SYNTHESIS AND MASS SPECTROMETRY OF SOME NEW BENZENESULFONYL SUBSTITUTED ISOXAZOLIDINES

CEVHER ALTUĞ

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SYNTHESIS AND MASS SPECTROMETRY OF SOME NEW BENZENESULFONYL SUBSTITUTED ISOXAZOLIDINES

by

CEVHER ALTUĞ

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Approval of the Graduate School of Natural and Applied Sciences.

Prof.Dr.Davut KÖŞKER
Director

..... I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

Prof. Dr. Mahmut ACIMIŞ
Head of Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Sciences.

Prof.Dr.Yaşar DÜRÜST
Supervisor

Examining Committee Members

1.Prof.Dr.Nihat ÇELEBİ .....

2.Prof.Dr.Necdet COŞKUN .....

3.Prof.Dr.Yaşar DÜRÜST .....

ABSTRACT

SYNTHESIS AND MASS SPECTROMETRY OF SOME NEW BENZENESULFONYL SUBSTITUTED ISOXAZOLIDINES

ALTUĞ, Cevher

M.Sc. , Department of Chemistry

Supervisor : Prof.Dr.Yaşar DÜRÜST

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In this work, the 1,3-dipolar cycloaddition (1,3 DC) reactions of some nitrones including a new one to the dipolarophile phenylvinyl sulfone are described. To our best knowledge of literature survey, nine new isoxazolidine compounds have been synthesized. Purification of the title compounds have been performed by means of flash column chromatography on silica gel.Also much attention was focused on the fragmentation ways of the cycloadducts, namely benzenesulfonyl substituted isoxazolidines, in electron impact mass spectrometry and the routes leading to described fragmentations were interpreted in terms of stability and substituents existing on the isoxazolidine ring. The structures of benzenesulfonyl substituted isoxazolidines were elucidated by means of IR, NMR (^{1}H , ^{13}C), MASS spectra and physical

characteristics (melting points and R_f values). The stereochemistry of the isoxazolidine ring was determined by n.O.e experiments and was found to be *trans* configuration according to the groups on C-3 and C-4 carbons. Regiochemistry is also determined as to have been formed only 4-regioisomers but not 5-regioisomers based on the *J* coupling constants in ^{1}H-NMR and n.O.e data.

Keywords: 1,3-Dipolar cycloaddition , nitrones , isoxazolidine.

ÖZET

BAZI YENİ BENZENSULFONİL SUBSTİTUE İZOKSAZOLİDİN BİLEŞİKLERİNİN SENTEZİ VE KÜTLE SPEKRUMLARININ İNCELENMESİ

ALTUĞ, Cevher

Yüksek Lisans Tezi , Kimya Bölümü

Tez Danışmanı : Prof.Dr.Yaşar DÜRÜST

Aralık 2004, 119 sayfa

Bu çalışmada, biri yeni olmak üzere 10 adet nitron bileşiğinin dipolarofil reaktif olarak fenilvinil sülfon ile 1,3 dipolar halkalı katılma tepkimeleri araştırılmıştır. En son literatür araştırması esas alınarak 9 adet yeni benzensülfonil sübstitue izoksazolidin bileşiğinin sentezi gerçekleştirilmiştir. Katılma ürünleri olan izoksazolidin bileşiklerinin tepkime karışımından ayrılmaları ve saf maddeler olarak elde edilmeleri silika jel üzerinde flaş kolon kromatografisi yardımıyla olanaklı olmuştur. Bileşiklerin yapı aydınlatılması IR, NMR (^{1}H, ^{13}C), Kütle spektrumları ve bazı fiziksel sabitler (erime noktası, R_f değerleri) yardımıyla yapılmıştır. Ayrıca sentezi gerçekleştirilen sübstitue izoksazolidin bileşiklerinin elektron impakt kütle spektrumları üzerinde de yoğunlaşılmış ve parçalanma yolları sübstituentler ve oluşan parçalanma ürünlerinin kararlılıkları esas alınarak yorumlanmıştır.

Bileşiklerin stereokimyası n.O.e (nükleer Overhauser etkisi) deneyleri ile belirlenmiş ve C-3, C-4 karbonları üzerindeki grupların *trans* konfigürasyonda oldukları bulunmuştur.

Anahtar Kelimeler: 1,3-Dipolar halkalıkatılma , nitron , izoksazolidin.

TO MY SISTER

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I would like to thank my family for their strong support and encouragement of my studies.

Finally I would like to thank Merve, who brings immeasurable joy to my life by simply being a part of it.

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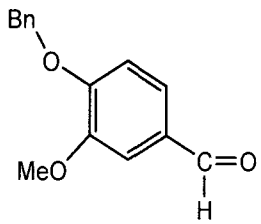

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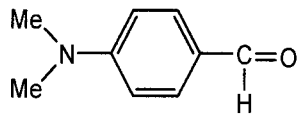

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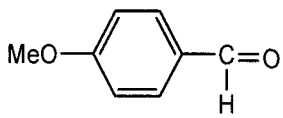

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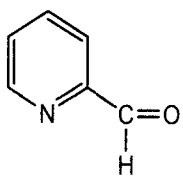

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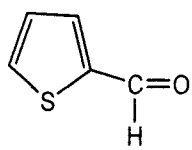

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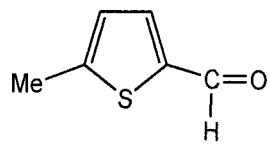

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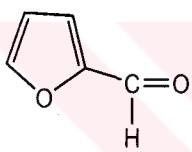

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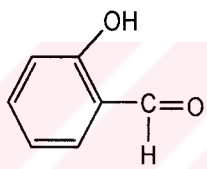

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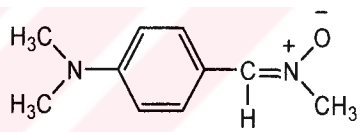

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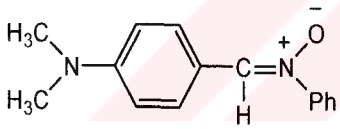

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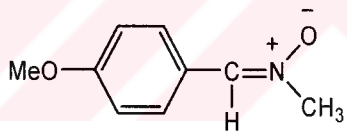

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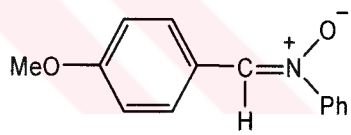

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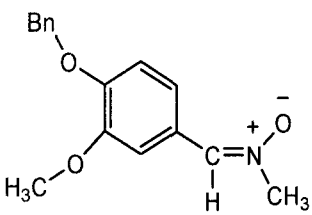

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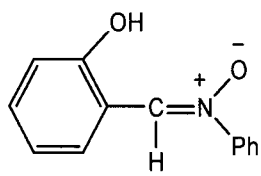

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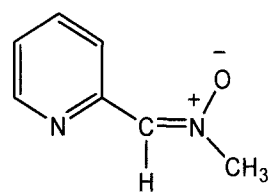

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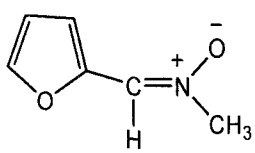

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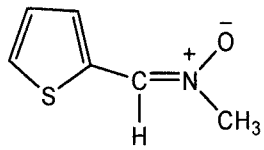

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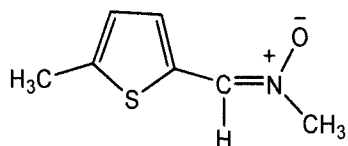

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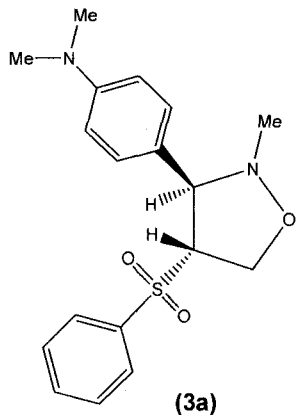

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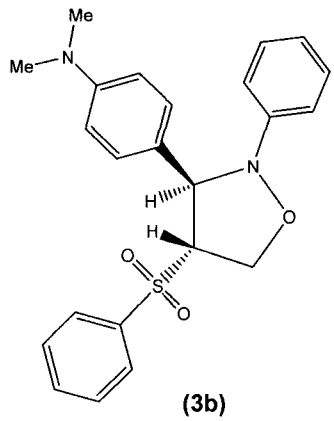

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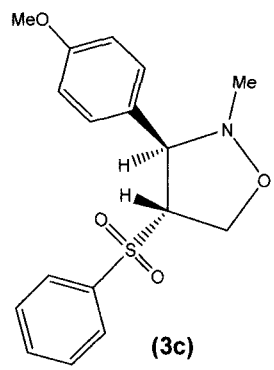

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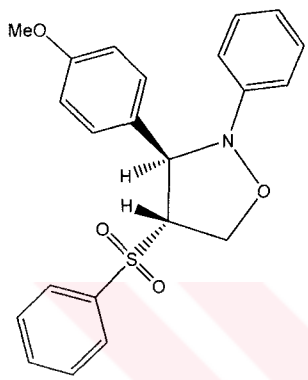

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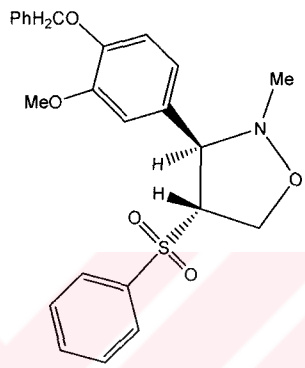

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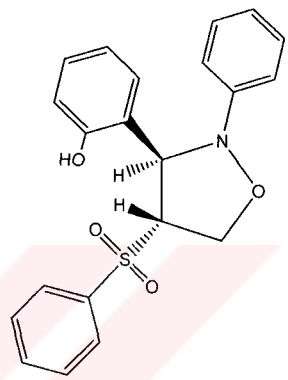

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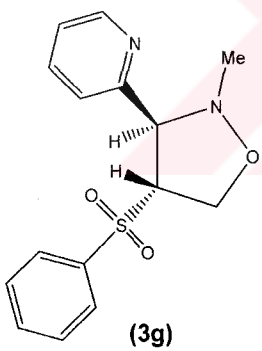

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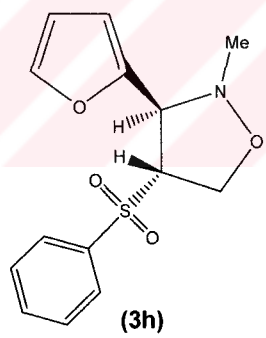

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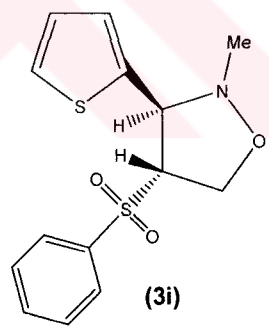

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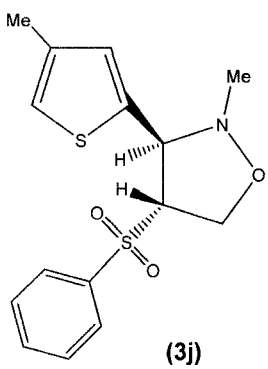

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LIST OF SYMBOLS AND ABREVIATIONS

Ph	Phenyl
Me	Methyl
E	Conformation
Z	Conformation
DC	Dipolar Cycloaddition
Et	Ethyl
MeO	Methoxy
Δ	Heat
CNDO	Complete Neglect of Differential Overlap
INDO	Intermediate Neglect of Differential Overlap
LUMO	Lowest Unoccupied Molecular Orbital
HOMO	Highest Unoccupied Molecular Orbital
EtOH	Ethyl Alcohol
THF	Tetrahydrofuran
EtOAc	Ethyl Acetate
Bn	Benzyl
NaOMe	Sodium Methoxide
MeOH	Methanol
IR	Infra Red
NMR	Nuclear Magnetic Resonance
MS	Mass Spectrometry

CHAPTER I :INTRODUCTION

1.1.THE 1,3-DIPOLAR CYCLOADDITION REACTION

The [3+2] 1,3-dipolar cycloaddition is a reaction where two organic compounds, a dipolarophile, and a 1,3-dipole (or ylide), combine to form a five membered heterocycle (Figure 1.1). From simple starting materials, the 1,3-dipolar cycloaddition (DC) reaction can furnish very complex heterocycles, containing multiple stereogenic centres. Therefore this reaction is often used as a key step in the syntheses of many natural products and pharmaceuticals. After its discovery in 1888[1], with diazoacetic ester as the 1,3-dipole, various other 1,3-dipoles have been used in this type of reaction.

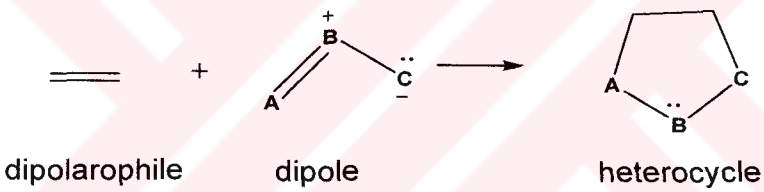


Figure 1.1

1.1.1.The 1,3-dipole/ylide

The 1,3-dipole, also known as an ylide, bears a positive and a negative charge distributed over three atoms and has 4π electrons. The most common atoms incorporated in the 1,3-dipole are nitrogen, carbon, oxygen or sulfur.

Representative examples of some 1,3-dipoles are shown in Figure 1.2, but other types of 1,3-dipoles also exist.[2] These are divided into two groups, the allyl anion type which has a bent structure and the propargyl/allenyl anion

type with a linear structure as shown in Figure 1.2. Each of these dipoles has four resonance structures as exemplified for the nitrone and the diazoalkane in Figure 1.2. The ylide can, depending on the nature of the 1,3-dipole exist in an equilibrium between an *E*-form and a *Z*-form. This can have consequences for the diastereoselectivity in reactions with dipolarophiles.

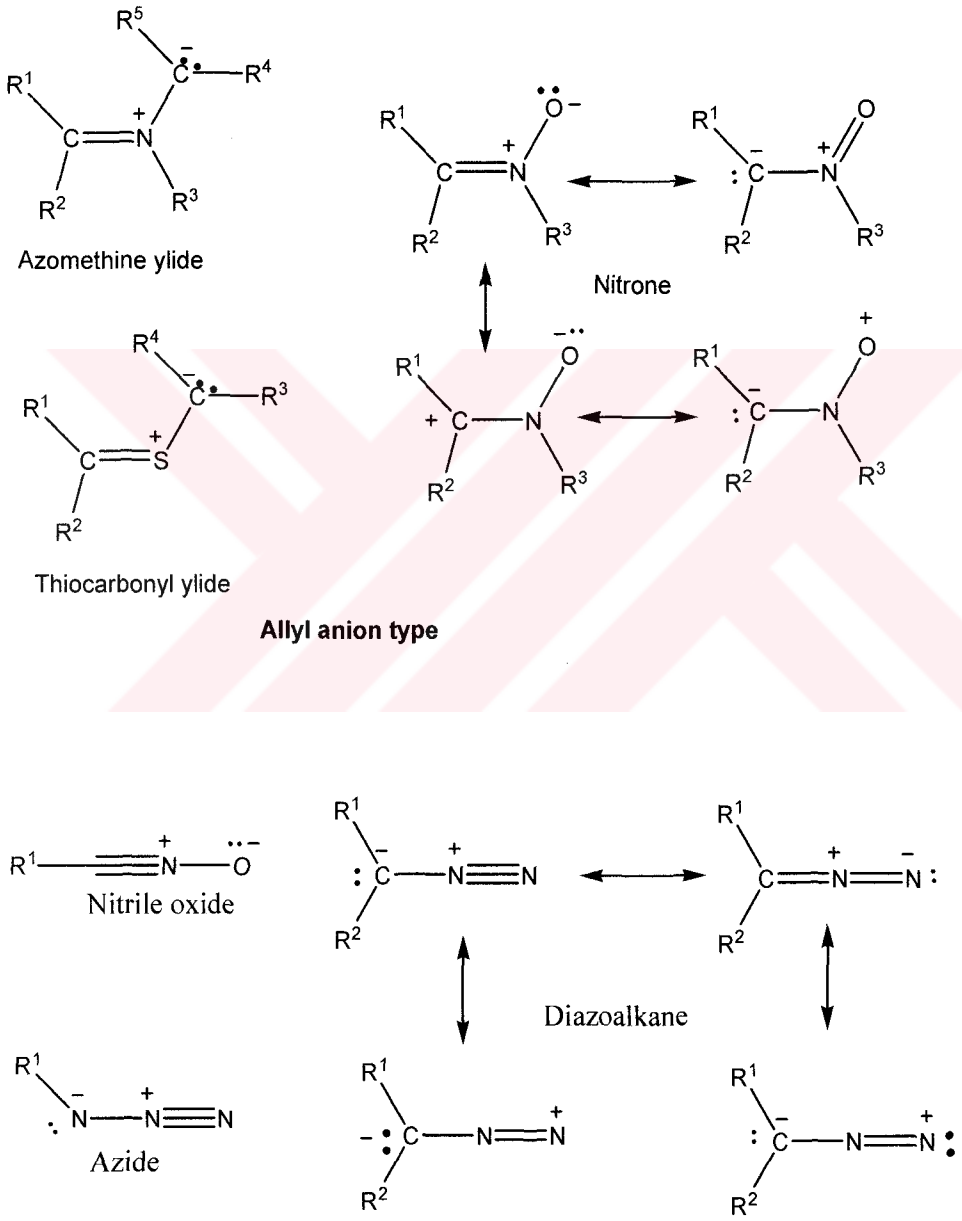
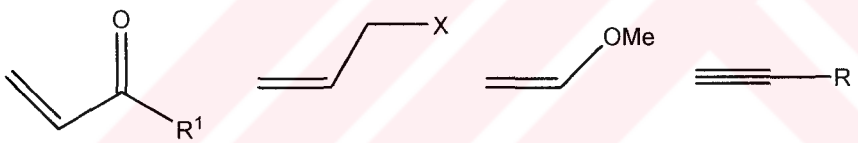


Figure 1.2.

1.1.2.The dipolarophile

The dipolarophile in a 1,3-dipolar cycloaddition is a reactive alkene moiety containing 2π electrons. Thus, depending on which dipole that is present, α,β-unsaturated aldehydes, ketones, and esters, allylic alcohols, allylic halides,vinylic ethers and alkynes are examples of dipolarophiles that react readily(Figure 1.3). It must be noted, however, that other 2π-moieties such as carbonyls and imines also can undergo cycloaddition with dipoles. The alkene moiety can be mono-, di-, tri- or even tetrasubstituted (only monosubstituted ones are shown here). However, mostly due to steric factors, tri- and tetrasubstituted ones often display very low reactivity in reactions with dipoles.



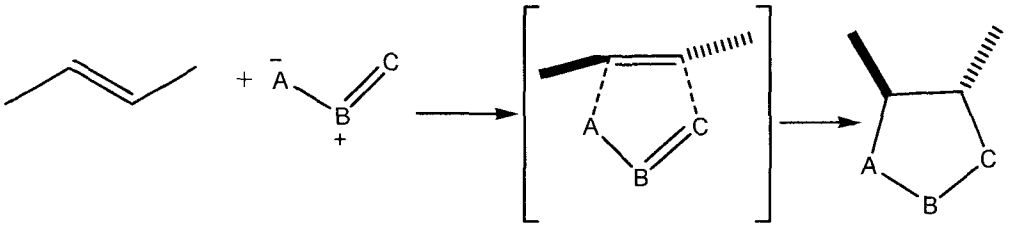
R^1 = H,Me or MeO X = OH or halogen

Figure 1.3.

1.1.3.Mechanistic aspects

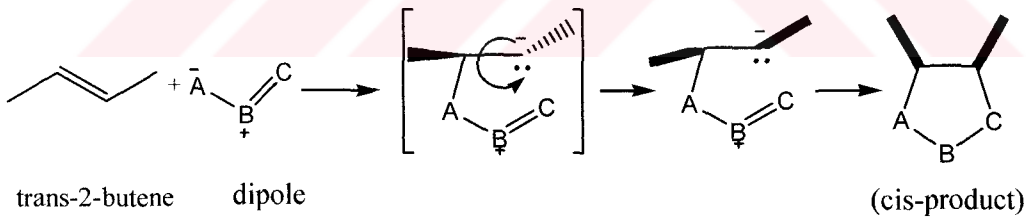
The 1,3-dipolar cycloaddition reaction of a 1,3-dipole with a dipolarophile involves the 4π electrons of the dipole/ylide and the 2π electrons of the dipolarophile . The reaction mostly proceeds in a concerted manner, which means that all bonds are created simultaneously, but not necessarily to the same extent at a certain time. Consequently, the stereochemistry of the dipolarophile is conserved in the final product. This is exemplified in Scheme

1.1 where *trans*-2-butene reacts with the hypothetical dipole furnishing exclusively *trans*-product. Starting from the cis-2-butene will thus yield the *cis* product.



Scheme 1.1

If, on the other hand, the reaction proceeds *via* a two step mechanism, the stereochemistry of the starting dipolarophile is not necessarily conserved throughout the whole reaction. This is exemplified in Scheme 1.2, where *trans*-2-butene reacts with the dipole in a two step fashion furnishing the diastereomer *cis*-product *via* isomerisation of the starting dipolarophile.

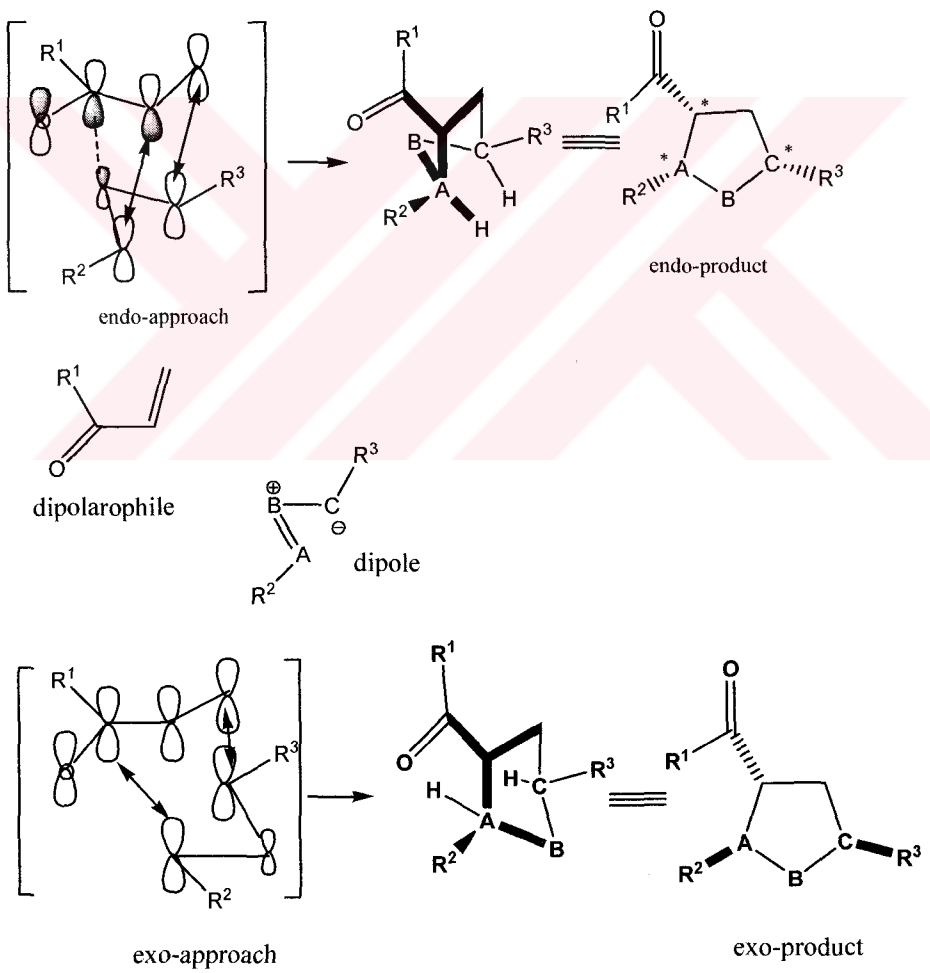


Scheme 1.2

Depending on the nature of the dipole and the dipolarophile, the 1,3-dipolar cycloaddition reaction is controlled either by a LUMO(dipolarophile)-HOMO (dipole) or a LUMO(dipole)-HOMO(dipolarophile) interaction but in some cases a combination of both interactions is involved.[3] An example of a LUMO(dipolarophile)-HOMO(dipole) controlled reaction is depicted in Scheme 1.3. The approach of the dipole to the dipolarophile can occur in an

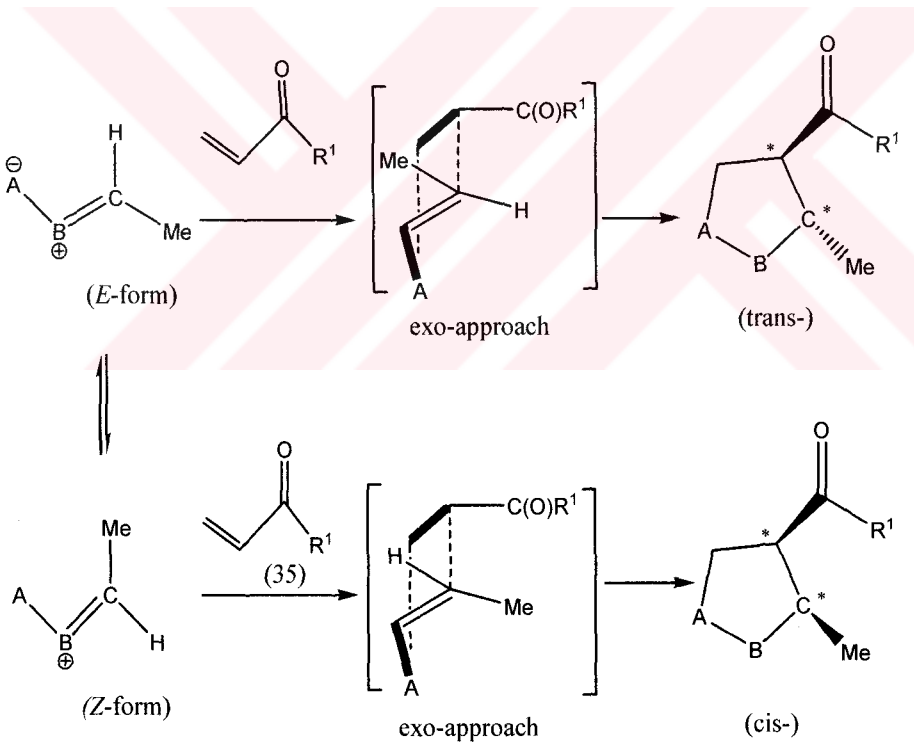
endo or exo mode resulting in two diastereomeric endo/exo cycloadducts, *endo*-cycloaddition product and *exo*-cycloaddition product, respectively. An overview over both these approaches is depicted in Scheme 1.3 where the endo approach is stabilised by small secondary π-orbital interactions, contributing to the endo/exo selectivity of the reaction.

However, other factors such as steric ones can have a major influence on this endo/exo selectivity and can often override this stabilising effect.



Scheme 1.3

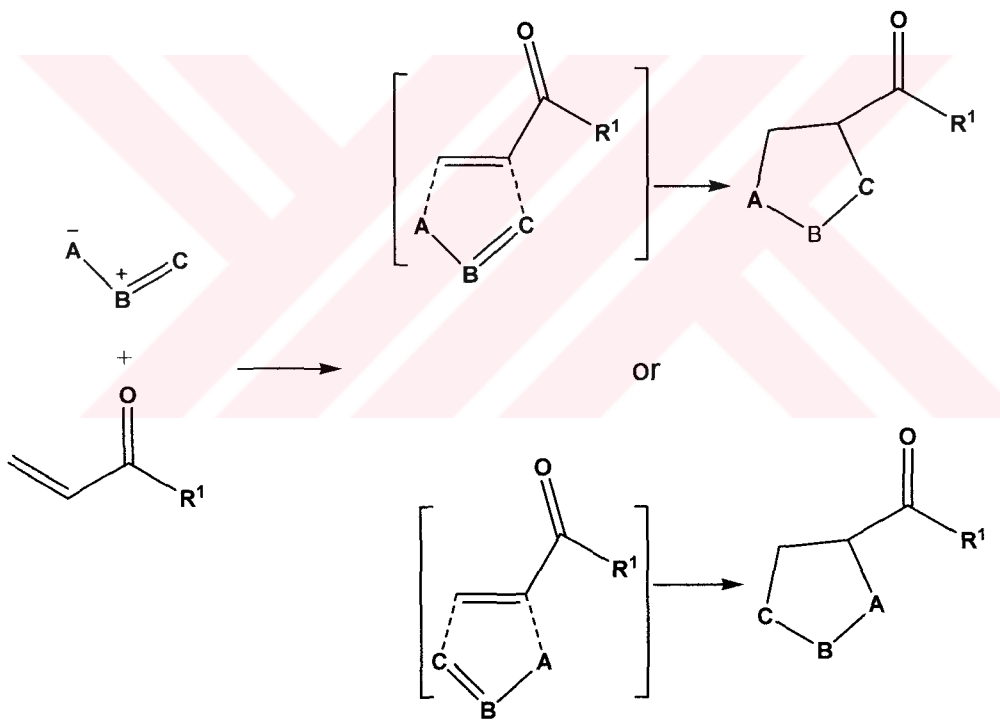
Moreover, depending on the substitution pattern of the ylide, this can exist in an equilibrium between a *Z*-form and an *E*-form. Reaction of each of these isomers with a dipolarophile, gives rise to diastereomeric cycloadducts, provided that the approach of these (endo or exo) is the same. This is exemplified in Scheme 1.4 where *E*-form and *Z*-form of ylides react with the dipolarophile *via* an exo-approach furnishing diastereomeric cycloadducts *trans*-product and *cis*-product respectively. The cis/trans nomenclature for the description of the stereochemistry of the cycloadducts is thus often used instead of the exo/endo one to avoid confusion when ylides existing as an equilibrating mixture of *Z*/*E* isomers are used.



Scheme 1.4. Reaction of two Z/E isomers of ylide with dipolarophile via an exo-approach.

In addition to the issues concerning diastereoselectivity discussed above,

regioselectivity related ones can also arise. Thus, when both the ylide and the dipolarophile are nonsymmetric, regioisomeric adducts can be formed. This is exemplified in Scheme 1.5, where the hypothetical ylide reacts in two different modes with dipolarophile, giving rise to the regioisomeric cycloadducts. Nitrones are examples of nonsymmetric ylides, which upon reaction with nonsymmetric dipolarophiles sometimes furnish two regioisomeric cycloadducts. Depending on electronic factors and the substitution pattern of the ylide and the dipolarophile, both modes of addition of the ylide to the dipolarophile can occur.[4-5]



Scheme 1.5- Two alternative approaches of a hypothetical ylide to dipolarophile giving rise to regioisomers.

1.2.NITRONES

1.2.1.Structure of Nitrones [6]

Nitrones are usually represented by formulae as shown in Figure 1.4, which imply that there is a positive charge on the nitrogen. However it has to be made clear that this positive charge is delocalized between the nitrogen and the α-carbon as represented in Figure1.4, resulting in a 1,3-dipolar structure.

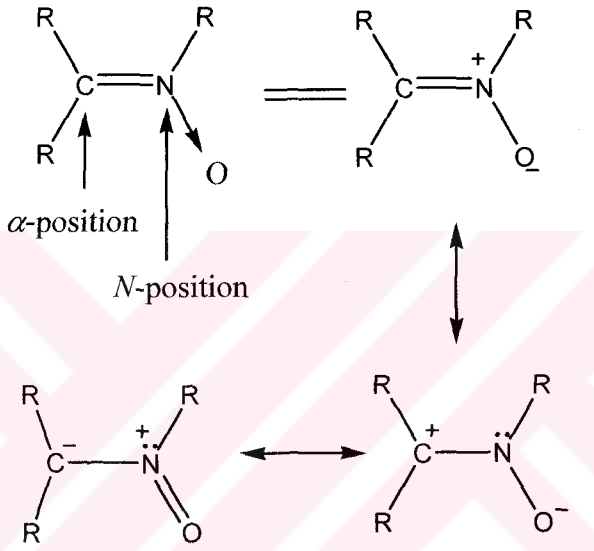


Figure 1.4.

The extent of this delocalization will naturally be influenced by the substituents in the α-position as well as on the nitrogen, which therefore will also have a marked influence upon the reactivity of the nitrone function.

It is necessary to make a general remark regarding the various nomenclatures used in nitrones. There are two positions in the parent nitrone molecule: the α-position and the *N*-position (see Figure 1.4.). The α-position is often referred to as the *C*-position. In addition nitrones are often called Schiff base *N*-oxides (e.g. *N*-benzylidene-*N*-methylamine *N*-oxide) or aldehyde *N*-alkyloximes or aldehyde *N*-alkyl nitrones. In the older literature

aldehyde *N*-alkyloximes or aldehyde *N*-alkyl nitrones. In the older literature nitrones were often called oxime *N*-alkyl ethers. The names of cyclic nitrones are usually derived from the name of the parent heterocycle.

1.2.1.1. Theoretical calculations

Ab initio molecular orbital calculations have been carried out for the parent molecule in Figure 1.5 and its eight isomers, showing that formamide is far more stable than the other isomers. However, the calculated dipole moment of 4.99 D was quite far from the experimental value of 3.37-3.47 D. Subsequent CNDO/2 and INDO calculations gave results closed to the experimental values CNDO/2 was also used to calculate the α- and π-electron density of α-phenyl *N*-methyl nitrone.

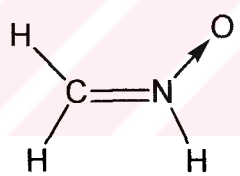


Figure 1.5. Example of a simple nitrone

1.2.1.2. Nonspectral physical methods

1.2.1.2.1. X-ray studies.

The structures of two nitrones have been determined by this method. Lipscomb and coworkers have determined the structures of *C*-*p*-chlorophenyl *N*-methyl nitrone Figure 1.6 and compared its bond lengths to those of the isomeric *O*-methyloximes of *p*-chlorobenzaldehyde(see Figure 1.7) [7].The

bond angles of *C*-*p*-chlorophenyl *N*-methyl nitrone are indicated in the formula. The N—O bond length in nitrone was found to be 1.284 Å. considerably shorter than the N—O distance in the isomeric syn oxime (1.408 A) indicating the partial double-bond character of this bond in

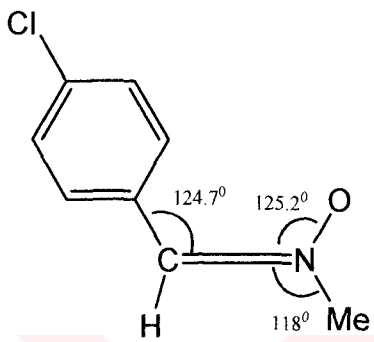


Figure 1.6. *C*-*p*-Chlorophenyl-N-methyl nitrone

the nitrone. Moreover the C=N distance of 1.309 Å in the nitrone is longer than the corresponding bond in the *O*-methyloxime (1.260 Å). The data found for α,α-*N*-triphenyl nitrone (see Figure 1.7) are indicated in the formula.

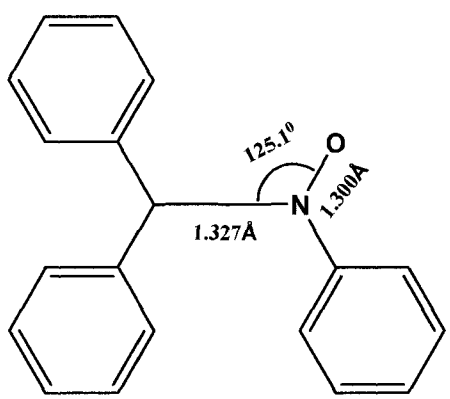


Figure 1.7

1.2.1.2.2. Mesomorphism

Some nitrones are found to exhibit mesomorphism. This property can be exploited for the formation of liquid crystals.

1.2.1.2.3. Dipole moment and acid base properties

Dipole moments have been determined for several series of nitrones and found to be 3.37-3.47 D; this confirms the dipolar structure indicated previously.

In a study of a series of *N*-phenyl nitrones having variously substituted aryl or heteroaryl groups in the α-position it was found that the *N*-oxide group is capable of acting either as an electron acceptor or as an electron donor contributing to the effects of electron-donating and electron-withdrawing substituents. This can be illustrated for α-(*p*-nitrophenyl) and α-(*p*-anisyl) nitrones in Figure 1.8. Similar results have been found in a series of *N*-methyl nitrones.

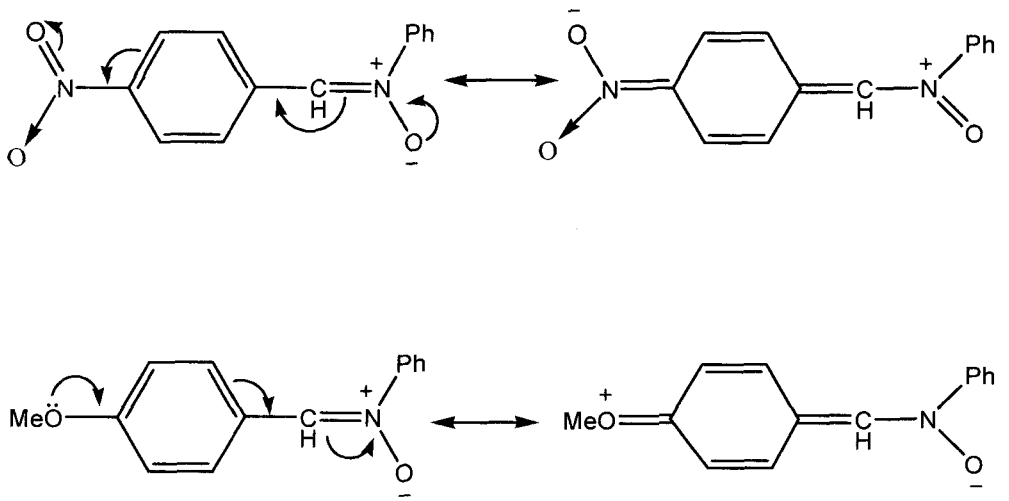


Figure 1.8.

The ionization constants of a series of conjugate acids of substituted phenyl nitrones (see Figure 1.9) and other aryl nitrones have been determined by potentiometric titration.

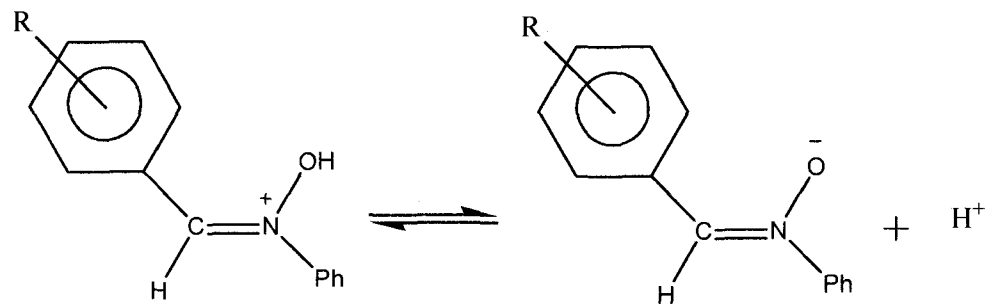
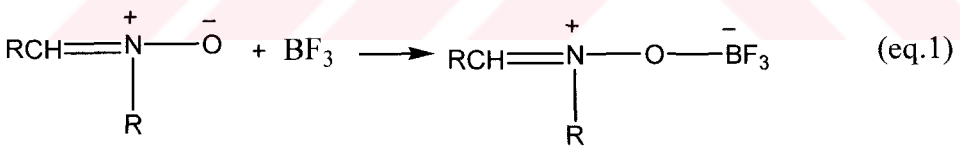


Figure 1.9

The values obtained could best be correlated with the δ^+ values of the substituent R.The basicity of a nitrones towards a Lewis acid (BF_3) has also been studied.Complexation with boron trifluoride(equation 1) increased the dipole moment by approximately 5 D. Calculations indicated that approximately 0.43 e was transferred from the oxygen to the boron.



(eq.1)

The rate constants of the exchange of α ,*N*-diaryl nitrones and the α -methyl hydrogens of α -aryl *N*-methyl nitrones with deuterium have also been correlated with the substituent constants of the groups in the aryl rings. The electron-withdrawing effect of the *N*-oxide group has been found to have strong influence on the sensitivity of the methine hydrogen exchange to substiuent effects.

1.2.1.3.Spectra of Nitrones

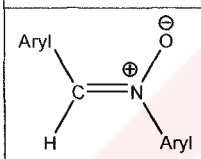
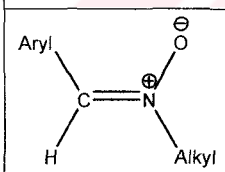
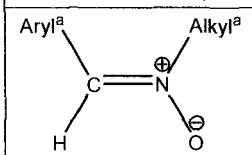
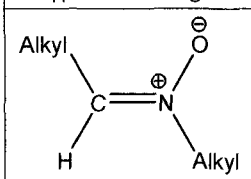
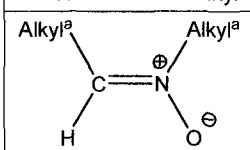
1.2.1.3.1.Photoelectron spectra

The photoelectron spectra of a number of nitrones have been measured and various ionization potentials have been assiged. The correlation of these with the mode of 1,3-cycloaadditions of nitrones has also been discussed.

1.2.1.3.2.Ultraviolet spectra

A large number of papers report that the influence of steric effects and of solvents effects upon the ultraviolet spectra of nitrones. Spectral data of various types of nitrones are summerized in Table1.

TABLE.1.Ultraviolet spectral data of various types of nitrones in alcohol solvents

Type	$\lambda_{max}\,(nm)$	$\varepsilon_{max} \times 10^{-3}$
	227-240 247-280 310-372	7-17 6-12 8-20
	205 221 290	8 7 14-17
	211 228 304	6 12 16
	244	6
	230-235	8-9

1.2.1.3.3.Infrared spectra.

It is generally accepted now that nitrones exhibit two characteristic bands resulting from N→O and C=N bond stretching vibrations. The N→O band appears in aromatic ketonitrones in the region of 1200-1300cm^{-1} while in aldonitrones it is seen between 1050-1170 cm^{-1} .The C=N stretching vibration appears in aromatic nitrones at 1350-1600cm^{-1} and in aliphatic and alicyclic nitrones at 1570-1620 cm^{-1}.

1.2.1.3.4.Nuclear Magnetic Resonance Spectra;

Only proton chemical shifts are available. Some typical chemical shifts of protons adjacent to the nitrones function are listed in Table 2.

In addition to these general data there are some additional features of interest in the NMR spectra of nitrones. The spectra of α-aryl aldonitrones and α,α-diaryl nitrones show signals corresponding to two hydrogens at a field lower than the rest of the aromatic hydrogens. These low field signals have been assigned to the two ortho hydrogens of the phenyl group situated syn to the nitrone oxygen (see Figure 1.10) and apparently arise from its deshielding influence. The magnitude of this deshielding influence has been found comparable to that of the nitro group. In contrast, the deshielding effect of the nitrone group upon the *meta* protons of aryl groups attached to it is very weak.

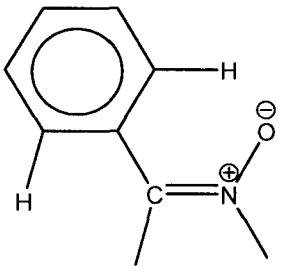
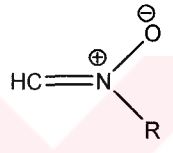
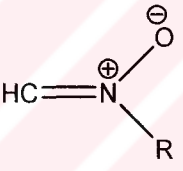
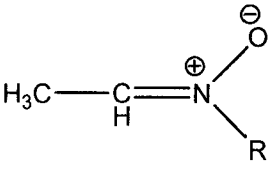
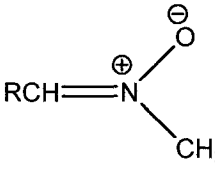
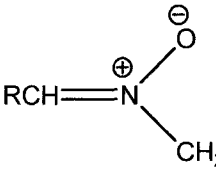


Figure 1.10

TABLE 2. Approximate chemical shifts of protons in the vicinity of the nitrone function

Position	**Chemical shift,** $\delta(ppm)$
Alkyl 	6.4-6.7
Aryl 	7-8
	2
	3.4-4
	5

From a study of a series of substituted α,*N*-diaryl nitrones it appears that

there are nonbonded interactions between the *ortho* substituent of the α-phenyl group and the *N*-oxygen as there are between the *ortho* substituent of the *N*-phenyl group and the α-hydrogen. As a consequence of this the stable conformation of 2.2'-dimethyl-α-*N*-diphenyl nitrone would be as indicated by Figure 1.11 and the hydrogen at position 6 appears at the unusually low field of 9.5 ppm due to the deshielding effect of the oxygen.

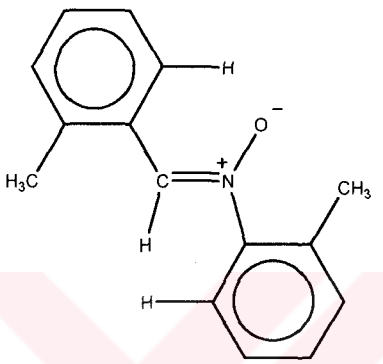


Figure 1.11

In 2.6-unsubstituted α-phenyl nitrones the phenyl group rotates freely and the two *ortho* hydrogens become magnetically equivalent. With more hindered 2.6-disubstituted aryl groups in the α-position of a nitrone it has been possible to obtain and isolate stable (*E*)-aldonitrones in addition to the predominant (*Z*) isomers (see Figure1.12). The NMR spectra show the *N*-methyl of *(E)*-isomer at higher field (3.4 ppm) than that of the (*Z*) isomer (3.90 ppm), while the opposite trend is observed for the vinyl proton [(*Z*)-isomer: 7.6 ppm; *(E)*-isomer; 7.9 ppm]

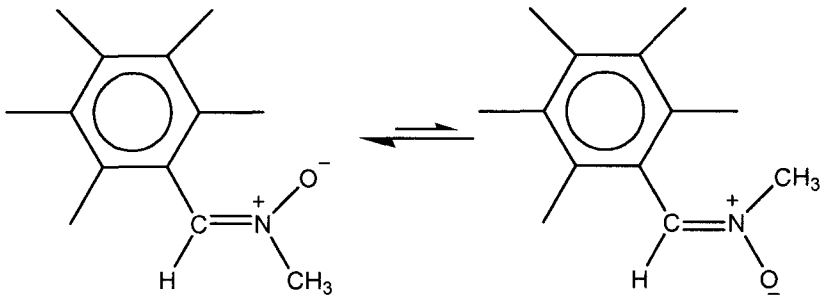


Figure 1.12

In cyclic nitrones of various ring-sizes it has been found that there is a homoallylic coupling between two groups that lie in a transoid fashion across the nitrone function. The magnitude of the coupling constant varies somewhat with the ring-size (see Figure 1.14).

