SYNTHESIS OF POTENTIAL BIOACTIVE HETEROCYCLES BY 1,3-DIPOLAR CYCLOADDITION OF NITRILIMINES WITH DIPOLAROPHILES

MUHAMMET YILDIRIM

JULY 2010

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by

MUHAMMET YILDIRIM

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Approval of the Graduate School of Natural and Applied Sciences

Prof. Dr. Nihat ÇELEBİ

Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Doctor of Philosophy.

Prof. Dr. Çetin BOZKURT

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 Doctor of Philosophy.

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ABSTRACT

SYNTHESIS OF POTENTIAL BIOACTIVE HETEROCYCLES BY 1,3-DIPOLAR CYCLOADDITION OF NITRILIMINES WITH DIPOLAROPHILES

Yıldırım, Muhammet
Ph.D., Department of Chemistry
Supervisor: Prof.Dr.Yaşar DÜRÜST
July 2010, 357 pages

1,3-Dipolar cycloadditive methodology occupies a prominent place due to its versatility in the construction of complex heterocylic systems. Pyrazole and pyrazoline containing heterocycles have been intensively synthesized for many years by the nitrilimine cycloaddition reactions with dipolarophilic compounds since the pyrazole or pyrazoline rings are the core structure of many natural products and drugs. For this reason, this Ph.D. dissertation study comprises the synthesis of potential bioactive pyrazoline derivatives by means of nitrilimine cyloaddition reactions. The outcomes of nitrilimine cyloaddition reactions were discussed in five parts;

In the first part, as the precursors of nitrilimines, wide range of aryl aldehyde hydrazones and hydrazonyl chlorides were efficiently prepared according to the modified literature methods and characterized.

The second part of the work was involved in the synthesis of novel biscycloadducts, namely, aryl substituted dihydro bispyrrolo[3,4-*c*]pyrazole-

4,6-diones, by the reaction of *C,N*-diarylnitrilimines with bismaleimide derivatives in excellent yields. It should be noted herein that the reaction was absolutely stereoselective and no other regioisomeric product was observed.

In the third part, the effect of the substituent groups on *para* positions of phenyl ring attached to azomethine carbon of biscycloadducts to the absorption maxima values of UV-VIS spectra was investigated by measuring their ultraviolet absorption spectra and by the correlating them with Hammett sigma para constants. Some significant correlation results have been obtained.

Fourth part covers the synthesis of novel dihydropyrrolo[3,4-*c*] pyrazole-4,5-diones by nitrilimine cycloaddition reactions with chiral (*R*)-*N*-(1-phenylethyl)maleimide. Regiocontrolled cycloaddition reactions gave rise to formation of either single regioisomer or mixture of regioisomers in some cases.

Last part of the thesis was devoted to the investigation of reactivity of nitrilimines with 2-methyl-2-vinyloxirane since there is no reported cycloaddition reaction of nitrilimines to the alkenes bearing epoxide moiety as far as we searched the literature. The reaction took place in regioselective manner and the formation of two diastereomers resulted in each reaction which differs only by the rotation of single bond between oxirane and pyrazoline ring, thus, novel 2-methyl-2-oxiranyl substituted dihydropyrazoles were obtained in low diastereoselectivity.

Keywords: Nitrilimine, bismaleimide, 2-methyl-2-vinyloxirane, (*R*)-*N*-(1-phenylethyl)maleimide, dihydropyrrolo[3,4-*c*] pyrazole-4,5-dione, Hammett.

ÖZET

NİTRİLİMİNLERİN ÇEŞİTLİ DİPOLARSEVENLERLE 1,3-DİPOLAR HALKA KATILMALARINDAN POTANSİYEL BİYOAKTİF HETEROHALKALI BİLEŞİKLERİN SENTEZİ

Yıldırım, Muhammet
Doktora, Kimya Bölümü
Tez Danışmanı: Prof.Dr.Yaşar DÜRÜST
Temmuz 2010, 357 sayfa

1,3-dipolar halkakatılma yöntemi, birçok kompleks heterohalkasal bileşiğin sentezinde yaygın olarak kullanılmasından dolayı çok önemli bir yere sahiptir. Birçok doğal ürün ve ilacın ana yapısının pirazol yada pirazolin halkalarını içermesinden dolayı, pirazol ve pirazolin heterohalkalı bileşikleri, yıllardan beri nitriliminlerin çeşitli dipolarseven maddelere katılmaları üzerinden yoğun bir şekilde sentezlenmektedir. Bundan dolayı, bu doktora tez çalışması, nitriliminlerin çeşitli dipolarofillerle tepkimesi aracılığıyla potansiyel biyoaktif maddelerin sentezini içermektedir. Nitrilimin halkakatılma reaksiyonlarının sonuçları, 5 kısımda tartışılmıştır;

İlk kısımda, nitriliminlerin başlangıç maddeleri olarak, birçok aril hidrazon ve hidrazonil klorür türevleri modifiye edilmiş literatür metotları kullanılarak sentezlendi ve karakterize edildi.

İkinci kısım, *C,N*-diaril nitriliminlerin, bismaleimid türevlerine 1,3-dipolar halka katılması sonucu elde edilen, sübstitüe dihidro bispirolo[3,4-*c*]pirazol-4,6-dion olarak isimlendirilen yeni çift taraflı heterohalkaların yüksek verimle sentezini içermektedir. Şunu vurgulamak gerekirse, tepkime tamamıyla stereoseçimlidir ve kesinlikle başka bir yerseçici izomer oluşumu gözlenmemiştir.

Üçüncü kısımda, çift taraflı ürünlerde bulunan azometin karbona bağlı olan fenil halkalarındaki para grupların etkisi, bu maddelerin UV soğurma spektrumlarının ölçülüp, Hammett para sübstitüent sabitleriyle korelasyonuna bakılarak incelenmiştir ve anlamlı doğrusal korelasyonlar elde edilmiştir.

Dördüncü kısım, dihidropirolo[3,4-*c*]pirazol-4,6-dion türevlerinin, nitriliminlerin kiral (*R*)-*N*-(1-feniletil)maleimid halkakatılma tepkimeleriyle sentezlenmesini içermektedir. Yerkontrollü halka katılma tepkimesi, bazı durumlarda tek ürün olarak yer seçici izomerin ya da yerseçici izomerlerin karışımlarının elde edilmesiyle sonuçlanmıştır.

Tezin son kısmı, yapılan literatür araştırmasına göre hiçbir örneği olmayan nitriliminlerin 2-metil-2-vinil oksirana 1,3-dipolar halka katılması tepkimesinin araştırılmasına ayrılmıştır. Tepkime yerseçici olsa da, bütün denemelerde pirazol ve oksiran halkaları arasındaki tek bağın dönmesiyle oluşan iki diyasteryoizomer gözlenmiştir. Böylelikle, yeni 2-metil-2-oksiran sübstitüte dihidropirazol türevleri düşük diyasteryoseçicilikle elde edilmiştir.

Keywords: Nitrilimin, bismaleimid, 2-metil-2-viniloksiran, (*R*)-*N*-(1-feniletil)maleimid, dihidropirolo[3,4-*c*] pirazol-4,5-dion, Hammett.

To my wife and daughter,

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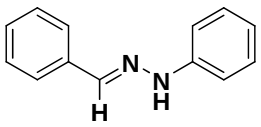
FORMULAE



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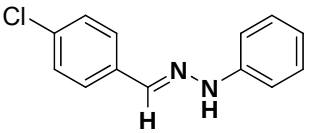

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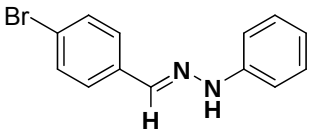

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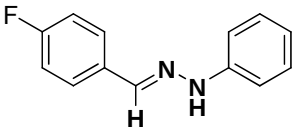

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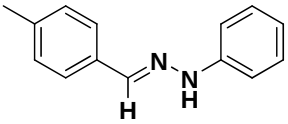

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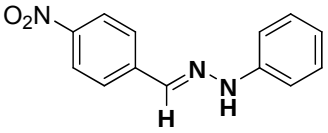

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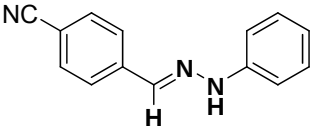

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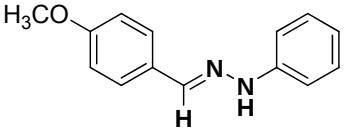

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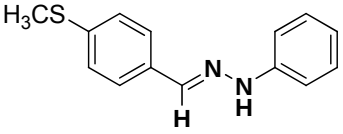

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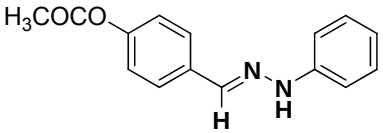

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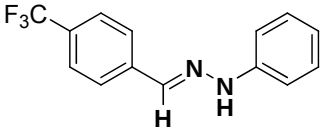

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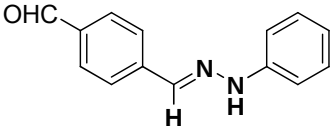

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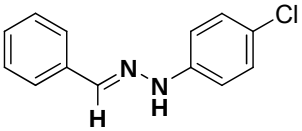

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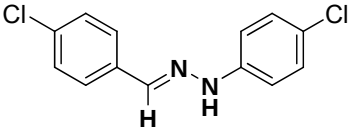

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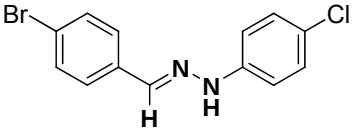

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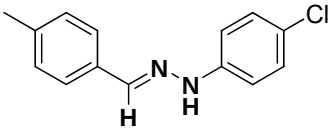

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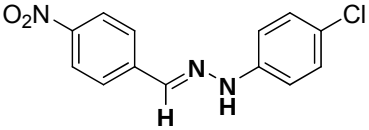

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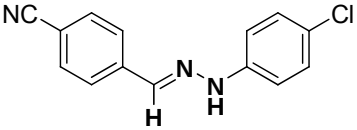

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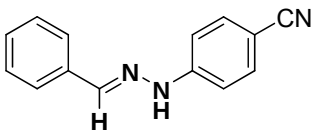

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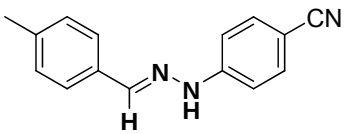

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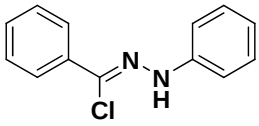

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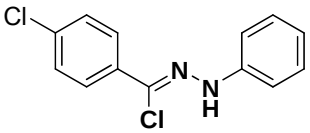

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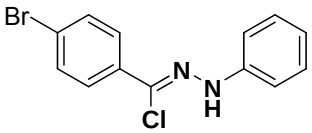

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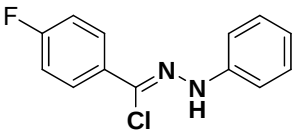

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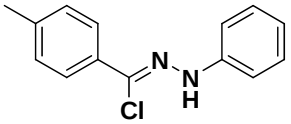

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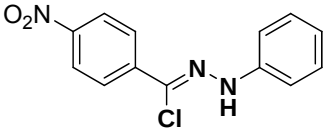

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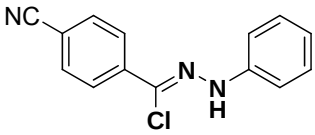

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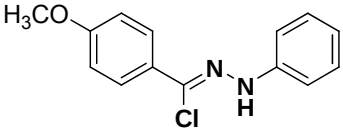

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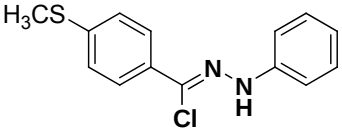

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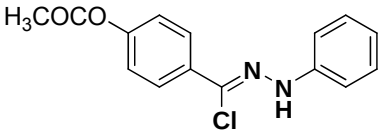

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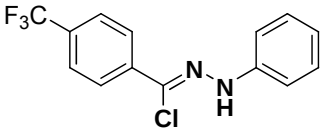

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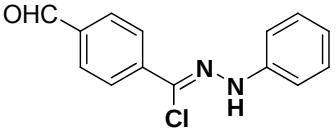

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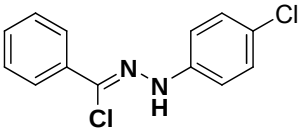

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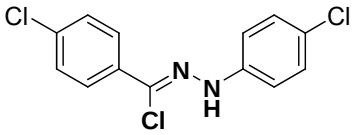

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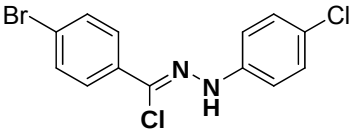

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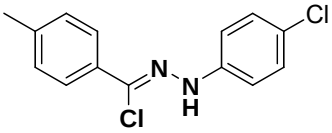

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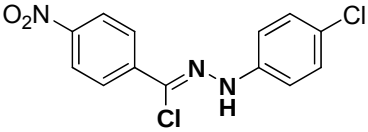

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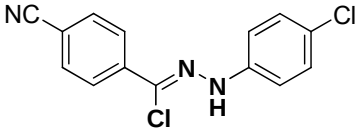

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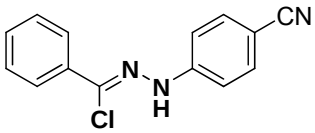

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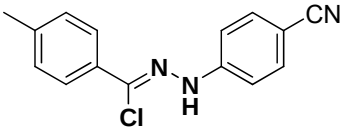

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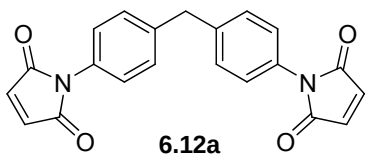

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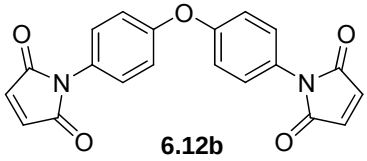

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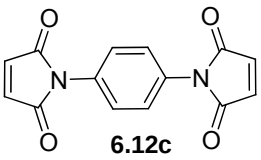

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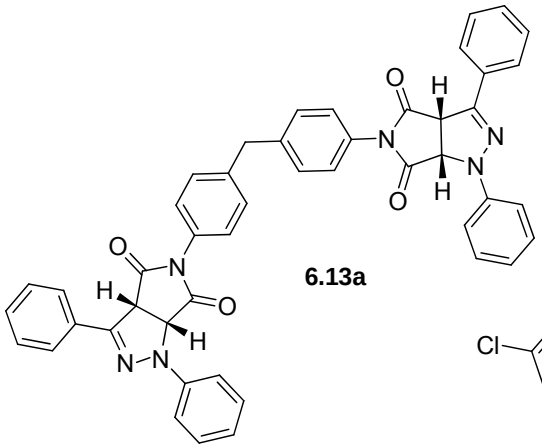

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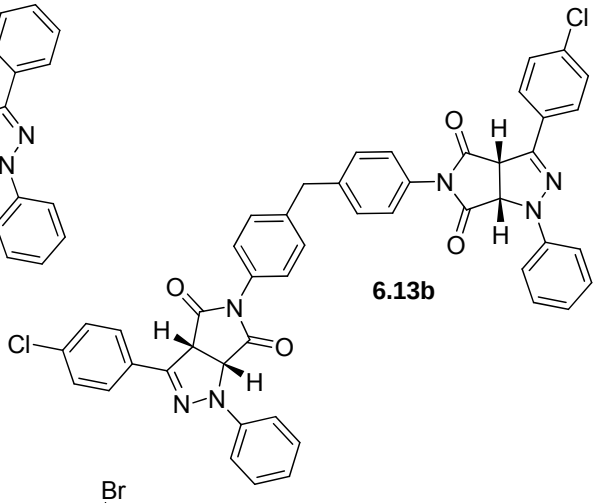

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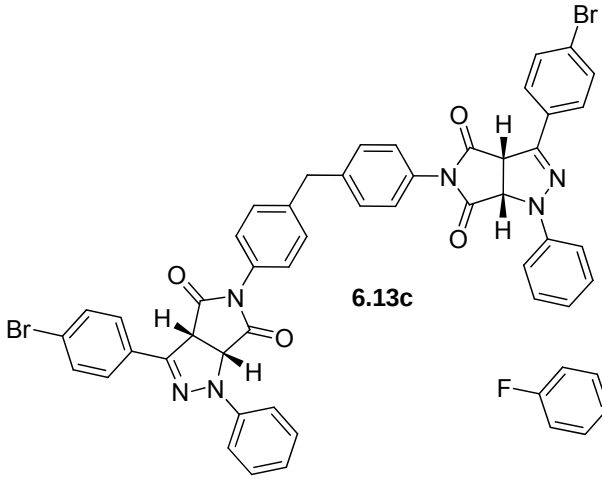

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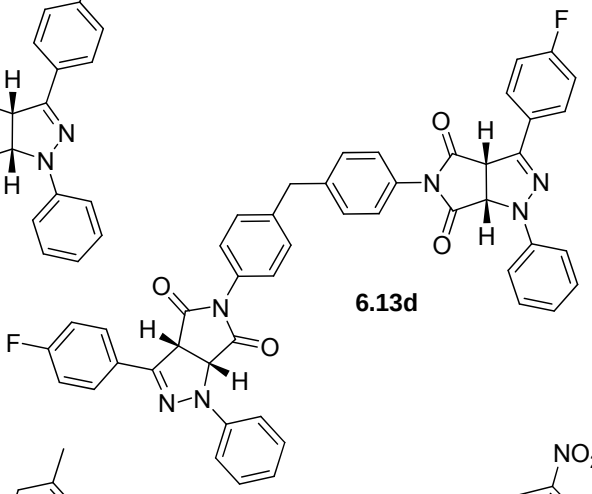

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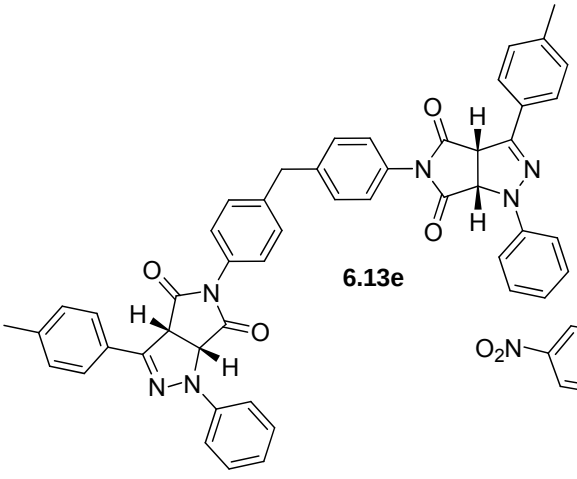

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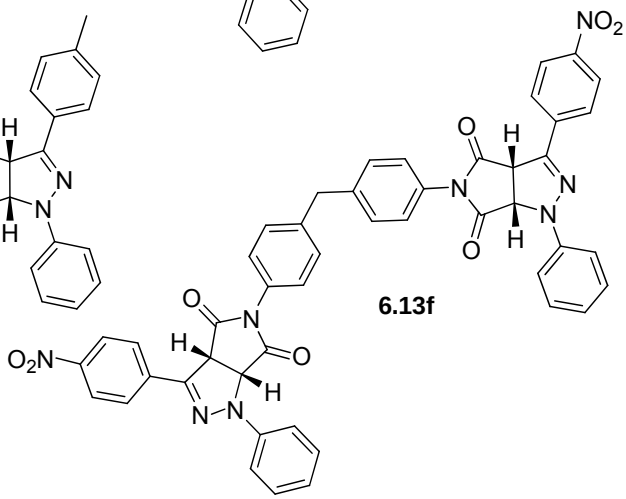

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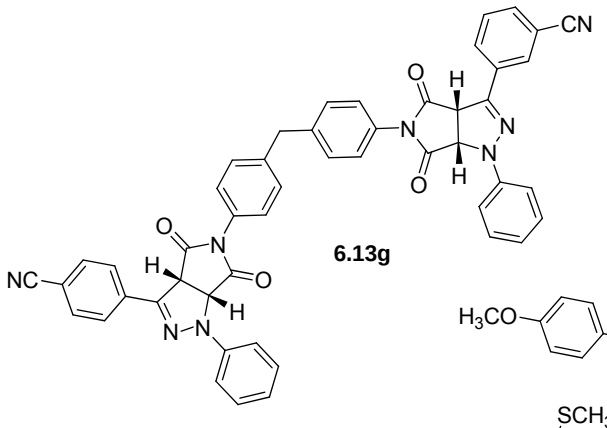

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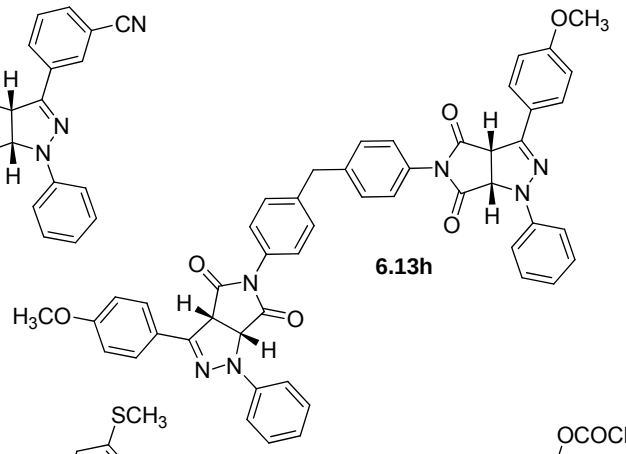

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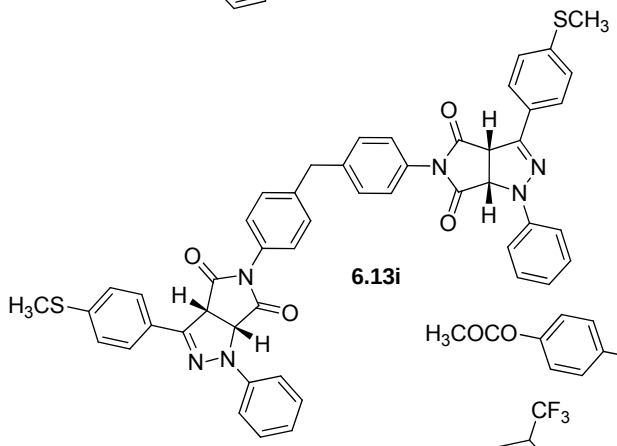

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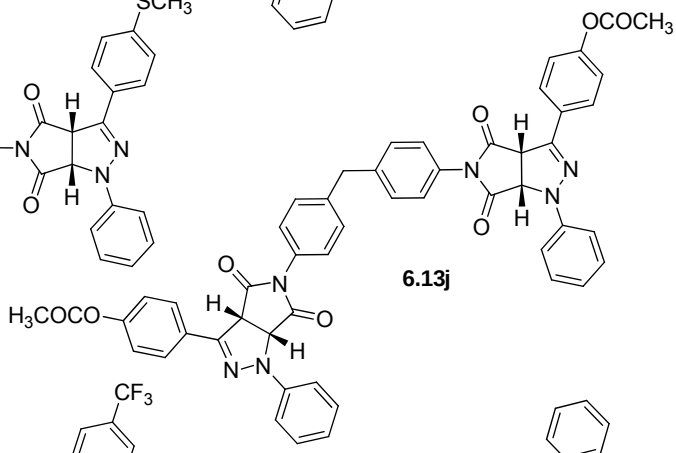

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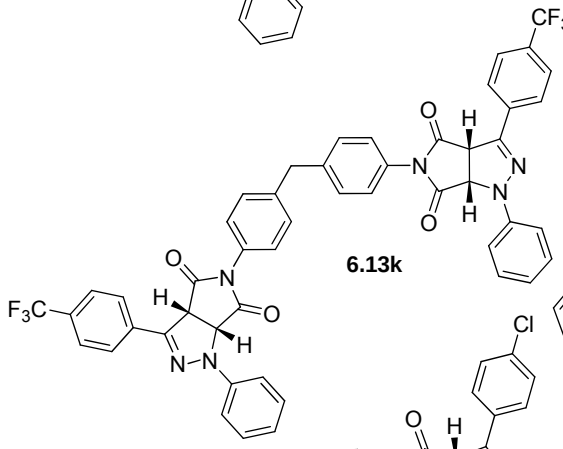

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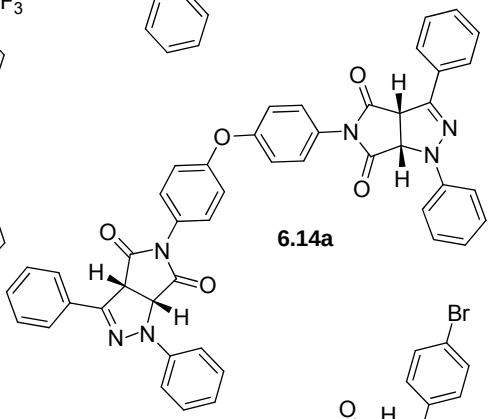

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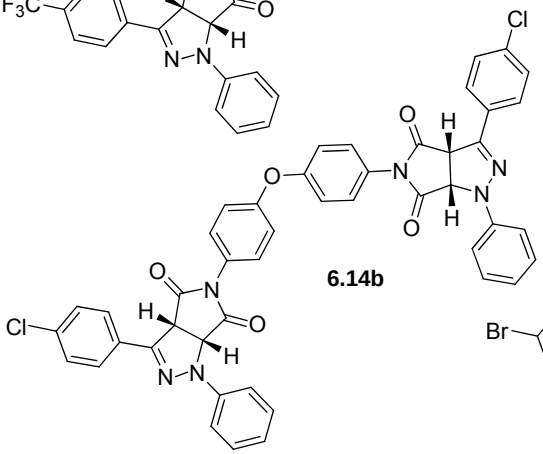

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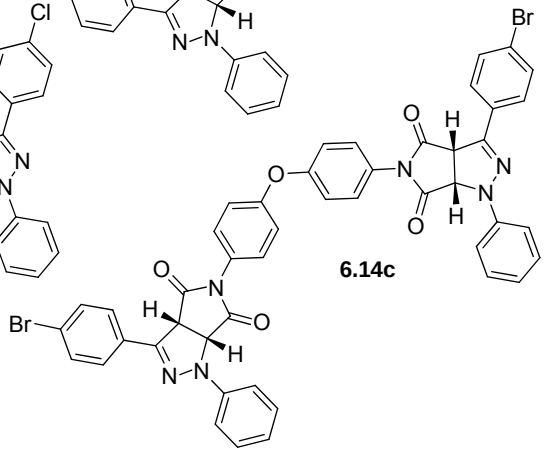

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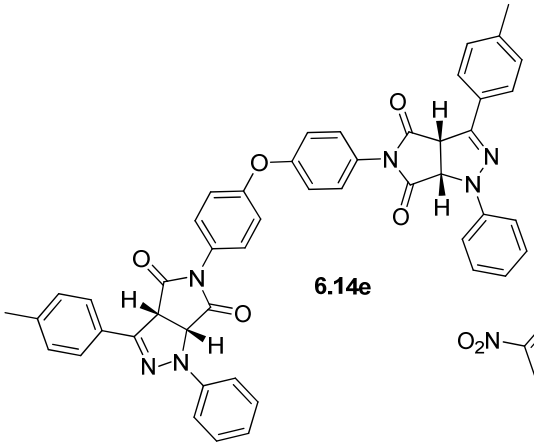

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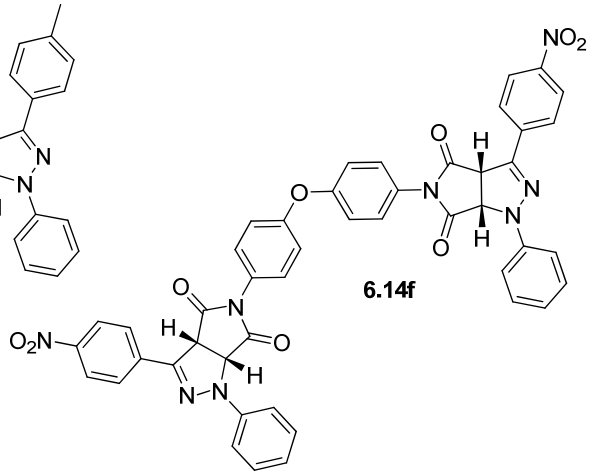

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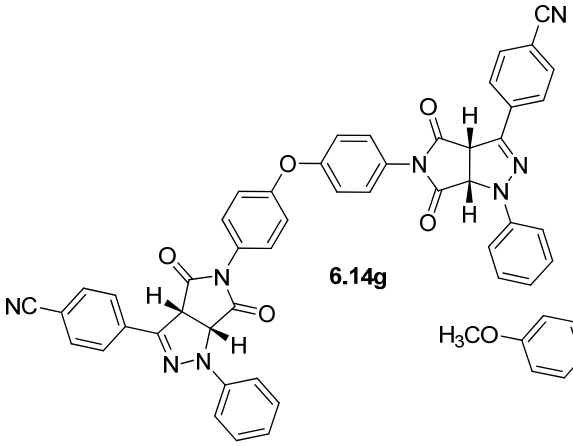

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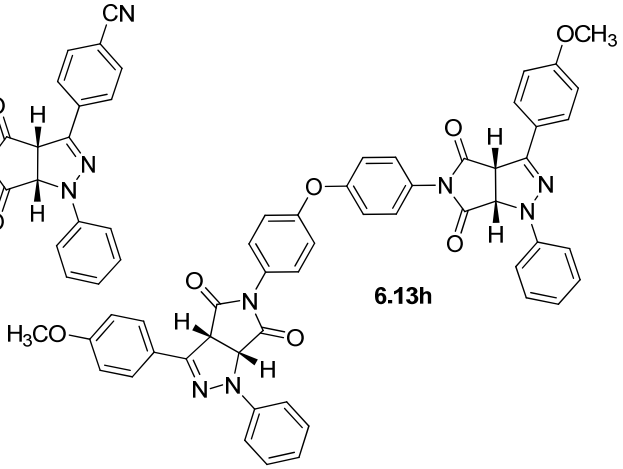

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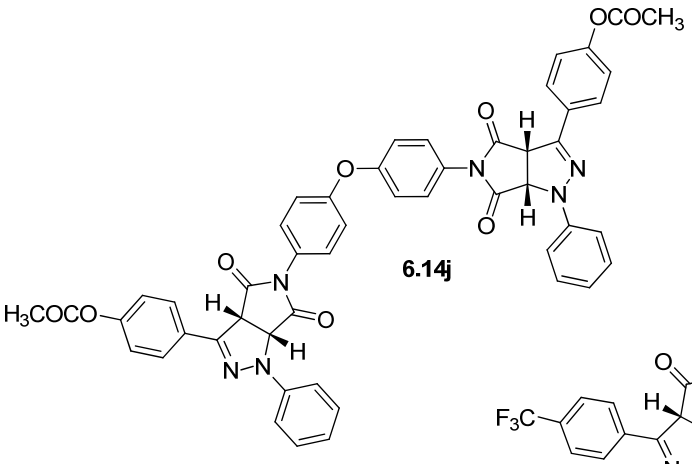

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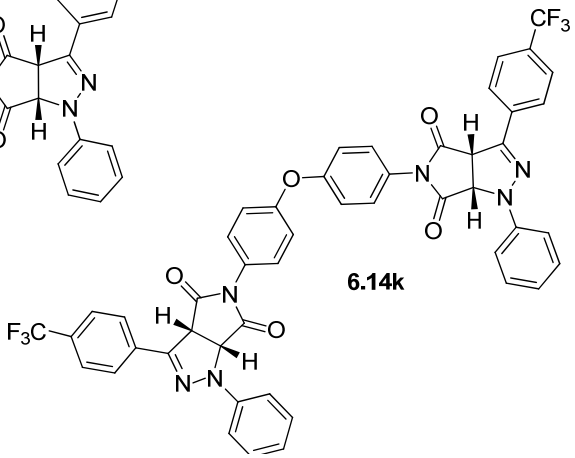

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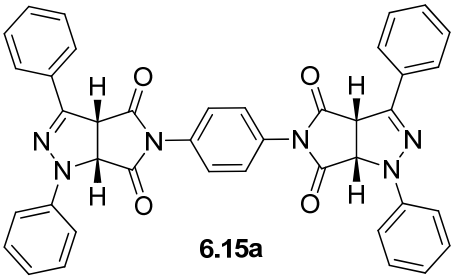

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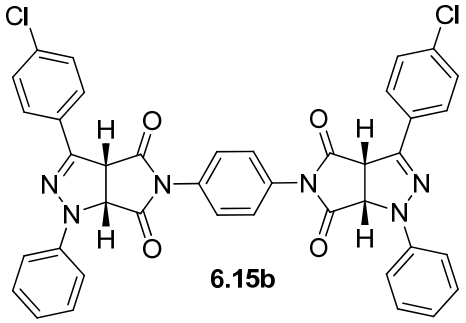

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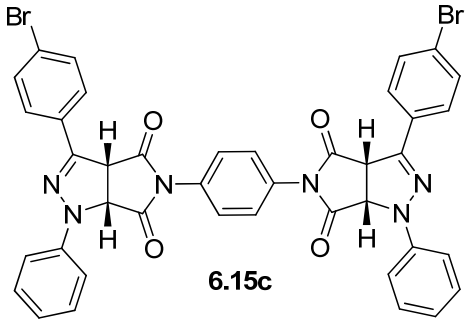

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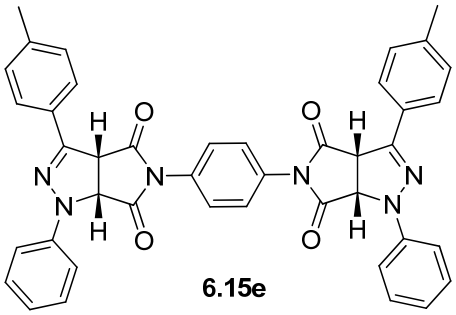

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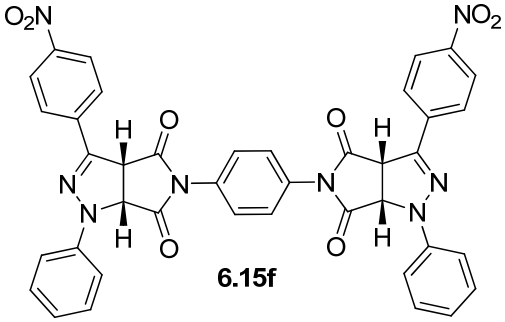

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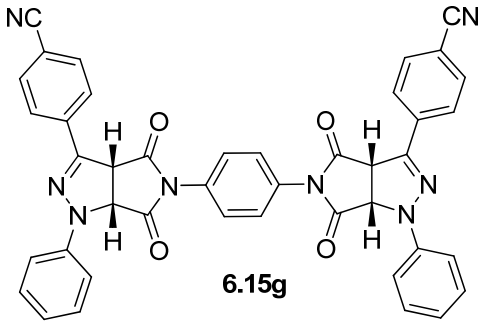

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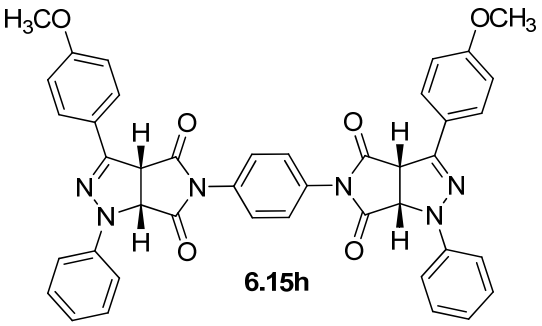

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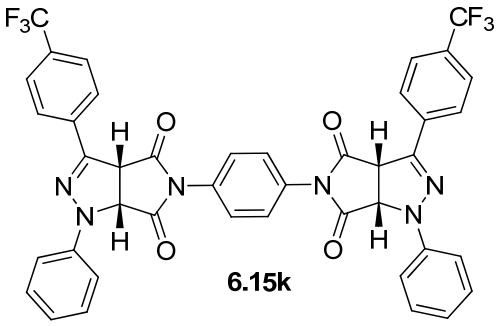

