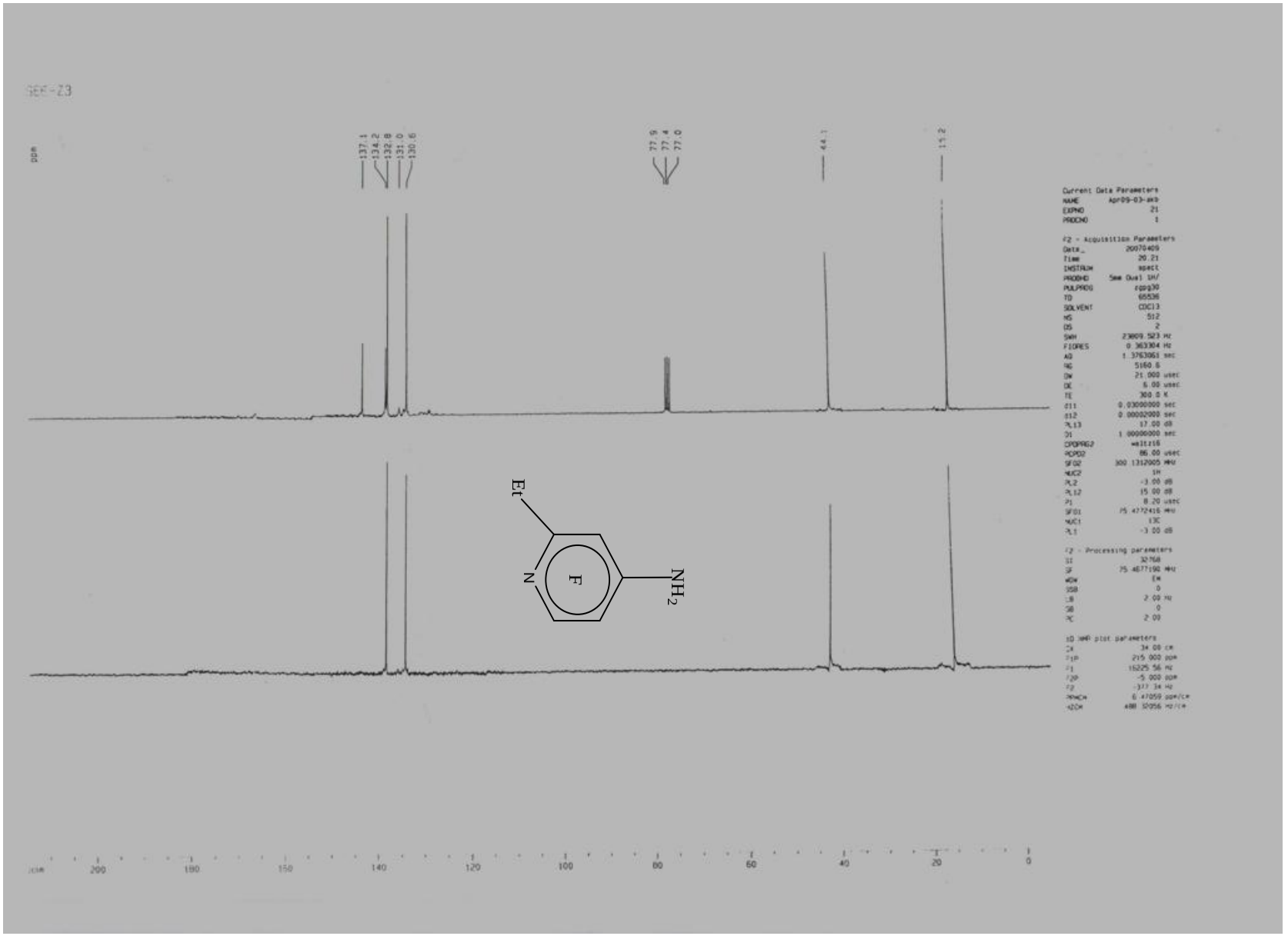
Current Data Para
NAME
EXPNO
PROCNO

F2 - Acquisition
Date_
Time
INSTRUM
PROBHD
PULPROG
TD
SOLVENT CDCl3
NS 17
DS 2
SWH 85106.383 Hz
FIDRES 0.649310 Hz
AQ 0.7700980 sec
RG 256
DW 5.875 usec
DE 8.39 usec
TE 300.0 K
D1 1.00000000 sec
P1 16.50 usec
SFO1 188.3104280 MHz
NUC1 19F
PL1 -3.00 dB