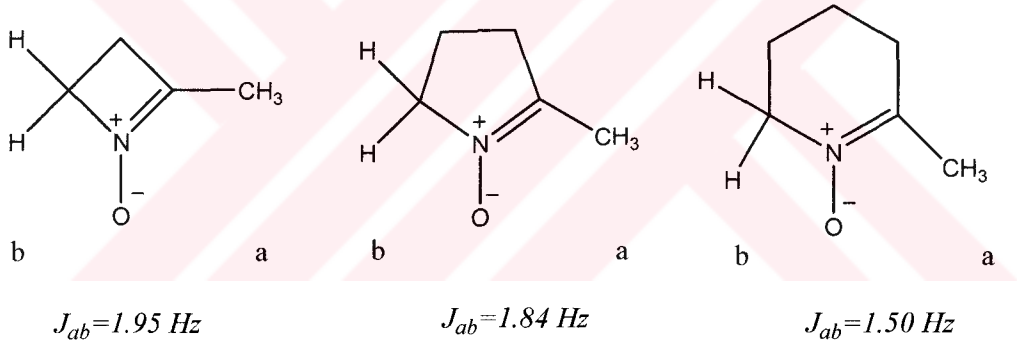


Figure 1.13

NMR spectroscopy has also become a convenient tool to study geometrical and other isomerizations of nitrones since the spectra of the pairs of compounds involved are often found sufficiently different. For example the interconversion between the (*Z*) and (*E*) isomers has been followed by examining the aromatic methyl signal, while the equilibrium composition of a series of α-aryl *N*-benzyl nitrones has been examined by integrating the *N*-benzyl CH_2 signal (equation 2)

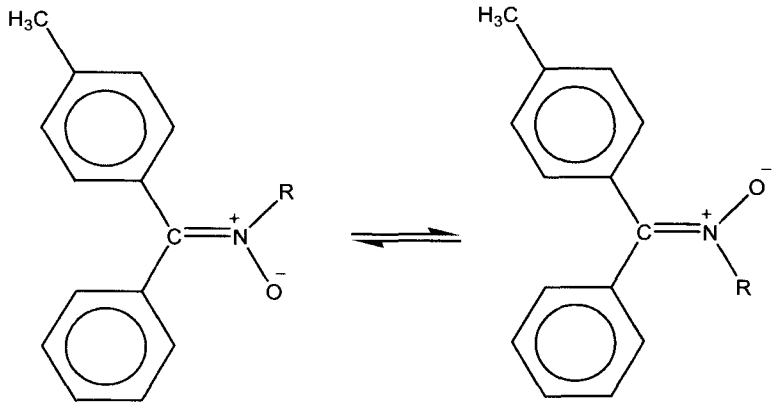
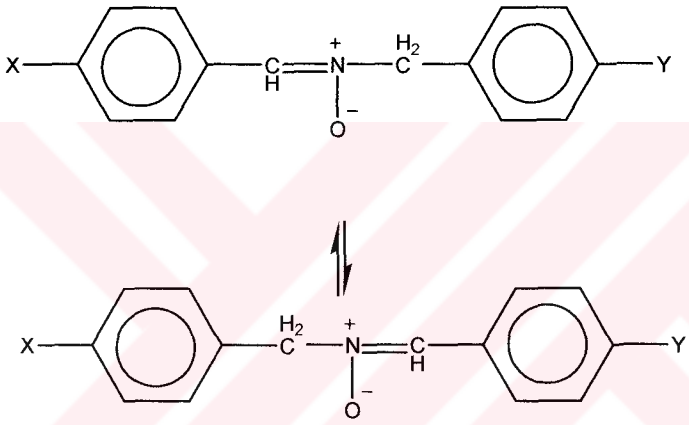


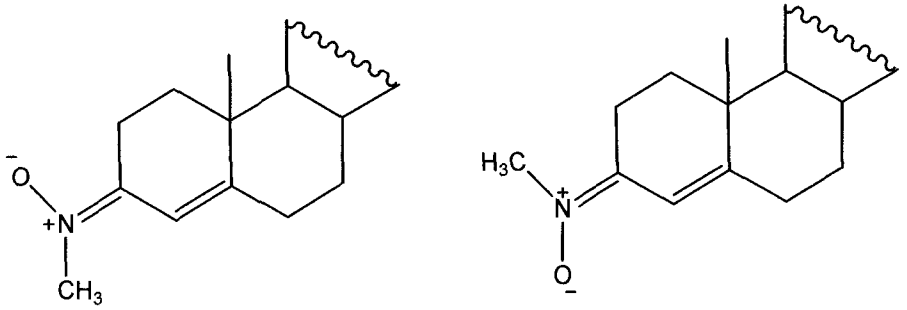
Figure 1.14



(eq. 2)

1.2.1.3.5. Mass spectra

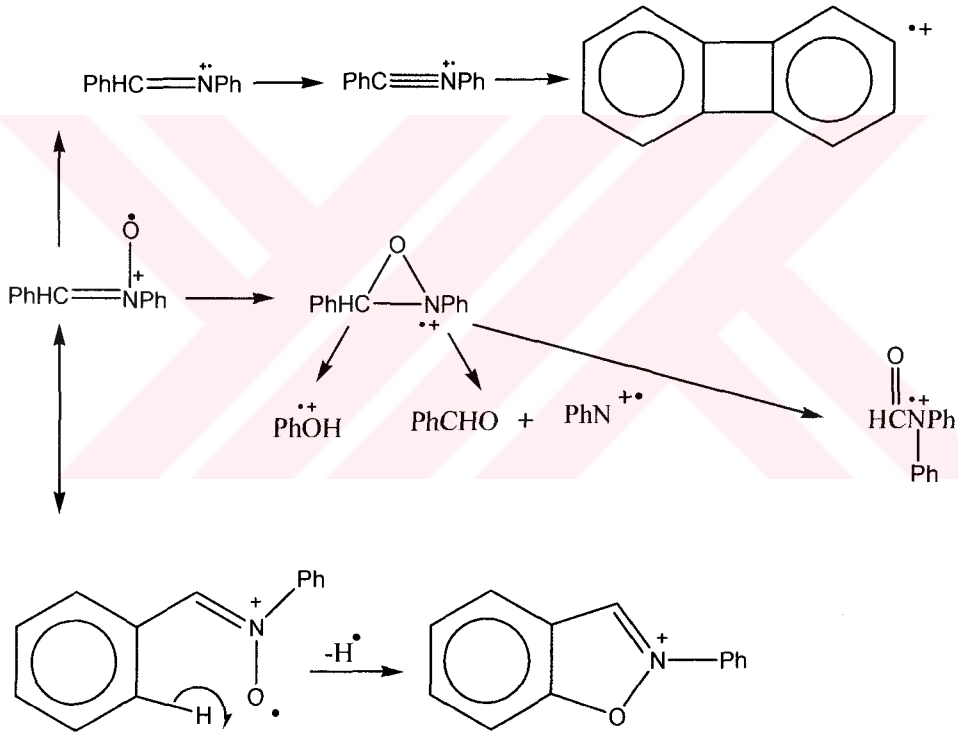
In all mass spectra variously substituted and deuterated α-*N*-diaryl nitrones (Figure 1.15) appears the M-16 peak, which results from the loss of oxygen.



(*E*-isomer) (*Z*-isomer)

Figure 1.15

This is a peak of some diagnostic value for *N*-oxides. A summary of the mass spectral processes which α-*N*-diaryl nitrones undergo is presented in Scheme 1. The presence of the benzoyl cation requires oxygen migration from nitrogen to carbon and presumably the intermediacy of an oxaziridine, which may rearrange to an amide, which in turn may provide the fragment $PhC{\equiv}O^+$ .In addition to this in all spectra the biphenylene radical cation and the 2-substituted benzisoxazolium cation are produced.

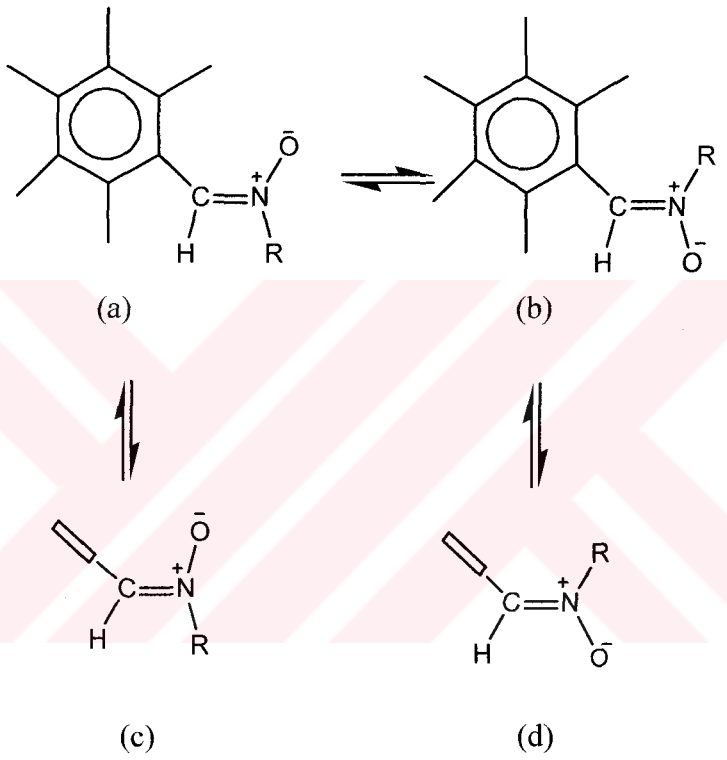


Scheme 1.6

1.2.1.4. Geometrical isomerism of nitrones

The phenomenon of geometrical isomerism in nitrones has long been recognized and in many instances pairs *(E)* and (*Z*) isomers have been separated and configurations assigned. However it is only recently that such

pairs of isomers have been successfully isolated in acyclic aldonitrones, which usually exist entirely as the (*Z*) isomers (a) (see Scheme 1.7). It has been found that in derivatives of (a) with highly substituted aryl groups it is possible to isolate the stable *(E)* isomers (b). Apparently in these cases the increased steric requirements of the α-aryl group cause it to twist out of its normal coplanar conformation (a) and assume an orthogonal orientation (b).



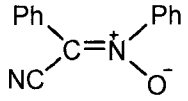
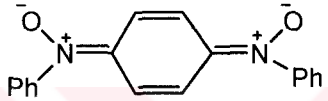
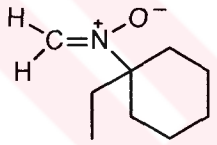
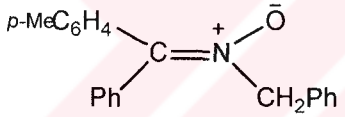
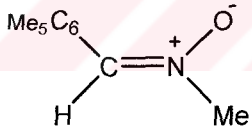
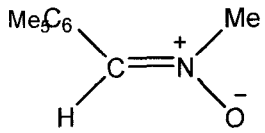
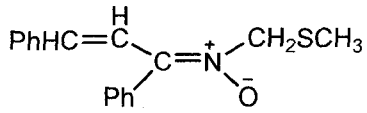
Scheme 1.7

In this conformation there is increased repulsion between the negative oxygen and the electron-rich aromatic ring, resulting in an increase in the ground-state energy of the (*Z*) isomer and greater ease of formation of the (*E*) isomer (b). This effect can be counteracted by the size of the, N-substituent. Indeed only one isomer *(Z) is* observed with nitrones (a) containing bulky R groups such as t-butyl, neopentyl or adamantyl.

There have been a number of investigations regarding $(E) \leftrightarrow (Z)$

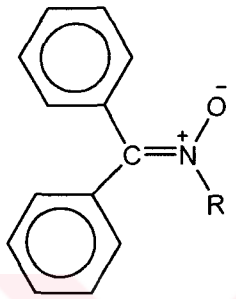
isomerizations. The activation energies of such isomerizations have been determined in a number of cases and some representative data are listed in Table 3.

TABLE3. The activation energies of some isomers of nitrones.

Nitrone	EA(kcal/mol)
	24.6
	12
	23.2
	33.6
	33.1
	34.6
	28.2

The influence of the *N*-substituent upon the rate of isomerization has been studied in the α,α-diphenyl nitrone series Figure 1.16. The approximately twofold rate of isomerization of b as compared to a is considered to be due to increased ground-state energies of the former caused by the stronger non-

bounded interactions between the benzyl and the α-phenyl groups. However the fact that the benzhydryl derivative *c* isomerizes 10 times faster than a is taken as an indication that a new mechanism is operating in this case. It has been suggested that the isomerization of *N*-benzhydryl nitrones proceeds, at least in part, via dissociation to iminoxy radicals followed by fast isomerization of the radical and recombination.



(a) R = Me
(b) R = CH_2Ph
(c) R = $CHPh_2$

Figure 1.16

The question of the mechanism of $(E) \leftrightarrow (Z)$ isomerization has been approached theoretically. CNDO/2 and INDO calculations on the parent nitrone, Figure 1.17, indicate a high charge density on the oxygen and are consistent with a major contribution of structure in the ground state. The twisted conformation, which is proposed to be the transition state for the rotation around the C=N bond, appears, however, to be well represented by isomer of that nitrone since there is a high electron density on the carbon. However the calculated rotational barriers of 60 and 80 kcal/mol by these methods are much higher than those observed experimentally.

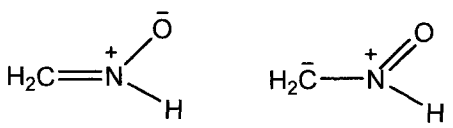
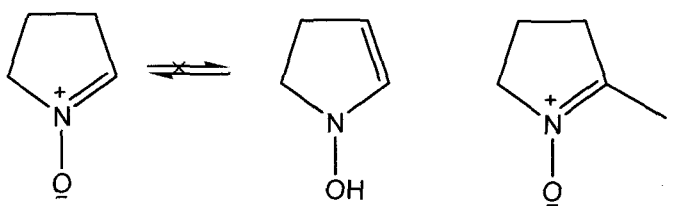


Figure 1.17

1.2.1.5. *Tautomerism of nitrones*

1.2.1.5.1. Nitrone-hydroxyenamine tautomerism.

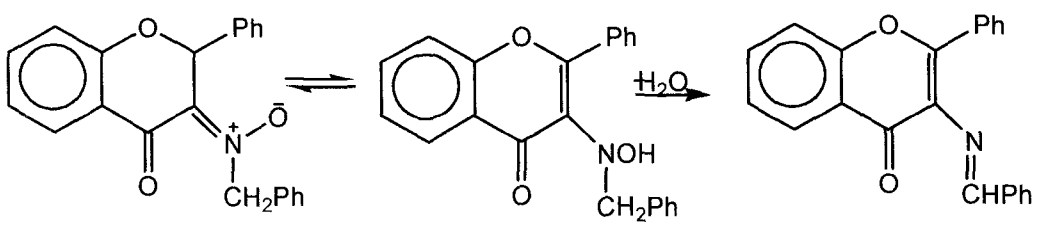
This type of tautomerism is analogous to the keto-enol tautomerism of carbonyl compounds. The question of such tautomerism has been the subject of a number of papers. *2,3-dihydropyrrol-1-ol* **(b)** , see Figure 1.18, are not detectable by NMR in pyrroline N-oxide **(a)**.



(a) **(b)** **(c)**

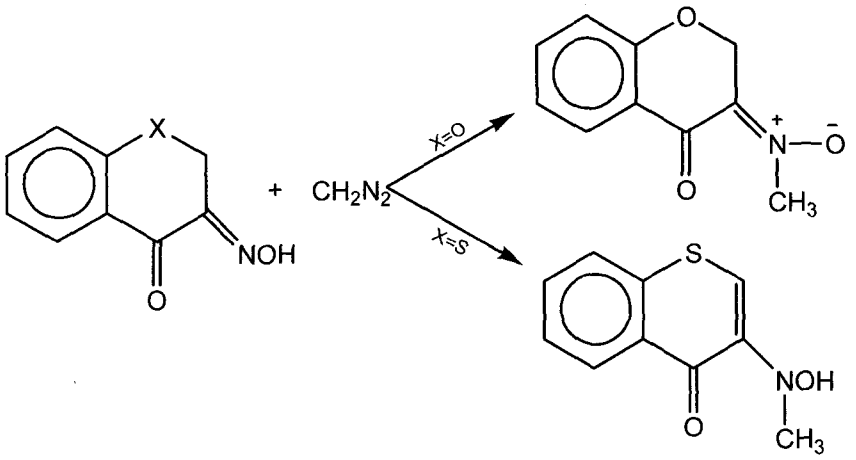
Figure 1.18

This type of tautomerization is assumed to be involved also in the base-catalysed reaction of the flavanononitrone, which leads to the Schiff base as one of the products (equation 7).



Interestingly the nitrone-hydroxyenamine equilibrium is found to be influenced by the heteroatom in the chromane system. Thus reaction of the oxime (X = O) with diazomethane leads to nitrone , whereas the thio

analogue (X = S) with the same reagent affords the hydroxylamino thiochromane.



Scheme 1.8

A keto group appropriately situated relative to the nitrone function will enhance tautomerism similarly to β-dicarbonyl compounds. Indeed the infrared spectrum of phenacylpyrroline N-oxide(Figure 1.19) shows bonds attributable to an intramolecular hydrogen bond which could result from either or both structures.

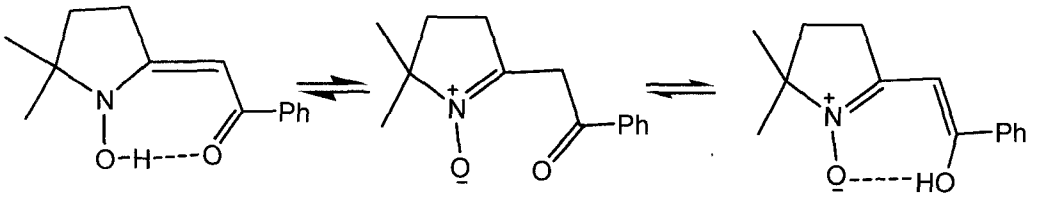
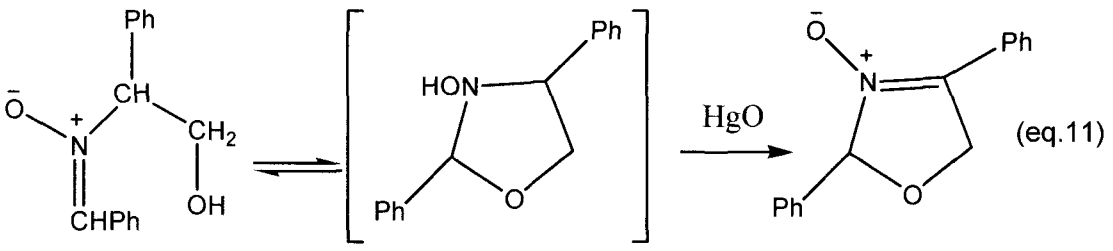


Figure 1.19

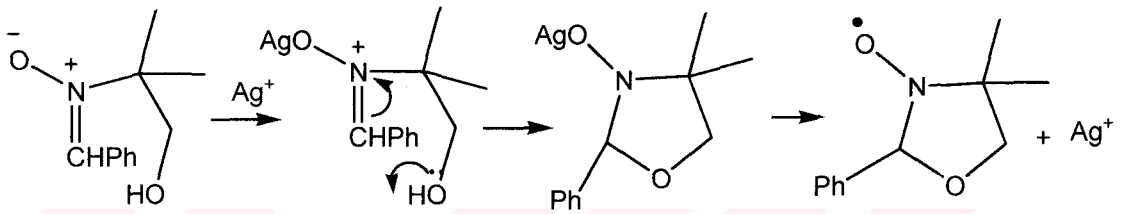
1.2.1.5.2. Ring-chain tautomerism.

Oxidation of an *N*-(2-hydroxyalkyl) nitrone of type with mercuric oxide leads to an oxazoline *N*-oxide indicating involvement of the cyclic tautomer in the reaction (equation 11). The gem-dimethyl nitrone is oxidized by silver ion to the cyclic nitroxide radical.



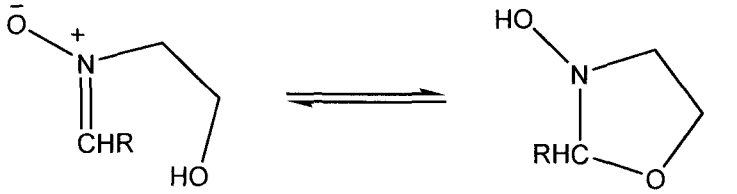
(eq.11)

It has been suggested that in this case the cyclization is facilitated by the silver ion acting as a Lewis acid.



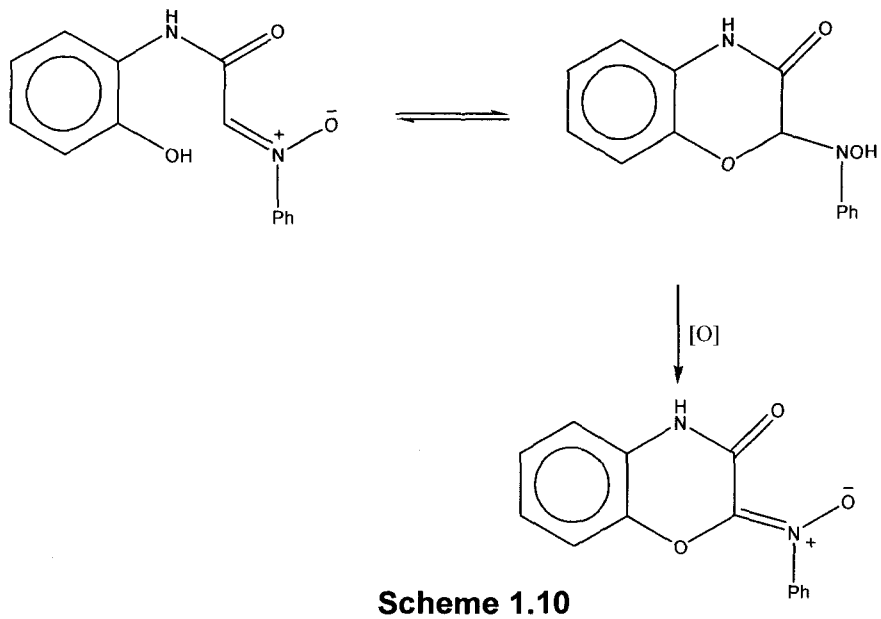
Scheme 1.9

In contrast to the α-aryl nitrones mentioned, examination of a series of aliphatic aldonitrones by spectroscopic methods has revealed the presence of the cyclic tautomers in the equilibrium mixture (equation 12).



(eq.12)

Acylation gives derivatives of the cyclic tautomer. Ring-chain tautomerism has also been studied in 2-hydroxynaphthalene derivatives Scheme 1.10. The equilibrium composition is influenced by R as well as by the medium. Acetylation gives derivatives of the cyclic tautomer. The *o*-hydroxyphenylaminoacyl nitrone could be converted to the cyclic tautomer which could be oxidized to the new nitrone. Acetylation of both tautomers is reported to lead to the derivative of the open-chain tautomer.

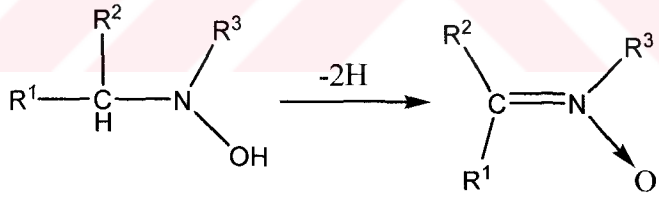


Scheme 1.10

1.2.1.6.Synthesis of Nitrones

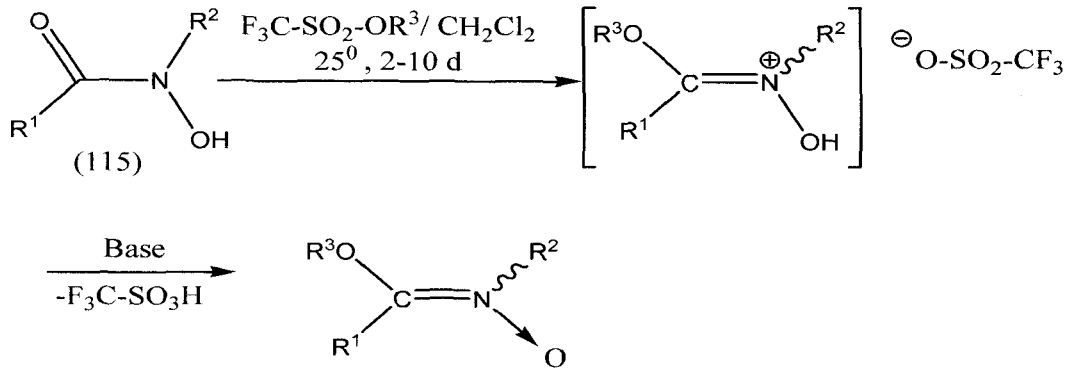
1.2.1.6.1.Oxidation Methods

1.2.1.6.1.1. From dehydrogenation of *N,N*-disubstituted-hydroxyl amines



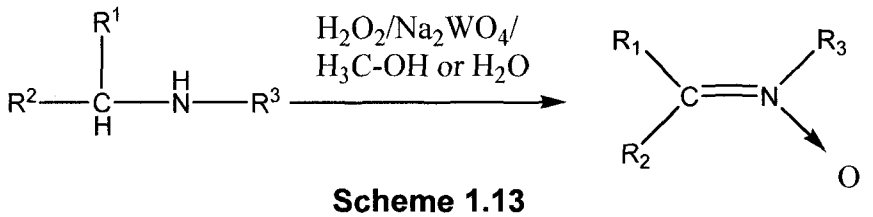
Scheme 1.11

1.2.2.6.1.2. From *N*-alkyl hydroxamic acid



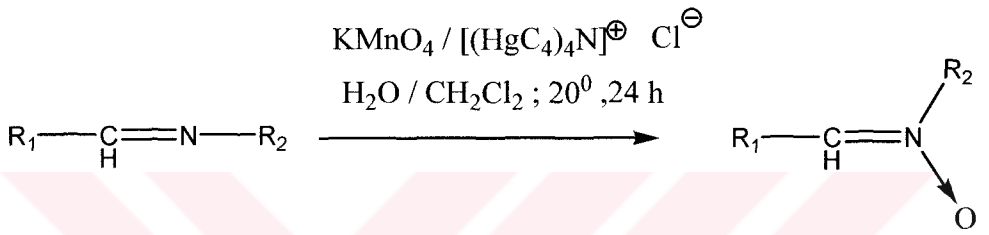
Scheme 1.12

1.2.2.6.1.3. By oxidation of secondary amines



Scheme 1.13

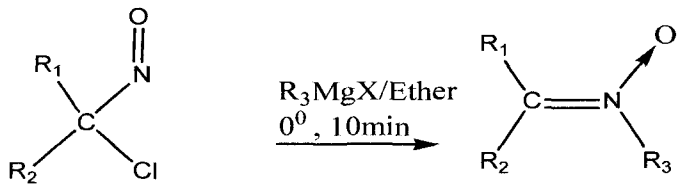
1.2.2.6.1.4. By oxidation of imines



Scheme 1.14

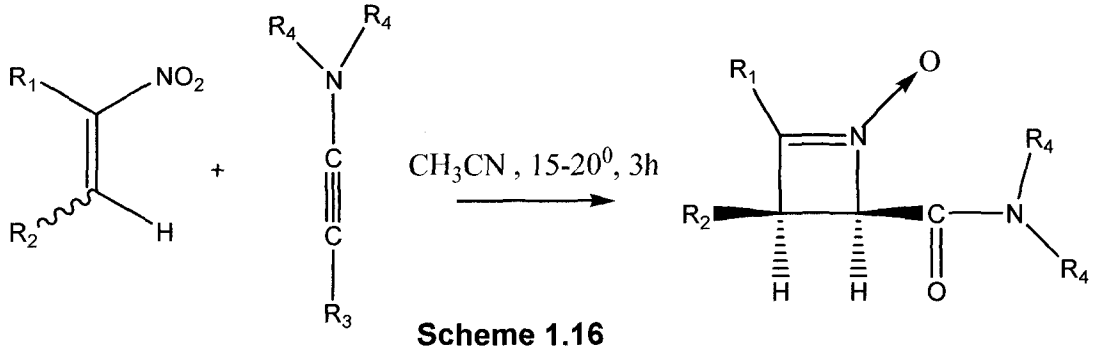
1.2.2.6.2.Alkylation Methods

1.2.2.6.2.1. By alkylation of α-chloronitroso alkenes



Scheme 1.15

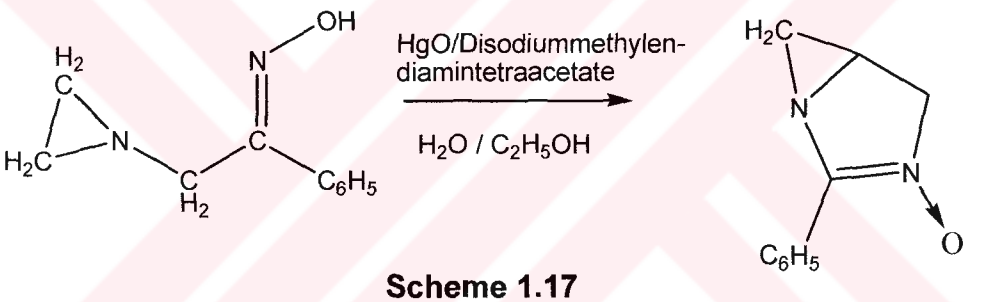
1.2.2.6.2.2. By alkylation of Nitro alkenes



Scheme 1.16

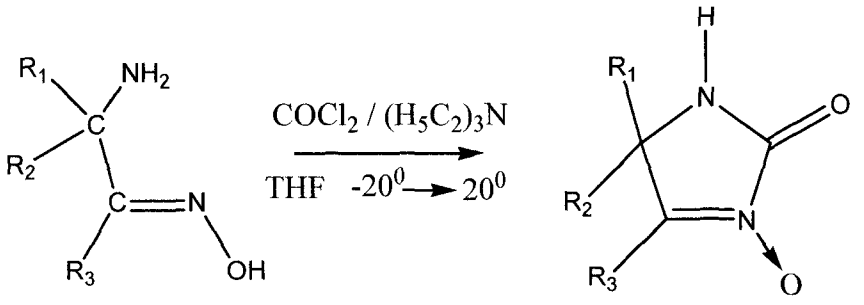
1.2.2.6.3.From Oximes

1.2.2.6.3.1. By intramolecular cyclization of oximes



Scheme 1.17

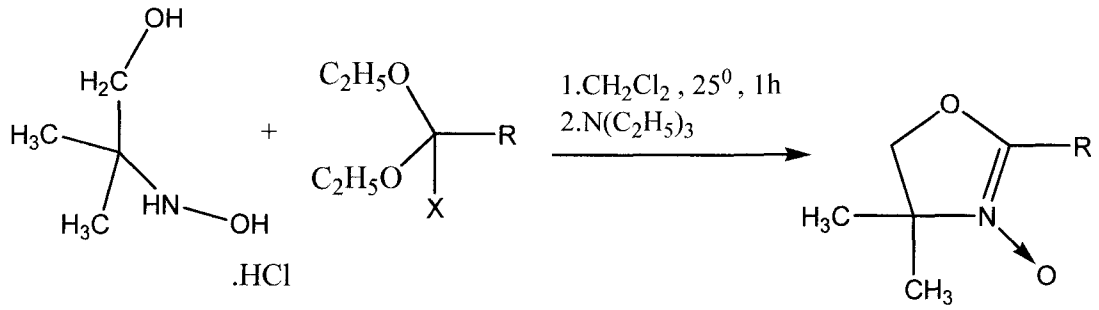
1.2.2.6.3.2. By intermolecular cyclization of oximes



Scheme 1.18

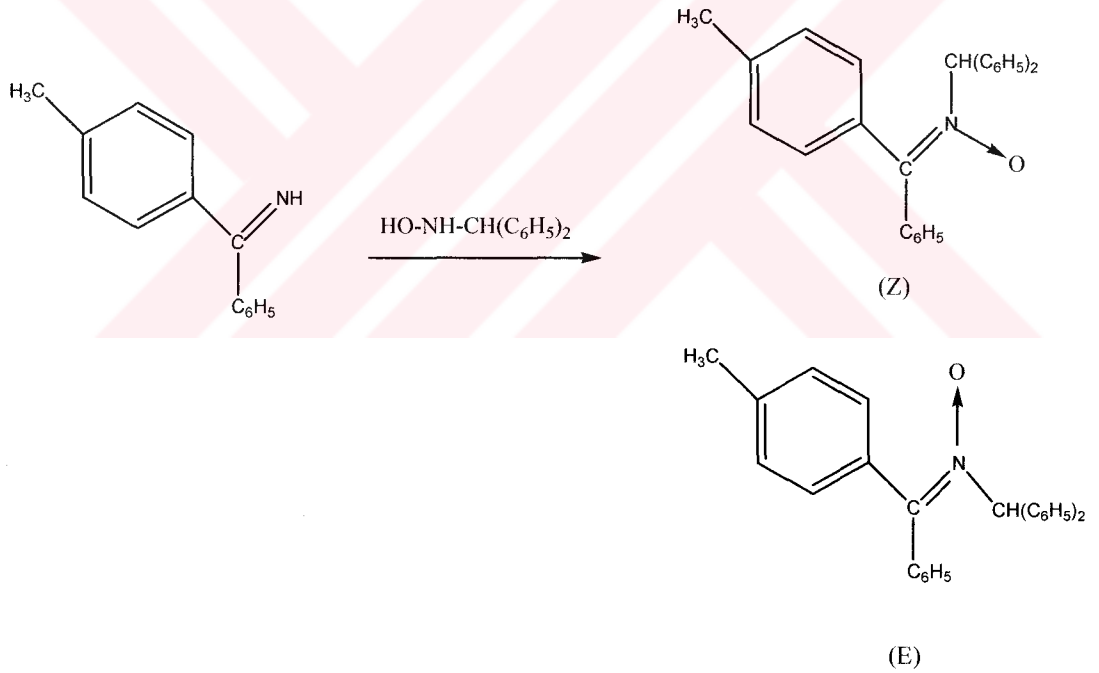
1.2.2.6.4.By condensation of hydroxylamine derivatives

1.2.2.6.4.1. With orthocarbonic acids



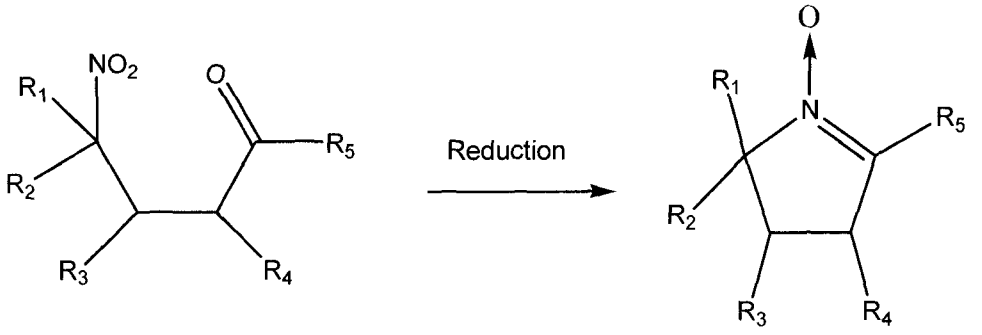
Scheme 1.19

1.2.2.6.4.2. With imines



Scheme 1.20

1.2.2.6.5.From Nitro Compounds

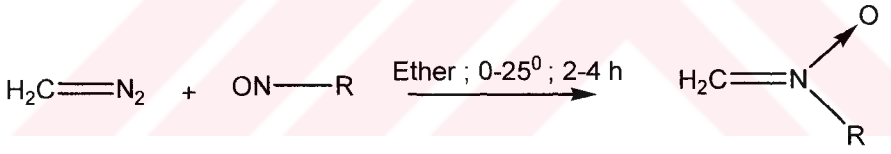


R_1=H , CH_3 ; R_2=H , Alkyl , Aryl
R_4=H,Aryl ; R_5=H, Alkyl , Aryl

Reduction:
$Zn/NH_4Cl/Water^1$·$Methanol^2$

Scheme 1.21

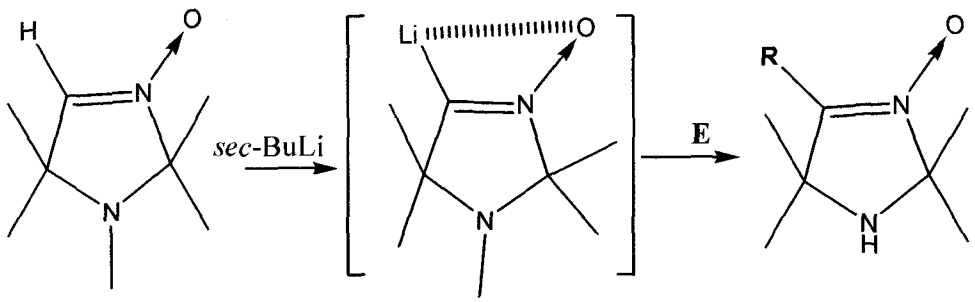
1.2.2.6.6.From Diazoalkanes



Scheme 1.22

1.2.2.6.7.Recent Publications

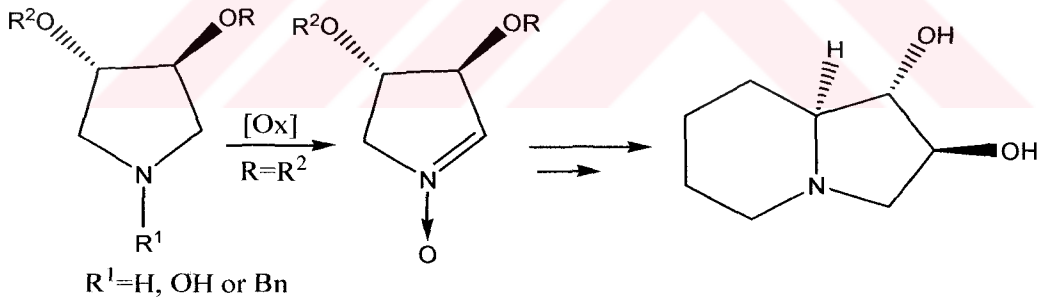
Recently , Voinov has been synthesized α-heteroatom substituted nitrones for the first time by the reaction of lithiated cyclic aldonitrone with $HgCl_2$, and α-Chloronitrone was prepared for the first time by direct chlorination of lithiated aldonitrone using TsCl.[6]



a) E=$HgCl_2$, R=HgCl, 55 %
b) E=TsCl, R=Cl, 90%

Scheme 1.23

Brandi and coworkers reported that a nitrone from the oxidation of a *C*2 symmetric piperidine, obtained through a ring enlargement process of the enantiopure protected (4*R*)-hydroxy-(2*S*)-hydroxymethyl pyrrolidine. Oxidation with *C*-phenyl-*N*-phenylsulfonyloxaziridine afforded the corresponding nitrone that is too unstable for isolation. [7]



Scheme 1.24

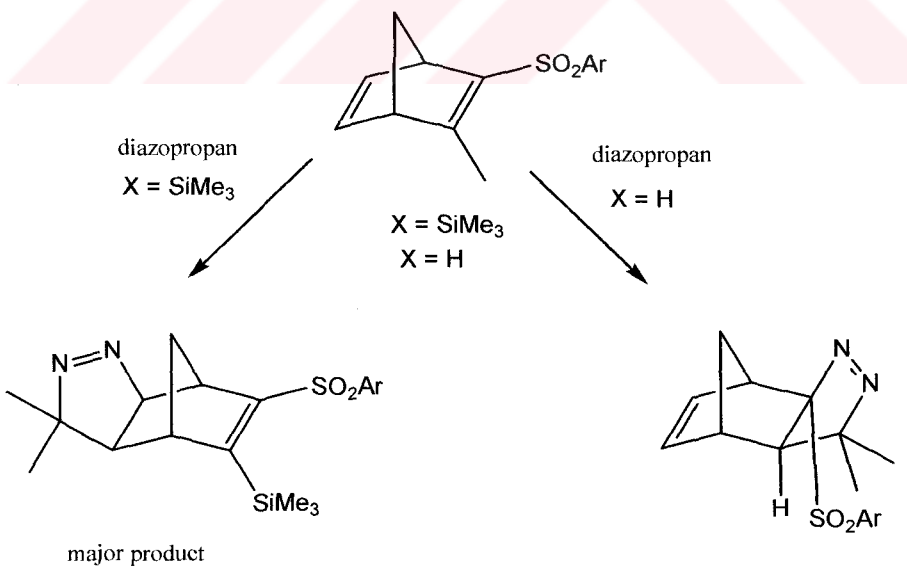
1.3.VINYL SULPHONES

Vinyl sulphones (α,β-unsaturated sulphones) have now become generally accepted as useful intermediates in organic synthesis. Thus vinyl sulphones serve efficiently as both Michael acceptors and as partners in cycloaddition reactions.[8]

In cycloaddition reactions, vinyl sulphones again serve a useful function as convenient equivalents for ethylene, acetylene, ketene, etc. Other notable features of sulphones, including their ease of handling (many are nicely crystalline) and ready removal (desulphonylation), have added to the attractions of vinyl sulphones as intermediates.

1.3.1.Vinyl Sulphones in [3+2] Cycloaddition Reactions

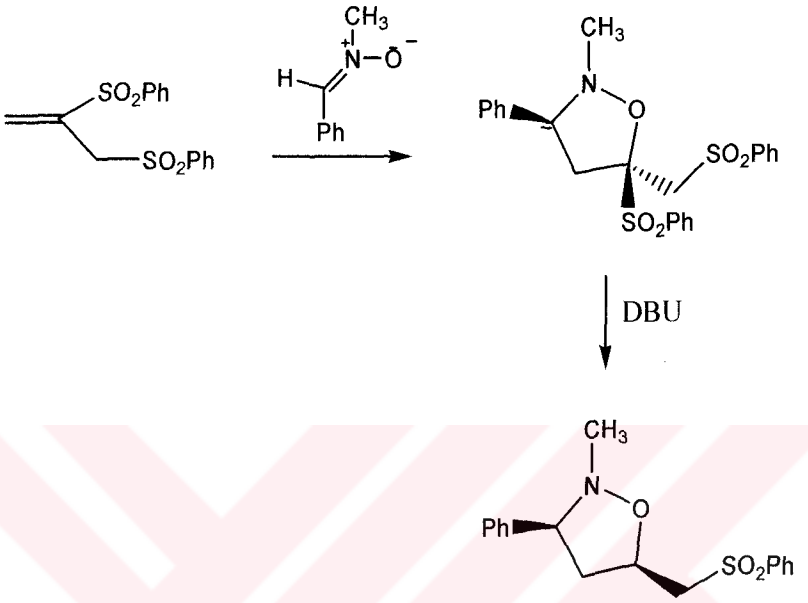
In one of a series of significant contributions to the cycloaddition chemistry of vinyl sulphones Padwa's group have examined the reaction of 2-diazopropane with the bicycloheptadiene.[9] This reaction followed a similar unexpected course to that observed with cyclopentadiene reaction occurring on the electronically less activated alkene. By contrast , the corresponding desilylated diene gave the product of addition to the vinyl sulphone(Scheme 1.25).



Scheme 1.25

Reactions of diazo compounds with allenylphenyl sulphone have also been examined by Padwa,[10] as have a variety of dipolar cycloadditions between

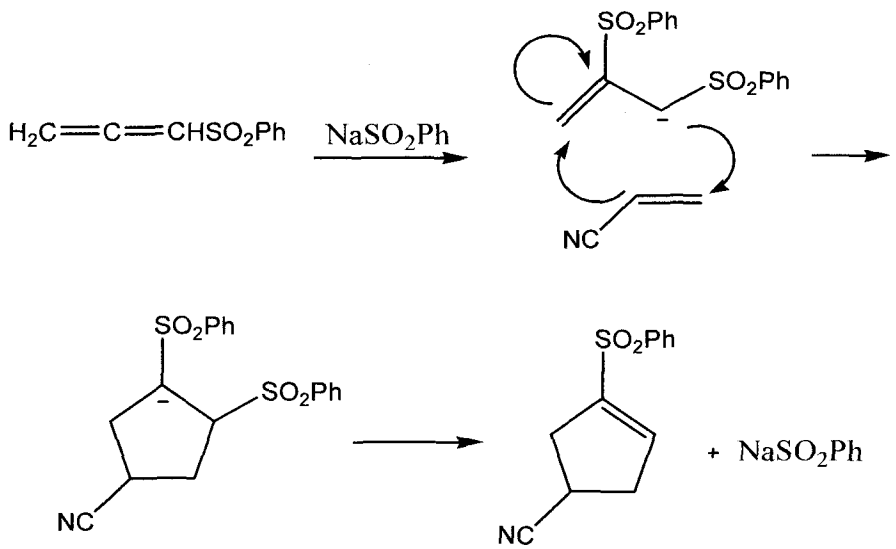
unsaturated sulphones and nitrones. An interesting development of the sulphonyl allene chemistry was the finding that the use of vinyl sulphone allows access to nitrone cycloadducts., formally derived from addition to the unactiviated double bond of a sulphonyl allene.(Scheme 1.26).[11]



Scheme 1.26

The anion derived from vinyl sulphone can be generated by conjugate addition of sodium benzenesulphinate to phenylsulphonyl allene.[12] This allows for a number of interesting cyclisation-elimination reactions with

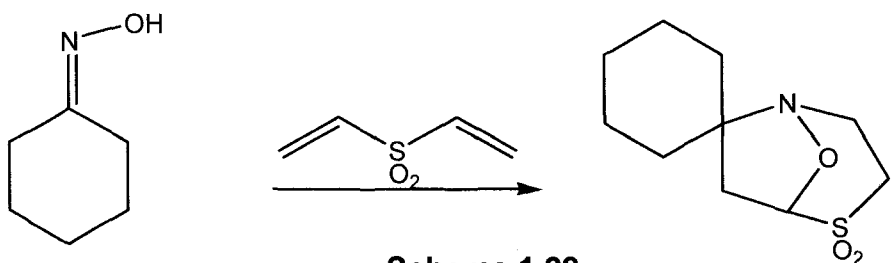
Michael acceptors to give [3+2] type products, e.g. Scheme 1.27 .