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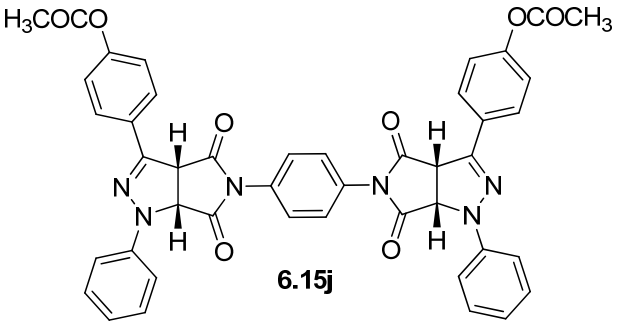

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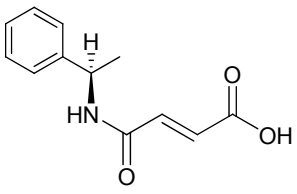

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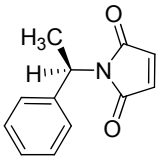

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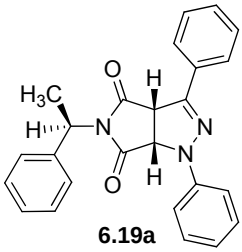

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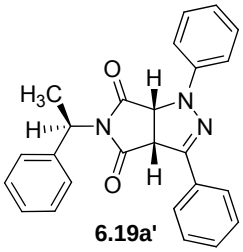

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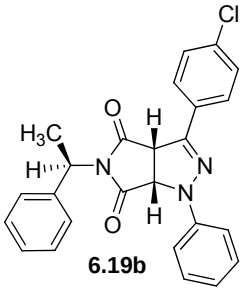

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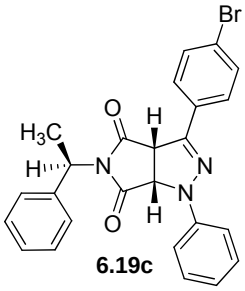

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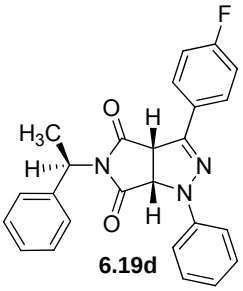

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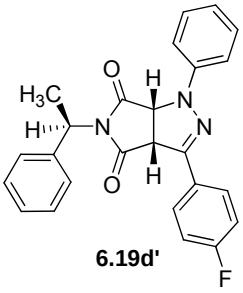

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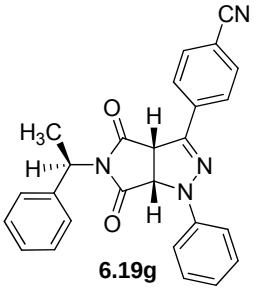

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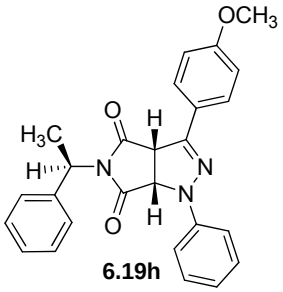

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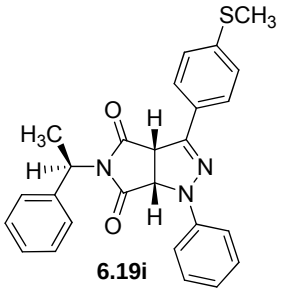

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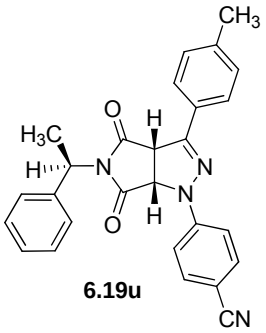

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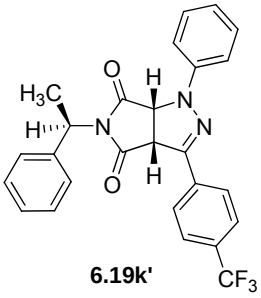

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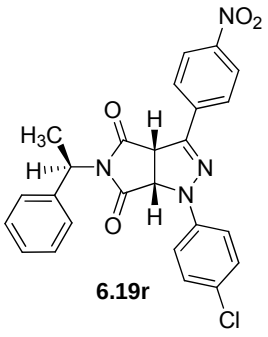

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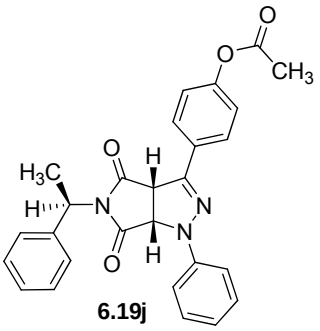

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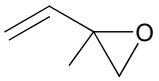

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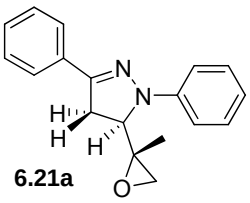

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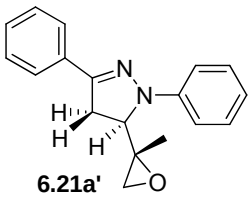

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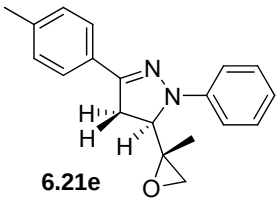

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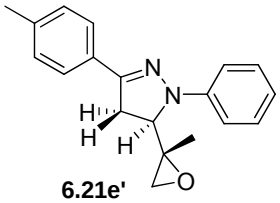

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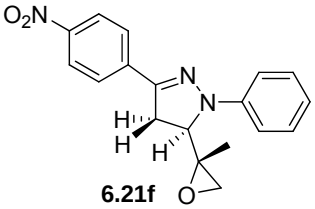

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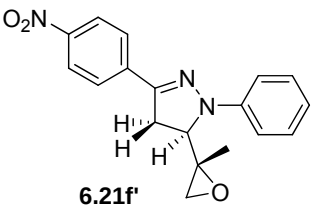

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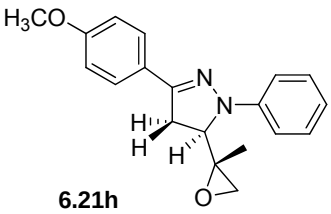

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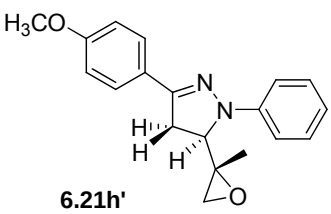

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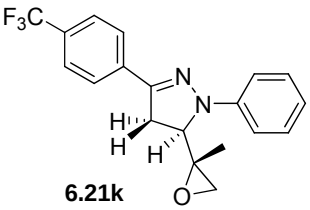

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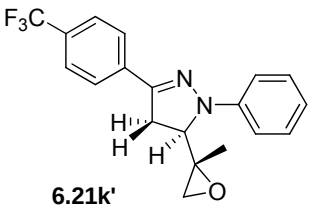

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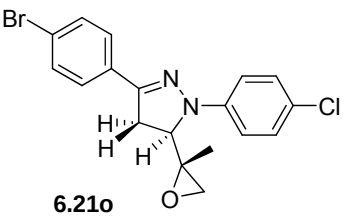

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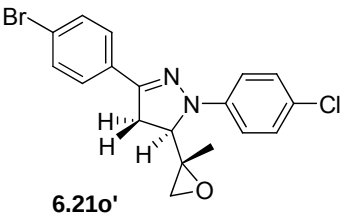

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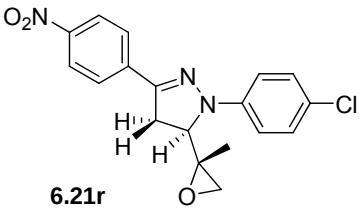

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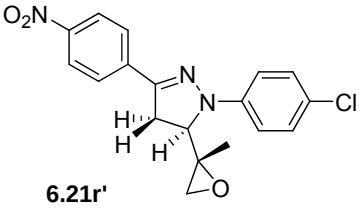

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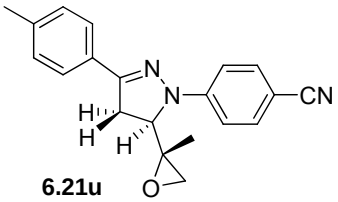

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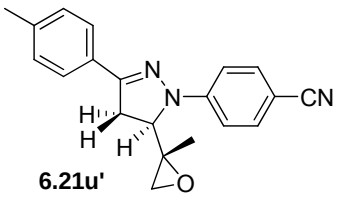

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ABBREVIATIONS

1,2-DCE	1,2-dichloroethane
1,3-DC	1,3-Dipolar cycloaddition
Ac_2O	Acetic anhydride
AcOH	Acetic acid
$APCI^+$	Atmospheric pressure chemical ionization (positive)
Ar	Aryl
b.p.	Boiling point
BBN	9-Borabicyclo(3.3.1)nonane
Boc	*tert*-Butoxycarbonyl
cat.	Catalyst
CDCl3	Deuterated chloroform
Chloranil	2,3,5,6-tetrachloro-*p*-benzoquinone
COSY	Correlation spectroscopy
d	Doublet (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
dd	Doublet of doublets (NMR)
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
de	Diastereomeric excess
DEPT	Distortionless enhancement by polarization transfer
DMAc	Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dq	Doublet of quartets (NMR)
dt	Doublet of triplets (NMR)
ED	Electron-donating

EI	Electron impact
eq.	Molar equivalents
ESI^-	Electrospray ionisation (negative)
ESI^+	Electrospray ionisation (positive)
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
EW	Electron-withdrawing
FMO	Frontier molecular orbital
HDMS	Bis(trimethylsilyl)amide
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
IR	Infrared spectroscopy
J	Coupling constant (NMR)
LUMO	Lowest unoccupied molecular orbital
m	Multiplet (NMR)
m.p.	Melting point
MALDI	Matrix assisted laser desorption/ionization
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
MS	Mass spectrometry
MW	Microwave radiation
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	Nuclear magnetic resonance
OAc	Acetate
OTf	Triflate
Ph	Phenyl

PPh_3	Triphenyl phosphine
ppm	Parts per million (NMR)
q	Quartet (NMR)
Rf	Retardation Factor
rt	Room temperature
s	Singlet (NMR)
t	Triplet (NMR)
td	Triplet of doublet
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TOF	Time of flight
tt	Triplet of triplets (NMR)
δ	Chemical shift (NMR)

CHAPTER 1

1. CYCLOADDITION REACTIONS

Cycloaddition reactions are one of the most important processes with both synthetic and mechanistic interest in organic chemistry. A concerted combination of two *π*-electron systems to form a ring of atoms having two new σ bonds and two fewer π bonds is called a “cycloaddition reaction” [1].

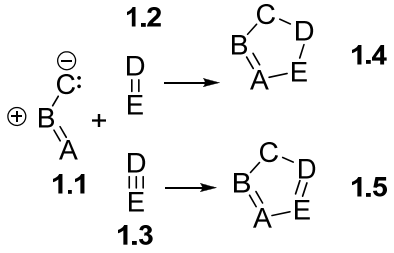
1.1. 1,3-Dipolar Cycloaddition Reactions

The concept of “*1,3-dipolar cycloaddition*” was first suggested in 1938 by Smith [2] but the general principles of the reaction was established by Huisgen and his co-workers [3] in 1960s. These reactions are one of the most important method for the construction of heterocyclic 5-membered rings in organic chemistry [1]. The term “dipolar” means the necessary formal charges in the structure of 4*π*-electron component. Generally, 2*π*-electron component is activated by being strained, highly polarizable.

1.2. The 1,3-Dipoles and Dipolarophiles

A *1,3-dipole*, **a-b-c**, such that atom **a** possesses an electron sextet, and that atom **c**, the negatively charged center, has an unshared electron pair. Combination of a 1,3-dipole with a multiple bond system **d-e**, *dipolarophile*, to form five-membered heterocycles (**1.4** and **1.5**) is referred as a *1,3-dipolar*

cycloaddition and dipolarophile may contain any double or triple bond (Scheme 1.1).



Scheme 1.1 General representation for a 1,3-dipolar cycloaddition reaction mechanism

The "*1,3-dipole*" is defined as a species which is represented by zwitterionic resonance structures (Figure 1.1) and consists of elements from main groups IV,V,VIA [4]. Four π-electrons are distributed over the system of three atoms. Two resonance canonical structures may be written. One is 1,2- charge separation(1,2-dipole), other is 1,3-charge separation (1,3-dipole). The 1,2-dipolar structure is the most representative Lewis structure for these compounds.

1,3-dipoles are generally divided into two categories by the incorporation of an additional *π* bond. This additional π bond makes 1,3-dipoles of propargyl-allenyl type linear while those of the allyl type are bent [5].

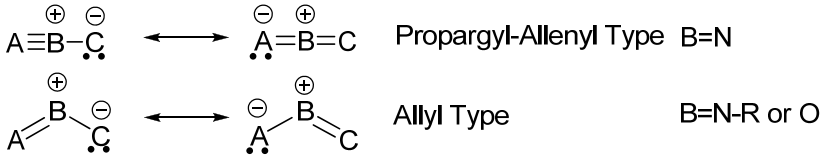


Figure 1.1 Types of 1,3-dipoles

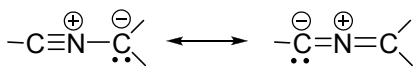
In the propargyl-allenyl type, **b** atom must be nitrogen. No other elements has an extra pair of electrons available while remaining in the triply bonded

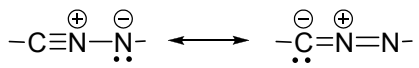
neutral state. In allyl type, **b** atom can be occupied by either a nitrogen or an oxygen atom.

If one restricts the atoms a, b, and c to carbon, nitrogen, and oxygen, the 1,3-dipoles representatives of all but two of these classes, many of them as short lived in situ intermediates, have been shown to undergo 1,3-dipolar cycloaddition. These dipoles were classified by Huisgen (Table 1.1) [6].

Table 1.1 Classification of 1,3-Dipoles consisting C, N and O Centers

A.Propargyl-Allenyl Type


Nitrile Ylides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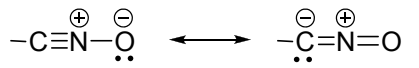
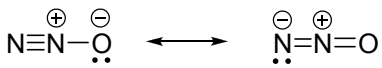
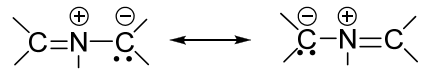
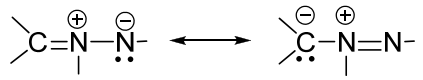
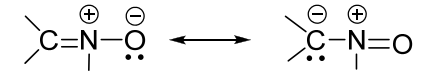

Nitrile Oxides

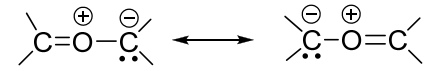

Nitrous Oxide

B. Allyl Type


Azomethine Ylides


Azomethine Imines


Nitrones


Carbonyl Ylides

The dipolarophile in a 1,3-dipolar cycloaddition is a reactive alkene moiety containing 2π-electrons. Thus, depending on type of dipole, α,β-unsaturated aldehydes, ketones, and esters, allylic alcohols, allylic halides, vinylic ethers and alkynes are examples of dipolarophiles that react readily. It must be

noted, however, that other 2π-moieties such as carbonyls and imines also can undergo cycloaddition with dipoles. Olefinic and acetylenic dipolarophiles are more reactive when they bear conjugating groups. Heterodipolarophiles (**1.9** and **1.10**) are generally less reactive than the corresponding C-C dipolarophiles.

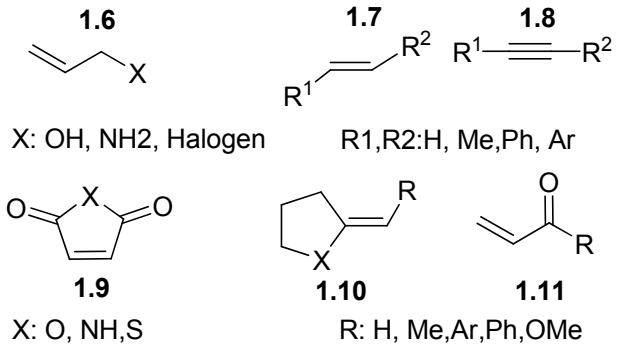
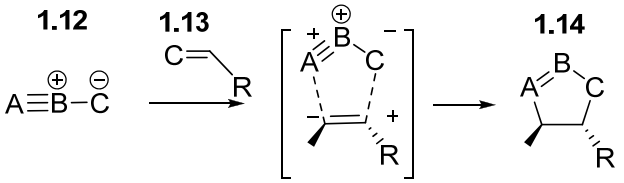


Figure 1.2 Examples of dipolarophiles

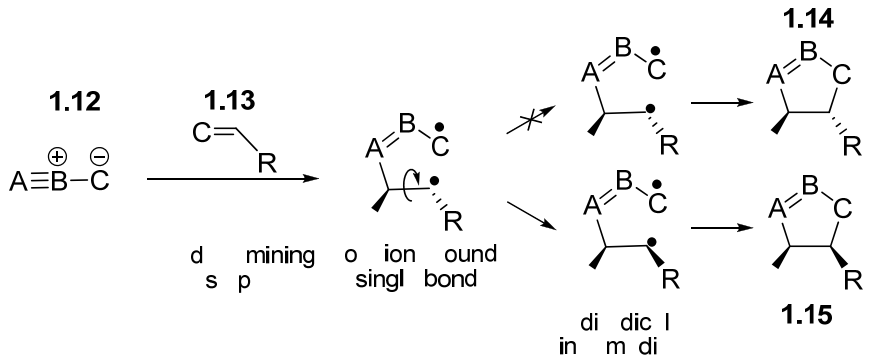
1.3. Reaction Mechanisms of 1,3-Dipolar Cycloaddition

The mechanism of 1,3-dipolar cycloaddition reactions has been discussed early 1960s by Huisgen [7] and Firestone [8]. However, concerted mechanism suggested by Huisgen was supported by many experimental results and generally accepted. It was an orbital symmetry-allowed (4π+2π) cycloaddition where the 1,3-dipole with its allyl anion type MO functions as 4π-reactant and the dipolarophile as 2π-reactant and net effect is retention of configuration in the course of reaction. This can be seen in Scheme 1.2 in the reaction of hypothetical dipole **1.12** with ethylenic dipolarophile **1.13** giving exclusively *trans*-product **1.14**.



Scheme 1.2 1,3-Dipolar cycloaddition in concerted manner

According to Firestone's argument, in place of a one-step pathway with a single transition state, two-step reaction with a discrete intermediate, a spin-paired diradical, with a rate-determining first step is proposed. In two-step mechanism, only one bond is partially formed in transition state and followed by rotation around single bond. Formation of *trans*- **1.14** or *cis*- **1.15** products depend on how fast the rotation occurred around single bond. This occurrence can be seen in Scheme 1.3 below.



Scheme 1.3 1,3-Dipolar cycloaddition in diradicalic manner

The transition state of the concerted 1,3-dipolar cycloaddition reaction is controlled by the frontier molecular orbitals (FMO) of substrates [9]. The LUMO of dipole interacts with HOMO of dipolarophile or HOMO of dipole interacts with LUMO of dipolarophile [10]. According to the relative dispositions of the HOMOs and LUMOs of the 1,3-dipole and the dipolarophile, 1,3-dipolar cycloaddition reactions are classified into three

categories [11] and the reactivity increases as the HOMO-LUMO energy distance decreases.

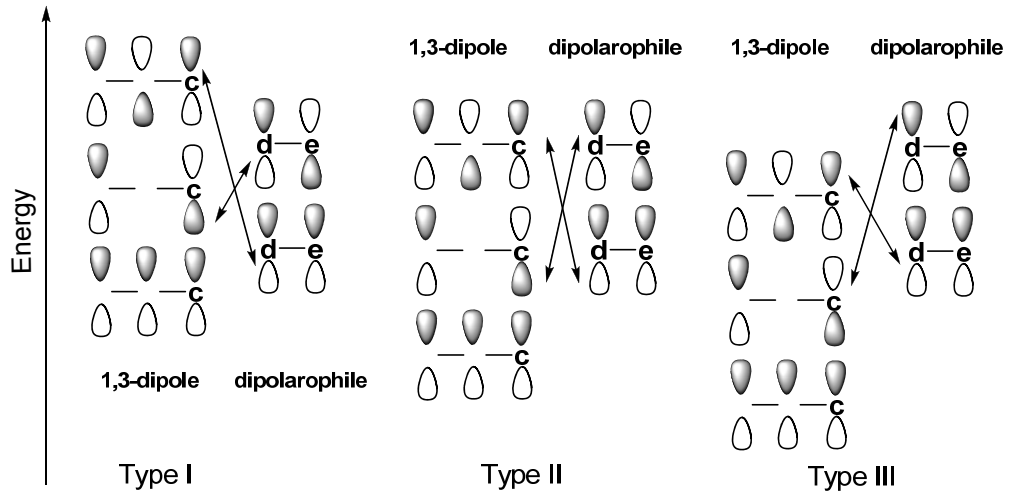


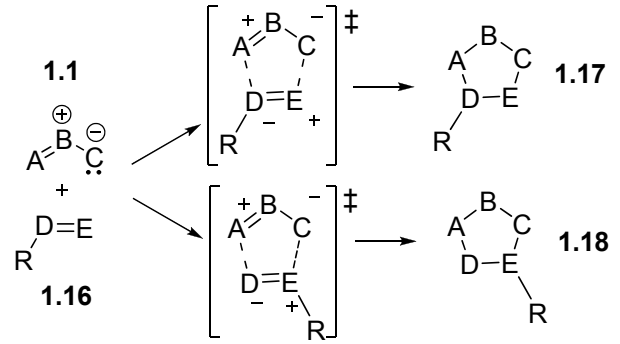
Figure 1.3 Possible interactions between 1,3-dipole and dipolarophile

The dominant FMO interactions in Type I reactions is that of HOMO (dipole)-LUMO(dipolarophile). In Type II reactions, FMO energies of both dipoles and dipolarophile are similar, so both HOMO-LUMO interactions of dipoles and dipolarophiles are important. In Type III reactions, HOMO (dipolarophile)-LUMO(dipole) interactions are dominant. According to Sustmann classification [12]**,** typical examples for Type I reactions are azomethines and carbonyl ylides, for Type II reactions are nitrones, nitrilimines, azides, and for Type III reactions are nitrile oxides which have relatively low LUMO energies -11 to -10 eV. Electron-donating and withdrawing substituents both on dipoles and dipolarophiles can change the relative FMO energies and reaction types [12].

1.3.1. Selectivity in 1,3-dipolar cycloaddition

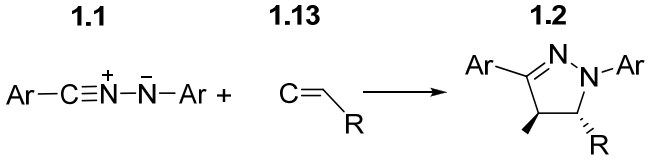
HOMO(dipole)-LUMO(dipolarophile) or HOMO(dipolarophile)-LUMO (dipole) interactions are important to determine the reactivity and regioselectivity of 1,3-dipolar cycloaddition reactions.

Three types of selectivity is generally considered in 1,3-dipolar cycloaddition chemistry and these are regioselectivity, diastereoselectivity and enantioselectivity. Both steric and electronic effects control the regioselectivity of the reaction [13]. When hypotetical 1,3-dipole **1.1** is reacted with an unsymmetrical dipolarophile **1.16**, two types of orientations are possible and two regioisomers (**1.17** and **1.18**) form. In a cycloaddition reaction of electron-rich or electron-neutral alkene, the reaction is primarily controlled by LUMO(dipole)-HOMO(dipolarophile) and 5-substituted regioisomer forms. LUMO(dipole) has the largest coefficient at the C atom and HOMO(dipolarophile) has the largest coefficient at the terminal C atom and this is supported by steric factor. On the other hand, cycloaddition reaction of electron-poor terminal alkenes is primarily controlled by LUMO(dipolarophile)-HOMO(dipole) and 4-substituted regioisomer forms. LUMO(dipolarophile) has the largest coefficient at the C atom and HOMO(dipole) has the largest coefficient at the terminal C atom but steric factor is not effective and the mixture of regioisomers is often obtained.



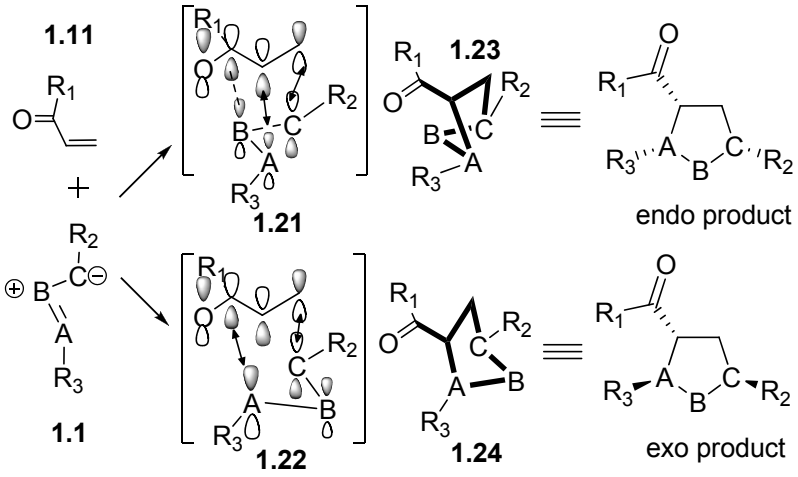
Scheme 1.4 Two possible regioisomers forming in 1,3-dipolar cycloaddition

In the course of addition to terminal alkenes, the sterically more crowded functionality of 1,3-dipole tends to add to the terminal C atom of alkene, giving rise the 5-substituted regioisomer. However, steric effect may overruled by strong electronic effects. Nitrilimines readily react with unsymmetrical electron-poor dipolarophiles (i.e. methyl acrylate, styrene) regioselectively to produce 5-substituted pyrazolines and this can be seen in Scheme 1.5 wherein diarylnitrilimine **1.19** reacts with unsymmetrical alkene **1.13** to give 5-substituted regioisomer **1.20**.



Scheme 1.5 Formation of 5-substituted regioisomer with nitrilimine dipole

Especially, in the reactions allyl anionic type dipoles with terminal alkenes, 1,3-dipole approaches alkene in two different modes giving rise to two diastereomers, *endo* product **1.23** and *exo* product **1.24** (Scheme 1.6).



Scheme 1.6 Diastereoselective approach in 1,3-dipolar cycloaddition reactions

Last type of selectivity in 1,3-dipolar cycloaddition is enantioselectivity, using of a chiral catalyst in the course of reaction controls the enantioselectivity of the reaction where different ratio of enantiomers or only one single enantiomer might be obtained.

CHAPTER 2

2. BACKGROUND OF NITRILIMINES AND SYNTHESIS OF PYRAZOLE AND PYRAZOLINES

2.1. Hydrazonyl Halides and Nitrilimines

The compounds “hydrazonyl or hydrazidoyl halides” **2.1** are solid compounds which contain a reactive halo group. Halo group participates readily in nucleophilic and elimination of hydrogen halide occurs prior to substitution. The elimination of hydrogen halide affords the highly reactive nitrilimines (**2.2-2.6**), which Huisgen and his co-workers have utilized in a wide variety of 1,3-dipolar cycloaddition reactions [4].

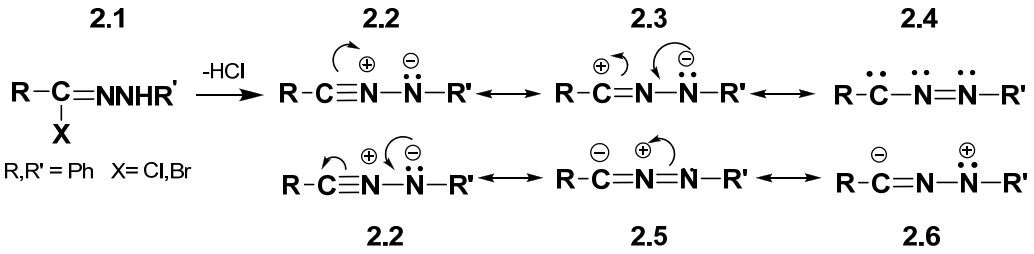
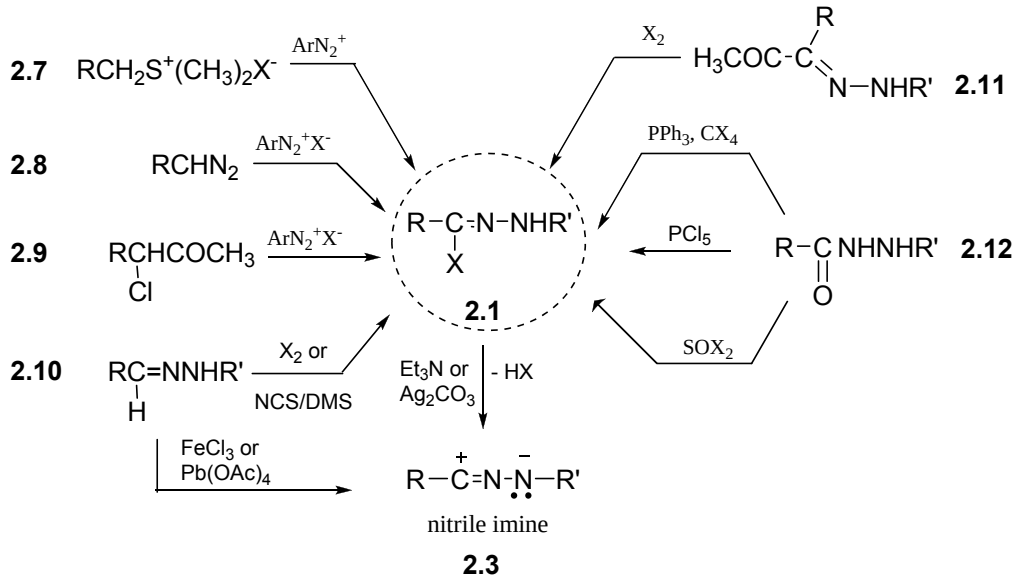


Figure 2. 1 The structure of hydrazonyl halides and octet zwitterionic structures of nitrilimines

Basically, a nitrilimine is a flexible system of three atoms over which four *π*-electrons are distributed (Figure 2.1) and five possible structures can be written but theoretical calculations indicated that all-octet-structure **2.2** is the most stable contributor to the resonance hybrid.

2.2. Synthesis of Hydrazonyl Halides as precursors of nitrilimines

N-Phenylbenzhydrazonyl chloride was first synthesized by v. Pechmann in 1894 [14]. Several different methods have been utilized in the past to synthesize hydrazonyl halides [15, 16, 17, 18, 19, 20]. Hydrazonyl chlorides have been used by Huisgen [21] and his students utilized this class of compounds to generate the highly reactive nitrilimines and synthesize a variety of pyrazole derivatives.



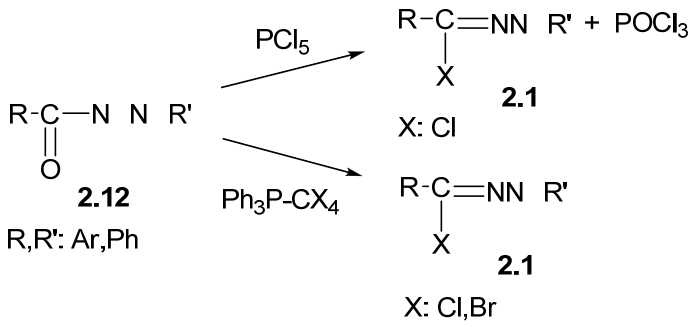
Scheme 2.1 The methods for the preparation hydrazonyl halides

The characteristic spectral feature of the hydrazidoyl halides is their C=N double bond absorption in the infrared, which appears at 1580-1610 cm^{-1}.

2.2.1. From Carboxylic acid hydrazides

The reaction of arylcarboxylic acid hydrazides **2.12** with phosphorus pentachloride is the classical method of synthesis of hydrazonyl chlorides

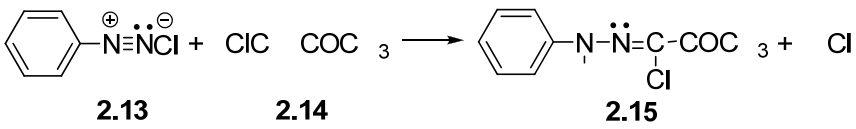
[14] (Scheme 2.2). Lately, a new method has been used by Wolkoff [20] by the use of aryl carboxylic acid hydrazides with triphenylphosphine-carbon tetrahalide system (Scheme 2.2).



Scheme 2.2 Conversion acid hydrazides into *N*-phenylbenzhydrazonyl chloride by PCl_5 and triphenylphosphine-carbon tetrahalide system.

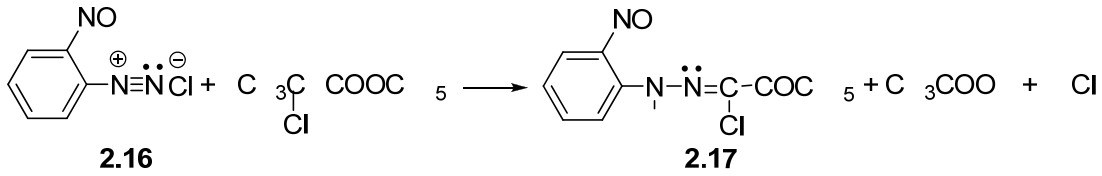
2.2.2. From Diazonium Halides

The coupling of diazonium halides **2.13** with suitable halogenated activated methylene groups is an excellent method of synthesis of acyl and aroyl hydrazonyl halides. The method has been used by Favrel [22] and by Dieckmann and Platz [23] to synthesize the acetyl derivatives **2.15**.



Scheme 2.3 Reaction of methyl chloroacetate with diazonium halide

Similarly, carboxyl and carbalkoxy hydrazonyl chlorides are readily synthesized by this method. For example, coupling of 2-nitrobenzdiazonium chloride **2.16** with ethyl chloroacetoacetate affords the carboxyhydrazonyl chloride **2.17**.

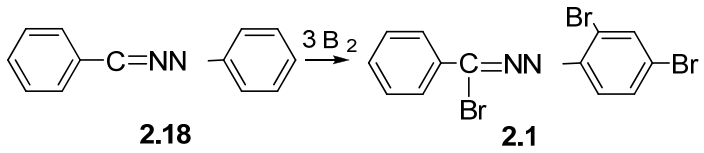


2.16 **2.17**

Scheme 2.4 Formation of carboxyhydrazidoyl chloride by coupling

2.2.3. By Halogenation of Hydrazones

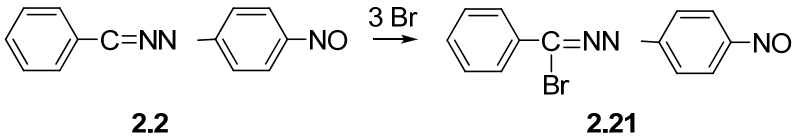
The halogenation of the aryl aldehyde hydrazones is also an excellent way for synthesis of hydrazonyl halides. However, halogenation of the ring attached to nitrogen cannot be avoided. Reaction of benzaldehyde phenylhydrazone **2.18** with bromine in glacial acetic acid yields benz-2,4-dibromophenylhydrazonylbromide **2.19** [24].



2.18 **2.1**

Scheme 2.5 The bromination of benzaldehyde phenylhydrazone

If the phenyl ring attached to nitrogen is deactivated, bromination to the hydrazidoyl bromides **2.21** without ring bromination can be achieved [25].

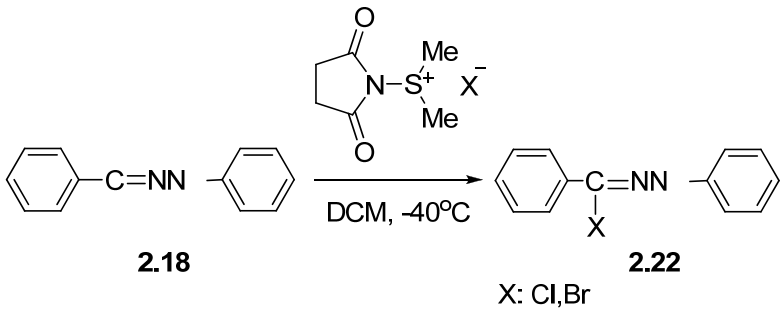


2.2 **2.21**

Scheme 2.6 Synthesis of hydrazidoyl halides from hydrazones

Benzaldehyde phenylhydrazone **2.18** is easily halogenated by the use of *N*-Chlorosuccinimide/*N*-Bromosuccinimide-dimethyl sulfide complex, the Corey-Kim reagent [26], a very reactive species and stable at low temperatures.