F2 - Processing parameters
SI 65536
SF 188.3104280 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

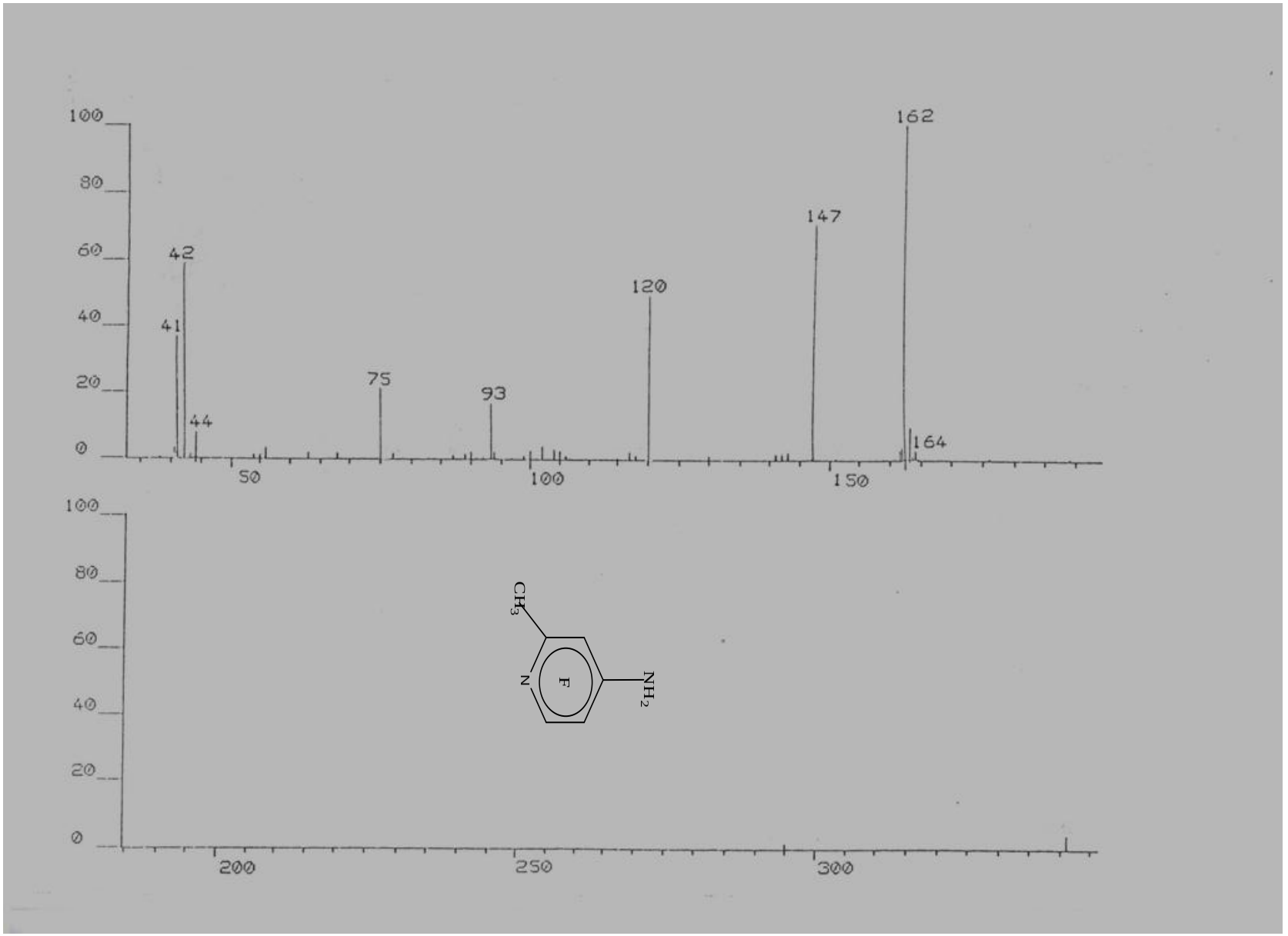
1D NMR plot parameters
CX 20.00 cm
F1P -102.205 ppm
F1 -19246.35 Hz
F2P -115.590 ppm
F2 -21766.87 Hz
PPMCM 0.66925 ppm/cm
HZCM 126.02612 Hz/cm