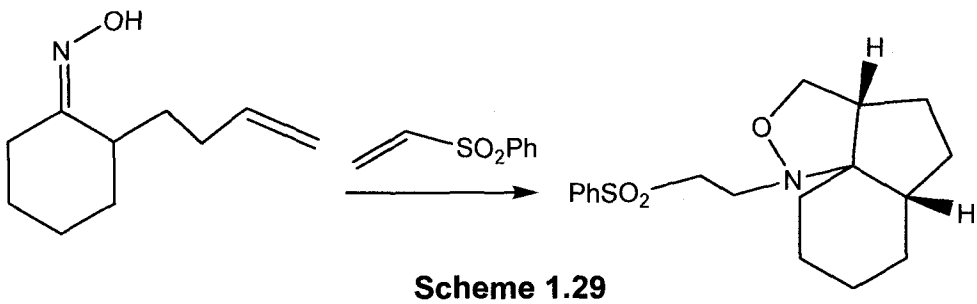
Scheme 1.27

The benzenesulphinate is regenerated in this sequence, and is required only in trace amounts. Analogous sequences were possible by using the addition of other anions to the starting allene to trigger cyclisation.

Grigg and coworkers have described the use of nitrones, generated from oximes by Michael addition, for cycloaddidon reactions.[13] Vinyl sulphones can be used as reaction partners, either to generate the nitrone, or to participate in the cycloaddition, or in both steps, e.g. Scheme 1.28-29.



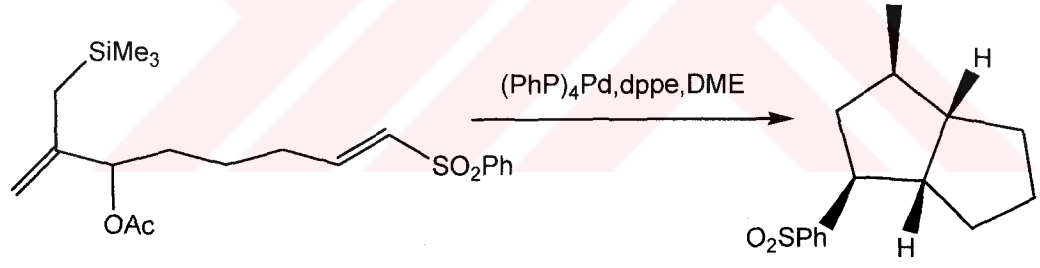
Scheme 1.28



Scheme 1.29

Both the initial Michael reaction and the cycloaddition reaction can be carried out intra- or intermolecularly, allowing a broad range of interesting functionalised polycyclic products to be prepared.

Trost has included vinyl sulphones amongst the partners that react with trimethylenemethane-palladium complexes to give [3+2] adducts. Scheme 1.30 highlights a particularly pleasing example in which two rings are constructed in a single step and with a high degree of stereocontrol.[14]



dppe = 1,2-bis(diphenylphosphino)ethane

Scheme 1.30

Caddick has studied 1,3-dipolar cycloaddition reaction of a variety of nitrones to pentafluorophenyl vinyl sulfonate and phenylvinyl sulphone. Compared it with cycloaddition of C-phenyl-N-methylnitrone and reported that the reversed 4C-substituted cycloadduct increasingly predominates when very electron-defficient dipolarophiles are involved. Actually the cycloaddition of nitrones to olefins generates 5C-substituted isoxazolidines [15].

Details of the reactivity of the factors affecting the regioselectivity in the cycloaddition of nitrones to unsaturated methyl sulfones possesing vicinal electron-withdrawing (CN or CO_2Me) substituents can be found in paper found by Chanet-Ray and coworkers.The cycloaddition product shows the 4-sulfonyl isomer is the sole or dominant cycloadduct. [16]

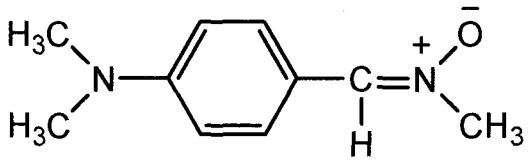
CHAPTER II

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on BRUKER and VARIAN spectrometers. IR spectra were recorded on a JASCO 430 FT/IR instrument (KBr pellet in case of solids and neat for oil or liquids using NaCl discs). Mass spectra were run on ZABSpec VG7070E instrument. Melting points were determined on a Meltemp apparatus and uncorrected. Flash Column chromatography was performed on Silica Gel (Merck, 230-400 mesh). TLC was done using precoated plates with fluorescent indicator (Merck 5735). Nitrones **2a-j** were synthesized according to the methods described in the literature [20-29].

2.1.Synthesis of Nitrones 2a-j

2.1.1. N-Methyl-4-(N,N-dimethylamino)-benzylidene amine N-oxide (2a)



A mixture of 4-(*N*,*N*-dimethylamino)benzaldehyde **(1b)** (298 mg , 2 mmol) and *N*-methylhydroxylamine hydrochloride (167 mg, 2 mmol) and potassiumhydroxide (123 mg, 2.2 mmol) in methanol (10 mL) was heated at reflux with molecular sieves (4 Å) in order to remove water for over night.Reaction monitored by TLC. After cooling a white precipitate (KCl) was

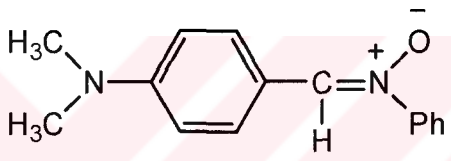
observed. The mixture were filtered and filtrate were concentrated under reduced pressure. A light yellow crystalline solid is obtained in benzene-petroleum ether(40-60 ^{0}C) mixture; yield 213 mg (60%), m.p. 95-98 ^{0}C.

Rf :0.37 (Ethanol-n-Hexane;3:1)

IR (KBr): ν (cm^{-1}) : 1612 (C=N), 1149 (N-O) .

^{1}H NMR (δ_H,400 MHz, $CDCl_3$):2.84 (s, 6H), 3.70(s,3H), 6.30 (d, 2H), 7.01 (s, 1H),7.90 (d, 2H).

2.1.2. N-Phenyl-4-(N,N-dimethylamino)-benzylidene amine N-oxide (2b)

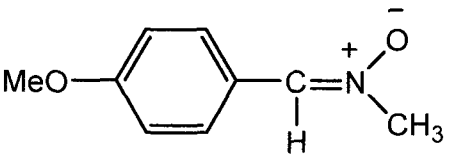


A mixture of 4-(*N*,*N*-dimethylamino)benzaldehyde **(1b)** (298 mg , 2 mmoL) and *N*-phenylhydroxylamine [17] (218 mg, 2 mmol) in methanol (10mL) was heated at reflux, with molecular sieves (4 Å) in order to remove water, for 6 hour reaction monitored by TLC. After cooling the mixture was filtered and filtrate was concentrated under reduced pressure. The crude product was kept in order to use in cycloaddition reaction; crude yield 310 mg .

R_f : 0.25 (Ethanol-n-Hexane;3:1)

IR (KBr): ν (cm^{-1}) : 1611 (C=N) , 1059 (N-O)

2.1.3. N-Methyl-4-(methoxy)-benzylidene amine N-oxide (2c)

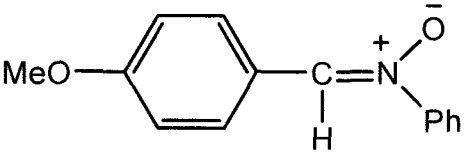


A mixture of 4-methoxy-benzaldehyde **1c** (1 mL , 8.2 mmoL) and *N*-methylhydroxylamine hydrochloride (687 mg, 8.2 mmoL) and potassiumhydroxide (508 mg, 9 mmoL) in methanol (10mL) was heated at reflux with molecular sieves in order to remove water for over night.Reaction monitored by TLC. After cooling a white precipitate (KCl) was observed. The mixture was filtered and filtrate was concentrated under reduced pressure. A white crystalline solid is obtained in benzene-petroleum ether mixture; yield 1.122 mg (83%).

Rf : 0.29 (Ethanol-n-Hexane;3:1)

IR (KBr): ν (cm^{-1}) : 1603(C=N) , 1148 (N-O).

2.1.4. N-Phenyl-4-(methoxy)-benzylidene amine N-oxide (2d)



A mixture of 4-methoxy-benzaldehyde **1c** (1 mL , 8.2 mmoL) and

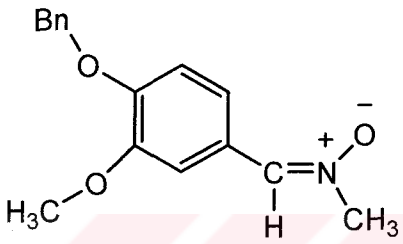
N-phenylhydroxyl amine (898 mg, 8.2 mmoL) in methanol (10mL) was heated under reflux temperature with molecular sieves to remove water for over night.Reaction monitored by TLC. After cooling , the mixture was filtered

and filtrate was concentrated under reduced pressure. A yellow crystalline solid is obtained in benzene-petroleum ether mixture; yield 877 mg (47%) m.p. 117-118 ^{0}C.

R_f : 0.21 (Ethanol-n-Hexane;4:1.5)

IR (KBr): ν (cm^{-1}) : 1604 (C=N) , 1065 (N-O)

2.1.5.N-Methyl-(4-benzyloxy-3-methoxy)-benzylidene amine N-oxide (2e)



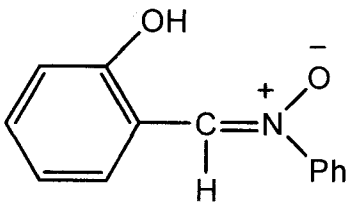
A mixture of 4-benzyloxy-3-methoxy benzaldehyde **1a** (242 mg , 1mmol) and *N*-methylhydroxylamine hydrochloride (83.5 mg , 1mmol) and potassiumhydroxide (61.7 mg , 1.1 mmol) in methanol (10mL) was heated at reflux with molecular sieves (4Å) in order to remove water for over night.The progress of the reaction was monitored by TLC. After cooling a white precipitate (KCl) was observed. The mixture was filtered and filtrate was concentrated under reduced pressure. A yellow crystalline solid is obtained in benzene-petroleum ether(40-60 ^{0}C) mixture; yield 181 mg (67%), m.p. 110-111 ^{0}C.

R_f : 0.31 (Ethanol-n-Hexane ; 4:1)

IR (KBr): ν (cm^{-1}) :1591 (C=N) , 1083 (N-O).

^{1}H NMR (δ, 400 MHz, $CDCl_3$): 3.82 (s,3H, NCH_3),3.93 (s, 3H, OCH_3), 5.19 (s, 2H, OCH_2), 6.90(d, 1H, J=8.47 Hz), 7.28-7.44 (m, 5H), 8.36 (s, 1H).

2.1.6. N-(2-Hydroxyphenyl)-benzylidene amine N-oxide (2f)

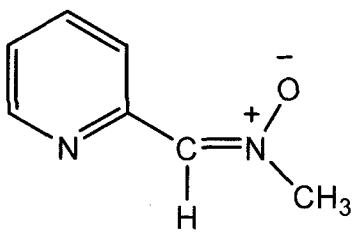


A mixture of 2-hyroxybenzaldehyde **(1h)** (122 mg, 0.21 mL , 2.0 mmoL) and *N*-phenylhydroxylamine (218 mg , 2.0 mmoL) in methanol (10mL) was heated at reflux, in the presence of molecular sieves (4 Å), for 6 h. The progress of the reaction was monitored by TLC. After cooling, the mixture was filtered and filtrate was concentrated under reduced pressure. The crude product was kept in order to use in cycloaddition reaction; crude yield 198 mg .

R_f : 0.21 (Ethylalcohol-n-Hexane;2:1)

IR (KBr): ν (cm^{-1}) :3500(O-H) , 1559 (C=N) , 1149 (N-O).

2.1.7. N-Methyl-1-(2-pyridyl)methanimine N-oxide (2g)



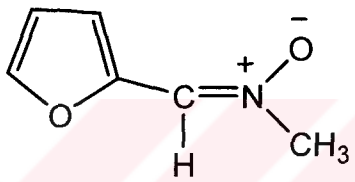
A mixture of pyridine-2-carbaldehyde **(1d)** (1.5 mL , 1.69 g , 15.8 mmoL) and *N*-methylhydroxylamine hydrochloride (1.349 g, 16 mmoL were added to a suspension of sodiumhydrogen carbonate (3.989 g , 47.4 mmoL) in dichloromethane(50 mL) in the presence of molecular sieves (4 Å). The mixture was heated under reflux with vigorous stirring for 5 h. Reaction monitored by TLC. After cooling, the reaction mixture was filtered and the

precipitate washed with CH_2Cl_2 . The combined CH_2Cl_2 filtrates were evaporated to dryness. The crude product was recrystallized from cyclohexane to give light yellow crystals : Yield 1.64 g (76.3 %) , m.p. 38^0C .

R_f : 0.22 (Ethanol-n-Hexane;3:1)

IR (KBr): ν (cm^{-1}) : 1583 (C=N) , 1087 (N-O)

2.1.8. N-Methyl-1-(2-furyl)methanimine N-oxide (2h)

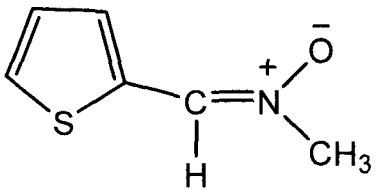


A mixture of furan-2-carbaldehyde **(1g)** (0.5 mL , 6 mmoL) and *N*-methylhydroxylamine hydrochloride (498 mg, 6 mmoL) were added to a suspension of magnesium sulfate (1.7 g , 12 mmoL) and molecular sieves (4 Å) in dichloromethane (15 mL). The mixture was heated under reflux with vigorous stirring for 3.5 h. The progress of the reaction was monitored by TLC.After cooling, the reaction mixture was filtered and the precipitate was washed with CH_2Cl_2 . The combined CH_2Cl_2 filtrates were evaporated to dryness. The crude product was kept in order to use in cycloaddition, crude yield 1.220 g.

R_f : 0.21 (Ethanol-n-Hexane;3:1)

IR (KBr): ν (cm^{-1}) : 1596 (C=N) , 1097 (N-O)

2.1.9. N-Methyl-1-(2-thienyl)methanimine N-oxide (2i)

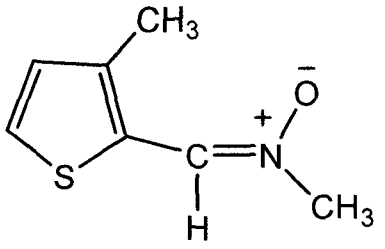


A mixture of thiophene-2-carbaldehyde **(1e)** (0.2 mL ,2.18 mmoL) and *N*-methylhydroxylamine hydrochloride (181 mg, 2.18 mmoL) were added to a suspension of sodiumhydrogen carbonate (1.16 g , 13.2 mmol) in dichloromethane (15 mL) in the presence of molecular sieves (4 Å). The mixture was heated under reflux with vigorous stirring for over night, reaction monitored by TLC , filtered and precipitate was washed with CH_2Cl_2 . The combined CH_2Cl_2 filtrates were evaporated to dryness. Crude product **(2i)** were used in the next step, without purification for the cycloaddition reaction.Crude yield 324 mg.

R_f : 0.28 (Ethylalcohol-n-Hexane;3:1)

IR (KBr): ν (cm^{-1}) : 1585 (C=N) , 1092 (N-O).

2.1.10. N-Methyl-1-(2-(3-methyl thienyl))methanimine N-oxide (2j)



A mixture of 3-methylthiophene-2-carbaldehyde **(1f)** (0.27 mL,2.5 mmoL) and *N*-methylhydroxylamine hydrochloride (209 mg, 2.5 mmoL) were added to a suspension of sodium hydrogen carbonate (630 mg , 7.5 mmoL) in

dichloromethane (15 mL) in the presence of molecular sieves (4 Å). The mixture was heated under reflux with vigorous stirring for over night, reaction monitored by TLC , filtered and precipitate was washed with CH_2Cl_2 . The combined CH_2Cl_2 filtrates were evaporated to dryness. Crude green products were kept to use in cycloaddition product.

R_f : 0.31 (Ethylalcohol-n-Hexane;3:1)

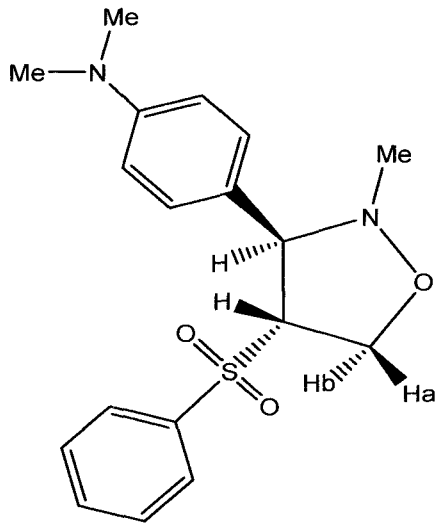
IR (KBr): ν (cm^{-1}) : 1590 (C=N) , 1087 (N-O).

^1H NMR (δ_H, 400 MHz, $CDCl_3$): 2.37 (s, 3H), 3.80(s, 3H),6.95 (d, 1H, J=8.5 Hz), 7.38 (d, 1H, J=8.3 Hz),7.78 (s, 1H).

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$,):14.4, 51.7, 125.4, 127.0, 128.1, 129.2, 131.1,138.9

2.2.Synthesis of benzenesulfonyl substituted isoxazolidines

2.2.1.4-Benzenesulfonyl-3-(4-*N*,*N*-dimethylphenyl)-2-methyl-isoxazolidine (3a)



To a solution of phenyl vinyl sulfone (168 mg, 1 mmoL) in dry toluene (10 mL) was added *N*-methyl-4-(*N*,*N*-dimethylamino)-benzylidene amine *N*-oxide **(2a)** (1.0 eq., 271 mg, 1 mmoL) and the mixture was heated to reflux for overnight. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 2:1) to give **(3a)** as a yellowish solid (190 mg, 55 %). Mpt 116-117 °C.

R_f : 0.55 (Ethylacetate-n-Hexane;2:1)

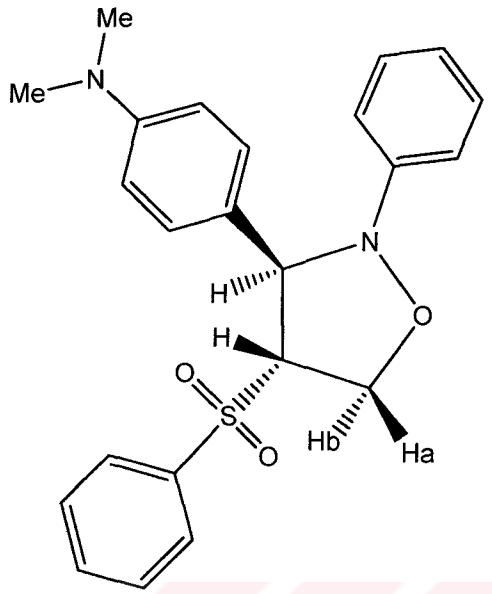
IR (KBr): $\nu(cm^{-1})$: 2922 , 1614, 1447, 1309 (SO_2 ,symmetric), 1147(SO_2,asymmetric) .

^1H NMR(δ_H, 300 MHz, $CDCl_3$): 7.98 (d, *J*=7.3 Hz, 2H), 7.75(t, *J*=7.4 Hz, 1H), 7.65 (t, *J*=7.9 Hz, 2H), 7.18 (d,*J*=8.7 Hz, 2H), 6.70 (d, *J*=8.5 Hz, , 2H), 4.66 (dd, *J*=9.9, 3.3 Hz,1H, 5-H_b), 4.45 (dd,*J*=9.9, 8.2 Hz, 1H, 5-H_a), 4.22 (ddd, *J*= 8.2, 6.0, 3.2 Hz,1H, 4-H), 3.92 (br d,*J*=6 Hz,1H, 3-H), 3.01 (s, 6H), 2.71(s, 3H).

^{13}C NMR(δ_C, 75 MHz, $CDCl_3$): 150.85, 138.52 , 134.31, 129.67, 129.01, 128.96, 128.74, 123.92, 112.84, 75.53 (C-4), 73.87 (C-3), 66.47 (C-5), 42.95 (NCH_3), 40.88 (NMe_2).

MS (m/z, %): 346 (M^+, 22), 178 (100), 160 (60), 77 (23).

2.2.2. 4-Benzenesulfonyl-3-(4-*N*,*N*-dimethylphenyl)-2-phenyl-isoxazolidine (3b)



To a solution of phenyl vinyl sulfone (298 mg, 2 mmoL) in dry toluene (10 mL) was added *N*-Phenyl-4-(*N*,*N*-dimethylamino)-benzylidene amine *N*-oxide **(2b)** (1.0 eq., 218 mg, 2 mmoL) and the reaction mixture was heated to reflux overnight. The reaction was monitored by TLC. The crude reaction mixture was concentrated *in vacuo*, and the residual material was purified by flash column chromatography (n-hexane:ethyl acetate;3:1) to give **(3b)** and recrystallized from benzene-light petroleum as yellow needles (208 mg, 51 %). Mpt 172-175 °C.

Rf : 0.46 (Ethylacetate-n-Hexane;1:1)

IR (KBr): ν (cm^{-1}) : 2922, 1614 , 1447 ,1309 (SO_2,symmetric), 1147 (SO_2,asymmetric) .

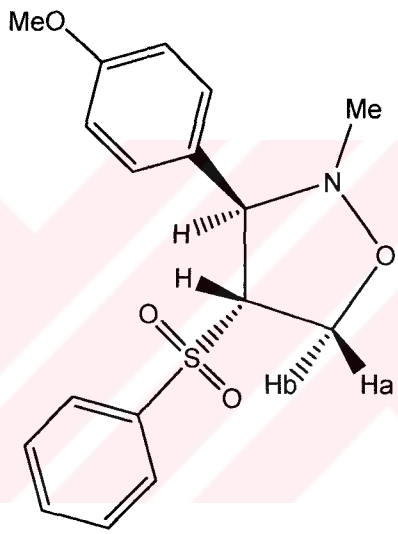
^1H NMR (δ_H, 300 MHz, $CDCl_3$,): 7.90-7.81 (m,2H), 7.71-7.57(m, 2H), 7.51-7.45 (m, 2H), 7.18 (m, 3H), 6.97-6.84 (m, 3H), 6.61 (m, 2H), 4.79 (d, *J*=4.9 Hz,1H, 3-H), 4.54 (dd, *J*=10.0 , 4.5 Hz, 1H, H-5_b), 4.38 (dd, J=10.0, 7.5 Hz,1H, H-5_a), 4.10 (ddd,J=7.5, 4.9, 4.5 Hz, 1H, H-4), 3.45 (s, 1H), 2.97 (s,

3H).

^{13}C NMR (δ_C'75MHz, $CDCl_3$): 150.5, 149.4, 137.9, 134.8, 134.4, 129.6, 129.0, 128.3, 127.9, 126.7, 123.1, 116.4, 112.8, 76.8 (C-4),70.4 (C-3), 66.7 (C-5), 40.7 (NCH_3).

MS (m/z, %): 408 (M^+, 21), 240(6) , 300 (21), 160 (100), 77 (57)

2.2.3. 4-Benzenesulfonyl-3-(4-methoxyphenyl)-2-methyl-isoxazolidine (3c)



To a solution of phenyl vinyl sulfone (42 mg, 0,25 mmoL) in dry toluene (10 mL) was added *N*-Methyl-4-(methoxy)-benzylidene amine *N*-oxide **(2c)**(1.0 eq., 68 mg, 0,25 mmoL) and the reaction mixture was refluxed overnight. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the remaining crude product was purified by flash column chromatography (n-hexane : ethyl acetate;2:1) to give **(3c)** as a yellow solid (62 mg, 55 %). Mpt 146-147 °C.

R_f : 0.62 (Ethylacetate-n-Hexane;1:1)

IR (KBr): ν (cm^{-1}) : 3050 , 2845 , 1615 , 1445 , 1295(SO_2,symmetric), 1142

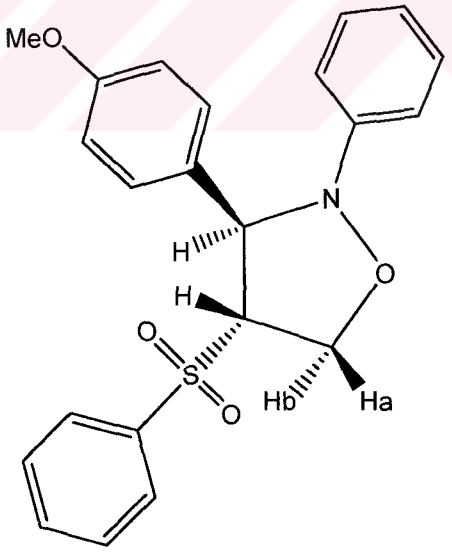
(SO_2,asymmetric).

^1H NMR (δ_H, 300 MHz, $CDCl_3$): 7.72 (d, *J*= 9.4 Hz, 2H), 7.49 (t, *J*=8.6 Hz,1H), 7.35 (t, J=7.5 Hz, 2H), 6.98 (d, *J*=8.7 Hz, 2H), 6.65 (d,J=8.7 Hz, 2H), 4.37 (dd, *J*=9.9, 3.3 Hz, 1H, H_b -5), 4.17 (dd, *J*=9.9, 8.2 Hz,1H,H_a-5), 3.89 (ddd, *J*=8.2, 7.0, 3.5 Hz,1H, H-4), 3.68 (br d, *J*=6.3 Hz, 1H,H-3), 3.65 (s, 3H, OCH_3), 2.41(s,3H, NCH_3).

^{13}C NMR (δ_C , 75 MHz, CDCl3): 160.0, 138.4, 134.4, 129.7, 129.3, 129.0, 128.9, 128.8, 114.4, 75.6 (C-4), 73.5 (C-3), 66.4 (C-5), 55.6 (OCH_3), 42.9 (NCH_3).

MS (m/z, %): 333 (M^+, 40), 190(100), 165(30) , 147 (27), 77 (38).

2.2.4. 4-Benzenesulfonyl-3-(4-methoxyphenyl)-2-phenyl-isoxazolidine (3d)



To a solution of phenyl vinyl sulfone (168 mg, 1 mmoL) in dry toluene (10 mL) was added *N*-phenyl-4-(methoxy)-benzylidene amine *N*-oxide **(2d)** (1.0 eq., 227 mg, 1 mmoL) and the mixture was heated to reflux overnight. The reaction was monitored by TLC. The reaction mixture was concentrated *in*

vacuo, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 3:1) to give **(3d)** and recrystallized from benzene-light petroleum as yellow needles (200 mg, 50 %). Mpt 145-146 °C.

R_f : 0.61 (Ethylacetate-n-Hexane;1:1)

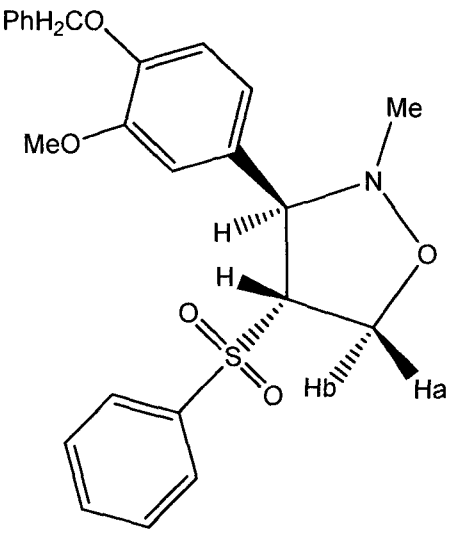
IR (KBr): ν (cm^{-1}) : 3415, 3056 , 1611 ,1486 ,1309 (SO_2,symmetric) ,1147 (SO_2,asymmetric).

^1H NMR (δ_H, 300 MHz, $CDCl_3$) ; 7.84 (d,2H), 7.61 (m,1H), 7.50 (t,2H), 7.24 (d, 3H),7.15 (t, 2H), 6.98 (m,1H), 6.80(m,4H), 4.85 (d, *J*=5.0 Hz,1H, H-3), 4.50(dd, J=10.0, 4.8 Hz,1H, H_b-5), 4.35 (dd, *J*=10.0, 7.5 Hz,1H, H_a-5), 4.15(ddd, *J*=7.5, 5.0, 4.8 Hz,1H, H-4), 3.79 (s,3H, OCH_3).

^{13}C NMR (δ_C, 75 MHz, $CDCl_3$):159.6, 149.2, 137.8, 134.5, 131.5, 129.7, 128.9,128.3, 123.3, 116.4, 114.5, 76.8 (C-4), 70.2 (C-3), 66.8 (C-5), 55.5 ($O\mathbf{C}H_3$).

MS (m/z, %): 395 (M^+, 31), 253(12) , 211(73), 147(32) , 77 (53).

2.2.5. 4-Benzenesulfonyl-3-(4-benzyloxy-3-methoxyphenyl)-2-methyl-isoxazolidine (3e)



To a solution of phenyl vinyl sulfone (168 mg, 1 mmoL) in dry toluene (10 mL) was added *N-m*ethyl-(4-benzyloxy-3-methoxy)-benzylidene amine *N*-oxide **(2e)** (1.0 eq., 271 mg, 1 mmoL) and the mixture was heated to reflux for 18 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (petroleum ether 40-60 °C : ethyl acetate;2 :1) to give **3e** as a yellow solid (276 mg, 63 %). m.p 115-117 °C.

R_f : 0.77 (Ethylacetate-n-Hexane;2:1)

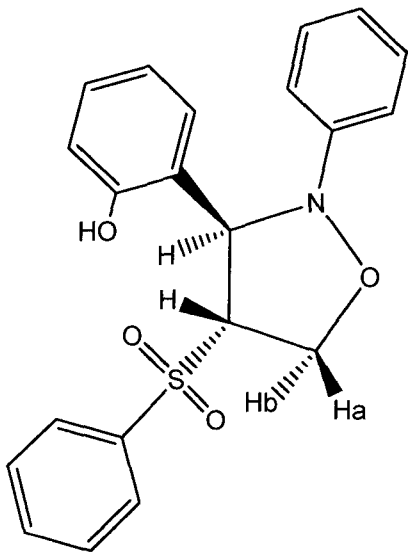
IR (KBr): ν (cm^{-1}) : 3050,2959,1604, 1454, 1305(SO_2,symmetric), 1153 (SO_2,asymmetric).

^1H NMR (δ_H, 500 MHz, $CDCl_3$): 7.80(2 doublets, 2H), 7.55-7.52 (3 triplets, 1H), 7.45-7.30 (m, 8H), 6.75(d, 1H), 6.68 (d, 1H,J=8.27 Hz), 6.59 (dd,*J*=8.2, 6.3 Hz,1H), 5.13 (s, 2H), 4.47 (dd, *J*=10.0, 3.4 Hz, H_b-5,1H) 4.25 (dd,*J*=10.0, 8.3 Hz, 1H, Ha-5), 4.03 (ddd,*J*=8.3, 7.1, 3.4 Hz, 1H,H-4), 43.80 (br d,*J*=7.1 Hz, 1H, H-3), 2.60 (s, 3H, NCH_3).

^{13}C NMR(δ_C, 125 MHz, $CDCl_3$): 149.6, 148.1, 138.0, 134.0, 129.5, 129.3, 128.5, 120.3, 113.6, 110.6, 75.3 (C-4), 73.2 (C-3), 70.8 (O**C**H_2Ph)66.0 (C-5), 56.0 (O**C**H_3), 42.7 (**NC**H_3).

MS (m/z, %): 439 (M^+, 11), 297(9) , 255(11), 91(100) , 77 (28).

2.2.6. 4-Benzenesulfonyl-3-(2-hydroxyphenyl)-2-phenyl-isoxazolidine (3f)



To a solution of phenyl vinyl sulfone (168 mg, 1 mmoL) in dry toluene (10 mL) was added *N*-(2-hydroxyphenyl)-benzylidene amine *N*-oxide **(2f)** (1.0 eq., 213 mg, 1 mmoL) and the reaction mixture was heated to reflux overnight. During this time the reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate 2:1) to give **3f** as a dark coloured oily product. (48 mg, 13 %).

R_f : 0.46 (Ethylacetate-n-Hexane;1:1)

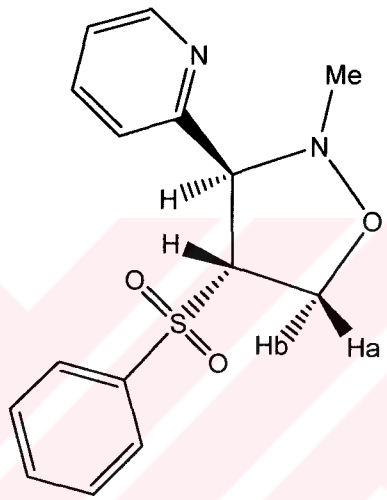
IR (KBr): ν (cm^{-1}) : 3411 (OH), 1596 , 1447 ,1307 (SO_2,symmetric), 1149 (SO_2,asymmetric).

^1H NMR (δ_H, 500 MHz ,$CDCl_3$): 8.98 (br s, 1H, OH), 7.84 (d, 2H, *J*=7.9 Hz),7.64 (m, 1H), 7.50 (t, 2H), 7.38 (s, 2H), 7.24 (m, 3H), 7.20 (m, 3H), 6.93 (d, 1H, J=8.2 Hz), 6.80 (d, 1H, *J*=7.8 Hz), 6.72 (t,1H), 4.82 (d, *J*=6.1 Hz,1H, H-3),4.68 (dd,*J*=10.1, 3.2 Hz, 1H,H_b-5), 4.47 (dd,*J*=10.1, 7.6 Hz, 1H, H_a-5), 4.25 (ddd,J=7.6, 6.1, 3.2, 1H, H-4).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 162.4, 160.1, 141.4, 134.9, 133.1, 130.7, 129.5,129.1,122.1, 120.6,119.5,117.1,116.6, 74.4 (C-4), 71.8 (C-3), 67.3 (C-5).

MS (m/z, %): 381 (M^+, 52), 239(37) , 196(28), 133(55) , 77 (100).

2.2.7. 4-Benzenesulfonyl-2-methyl-3-pyridyl-isoxazolidine (3g)



To a solution of phenyl vinyl sulfone (168 mg, 1 mmoL) in dry toluene (10 mL) was added *N*-methyl-1-(2-pyridyl)methanimine *N*-oxide **(2g)** (1.0 eq., 271 mg, 1 mmoL) and the reaction mixture was refluxed overnight. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was subjected to flash column chromatography (n-hexane:ethyl acetate 2:1) to give **3g** as a black solid (126 mg, 41 %). Mpt 119-122 °C.

R_f : 0.62 (Ethylacetate-n-Hexane;1:1)

IR (KBr): ν (cm^{-1}) : 2853, 1591, 1443, 1302 (SO_2,symmetric),1154 (SO_2,asymmetric).

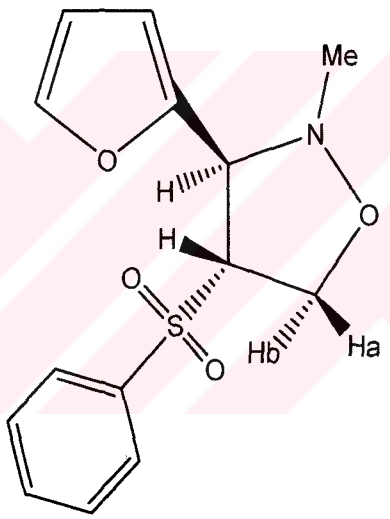
^1H NMR (δ_H: 500 MHz, $CDCl_3$) ; 8.46(d,1H), 7.49 (d,2H), 7.37 (m,2H), 6.98

(m,2H), 7.10 (t,2H), 4.79 (very broad,1H, H-4), 4.55 (dd, *J*=9.8, 4.0 Hz,1H, H_b-5), 4.33 (dd, *J*=9.8, 8.2 Hz, 1H, H_a-5), 4.06 (very broad,1H, H-3), 2.69 (s, 3H, *N*-CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 154.9 , 149.9, 138.2, 136.7, 133.9, 128.4, 123.8, 123.3, 74.4 (C-3), 73.1 (C-4), 66.2 (C-5), 43.0 (*N*-**C**H_3).

MS (m/z, %): 304 (M^+, 18), 246(100) , 134(69), 118(92) , 77 (55).

2.2.8. 4-Benzenesulfonyl-3-furyl-2-methyl-isoxazolidine (3h)



To a solution of phenyl vinyl sulfone (168 mg, 1 mmoL) in dry toluene (10 mL) was added *N*-methyl-1-(2-furyl)methanimine *N*-oxide **(2h)** (1.0 eq., 125 mg, 1 mmoL) and the mixture was heated to reflux overnight. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the remaining crude residue was purified by flash column chromatography (n-hexane:ethyl acetate;2:1) to give **(3h)** and recrystallized from benzene-light petroleum as a white needles (125 mg, 40 %). Mpt 122-124 °C.

R_f : 0.50 (Ethylacetate-n-Hexane;1:1)

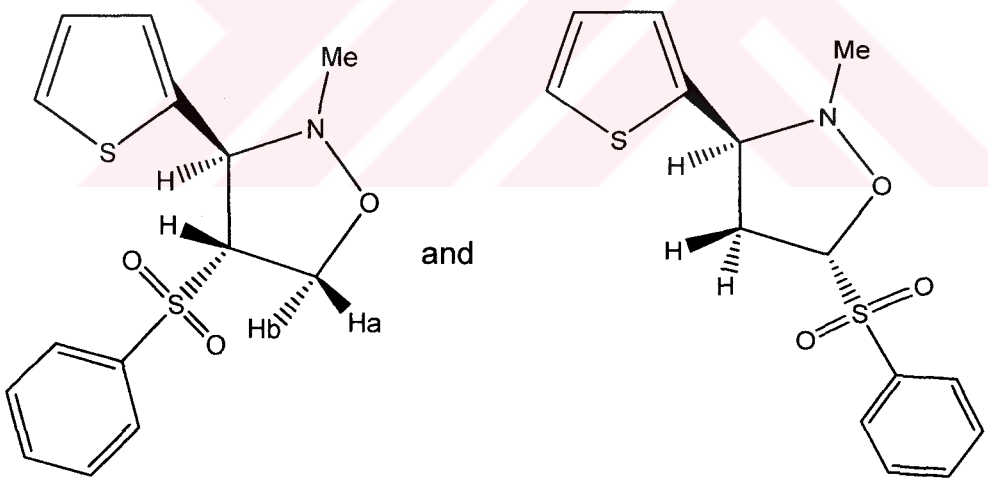
IR (KBr): ν (cm^{-1}) : 3137, 2967 , 1448 ,1315 (SO_2,symmmetric), 1149(SO_2,,asymmetric).

^1H NMR (δ_H, 500 MHz, $CDCl_3$):7.83 (dd,2H), 7.60 (3 triplets,1H), 7.49 (t, 2H), 7.25 (dd, 2H), 6.17-6.06 (br t and d , 1H), 4.54 (dd, *J*= 9.9, 3.3 Hz, 1H, H_b-5), 4.37 (ddd, *J*=8.6,7.5, 3.3 Hz),1H, H-4), 4.29 (dd, *J*=9.9,8.6 Hz, 1H, H_a-5),3.91 (very br, 1H, H-3),2.66 (s, 3H, *N*CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$):147.6 , 137.8, 134.0, 129.3, 128.4, 110.5, 110.0, 71.3 (C-4), 67.4 (C-3), 65.8 (C-5), 42.4 (*N*-CH_3).

MS (m/z, %): 293 (M^+, 16), 150(100) , 125(22), 107(25) , 77 (45).

2.2.9. 4-Benzenesulfonyl-2-methyl-3-thienyl-isoxazolidine (3i-a) and 5-Benzenesulfonyl-2-methyl-3-thienyl-isoxazolidine (3i-b)



3i-a **3i-b**

To a solution of phenyl vinyl sulfone (168 mg, 1 mmoL) in dry toluene (10 mL) was added *N*-methyl-1-(2-thienyl)methanimine *N*-oxide **(2i)**(1.0 eq., 141 mg, 1 mmoL) and the reaction mixture was heated to reflux overnight.The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography

(n-hexane:ethyl acetate ;2:1) to give a mixture of 4- and 5- regioisomers which can not be separated and recrystallized from benzene-light petroleum as white needles (126 mg, 41 %). Mpt 99-101 °C.

R_f : 0.49 (Ethylacetate-n-Hexane;3:2)

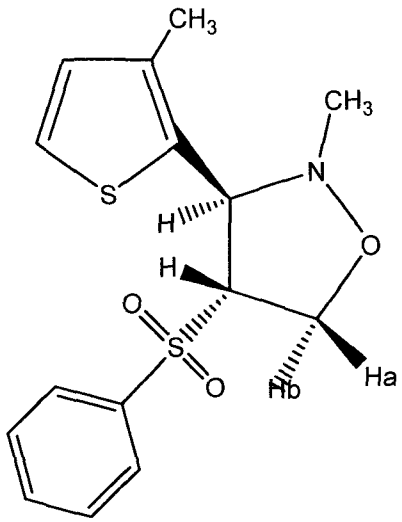
IR (KBr): ν (cm^{-1}) : 1581 , 1446, 1307(SO_2,symmmetric) ,1147 (SO_2,asymmetric).

^1H NMR (δ_H 500 MHz, $CDCl_3$): 7.95 (d, 2H), 7.86 (d, 4H), 7.71-7.59 (m, 5H), 7.52 (t, 4H), 7.28 (d, 1H), 7.20 (d,2H),7.02 (br s, 1H), 6.97 (dd, 1H), 6.81 (dd, 2H), 6.66 (d,2H), 4.50 (dd, *J*=10.0, 3.3 Hz, 1H, H_b-5), 4.26 (dd, *J*=10.0, 8.2 Hz, 1H, H_a-5), 4.21 (very broad, 1H, H-3), 4.03 (ddd, 8.2, 7.0, 3.3 Hz, 1H, H-4), 2.68 (s, 3H, NCH_3).

^{13}C NMR (δ_C , 125 MHz, $CDCl_3$): 139.5, 137.1, 134.2, 129.4, 128.6, 126.8, 126.6, 126.1, 91.6 (C-5 of 5-regioisomer),75.6 (C-4), 69.1 (C-3), 65.9 (C-5 of 4-regioisomer), 42.8 (NCH_3).

MS (m/z, %): 309 (M^+, 25), 166(100) , 140(37), 125(100) , 97 (50) , 77(97).

2.2.10. 4-Benzenesulfonyl-2-methyl-3-(3-methylthienyl)-isoxazolidine (3j)



To a solution of phenyl vinyl sulfone (168 mg, 1 mmoL) in dry toluene (10 mL) was added *N*-methyl-1-(2-(3-methyl thienyl))ethanimine *N*-oxide **(2j)** (1.0 eq., 155 mg, 1 mmoL) and the reaction mixture was heated to reflux overnight.The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography (n-hexane:ethyl acetate;2:1) to give **3j** and recrystallization from hexane yielded white needles (126 mg, 41 %). Mpt 87-89 °C.

R_f : 0.46 (Ethylacetate-n-Hexane;1:1)

IR (KBr): ν (cm^{-1}) : 3058, 2877 , 1447 ,1307 (SO_2,symmetric) , 1153(SO_2,asymmetric).

^{1}H NMR (δ_H, 500 MHz, $CDCl_3$): 7.84 (d, 2H), 7.61 (t, 1H), 7.49 (t, 2H),7.14 (s, 1H), 6.68 (d, 2H), 4.43 (dd, *J*=10.0, 3.3 Hz, 1H, H_b-5), 4.28 (very broad, 1H, H-3), 4.26 (dd, *J*=10.0, 8.3 Hz, 1H, H_a-5), 4.11 (ddd, *J*=8.3, 7.0, 3.3 Hz, 1H, H-4), 2.62 (s, 3H, *N*-CH_3), 2.19 (s, 3H).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$):137.9, 137.1, 134.0, 132.3, 130.0, 129.3, 128.3, 125.0, 75.3 (C-4), 67.0 (C-3), 66.2 (C-5), 42.4 (*N*-CH_3), 14.4 .

MS (m/z, %): 323 (M^+, 51), 181(100) , 164(32), 137(55) , 77 (50).

CHAPTER III : RESULTS AND DISCUSSION

More than a century since the original discovery and four decades since the systematic organization of the field 1,3-dipolar cycloaddition chemistry has greatly evolved as an exceptionally versatile strategic tool for assembling the organic molecules especially heterocyclic compounds which can be found naturally,1,3-dipoles, are structurally grouped into more than a dozen classes and according to intermolecular or intramolecular pathways lead in a feasible manner to heterocyclic systems[29].

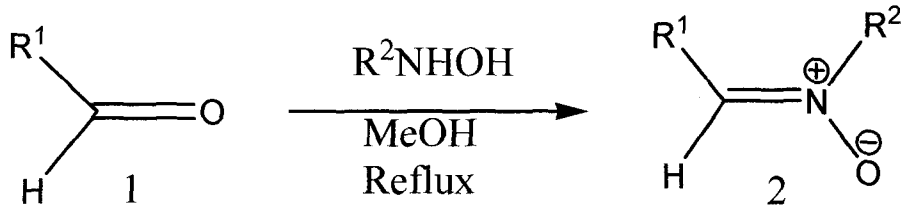
On the other hand , to our best knowledge of the literatute survey involved in the above mentioned area revealed that the 1,3-dipolar cycloaddition reactions of nitrones to the dipolarophile phenyl vinyl sulfone were the one that was rarely incorporated among this class of reactions. This encouraged us to perform this work. The work under investigation is essentially consisted of three parts.

1) Synthesis of various aldehyde nitrones**(2a-j),**

2) Synthesis of 3-substituted 4-benzenesulfonyl isoxazolidines **(3a-j)**

3) Mass spectral study of the new cycloadducts.