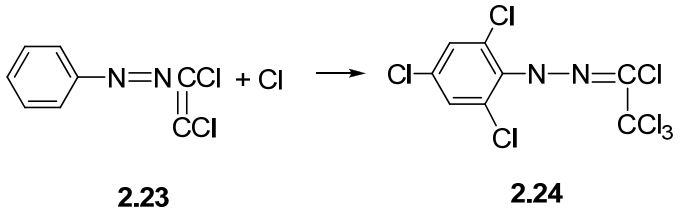
Treatment of this complex with arylhydrazones at -40°C resulted the formation of *C*,*N*-diphenylhydrazonyl halides **2.22** in good yields [21].



Scheme 2.7 Preparation of hydrazonyl halides using NCS/DMS complex

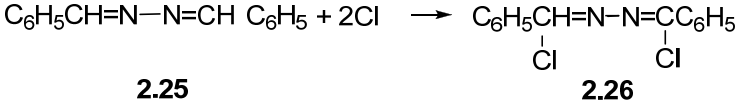
2.2.4. By Halogenation of Azo Compounds and Azines

In the reaction of chloral with phenylhydrazine, the azoethylene compound **2.23** is obtained and further chlorination yields the corresponding hydrazonyl chloride **2.24** [27].



Scheme 2.8 Halogenation of azo compounds

The chlorination of azines gives the corresponding bis-hydrazonyl chlorides **2.26** in good yields [28].



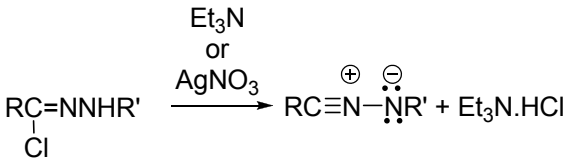
Scheme 2.9 The chlorination of benzalazine with chlorine

2.3. Generation of nitrilimines

The ease of generation of nitrilimines from different precursors coupled with the highly regio and stereoselective nature of their cycloaddition reactions has resulted in extensive use as key synthons in many heterocyclic syntheses [29]. Due to their instability, the reactions of nitrilimines **2.2** are always carried out by their in situ generation from suitable precursors.

2.3.1. From Hydrazonyl Halides

The dehydrochlorination of hydrazonyl chlorides **2.1** is usually affected by the treatment of the latter with the base such as triethylamine in an inert solvent [15, 21, 30, 31]. Dehydrohalogenation of **2.1** is also affected by silver nitrate [32, 33, 34].

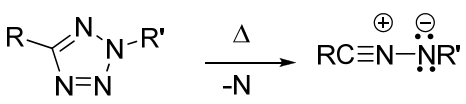


2.1 **2.2**

Scheme 2.10 Generation of nitrilimines from hydrazonyl chloride

2.3.2. From 2,5-disubstituted tetrazoles

The precursors of 2,5-disubstituted tetrazoles **2.27** are easily available but they all involve the preparation and handling of some hazardous azides. Generation of nitrimine **2.2** is performed by either photolysis or thermolysis [35].

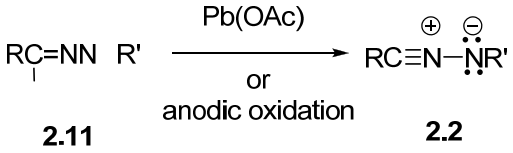


2.27 **2.2**

Scheme 2.11 Generation of nitrilimines from tetrazoles

2.3.3. From arylhydrazones

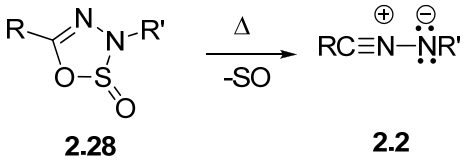
Aldehyde arylhydrazones **2.11** are also used as nitrilimine precursors. Generation is performed either chemically with lead tetraacetate [36] or electrically by anodic oxidation [37].



Scheme 2.12 Generation of nitrilimine from aldehyde arylhydrazones

2.3.4. By thermolysis of 3*H*-1,2,3,4-Oxathiadiazole S-oxides

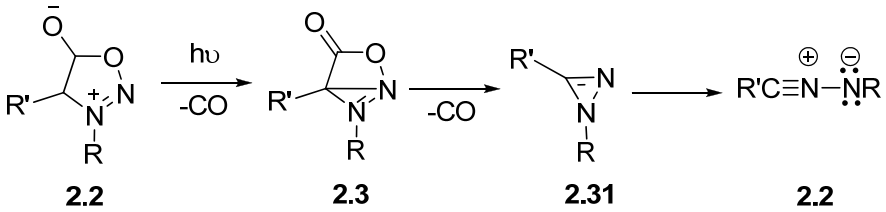
Thermolysis of 3*H*-1,2,3,4-oxathiadiazole *S*-oxides **2.28** in toluene results in the elimination of sulfur dioxide and formation of nitrilimine [38].



Scheme 2.13 Generation of nitrilimine from 3*H*-1,2,3,4-oxathiadiazole S-oxides

2.3.5. From 3,4-Substituted Sydnones

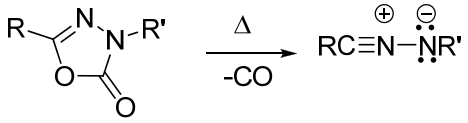
Photolysis of 3,4-substituted sydnones **2.29** leads to corresponding nitrilimines [39].



Scheme 2.14 Generation of nitrilimine by photolysis of 3,4-substituted sydnones

2.3.6. From Δ^2-1,3,4-Oxadiazolin-5-one

Δ^2-1,3,4-Oxadiazolin-5-one affords corresponding nitrilimines by flash vacuum thermolysis [40].

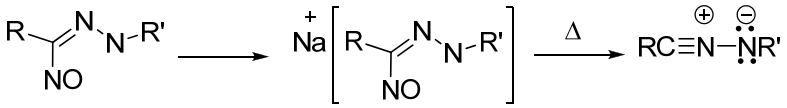


2.32 **2.2**

Scheme 2.15 Generation of nitrilimine by Flash vacuum thermolysis

2.3.7. From *α*-Nitrohydrazones

α-Nitrohydrazones **2.33** are prepared by either direct nitration of corresponding aldehyde arylhydrazones [41] or azo coupling or corresponding nitroalkanes [42] and nitrilimines are generated by thermolysis of sodium salt of *α*-nitrohydrazones [43].

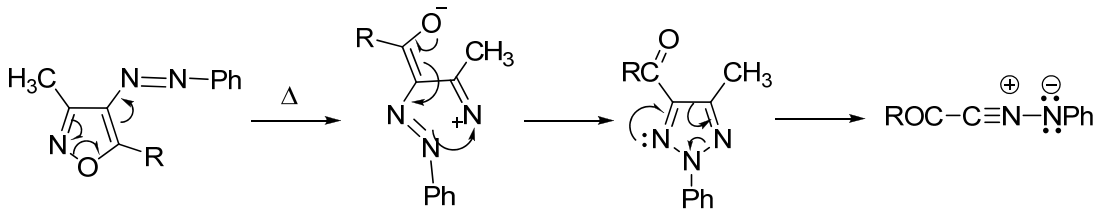


2.33 **2.2**

Scheme 2.16 Generation of nitrilimine from *α*-Nitrohydrazones

2.3.8. By thermal decomposition of 5-aryl-4-arylazoisoxazoles

The thermal decomposition of 5-aryl-4-arylazoisoxazoles **2.34** leads to two competitive reactions. The cleavage of N-O bond give a triazole derivative *via* Wittig-rearrangement, where the 1,3-dipolar cycloreversion gives nitrilimine [44].



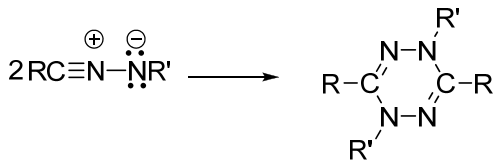
2.34 **2.35** **2.36**

Scheme 2.17 Generation of nitrimines by 1,3-dipolar cycloreversion

2.4. Reactions of Nitrilimines

2.4.1. Addition and Elimination Reactions of Nitrilimines

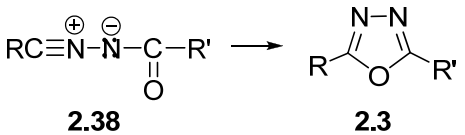
In the absence of a substrate the generated dipole dimerizes to yield the 1,4-dihydro-1,2,4,5- tetrazine derivative [45].



2.2 **2.37**

Scheme 2.18 Dimerization of nitrilimines

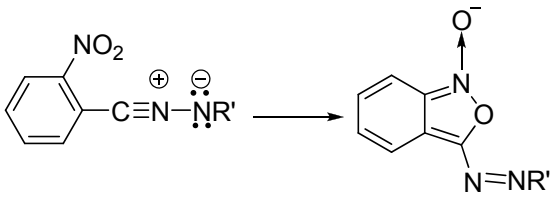
When *N*-acylnitrilimines **2.38** are generated, cyclization occurs with formation of 1,3,4-oxadiazole **2.39** occurs [46].



2.38 **2.3**

Scheme 2.19 1,3,4-oxadiazoles from *N*-acylnitrilimines

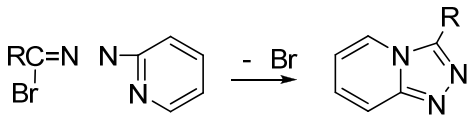
The cyclization of nitrilimines having *o*-nitro group attached on the phenyl ring **2.39** was already observed by Chattaway and Walker [24].



2.39 **2.40**

Scheme 2.20 Intramolecular cyclization of *o*-nitroarylnitrilimines

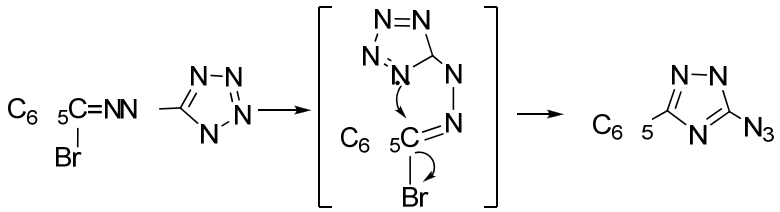
The heterocyclic hydrazonyl bromide also undergoes ready cyclization to yield bicyclic heterocycles [47].



2.41 **2.42**

Scheme 2.21 Formation of bicyclic heterocycles

Similarly, the heterocyclic-substituted hydrazonyl bromide **2.43** eliminates bromide ion in 95% ethanol at 25ºC. This cyclization occurs *via* the intermediate nitrilimine **2.44** and the major product is 5-azido-3-phenyl-1,2,4-triazole **2.45**, resulting from tetrazoyl anchimerism *via* a cyclic transition state [48].

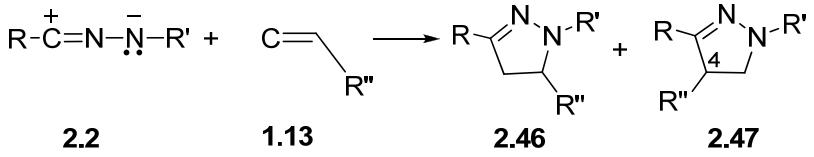


2.43 **2.44** **2.45**

Scheme 2.22 Conversion of heterocyclic substituted hydrazonyl bromide into 1,2,4-triazoles

2.4.2. 1,3-Dipolar Cycloaddition Reactions of Nitrilimines and Synthesis of Pyrazole and Pyrazoline derivatives

The 1,3-dipolar cycloaddition reactions of nitrilimines are generally [π_s^4+ π_s^2] thermally allowed pericyclic reactions. Use of a dipolarophile having nonidentical terminal *π*-centers such as monosubstituted ethylenes in such reactions with nitrilimines can lead theoretically to two orientationally different cycloadducts (referred to as regioisomers), namely the 5- and 4-substituted 2-pyrazolines.

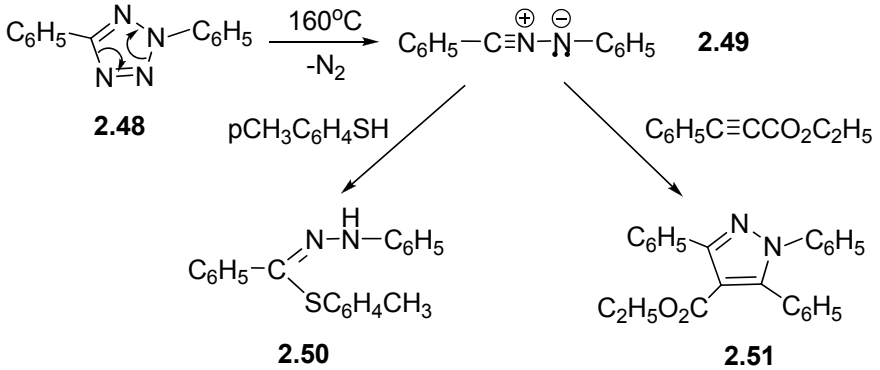


2.2 **1.13** **2.46** **2.47**

Scheme 2.23 Formation of 5- and 4-substituted 2-pyrazolines

2.4.2.1. By the use of different olefinic and acetylenic dipolarophiles

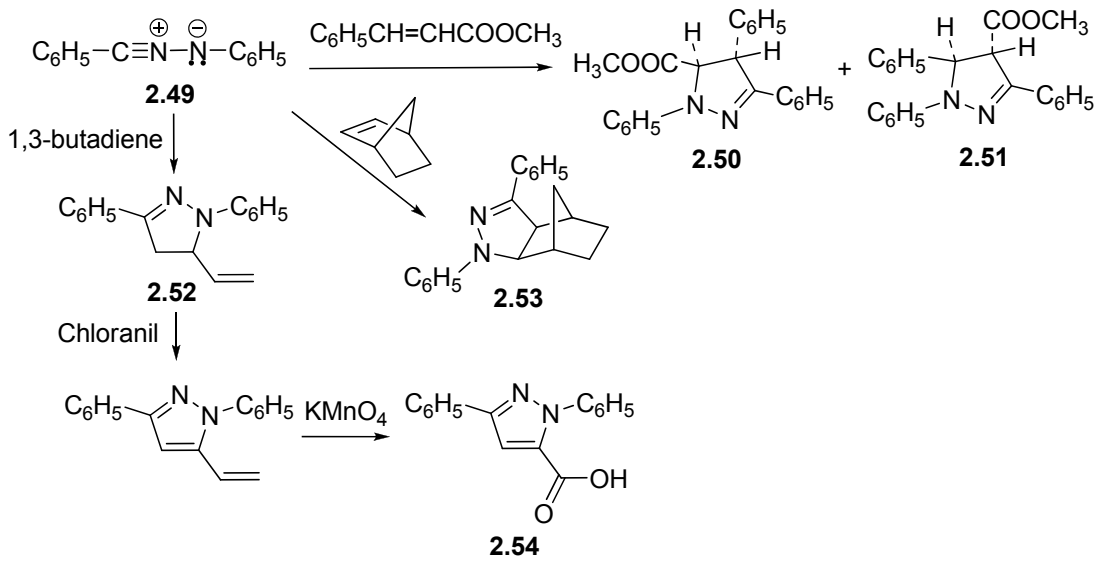
After obtaining diphenylnitrilimines **2.49** by thermolysis of 2,5-diphenyl tetrazole **2.48**, the [*α*-(*p*-tolylmercapto)benzal]phenylhydrazine **2.50** is formed by the addition of the thiol and ethyl 1,3,5-triphenyl-1*H*-pyrazole-4-carboxylate **2.51** is obtained with ethyl 3-phenylpropiolate in 84% yield [4].



2.50 **2.51**

Scheme 2.24 Decomposition of the tetrazole and formation of new cycloadducts

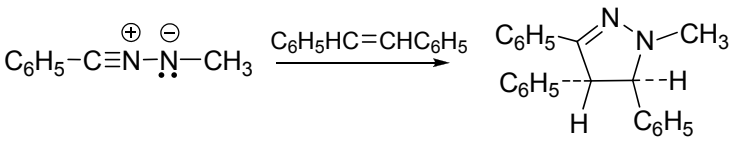
The opening of the aromatic tetrazole ring at high temperatures is a serious disadvantage and restrict the choice of dipolarophile. If the nitrilimines are generated in the presence of a nuchleophilic olefin, the corresponding 1,3-dipolar cycloaddition products are isolated usually in good yields [49].



Scheme 2.25 Reaction of nitrilimines with nucleophilic olefins and norbornene

In analogous manner, addition of nitrilimines **2.49** to methyl 3-phenylacrylate, a mixture of pyrazoline-4 and 5-carboxylates **2.50, 2.51** is obtained and to norbornene affords a bridged *exo*-Δ^2-pyrazoline **2.53** [30]. Reaction with 1,3-butadiene gives 1,3-diphenyl-5-vinyl-Δ^2-pyrazoline **2.52** and oxidation of latter with chloranil and $KMnO_4$ gives 1,3-diphenyl pyrazole-5-carboxylic acid **2.54**.

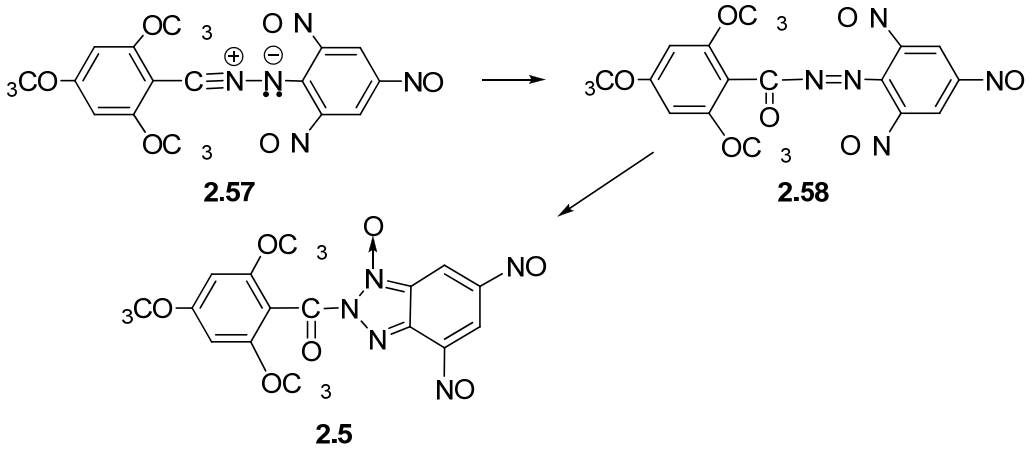
The cycloaddition of *C*-phenyl-*N*-methyl nitrilimine **2.55** onto *trans*-stilbene is accomplished smoothly in 74% yield by Huisgen et.al.



2.55 **2.56**

Scheme 2.26 Formation of 1-methyl-3,4,5-triphenyl-4,5-dihydropyrazoline **2.56**

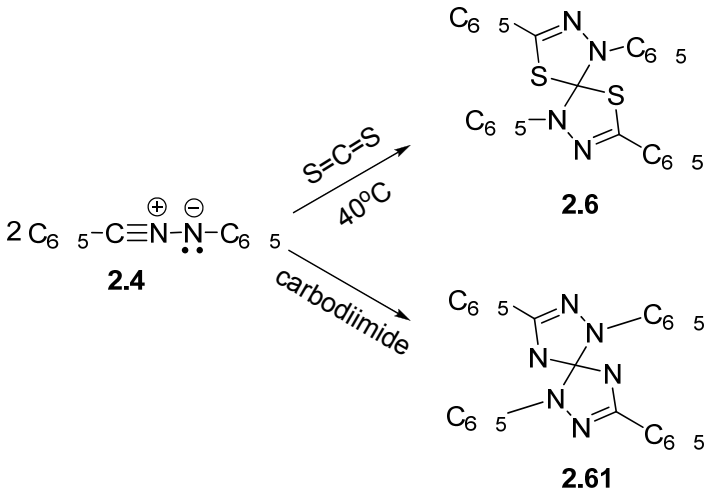
C-2,4,6-trimethoxy-*N*-2,4,6-trinitroaryl nitrilimine, generated from the corresponding hydrazonyl chloride and triethylamine, undergoes an intramolecular redox reaction to yield benztriazole derivative [32].



2.57 **2.58** **2.5**

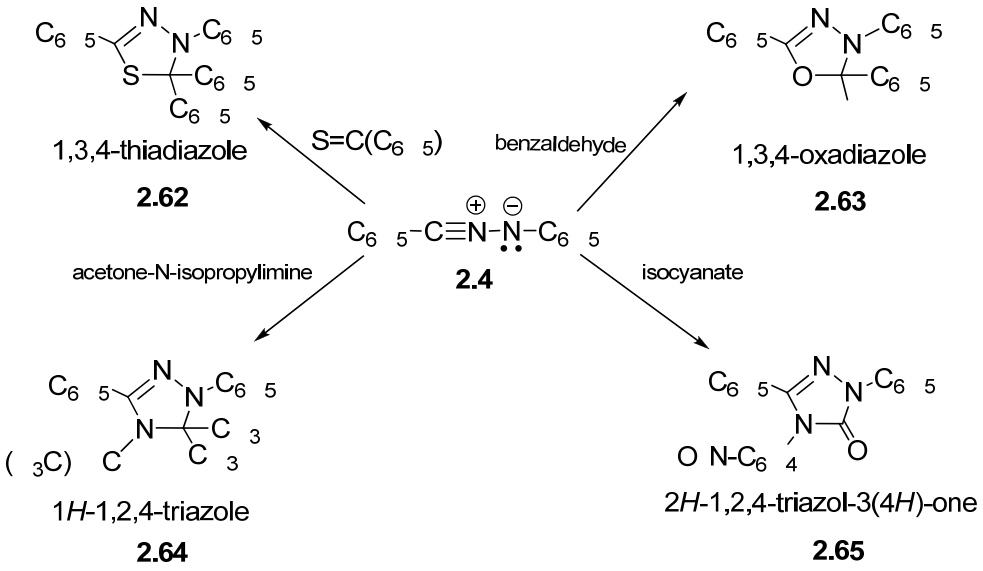
Scheme 2.27 Intramolecular redox reaction of nitrilimines

In addition to activated olefins, other double-bond substrates, such as carbonyl and thiocarbonyl compounds and azomethines have been used. Heterocumulenes such as carbon sulfide, isocyanates, isothiocyanates, carbodiimides and *N*-sulfinylamines have been added to nitrilimines [4].



Scheme 2.28 Formation of spiro bis-adduct with carbon disulfide and carbodiimide

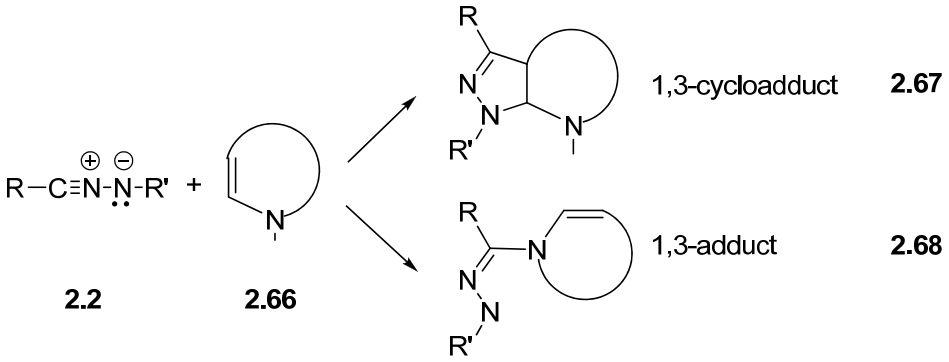
The C=O group may act as dipolarophile, e.g. benzaldehyde always yields 2,4,5- triphenyl-1,3,4-oxadiazoline **2.63**. As a dipolarophile, the C=S double bond has unusually great activity, but tetraphenyl derivative of 1,3,4-thiadiazoline **2.62** was formed [30]. Aliphatic and aromatic azomethines (Shiff bases) are able to add nitrilimines. Although acetone itself fails to add dipenhylnitrilimine, acetone-*N*-isopropylimine gives the cycloadduct **2.64** in 84% yield. The same orientation is observed in the addition of diphenylnitrilimine to isocyanates.



Scheme 2.29 Formation of several heterocycles using different dipolarophiles

2.4.2.2. By the use of different heterocyclic dipolarophiles

In general, nitrilimines react with heterocyclic dipolarophiles with two modes, namely the 1,3-dipolar cycloaddition and the 1,3-electrophilic addition, as indicated below.

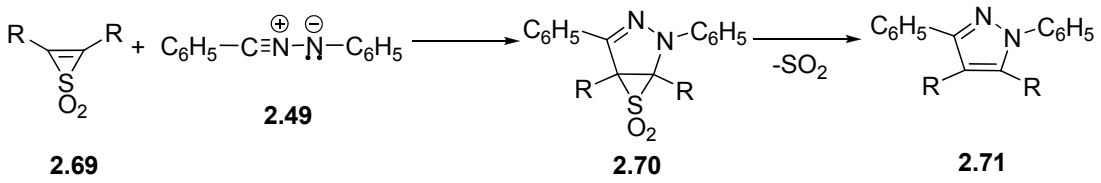


Scheme 2.30 Reaction of nitrilimines with heterocyclic dipolarophile in two modes

Significant amounts of the 1,3-addition product are usually formed when the dipolarophilic activity of the heterocyclic reactant is remarkably decreased as in the case of the more heteroaromatics like imidazole.

2.4.2.2.1. With Three-membered heterocycles

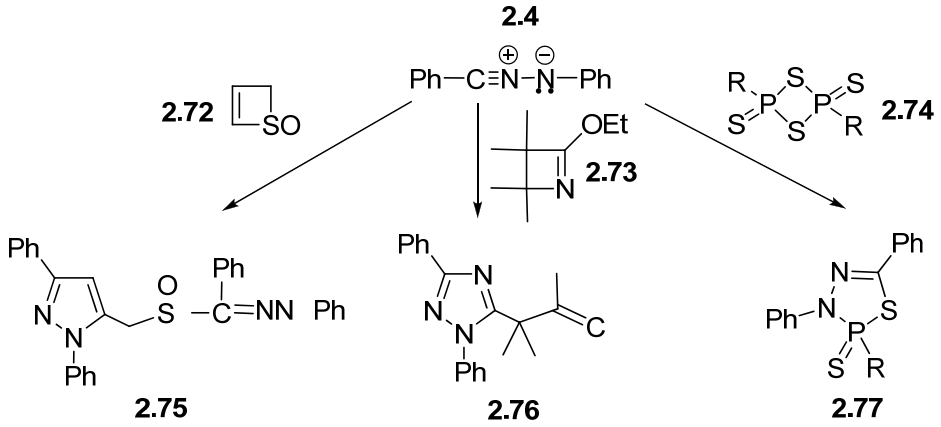
The reaction of diphenylnitrilimine **2.49** with 2,3-disubstituted thirene dioxides **2.69** in benzene affords the pyrazole derivatives **2.71** *via* loss of sulfur dioxide [50].



Scheme 2.31 Reaction of diphenylnitrilimine with 3-membered heterocycles

2.4.2.2.2. With Four-membered heterocycles

Reaction of diphenylnitrilimine **2.49** with thiete 1,1-dioxide **2.72** in acetonitrile to give pyrazole derivative **2.75** [51] and with tetramethyl-1-azetine **2.73** to give the 1,2,4-triazole derivative **2.76** [52] accompanied by ring opening and loss of EtOH. Also, perthiophosphonic anhydrides **2.74** reacts with diphenylnitrilimine in benzene to yield 1,3,4,2-thiadiaza-phospholine-2-thiones **2.77** [53].

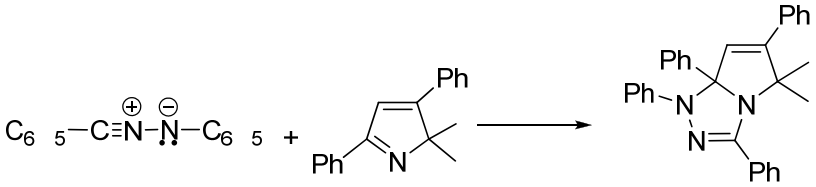


Scheme 2.32 Reaction of diphenylnitrilimine with 4-membered heterocycles

2.4.2.2.3. With Five-membered heterocycles

Nitrilimines react with variety of five-membered heterocyclic dipolarophiles e.g. pyrroles, furans, pyrazoles, imidazoles, oxazoles, thiazoles, triazoles and thiadiazole derivatives and it is not possible to include all the synthetic literature here but a general outline will be given.

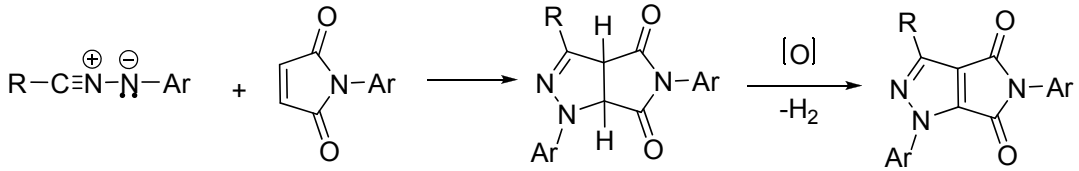
The reaction of diphenylnitrilimine **2.49** with 2,2-dimethyl-3,5-diphenyl-2*H*-pyrrole **2.78** is completely regioselective, giving the cycloadduct **2.79** [54].



2.4 **2.78** **2.7**

Scheme 2.33 Regioselective 1,3-dipolar cycloaddition of nitrilimine with pyrroles

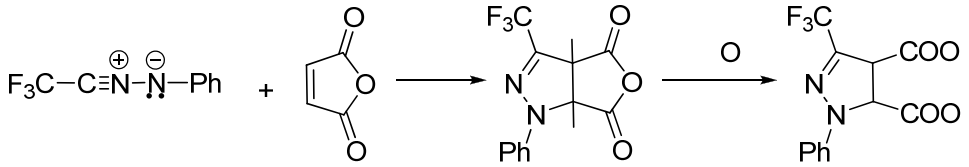
N-arylnitrilimines **2.80** react with *N*-arylmaleimides **2.81** in benzene of DCM to give corresponding pyrrolo[3,4-*c*]pyrazoline derivatives **2.82** which can be oxidized to pyrrolo[3,4-c]pyrazole-4,6-diones **2.83** with chloranil in refluxing xylene [55].



2.80 **2.81** **2.82** **2.83**

Scheme 2.34 Synthesis of pyrrolo[3,4-c]pyrazole-4,6-diones

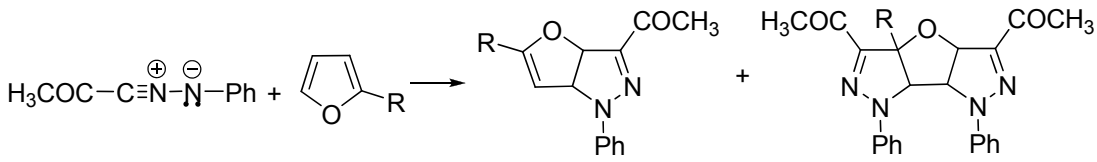
The reaction of *C*-(trifluoromethyl)-*N*-phenylnitrilimine **2.84** with maleic anhydride **2.85** yields the cycloadduct **2.86**, then, undergoes hydrolysis giving dicarboxylic acids **2.87** [56].



2.84 **2.85** **2.86** **2.87**

Scheme 2.35 Formation of dicarboxylic acids using nitrilimine and maleic anhydride

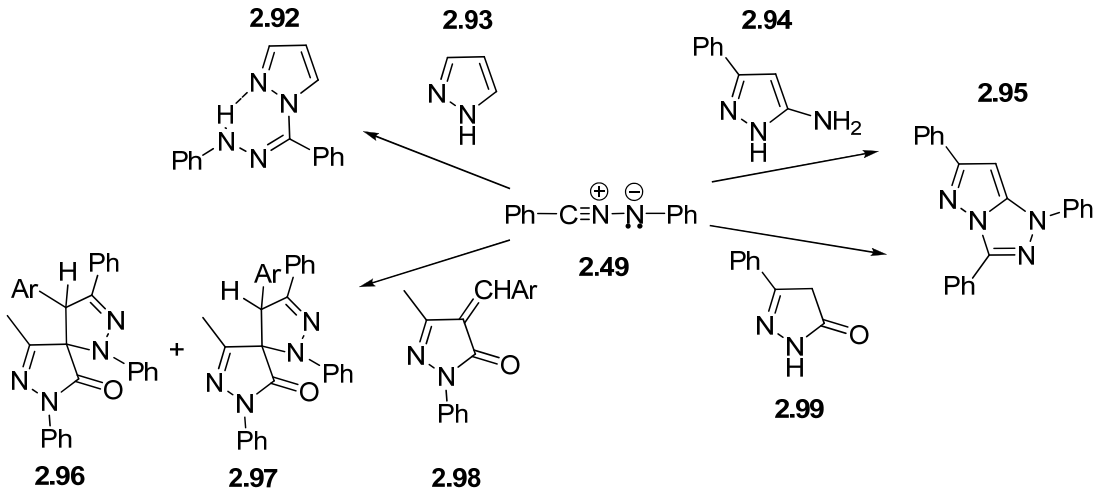
The mixture of mono- and bis-cycloadducts (**2.90-2.91**) are formed by the reaction of 2-alkylfurans **2.89** with *C*-acetylnitrilimines **2.88** [57].



2.88 **2.89** **2.90** **2.91**

Scheme 2.36 Reaction of substituted furans with *C*-acetylnitrilimines

Unsubstituted pyrazoles **2.93** reacts with diphenylnitrilimines to give the mainly the arylhydrazones derivatives **2.92** [58], however, when diphenylnitrilimines react with 5-amino-3-phenylpyrazoles **2.94** to give pyrazolo[3,4-*c*]pyrazoles **2.95** *via* elimination of ammonia [59].

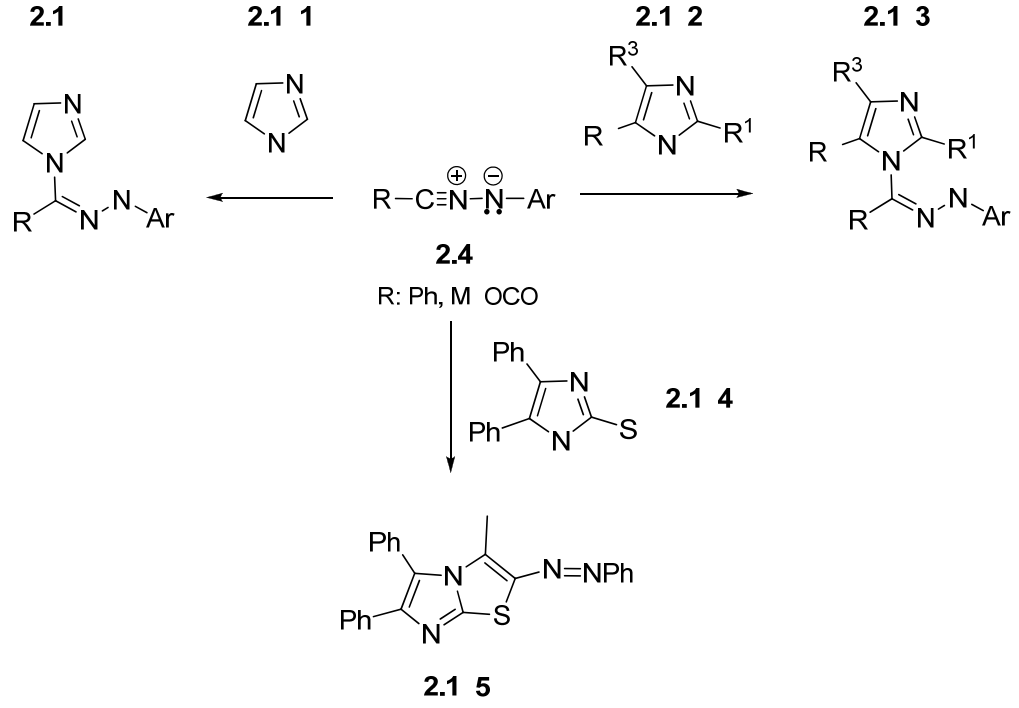


2.92 **2.93** **2.94** **2.95** **2.49** **2.96** **2.97** **2.98** **2.99**

Scheme 2.37 Reactions of diphenylnitrilimine with pyrazole derivatives

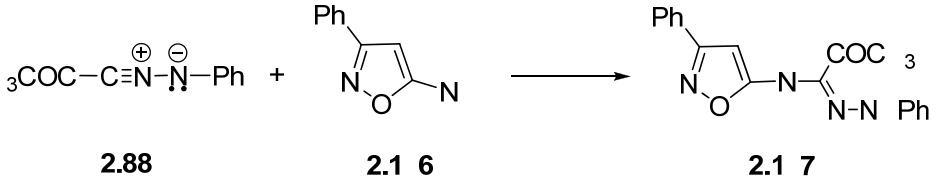
In another study, the reaction with 3-phenyl-5-pyrazolones **2.99** gives pyrazolo[3,4-*c*]pyrazoles **2.95** [60] via elimination of water. 4-Arylidene-1-phenylpyrazolin-5-one **2.98** reacts with diarylnitrilimines at room temperature in chloroform and gives in each case a mixture of two diastereomeric spiropyrazolinyl-5-ones **2.96**,**2.97**.