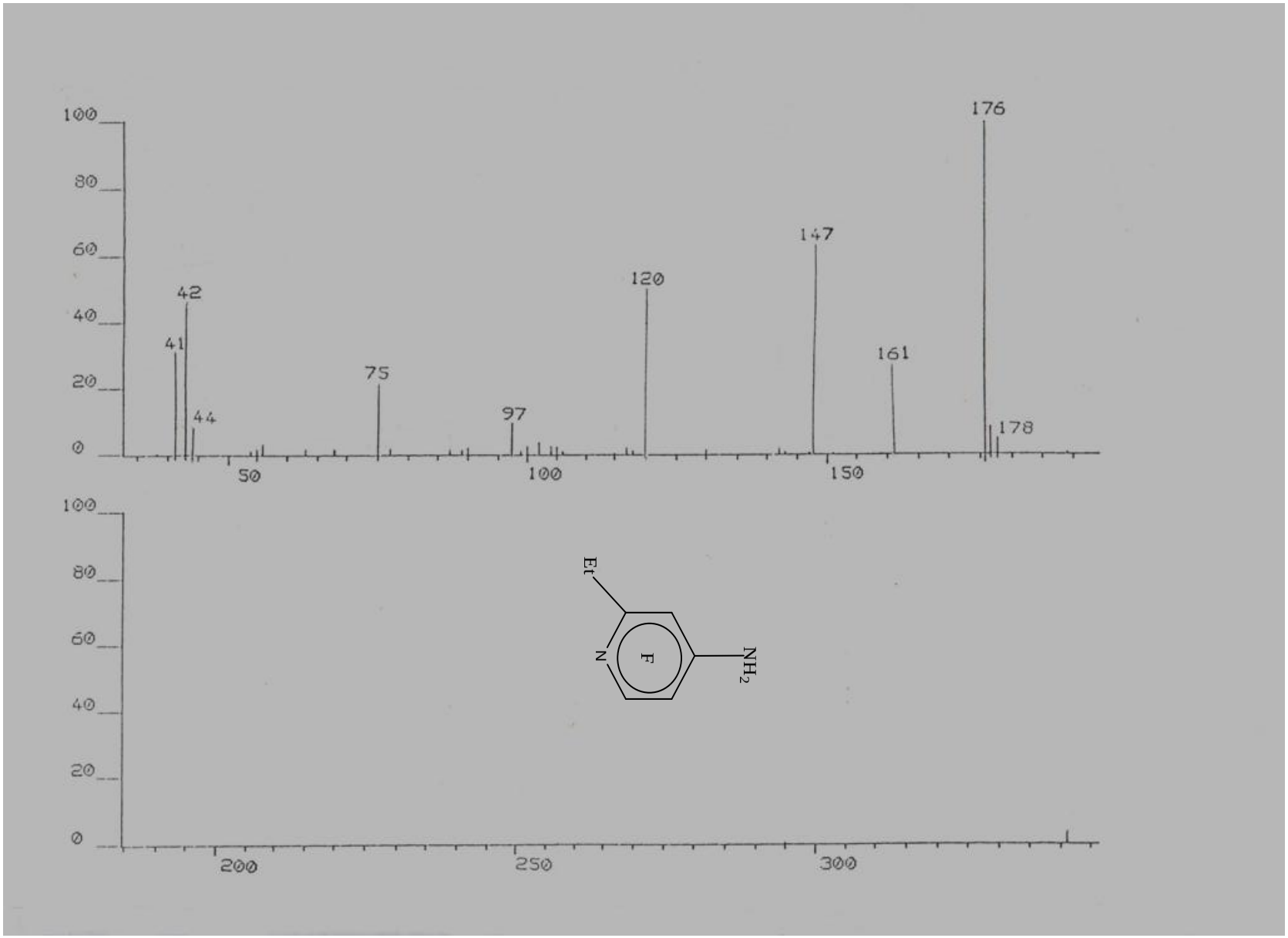
^{13}C spectrum

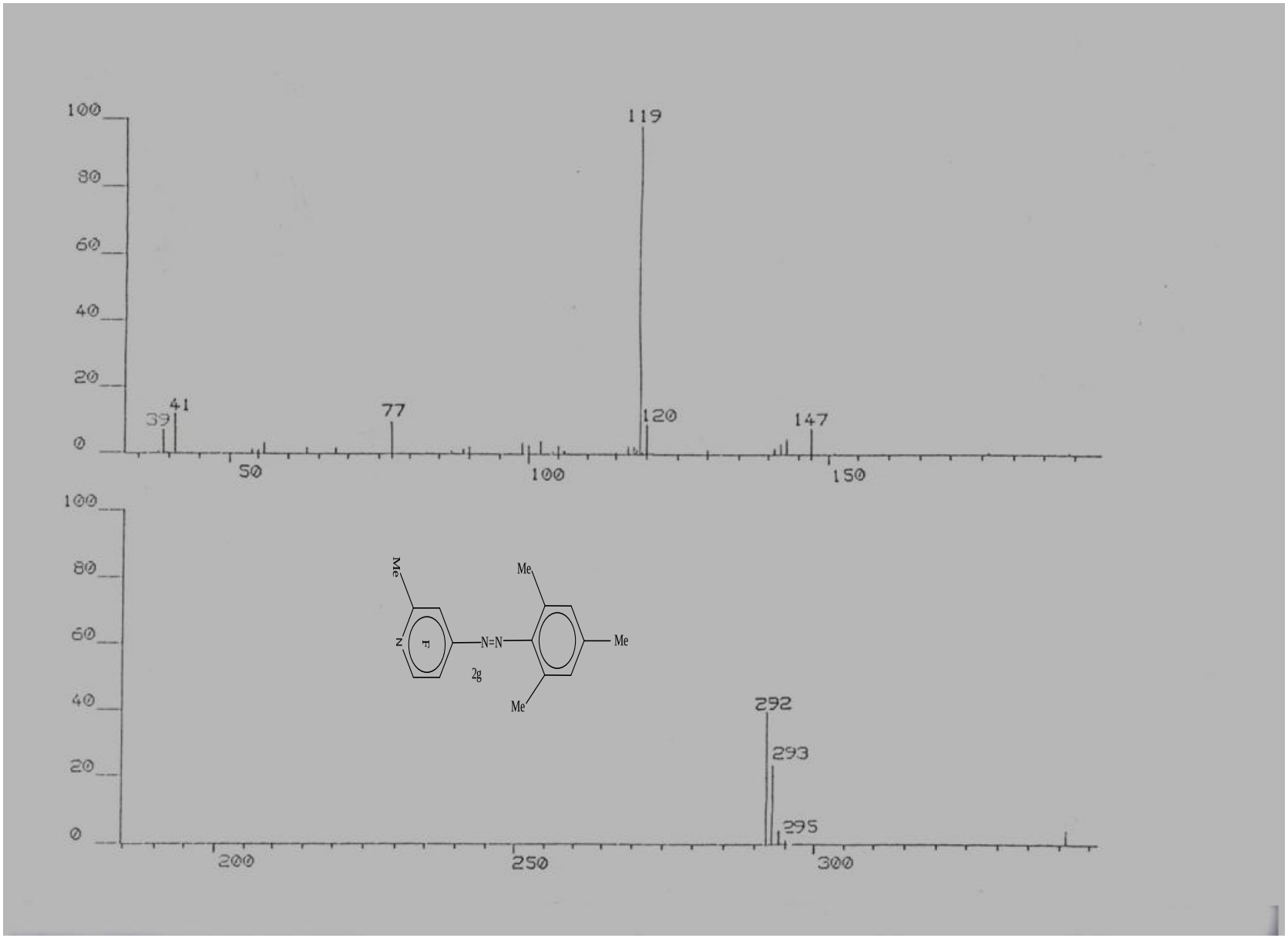

137.1
134.2
132.8
131.0
130.6
77.9
77.4
77.0
44.1
15.2
ppm
Et
N
F
NH2
200
180
160
140
120
100
80
60
40
20
0


SEK-Z2
ppm
207.6
172.7
132.1
131.9
131.5
130.9
78.0
77.6
77.2
47.8
24.1
18.2
nPr
N
F
NH2
Current Data Parameters
NAME Apr09-03-ak5
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20030409
Time 19.42
INSTRUM spect
PROBHD 5mm Dual (H/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 2
SWH 23809.523 Hz
FIDRES 0.363304 Hz
AQ 1.3763061 sec
RG 13004
DW 21.000 usec
DE 6.00 usec
TE 300.0 K
D11 0.03000000 sec
D12 0.00002000 sec
PL13 17.00 dB
D1 1.00000000 sec
CPDPRG2 waltz16
PCPD2 80.00 usec
SFO2 300.1312005 MHz
NUC2 1H
PL2 -3.00 dB
PL12 15.00 dB
P1 8.20 usec
SFO1 75.4772416 MHz
NUC1 13C
PL1 -3.00 dB
F2 - Processing parameters
SI 32768
SF 75.4677190 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 34.00 cm
F1P 215.000 ppm
F1 16225.56 Hz
F2P -5.000 ppm
F2 -377.34 Hz
PPMCM 6.47059 ppm/cm
HZCM 486.32056 Hz/cm
ppm
200
180
160
140
120
100
80
60
40
20
0