Synthesis of the nitrones **(2a-j)** were carried out by reacting the corresponding aromatic or heteroaromatic aldehyde with *N*-methylhydroxyl amine hydrochloride or *N*-phenyl hydroxyl amine in the presence of a desiccant (i.e. molecular sieves 4 Å or magnesium sulfate) according to the procedures described in the literature [20-29].(Scheme 3.1)



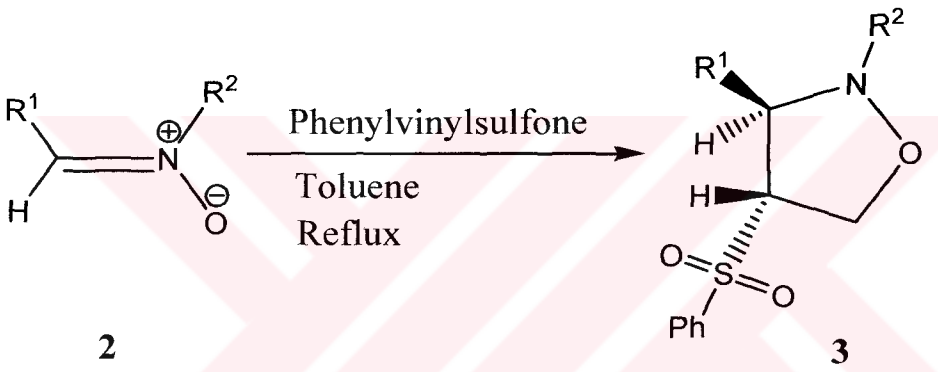
	R^1	R^2
2a	4-Me_2N-C_6H_4	Me
2b	4-Me_2N-C_6H_4	Ph
2c	4-MeO-C_6H_4	Me
2d	4-MeO-C_6H_4	Ph
2e	(4-$PhCH_2O$-3-MeO)-C_6H_3	Me
2f	2-OH-C_6H_4	Ph
2g	2-pyridyl	Me
2h	2-furyl	Me
2i	2-thienyl	Me
2j	2-(3-methyl)-thienyl	Me

Scheme 3.1

Some of the nitrones could be crystallized but some of them were used in the next step (1,3 DC with phenylvinylsulfone) as oils without any purification. Nitrone **(2j)** is a new one and not registered as far as we searched the literature (WEBOFSCIENCE and SCIFINDER electronic databases). The nitrone compounds were identified by IR, NMR, m.p and R_f characteristics. The very basic proof of the generation of the nitrone is the disappearance of the carbonyl absorption of the corresponding aldehyde in the IR spectrum of the crude product during the course of reaction.On the other hand, the very polar structure of the nitrone in comparison with the aldehyde prevents it ascending much higher point on thin layer

chromatography plates.The nitrones have strecting vibrations of C=N at around 1620-1550 cm^{-1}. N-O streching vibrations appear at 1070-1050 cm^{-1} which are higher (ca. 1300-1200 cm^{-1}) in the case of ketonitrones. In the NMR spectra , iminic proton of the nitrones arise at lowerfield values like 8.5-6.5 ppm. This is another indicative proof of the nitrone since aldehydic protons arise at much lowerfield region.

Secondly, 1,3-dipolar cycloaddition reactions were performed by refluxing the nitrones and dipolarophile phenylvinyl sulfone (Scheme 3. 2).



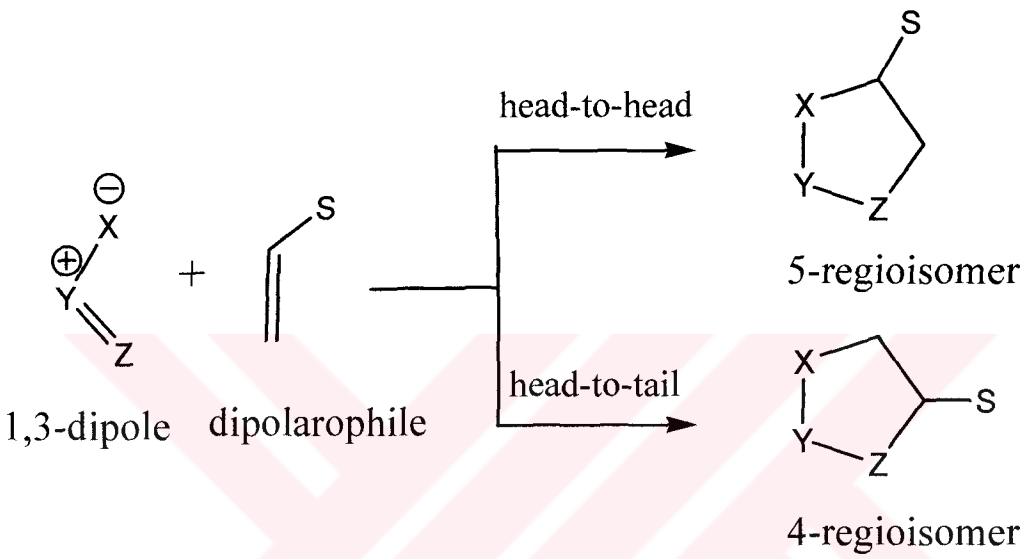
2 3

	R^1	R^2
3a	4-Me_2N-C_6H_4	Me
3b	4-Me_2N-C_6H_4	Ph
3c	4-MeO-C_6H_4	Me
3d	4-MeO-C_6H_4	Ph
3e	(4-$PhCH_2O$-3-MeO)-C_6H_3	Me
3f	2-OH-C_6H_4	Ph
3g	2-pyridyl	Me
3h	2-furyl	Me
3i	2-thienyl	Me
3j	2-(3-methyl)-thienyl	Me

Scheme 3.2

From the theoretical background of the 1,3-dipolar cycloaddition of a 1,3-

dipolar compound and a dipolarophile like phenylvinyl sulfone , it can be deduced that we might obtain two isomeric cycloadducts depending on the relative position of the substituent (S) in the cycloadduct, head-to-head, 5-regioisomer, or head-to-tail, 4-regioisomer (Scheme 3.3)[32,33].

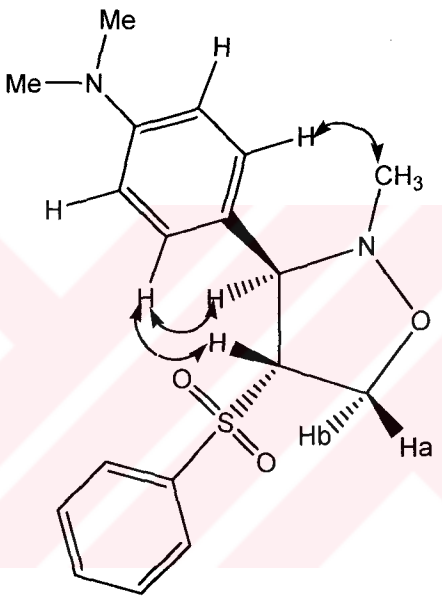


Scheme 3.3

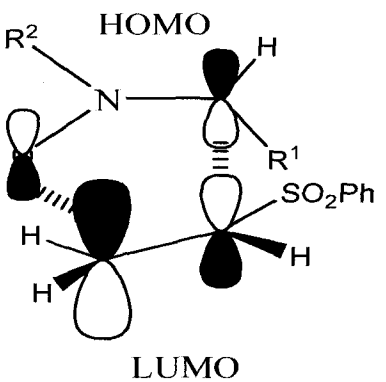
The chemical shift positions of the methylene protons of isoxazolidines **3a-j** (δ 4.30-4.50) were consistent with the presence of a directly bonded oxygen atom and not with a vicinal carbon attachment which would produce a resonance at higher field. As for the carbon chemical shift positions of the isoxazoline compounds, a representative sample **3a, 3c,** carbons C-5, C-4 and C-3 resonated at deshielded regions as expected.

	C-5	C-4	C-3
3a	**66.47**	**75.53**	**73.87**
3c	**66.88**	**76.86**	**70.22**

All the cycloadducts obtained were found to be 4-regioisomeric structure based on the NMR and MASS spectral measurements. The stereochemistry of the new benzenesulfonyl substituted isoxazolidines were determined as *trans* configuration based on both *J* coupling constants of hydrogen atoms on the carbons 3 and 4 by isoxazolidine ring numbering and 2 D NMR measurements (NOESY, HSQC, HMBC spectra). A representative example for n.O.e enhancements of related protons in **3a** was shown below.



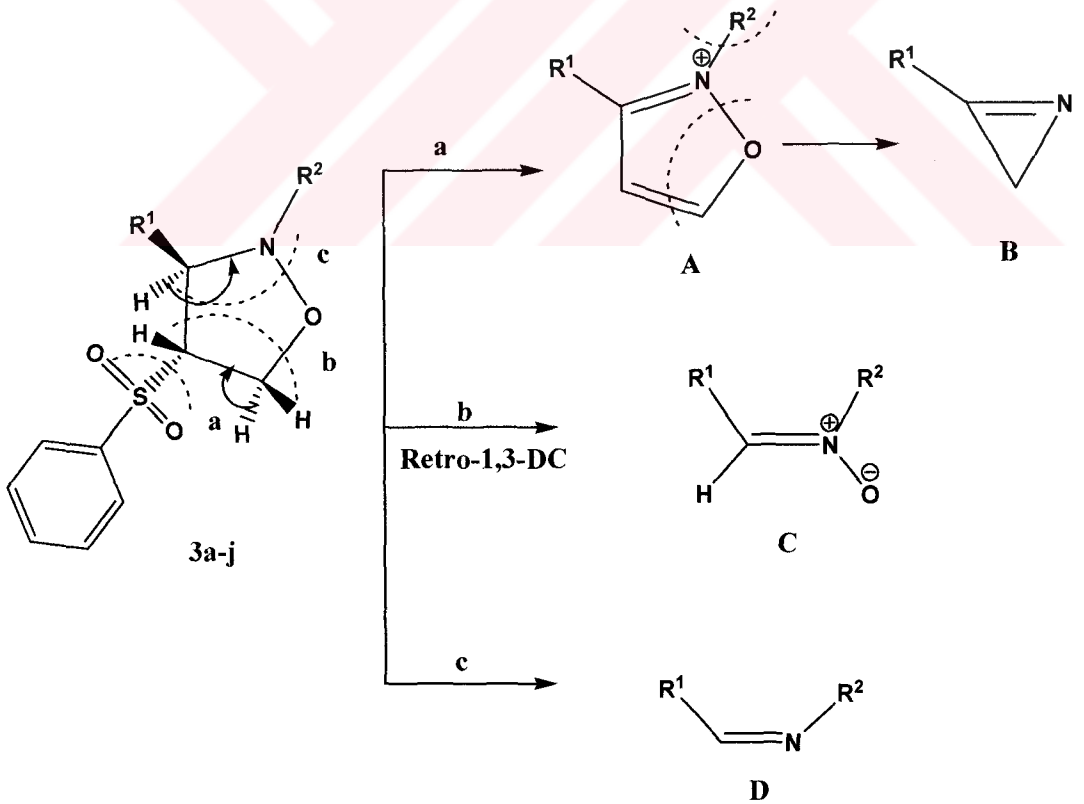
The predominant regioisomer formation can be accounted for the following frontier molecular orbital interaction between nitrone and phenyl vinyl sulfone (Scheme 3.4) [29,30].



Scheme 3.4

However, the reaction between nitrone **2i** and phenyl vinyl sulfone gave a mixture of 4- and 5- regioisomers (**3i-a** and **3i-b**) (ratio:2:1) which was determined by ^{1}H NMR and ^{13}C NMR spectra. The carbon chemical shift of C-5 of the 5-regioisomer **(3i-b)** appeared at 91.6 ppm whereas that of C-5 of the 4-regioisomer (**3i-a)** was found at 65.9 ppm. H-4 of 4-regioisomer **(3i-a)** was observed at 4.03 ppm, but, H-5 of 5-regioisomer **(3i-b)** appeared at 5.04 ppm.

In addition to the synthetic part of this work, a mass spectral study was carried out to investigate the fragmentation pathways of the target isoxazolidines under electron impact conditions. From the data it can be ruled out that there have been following routes to lead the peaks observed in the mass spectra of the compounds (Scheme 3.5).



Scheme 3.5

Table 4.MASS Spectral Data for Isoxazolidine Compounds

	m/z (%) A	m/z (%) B	m/z (%) C	m/z (%) D
3a	204/10	160/59	178/100	162/2
3b	-	160/100	240/6	223/11
3c	190/100	146/27	165/30	149/9
3d	253/12	147/28	-	211/73
3e	297/9	255/14	very low	254/2
3f	239/37	133/56	very low	196/28
3g	163/28	118/91	136/40	120/10
3h	150/100	107/24	very low	109/2
3i	166/100	123/46	141/37	125/49
3j	181/100	137/54	155/20	139/8

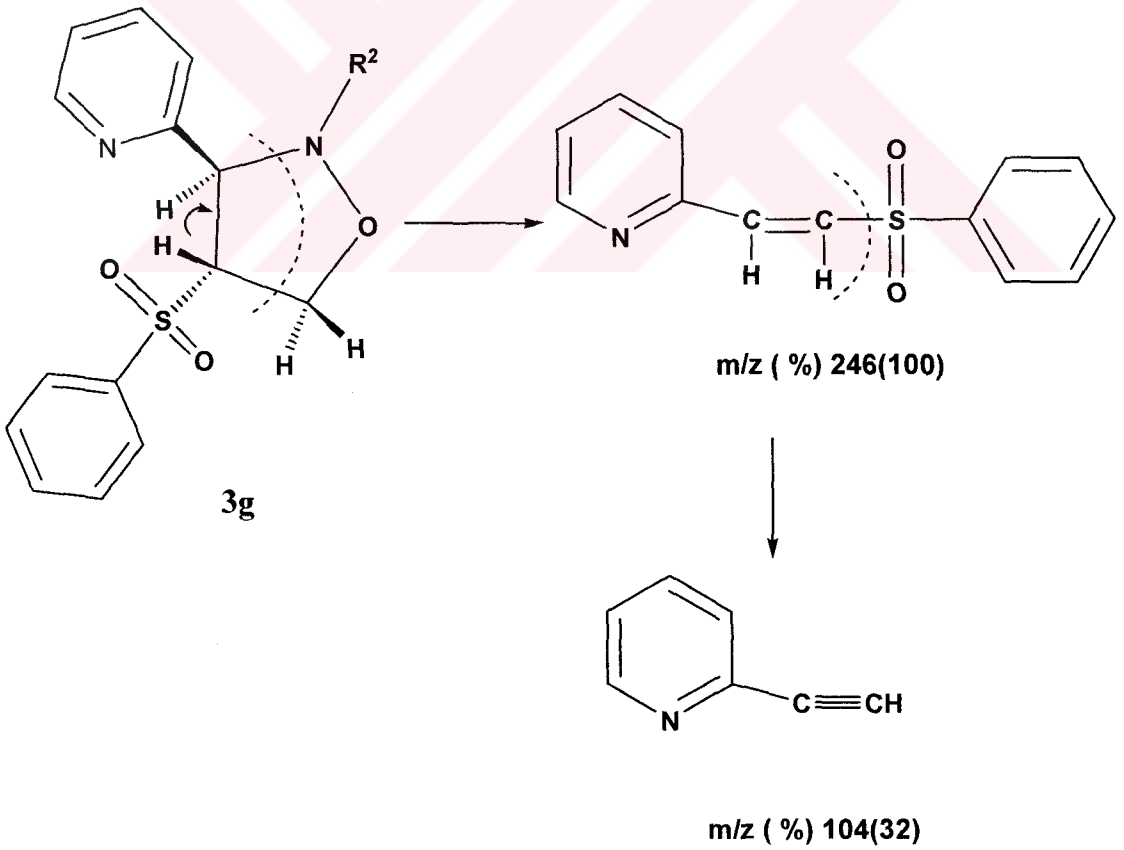
Route (a) in the fragmentation of isoxazolidines **(3a-j)** under electron impact conditions gives rise to the formation of oxazolium cations (A) which may be considered as resonance-stabilized aromatic rings. There have not been observed an oxazolium species in the fragmentation of **3b**.The relative abundances of the oxazoliums were the highest (as base peaks) in **3c, 3h, 3i and 3j** . The account for this could be the aromatic stabilization of furan and thiophene and also contribution from the electron donating effect of methoxy group on the phenyl ring of **3c**.

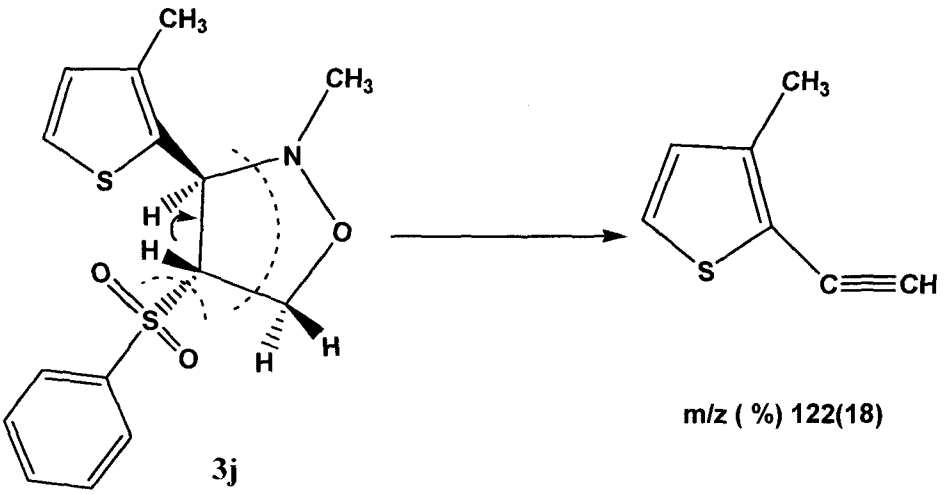
A further fragmentation might be occurred since the peaks were observed due to the existence of the m/z **(B)** ; azirine species. The highest abundances for the corresponding aziridines are those of having *N,N*-dimethyl phenyl on

C-3 and phenyl on N-2 of **3b** and 2-pyridyl on C-3 and methyl on N-2 of **3g**.

In addition, a retro-1,3-dipolar cycloaddition reaction (pathway b) would generate the nitrone which could be attributed to the masses depicted in Scheme 3.5 (C). Imine formation seemed to be in highest abundance in the case of isoxazolidine **(3d)** where methoxy subtiuent is attached on the phenyl of carbon-3.

An interesting fragmentation due to the existence of alkyne moieties (Scheme 3.6) have been concluded which may be accounted for the resizing of the isoxazolidines **3g and 3j** can be seen below .





3j

m/z (%) 122(18)

CONCLUSION

This work describes a simple and one-pot synthesis of the 9 new benzenesulfonyl substituted isoxazolidines. The structure and sterochemistry of the compounds are determined by means of IR,NMR and Mass Spectra. A detailed mass spectral study was also conducted on the compounds newly synthesized.

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APPENDIX : IR , NMR(^{1}H , ^{13}C , NOESY, HSQC, HMBC)