Diarlynitrilimines react with unsubtituted imidazole derivatives **2.101**, **2.102** to give mainly 1,3-addition products **2.100**, **2.103** [61], however, with 2-mercapto substituted imidazole derivatives **2.104** to afford the 1,3-dipolar cycloaddition products **2.105** by the cyclization of intermediate 1,3-adduct [62].



Scheme 2.38 Reactions of diarylnitrilimines with imidazole derivatives

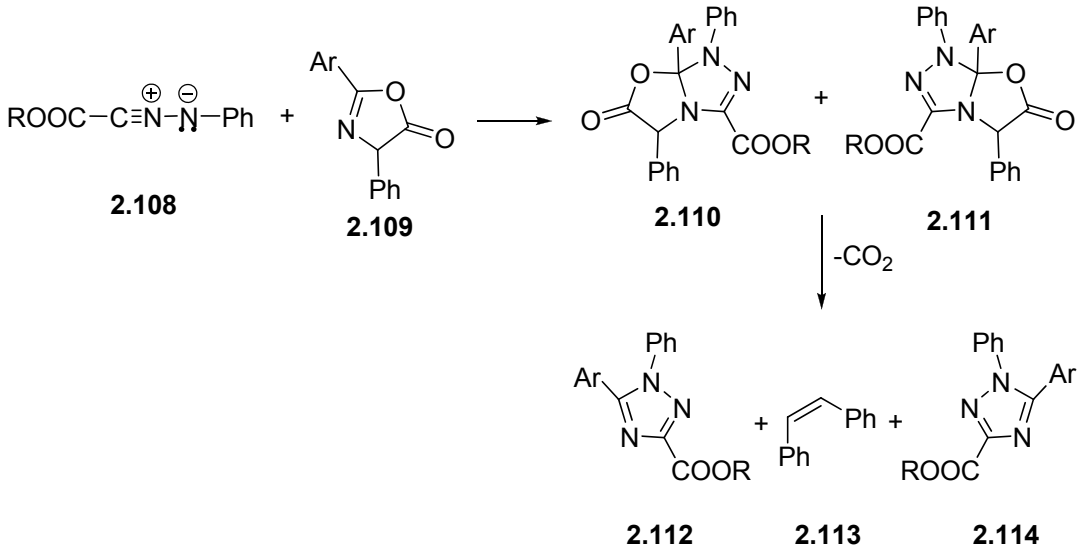
5-amino-3-pheylisoxazole **2.106** reacts with *C*-acetyl-*N*-phenylnitrilimine **2.88** to afford the amidrazones **2.107** [59].



2.88 **2.1 6** **2.1 7**

Scheme 2.39 Reaction of *C*-acetyl-*N*-phenylnitrilimine with 5-amino-3-phenyl isoxazole

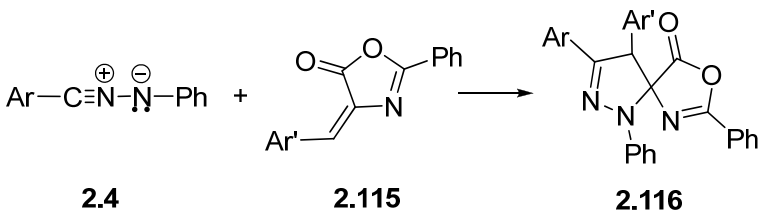
5-(4*H*)-oxazolones **2.109** were reported to react with nitrilimines to afford 1,2-diarylethylenes **2.113** and the two isomeric 1*H*-1,2,4-triazoles **2.112**, **2.114** [63].



2.108 **2.109** **2.110** **2.111** **2.112** **2.113** **2.114**

Scheme 2.40 Reaction of 5-(4*H*)-oxazolone derivatives with nitrilimines

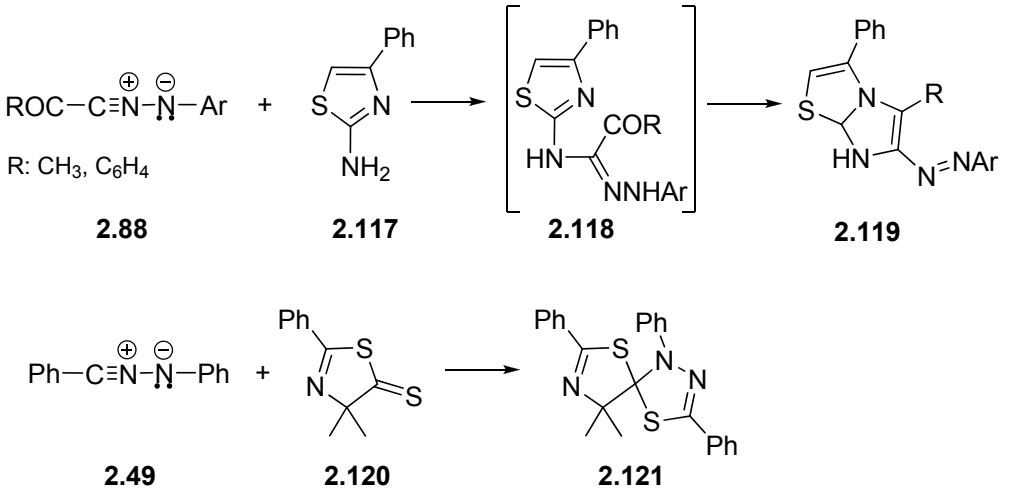
However, (*Z*)-4-Arylidene-2-phenyloxazol-5(4*H*)ones **2.115** react with diarylnitrilimines to give the spirocycloadduct **2.116** [64].



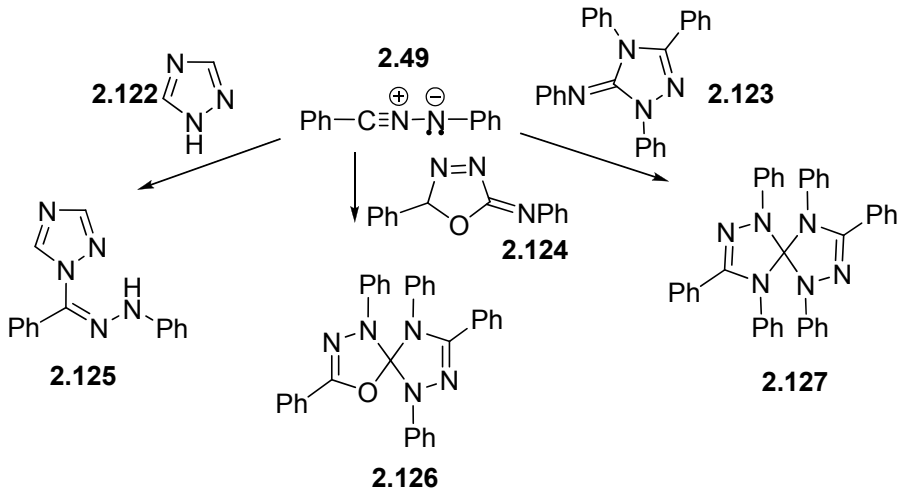
2.4 **2.115** **2.116**

Scheme 2.41 Reaction of 4-arylidene-5-oxazolones with nitrilimines

2-Amino-4-phenylthiazole **2.117** reacts with *C*-acylnitrilimines **2.88** in EtOH and yields the amidrazone **2.118,** which cyclize to the final bicyclic products **2.119**. 2-thiazoline-5-thione **2.120** yields the spirocycloadduct **2.121** when treated with diphenylnitrilimine [65,66].



Scheme 2.42 Reactions of nitrilimines with thiazoline derivatives



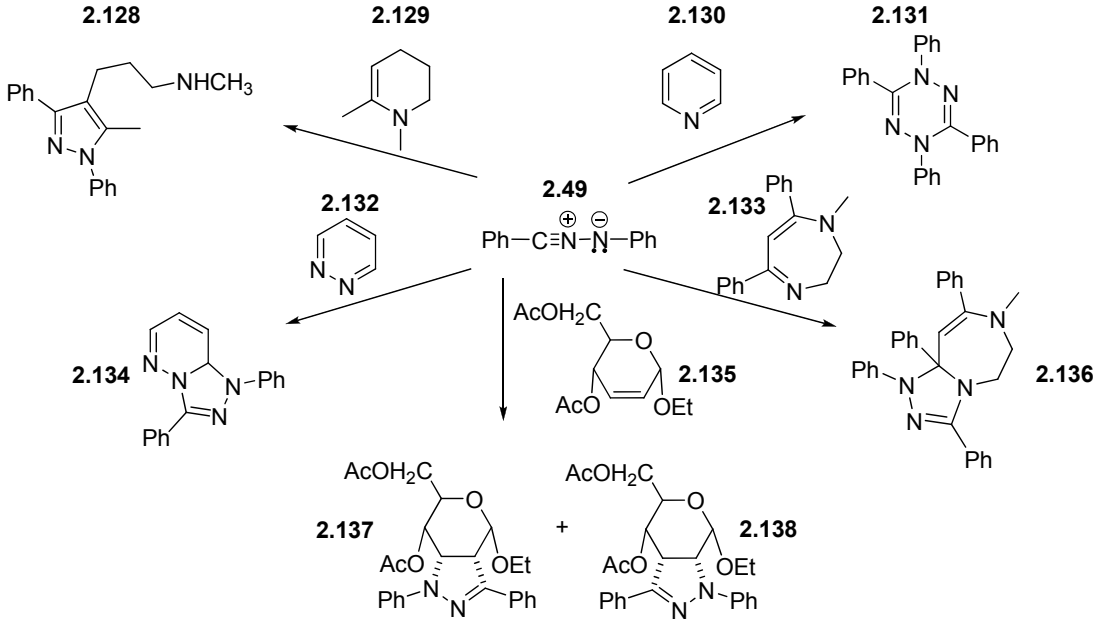
Scheme 2.43 Reactions of nitrilimines with triazole and oxadiazole derivatives

Unsubstituted 1,2,4-triazoles **2.122** was reported to react with nitrilimines and gives only a single 1,3-adduct **2.125** [58]. Reactions of the nitrilimines with

imino-1,3,4-oxadiazole **2.124** and imino-1,2,4-triazole **2.123** yields the corresponding spirocycloadducts **2.126**, **2.127** [30].

2.4.2.2.4. With Six and Seven-membered heterocycles

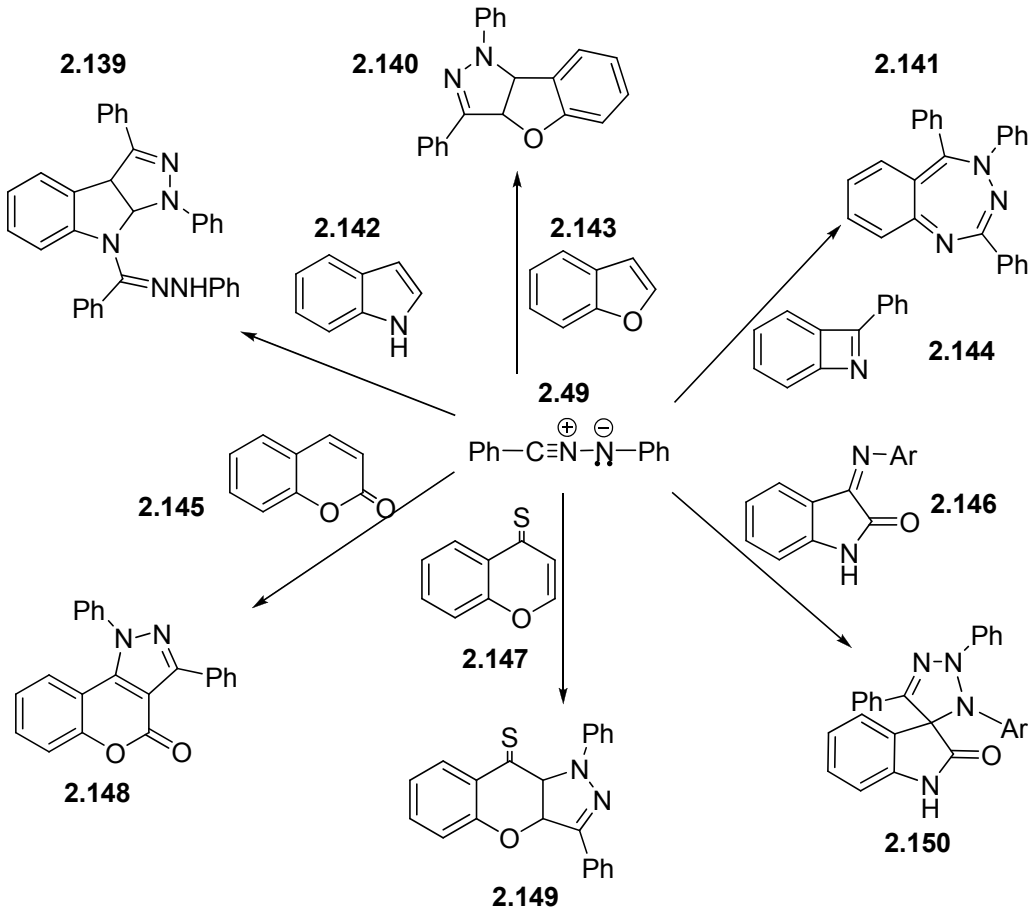
Diarylnitrilimines **2.49** react with 1,2-dimethyl-1,4,5,6-tetrahydropyridine **2.129** to give the derivatives of 4-[3-(*N*-methylamino)propyl]-5-methyl-1-phenylpyrazoles **2.128** *via* ring cleavage of the corresponding 1,3-cycloaddition intermediate. Unsubstituted pyridines **2.130** reacts with nitrilimines yield the tetrazine derivatives **2.131** upon heating in ethanol [67], however, with pyridazine derivatives **2.132** yield the 1,3-cycloadduct **2.134** [68]. Similarly, reaction of nitrilimines with pyranoside derivatives **2.135** affords a mixture of two regioisomeric cycloadducts **2.137**, **2.138** [69]. The treatment of diazepine derivative **2.133** yields 1,2,4-triazolo[4,3-*d*]diazepines **2.136** [70].



Scheme 2.44 Reactions of nitrilimines with 6-and 7-membered heterocyclic derivatives

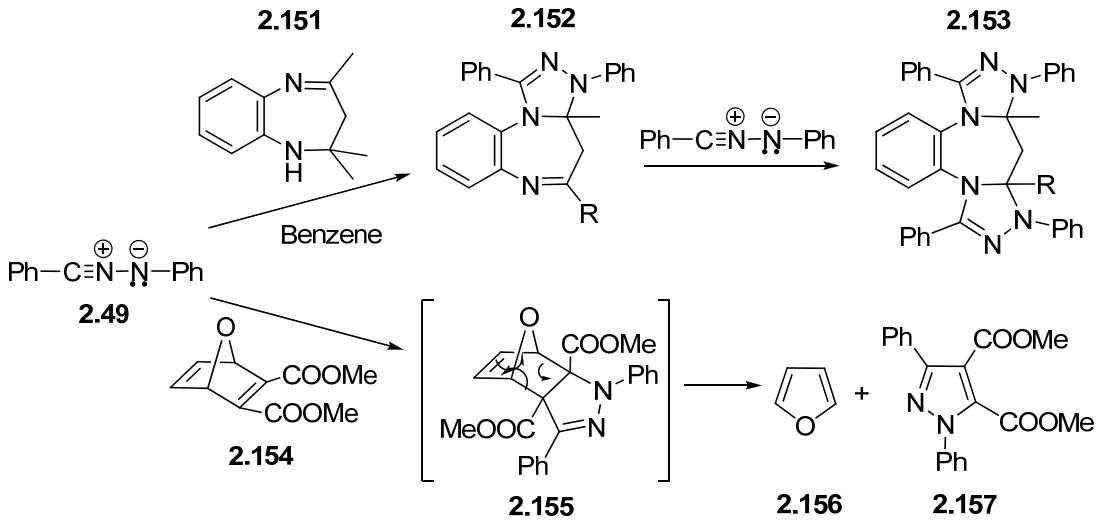
2.4.2.2.5. With bicyclic heterocycles

Addition of nitrilimines to 2-phenylbenzazete **2.144** gives the cycloadducts, which undergo ring opening to the corresponding benzo[*e*]-1,2,4-triazepines **2.141** [71]. Unsubstituted indole **2.142** reacts with the nitrilimines and gives the corresponding bis-adducts **2.139**. Reaction of benzofuran **2.143** with diarylnitrilimines was reported to give the cycloadducts **2.140** [72]. Unsubstituted coumarin **2.145** reacts with nitrilimines and yields the corresponding 1,3-disubstituted 4-oxo-1*H*-benzopyrano[4,3-*c*]pyrazoline derivatives **2.148** [73].



Scheme 2.45 Reactions of nitrilimines with bicyclic heterocycles

4*H*-1-benzopyran-4-thione **2.147** reacts smoothly with various nitrilimines regioselectively to yield the cycloadducts **2.149** and none of the other regioisomers could be detected [74]. Spiro tricyclic heterocycle **2.150** was obtained by the reaction of corresponding isatinimine **2.146** with nitrilimines [75]. On the other hand, reaction of 2,4-disubstituted-3*H*-1,5-benzo diazepines **2.151** with diphenylnitrilimine affords the bis-cycloadducts **2.153** [76]. The reaction of nitrilimines with 2,3-bis(methoxycarbonyl)-7-oxa bicyclo[2.2.1]hepta-2,5-diene **2.154** affords furan **2.156** and pyrazole **2.157** derivatives as major products [77].

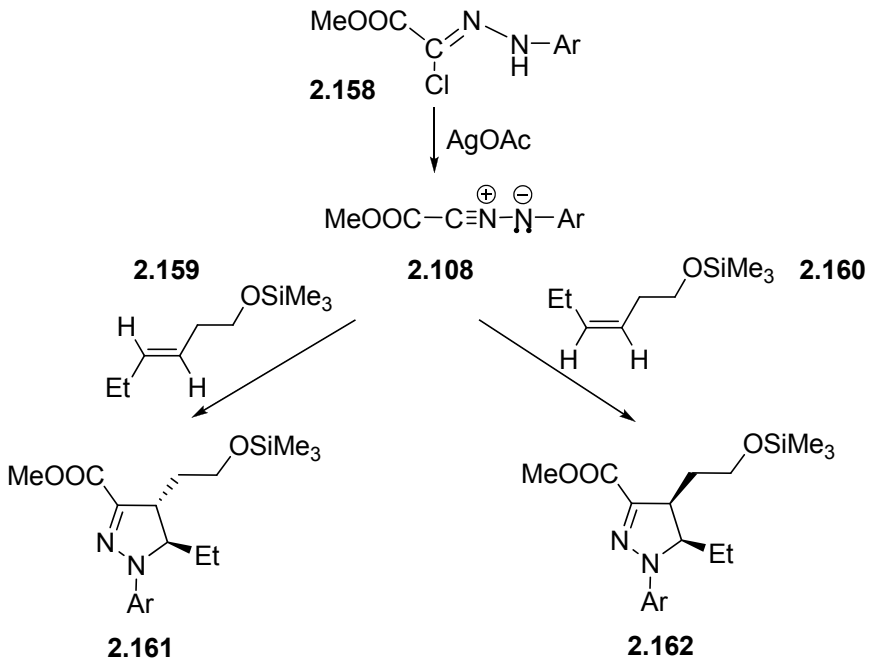


Scheme 2.46 Formation of bis-cycloadducts with benzodiazepines and stereo selectivite reaction with 2,3-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene.

2.4.2.3. Recent Applications of 1,3-Dipolar Cycloaddition Reactions of Nitrilimines

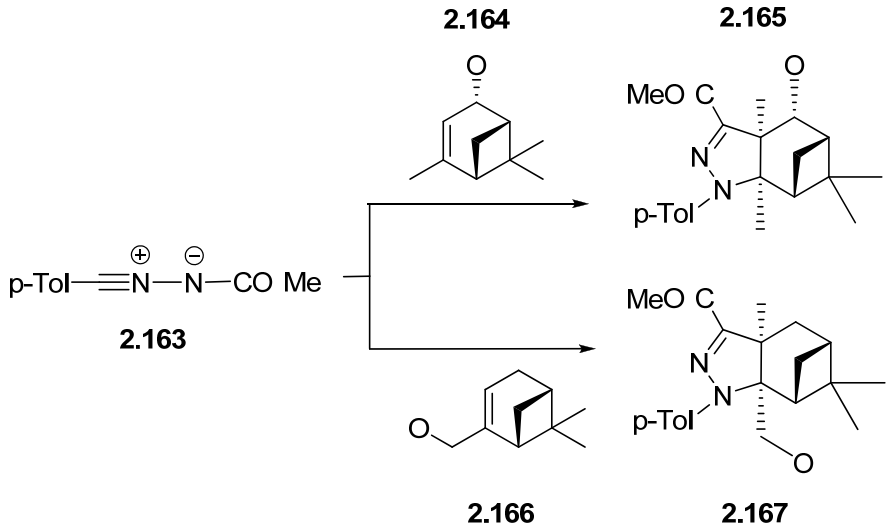
2.4.2.3.1. Silver(I)-Catalyzed Stereo- and Regioselective Cycloadditions of Nitrilimines

Huge variety of pyrazole-containing molecules by Ag-promoted 1,3-dipolar cycloaddition reactions of nitrilimines were prepared by starting with different precursors. The reactions of hydrazonoyl chlorides **2.158** with homoallyethers **2.159**, **2.160** as dipolarophiles in the presence of silver(I) acetate, major cycloadducts **2.161** and **2.162** are highly preferred, having the regioisomeric ratio between 90:10 and 92:8 [78].



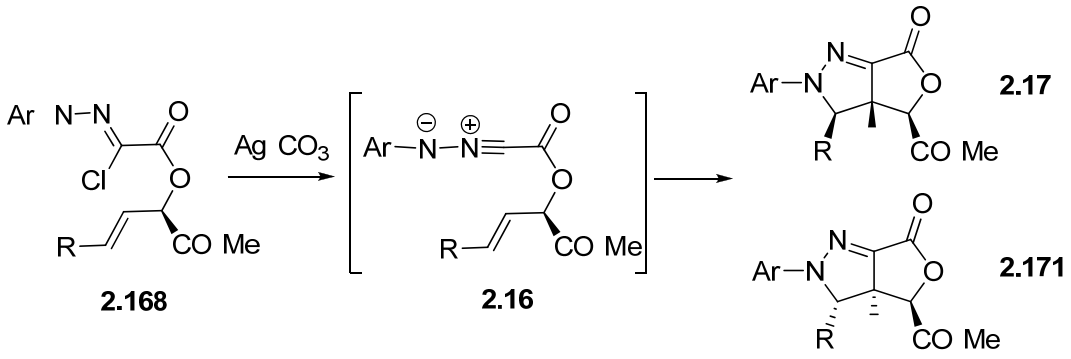
Scheme 2.47 Silver catalyzed regioselective reactions of homoallylethers with nitrilimines

A variety of naturally-occuring oxygenated monoterpenes, e.g. (*S*)-cis-verbenol **2.164**, (1*R*)-(-)-myrtenol **2.166** have been submitted in nitrilimine cycloaddition in the presence of silver (I) salts. Fully stereoselective cycloadducts **2.165**, **2.167** were obtained [79].



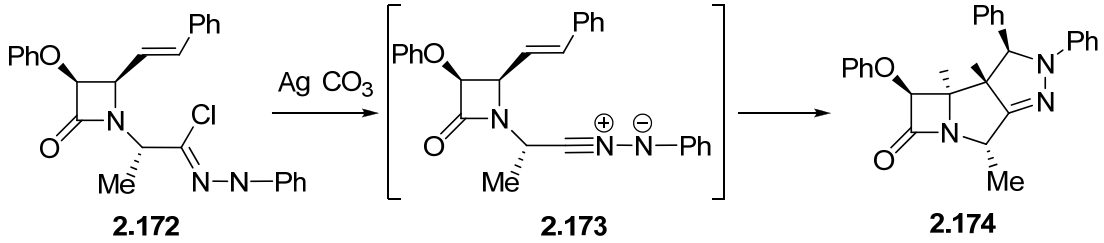
Scheme 2.48 Stereoselective silver-catalyzed nitrilimine cycloaddition with naturally-occuring dipolarophiles

The asymmetric induction in intramolecular cycloaddition reactions of nitrilimines **2.168** promoted by silver(I) carbonate was reported [80], giving rise to a mixture of enantiopure furo[3,4-*c*]pyrazole cycloadducts **2.171** and **2.172** in moderate degree of diastereoselectivity.



Scheme 2.49 Sythesis of furo[3,4-*c*]pyrazoles by Ag-catalyzed intramolecular nitrilimine cycloaddition reactions

A further example of pyrazoline annulated to a five-membered ring is given by the tricyclic *β*-lactam **2.174**, which was obtained with full stereoselectivity manner [81].

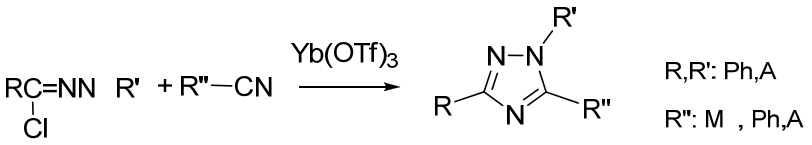


2.172 **2.173** **2.174**

Scheme 2.50 Stereoselective silver-catalyzed intramolecular nitrilimine cyclo-addition affording tricyclic *β*-lactam derivatives

2.4.2.3.2. 1,3-Dipolar Cycloadditon Reactions of Nitrilimines using $Yb(OTf)_3$, Chiral Catalysts and Microwave Irradiation

A series of 1,3,5-trisubstituted 1,2,4-triazoles **2.176** were synthesized by Su et al. *via* the intermolecular cyclization of hydrazonyl chlorides **2.1** with nitriles **2.175** catalyzed by ytterbium triflate, $Yb(OTf)_3$ in good yields [82].

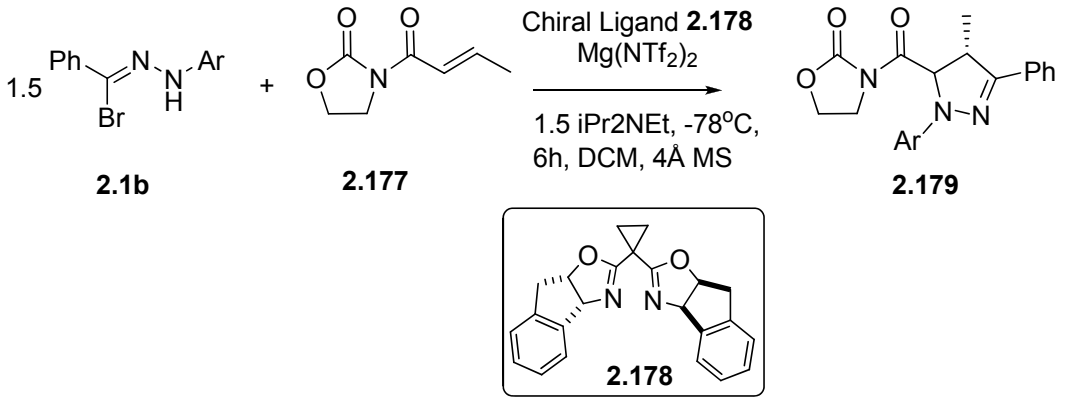


2.1 **2.175** **2.176**

Scheme 2. 51 $Yb(OTf)_3$ catalyzed reaction of nitrilimines and formation of 1,2,4-triazole derivatives

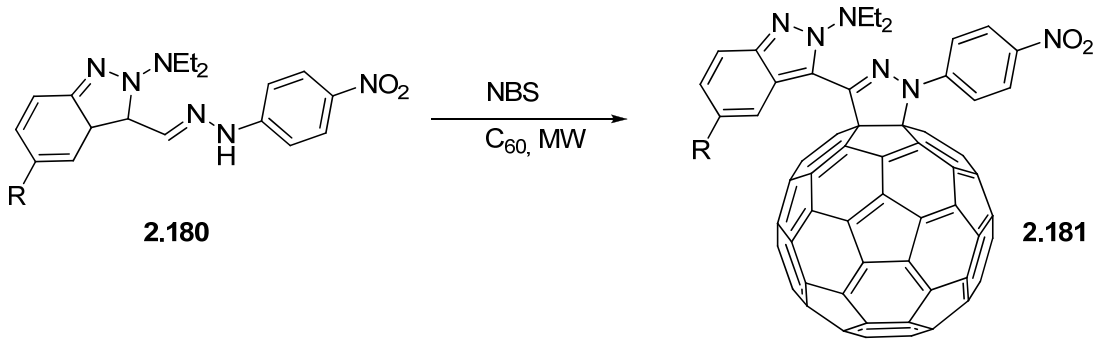
Diastereoselective inter- and intramolecular cycloaddition of nitrilimines to olefin is discussed before, however, the catalytical enantioselective [3+2] cycloaddition of nitrilimines to olefins was reported first by Sibi et al [83].

Hydrazonyl bromide **2.1b**, oxazolidinone crotonate **2.177**, noncoordinating diisopropylethylamine and chiral organic catalyst, bisoxazoline, **2.178** in combination with magnesium lewis acid provided cycloaddition product **2.179** in high yield and excellent enantioselectivity and best catalytic amount was found as 10% , also, yield has lowered by increasing temperature.



Scheme 2. 52 Highly enantioselective synthesis of pyrazoline derivatives using chiral catalyst under mild conditions

1,3-Dipolar cycloaddition reaction of isoindazolylnitrilimines, generated *in situ* from corresponding hydrazone **2.180**, with C_{60} fullerenes was carried out under microwave radiation and the formed pyrazolino[60]fullerene adduct **2.181** can be considered as a molecular switch [84].

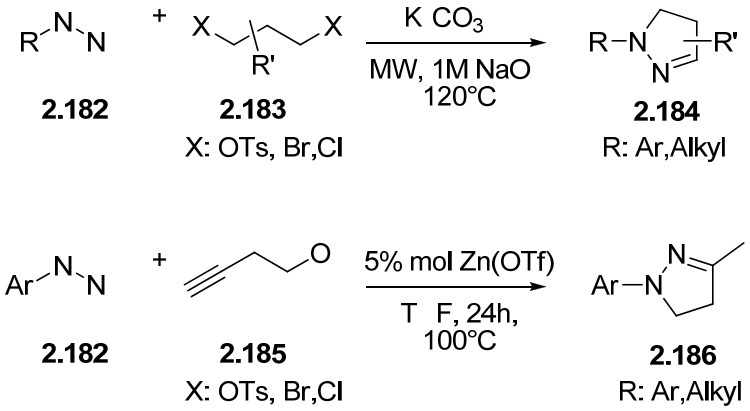


Scheme 2.53 Synthesis of isoindazole-C_{60} dyads by 1,3-dipolar cycloaddition reactions of nitrilimines

2.5. Other Methods for Preparation of Pyrazolines and Pyrazole Derivatives

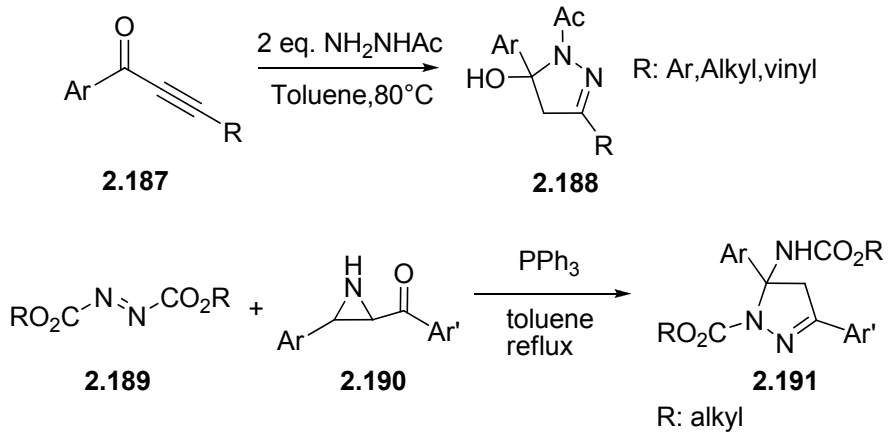
A one-pot synthesis of nitrogen-containing heterocycles from alkyldihalides **2.183** and hydrazines **2.182** occurs under microwave irradiation *via* a simple and efficient cyclocondensation in an alkaline aqueous medium [85]

Arylhydrazines **2.182b** regioselectively react with 3-butynol **2.185** in the presence of a catalytic amount of zinc triflate to give aryl-substituted pyrazolines **2.186**. The resulting products are easily oxidized in a one-pot procedure to the corresponding pyrazoles [86].



Scheme 2.54 One-pot synthesis of pyrazoline derivatives using hydrazines

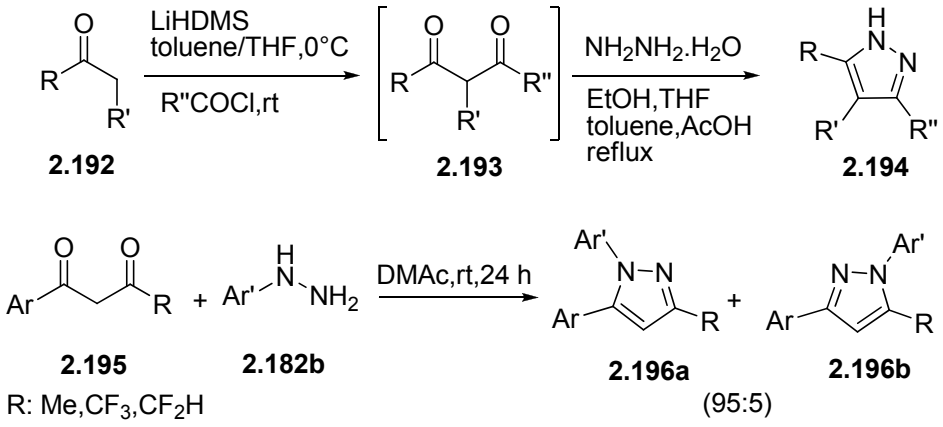
Various 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles **2.188** have been prepared in good yields from the corresponding 2-alkyn-1-ones **2.187** [87]. A novel, efficient, and general domino reaction of 2-acylaziridines **2.190** with the Huisgen zwitterions furnishes **2.191** pyrazolines. A possible mechanism for the domino sequence is proposed [88].