Appendix VI
Mass spectra


100
80
60
40
20
0
42
41
44
75
93
120
147
162
164
50
100
150
200
250
300
CH3
N
F
NH2


100
80
60
40
20
0
176
147
120
42
41
161
75
97
44
178
50
100
150
200
250
300
Et
N
F
NH2


100
80
60
40
20
0
119
41
39
77
120
147
50
100
150
Me
Me
N
F
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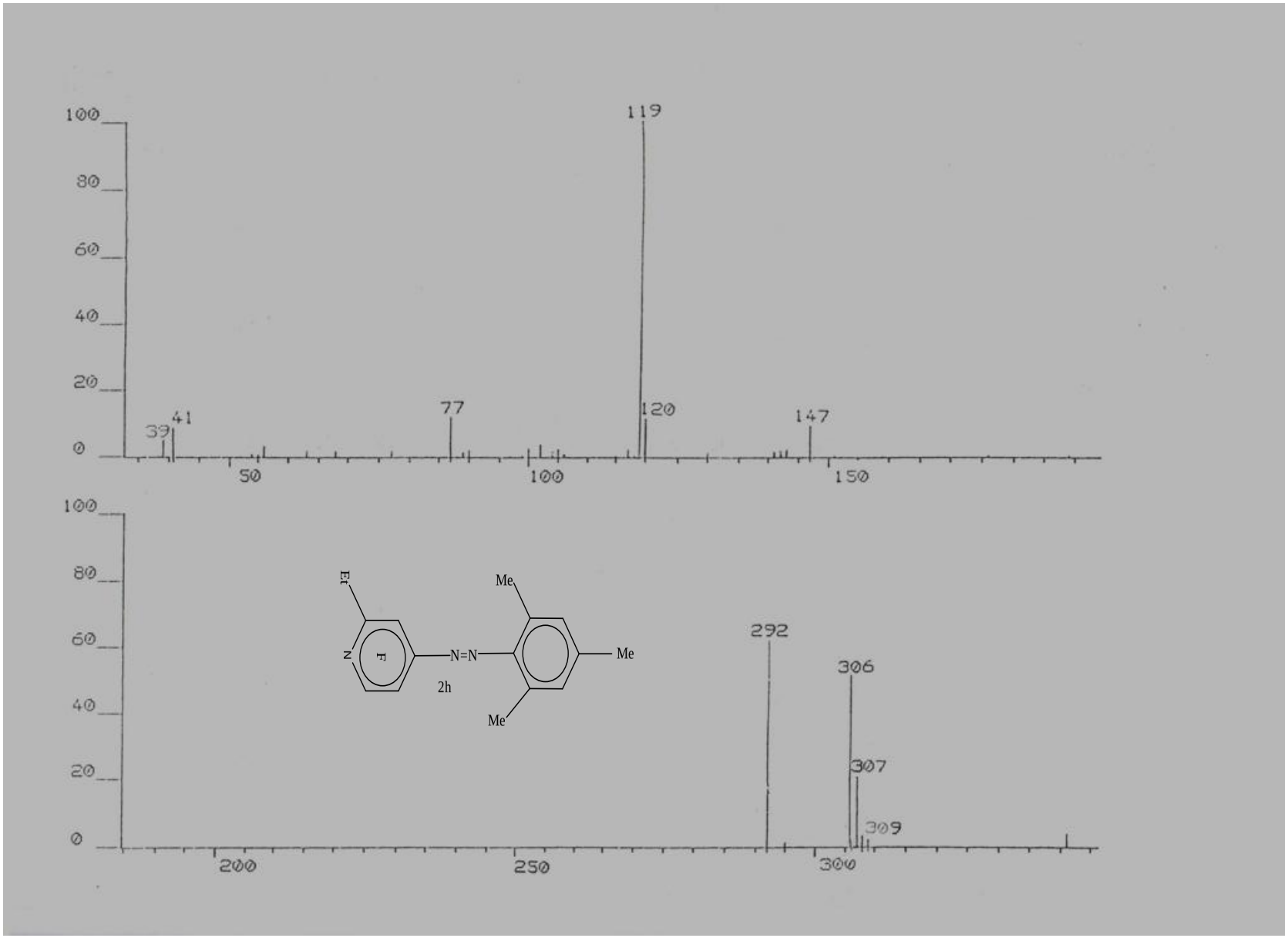
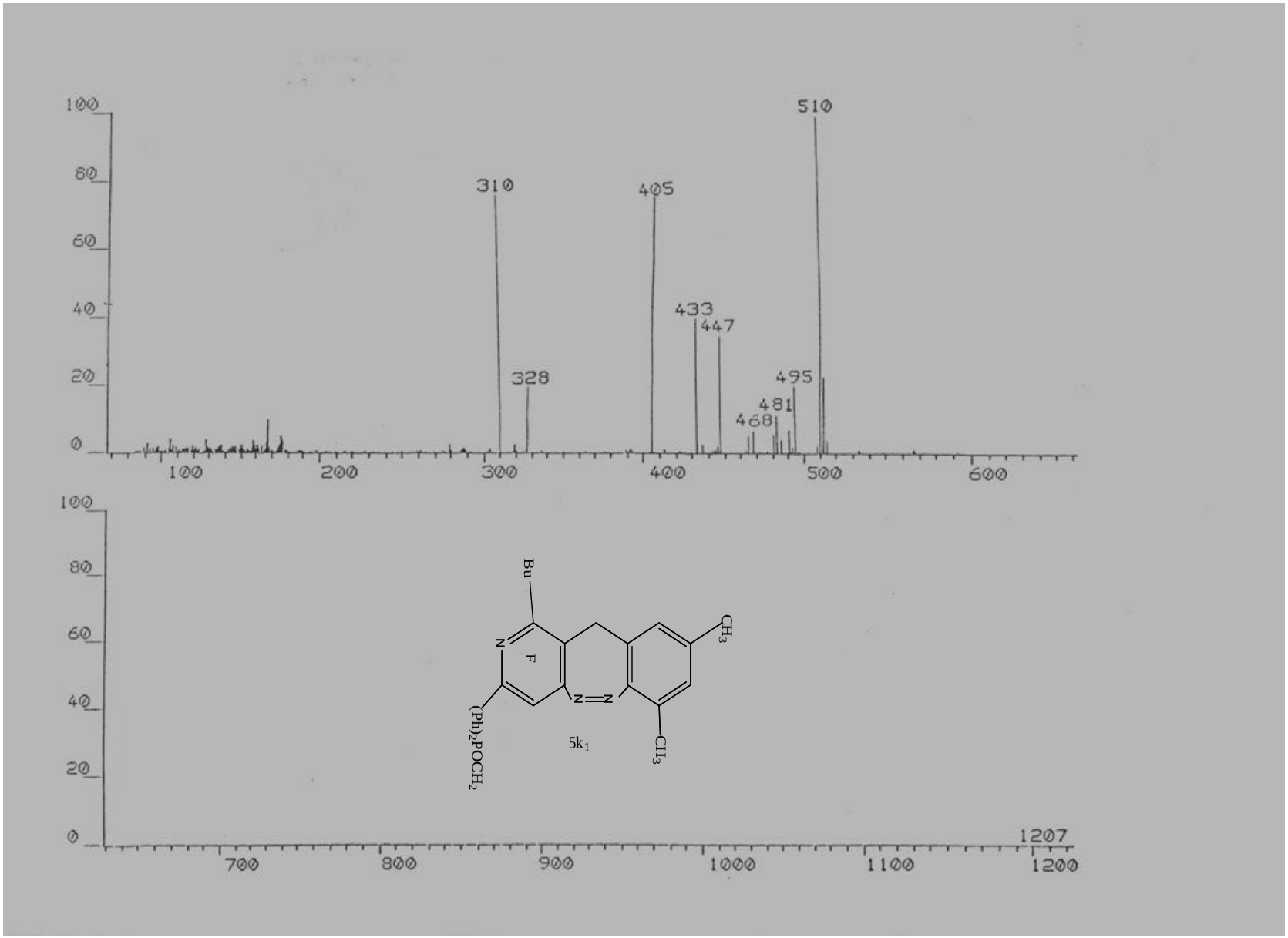
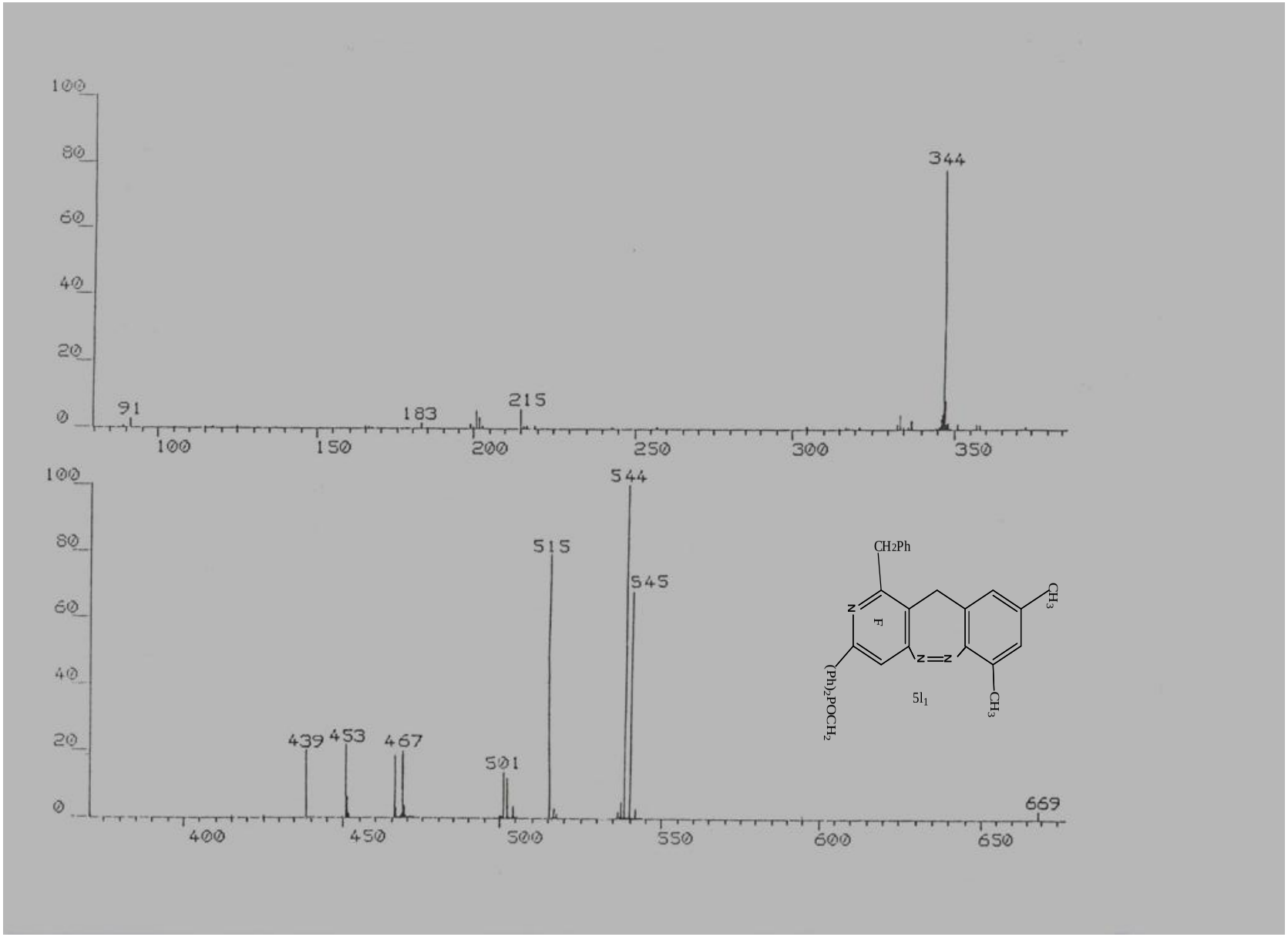
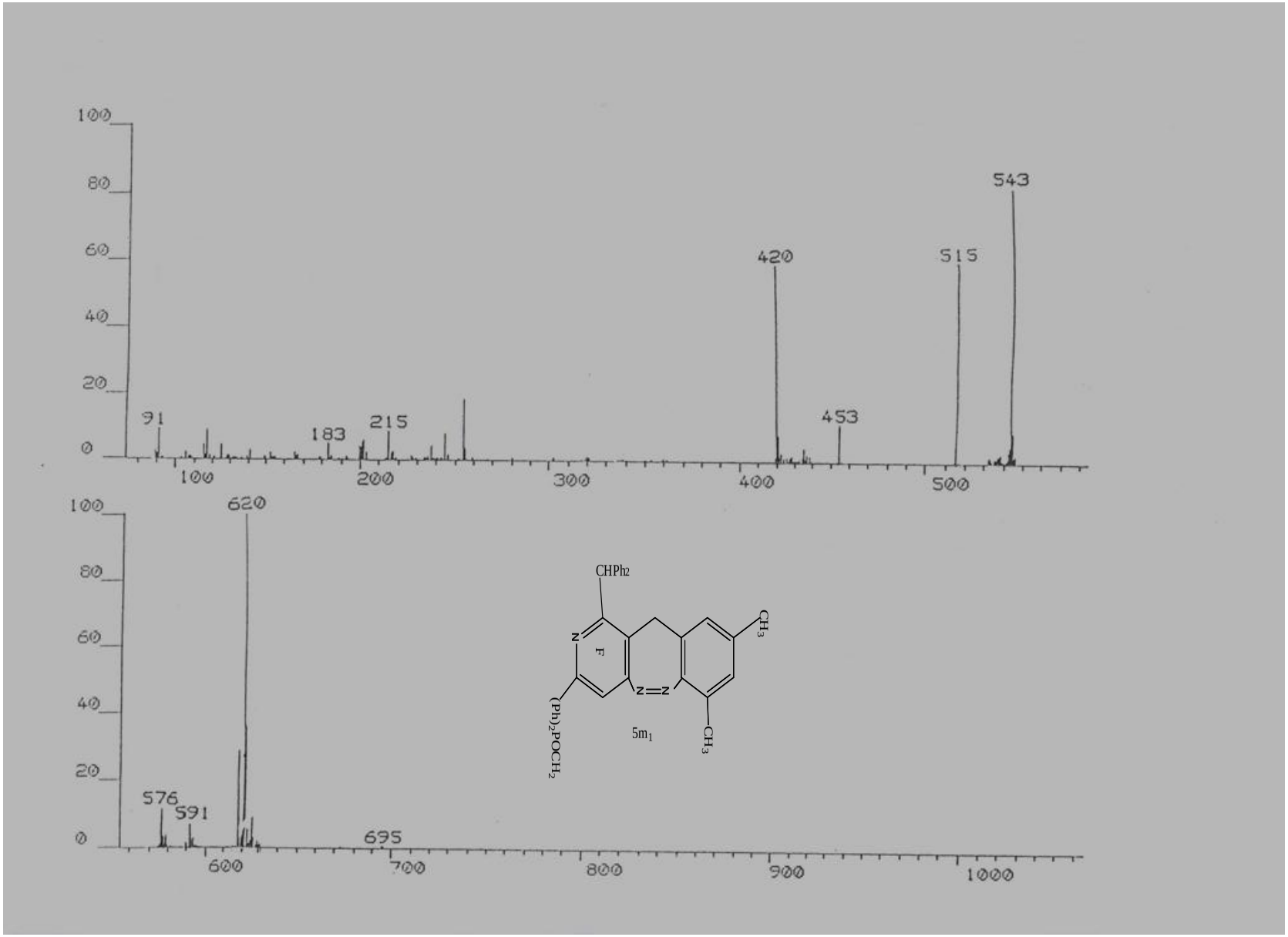
Me
Me
2g
292
293
295
200
250
300


100
80
60
40
20
0
119
41
39
77
120
147
50
100
150
100
80
60
40
20
0
Et
N
F
N=N
Me
Me
Me
2h
292
306
307
309
200
250
300


100
80
60
40
20
0
100
200
300
400
500
600
310
328
405
433
447
468
481
495
510
100
80
60
40
20
0
700
800
900
1000
1100
1200
1207
Bu
N
F
Z=Z
CH3
CH3
(Ph)2POCH2
5k1


100
80
60
40
20
0
91
183
215
344
100
150
200
250
300
350
544
515
545
439
453
467
501
669
400
450
500
550
600
650
CH2Ph
CH3
N
F
N=N
(Ph)2POCH2
5l1
CH3


100
80
60
40
20
0
91
183
215
420
453
515
543
100
200
300
400
500
620
576
591
695
600
700
800
900
1000
CHPh2
CH3
F
Z=Z
(Ph)2POCH2
CH3
5m1

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Part II

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