AND MASS SPECTRA

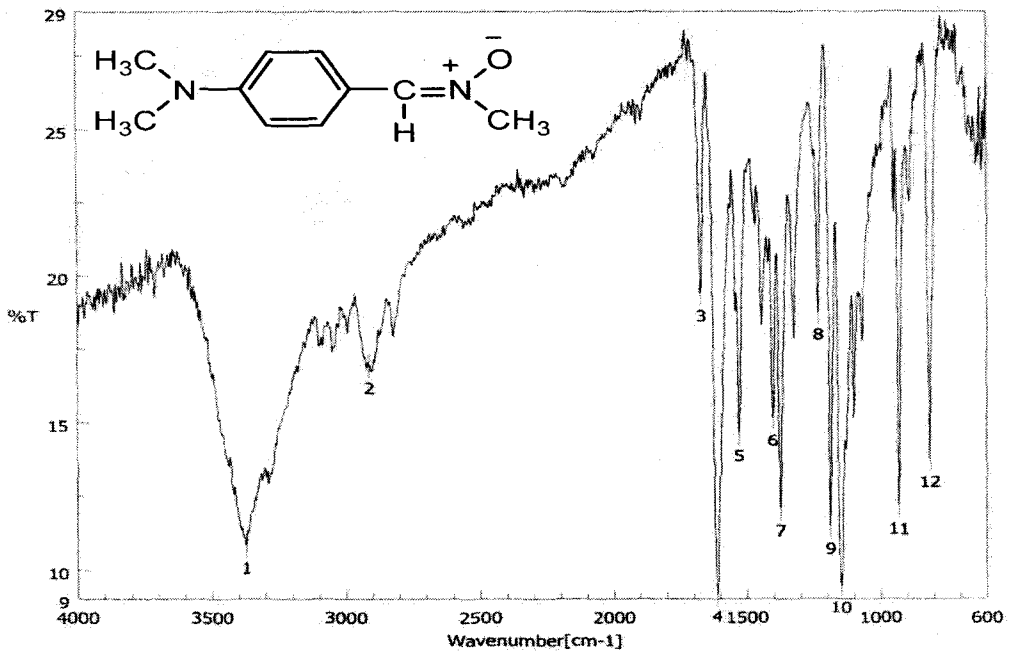


Figure 4.1. IR Spectrum of **2a**

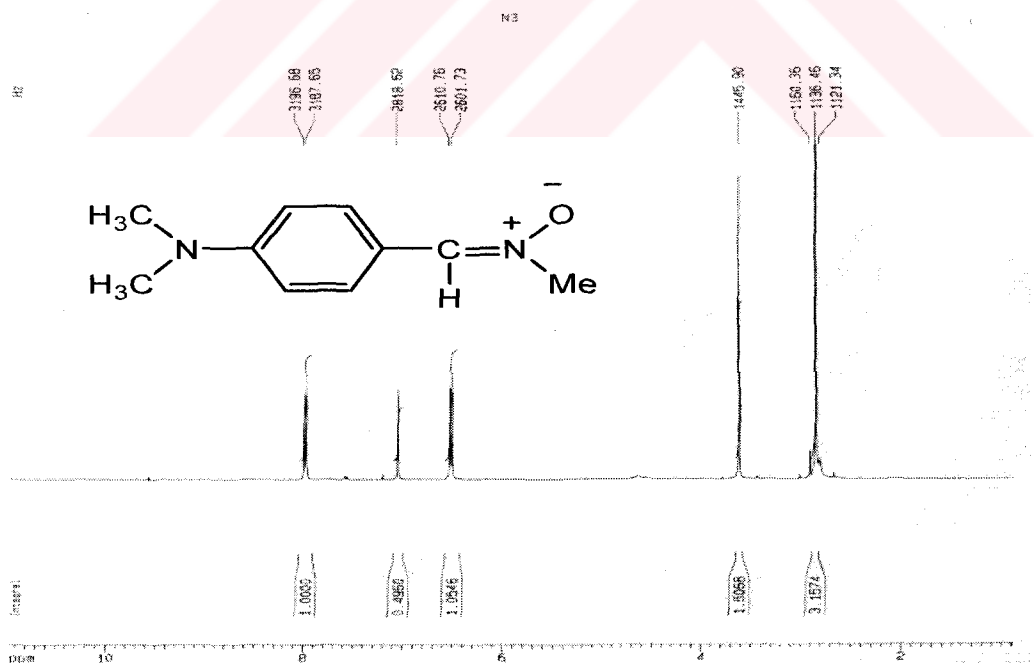


Figure 4.2. ^{1}H NMR Spectrum of 2**a**

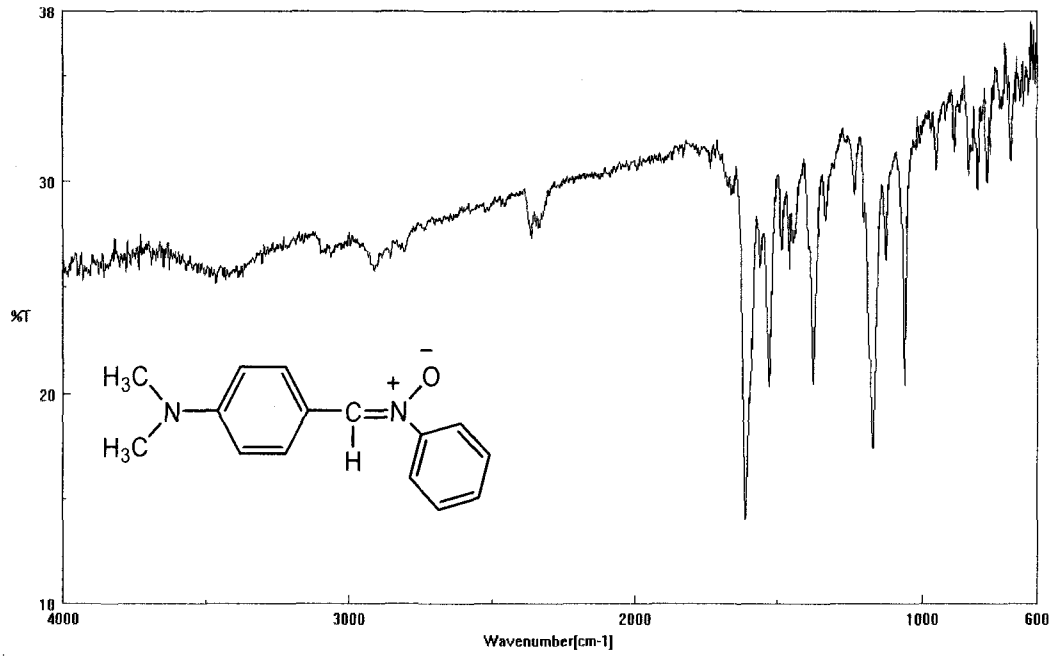


Figure 4.3. IR Spectrum of **2b**

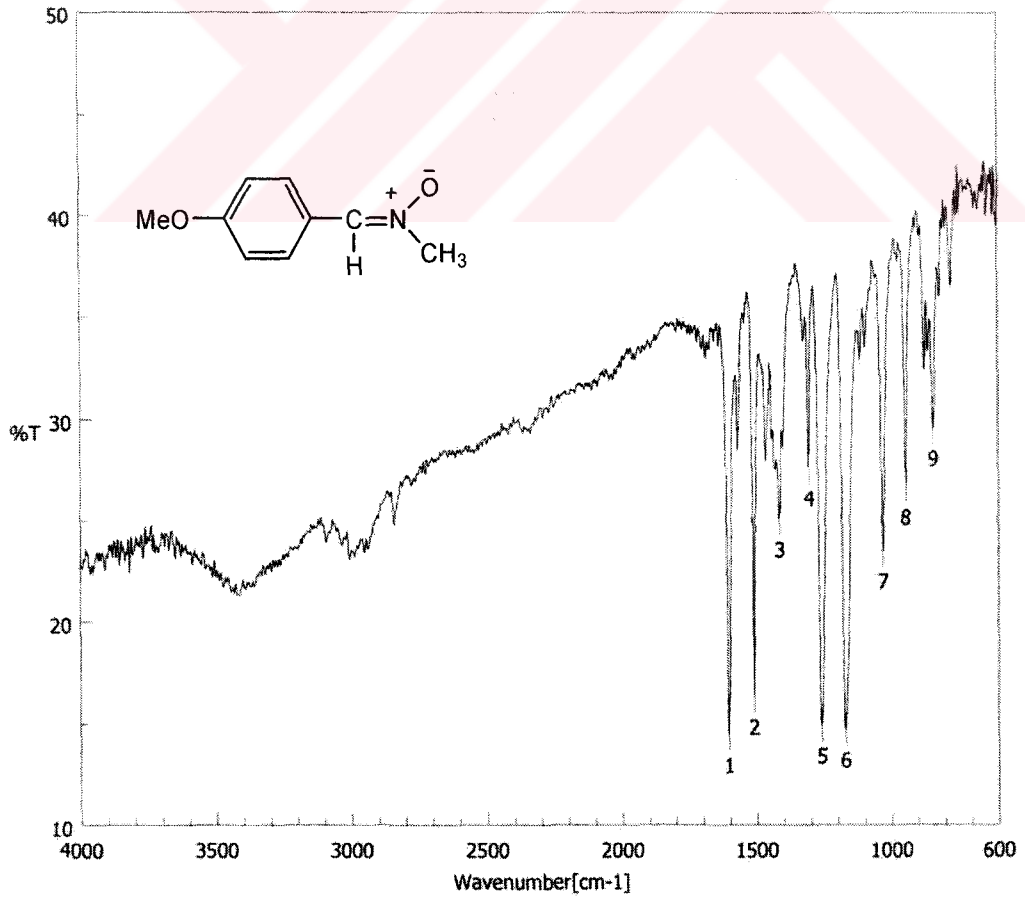


Figure 4.4. IR Spectrum of **2c**

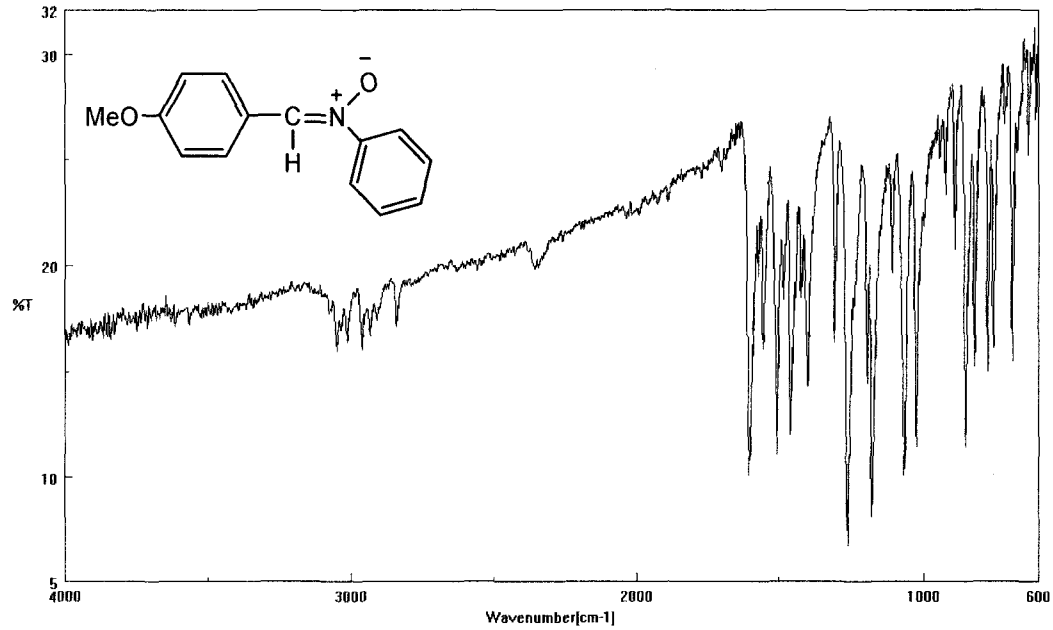


Figure 4.5. IR Spectrum of **2d**

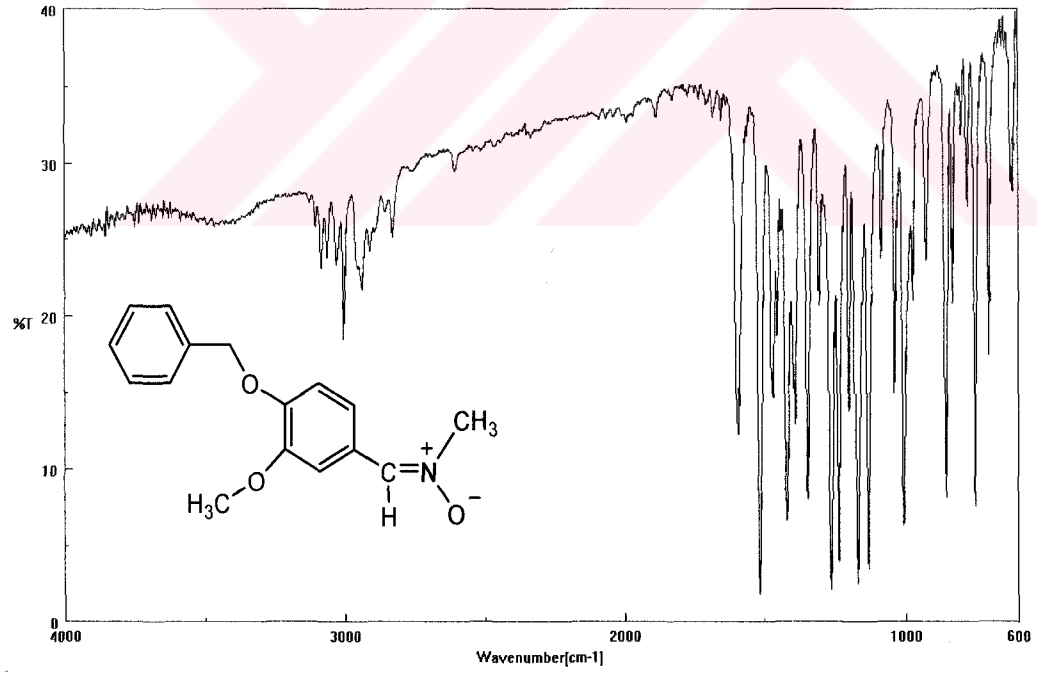


Figure 4.6. IR Spectrum of **2e**

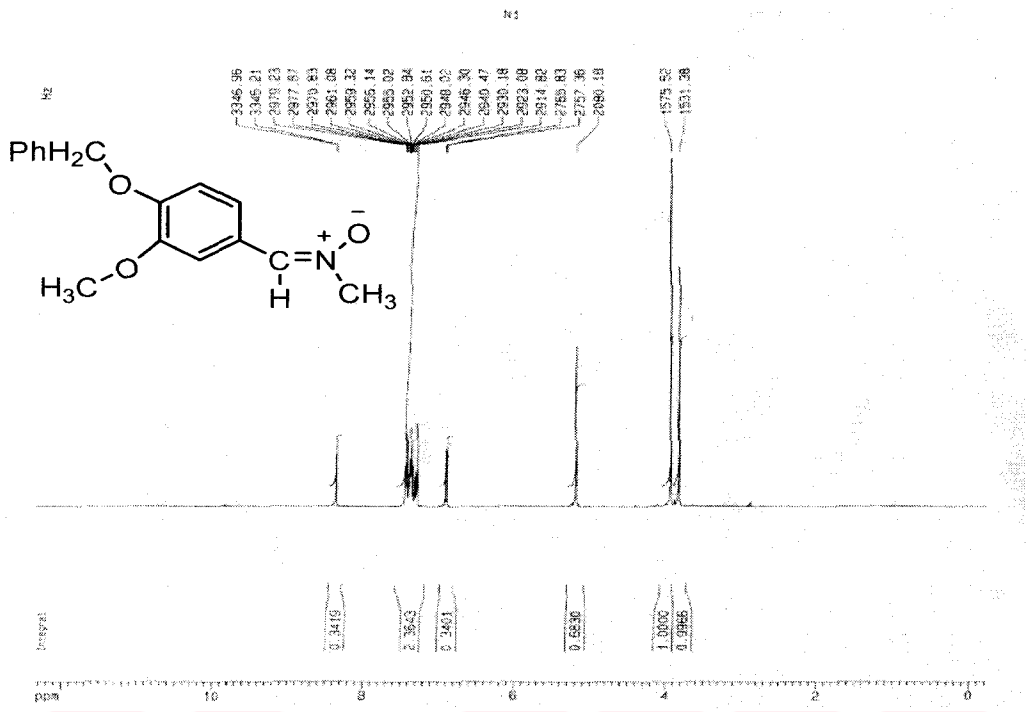


Figure 4.7. ^{1}H NMR Spectrum of **2e**

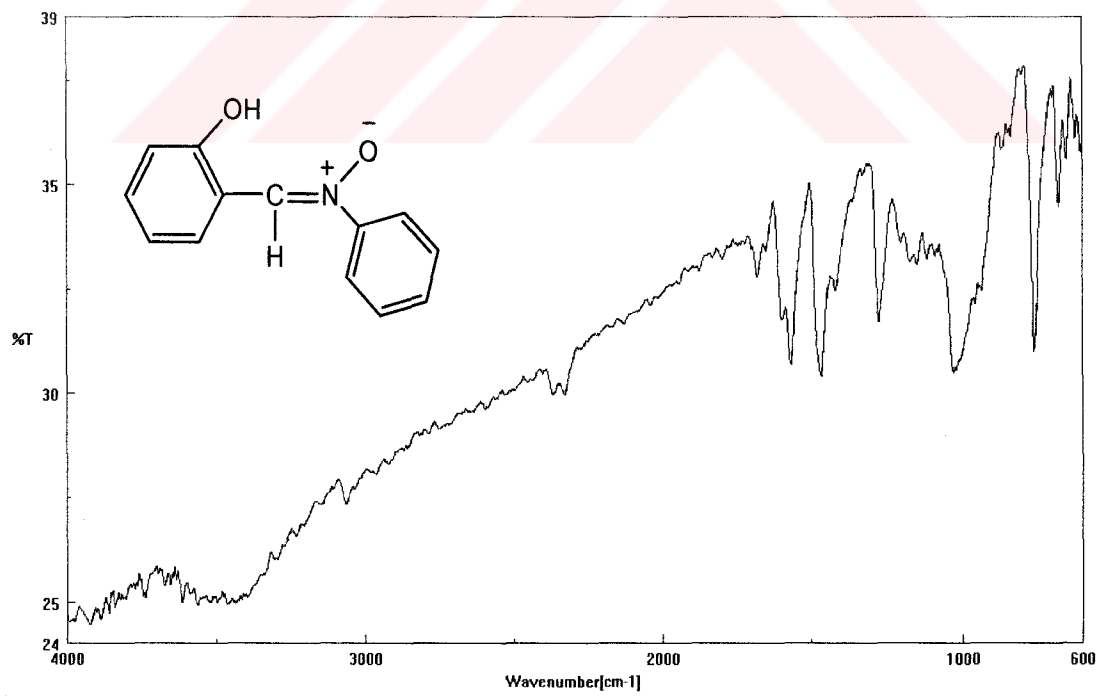


Figure 4.8. IR Spectrum of **2f**

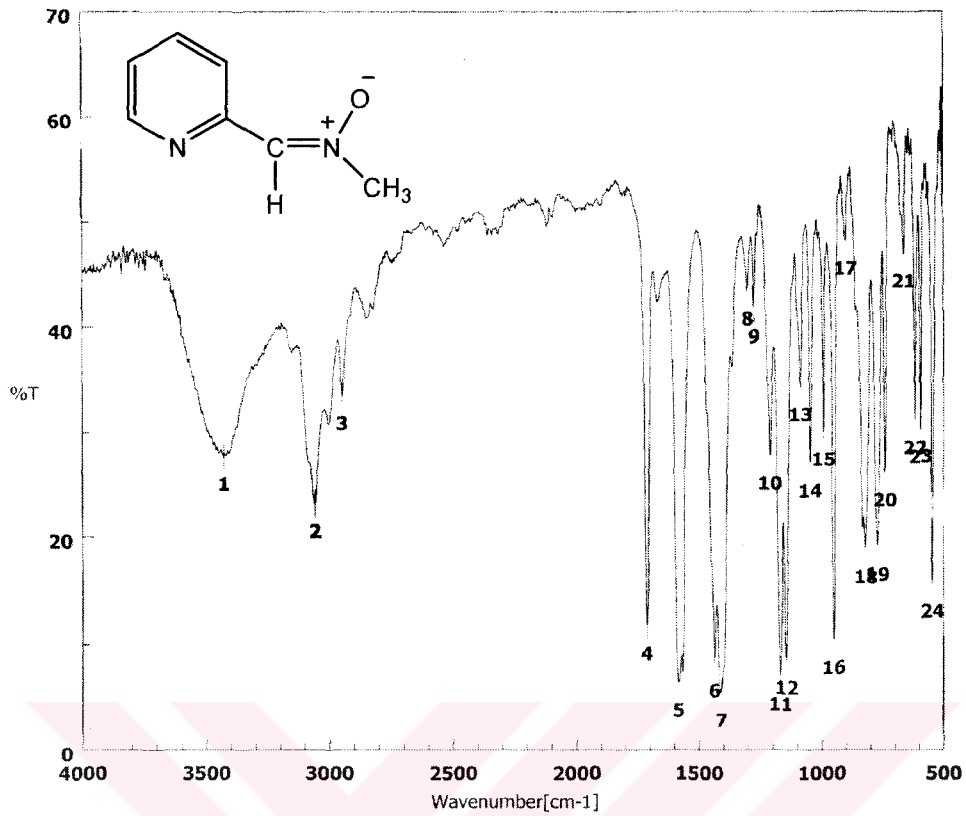


Figure 4.9. IR spectrum of **2g**

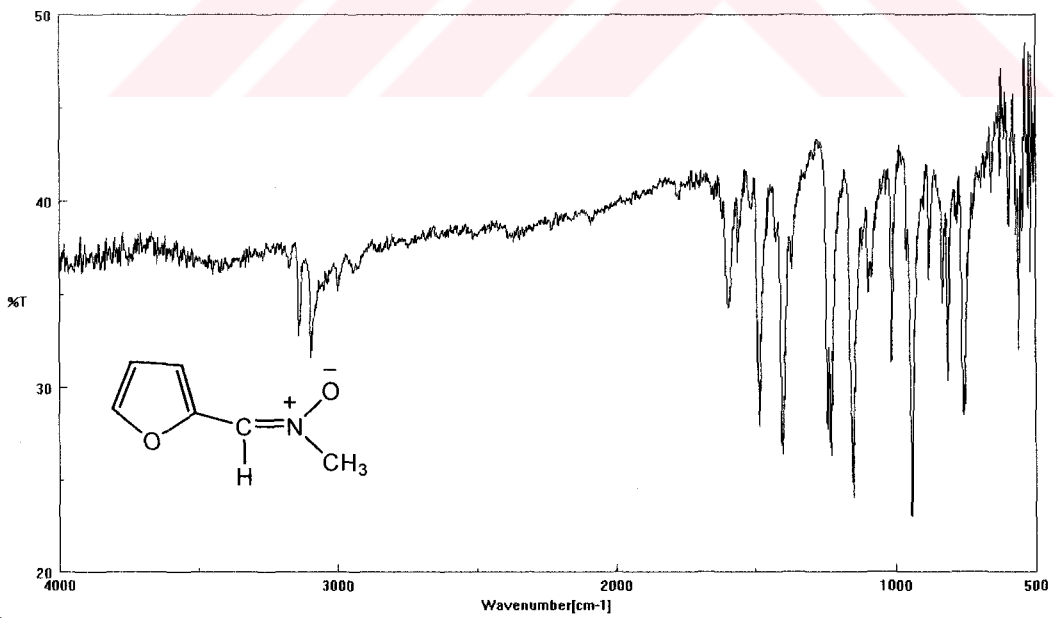


Figure 4.10. IR Spectrum of **2h**

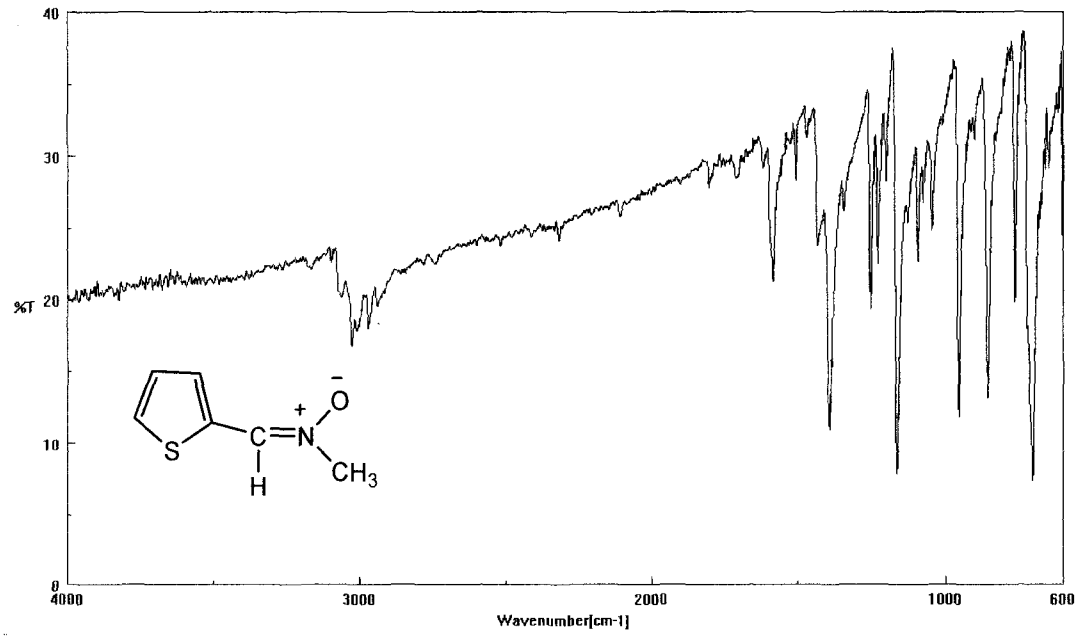


Figure 4.11. IR spectrum of **2i**

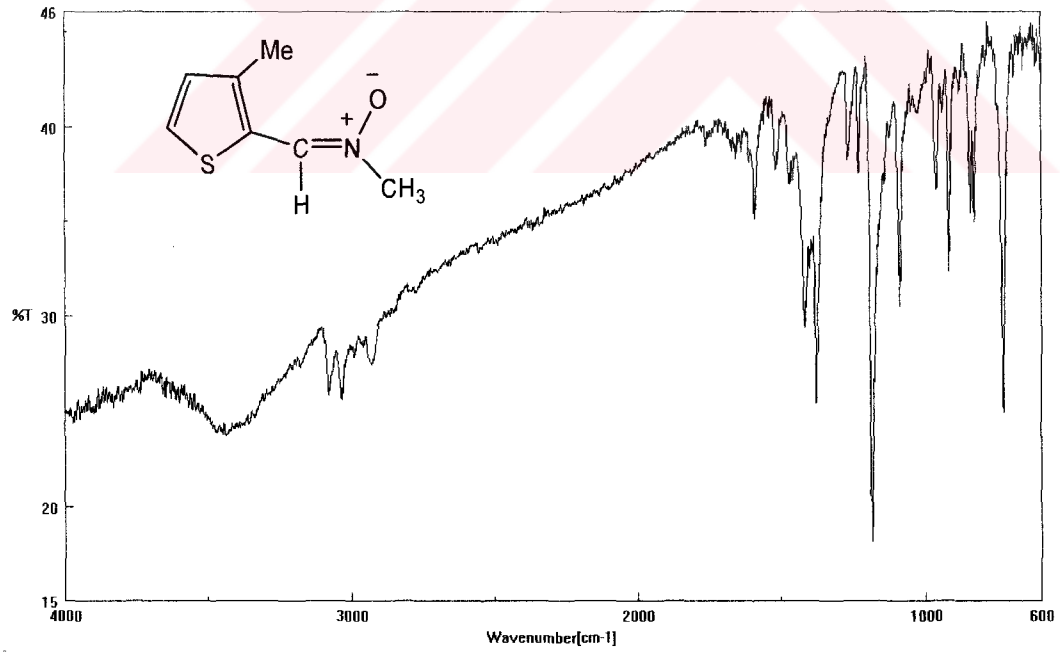


Figure 4.12. IR Spectrum of **2j**

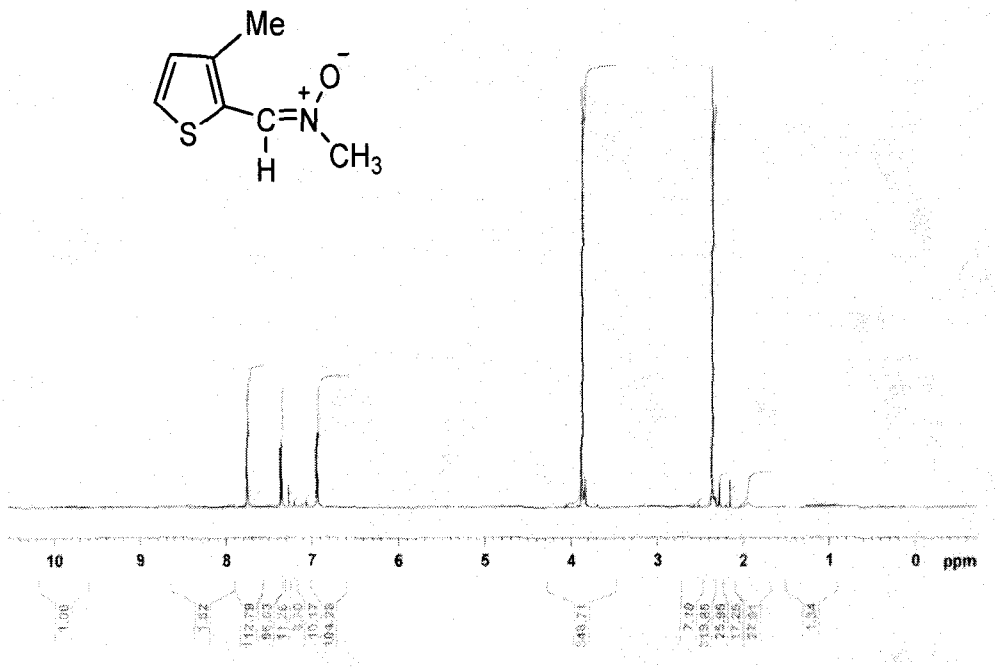


Figure 4.13. ^{1}H NMR Spectra of **2j**

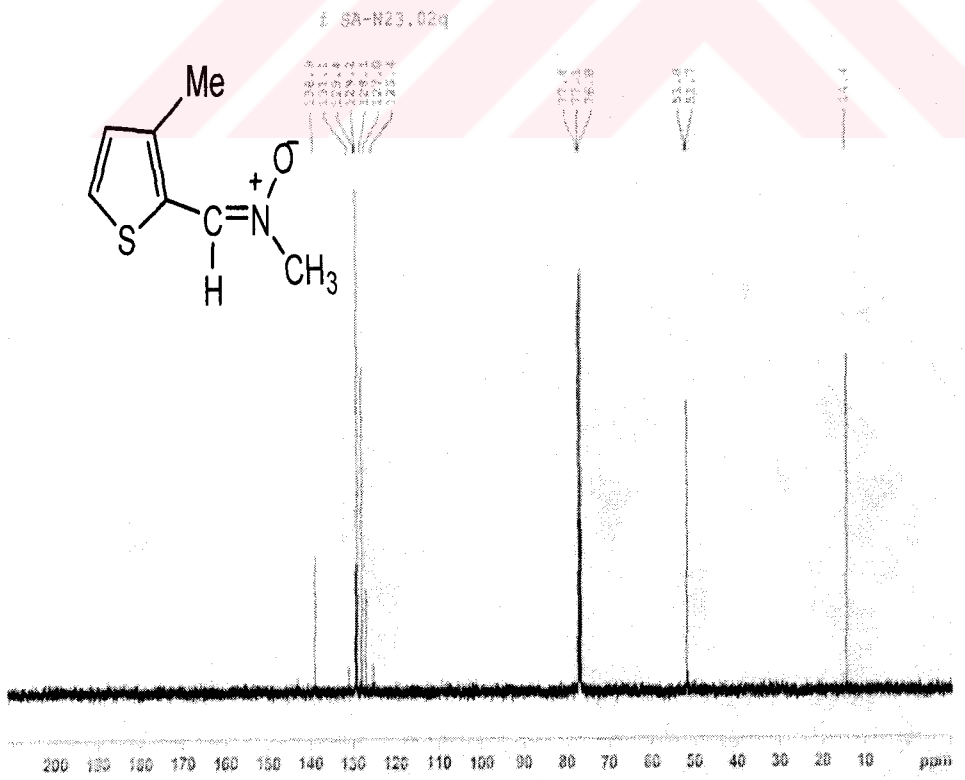


Figure 4.14. ^{13}C NMR Spectra of **2j**

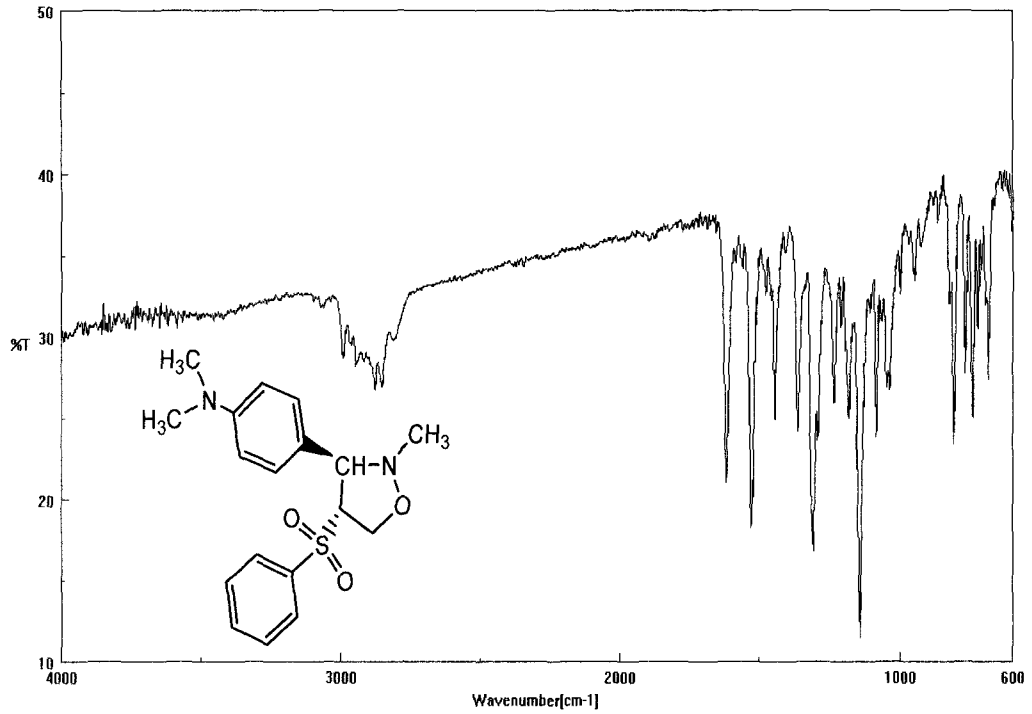
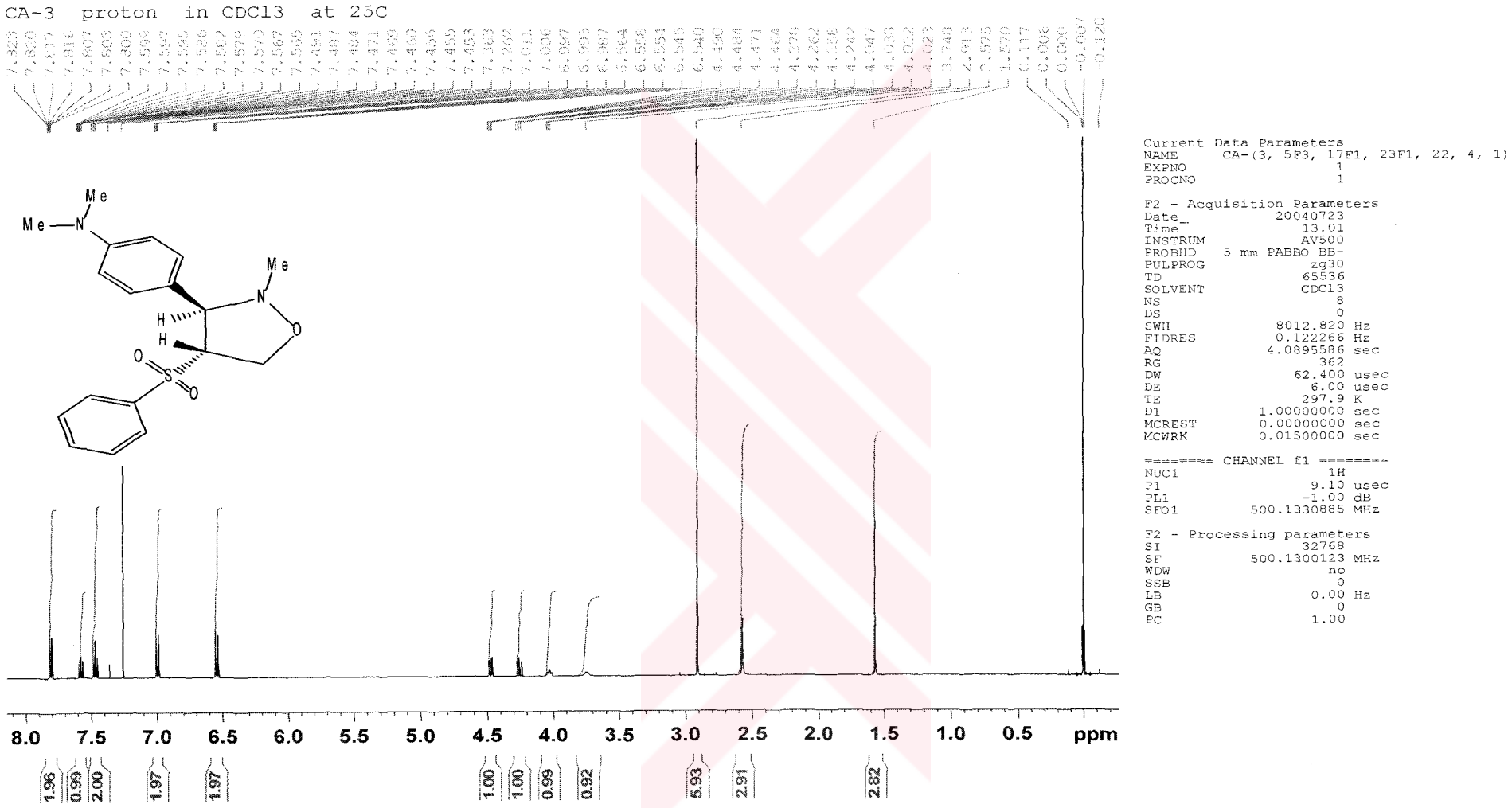