Scheme 2.55 Synthesis of 4-pyrazolines using alkyn-1-ones and acylaziridines

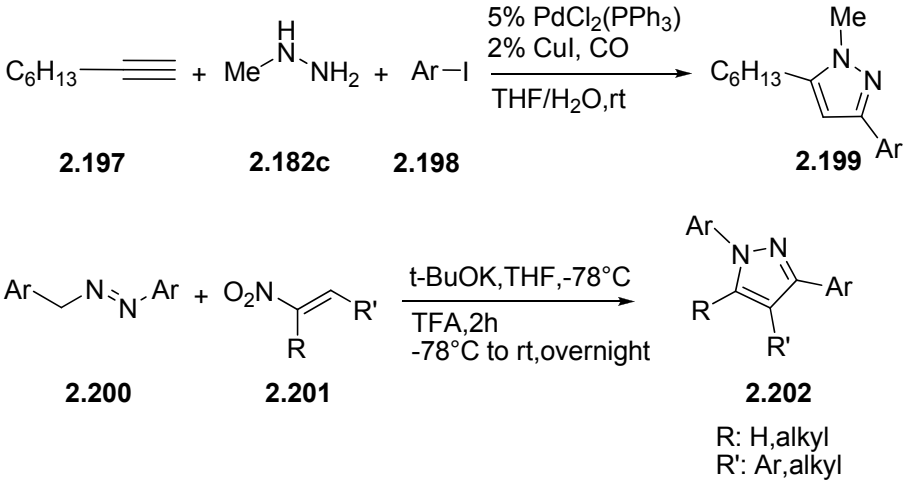
1,3-Diketones **2.193**, which were synthesized *in situ* from ketones **2.192** and acid chlorides, were converted into pyrazoles **2.194** by the addition of hydrazine. This method allows a fast and general synthesis of pyrazoles and synthetically demanding pyrazole-containing fused rings [89].

A highly regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles based on the condensation of 1,3-diketones **2.195** with arylhydrazones **2.182b** at room temperature in *N,N*-dimethylacetamide was reported to furnish pyrazoles **2.196** in good yields [90].



Scheme 2.56 One-pot synthesis of pyrazole using ketone and diketone derivatives

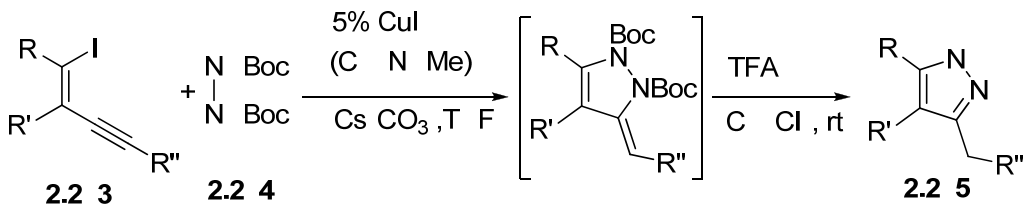
Pyrazole derivatives **2.199** are prepared by a palladium-catalyzed four-component coupling of a terminal alkyne **2.197**, hydrazine **2.182c**, carbon monoxide under ambient pressure, and an aryl iodide **2.198** [91].



Scheme 2.57 Preparation of substituted pyrazoles by Pd-catalyst and t-BuOK in two or more steps

A regioselective synthesis of tri- or tetrasubstituted pyrazoles **2.202** by the reaction of hydrazones **2.200** with nitroolefins **2.201** mediated with strong bases such as *t*-BuOK exhibits a reversed, exclusive 1,3,4-regioselectivity. Subsequent quenching with strong acids such as TFA is essential to achieve good yields [92].

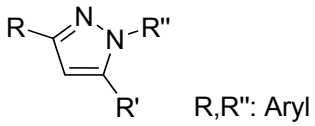
A general, highly flexible Cu-catalyzed domino C-N coupling/hydro-amination reaction constitutes a straightforward alternative to existing methodology for the preparation of pyrazoles [93].



Scheme 2.58 Cu-catalyzed synthesis of substituted pyrazoles

2.6. Biological Importance of pyrazole and pyrazoline derivatives

Due to its wide occurrence in the field of heterocyclic chemistry, the pyrazole ring constitutes a relevant synthetic target in both academia and industry. *N*-Arylpyrazole derivatives **2.196c** are a very interesting class of heterocyclic compounds that have remarkable pharmacological activities as antibacterial, antifungal [94], tumor necrosis inhibitor, antiangiogenic agent, A3 adenosine receptor antagonist, kinase inhibitor for treatment of type 2 diabetes, hyperlipidemia, and obesity, thrombopiotin mimetics, and anti-inflammatory.



2.196c

Figure 2.2 *N*-Substituted pyrazole core of molecules having diverse pharmacological activities

Celecoxib (Celebrex) is one of the *N*-aryl substituted pyrazole derivatives and a sulfa non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms [95].

Sildenafil citrate, sold as Viagra or Revatio and under various other trade names, is another drug, having pyrazole moiety, used to treat erectile dysfunction and pulmonary arterial hypertension (PAH). It was developed and is being marketed by the pharmaceutical company Pfizer [96].

In 2000, Antizol was approved by Health Canada as an antidote for ethylene glycol poisoning, followed by approval in 2001 as an antidote for methanol poisoning [97] and Antizol is the simplest pyrazole based drug.

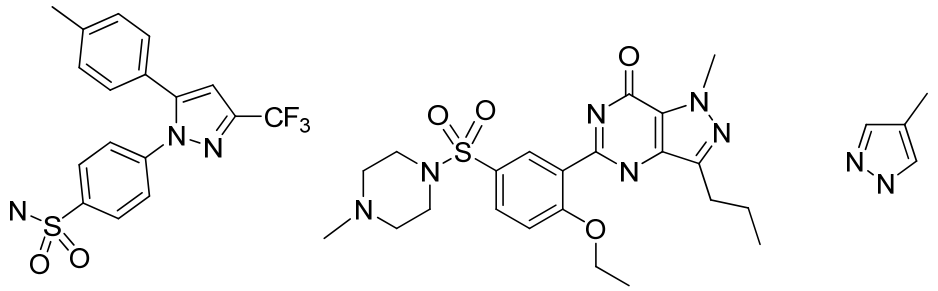


Figure 2.3 Structures of Celebrex, Viagra and Antizol

Betazole is a histamine H_2 receptor agonist and also known as Ametazole. Betazole hydrochloride, in which the main core is pyrazole, is known as gastramine and histalog, it has been used as a gastric stimulant to test for maximal production of gastric secretion activity [98].

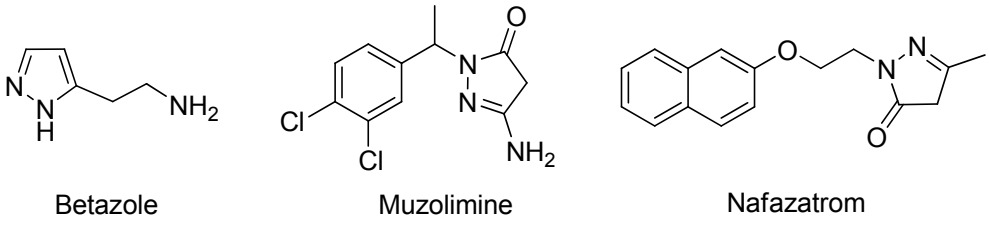


Figure 2.4 Structures of Betazole, Muzolimine and Nafazatrom

Muzolimine is a pyrazole diuretic which was used for treatment of hypertension but was withdrawn worldwide because of severe neurological side effects. Also, Nafazatrom is a pyrazolinone derivative that increases endogenous prostacyclin (PGI_2) and has experimental anti-cancer activity [99].

Benzydamine, available as the hydrochloride, is a locally-acting nonsteroidal anti-inflammatory drug with local anesthetic and analgesic properties providing both rapid and extended pain relief as well as a significant anti-inflammatory treatment for the painful inflammatory conditions of the mouth and throat [100].

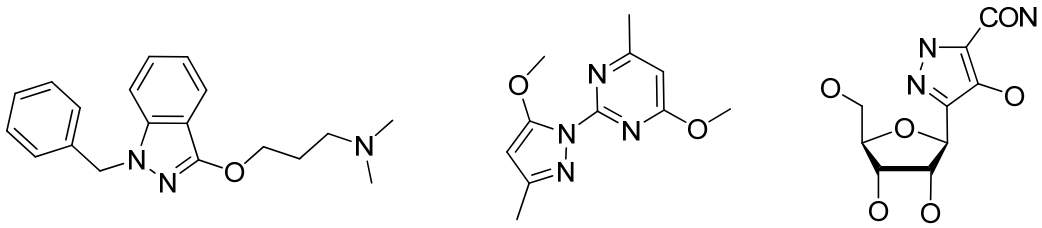


Figure 2.5 Structures of Benzidamine, Epirizole and Pyrazofurin

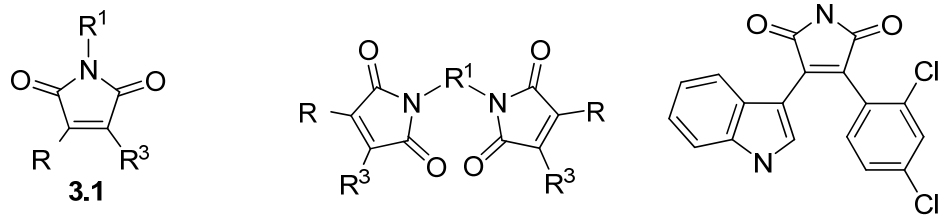
Epirizole, 4-methoxy-2-(5-methoxy-3-methylpyrazol-1-yl)-6-methyl pyrimidine, is a non-steroidal pyrimidinyl pyrazole with antipyretic, analgesic, and anti-inflammatory activity. Pyrazofurin having pyrazole moiety is one of four naturally occurring *C*-nucleoside antibiotics and it is elaborated by Streptomyces candidus and its antiviral efficacy is present against selected RNA viruses [101].

In fact, due to pyrazole or pyrazoline moiety being the core structure of a number of drugs including the widely prescribed Celebrex and Viagra, the interest for the synthesis of the molecules containing such moieties will be increasingly going on from now onward.

CHAPTER 3

3. MALEIMIDES AND BISMALEIMIDES

Maleimides **3.1** are unsaturated imides and belongs to an important class of substrates for chemical applications especially in biological [102], synthetic [103] and polymer chemistry [104]. The maleimide core is privileged natural product motif that has wide variety of biological activities e.g. disubstituted maleimide **3.3** is highly effective inhibitor of GSK3 [105].



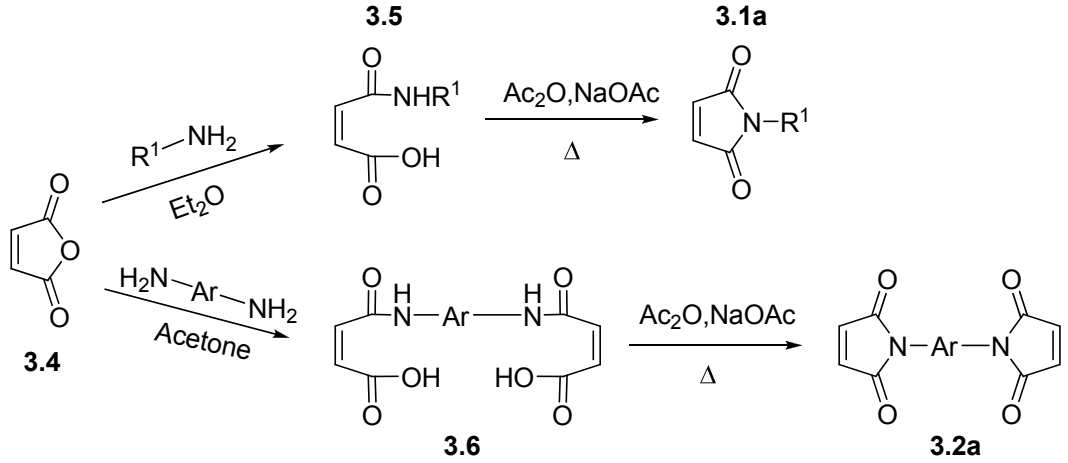
3.1 R^1,R^2,R^3: H,Alkyl,A yl **3.2** **3.3**

Figure 3.1 Core structure of maleimides, bismaleimides and biologically active disubstituted maleimide

Bismaleimides **3.2** are a class of compounds with two maleimide groups connected through a molecular unit and used as crosslinking reagents in polymer chemistry [106]. Also, thermally induced homopolymerized bismaleimides give rise to resins with good thermooxidative stability and low moisture absorption characteristics [107].

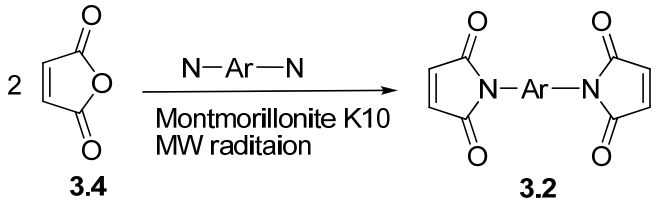
3.1. Synthesis of Maleimides and Bismaleimides

Despite their wide applicability, available routes for the synthesis of these compounds are limited. The maleimide or bismaleimide derivatives are easily prepared firstly by the treatment of maleic anhydride **3.4** with a suitable primary amine or diamine, then followed by dehydration of corresponding maleamic acid **3.5** using a base and by heating in acetic anhydride [108] and this reaction yields *N*-substituted maleimides **3.1a** and bismaleimides **3.2a** in high yields.



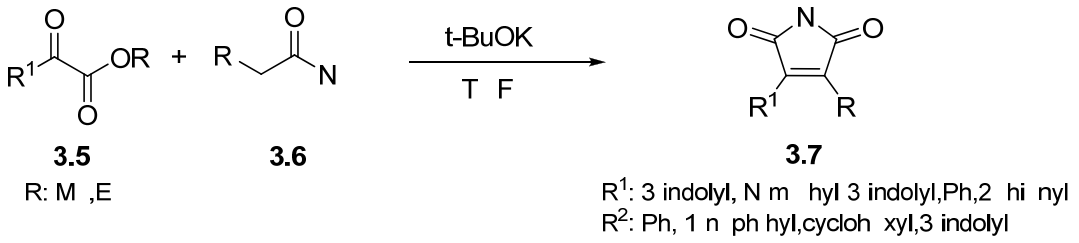
Scheme 3.1 Synthesis of *N*-substituted maleimides and bismaleimides using amine derivatives

In a microwave-assisted study [109], instead of two-step synthesis, bismaleimides **3.2a** derivatives are prepared by the condensation of maleic anhydride **3.4** and suitable diamine on montmorillonite KSF and K-10 clays without using solvent in good yields.



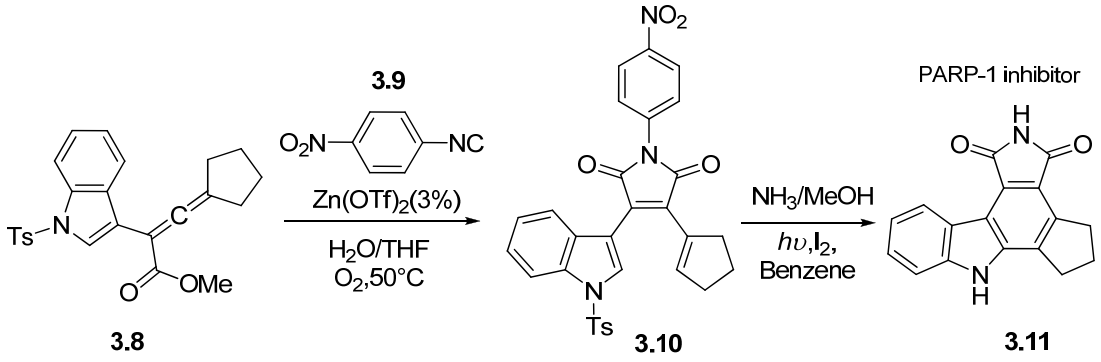
Scheme 3.2 MW-assisted synthesis of bismaleimide derivatives

Bisphenyl, bisheteroaryl, indolylaryl and indolylcycloalkyl maleimides **3.7** can be prepared in one step and 67-99% yield by condensation of glyoxylate esters **3.5** with acetamides **3.6** using a 1.0 M solution of potassium *tert*-butoxide in THF.



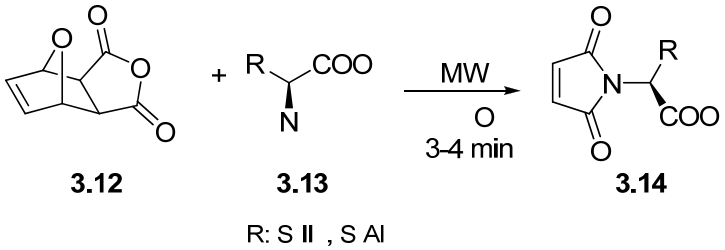
Scheme 3.3 Synthesis of maleimides by condensation of glyoxylate and acetamides

Lewis acid $Zn(OTf)_2$-catalyzed tandem annulations of isonitriles **3.9** and allenic esters **3.8** which lead to efficient and flexible syntheses of a range of biologically significant maleimides **3.10** and PARP-1 inhibitor carbazoles **3.11** and related compounds are reported [110].



Scheme 3.4 $Zn(OTf)_2$-catalyzed synthesis of biologically important maleimides using isonitriles

exo-Diels-Alder adduct of furan and maleic anhydride **3.12** reacts with amino acids **3.13** in water under classical heating or microwave irradiation with the release of furan to give maleimides **3.14** in good to excellent yields [111].

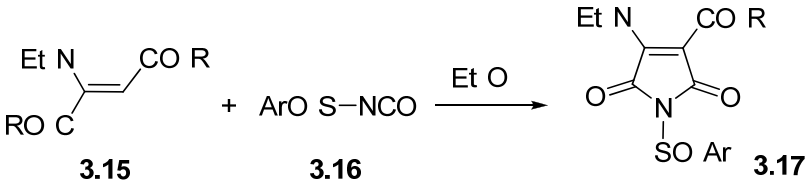


3.12 **3.13** **3.14**

R: S Ⅱ , S Al

Scheme 3.5 Synthesis of chiral maleimides using amino acids by micro-wave radiation

An effective route to novel maleimides **3.17** is described in another study, which involves the reaction of an enamine **3.15** derived from the addition of a secondary amine to a dialkyl acetylenedicarboxylate with an arylsulfonyl isocyanate **3.16** [112].

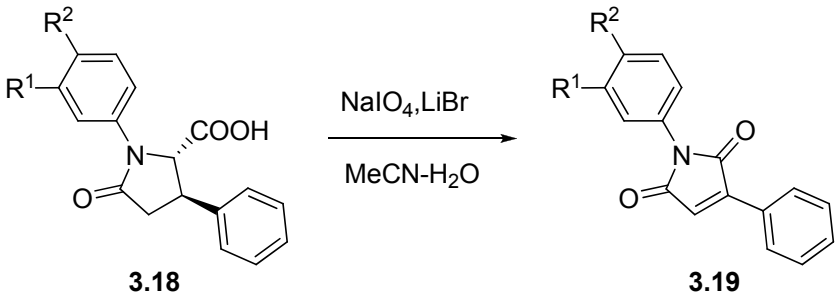


3.15 **3.16** **3.17**

R: Ph,A

Scheme 3.6 Synthesis of maleimides by the reaction of enamines and arylsulfonyl isocyanates

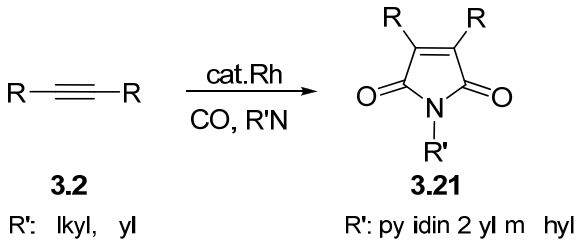
N-arylmaleimides **3.19** from *N*-aryl γ-lactam-2-carboxylic acids **3.18** can simply derived by decarboxylative oxidation and dehydrogenation with the oxidant $NaIO_4$/LiBr in refluxing acetonitrile-water solvent [113].



3.18 **3.19**

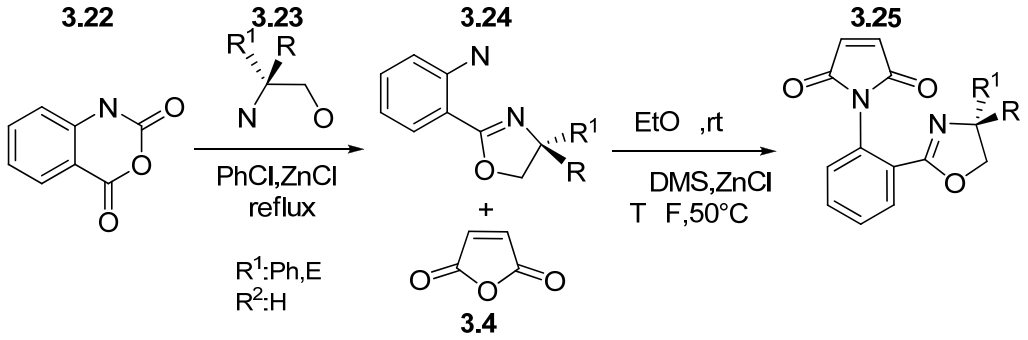
Scheme 3.7 Synthesis of *N*-Aryl Maleimides from γ-Lactam-2-carboxylic acids

The reaction of alkynes **3.20** with CO and pyridin-2-ylmethylamine in the presence of $Rh_4(CO)_{12}$/$P(OEt)_3$ results in the incorporation of two molecules of CO leading to maleimide derivatives **3.21** [114].



Scheme 3.8 The $Rh_4(CO)_{12}$-catalyzed carbonylation of alkynes with CO and pyridin-2-ylmethylamine

Chiral *N*-phenylmaleimide derivatives bearing an oxazoline ring **3.25** can be synthesized from isatoic anhydride **3.22**, 2-amino alcohols **3.23**, and maleic anhydride **3.4** in three-step pathway [115].

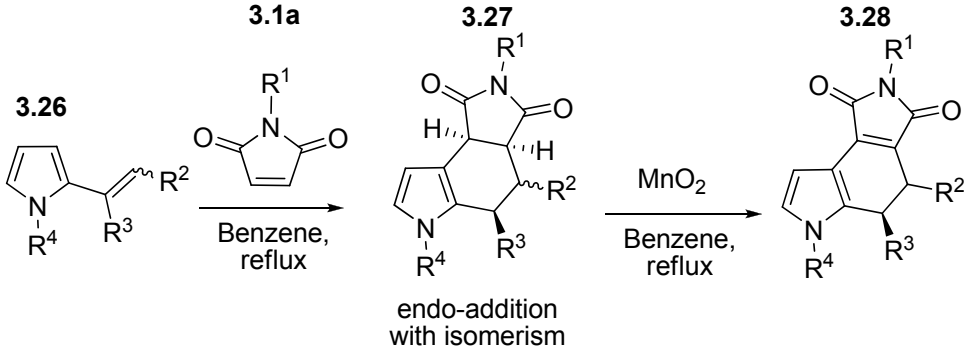


Scheme 3.9 Synthesis of *N*-phenylmaleimides bearing chiral oxazoline ring

3.2. Various Reactions of Bismaleimides And Maleimides

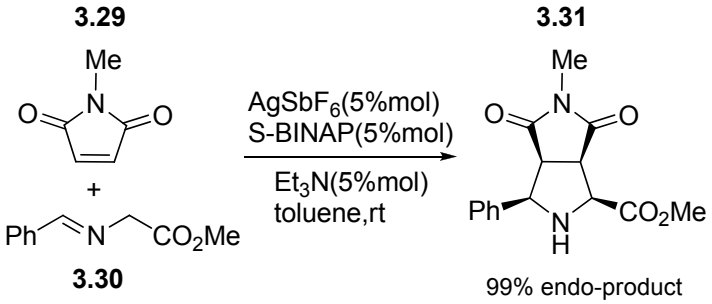
In recent years, maleimides have been extensively studied as functional compounds because of their unique chemical properties, such as the ability to undergo Michael additions with amine, alcohol [116] or thiol groups [117] and Diels-Alder additions with cyclopentadiene [118] or furan groups [119] .

In a Diels-Alder reaction, maleimides with substituted 2-vinylpyrroles **3.26** underwent an *endo*-addition [4+2] cycloaddition, followed by a spontaneous highly diastereoselective (93–98% *ee*) isomerization to give tetrahydroindole **3.27** in moderate to excellent yield. Treatment with activated MnO_2 in refluxing toluene provided the corresponding indole **3.28** in moderate to good yield [120].



Scheme 3.10 Diels-Alder reactions of maleimides with 2-vinylpyrroles

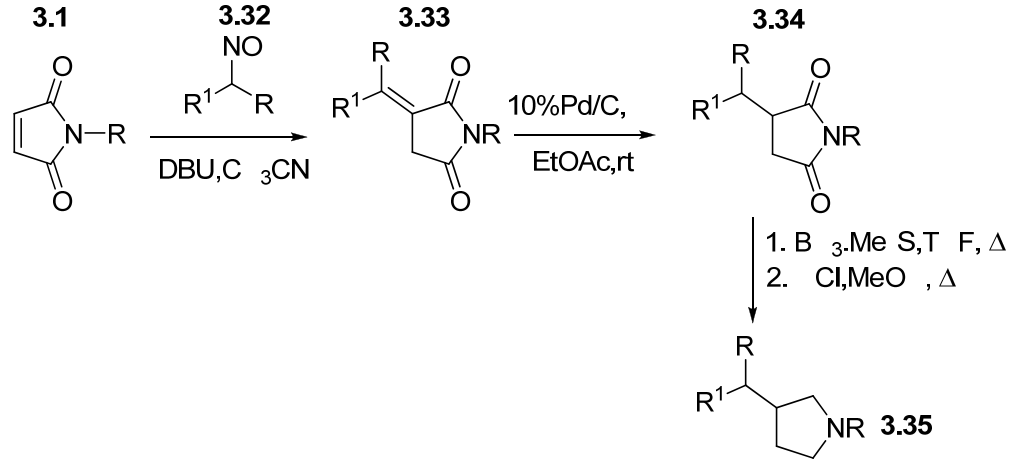
In a $AgSbF_6$-BINAP catalyzed enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides **3.30** and *N*-methylmaleimide **3.29** afforded extensively *endo*-cycloadduct **3.31** in high yields [121].



Scheme 3.11 1,3-DC of maleimides and several iminoglycinate derivatives

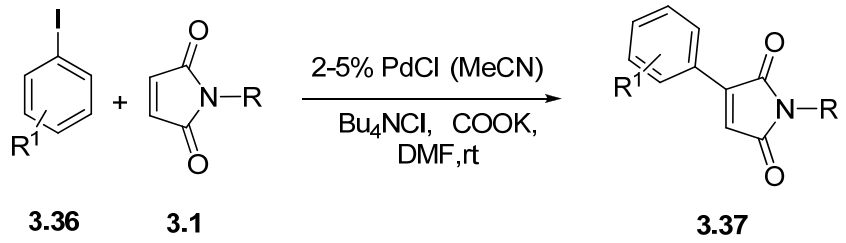
In the conjugate addition reactions of nitroalkanes **3.32** to *N*-substituted maleimides, obtained 3-alkylidenesuccinimides **3.33** which can be reduced to

the corresponding 3-alkyl derivatives **3.34** by catalytic hydrogenation and they can be further reduced using $BH_3.Me_2S$ complex to afford 3-alkyl pyrrolidines **3.35** in good yields [122].



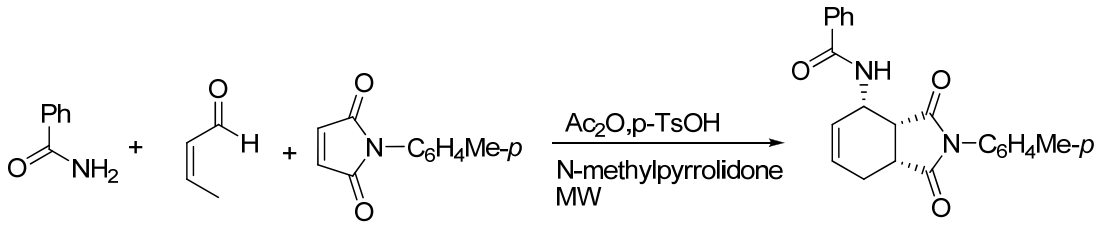
Scheme 3.12 Congugate addition of nitroalkanes to N-substituted maleimides

Similarly, Pd-coupling reactions (Heck reaction) of maleimides with aryl iodides **3.36** in the presence of $PdCl_2(MeCN)_2$, Bu_4NCl and HCOOK affords the corresponding 2-arylmaleimides **3.37** in moderate yields [123].



Scheme 3.13 Pd-coupling reactions of *N*-substituted maleimides with aryl iodides

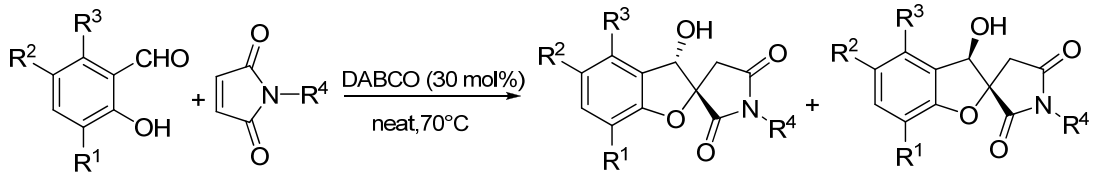
A rapid and facile synthesis of *N*-substituted 2,3,3a,4,7,7a-hexahydro isoindole-1,3-dione derivatives **3.40** can be prepared *via* microwave-promoted Beller three-component domino reaction of *α,β*-unsaturated aldehydes **3.39**, amides **3.38** and *N*-substituted maleimides [124].



3.38 **3.39** **3.1a** **3.40**

Scheme 3.14 Microwave-assisted three-component reaction of maleimide

For the synthesis of chromenes by Baylis-Hillman reaction of salicylaldehydes **3.41** with *N*-aryl/alkyl maleimides under neat conditions results in an unusual cyclization to form spirobenzofuranol **3.42** derivatives in moderate to good yield [125].



3.41 **3.1a** **3.42a** (90:10) **3.42b**

Scheme 3.15 Formation of unusual spirobenzofuranols by Baylis-Hilman reactions of N-substitutedmaleimides with salicylaldehydes

CHAPTER 4

4. VINYL OXIRANES

Vinyloxiranes **4.1** are simple 2-alkenyl substituted epoxides which are versatile building blocks and precursors of functionalized four-carbon sequences [126].

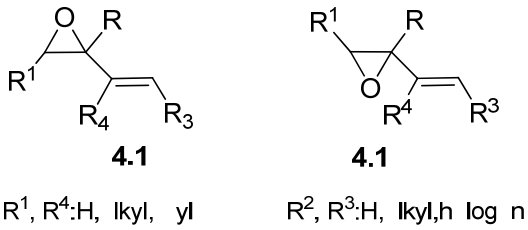
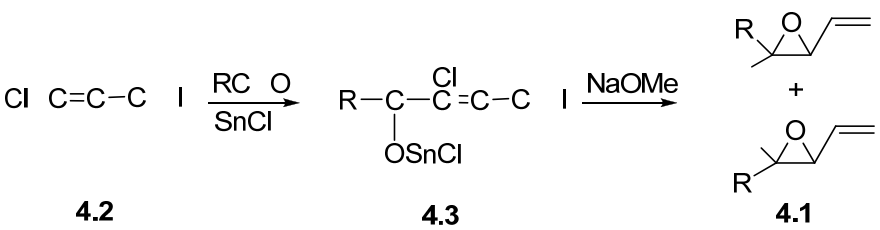


Figure 4.1 General structures of 2-vinyl oxiranes

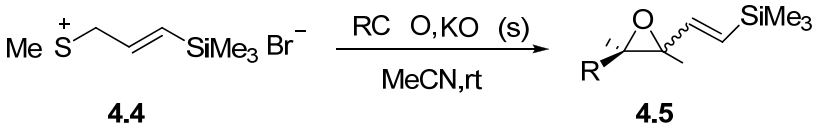
4.1. Synthesis of Vinyl Oxiranes

Vinyl oxiranes are simply prepared by the reaction of organotin reagent **4.3** from 1-chloro-3-iodoprop-1-ene **4.2** and $SnCl_2$ in dimethyformamide reacted with aldehydes by its chlorine-substituted carbon atom. Treatment with NaOMe then gave *cis*-vinyloxiranes **4.1b** (50-53%) with good stereoselectivity [127].



Scheme 4.1 Synthesis of *cis*-2-vinyl oxiranes by using organotin reagents

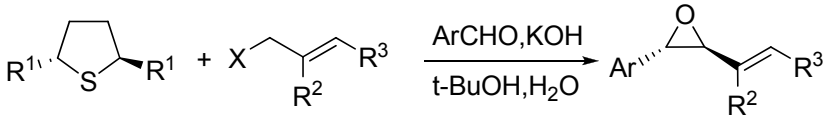
Recently, a one-pot strategy was reported [128] for the synthesis of β-trimethylsilylvinyloxiranes **4.5** by the reaction of aldehydes with a 3-trimethylsilylated dimethylsulfonium allylide **4.4** under phase-transfer conditions in excellent yields (81-95%) and high stereoselectivity.



4.4 **4.5**

Scheme 4.2 Synthesis of β-trimethylsilylvinyloxiranes

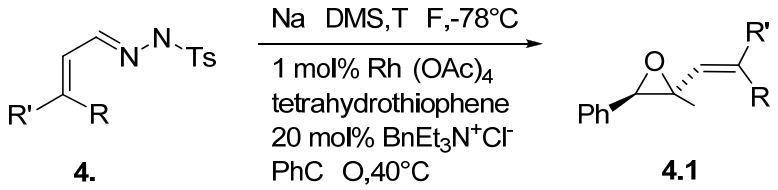
Very recently, Metzner et al. described the first enantioselective synthesis of vinyl oxiranes from allylic chiral sulfur ylides [129]. One-pot reaction of (2*R*,5*R*)-dimethylthiolane **4.6** with allyl halides **4.7**, aldehydes, and sodium hydroxide in *tert*-butyl alcohol affords vinyl oxiranes **4.8** in good yields (55-85%).



4.6 **4.7** **4.8**

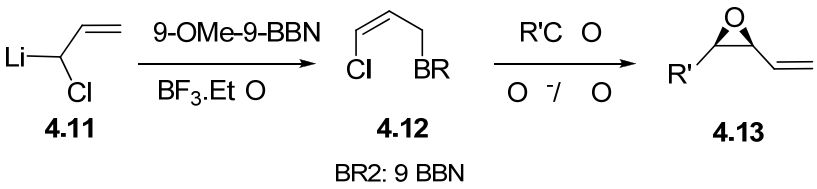
Scheme 4.3 Enantioselective synthesis of vinyl oxiranes

First catalytic ylide epoxidation *via* allylic sulfur ylide has been reported in a recent study where benzaldehyde reacted with (3,3-diphenyl)alkenyl sulfonyl hydrazone **4.9** to afford diphenyl vinyl epoxide **4.10** (60-95%) in the presence of 20 mol% tetrahydrothiophene [130].



Scheme 4.4 Synthesis of vinyl oxiranes by catalytic ylide epoxidation

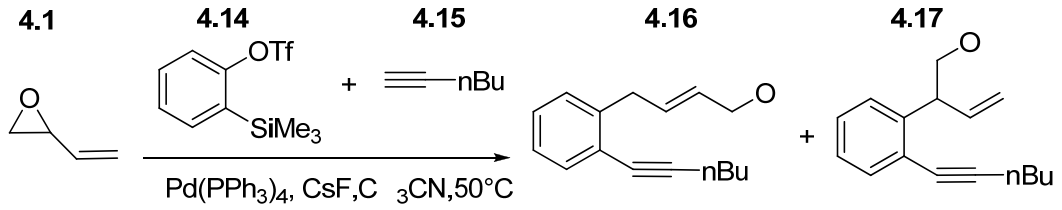
In another method, reaction of (*α*-haloallyl)lithium **4.11** with methoxy-9-BBN followed by treatment with $BF_3.Et_2O$ leads to (*Z*)-(γ-haloallyl)borane **4.12** which reacts with aldehydes to yield *cis*-vinylepoxides **4.13** (de ≥ 90%) upon oxidative workup (95-98%) [131].



Scheme 4.5 Synthesis of cis 2-vinyl oxiranes by using borane reagents

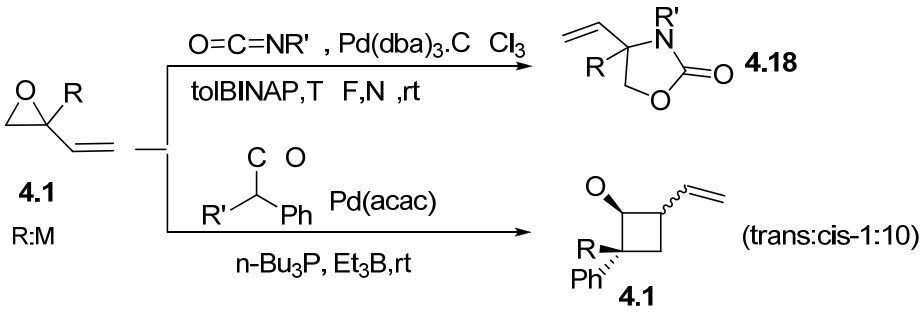
4.2. Various Reactions of Vinyl Oxiranes

Vinyl oxiranes give rise to the formation of new C-C in the presence of Pd(0) catalysts, leading to a variety of products such as allylic alcohols and new heterocyclic rings. A palladium-catalyzed highly regio- and chemo-selective three-component coupling of benzynes **4.14** with vinyl epoxides **4.1a** and terminal alkynes **4.15** provides an efficient synthesis of *ortho*-disubstituted arenes (79-87%) **4.16**, **4.17** containing alkynyl and 4-hydroxy-2-butenyl groups [132].



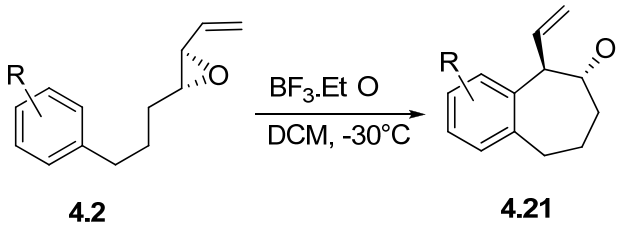
Scheme 4.6 Pd coupling reactions of vinyl oxiranes

In another Pd-catalyzed reaction, 4-vinyl-1,3-oxazolidin-2-one **4.18** derivatives can be synthesized by cycloaddition reactions of 2-vinyl oxiranes **4.1a** with unsymmetrical carbodiimides catalyzed by palladium(0) and chiral *tol*-BINAP complexes in excellent total isolated yields (69-94%) [133]. Moreover, vinyl oxirane is also capable of undergoing amphiphilic allylation of aldehydes where, under the catalysis of Pd(0)-Et_3B and furnishes 2-vinylcyclobutanols **4.19** in good-to-modest yields (50-80%) [134].



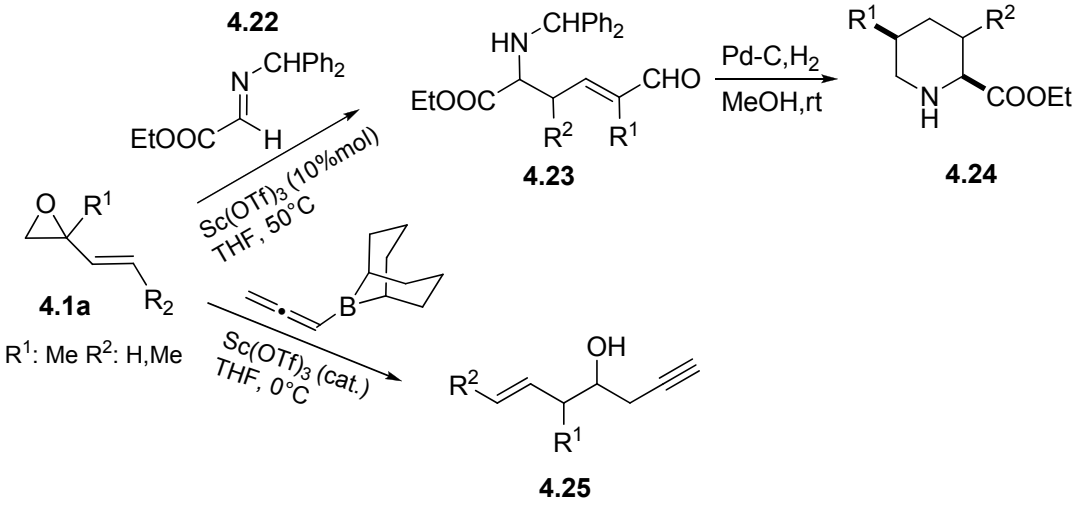
Scheme 4.7 Pd-catalyzed cyclization reactions of vinyl oxiranes with different substrates

Intramolecular 7-*endo* Friedel-Craft reaction of vinyloxirane **4.20** was carried out upon treatment with $BF_3.Et_2O$ at −30°C to give an inseparable mixture (ca. 1:1) of two seven-membered ring compounds **4.21** in high yield (80-85%) at which the cyclization proceeded non-stereoselectively [135].



Scheme 4.8 Intramolecular Friedel-Craft reactions of vinyl oxirane derivatives

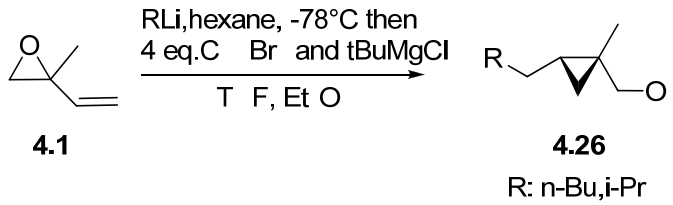
Reaction of 2-methyl-2-vinyloxirane **4.1a** with an *α*-imino ester **4.22** as an electrophile in the direct vinylogous Mannich-type reaction has been reported. The Mannich adduct **4.23** was a useful intermediate en route to *cis*-5-substituted pipecolinic acid ethyl ester (80-84%) **4.24** under simple hydrogenation conditions [136]. However, *α,β*-unsaturated aldehydes generated *in situ* by treatment of 2-vinyloxiranes with a catalytic amount of $Sc(OTf)_3$ are effectively trapped by B-allenyl-9-BBN to afford homoallylic homopropargylic alcohols **4.25** in high yield (70-95%) [137].



Scheme 4.9 Ring-opening reactions of vinyl oxiranes with different electrophiles

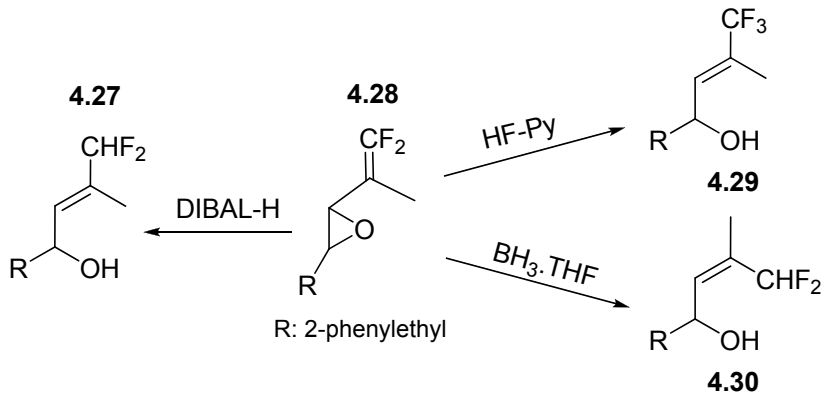
Alkyl lithium reagents were employed, which are known to open vinyl oxirane **4.1a** without additives by 1,3-allylic substitution, giving mainly (*Z*)-configurated 4-alkyl-2-methylbut-2-en-1-ols, was cleanly cyclopropanated

under Grignard conditions giving the corresponding cyclopropylcarbinols **4.26** (83-84%) with the expected *cis*, *syn*-configuration [138].



Scheme 4.10 Synthesis of cyclopropylcarbinols using vinyl oxiranes

The reaction of *gem*-difluorinated vinyloxiranes by the use of HF-pyridine furnishes trifluoromethylated allylic alcohols with exclusive *E*-selectivity, by the reduction with DIBAL-H affords difluoromethylated *E*-allylic alcohols predominantly and by treatment with BH_3.THF, the corresponding *Z* isomers forms exclusively [139].



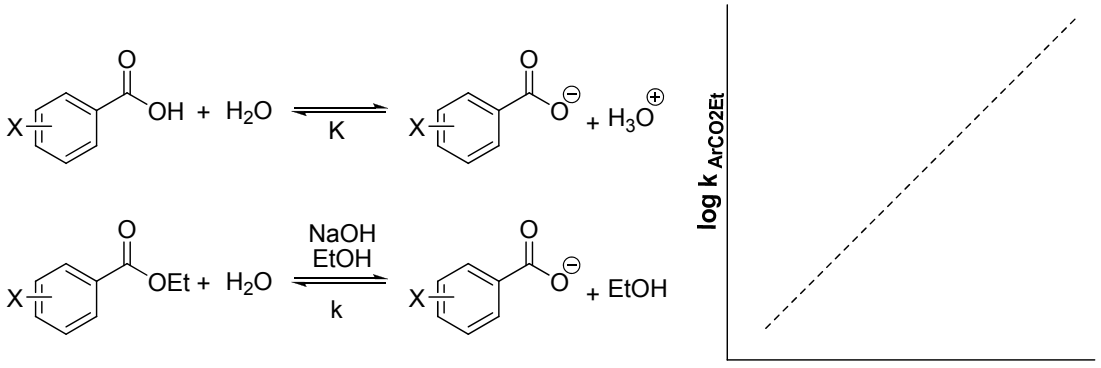
Scheme 4.11 Synthesis of trifluoro- or difluoromethylated olefins using vinyl oxiranes

CHAPTER 5

5. HAMMETT CORRELATION AND EFFECT OF SUBSTITUENTS ATTACHED TO THE AROMATIC RINGS ON ACIDITY

5.1. Hammett Equation

In 1937, Hammett reported the linear correlations between the logarithms of rate constants for reactions of *meta*- and *para*-substituted phenyl derivatives ($\log k_x$) and pK_a values of the corresponding substituted benzoic acids [140].



$$\log k = \rho \log K + c$$

$$\log \frac{k_x}{k_0} = \sigma_x \rho \qquad \log \frac{K_x}{K_0} = \sigma_x \rho$$

Kinetic equation — Equilibria equation

k_x: rate constant (X≠H); k_o: rate constant (X=H); K_x: equilibrium constant (X≠H); K_o, equilibrium constant (X=H); σ_x: Hammett substituent constant; ρ: Hammett reaction constant

$$\log \frac{k_x}{k_H} = \rho \log \frac{K_x}{K_H} = \rho\sigma_x$$

$$\sigma_x = \log \frac{K_x}{K_H} \quad \text{or} \quad \sigma_x = \log K_x - \log K_H = \mathbf{pKa_{(H)} - pKa_{(x)}}$$

Figure 5.1 Linear correlation between logarithms of k_x and pK_a

5.1.1. Hammett constants and correlations with substituents

Hammett relationship only applies to the systems where the substituents are attached to the reaction centre *via* aromatic rings and are situated *-meta* and *-para*. The substituent constant (σ) is a collective measure of **total electronic effects** (resonance and inductive effects) of *-meta* or *-para*-substituents on benzene derivatives. σ is defined separately, σ_m, for *meta*-substituents and σ_p, for *para*-substituents.

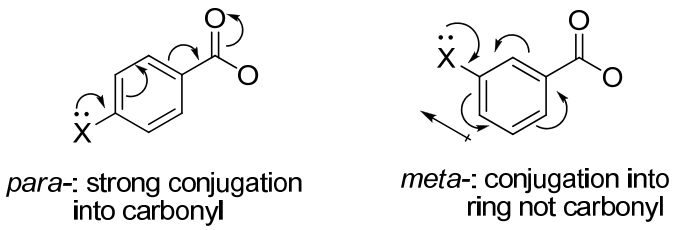
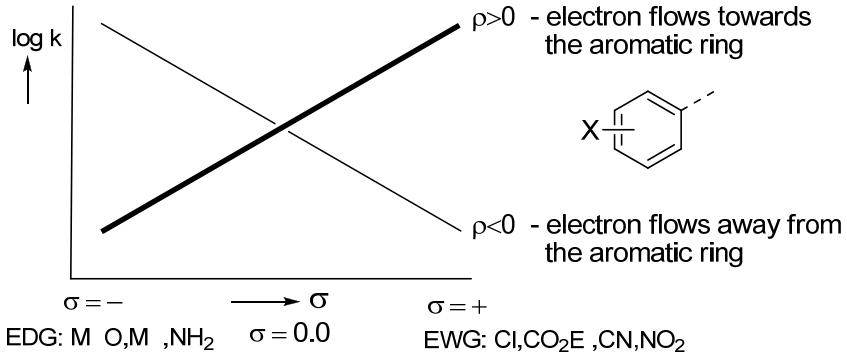


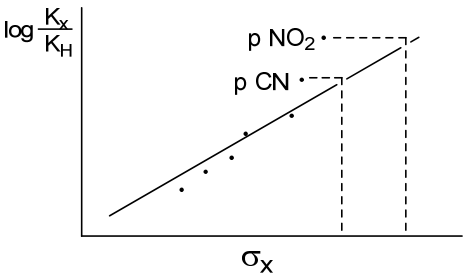
Figure 5.2 Inductive and resonance effects on benzoic acid

If magnitude of σ is minus(-), it means the effect due to electron-donating (ED) substituent, if positive(+), it means the effect due to electron-withdrawing (EW) substituent, if σ=0, substituent has no effect same as X=H. The ionisation of *meta*- and *para*-benzoic acids in water (25°C) is defined as the standard reference reaction with the reaction constant ρ=1. The magnitude of ρ reflects how sensitive a particular reaction is to the electronic effects of the substituents. Sign of ρ (the slope) shows whether a reaction is accelerated by EW or ED substituents. If the sign of ρ is positive, that means rate will be accelerated by EW susbtituents, if negative, means the rate will be accelerated by ED substituents.

In many cases a breakdown in linearity between log K's and σ's is observed for strongly EW-/ED-substituents as predicted by the Hammett relationship.

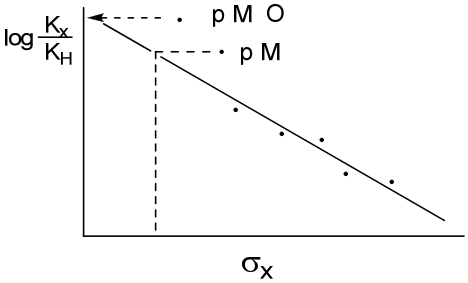
The amount by which certain substituents deviate from the line can be added or subtracted from their σ-values to produce σ_x^- and σ_x^+ modified substituent constants.





σ_x^- strongly EW groups

Subsiun	σ_p	σ_p^-
CO_2E	0.45	0.68
CO_2M	0.50	0.84
CN	0.66	0.88
CHO	0.43	1.03
NO_2	0.78	1.27



σ_x^+ strongly ED groups

Subsiun	σ_p	σ_p^+
C_2H_5	0.01	0.18
M	0.17	0.31
M O	0.27	0.78
NH_2	0.66	1.30
NM_2	0.83	1.70

Figure 5.3 Correlations between Hammett constants σ, σ^-, σ^+ and effects of substituents on aromatic ring

Choosing between σ, σ^-, and σ^+ presupposes the mechanism of the reaction. Generally, S_NAr reactions correlate well with σ^- ; S_EAr reactions correlate well with σ^+ .

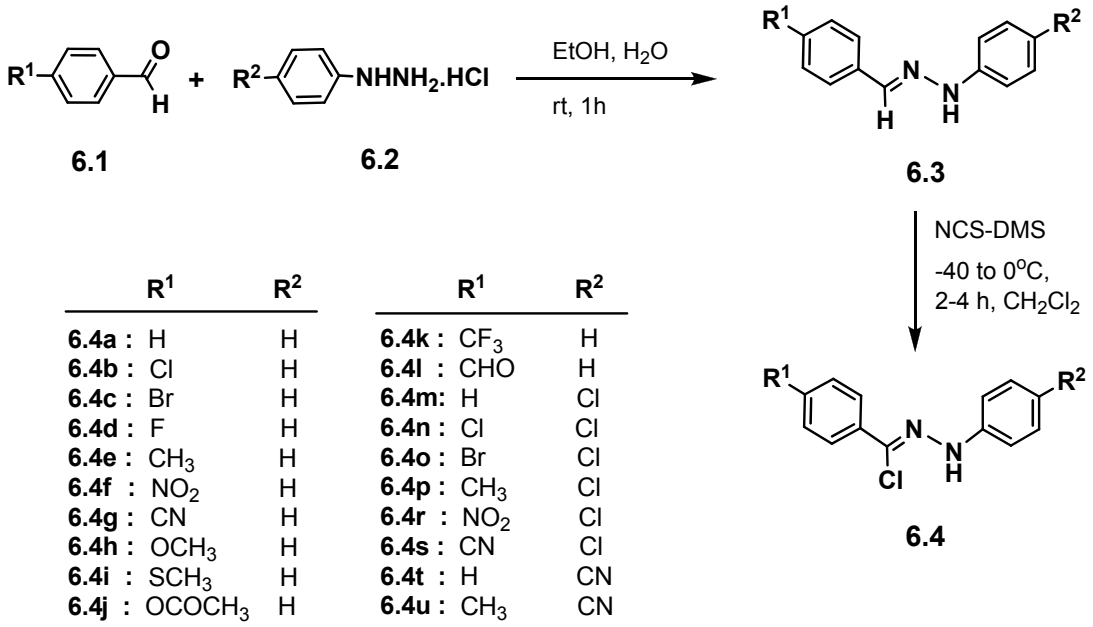
CHAPTER 6

6.1. RESULTS AND DISCUSSION

Part 1: Synthesis of Hydrazones and Hydrazonyl Chlorides

Hydrazonyl chlorides (*α*-chloro benzaldehyde arylhydrazones) **6.4** are important precursors of nitrile imines and they can be prepared starting from aldehyde hydrazones **6.3**.

In our work, *C,N*-diaryl substituted hydrazones **6.3 a-u** were simply prepared by condensation of corresponding substituted aromatic aldehydes **6.1** with phenyl substituted hydrazine hydrochlorides **6.2** in water-ethanol mixture (1:1). The advantage of using hydrazones to access hydrazonyl chlorides is being the great variety of aldehydes and simple and fast synthesis of hydrazones without any need of heating or cooling. Besides, *C,N*-diaryl substituted hydrazonyl chlorides **6.4 a-u** were prepared by the treatment of corresponding hydrazones with NCS-DMS complex, Corey-Kim reagent, prepared prior to the reaction, at -40°C and followed by gradually warming up the reaction to room temperature [21]. This is the most convenient method for the preparation of hydrazonyl chlorides in the literature.



6.1 6.2 6.3 6.4

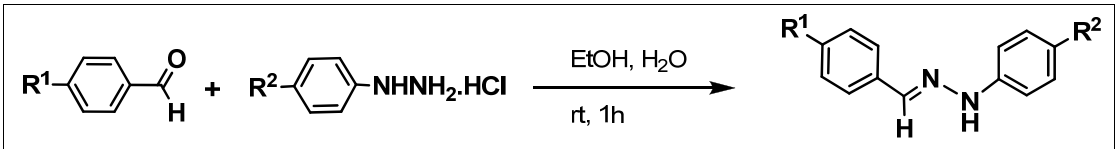
	R^1	R^2
6.4a :	H	H
6.4b :	Cl	H
6.4c :	Br	H
6.4d :	F	H
6.4e :	CH_3	H
6.4f :	NO_2	H
6.4g :	CN	H
6.4h :	OCH_3	H
6.4i :	SCH_3	H
6.4j :	$OCOCH_3$	H

	R^1	R^2
6.4k :	CF_3	H
6.4l :	CHO	H
6.4m:	H	Cl
6.4n :	Cl	Cl
6.4o :	Br	Cl
6.4p :	CH_3	Cl
6.4r :	NO_2	Cl
6.4s :	CN	Cl
6.4t :	H	CN
6.4u :	CH_3	CN

Scheme 6.1 Synthetic route for the preparation of hydrazones and hydrazonyl chlorides

However, the application of NCS-DMS system onto arylhydrazones having ED groups i.e. NH_2, $N(CH_3)_2$, OH, did not give expected hydrazonyl chloride derivatives. The reaction yields for both hydrazone and hydrazonyl chloride derivatives are found relatively high (Table 6.1 and 6.2). In addition, both hydrazones and hydrazonyl chlorides are air-stable compounds and do not need special conditions for long-term storage.

The structure elucidations of hydrazone and hydrazonyl chlorides were performed by means of spectroscopic methods IR, ^{1}H NMR, ^{13}C NMR and MS measurements.



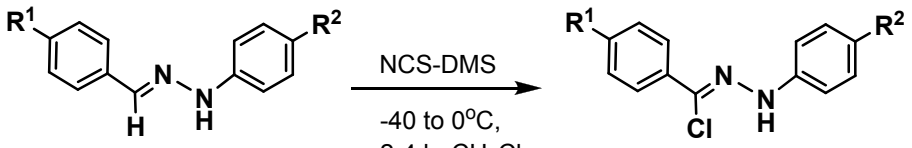
6.1 6.2 6.3

Compound	R^1	R^2	$\nu_{NH\ (cm-1)}$	$\nu_{C=N\ (cm-1)}$	Yield(%)
6.3a	H	H	3311	1602	97
6.3b	Cl	H	3311	1599	89
6.3c	Br	H	3304	1593	94
6.3d	F	H	3311	1600	87
6.3e	CH_3	H	3309	1595	87
6.3f	NO_2	H	3302	1595	96
6.3g	CN	H	3277	1602	95
6.3h	CH_3O	H	3313	1597	93
6.3i	CH_3S	H	3294	1602	95
6.3j	$OCOCH_3$	H	3308	1602	95
6.3k	CF_3	H	3292	1595	94
6.3l	CHO	H	3296	1600	85
6.3m	H	Cl	3317	1602	73
6.3n	Cl	Cl	3296	1597	91
6.3o	Br	Cl	3308	1599	88
6.3p	CH_3	Cl	3317	1599	88
6.3r	NO_2	Cl	3288	1593	90
6.3s	CN	Cl	3304	1602	48
6.3t	H	CN	3294	1608	76
6.3u	CH_3	CN	3252	1608	93

Table 6.1 Physical and IR data of compounds **6.3a-u**

In the IR spectra of aryl hydrazones **6.3a-u**, the N-H strectching vibrations arose between 3252-3317 cm^{-1} and the C=N stretching vibrations appeared between 1593-1608 cm^{-1}. Mass spectra of hydrazones revealed that the base peak is also molecular ions of the compounds.

C,N-diaryl hydrazonyl chlorides **6.4a-u** showed the N-H and C=N stretching vibrations in their IR spectra around 3273-3338 cm^{-1} and 1585-1606 cm^{-1}, respectively. There is a slight shift in wavenumbers of both N-H and C=N stretching vibrations due to inductive effect of chlorine atom attached to azomethine carbon of hydrazonyl chlorides in comparison with hydrazones.



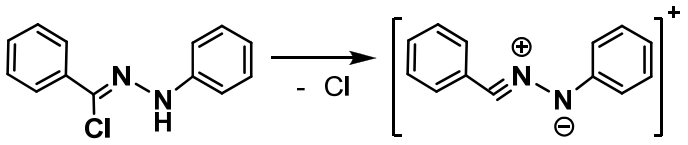
6.3 **6.4**

Compound	R^1	R^2	ν_{NH} (cm-1)	$\nu_{C=N}$ (cm-1)	Yield (%)	m.p. (°C)	δ_{NH} (ppm)	$\delta_{C=N}$ (ppm)
6.4a	H	H	3306	1600	90	128-130	8.08	134.5
6.4b	Cl	H	3309	1600	83	143-145	8.06	135.1
6.4c	Br	H	3309	1600	75	146-148	8.07	133.4
6.4d	F	H	3309	1595	88	117-119	8.02	130.6
6.4e	CH_3	H	3313	1602	90	134-135	7.91	139.4
6.4f	NO_2	H	3319	1602	91	151-153	8.20	141.0
6.4g	CN	H	3311	1602	60	145-146	8.23	138.4
6.4h	CH_3O	H	3315	1602	76	109-111	7.97	129.3
6.4i	CH_3S	H	3313	1600	81	132-133	8.03	140.3
6.4j	$OCOCH_3$	H	3317	1585	80	123-125	7.94	132.1
6.4k	CF_3	H	3309	1602	45	124-126	8.16	137.7
6.4l	CHO	H	3331	1600	50	166-168	8.24	134.9
6.4m	H	Cl	3315	1597	82	108-109	8.05	134.2
6.4n	Cl	Cl	3329	1593	83	144-145	8.04	135.4
6.4o	Br	Cl	3331	1579	90	146-148	8.04	133.1
6.4p	CH_3	Cl	3338	1593	71	109-111	8.00	139.7
6.4r	NO_2	Cl	3284	1599	96	219-220	8.29	143.4
6.4s	CN	Cl	3279	1600	94	215-217	8.21	138.2
6.4t	H	CN	3273	1606	80	138-140	8.30	140.2
6.4u	CH_3	CN	3282	1602	95	192-194	8.26	140.5

Table 6.2 Physical constants, IR data and ^{1}H NMR chemical shifts of N-H protons and ^{13}C NMR chemical shifts of C=N azomethine carbon atom of the compounds **6.4a-u**

In the proton NMR spectra of hydrazonyl chlorides **6.4a-u**, NH chemical shifts appear between 7.91-8.30 ppm as singlets depending on EW or ED groups on the phenyl ring which is bonded to azomethine carbon atom. EW groups i.e. NO_2, CN in *para* position shift NH proton signals to low field, however, ED groups i.e. CH_3, CH_3O cause shifting of NH protons to high field. Attachment of EW groups to the *para* position of phenyl ring bonded to NH strengthens the shifting effect to low field region. Upon examination of ^{13}C NMR spectra, it can be seen that C=N azomethine carbon signals are slightly affected by *para*-substitution on the phenyl ring bonded C=N carbon.

Electron impact mass spectra of hydrazonyl chlorides with 70 eV showed that the base peak is that of more stable nitrilimine species generated upon loss of HCl from the molecular ion; no molecular ion peak has been observed.



6.4

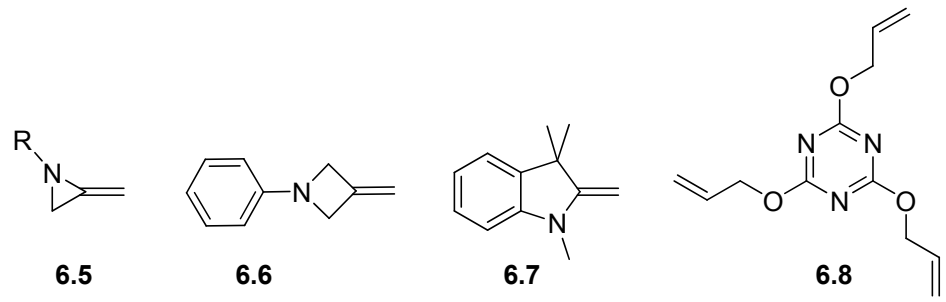
Scheme 6.2 EI mass fragmentation pattern of compound **6.4a**

Part 2: Synthesis of Novel Dihydro Bispyrrolo[3,4-*c*]Pyrazole-4,6-dione derivatives

Considerable attention has been focused on pyrazolines and substituted pyrazolines due to their interesting biological activities [141,164]. Several heterocylic systems have been synthesized by the cycloaddition of nitrilimines, generated *in situ* from the corresponding hydrazonyl halides by the action of a suitable base, to carbon-carbon double bonds of a suitable dipolarophiles as described in Chapter 2.

As a connection of our interest in the preparation of heterocyclic compounds from hydrazonyl chlorides, the present work herein was aimed at the preparation of some new pyrazoline derivatives with anticipated biological activities. In this respect, we have been focused on the cycloaddition reactions of *C,N*-diaryl substituted nitrilimines to the various heterocyclic dipolarophiles having exocyclic double bond such as *N*-substituted methylene aziridines **6.5**, 3-methylene 1-phenylazetidine **6.6**, 1,3,3-trimethyl-2-methyleneindoline **6.7**, 2,4,6-tris(allyloxy)-1,3,5-triazine **6.8**. The attempted

cycloaddition reactions of diaryl nitrilimines with those mentioned dipolarophiles (**6.5**-**6.8**) didn't give targeted cycloadducts and adequate results despite using of several conditions, solvents and sometimes utilization of silver salts and some metal catalysts.



6.5 **6.6** **6.7** **6.8**

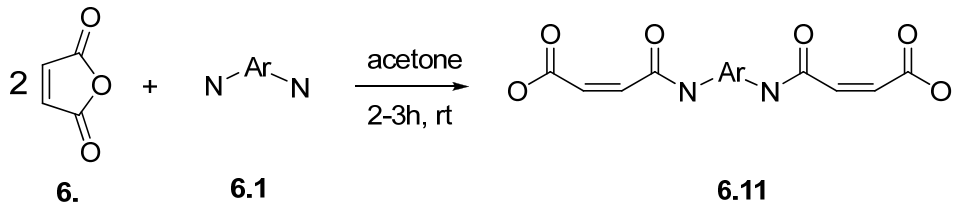
Figure 6.1 Utilized heterocyclic dipolarophiles for nitrilimine cycloadditions in attempted assays.

Failure in nitrilimine cycloaddition reactions to *N*-substituted methyleneaziridine **6.5** can be accounted for many reasons, there are some interpretations; methyleneaziridine is a ring-strained species and prone to ring-opening reactions with strong bases [142]. In addition, due to methylene aziridines not having EW groups on exocyclic double bond and being an unactivated dipolarophile, it may not be suitable for nitrilimine cycloaddition reactions.

However, reactions with dipolarophiles **6.7** and **6.8** gave some unexpected products but in very low yields, even many attempts to optimize the reaction yields has been conducted, it failed to lead better results. For this reason, we have been prompted in the preparation and nitrilimine cycloaddition reactions of bismaleimide derivatives. Commonly, bismaleimide (or maleimides) derivatives are special class of dipolarophiles with strong electron-accepting ability due to two carbonyl groups attached to C=C bond and they are

important precursors in the synthesis of polymeric materials [143] and the DNA minor-groove binding ligands [144].

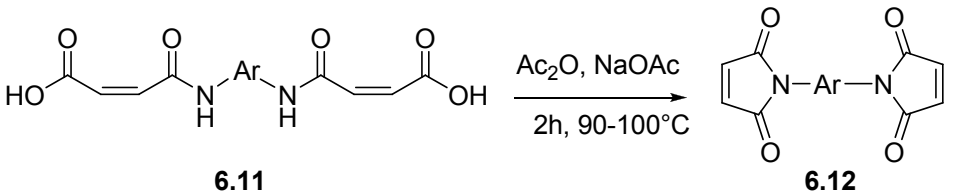
Suitable ways for the preparation of bismaleimides are limited. The best way for synthesis of bismaleimide derivatives is a two-step procedure [145]. In the first step, one equivalent of *N*-substituted aromatic diamine **6.10** is reacted with two equivalents of maleic anhydride **6.9** in acetone at room temperature to give corresponding bismaleamic acid **6.11**. This is a straightforward reaction and precipitated product is directly used in next step without any further purification.



6. **6.1** **6.11**

Scheme 6.3 Preparation of maleamic acid using maleic anhydride and diamines

Then, the maleamic acid derivative **6.11** is subjected to cyclization in acetic anhydride with sodium acetate as catalyst at 100˚C to yield corresponding bismaleimide derivatives **6.12** in relatively high yields (80-85%). This procedure is only applicable method for the preparation of bis(arylmaleimide) derivatives in the reported literature.



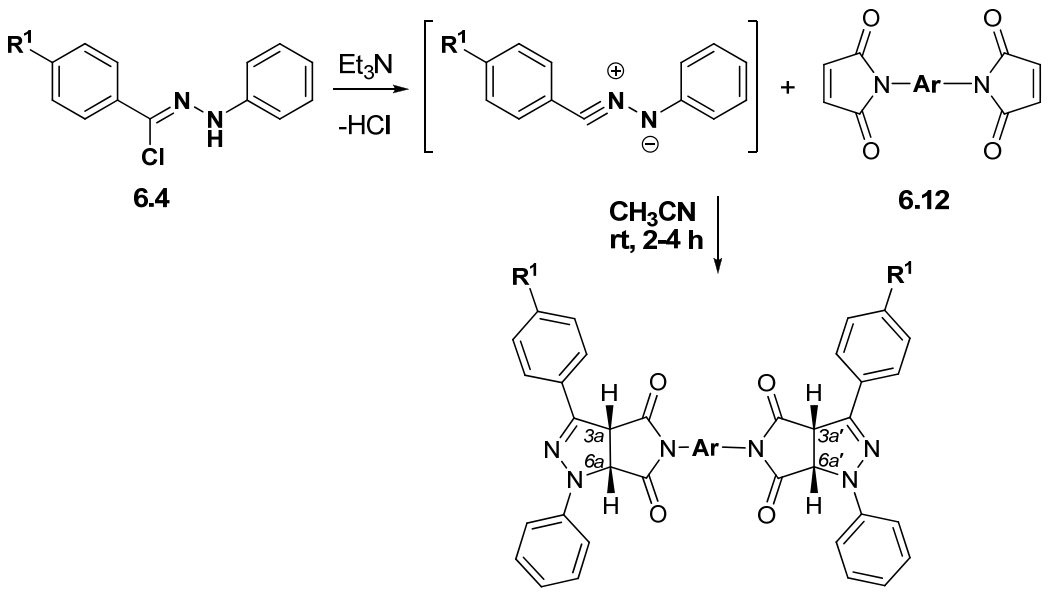
6.11 **6.12**

6.12a. Ar**:** -Ph-CH_2-Ph-
6.12b. Ar: -Ph-O-Ph-
6.12c. Ar: -Ph-

Scheme 6.4 Cyclization of bismaleamic acid to afford bismaleimide derivatives

Characteristic C=O stretching vibrations of bismaleimide products appeared around 1705-1720 cm^{-1} in the IR spectra and olefinic proton signals of the products were observed between 6.85-6.95 ppm in proton NMR spectra.

1,3-Dipolar cycloaddition reaction of *C,N*-diarylsubstituted nitrilimines (two eq.), generated from hydrazonyl chlorides **6.4** *in situ*, with one equivalent of bis(*N*-substituted maleimides) **6.12**, in dry acetonitrile at room temperature yielded three series of aryl substituted dihydrobispyrrolo[3,4-*c*]pyrazole-4,6-diones **6.13**, **6.14**, **6.15** in excellent yields without needed any chromatographic separation (Scheme 6.5, Table 6.3).