Figure 4.15. IR Spectrum of **3a**

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PROCNO                  1

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PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                      8
DS                      0
SWH              8012.820 Hz
FIDRES           0.122266 Hz
AQ               4.0895586 sec
RG                    362
DW                 62.400 usec
DE                  6.00 usec
TE                 297.9 K
D1              1.00000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  9.10 usec
PL1                -1.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
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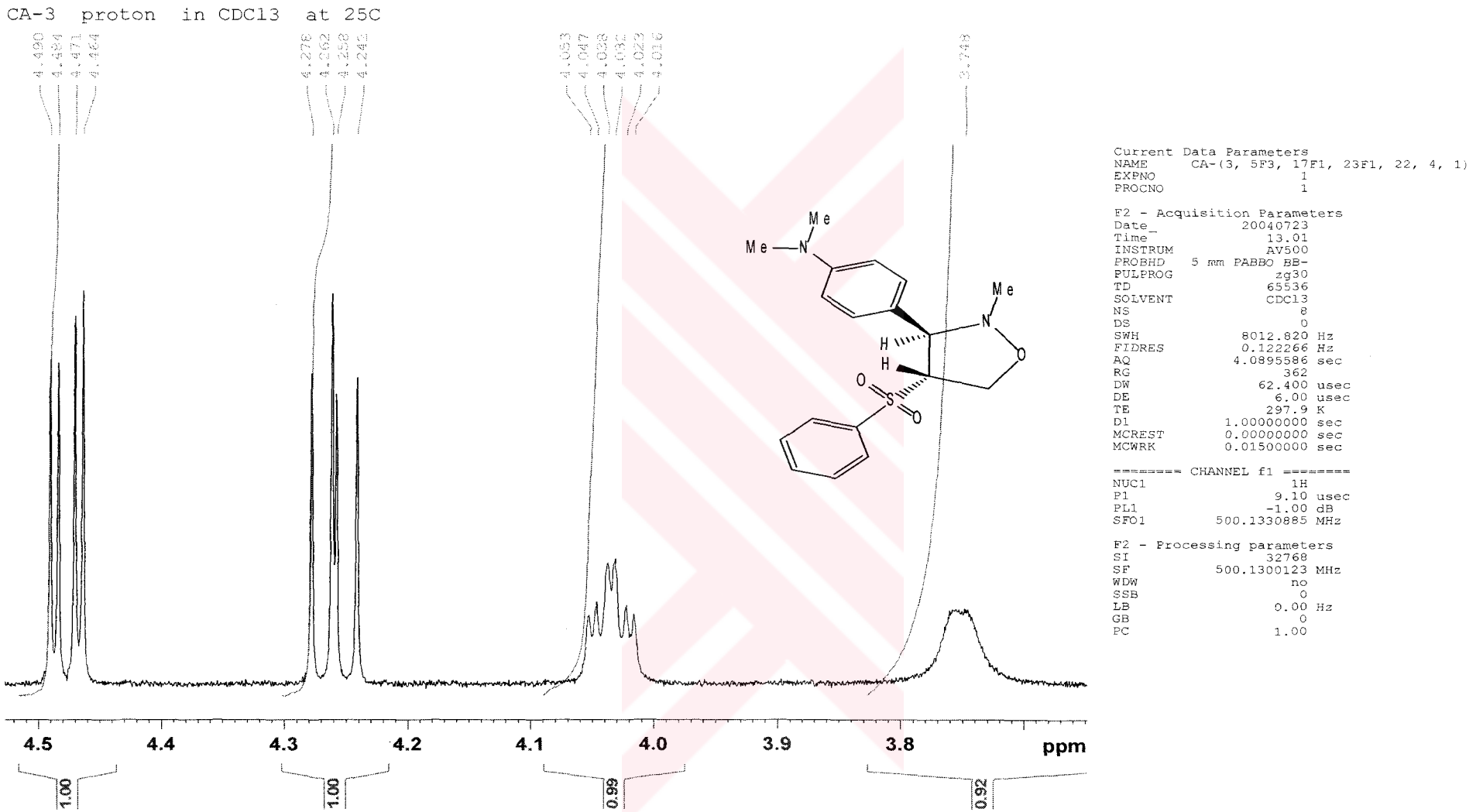
SF           500.1300123 MHz
WDW                    no
SSB                     0
LB                 0.00 Hz
GB                      0
PC                  1.00
```

Figure 4.16 A. ^{1}H NMR Spectrum of **3a**

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EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20040723
Time              13.01
INSTRUM           AV500
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    0
SWH            8012.820 Hz
FIDRES        0.122266 Hz
AQ            4.0895586 sec
RG                  362
DW               62.400 usec
DE                6.00 usec
TE               297.9 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.10 usec
PL1               -1.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                32768
SF          500.1300123 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```

Figure 4.16 B. Expanded (4.8-3.7 ppm) ^{1}H NMR Spectrum of **3a**

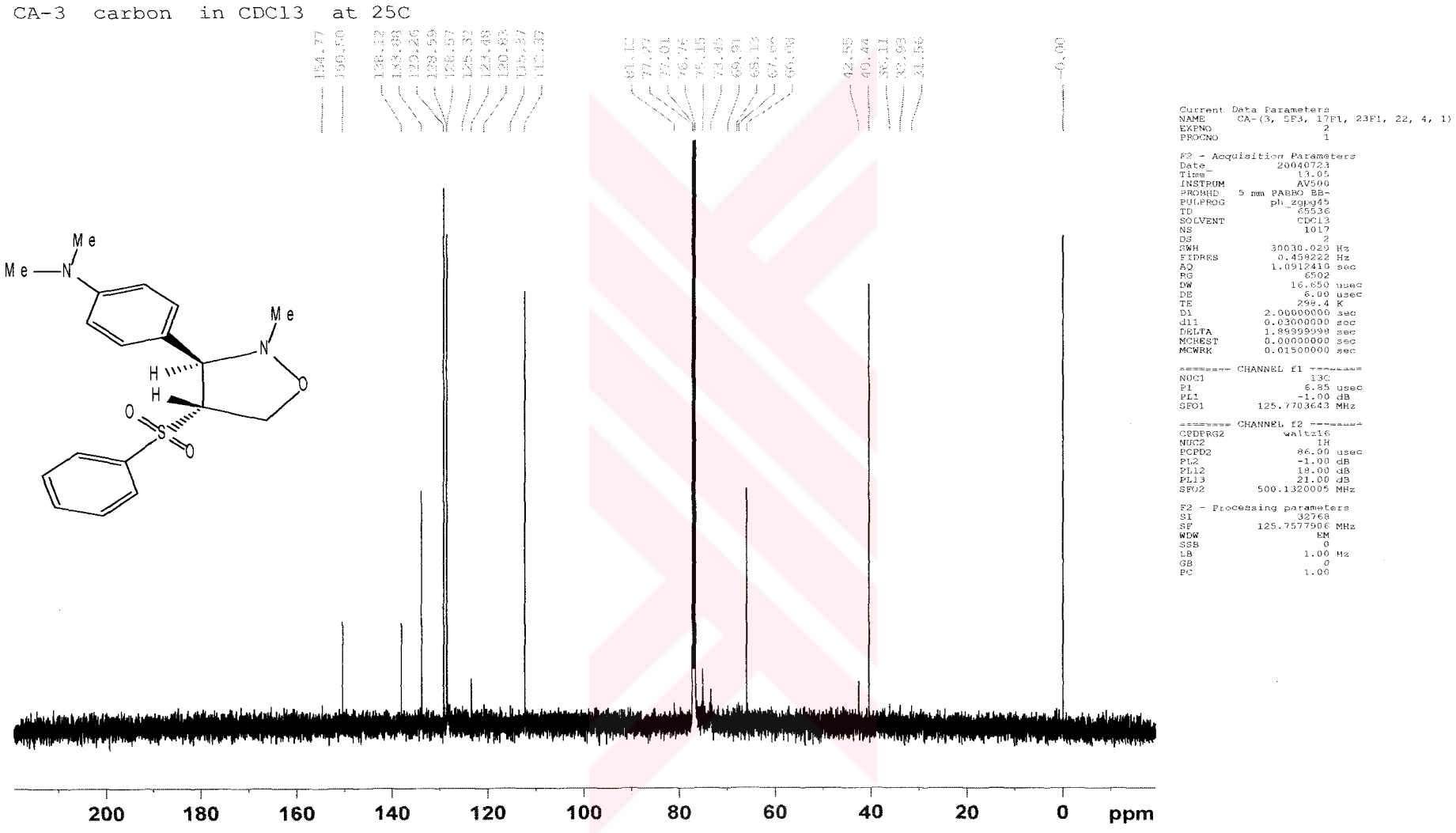


Figure 4.17. ^{13}C NMR Spectrum of **3a**

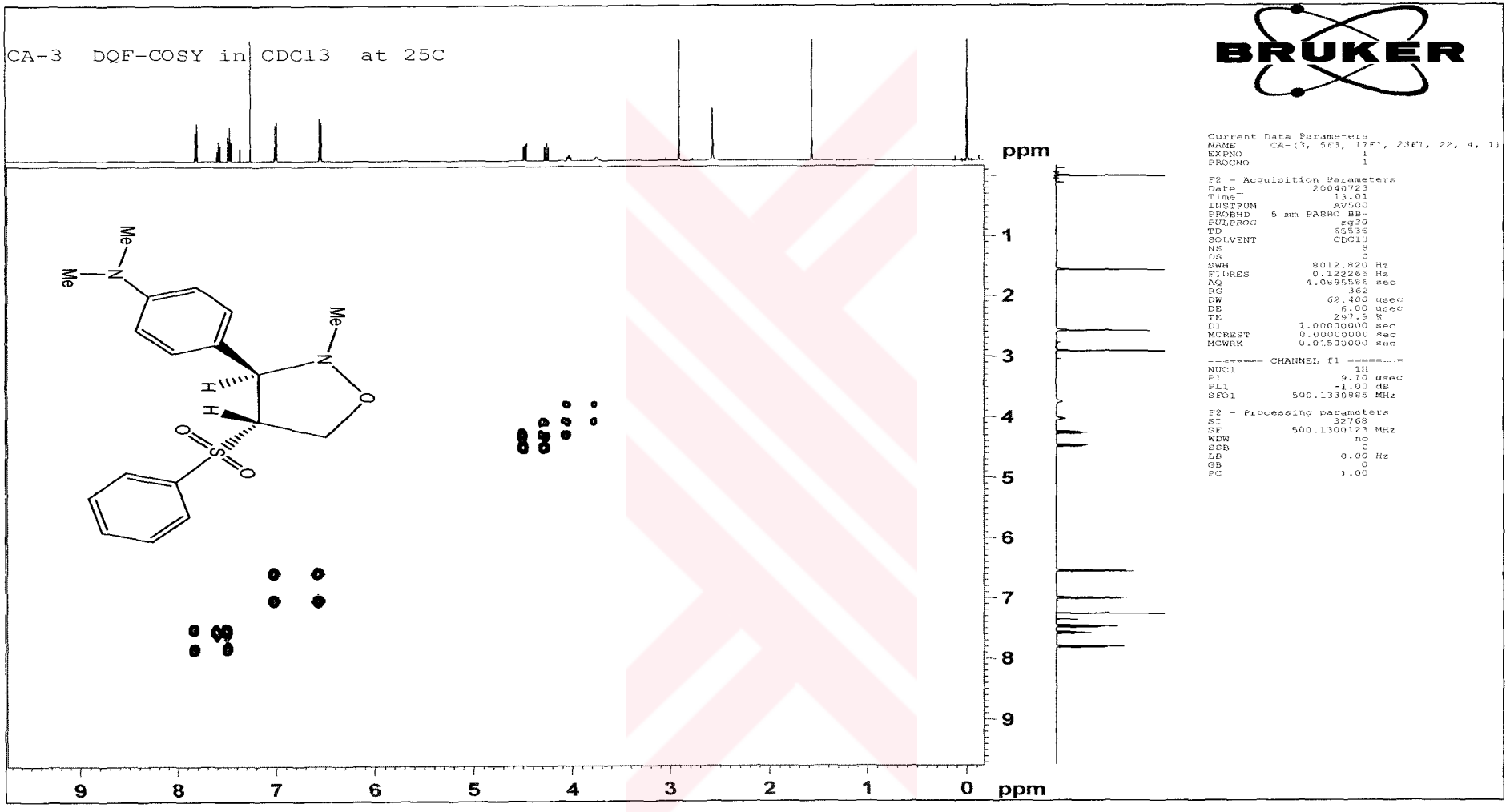


Figure 4.18 A. DQF-COSY NMR Spectrum of **3a**

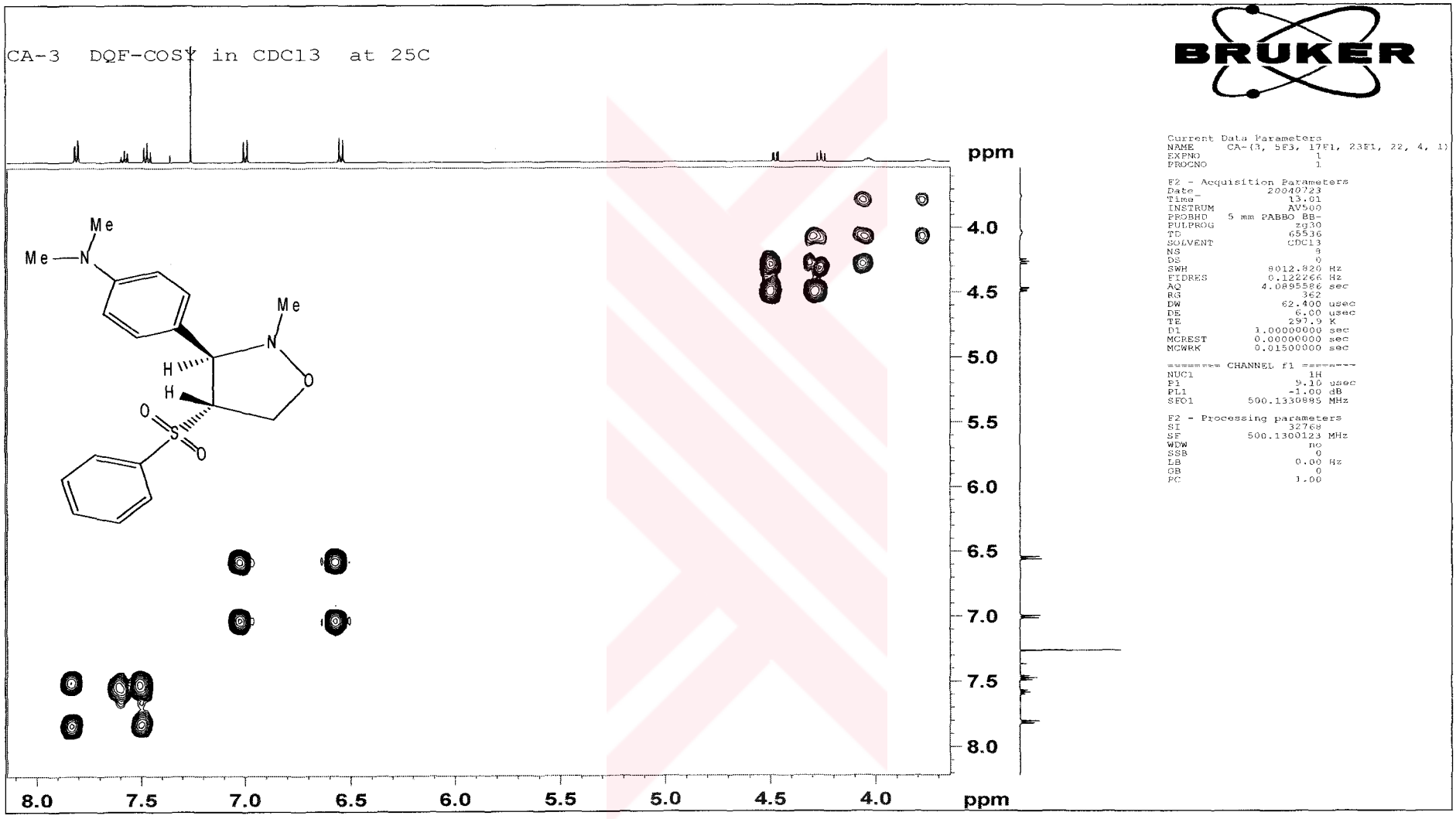


Figure 4.18 B. Expanded (8.0-4.0 ppm) DQF-COSY NMR Spectrum of **3a**

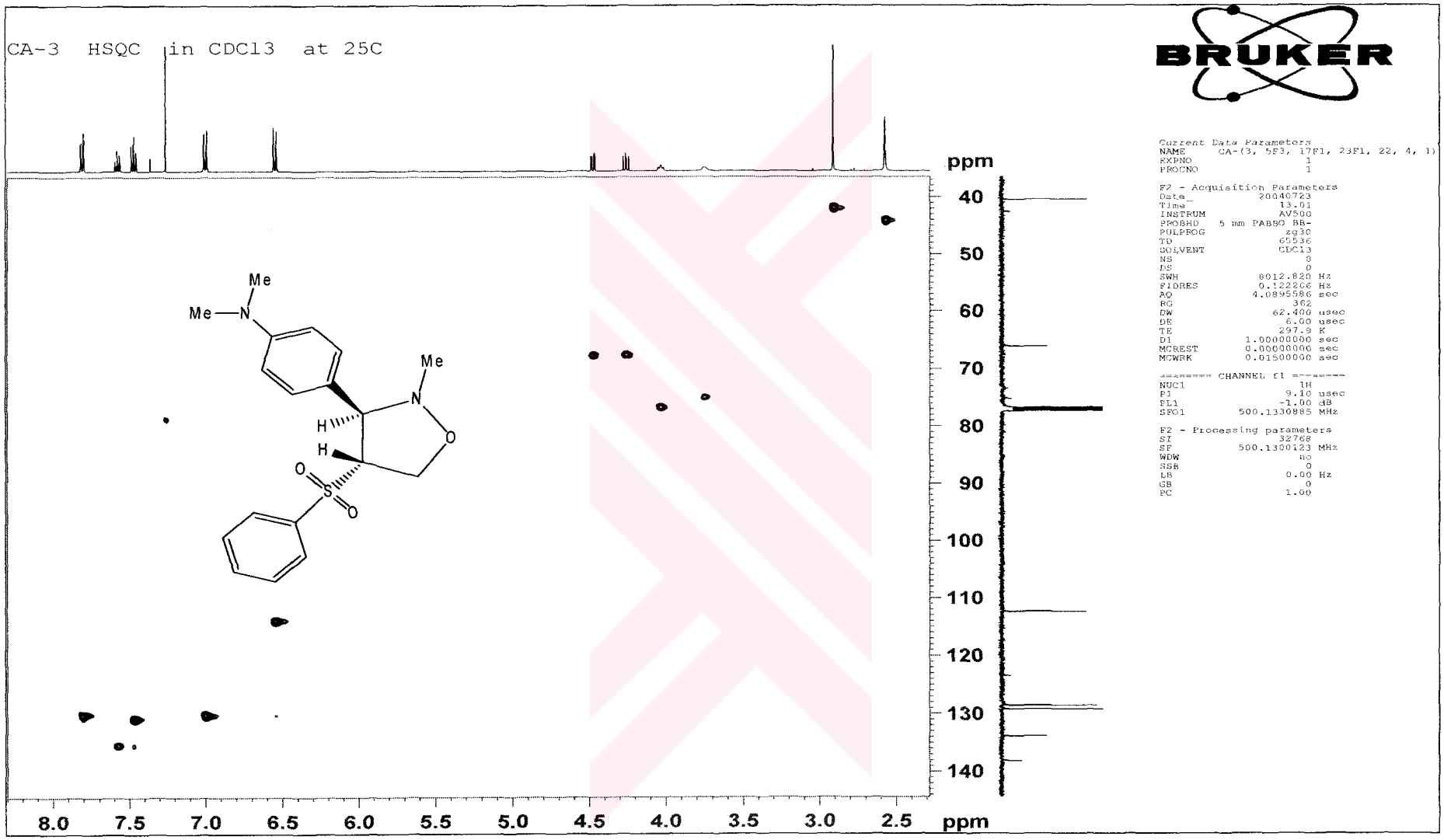


Figure 4.19. HSQC NMR Spectrum of **3a**

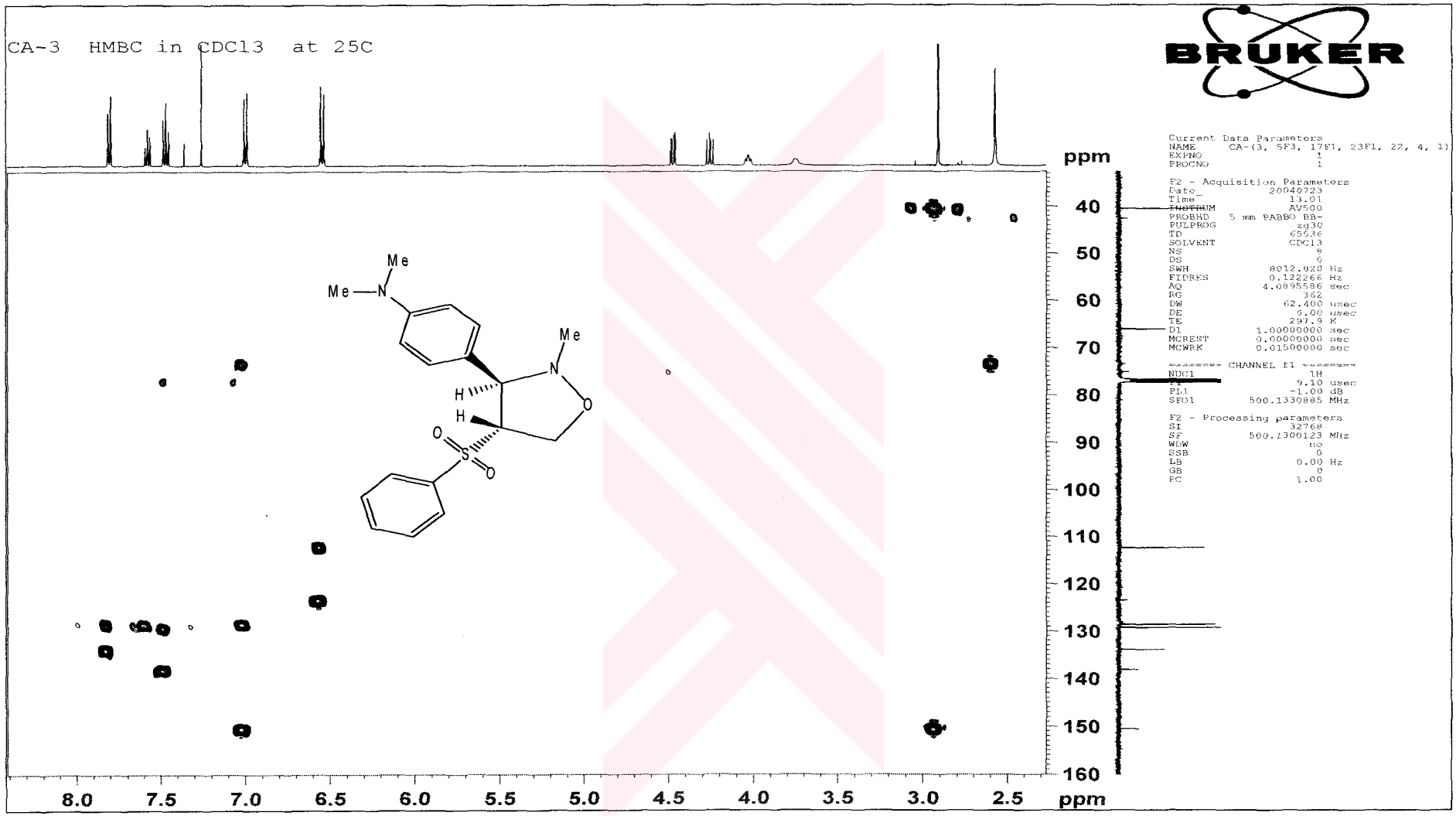


Figure 4.20A. HMBC NMR Spectrum of **3a**

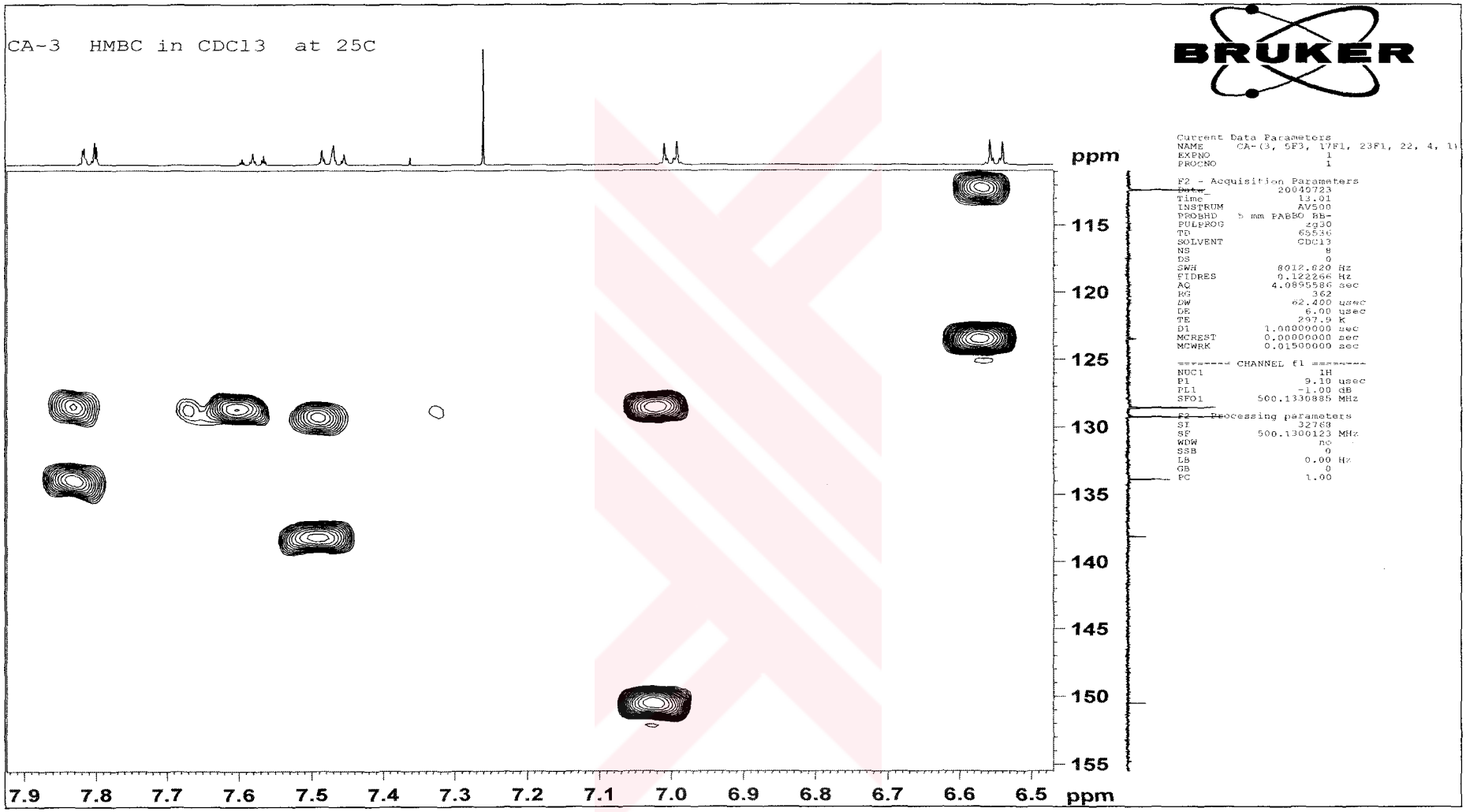


Figure 4.20B. Expanded (7.9-6.5 ppm) HMBC NMR Spectrum of **3a**

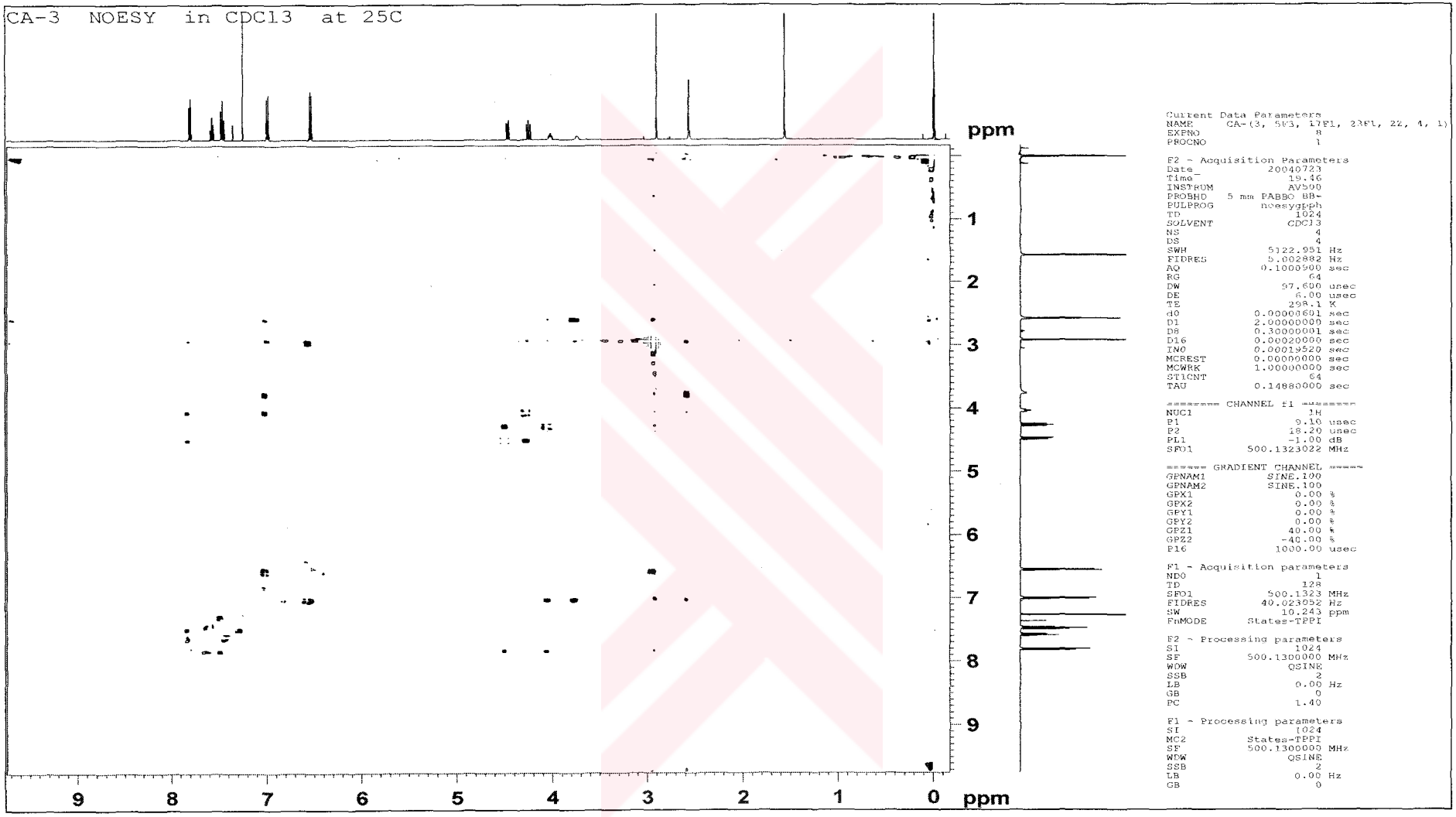


Figure 4.21 A. NOESY NMR Spectrum of **3a**

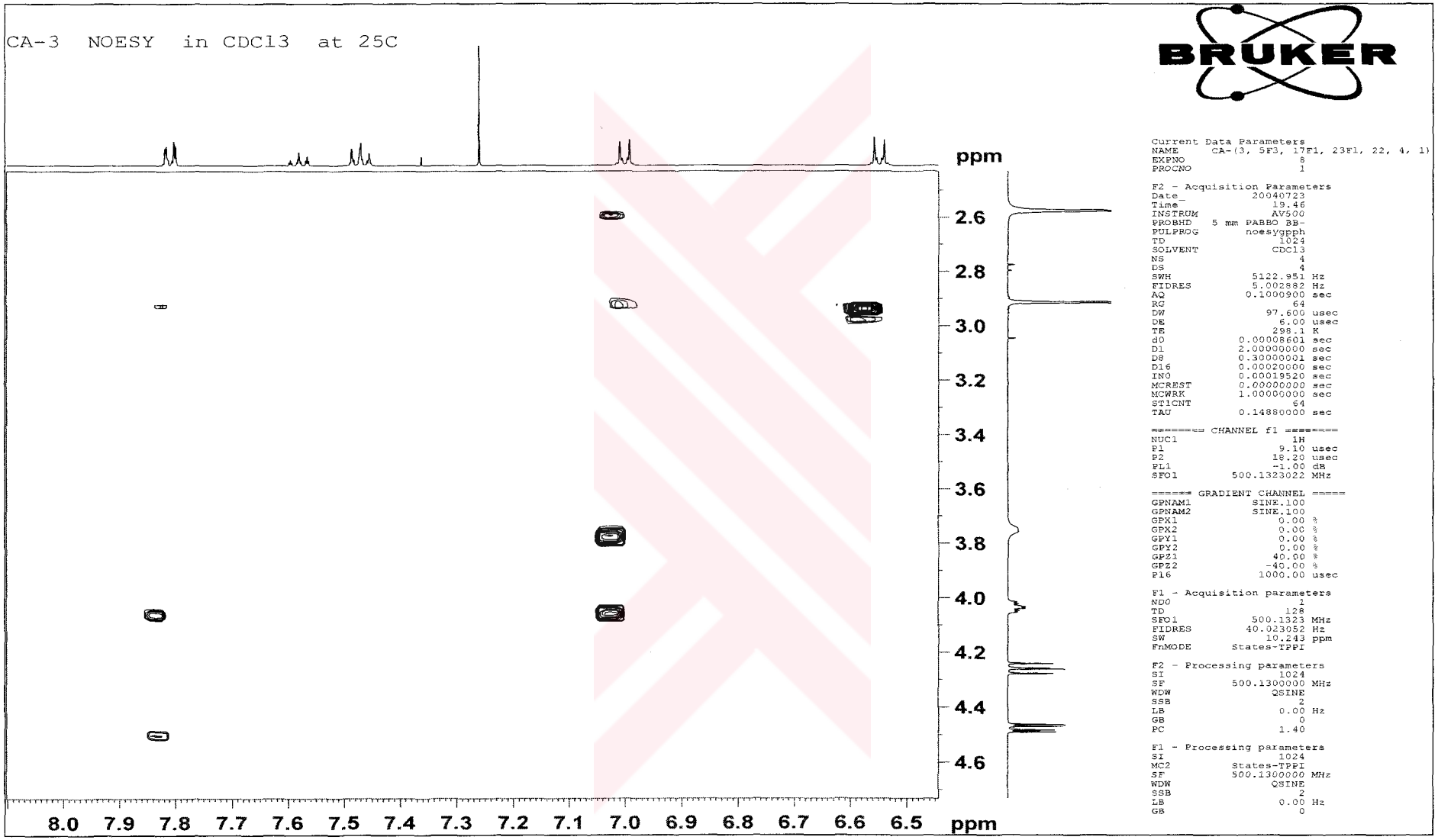


Figure 4.21 B. Expanded (8.0-6.5 ppm) NOESY NMR Spectrum of **3a**

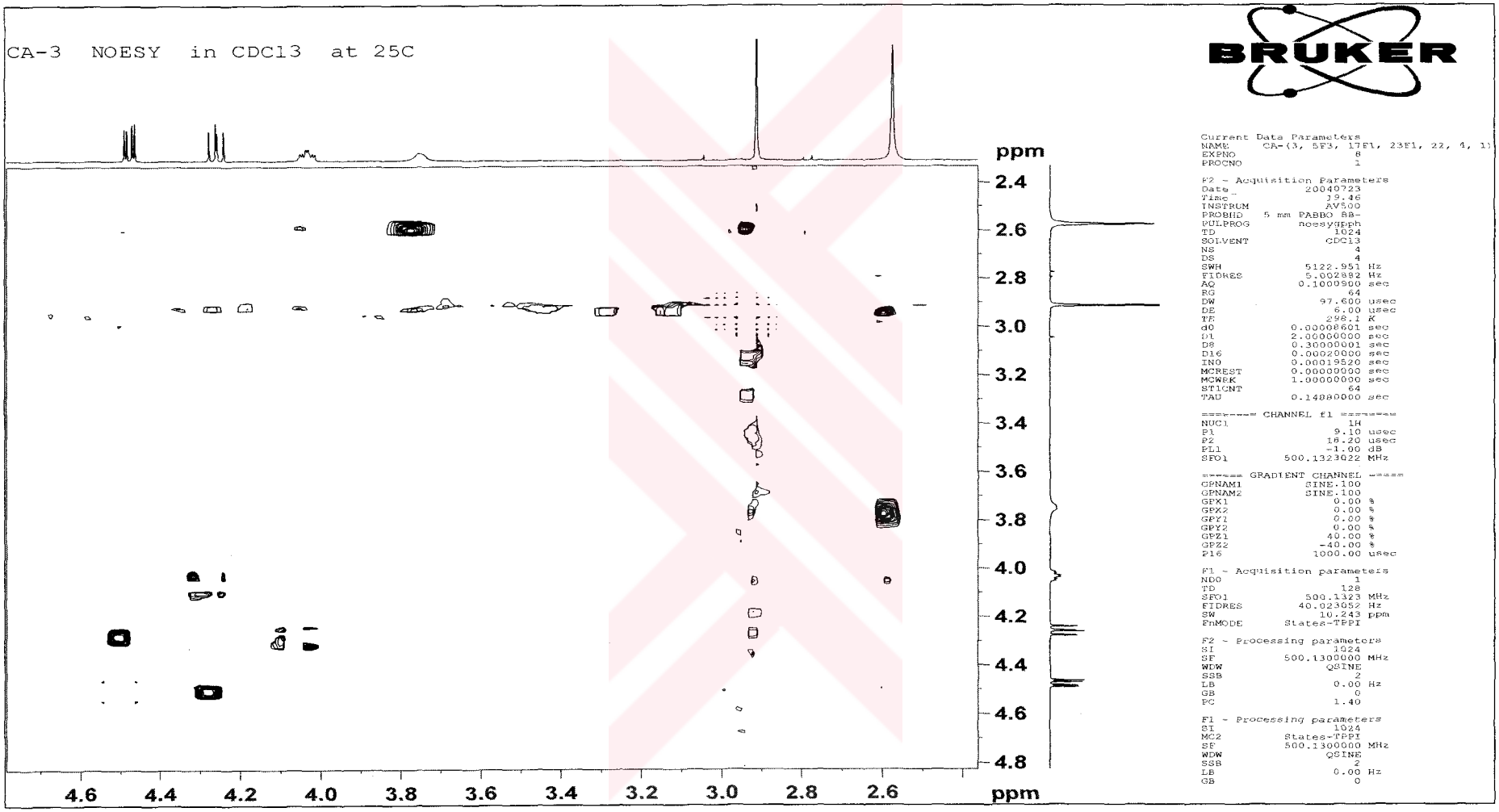


Figure 4.21.C. Expanded (4.6-2.6 ppm) NOESY NMR Spectrum of **3a**

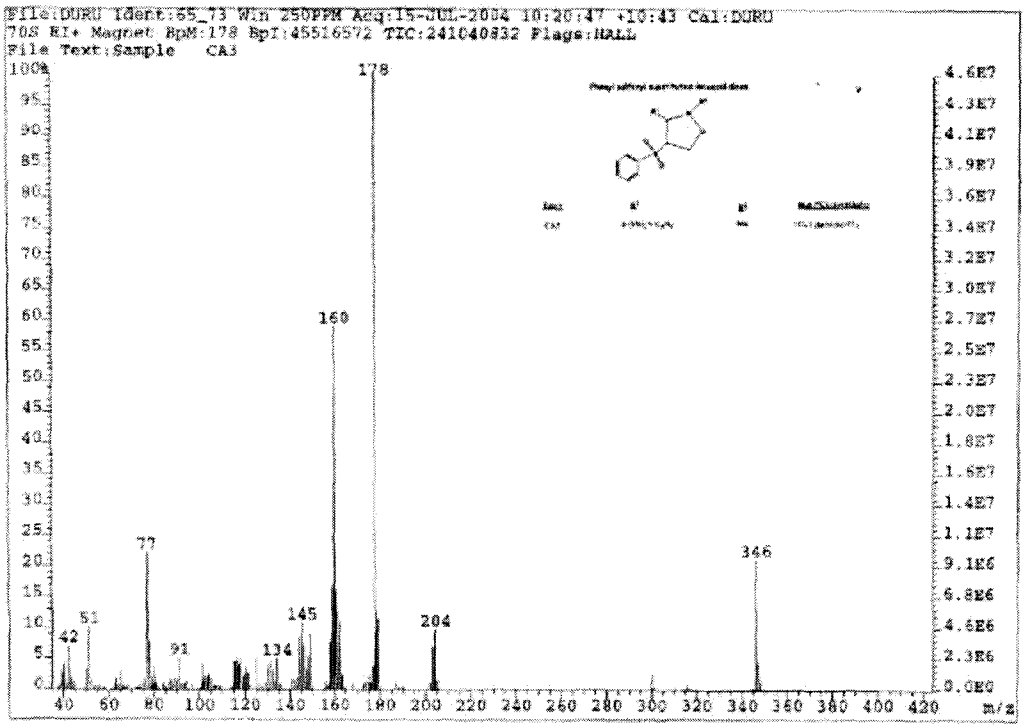


Figure 4.22 MASS Spectrum of **3a**

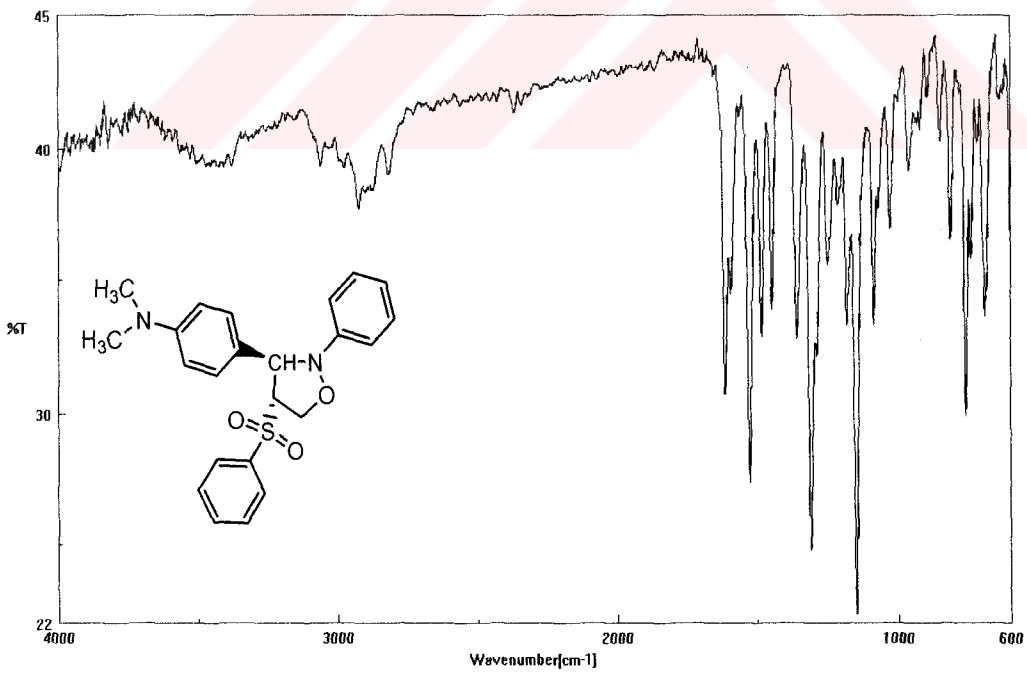


Figure 4.23. IR Spectrum of **3b**

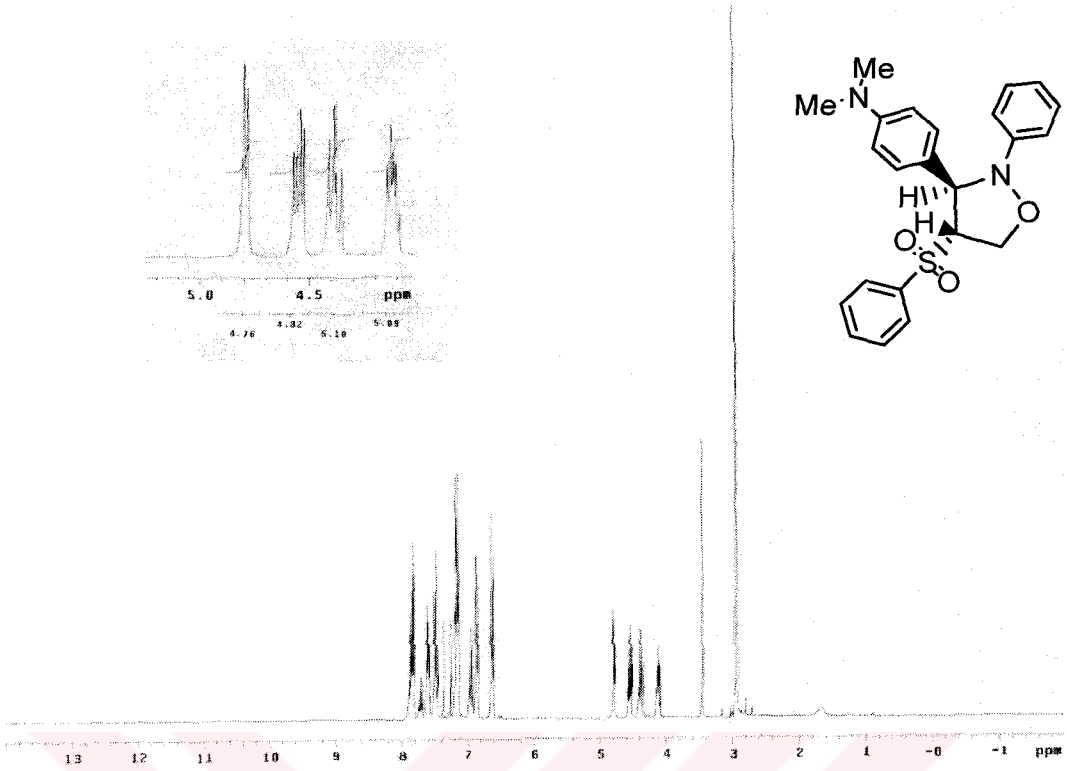


Figure 4.24 ^{13}C NMR Spectrum of **3b**

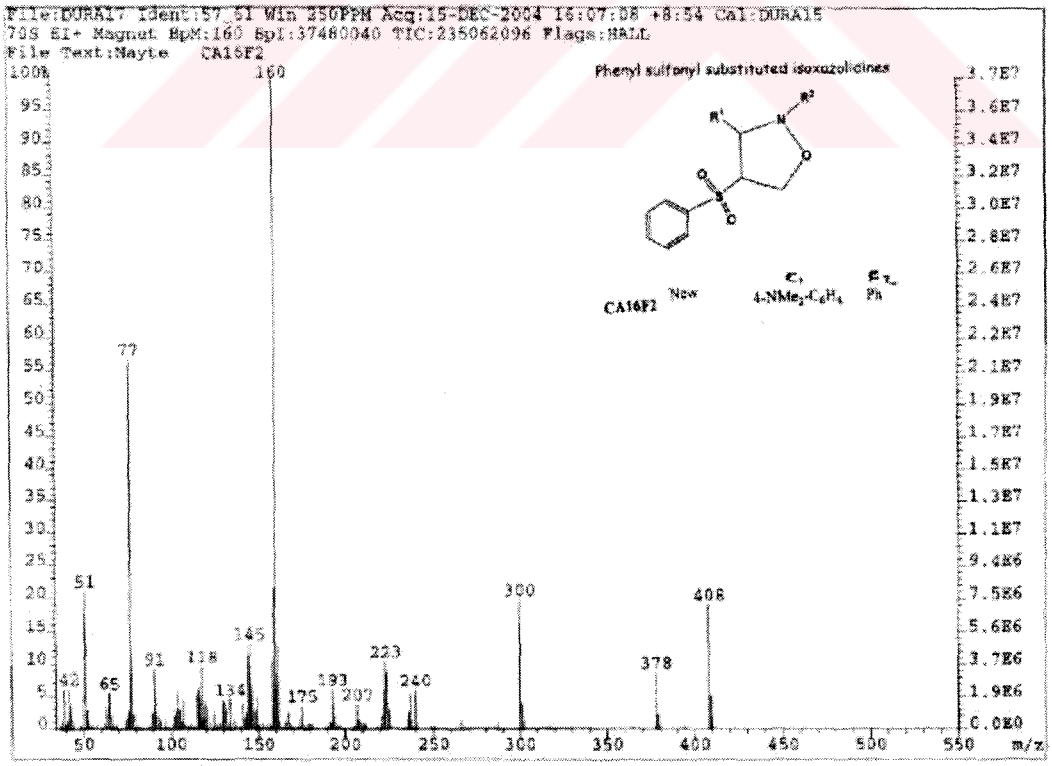


Figure 4.25 MASS Spectrum of **3b**

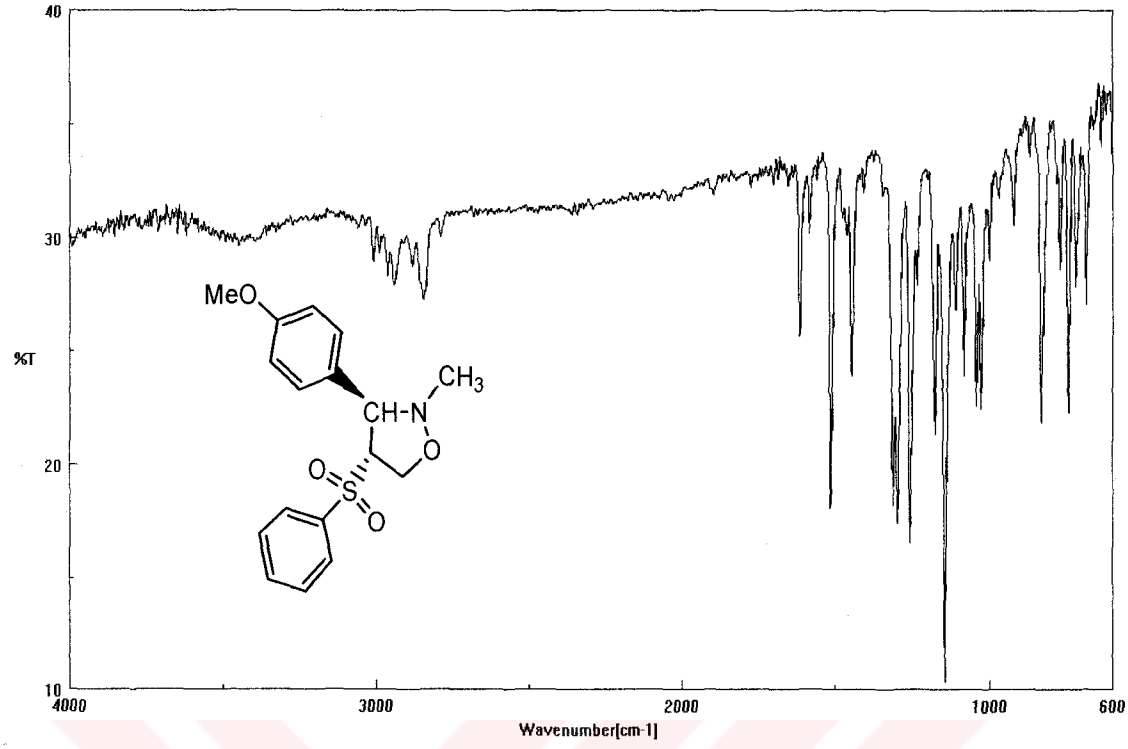


Figure 4.26. IR Spectrum of **3c**

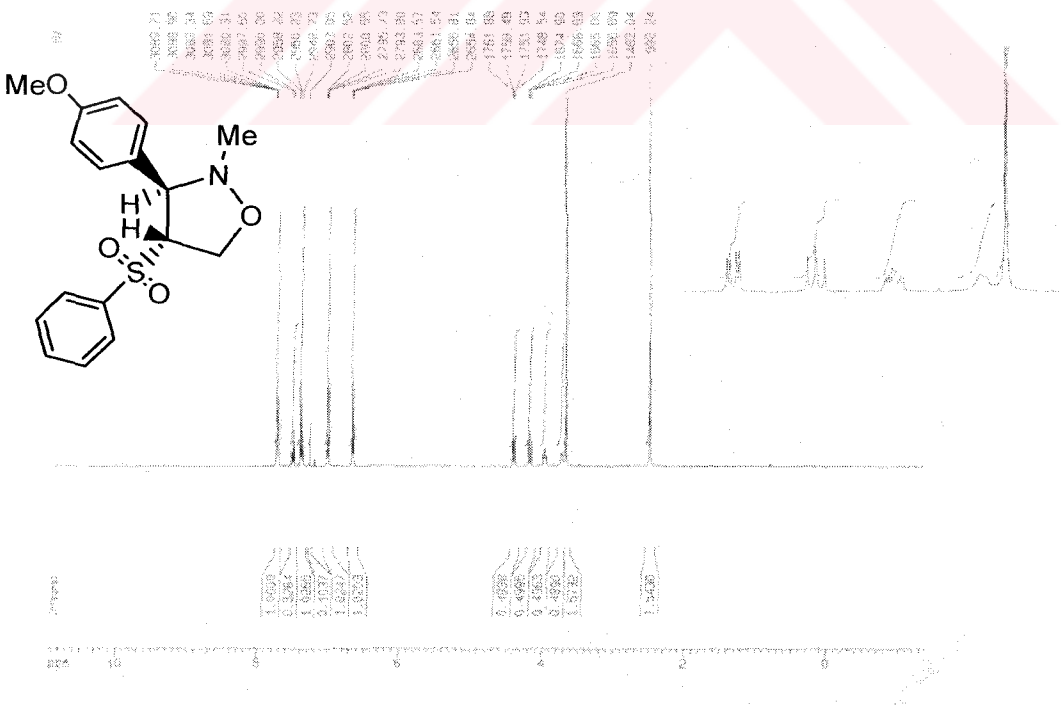


Figure 4.27. ^{1}H NMR Spectrum of **3c**

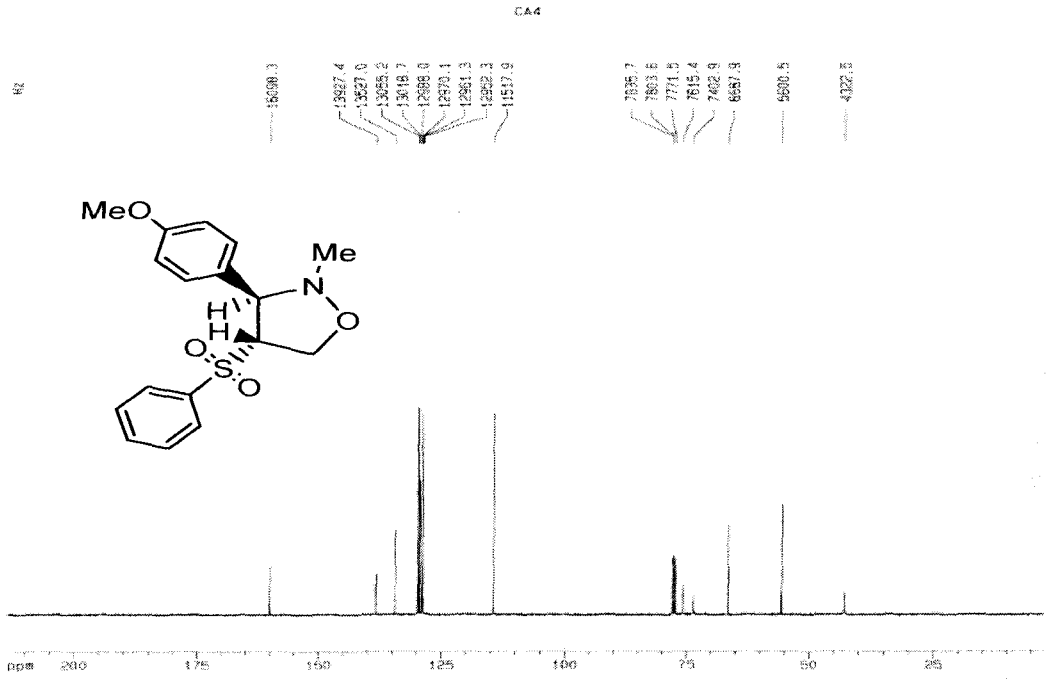


Figure 4.28. ^{13}C NMR Spectrum of **3c**

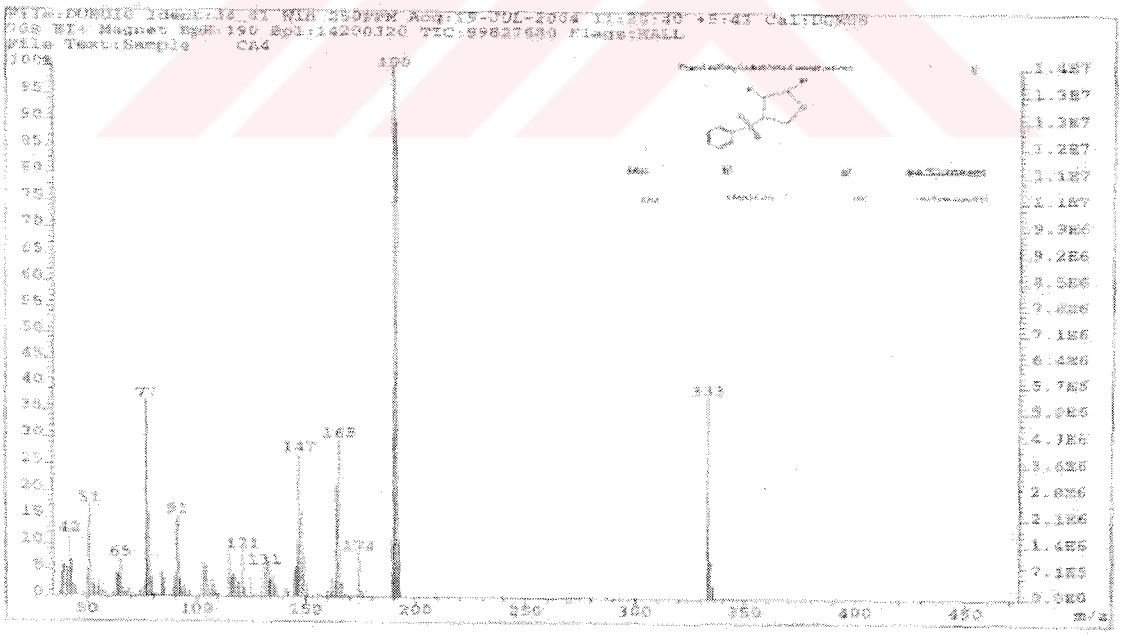


Figure 4.29. MASS Spectrum of **3c**

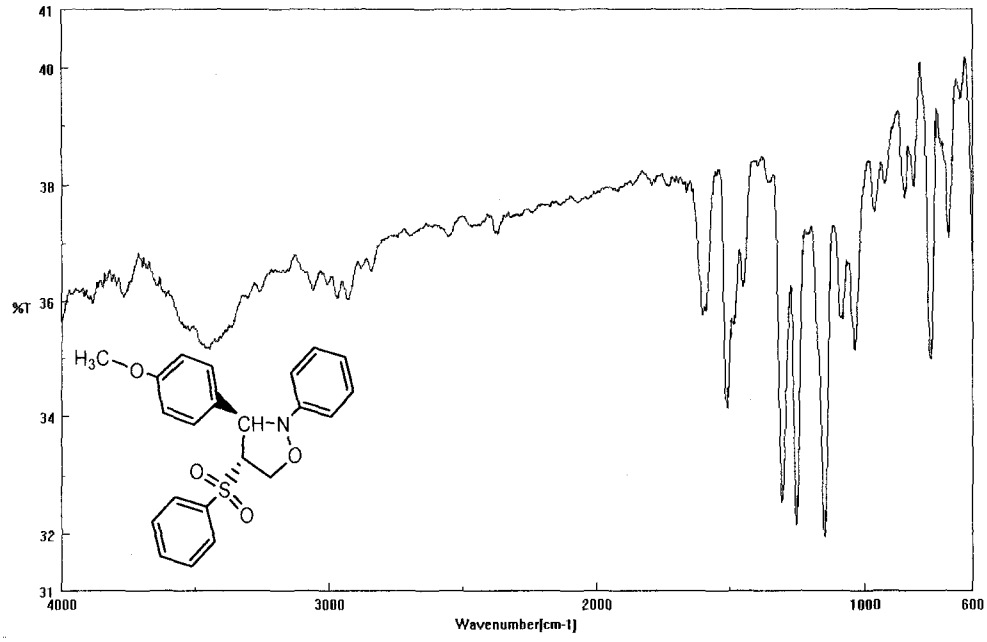


Figure 4.30. IR Spectrum of **3d**

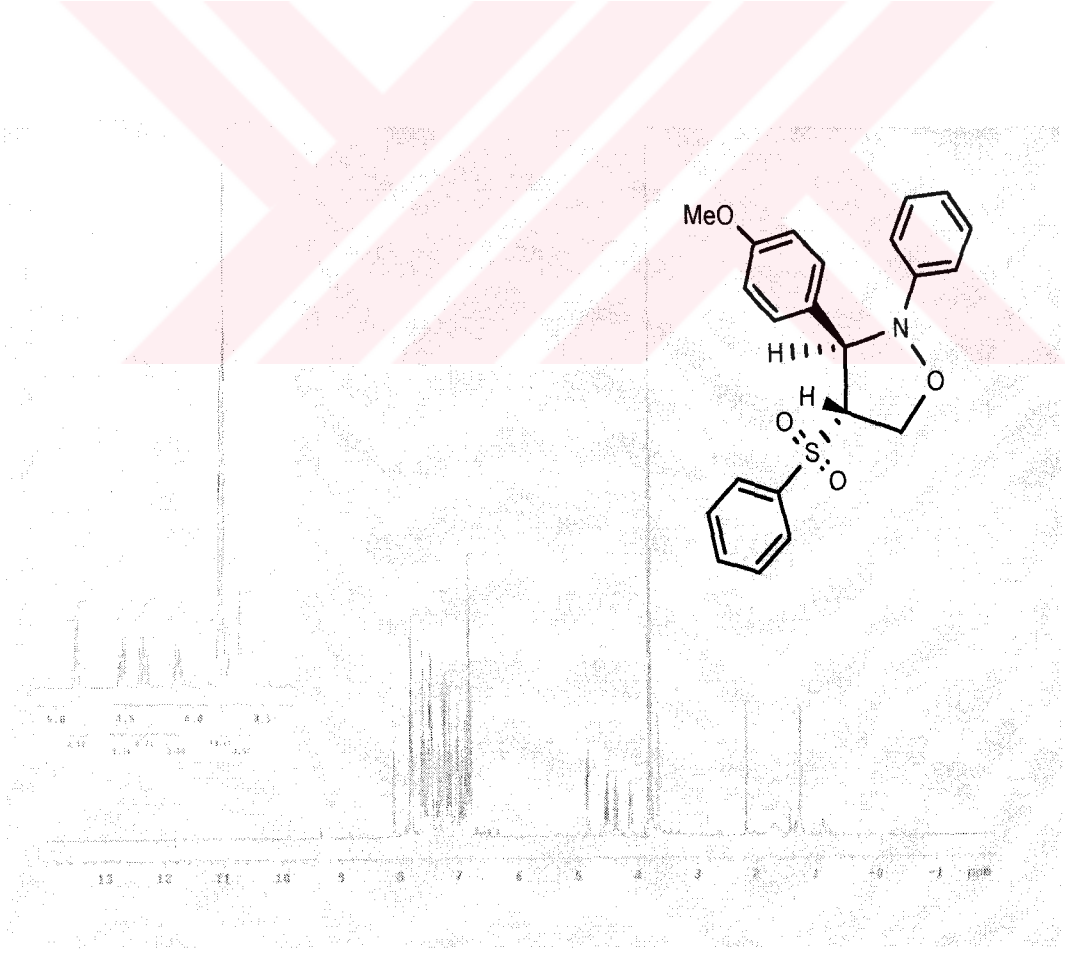


Figure 4.31. ^{1}H NMR Spectrum of **3d**

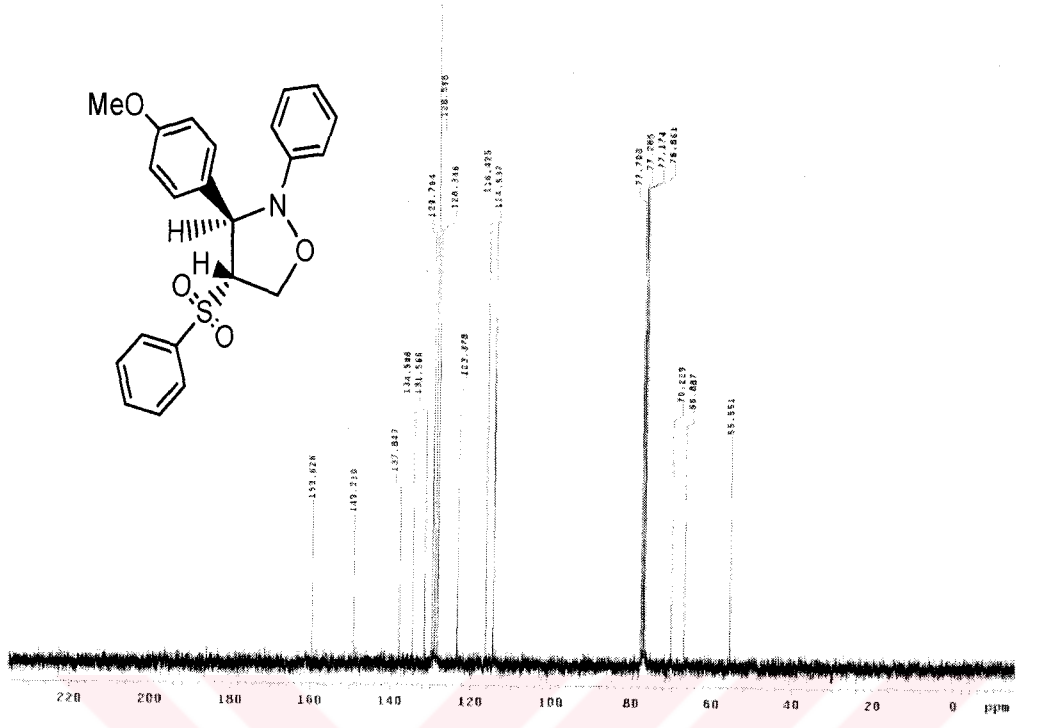


Figure 4.32. ^{13}C NMR Spectrum of **3d**

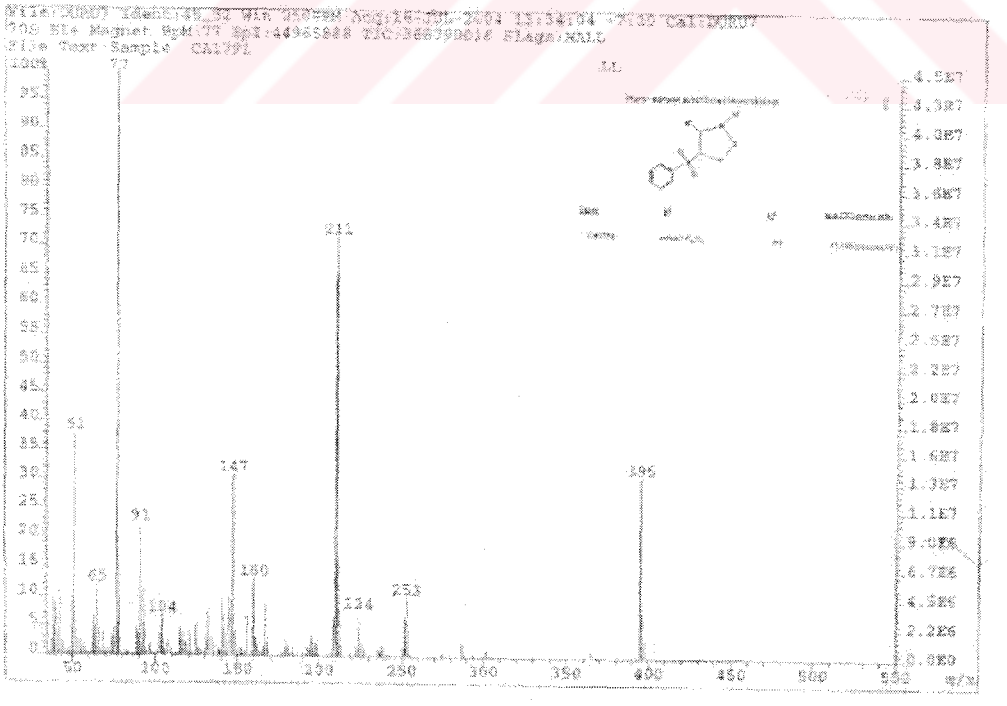


Figure 4.33 MASS Spectrum of **3d**

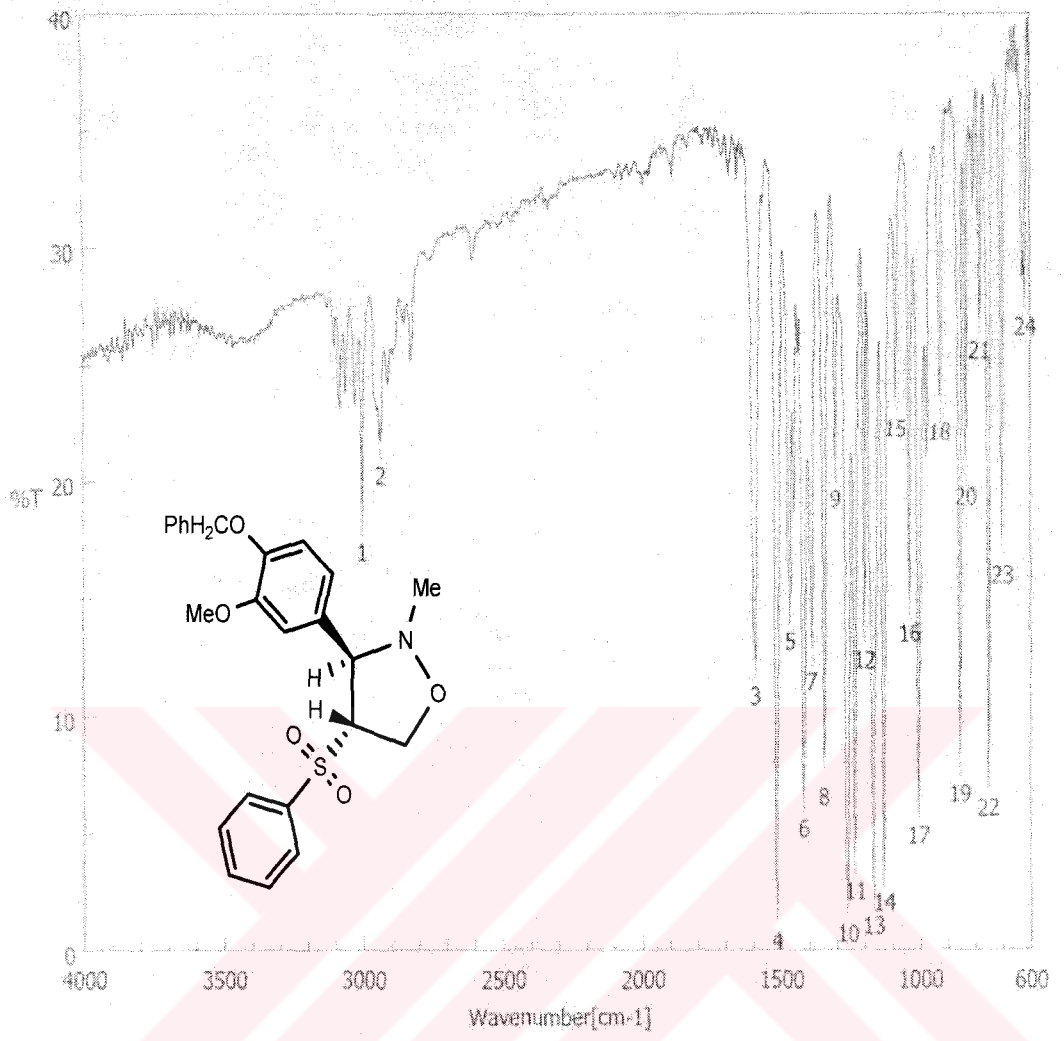
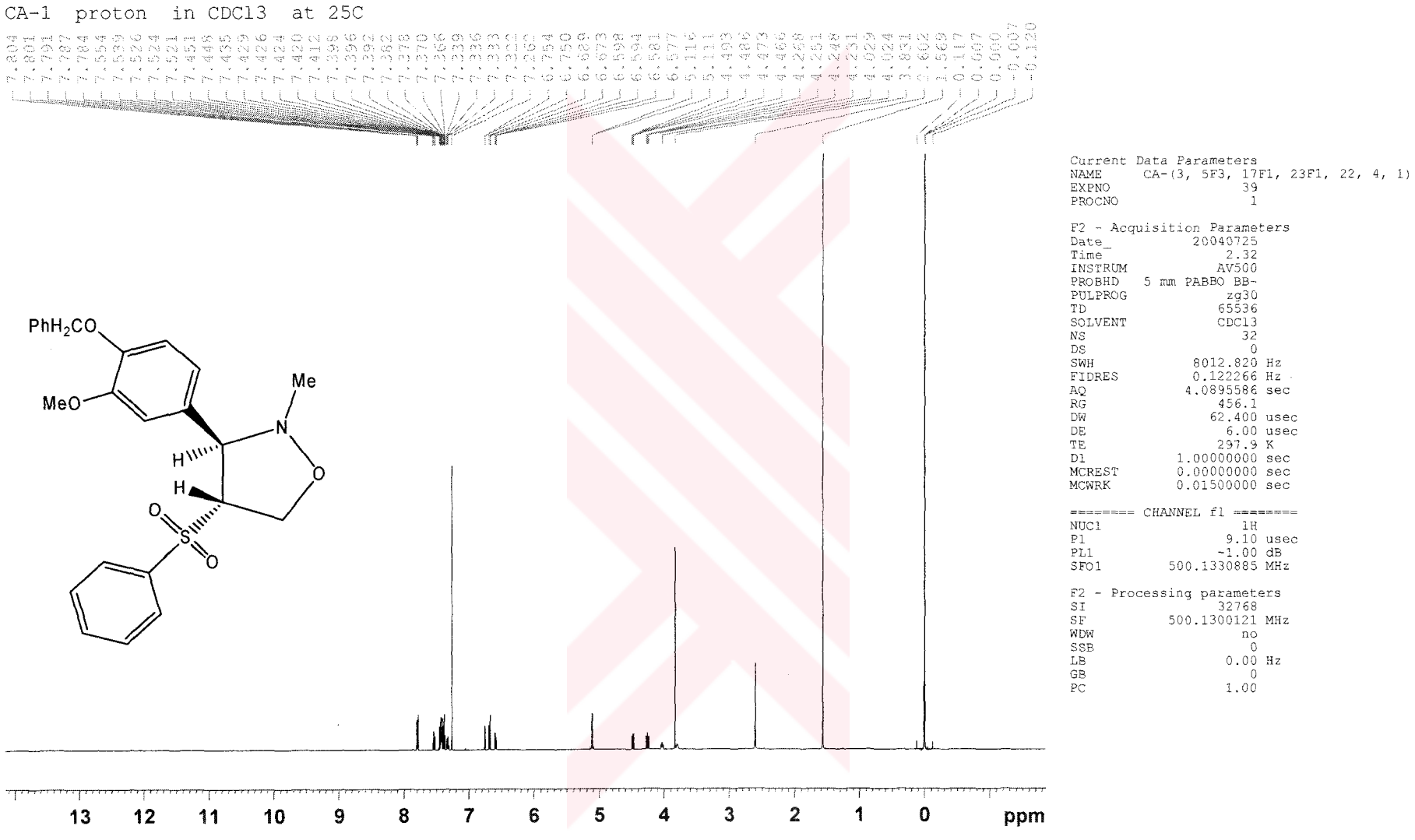


Figure 4.34. IR Spectrum of **3e**

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TD                 65536
SOLVENT            CDCl3
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DS                     0
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0895586 sec
RG                 456.1
DW                62.400 usec
DE                 6.00 usec
TE                297.9 K
D1             1.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.10 usec
PL1                -1.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF          500.1300121 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
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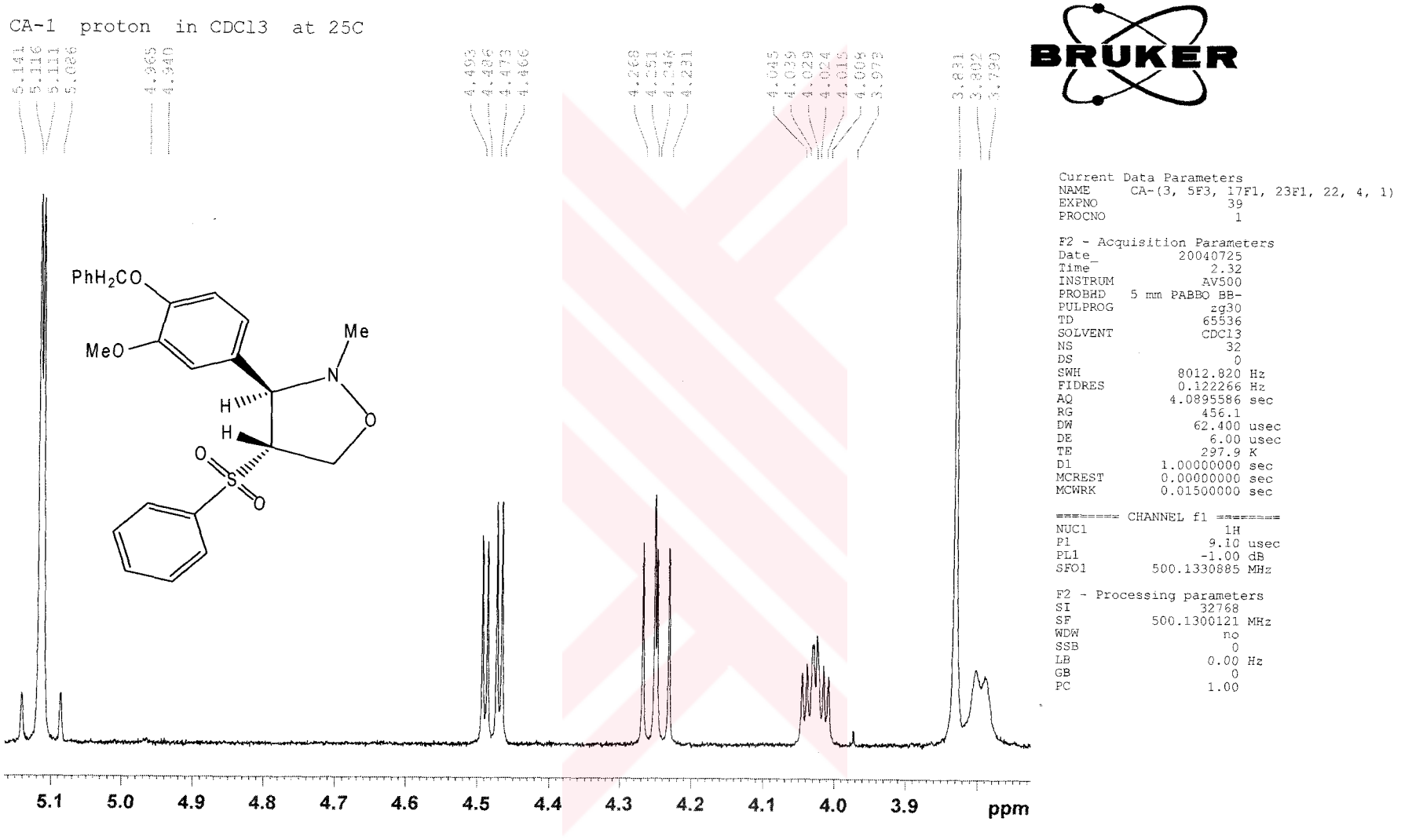
Figure 4.35 A. ^{1}H NMR Spectrum of **3e**



BRUKER

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Current Data Parameters
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PROCNO                1

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PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   32
DS                    0
SWH           8012.820 Hz
FIDRES        0.122266 Hz
AQ            4.0895586 sec
RG                456.1
DW             62.400 usec
DE              6.00 usec
TE              297.9 K
D1          1.00000000 sec
MCREST      0.00000000 sec
MCWRK       0.01500000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.10 usec
PL1              -1.00 dB
SFO1       500.1330885 MHz

F2 - Processing parameters
SI                32768
SF         500.1300121 MHz
WDW                  no
SSB                   0
LB                0.00 Hz
GB                    0
PC                 1.00
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Figure 4.35 B. Expanded(5.1-3.9 ppm) ^{1}H NMR Spectrum of **3e**

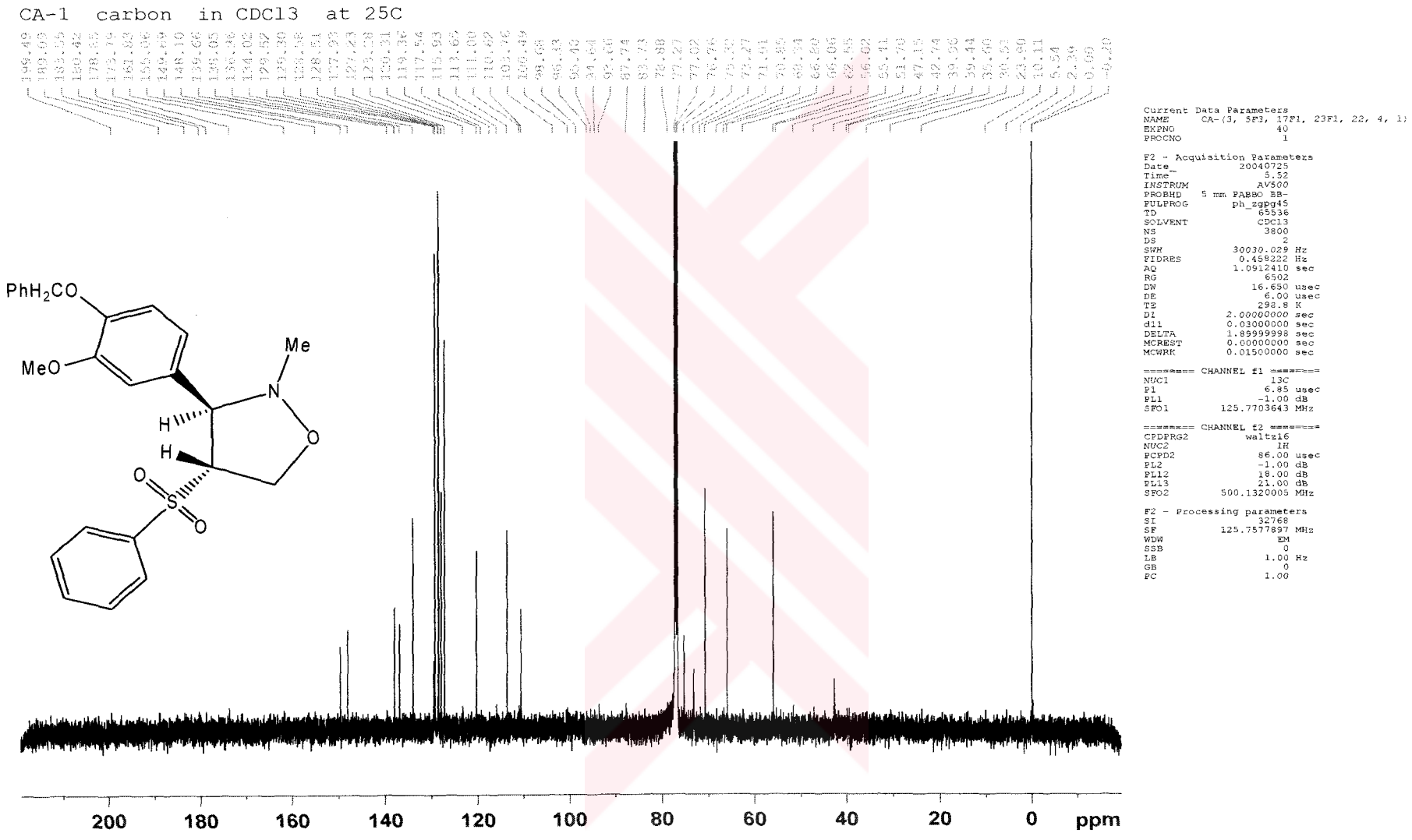


Figure 4.36. ^{13}C NMR Spectrum of **3e**

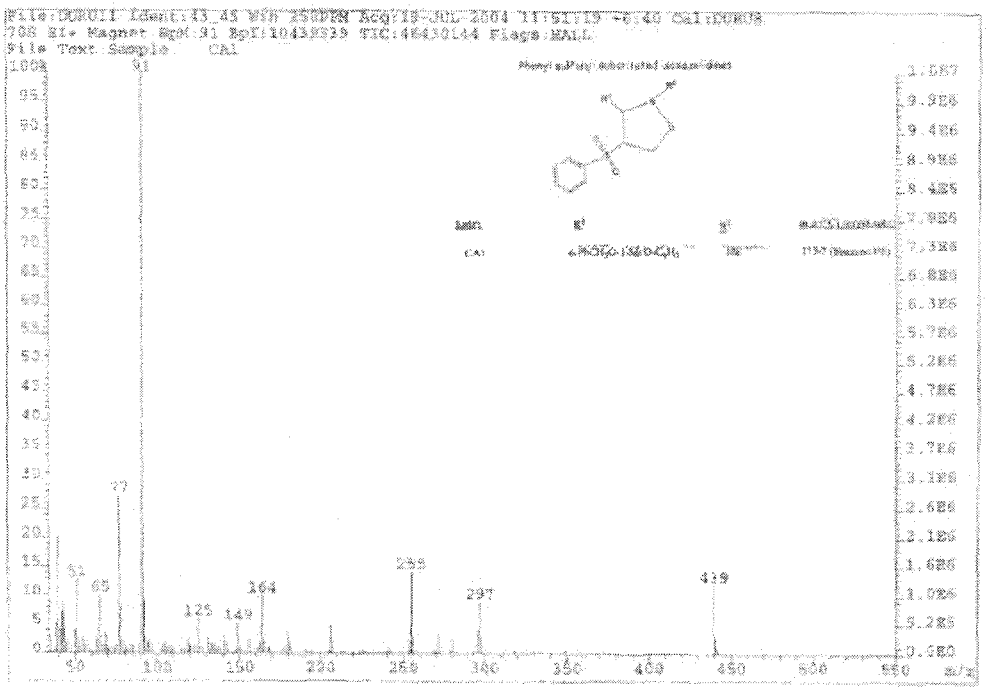


Figure 4.37 MASS Spectrum of **3e**

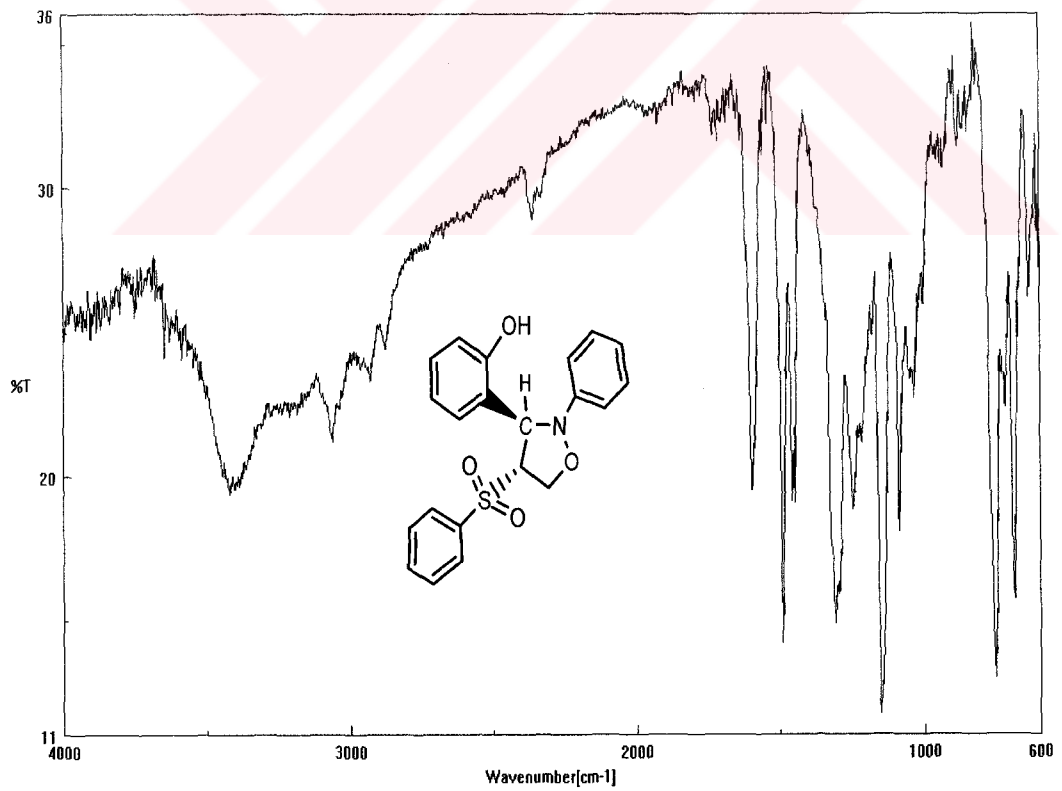


Figure 4.38 IR Spectrum of **3f**

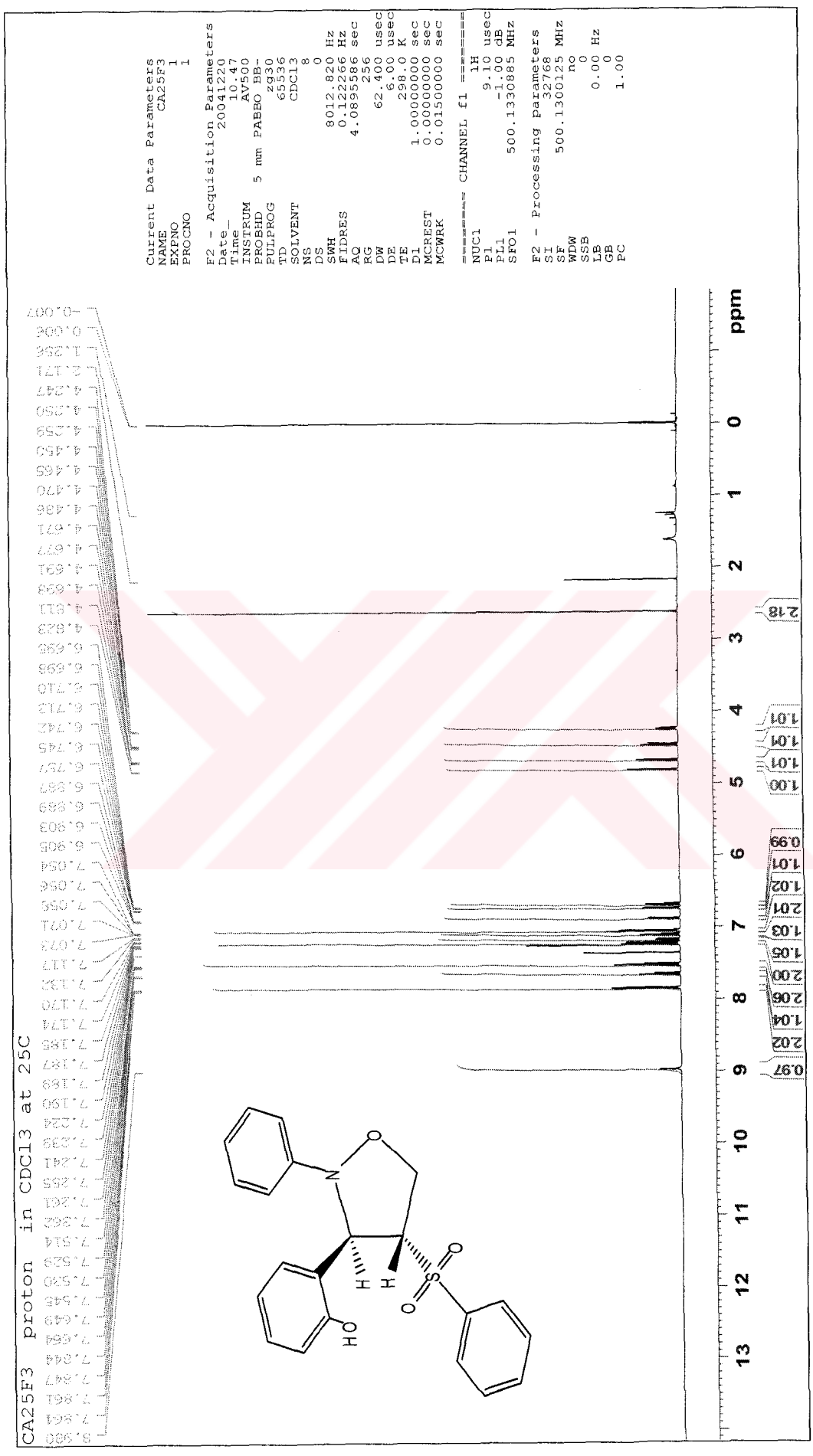


Figure 4.39 A. ^{1}H NMR Spectrum of **3f**

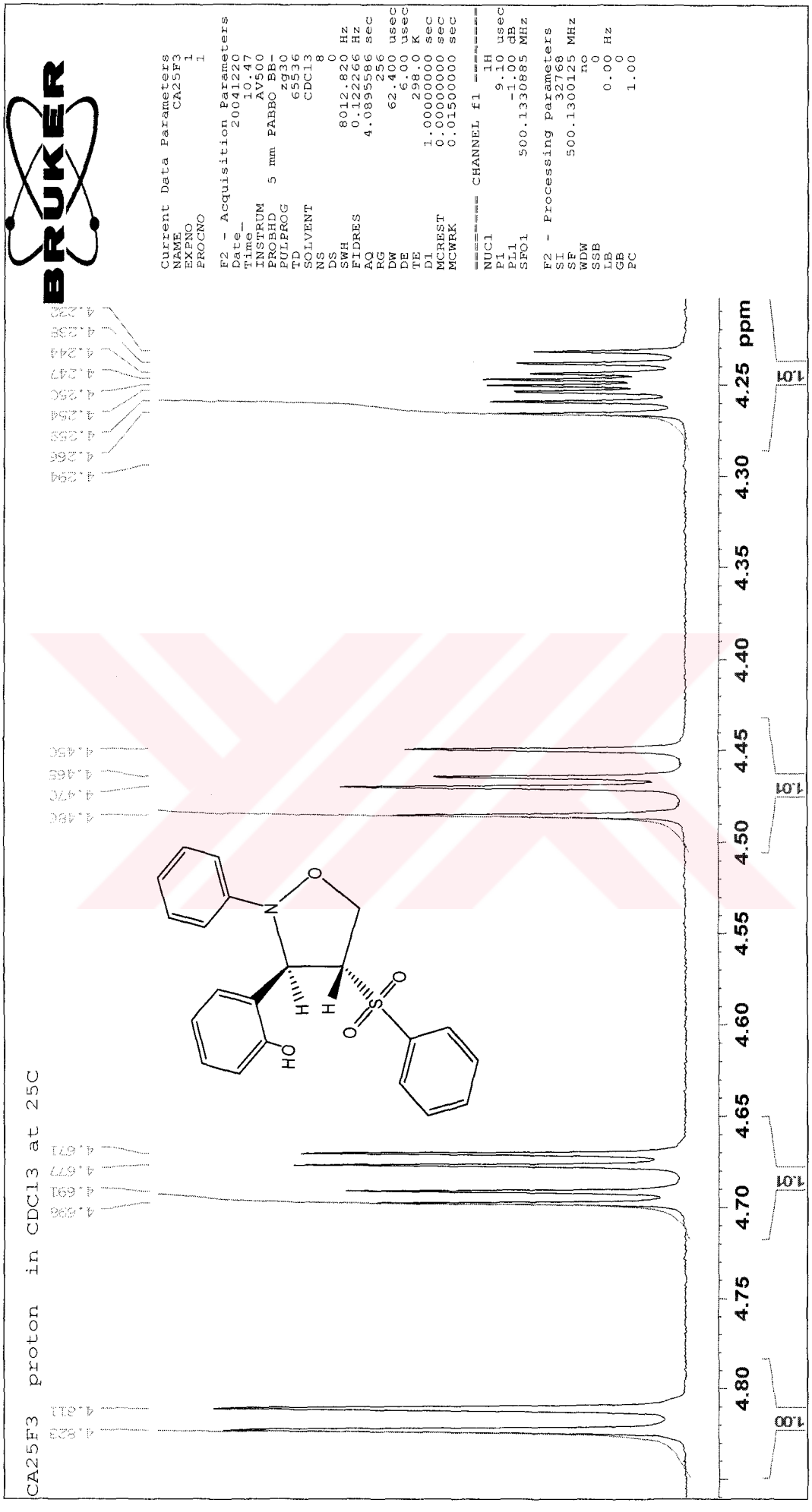
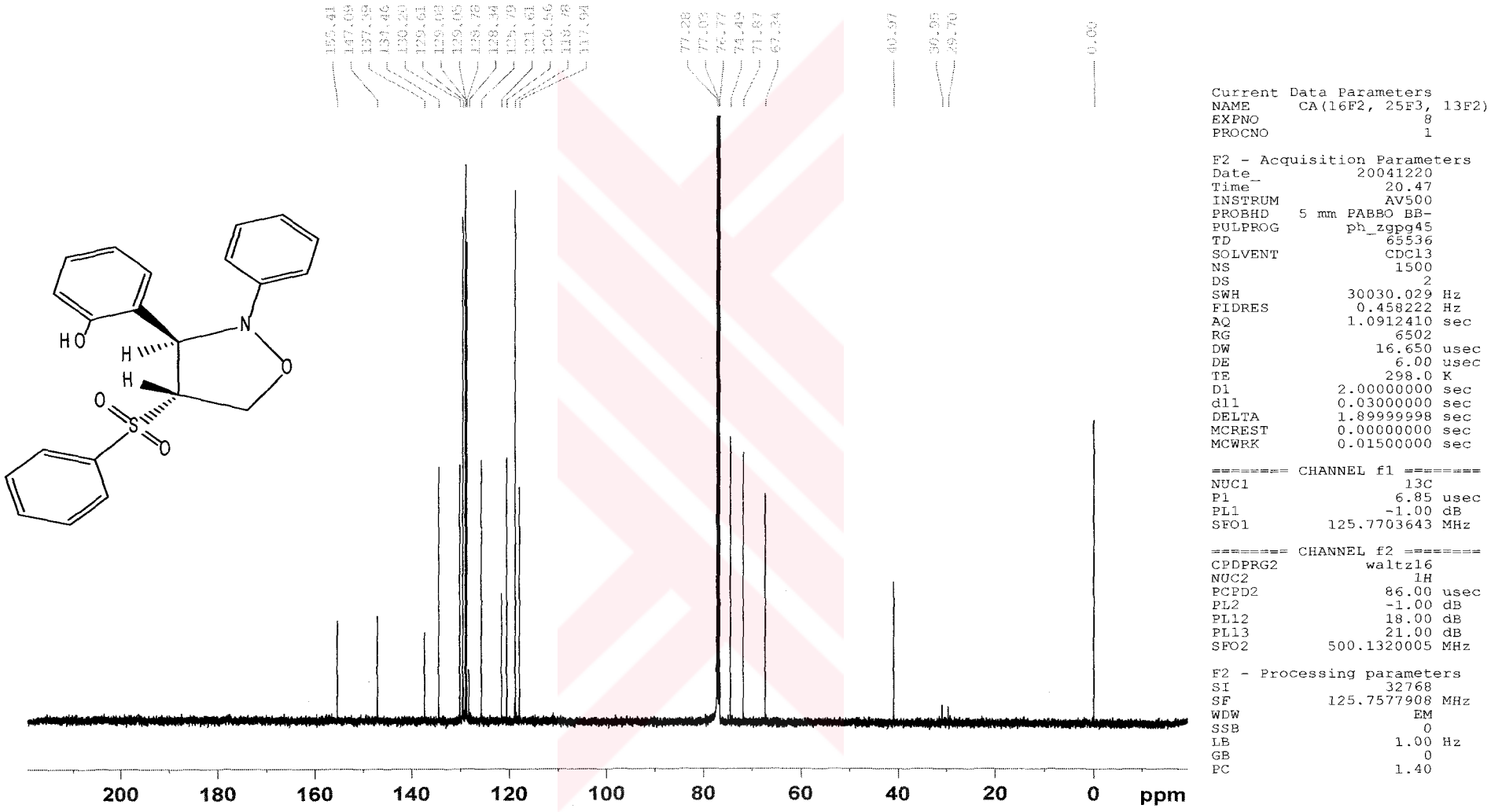


Figure 4.39 B. Expanded (4.80-4.25) ^{1}H NMR Spectrum of **3f**

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PROCNO                       1

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PULPROG          ph_zgpg45
TD                     65536
SOLVENT                CDCl3
NS                      1500
DS                         2
SWH               30030.029 Hz
FIDRES             0.458222 Hz
AQ                 1.0912410 sec
RG                      6502
DW                    16.650 usec
DE                     6.00 usec
TE                    298.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                       6.85 usec
PL1                     -1.00 dB
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                  86.00 usec
PL2                     -1.00 dB
PL12                    18.00 dB
PL13                    21.00 dB
SFO2           500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF             125.7577908 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

Figure 4.40. ^{13}C NMR Spectrum of **3f**

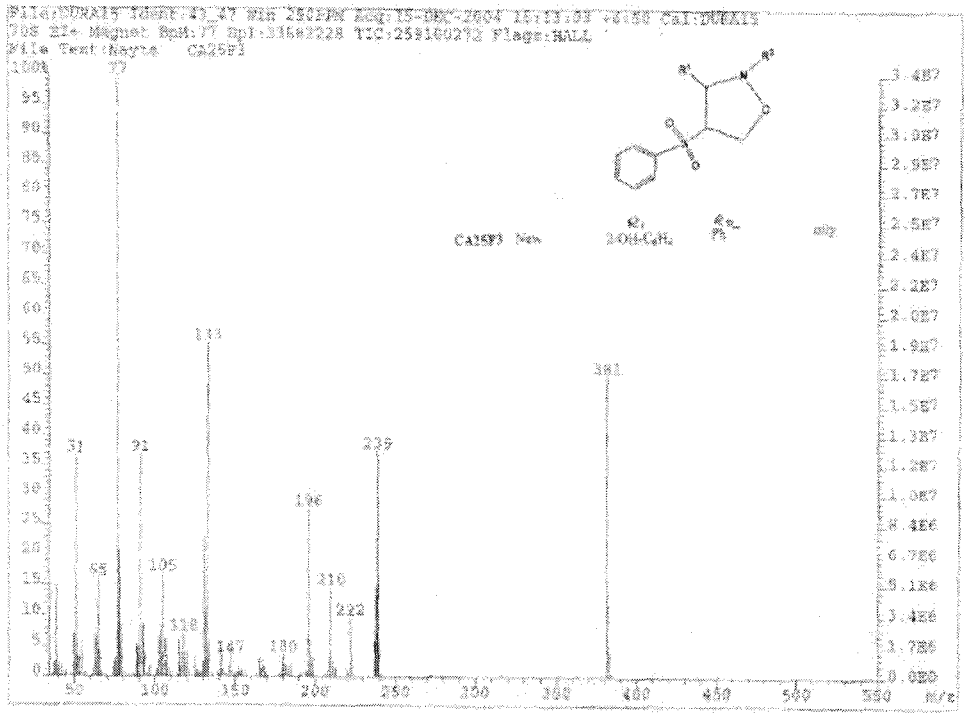


Figure 4.41 MASS Spectrum of **3f**

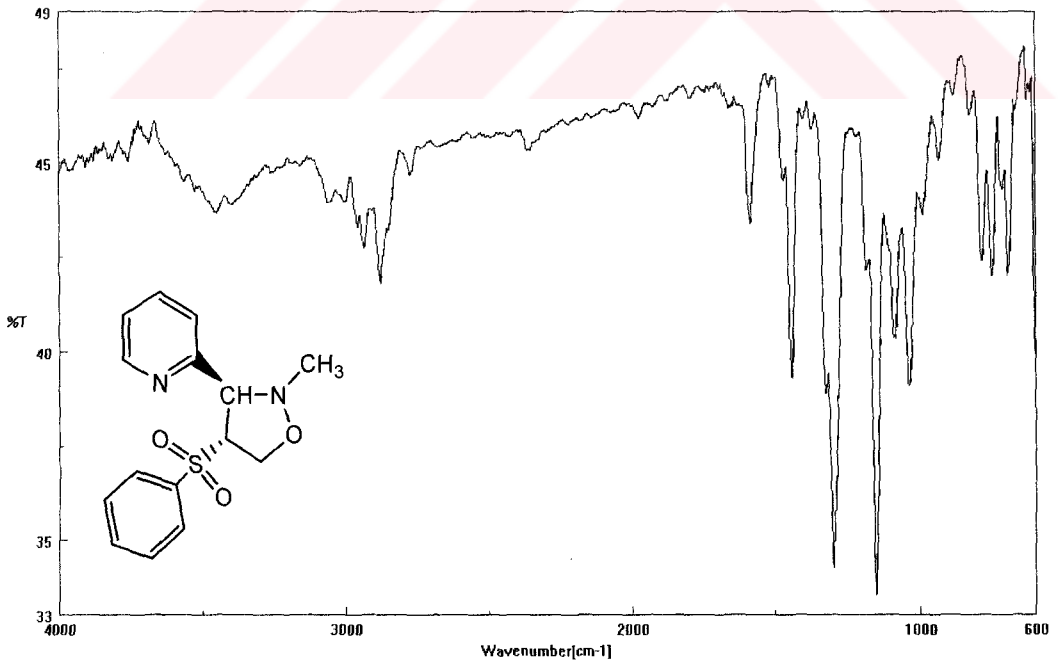


Figure 4.42. IR Spectrum of **3g**

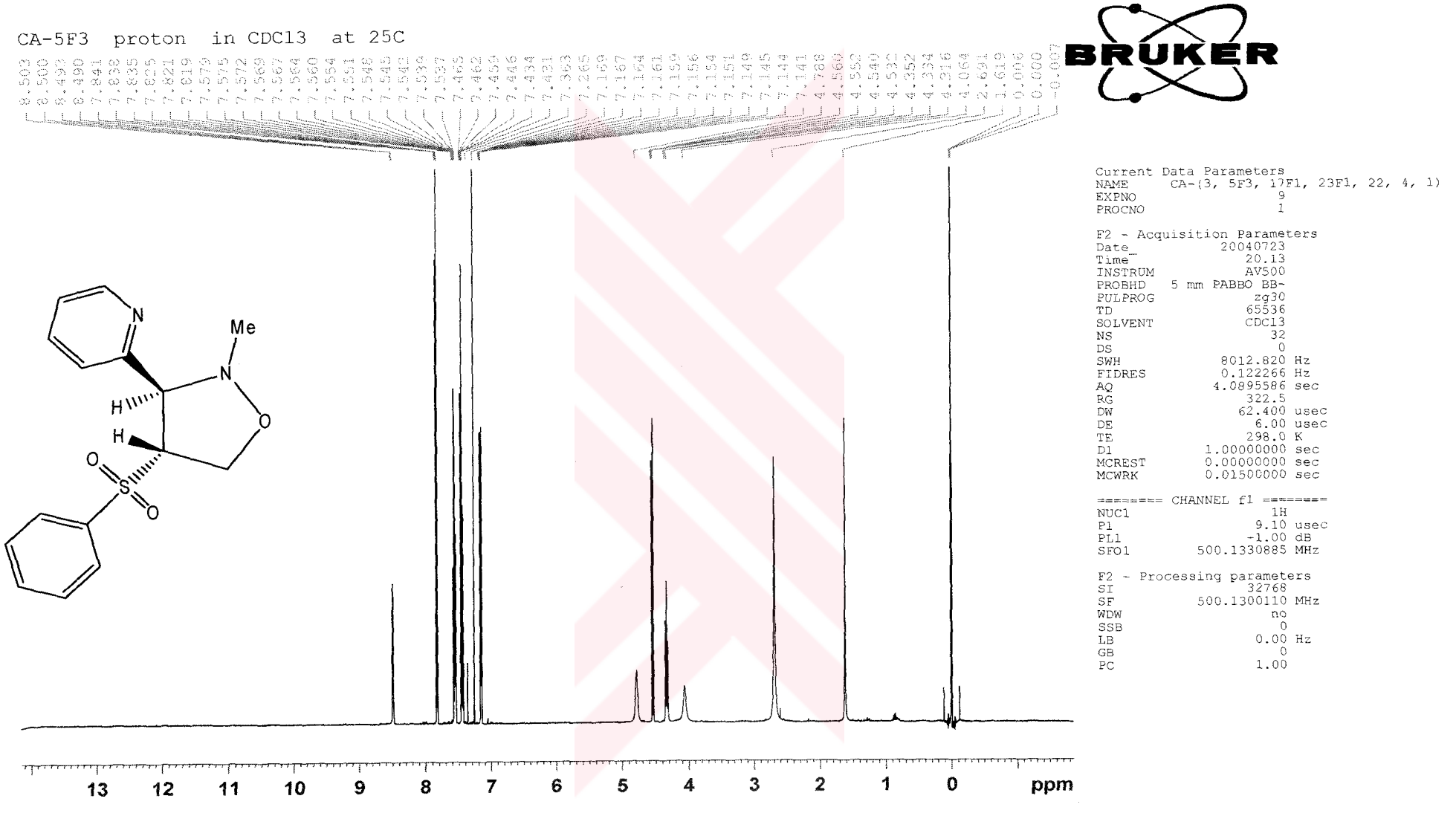
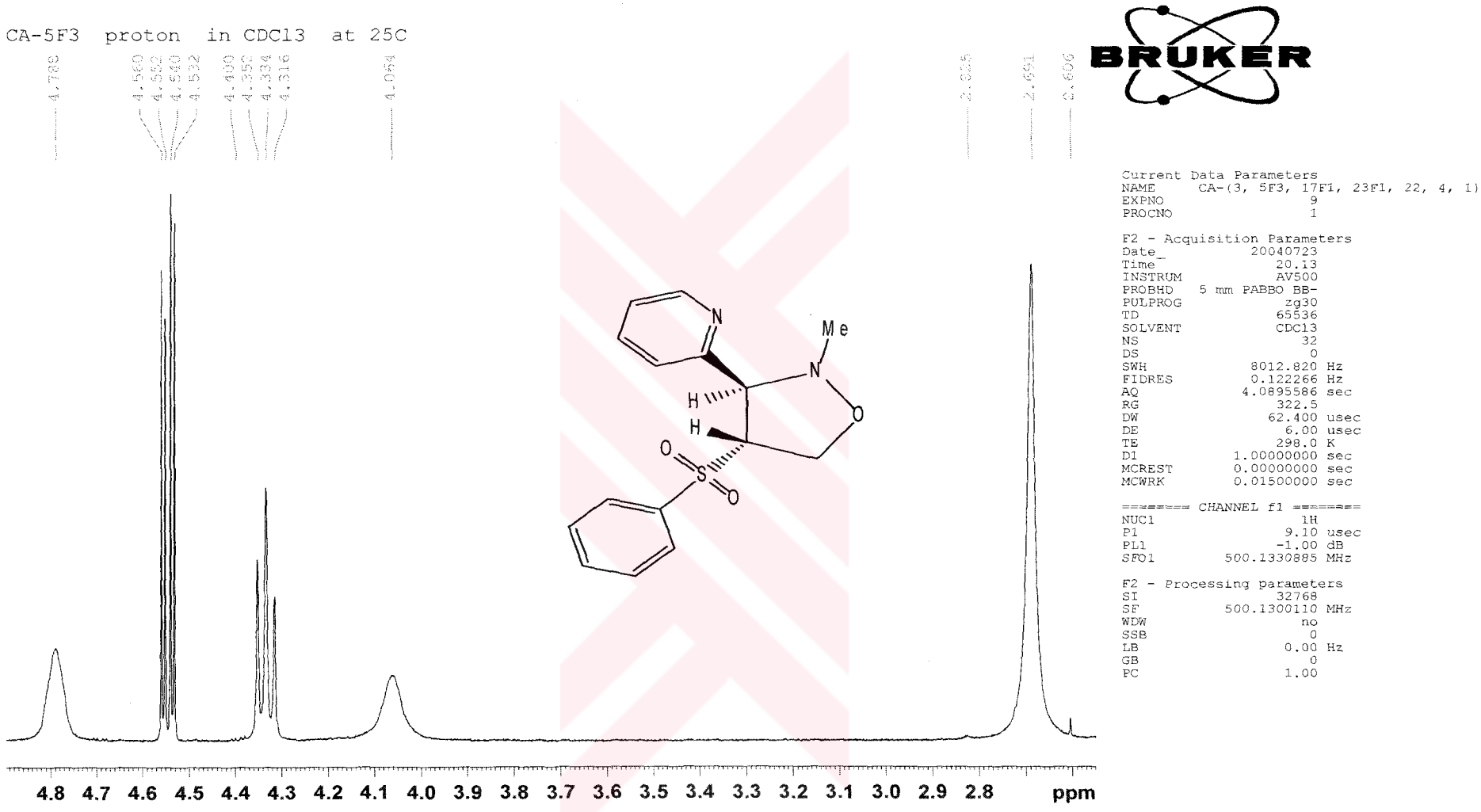


Figure 4.43 A. ^{1}H NMR Spectrum of **3g**

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PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   32
DS                    0
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0895586 sec
RG                322.5
DW              62.400 usec
DE               6.00 usec
TE              298.0 K
D1         1.00000000 sec
MCREST     0.00000000 sec
MCWRK      0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.10 usec
PL1               -1.00 dB
SFO1       500.1330885 MHz

F2 - Processing parameters
SI                32768
SF         500.1300110 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```

Figure 4.43 B. Expanded (4.8-2.8 ppm) ^{1}H NMR Spectrum of **3g**

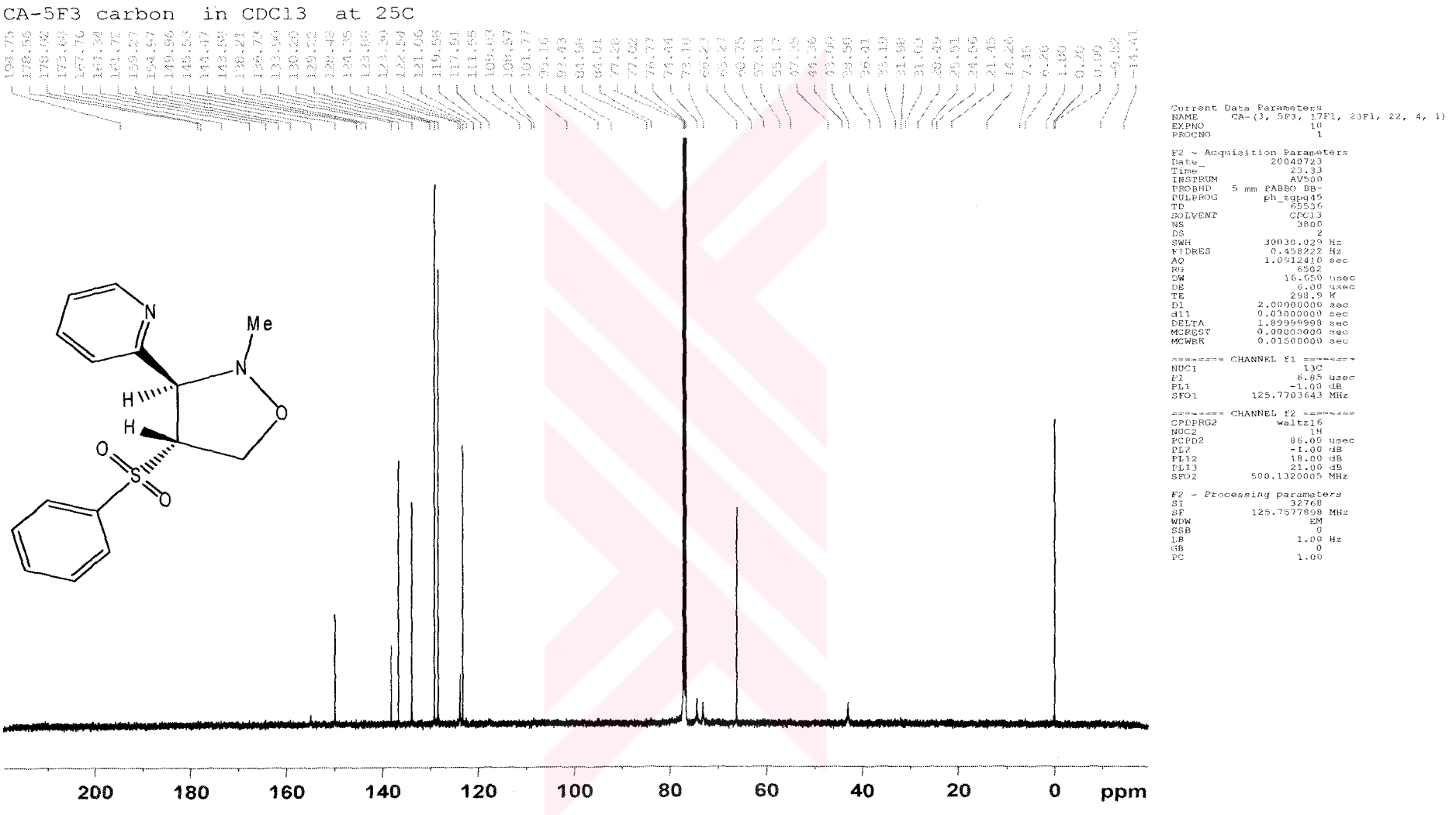


Figure 4.44. ^{13}C NMR Spectrum of **3g**

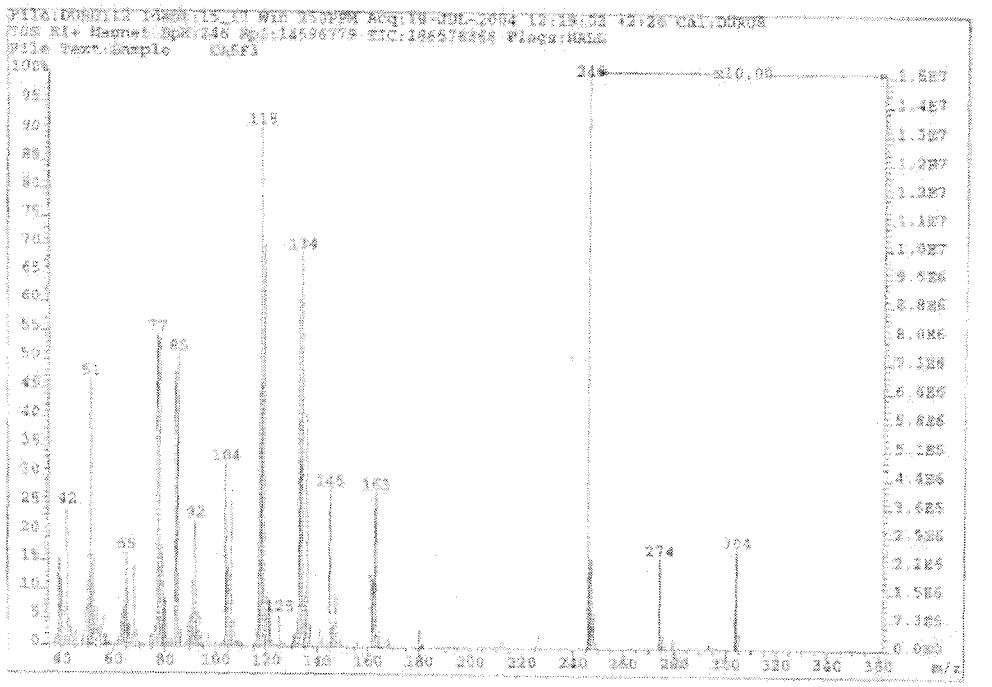


Figure 4.45. MASS Spectrum of **3g**

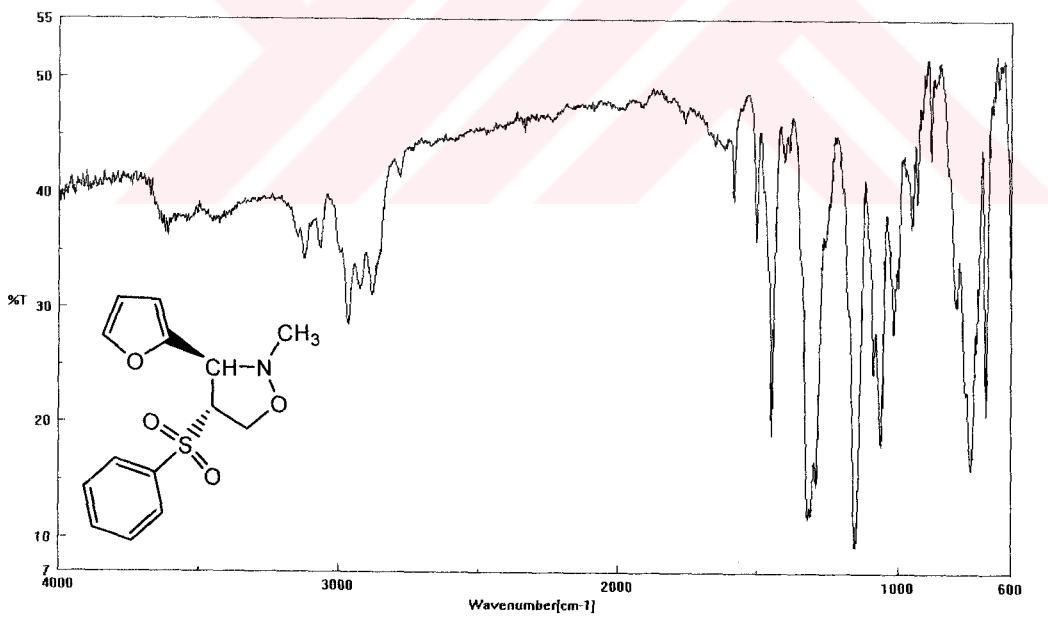
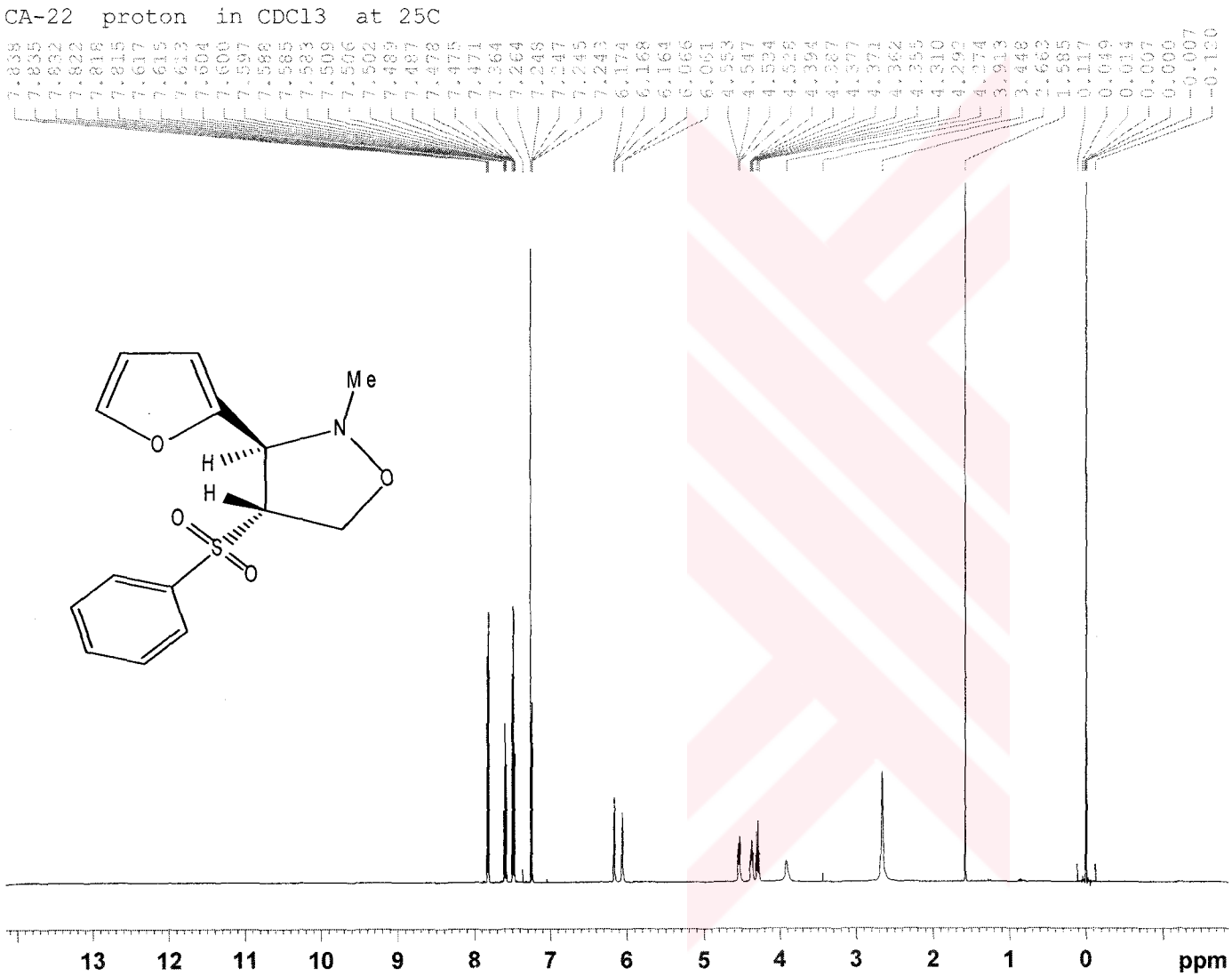


Figure 4.46. IR Spectrum of **3h**



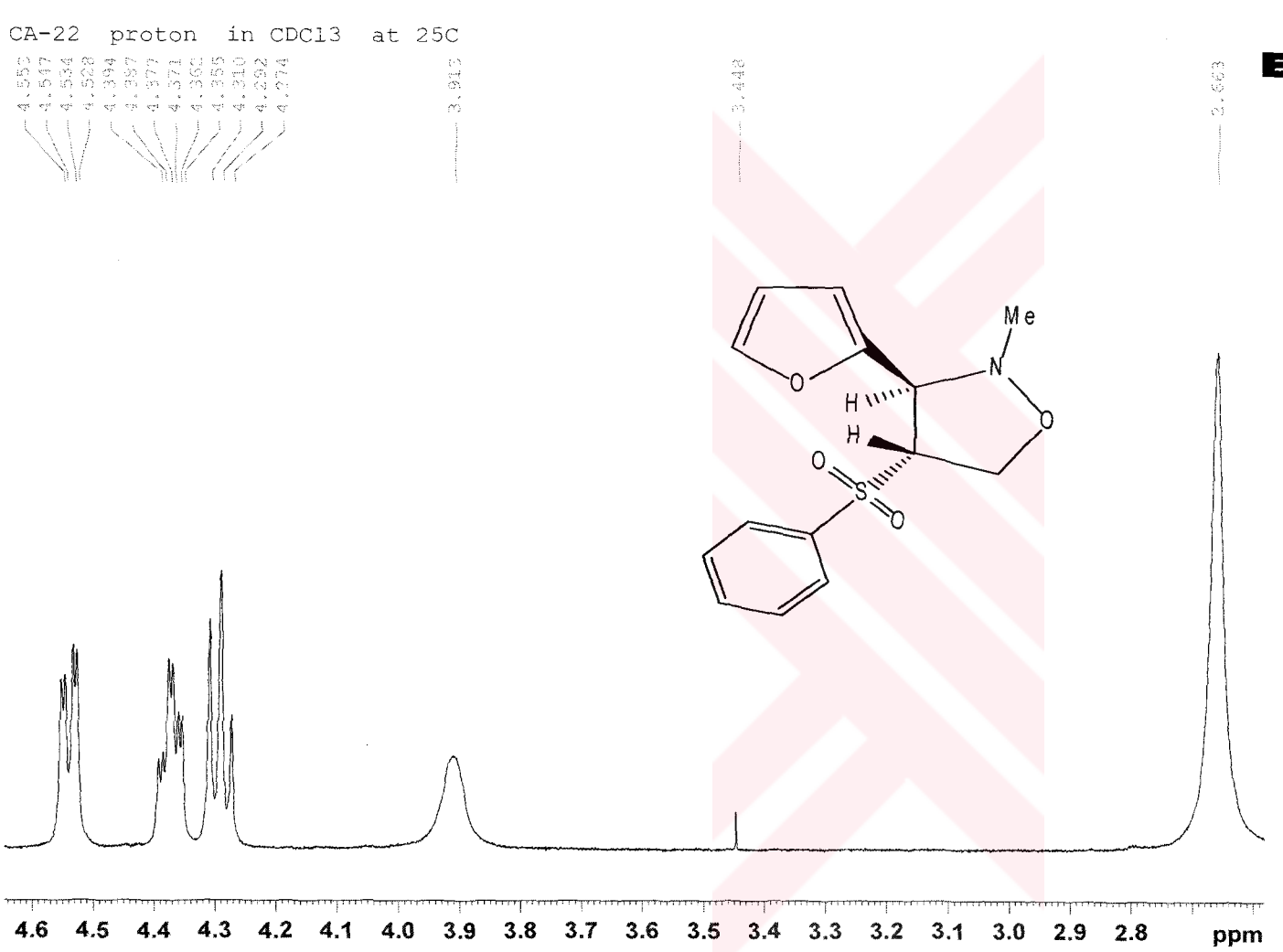