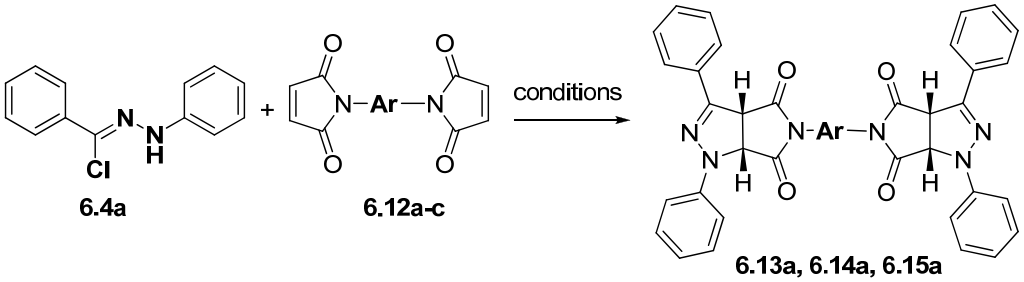


Scheme 6.5 Synthesis of aryl substituted dihydro bispyrrolo[3,4-*c*]pyrazole-4,6-diones

Entry	Product	R^1	Yield,%	Entry	Product	R^1	Yield ,%
1	**6.13a**	H	100	16	**6.14f**	NO_2	95
2	**6.13b**	Cl	92	17	**6.14g**	CN	100
3	**6.13c**	Br	100	18	**6.14h**	OCH_3	100
4	**6.13d**	F	100	19	**6.14j**	$OCOCH_3$	96
5	**6.13e**	CH_3	100	20	**6.14k**	CF_3	100
6	**6.13f**	NO_2	100	21	**6.15a**	H	96
7	**6.13g**	CN	100	22	**6.15b**	Cl	98
8	**6.13h**	OCH_3	100	23	**6.15c**	Br	90
9	**6.13i**	SCH_3	100	24	**6.15e**	CH_3	96
10	**6.13j**	$OCOCH_3$	95	25	**6.15f**	NO_2	95
11	**6.13k**	CF_3	100	26	**6.15g**	CN	99
12	**6.14a**	H	95	27	**6.15h**	OCH_3	92
13	**6.14b**	Cl	100	28	**6.15j**	$OCOCH_3$	100
14	**6.14c**	Br	100	29	**6.15k**	CF_3	91
15	**6.14e**	CH_3	97				

Table 6.3 Reaction yields of dihydro bispyrrolo[3,4-*c*]pyrazole-4,6-diones **6.13**, **6.14**, **6.15**

In order to optimize the reaction yields, different conditions have been assayed such as refluxing in DCM, toluene and CH_3CN but the best conditions have been found in CH_3CN at room temperature, owing to the low solubility of bismaleimide derivatives in DCM or toluene at room temperature and inefficiency of refluxing temperatures on reaction yields (Table 6.4).



Comp.	Bismaleimide	Eq. of 6.4a	Product	Solvent	Time	Yield (%)
6.4a	6.12a	2.05	6.13a	DCM	rt,6h	73
6.4a	6.12a	2.1	6.13a	DCM	reflux,2h	75
6.4a	6.12a	2.2	6.13a	toluene	reflux,6h	45
6.4a	6.12a	2.0	6.13a	CH_3CN	rt, 3h	100
6.4a	6.12c	2.1	6.15a	DCM	reflux,10h	87
6.4a	6.12c	2.3	6.15a	toluene	reflux,24h	36
6.4a	6.12c	2.0	6.15a	CH_3CN	rt, 4h	96

Table 6.4 Optimization of reaction conditions for biscycloadducts **6.13a**, **6.15a**

The cycloaddition reactions were monitored by TLC and found completely to have been converted into single diastereomer. Since 1,3-dipolar component of the reaction is necessarily unsymmetrical, we may expect the possible two diastereomers due to double cycloaddition. But, however, it was not found any indication of other diastereomer upon checking the ^{1}H NMR spectra of crude reaction mixture and also upon monitoring the progress of the reaction by thin layer chromatography.

All of the new compounds were identified by means of spectroscopic and physical data including IR, NMR, HRMS measurements and CHN analyses. The cycloadducts **6.13, 6.14** and **6.15** showed strong C=O absorptions at around 1720 cm^{-1} and C=N absorptions at around 1595-1600 cm^{-1} in the IR spectra.

Assignment of the structures **6.13, 6.14** and **6.15** was performed based on the data obtained from ^{1}H, ^{13}C, COSY, HSQC and NOE NMR spectra. Although many attempts to obtain fine crystals to have a better view of the absolute configurations of the cycloadducts by means of X-ray diffraction were performed, it failed each time. The relative stereochemistries of the cycloadducts were assigned to be all *cis* based on the coupling constants (*J*= 11.0 Hz) of the the bridge protons (3a-H/3a'-H and 6a-H/6a'-H) resonating at around 5.20-5.50 ppm as two doublets (Table 6.5) and HSQC and NOE NMR experiments. The chemical shifts of 3a-H(3a'-H) bridge protons showed remarkable differences than the bridge protons 6a-H(6a'-H) did due to the *p*-substitution of the EW and ED groups on the phenyl ring attached to the azomethine carbon. However, in the case of EW groups in *para* position of

the phenyl ring, 3a-H(3a'-H) protons are found to resonate at more deshielded chemical shifts (Table 6.5). Due to the molecular symmetry, only two doublets regarding 3a-H(3a'-H) protons and for 6a-H(6a'-H) protons were observed in compounds **6.13, 6.14** and **6.15** (Figure 6.2). Having been obtained the distinct doublets at the specified chemical shift positions may be considered as the proof of the yielding only one cycloadduct, *meso* form, from this reaction (Figure 6.2).

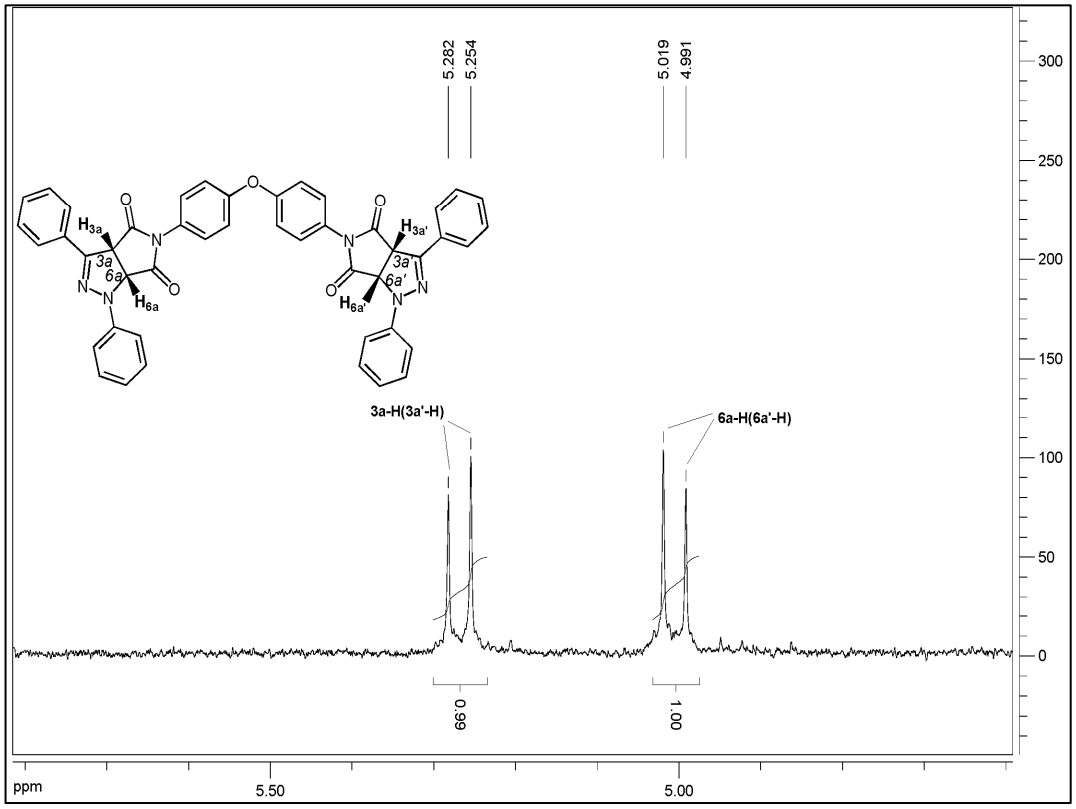
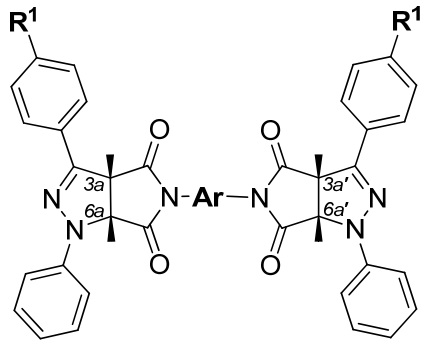


Figure 6.2 Typical 3a-H(3a'-H) and 6a-H(6a'-H) distinct doublet signals of compound 6.14a in ^{1}H NMR

Methylenic proton NMR signals of compounds **6.13 a-k** resonated around at 3.97-4.04 ppm as singlets since two protons are identical (homotopic) and giving resonance at the same frequency.

Table 6.5 3a-H(3a'-H) and 6a-H(6a'-H) proton NMR chemical shifts and coupling constants of compounds **6.13**, **6.14**, **6.15 a-k** depending on *p*-substitutents



6.13 Ar= Ph CH_2 Ph

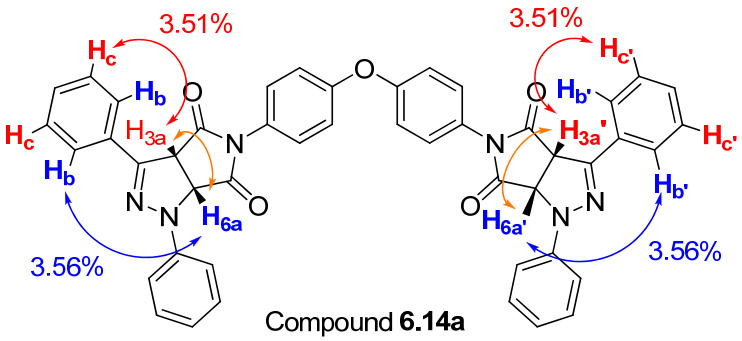
6.14 Ar= Ph O Ph

6.15 Ar= Ph

Compound	**R^1**	**δ(3aH)** (ppm)	**J** (Hz)	**δ(6a-H)** (ppm)	**J** (Hz)
6.13a	H	5.30,d	11.0	5.05, d	10.9
6.13b	Cl	5.30,d	10.9	4.97, d	10.9
6.13c	Br	5.34,d	11.1	5.01, d	11.0
6.13d	F	5.22,d	11.3	4.92, d	10.9
6.13e	CH_3	5.29,d	11.1	5.03, d	10.9
6.13f	NO_2	5.47,d	11.2	5.08, d	11.2
6.13g	CN	5.46,d	11.2	5.06, d	11.2
6.13h	OCH_3	5.20,d	10.9	4.93, d	10.9
6.13i	SCH_3	5.22,d	10.9	5.91, d	10.9
6.13j	$OCOCH_3$	5.25,d	11.0	4.90, d	10.9
6.13k	CF_3	5.40,d	11.1	5.06, d	11.1
6.14a	H	5.27,d	10.8	5.00, d	10.8
6.14b	Cl	5.55,d	10.9	5.36, d	10.8
6.14c	Br	5.55,d	11.0	5.35, d	10.9
6.14e	CH_3	5.50,d	10.8	5.34, d	10.8
6.14f	NO_2	5.68,d	11.1	5.42, d	11.1
6.14g	CN	5.45,d	11.1	5.10, d	11.1
6.14h	OCH_3	5.22,d	10.8	4.96, d	10.8
6.14j	$OCOCH_3$	5.26,d	11.1	4.95, d	10.8
6.14k	CF_3	5.40,d	11.1	5.07, d	11.1
6.15a	H	5.52,d	10.9	5.35, d	10.8
6.15b	Cl	5.57,d	10.1	5.38, d	10.2
6.15c	Br	5.26,d	11.1	4.94, d	11.0
6.15e	CH_3	5.30,d	10.9	5.06, d	10.9
6.15f	NO_2	5.70,d	10.9	5.40, d	11.0
6.15g	CN	5.51,d	11.4	5.22, d	10.9
6.15h	OCH_3	5.44,d	11.5	5.32, d	10.8
6.15j	$OCOCH_3$	5.54,d	11.1	5.37, d	11.1
6.15k	CF_3	5.63,d	11.4	5.43, d	11.1

The strong electron delocalization through aromatic ring by the effect of strong EW groups (NO_2 and CN) in *para* positions which remarkably diminishes the electron density on azomethine carbon bonded to carbon having bridge proton (3a-H/3a'-H) can be attributed for this (Table 6.5).

In addition, NOE experiments showed strong enhancements (3.51-3.56%) by irradiation of the bridge protons 3a-H(3a'-H) and 6a-H(6a'-H) confirming *cis* stereochemistry of these (Figure 6.3). This conformation is in accord with the structure reported by Noguchi et al. [146] for a similar structure.



Compound **6.14a**

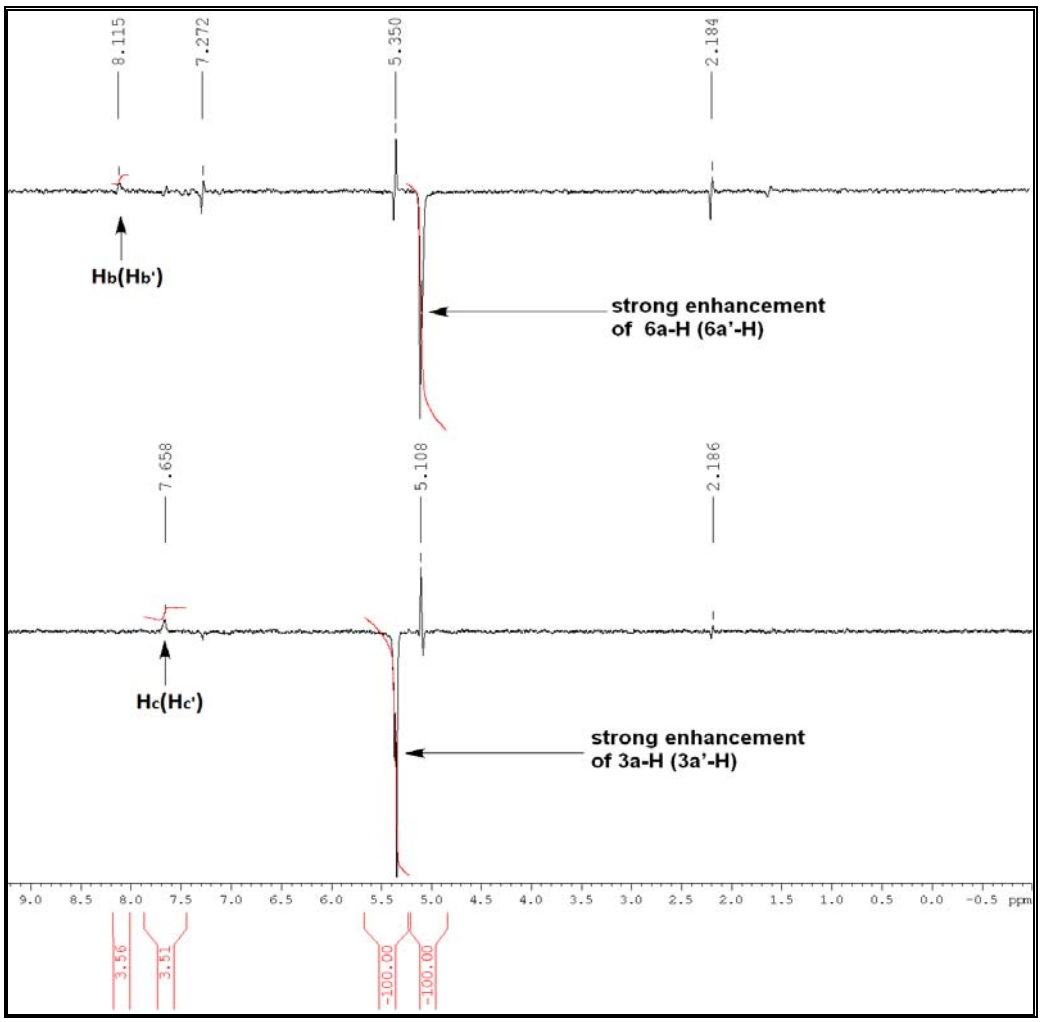


Figure 6.3 Typical NOE difference spectra of **6.14a** indicating strong enhancement of both bridge protons 3a-H(3a'-H) and 6a-H (6a'-H).

Moreover, the C=O carbons chemical shifts appeared at around 170-175 ppm and azomethine carbons around 145-155 ppm depending on the *p*-substituents in the ^{13}C NMR spectra of the title compounds.

When we subjected the cycloadducts for EI mass analyses, many fragments as a result of decomposition have been observed but no molecular ions, therefore, MALDI-TOF, ESI, or APCI techniques were used to detect the molecular ions as base peak with high precision.

The following transition state may be proposed for the formation of cycloadducts which is principally *exo* controlled (Figure 6.4).

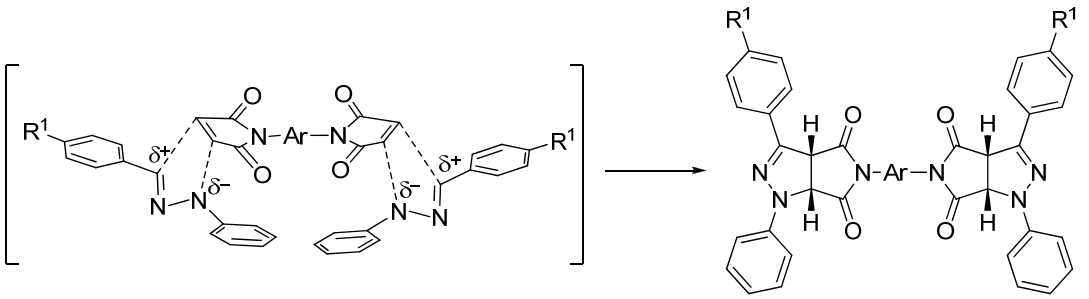


Figure 6.4 Formation of biscycloadducts in *exo* fashion

In addition to the synthesis of partially unsaturated cycloadducts, we have tried to obtain fully aromatized pyrazoles for obtaining deeper insight of the structures by conducting dehydrogenation reactions for the bridge protons with DDQ, chloranil, iodine pentoxide in different reaction conditions with literature methods [147] but no aromatized cycloadducts could be obtained.

As a final remark, since these heterocycles can be expected for their biological activities, some biological activity screening studies of cycloadducts have been performed in collaboration with School of Pharmacy, University of London and some preliminary results have been obtained for cycloadducts **6.13, 6.14 and 6.15** (Table 6.6).

Table 6.6 Antituberculotic activity studies of the compounds

Compound	MIC (μg/mL)
Strep (Streptomycin)	0.125
INH (Isoniazid)	0.025
6.13a	>256
6.13b	>256
6.13c	**64**
6.13d	>256
6.13e	>256
6.13f	>256
6.13g	**64**
6.13h	>256
6.13i	>256
6.13j	>256
6.13k	>256
6.15a	>256
6.15b	>256
6.15c	>256
6.15e	>256
6.15f	>256
6.15g	>256
6.14a	>256
6.14b	>256
6.14c	>256
6.14e	>256
6.14f	>256
6.14g	>256

As it can be seen from these results, only Br and CN substituted bispyrrolo pyrazolines **6.13c** and **6.13g** showed some antituberculotic activity. These compounds are currently being investigated for some other bioactivities like anti-parasitic, antibacterial, anti-malarial and anti-tumoral.

Part 3: The UV-VIS Spectra and Hammett Correlation Studies of dihydro bispyrrolo[3,4-*c*]pyrazole-4,6-diones

Linear Hammett correlation is only applicable to the systems where the substituents are attached to the reaction centre *via* aromatic rings and are situated in *meta* and *para* positions. In order to see if a Hammett correlation can be set up, the proton NMR chemical shifts (Table 6.5) of bridge protons of the cycloadducts **6.13a-k** were plotted against Hammet sigma para constants (σ_p) [148], and a good linear correlation has been observed (Figure 6.5).

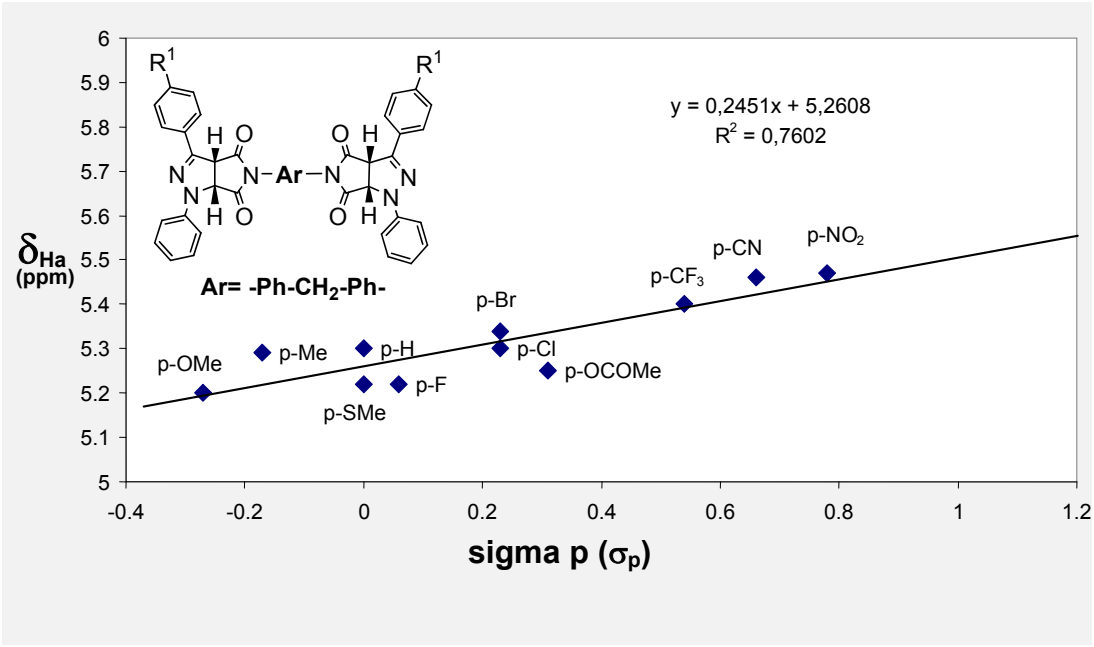


Figure 6.5 Correlation of the chemical shifts of 3a-H of compounds **6.13 a-k** vs. Hammett σ_p constants

The UV-VIS spectra of the compounds **6.13**, **6.14**, **6.15** in various solvents i.e. 1,4-dioxane, THF and 1,2-DCE were run and the most reproducible and interpretable ones were those obtained in very dilute solutions of 1,2-DCE (Table 6.7).

Table 6.7 UV absorption maxima (λ_{max}) and molar absorptivity (Є) of compounds **6.13**, **6.14**, **6.15** in 1,2-DCE

Comp.	R^1	λ_{max} (nm)	Є/10^4 1,2-DCE	Comp.	R^1	λ_{max} (nm)	Є/10^4 1,2-DCE
6.13a	p-H	350.0	3.36	**6.14f**	p-NO_2	418.5	3.20
6.13b	p-Cl	357.0	3.72	**6.14g**	p-CN	383.0	3.49
6.13c	p-Br	358.0	3.45	**6.14h**	p-OMe	349.0	3.24
6.13d	p-F	348.5	3.00	**6.14j**	p-OCOMe	353.0	3.42
6.13e	p-Me	349.0	3.77	**6.14k**	p-CF_3	365.0	3.44
6.13f	p-NO_2	419.0	3.37	**6.15a**	p-H	349.0	3.25
6.13g	p-CN	378.5	3.65	**6.15b**	p-Cl	357.0	3.12
6.13h	p-OMe	349.5	3.23	**6.15c**	p-Br	358.5	3.11
6.13i	p-SMe	362.0	3.44	**6.15e**	p-Me	348.5	3.45
6.13j	p-OCOMe	353.5	3.48	**6.15f**	p-NO_2	417.0	3.10
6.13k	p-CF_3	364.5	2.93	**6.15g**	p-CN	378.5	4.13
6.14a	p-H	350.0	3.06	**6.15h**	p-OMe	349.0	3.22
6.14b	p-Cl	357.5	3.35	**6.15j**	p-OCOMe	353.0	3.01
6.14c	p-Br	358.0	3.44	**6.15k**	p-CF_3	364.0	3.09
6.14e	p-Me	349.0	3.40				

It was clearly found that EW groups (CF_3, CN and NO_2) on phenyl ring attached to the azomethine carbon atom caused λ_{max} values to shift longer wavelengths (bathochromic shift) and ED groups (Me, OMe, SMe) to shorter wavelenghts (hypsochromic shift) (Figure 6.6-6.7).

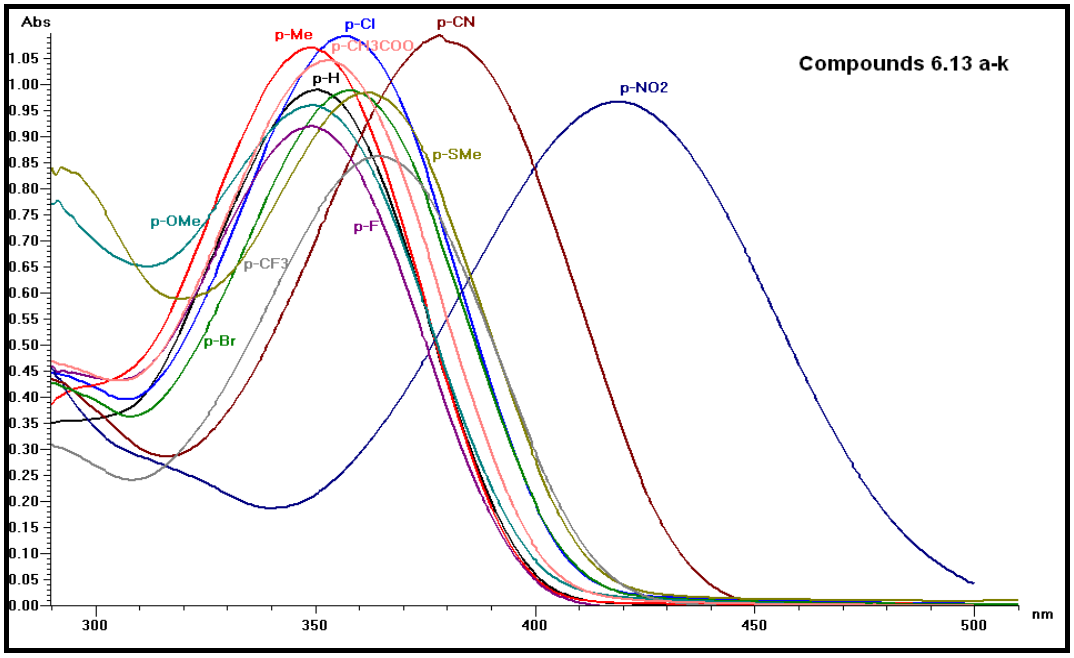


Figure 6.6 UV-VIS spectra of compounds **6.13 a-k** in 1,2-DCE

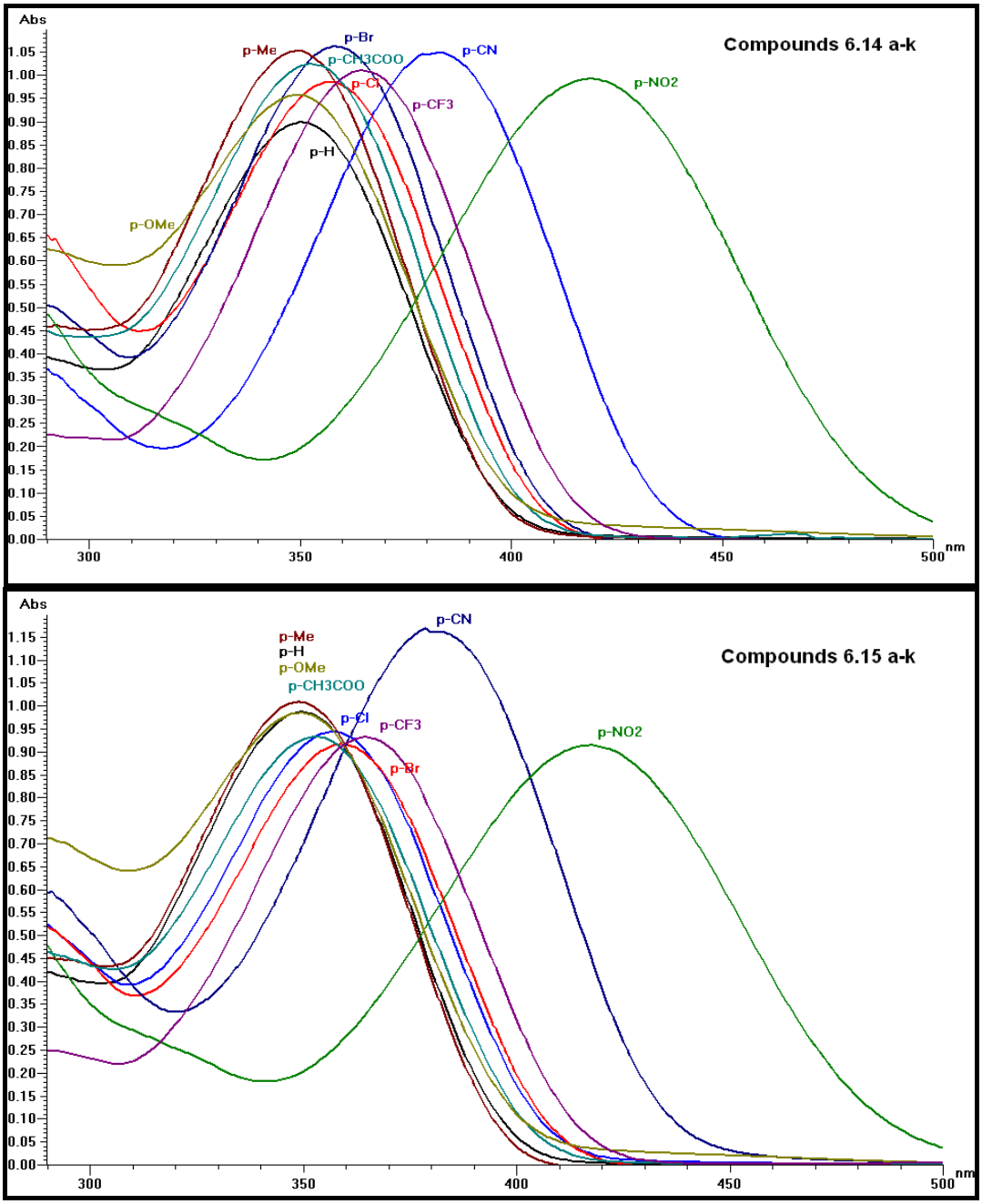


Figure 6.7 UV-VIS spectra of compounds **6.14 a-k**, **6.15 a-k** in 1,2-DCE

In addition, good linear correlations between λ_{max} values and the Hammett substituent constants, σ_p, were obtained for the compounds **6.13**, **6.14** and **6.15** (Figure 6.8-6.10) and the positive correlation results showed EW groups on phenyl ring of nitrilimines have accelerated the cycloaddition reactions with bismaleimides.

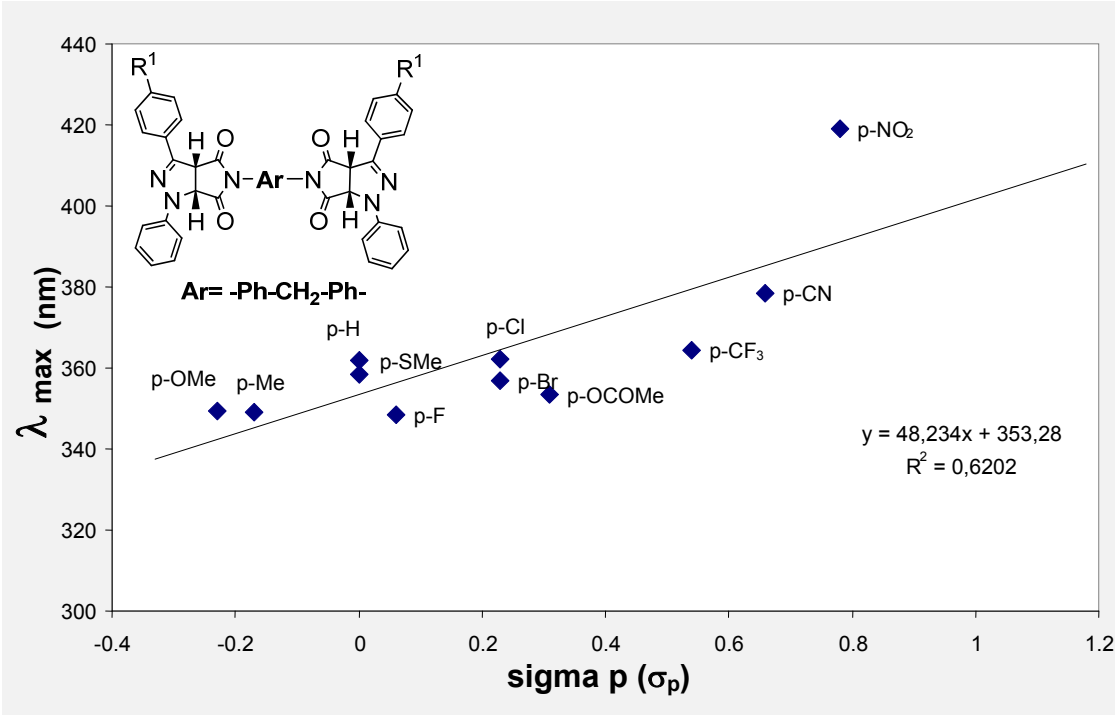


Figure 6.8 Correlation between Hammett σ_p Constants and λ_{max} of compounds **6.13 a-k**

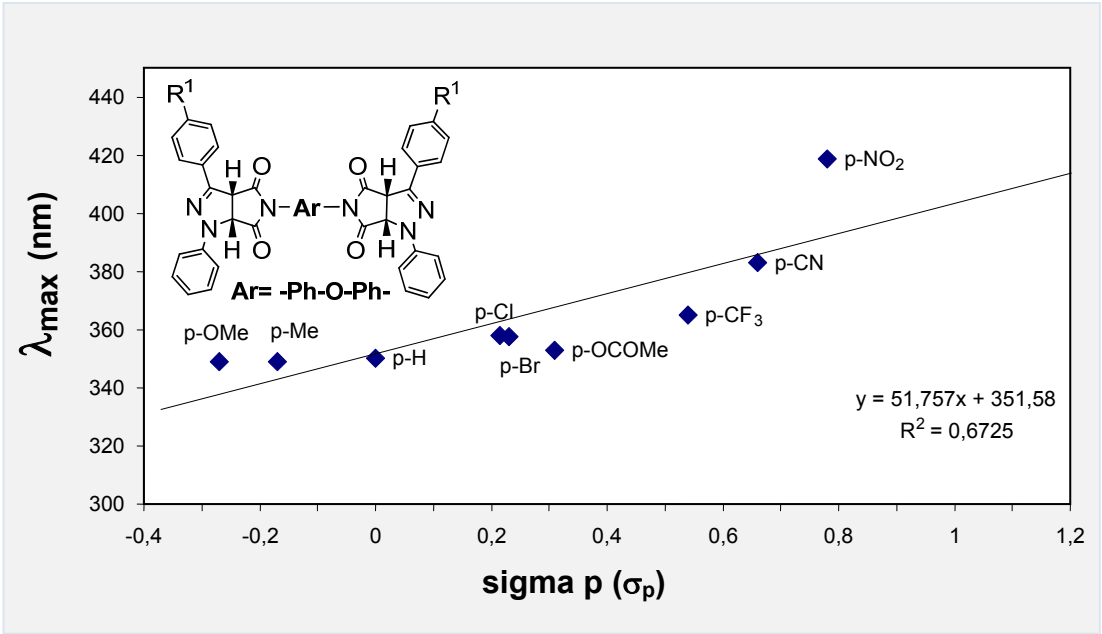


Figure 6.9 Correlation between Hammett σ_p Constants and λ_{max} of compounds **6.14 a-k**

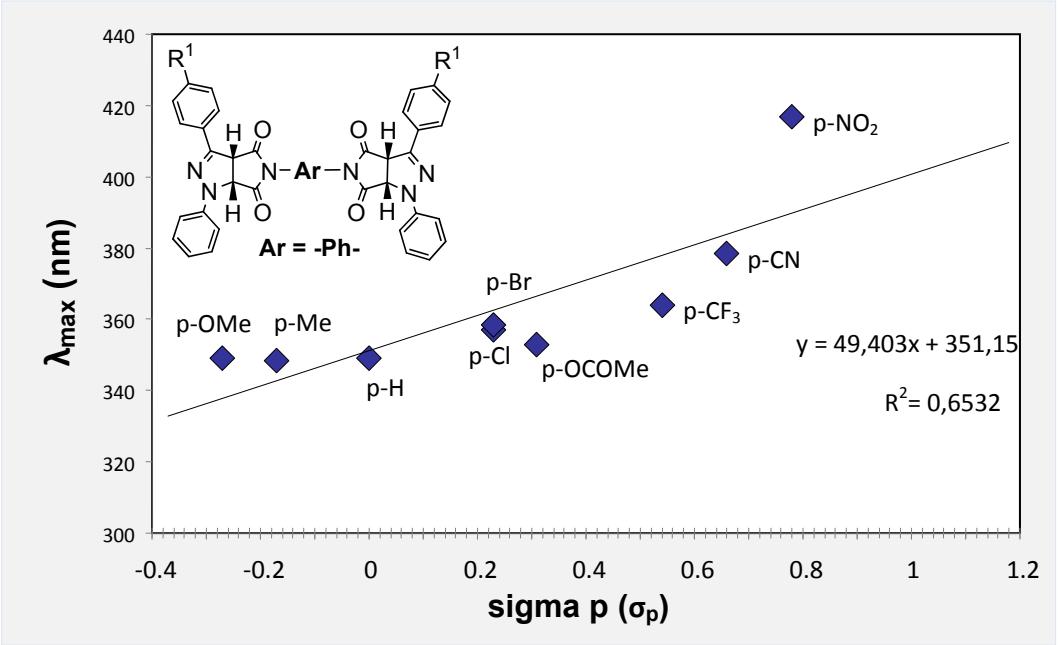
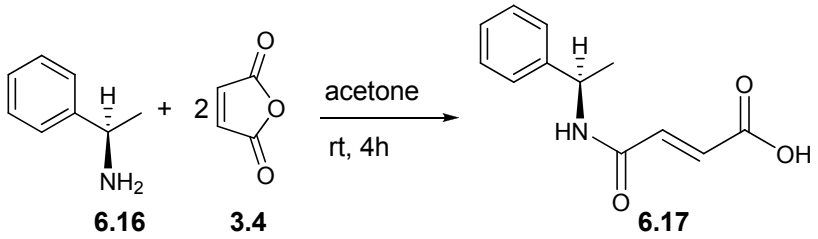


Figure 6.10 Correlation between Hammett σ_p Constants and λ_{max} of compounds **6.15 a-k**

Part 4: 1,3-Dipolar cycloaddition reactions of nitrilimines to chiral *(R)*-*N*-(1-phenylethyl)maleimide

N-Substituted maleimide derivatives find significant applications in synthetic organic chemistry particularly as a source of functionalized *β*-lactams [149], as Diels-Alder dienophiles [150] and as Michael acceptors. In recent literature, there are a few examples of nitrilimine cycloadditions with *N*-substituted maleimide derivatives [151]. The typical method of the preparation of these compounds is the dehydrative condensation of an anhydride and an amine at high temperature and the cyclization of the amic acid in the presence of acidic reagents. Thus, a chiral maleimide, *(R)*-(+)-*N*-(1-phenylethyl) maleimide, was prepared starting from the reaction of (*R*)-(+)-

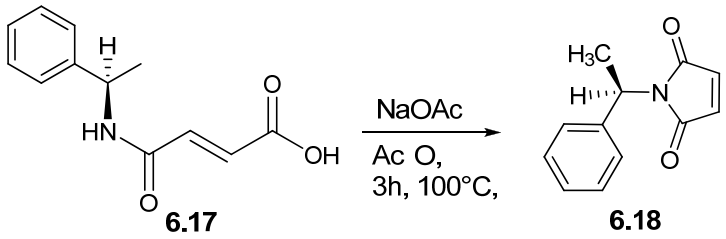
N-(1-phenylethyl) amine **6.16** with maleic anhydride **3.4** yielding *(R,E)*-4-oxo-4-(1-phenylethyl amino) but-2-enoic acid **6.17** in high yield.