```
Current Data Parameters
NAME      CA-(3, 5F3, 17F1, 23F1, 22, 4, 1)
EXPNO                  27
PROCNO                  1

F2 - Acquisition Parameters
Date_           20040724
Time               14.24
INSTRUM            AV500
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    32
DS                     0
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ             4.0895586 sec
RG                 322.5
DW                62.400 usec
DE                 6.00 usec
TE                297.9 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.10 usec
PL1               -1.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF          500.1300113 MHz
WDW                   no
SSB                    0
LB                 0.00 Hz
GB                     0
PC                  1.00
```

Figure 4.47 A. ^{1}H NMR Spectrum of **3h**



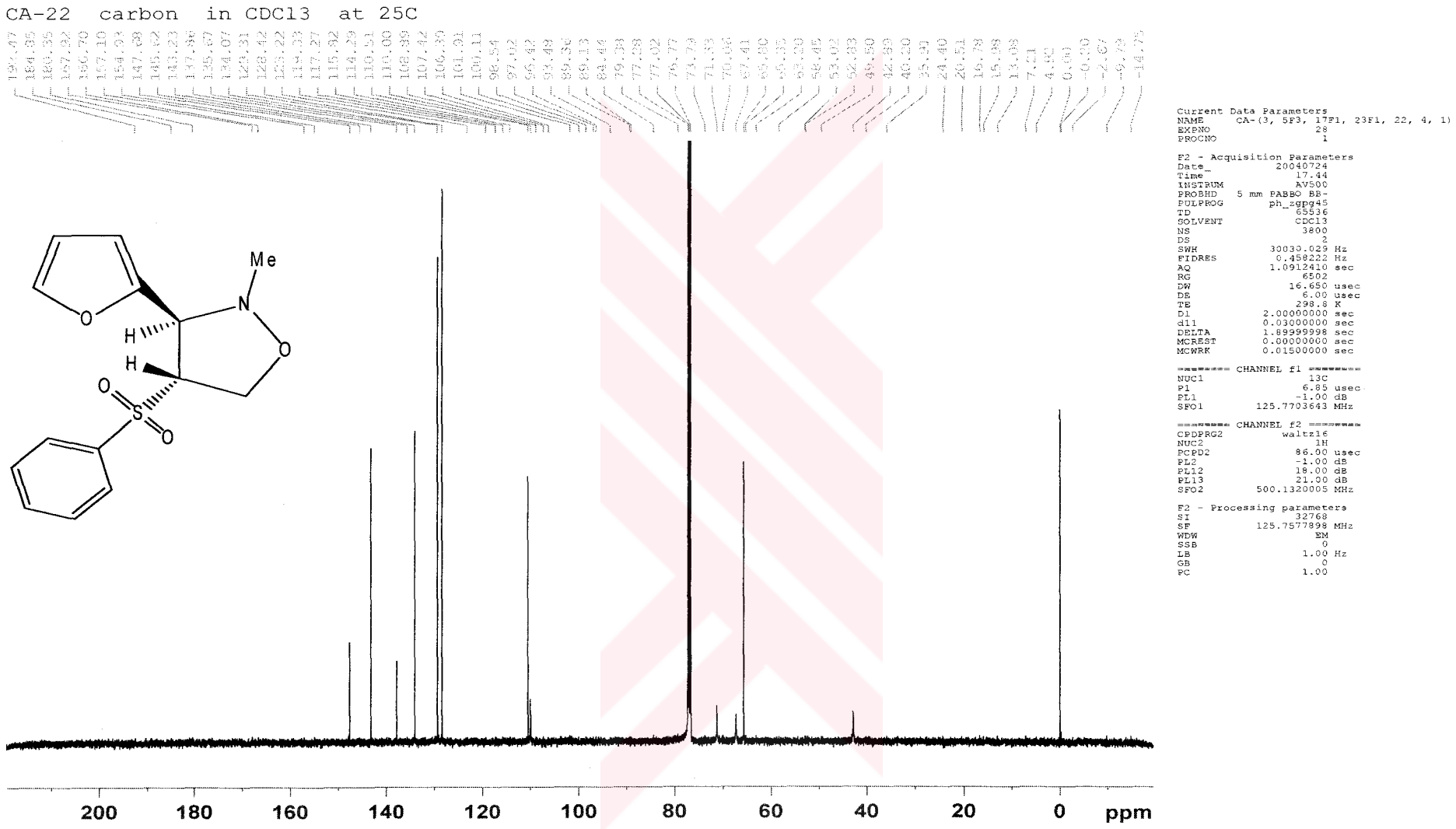

```
Current Data Parameters
NAME      CA-(3, 5F3, 17F1, 23F1, 22, 4, 1)
EXPNO                 27
PROCNO                 1

F2 - Acquisition Parameters
Date_           20040724
Time              14.24
INSTRUM           AV500
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   32
DS                    0
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0895586 sec
RG                322.5
DW               62.400 usec
DE                6.00 usec
TE                297.9 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.10 usec
PL1                -1.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                32768
SF          500.1300113 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```

Figure 4.47 B. Expanded (4.6-2.8 ppm) ^{1}H NMR Spectrum of **3h**



110

Figure 4.48. ^{13}C NMR Spectrum of **3h**

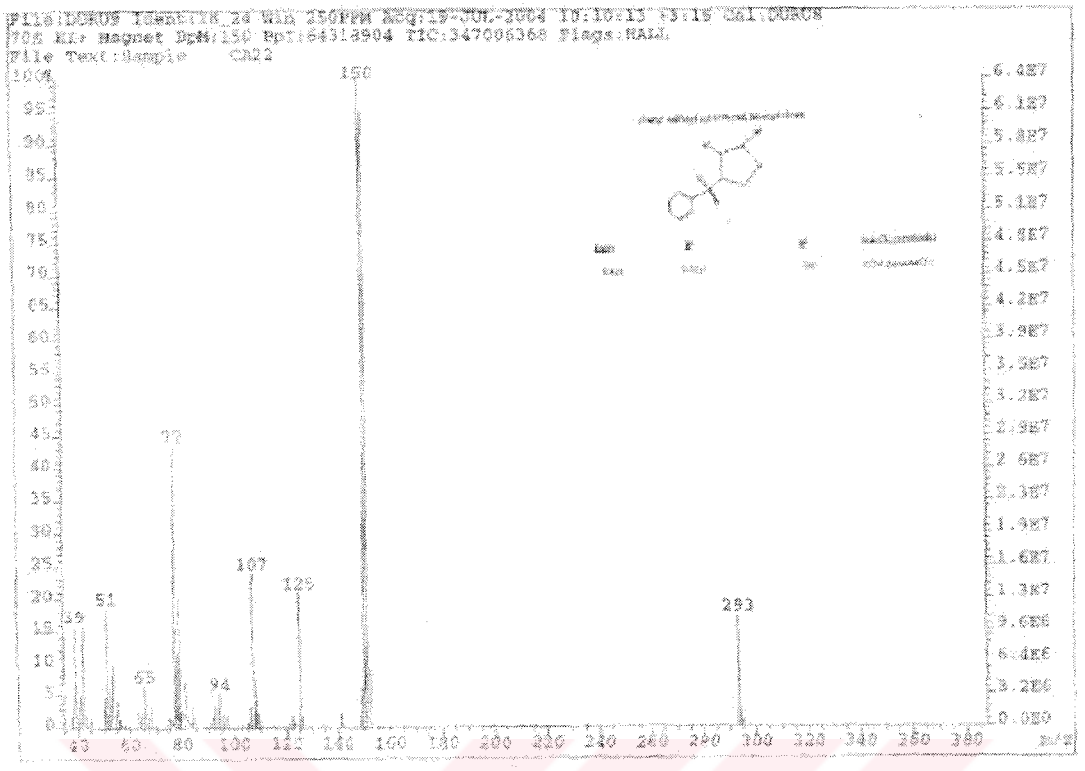


Figure 4.49 MASS Spectrum of **3h**

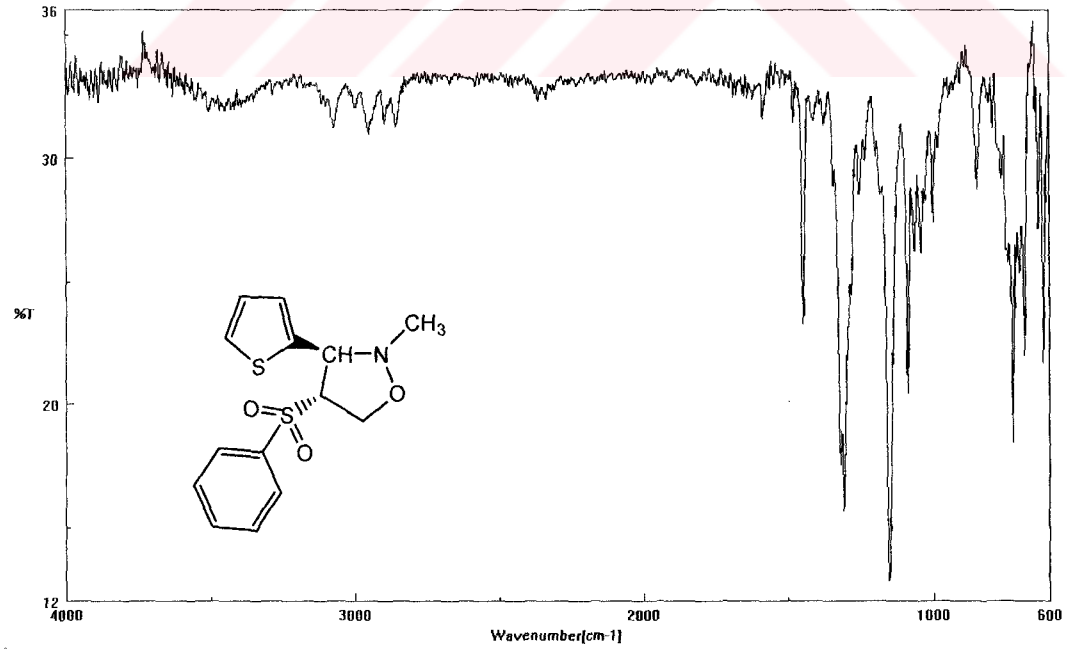
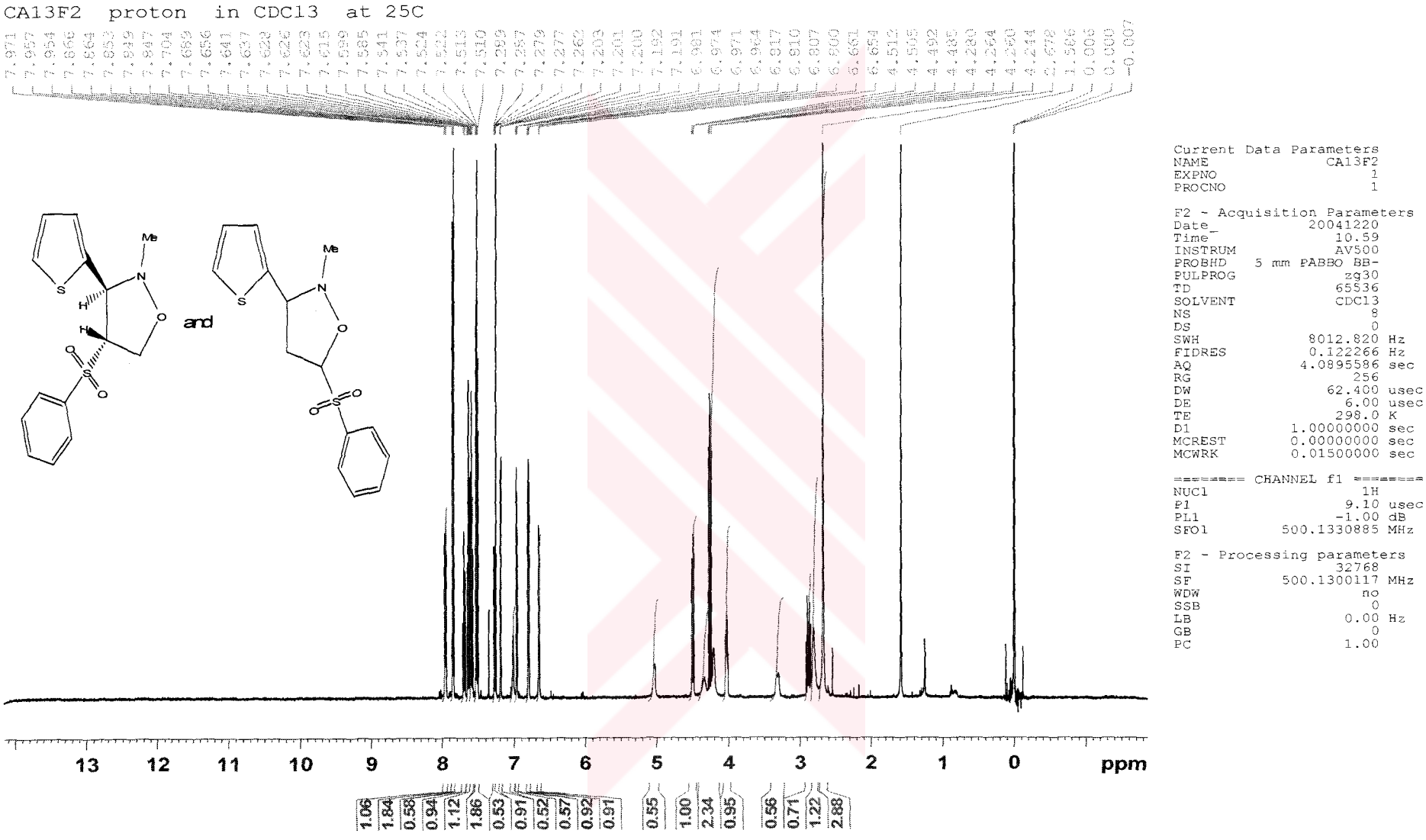


Figure 4.50. IR Spectrum of **3i**



Current Data Parameters

NAME	CA13F2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041220
Time	10.59
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	0
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0895586 sec
RG	256
DW	62.400 usec
DE	6.00 usec
TE	298.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	9.10 usec
PL1	-1.00 dB
SFO1	500.1330885 MHz

F2 - Processing parameters

SI	32768
SF	500.1300117 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

Figure 4.51 A. ^{1}H NMR Spectrum of **3i**

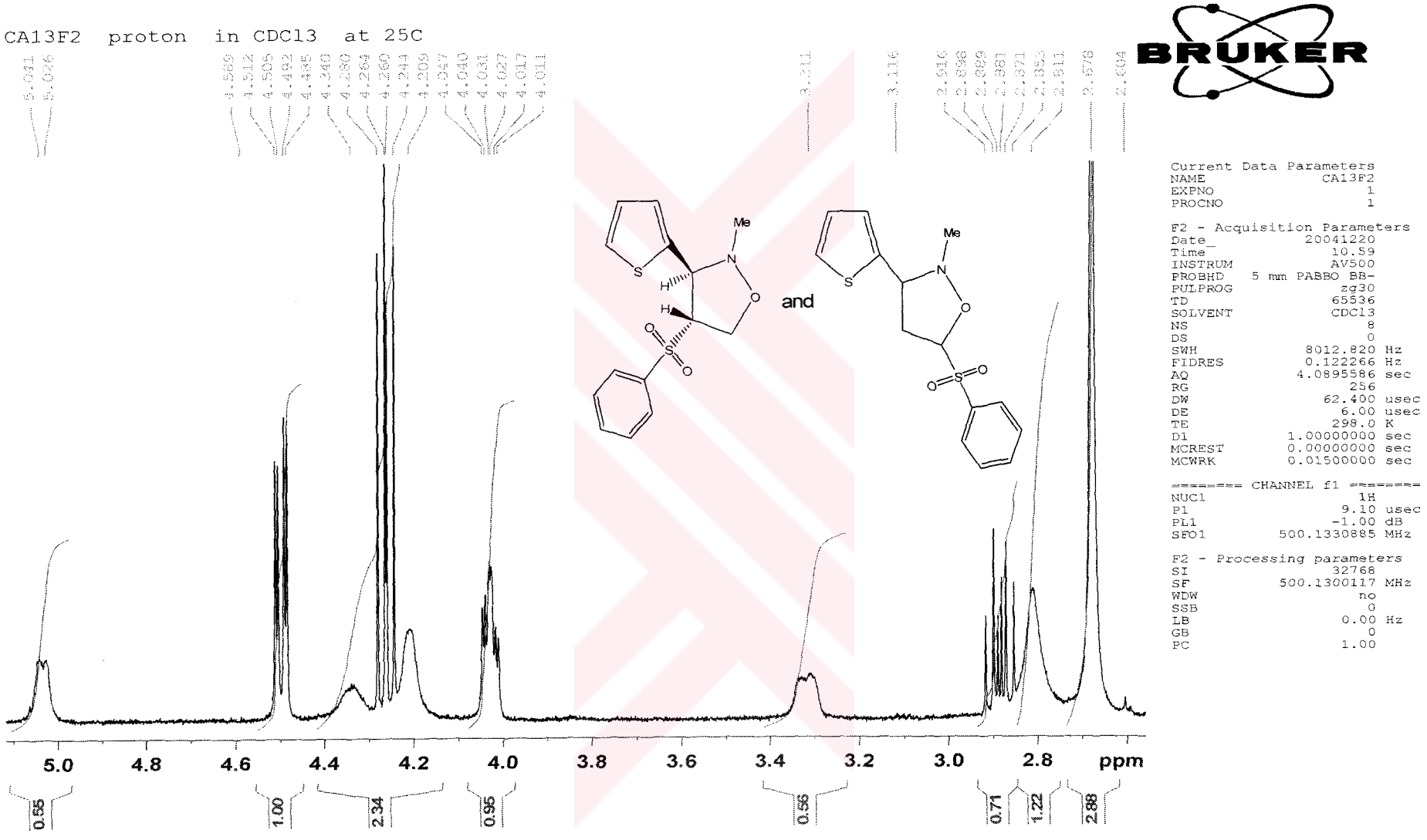
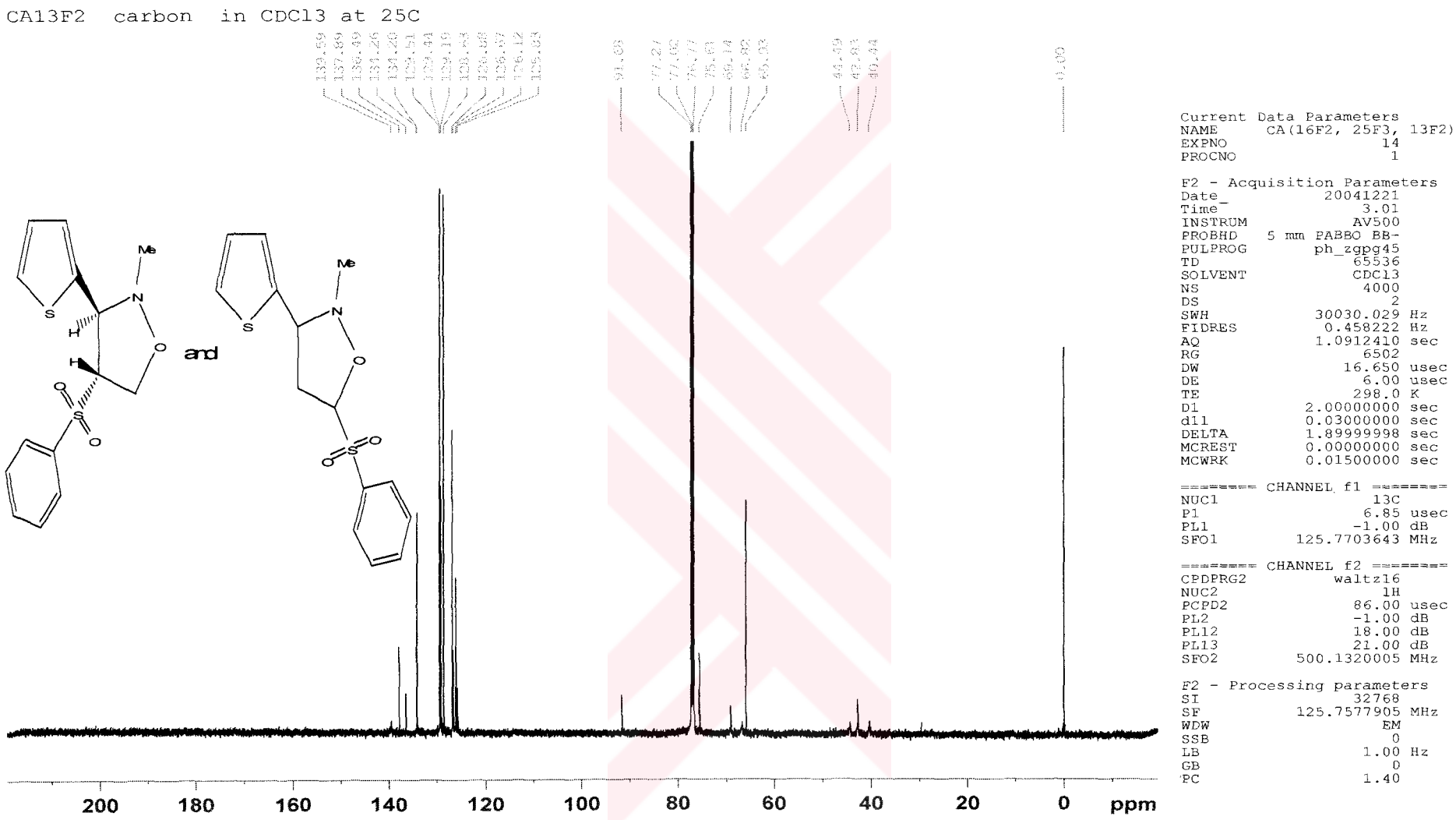


Figure 4.51 B. Expanded (5.0-2.8 ppm) ^{1}H NMR Spectrum of **3i**




```
Current Data Parameters
NAME      CA(16F2, 25F3, 13F2)
EXPNO                       14
PROCNO                       1

F2 - Acquisition Parameters
Date_              20041221
Time                   3.01
INSTRUM               AV500
PROBHD    5 mm PABBO BB-
PULPROG         ph_zgpg45
TD                     65536
SOLVENT                CDCl3
NS                      4000
DS                         2
SWH               30030.029 Hz
FIDRES            0.458222 Hz
AQ                1.0912410 sec
RG                      6502
DW                  16.650 usec
DE                   6.00 usec
TE                   298.0 K
D1              2.00000000 sec
d11             0.03000000 sec
DELTA           1.89999998 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                   6.85 usec
PL1                 -1.00 dB
SFO1          125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                      1H
PCPD2               86.00 usec
PL2                 -1.00 dB
PL12                18.00 dB
PL13                21.00 dB
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                     32768
SF            125.7577905 MHz
WDW                       EM
SSB                        0
LB                  1.00 Hz
GB                         0
PC                  1.40
```

Figure 4.52 ^{13}C NMR Spectrum of **3i**

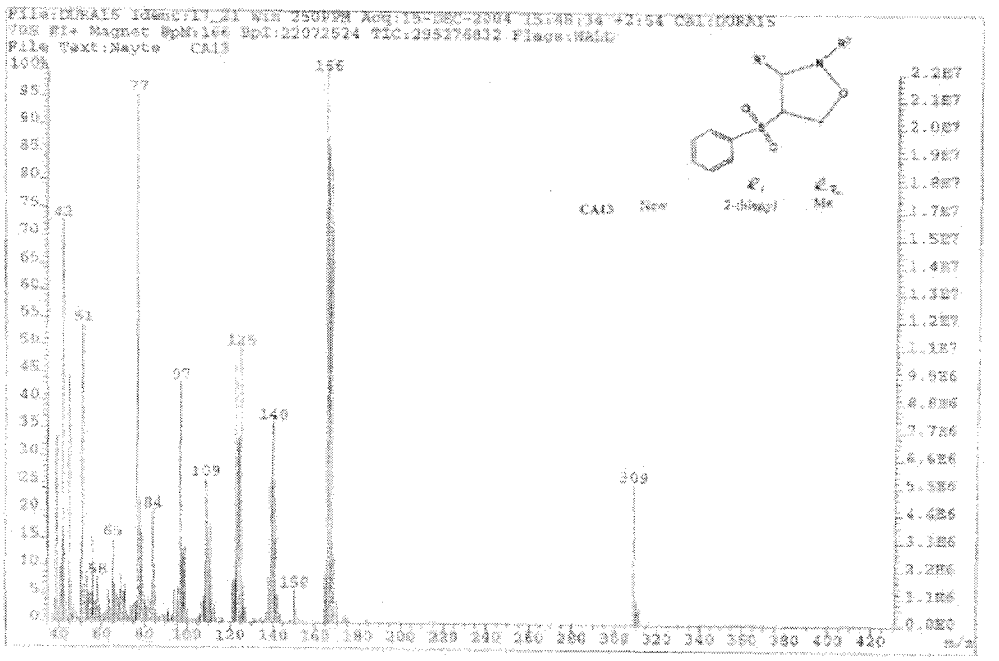


Figure 4.53.MASS Spectrum of **3i**

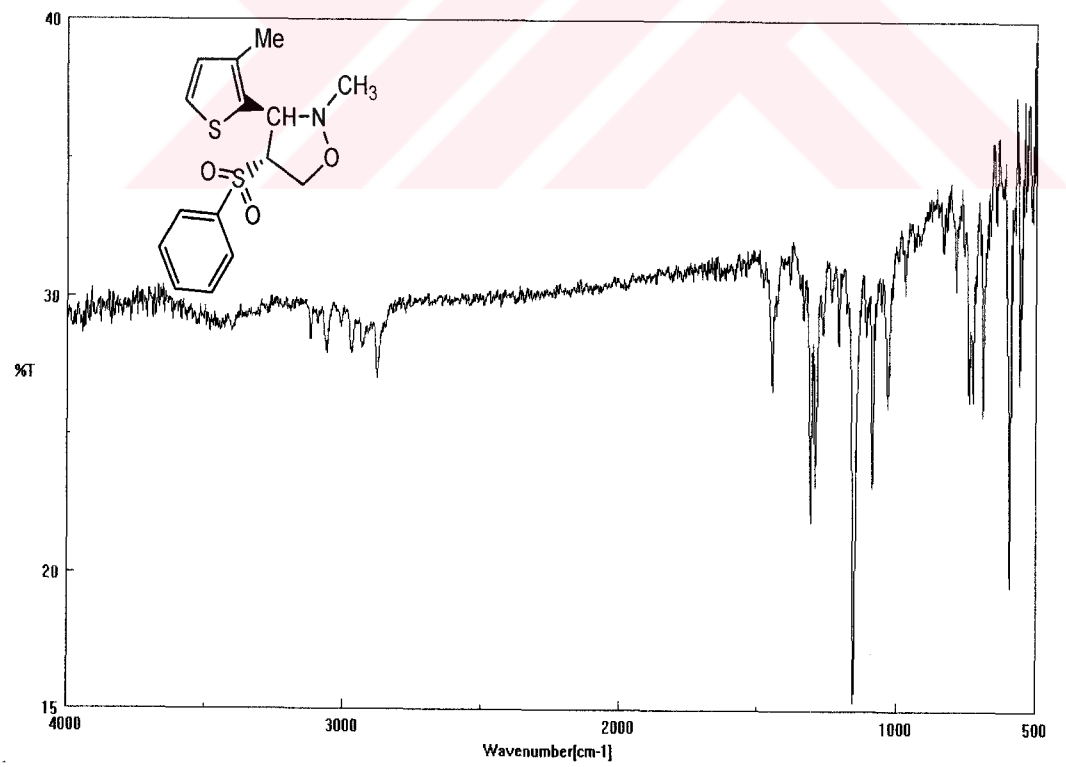
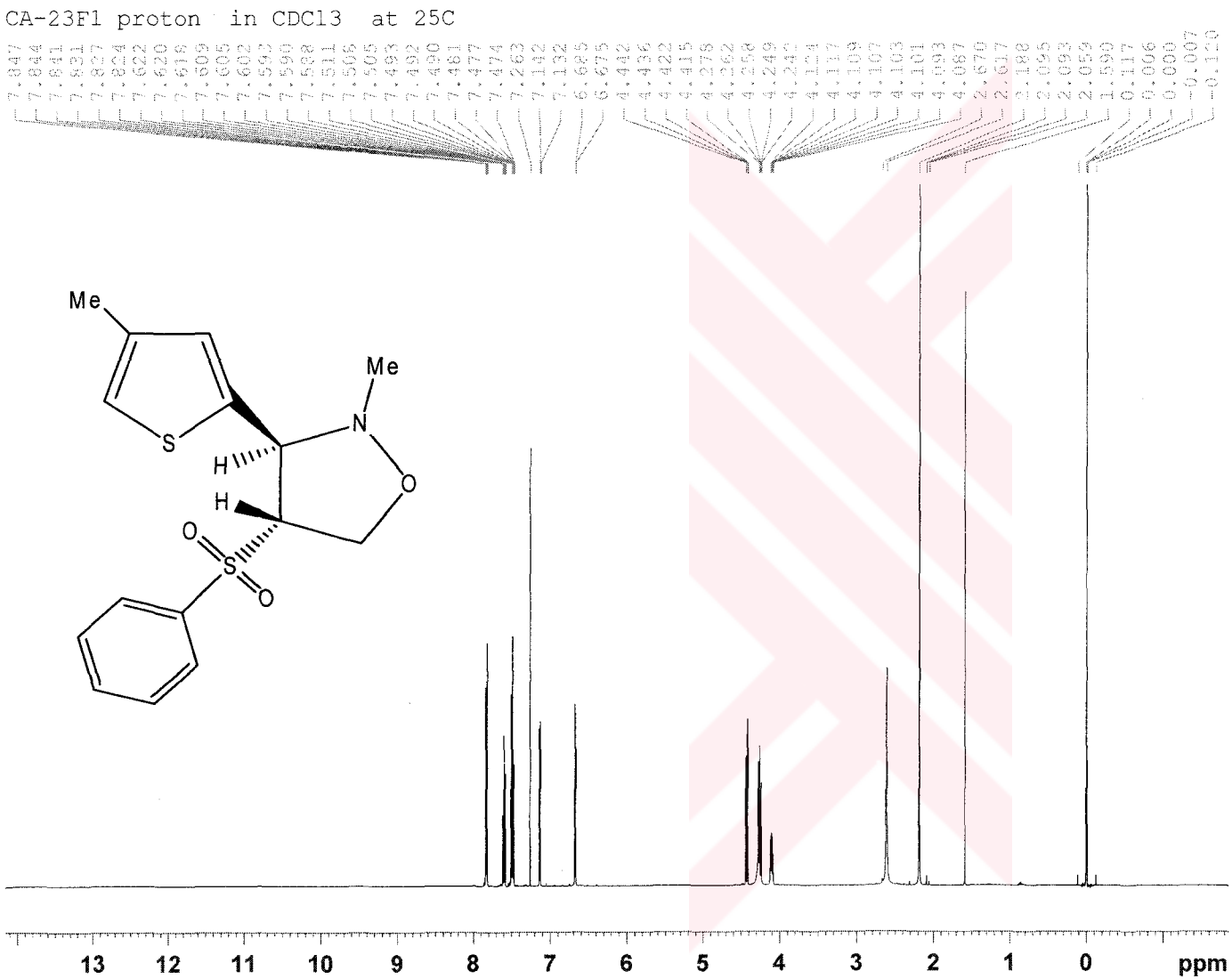


Figure 4.54. IR Spectrum of **3j**




```
Current Data Parameters
NAME      CA-(3, 5F3, 17F1, 23F1, 22, 4, 1)
EXPNO                  21
PROCNO                  1

F2 - Acquisition Parameters
Date_           20040724
Time                8.21
INSTRUM            AV500
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    32
DS                     0
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ             4.0895586 sec
RG                   256
DW                62.400 usec
DE                 6.00 usec
TE                297.9 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.10 usec
PL1               -1.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF          500.1300116 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```

Figure 4.55 A. ^{1}H NMR Spectrum of **3j**

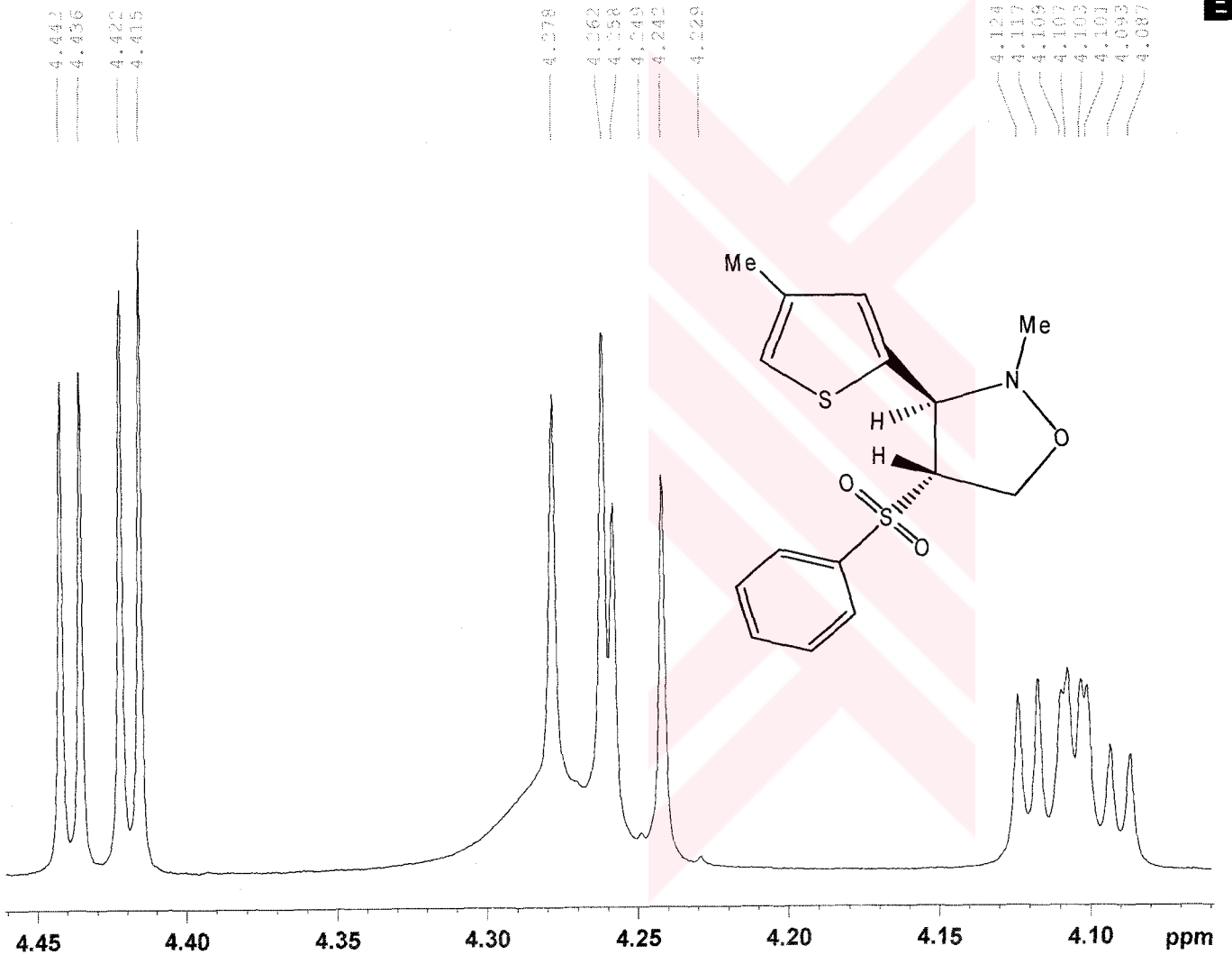


Figure 4.55 B. Expanded(4.45-4.05) ^{1}H NMR Spectrum of **3j**

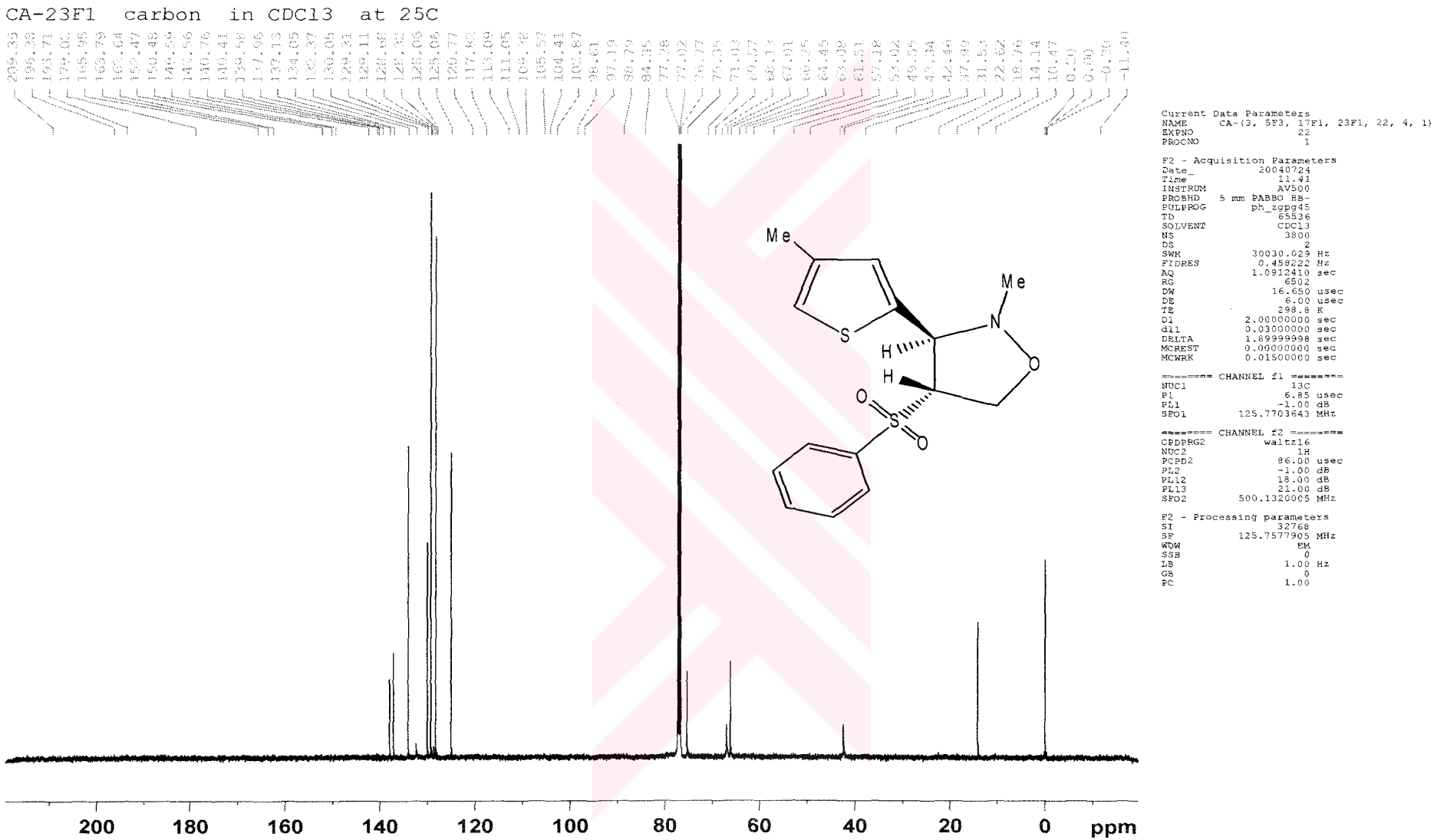
BRUKER

```
Current Data Parameters
NAME      CA-(3, 5F3, 17F1, 23F1, 22, 4, 1)
EXPNO                  21
PROCNO                  1

F2 - Acquisition Parameters
Date_           20040724
Time               8.21
INSTRUM           AV500
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    32
DS                     0
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0895586 sec
RG                   256
DW                62.400 usec
DE                 6.00 usec
TE                297.9 K
D1             1.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.10 usec
PL1                 -1.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF          500.1300116 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```




```
Current Data Parameters
NAME      CA-(3, 5F3, 17F1, 23F1, 22, 4, 1)
EXPNO                 22
PROCNO                 1

F2 - Acquisition Parameters
Date_           20040724
Time              11.41
INSTRUM           AV500
PROBHD   5 mm PABBO BB-
PULPROG       ph_zgpg45
TD               65536
SOLVENT          CDCl3
NS                3800
DS                   2
SWH          30030.029 Hz
FIDRES        0.458222 Hz
AQ           1.0912410 sec
RG                6502
DW              16.650 usec
DE               6.00 usec
TE              298.8 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1               13C
P1               6.85 usec
PL1              -1.00 dB
SFO1       125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2           86.00 usec
PL2              -1.00 dB
PL12             18.00 dB
PL13             21.00 dB
SFO2       500.1320005 MHz

F2 - Processing parameters
SI                32768
SF         125.7577905 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.00
```

Figure 4.56. ^{13}C NMR Spectrum of **3j**

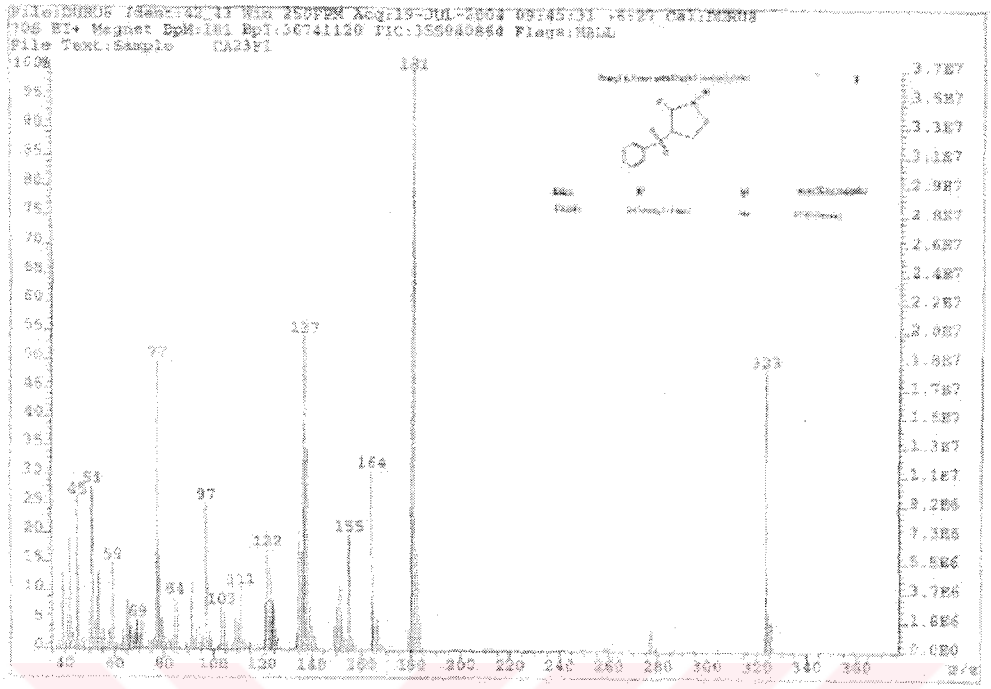


Figure 4.57 MASS Spectrum of **3j**