6.16 **3.4** **6.17**

Scheme 6.6 Synthesis of precursor of chiral maleimide

In the next step, by thermal cyclisation of intermediate amic acid in acetic anhydride, pure *(R)*-(+)-*N*-(1-phenylethyl)maleimide **6.18** was isolated by column chromatographic separation in moderate yield.



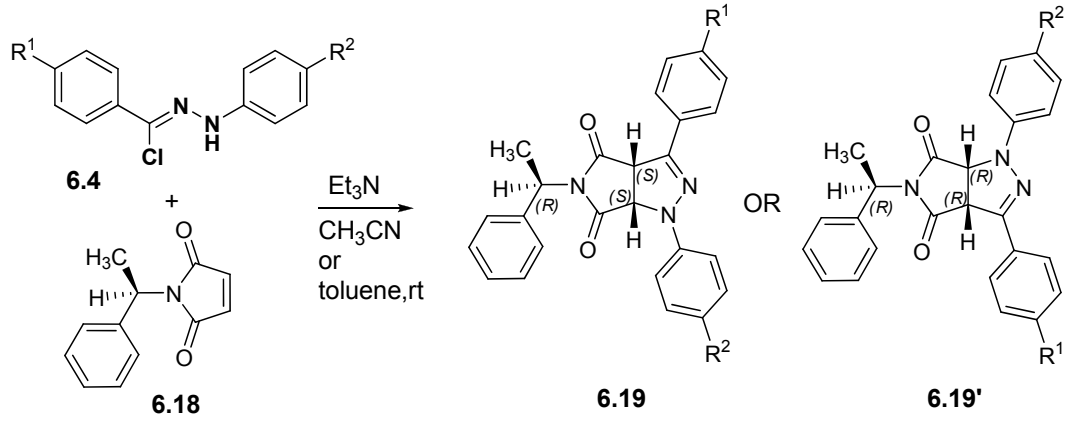
6.17 **6.18**

Scheme 6.7 Preparation of *(R)*-*N*-(1-phenylethyl)maleimide

Absolute configuration of compound **6.18** was determined by measuring its optical rotation which was found as +88.7˚ at 589 nm and 21˚C. Comparison of this result with the literature value (-87.5˚) of *(S)*-(-)-*N*-(1-phenylethyl) maleimide isomer [152], and it was confirmed as the *R*-configuration of our product. Since the product was an oil, it was kept sealed in the fridge for avoiding decomposition.

Nitrilimines which were generated *in situ* from corresponding hydrazonyl chlorides **6.4** by treating with excess Et_3N were reacted with chiral maleimide

6.18 giving either single regioisomer or mixture of regioisomers of pyrrolo[3,4-*c*] pyrazole-4,6-diones **6.19**, **6.19'** in high yields (Table 6.8).

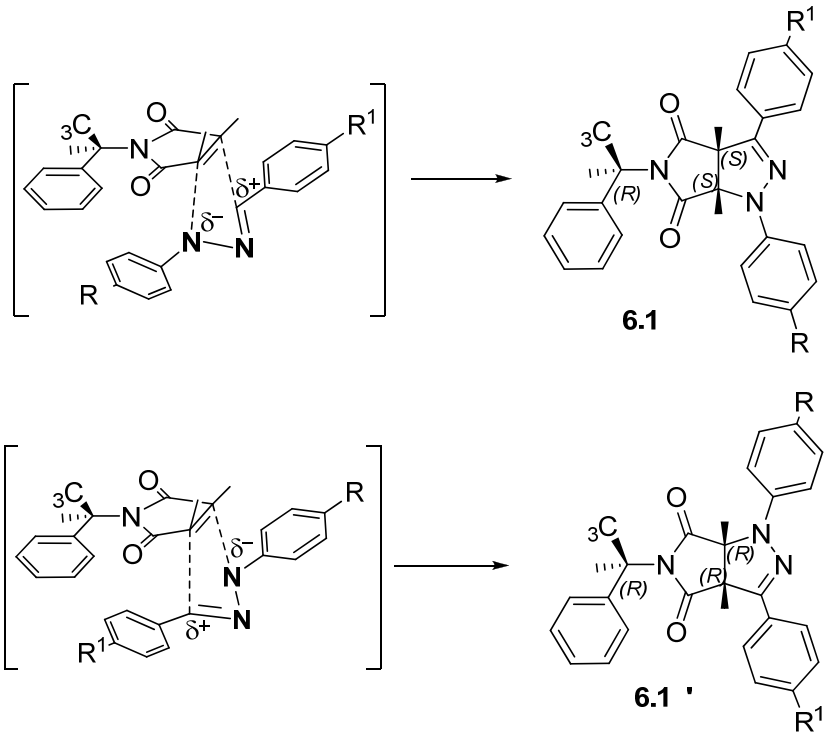


Scheme 6.8 1,3-Dipolar cycloaddition reaction of nitrilimines with chiral maleimide and formation of regioisomers **6.19** and **6.19'**

Comp.	R^1	R^2	Reaction conditions			Yield (%)	$[\alpha]_{589}^{21^oC}$ (c=0.01, acetone)	Regioisomeric ratio 6.19 : 6.19'
6.19a	H	H	Toluene	rt	12h	51	+80.0	50:50
6.19b	Cl	H	CH_3CN	rt	20h	84	+70.0	undetermined
6.19c	Br	H	CH_3CN	rt	48h	72	+60.0	undetermined
6.19d	F	H	CH_3CN	rt	20h	85	+60.0	57:43
6.19g	CN	H	CH_3CN	rt	12h	92	+68.0	undetermined
6.19h	OCH_3	H	CH_3CN	rt	20h	97	+40.0	undetermined
6.19i	SCH_3	H	CH_3CN	rt	20h	91	+44.0	undetermined
6.19j	$OCOCH_3$	H	CH_3CN	rt	3h	71	+79.0	100:0
6.19k	CF_3	H	CH_3CN	rt	8h	70	+12.0	0:100
6.19r	NO_2	Cl	CH_3CN	rt	12h	88	+53.0	undetermined
6.19u	CH_3	CN	CH_3CN	rt	12h	96	+80.0	undetermined

Table 6. 8 Cycloaddition products **6.19 a-u** and reaction conditions

Theoretically, unsymmetrical nitrilimine dipole may approach to chiral maleimide by orientially in two different ways leading to the formation of *exo*-cycloadducts **6.19** and **6.19'** regioselectively.



Scheme 6.9 Regioselective formation of chiral *exo*-cycloadducts

The structures of chiral cycloadducts were identified by means of spectroscopic and physical data including IR, NMR, GC-MS and CHN analyses. After recrystallization of the cycloadducts from suitable solvents, fine crystals could be obtained and then the absolute stereochemistries and regioisomeric ratios of some cycloadducts were determined by X-Ray crystallography. The results of X-Ray single crystal diffraction measurements indicated that the compounds **6.19a**/**6.19a'** and the compounds **6.19d**/**6.19d'** were as a regioisomeric mixture about 1:1 ratio (Figure 6.11). This result also revealed that these cycloaddition reactions are stereospecific due to formation of two regioisomers depending on starting chiral maleimide with *R*-configuration.

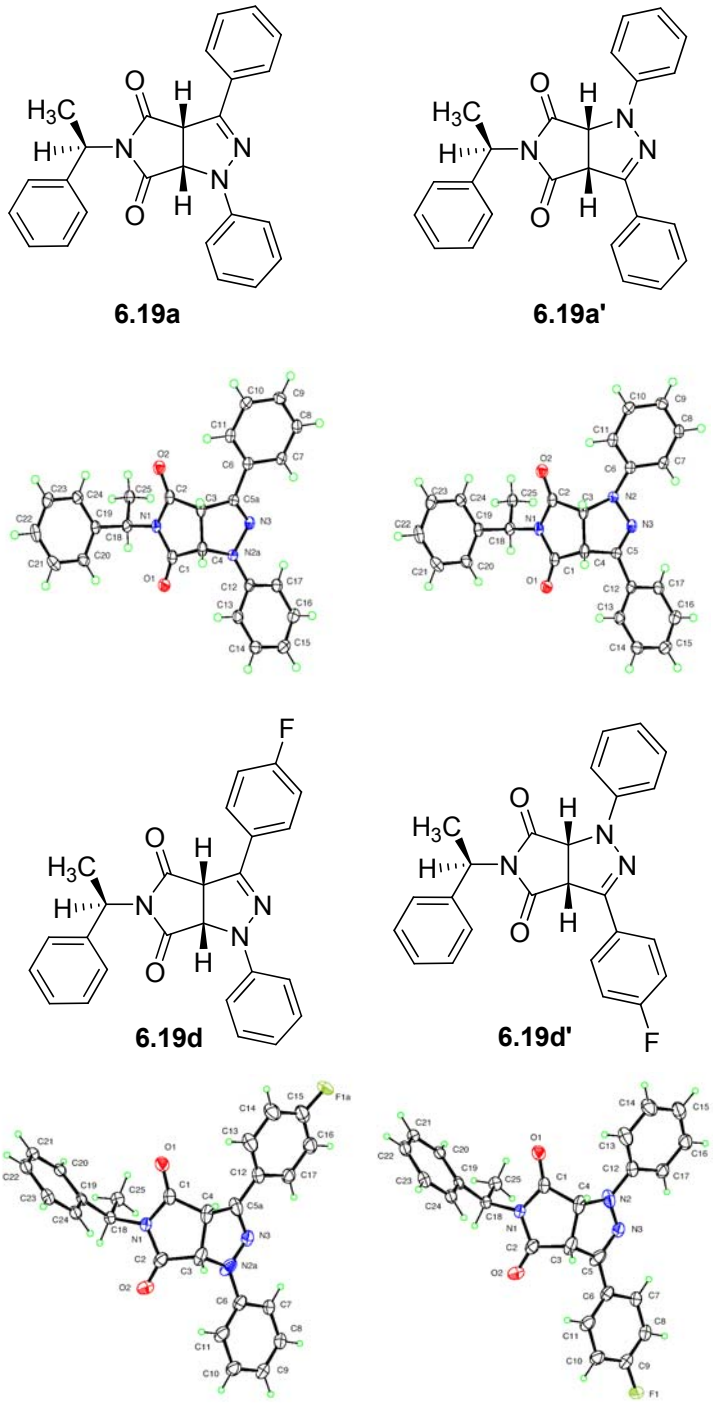


Figure 6.11 Regioisomers **6.19a** and **6.19a'**, **6.19d** and **6.19d'** with X-ray views

The formation of single regioisomer of the compounds **6.19j** and **6.19k'** was demonstrated by their X-Ray diffraction data (Figure 6.12). According to these results, the cycloaddition reactions yielded the cycloadducts **6.19j** and

6.19k' as major product with fully regiocontrolled manner by the orientation of unsymmetrical dipole.

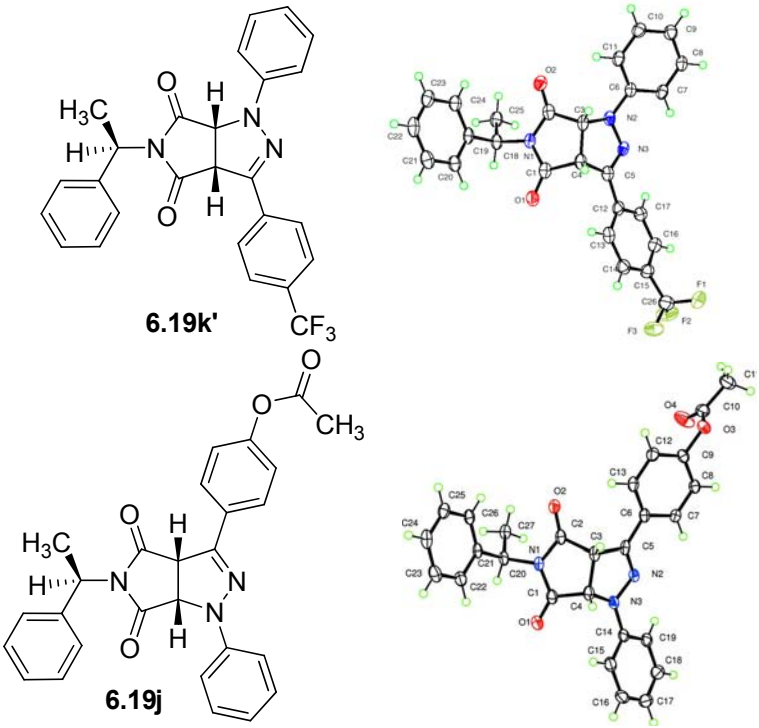


Figure 6.12 Single regioisomers **6.19j** and **6.19k'** with X-ray views

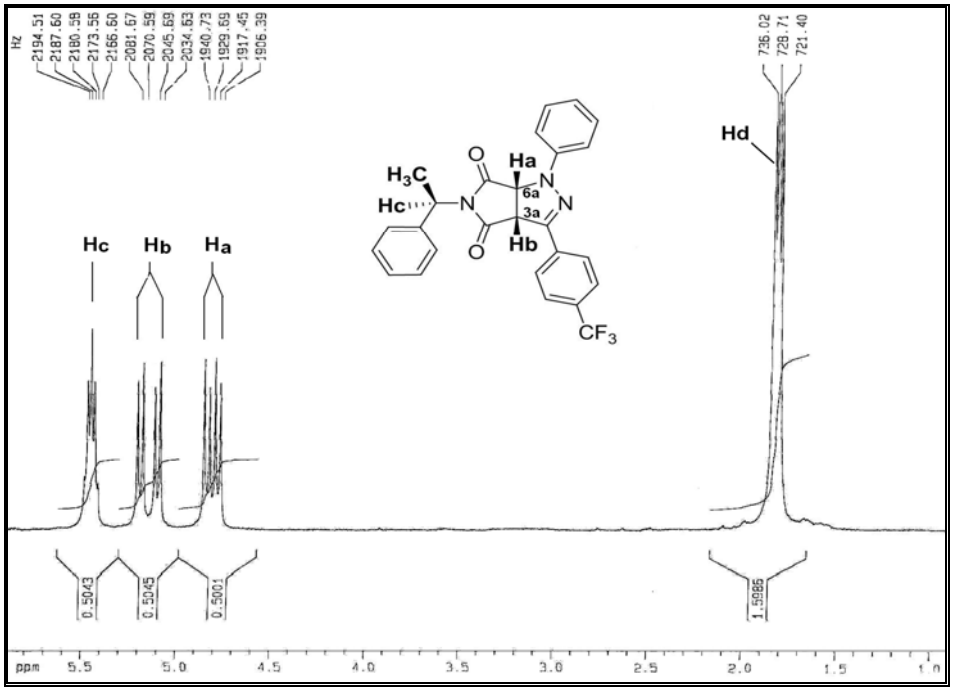


Figure 6.13 Representative expanded ^{1}H-NMR spectrum of compound **6.19k'** indicating splitting patterns of the aliphatic protons

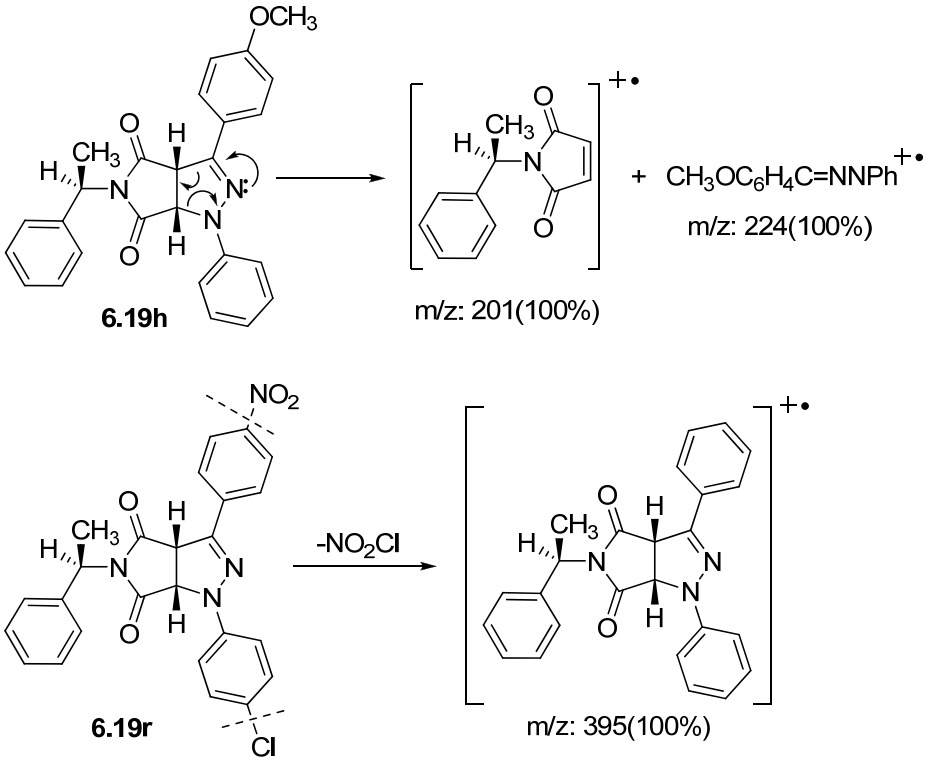
Table 6.9 ^{1}H NMR chemical shifts and coupling constants for aliphatic protons of compounds **6.19a-u** in $CDCl_3$

Comp.	Hc (ppm)	J (Hz)	Hb (ppm)	J (Hz)	Ha (ppm)	J (Hz)	Hd (ppm)	J (Hz)
6.19a	5.30,q	7.2	5.42,dd	10.8, 3.3	5.24,dd	10.8,1.7	1.70,t	4.2
6.19b	5.44,t	7.0	5.01,dd	35.7, 10.9	4.70,dd	22.1, 10.9	1.80,t	7.2
6.19c	5.43,t	7.0	5.01,dd	34.8, 11.0	4.70,dd	22.9, 10.9	1.81,t	7.3
6.19d	5.44, quintet	7.4	5.01,dd	34.6, 10.9	4.70,dd	20.9, 10.9	1.83,t	7.1
6.19g	5.44, quintet	6.7	5.15,dd	32.2, 11.1	4.76,dd	20.1, 11.1	1.81,t	7.0
6.19h	5.37, quintet	7.4	4.95,dd	33.4, 10.7	4.75,dd	24.1, 10.7	1.81,t	7.1
6.19i	5.43, quintet	7.3	4.98,dd	32.7, 10.9	4.75,dd	24.4, 10.9	1.80,t	7.4
6.19j	5.44,t	7.1	4.95,dd	51.1, 10.9	4.70,dd	21.5, 11.0	1.80,t	6.8
6.19k	5.44, quintet	7.0	5.08,dd	29.8, 11.0	4.76,dd	23.2, 11.0	1.82,t	7.3
6.19r	5.57,t	9.7	5.28-5.34, td	10.8,3.3	overlap with H_b signal	-	1.69,t	6.5
6.19u	5.42, quintet	5.8	5.10,dd	29.7, 10.7	4.86, dd	23.2, 10.7	1.80,t	5.7

The ^{1}H-NMR spectra of all the new compounds showed, in each case, two doublets at around 4.7 and 5.0 ppm, assignable to the protons at C-6a and C-3a, respectively. EW or ED substituents on *para* position of phenyl ring attached to azomethine carbon have only slight shielding or deshielding effect on H_b bridge protons. However, the vicinal coupling constants have been shown to be diagnostic, J_{trans} < (6 Hz), J_{cis} (9-12 Hz) [153], so observed coupling constants for H_a and H_b protons are compatible with *cis*-configuration which have been supported by the X-ray ortep views. The IR

spectra of the compounds **6.19a-u** exhibited amide carbonyl absorption bands at around 1705-1710 cm^{-1}. The ^{13}C NMR spectra of all chiral products showed the signals corresponding to amide carbonyl carbons at around 170-174 ppm and the signals corresponding to C=N carbon at around 143-147 ppm.

Upon investigation of EI mass spectra of cycloadducts **6.19a-u**, the vast majority of mass spectra displayed molecular ions as base peak. Only the compounds **6.19h** and **6.19r** showed different fragmentation pattern and ionic species; *m/z*: M^+-$CH_3OC_6H_5C{=}NNC_6H_5$, by retrocycloaddition reaction of cycloadduct **6.19h**, and *m/z*: M^+-NO_2Cl, by producing more stable unsubstituted pyrrolo[3,4-*c*]pyrazole-4,6-dione from cycloadduct **6.19r**.



Scheme 6.10 Mass fragmentation of cycloadducts **6.19h** and **6.19r**

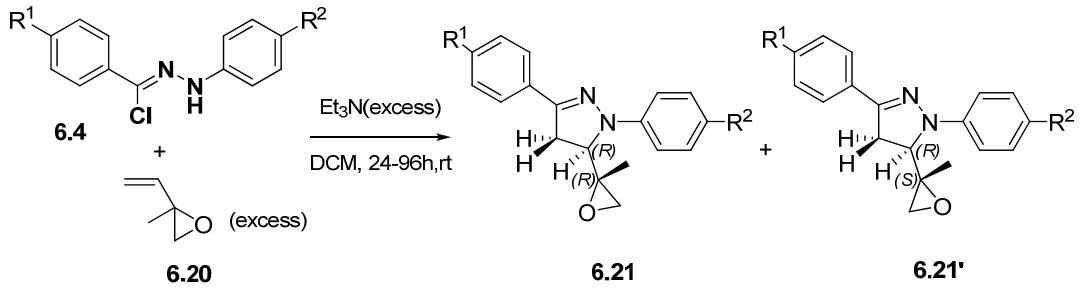
Since the chiral products may have potential biological activities, some biological screening studies are currently being conducted in collaboration with School of Pharmacy, University of London.

Part 5: Nitrilimine Cycloaddition Reactions with 2-methyl-2-vinyl oxirane

In continuation of our interest in the synthesis of heterocycles containing pyrazoline moiety, we attempted to carry out the reaction of nitrilimines with unsymmetrical dipolarophiles which are widely used as key starting materials in the cycloaddition reactions for decades.

To our best knowledge, as a new and unstudied ethylenic dipolarophile, 2-methyl-2-vinyl oxirane **6.20** has been found quite interesting for nitrilimine cycloaddition reactions in some respects. Vinyl oxirane derivatives are attractive precursors for the construction of functionalized 4- and 5-membered or larger rings by Pd-catalyzed or intramolecular Friedel-Craft reactions. However, the examples of cycloaddition reactions of vinyl oxiranes are merely found in literature [154]. Hereby, we will discuss the first example of nitrilimine cycloaddition reactions with vinyl oxiranes.

In theory, the cycloaddition of diarylnitrilimines with unsymmetrical ethylenic dipolarophiles gave rise to formation of 5-regioisomer mostly [155]. However, all *C,N*-diarylsubstituted nitrilimines were generated *in situ* with excess triethylamine **6.4** in dry solvents and afterwards, addition of excess 2-methyl-2-vinyl oxirane **6.20** yielded diastereomers **6.21** and **6.21'** (Scheme 6.11).



Scheme 6.11 1,3-dipolar nitrilimine cycloaddition reaction with 2-methyl-2-vinyl oxirane and formation of diastereomers **6.21** and **6.21'**

Table 6.10 Optimization of reaction conditions to yield compound **6.21** derivatives

Comp.	R^1	R^2	Reaction conditions			Et_3N (eq.)	2M2VO (eq.)	Yield (%)
6.21a-a'	H	H	CH_3CN	reflux	96h	8	1.5	28
6.21a-a'	H	H	CH_3CN	rt	120h	2	1.0	28
6.21f-f'	NO_2	H	CH_3CN	rt	56h	4	1.2	25
6.21f-f'	NO_2	H	DCM	rt	48h	8	2.0	40
6.21f-f'	NO_2	H	DCM	rt	24h	4	2.0	n.r
6.21g-g'	CN	H	DCM	rt	48h	8	2.0	33
6.21u-u'	CH_3	CN	CH_3CN	rt, catalyst	24h	4	1.2	n.r

2M2VO: 2-methyl-2-vinyloxirane

After several trials for the optimization of the reaction conditions, best yields and results were achieved by using three equivalents of 2-methyl-2-vinyl oxirane and eight equivalents of triethylamine at room temperature in DCM (Table 6.10). Although excess amount of triethylamine were used, it did not effect the formation of products in higher yields during the course of reaction.

Table 6.11 Reaction conditions, diastereomeric ratio and yields of title compounds **6.21a-u (a'-u')**

Comp.	R^1	R^2	Reaction conditions		Eq. of Et_3N	Eq. of 2M2VO	Yield* (%)	Diaseteromeric ratio 6.21 : 6.21'
6.21a-a'	H	H	DCM,rt	24h	10	3	92	54:46(i)**
6.21e-e'	CH_3	H	DCM,rt	64h	8	3	80	62:38(i)**
6.21f-f'	NO_2	H	DCM,rt	48h	8	2	40	50:50(s)
6.21h-h'	OCH_3	H	DCM,rt	20h	10	3	65	57:43(i)**
6.21k-k'	CF_3	H	DCM,rt	96h	8	3	84	53:47(s)
6.21o-o'	Br	Cl	DCM,rt	44h	8	3	95	58:42(i)**
6.21r-r'	NO_2	Cl	DCM,rt	64h	9	3	64	36:64(s)
6.21u-u'	CH_3	CN	DCM,rt	96h	8	3	84	56:44(i)**

***** Total yields of two isomers. **Assigned isomeric ratio using ^{1}H-NMR. i=inseparable s=separated

The structure elucidation of the cycloaddition products, namely, 2-methyl-2-oxiranyl-substituted 4,5-dihydro-(*1H*)-pyrazoles were performed by means of physical and spectroscopic methods, principally ^{1}H and ^{13}C NMR, COSY and HSQC NMR, IR, HRMS and X-Ray single crystal diffraction spectra.

Only diastereomers **6.21f-f'**, **6.21k-k'** and **6.21r-r'** could be separated by chromatographic techniques and they were obtained as single diastereomer, the rest of cycloadducts were handled as inseparable diastereomeric mixtures, in this regard, the ratio of diastereomers were assigned based on the integral values of the relevant protons in the proton NMR spectra.

Diastereoselectivity and absolute configurations of the cycloadducts bearing two stereocenters **6.21f**, **6.21f'**, **6.21r'** were established by single crystal X-ray diffraction and 2D-NMR spectra.

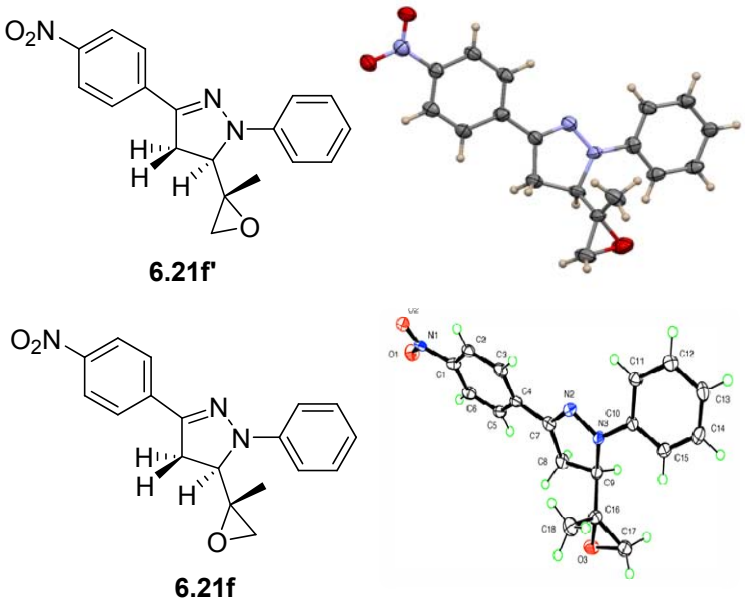


Figure 6.14 Absolute configuration of diastereomers **6.21f** and **6.21f'**

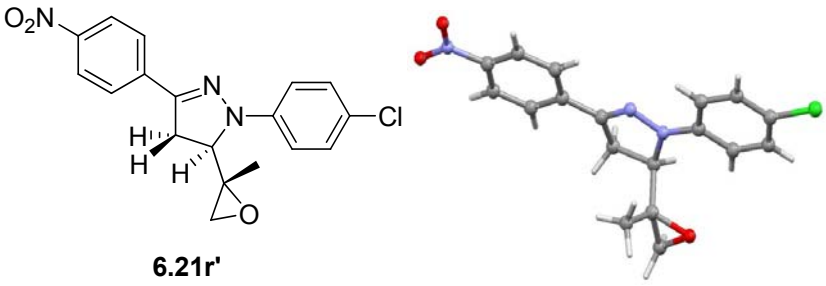


Figure 6.15 Absolute configuration of diastereomer **6.21r'**

Based on the chemical shifts and coupling constants of aliphatic protons in proton NMR, simultaneous formation of two diastereomers in nearly same amounts has been observed and exact ratio of diastereomers has been established by comparing the integral values of aliphatic protons, especially, methyl protons.

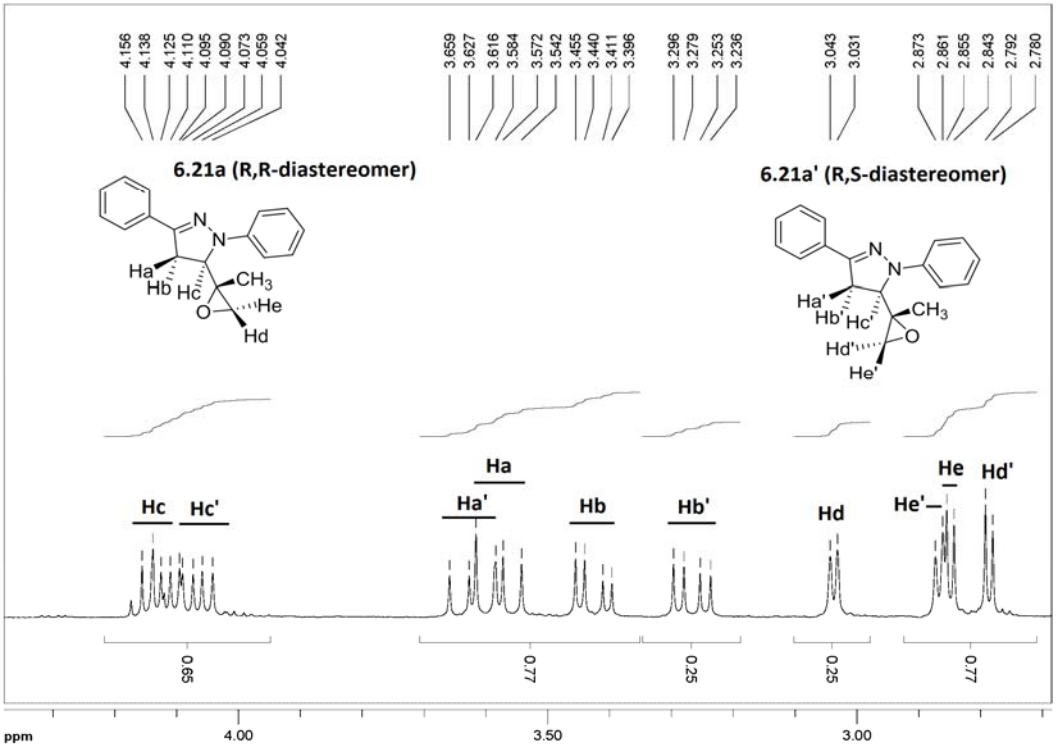


Figure 6.16 Chemical shifts of the aliphatic protons of inseparable diastereo-isomers **6.21a** and **6.21a'** in partial ^{1}H NMR spectrum

As for the ^{1}H NMR spectra of the separated diastereomers, H_a and H_b and also, H_d and H_e protons of compounds **6.21k** and **6.21k'** are diastereotopic, and since they are chemically nonequivalent, it is not suprising that they resonate at slightly different chemical shifts in the proton NMR spectra. However, H_b and H_d protons are found to have been more deshielded in the proton NMR spectrum of *R*,*R*-diastereomer because of the new position of oxygen atom in oxirane ring formed by the rotation around single bond (Figure 6.16). In addition, H_a-H_a', H_c-H_c' and H_e-H_e' proton chemical shifts were clearly seen as overlapped in ^{1}H NMR spectra of inseparable diastereomeric mixture of compounds **6.21a-a'**.

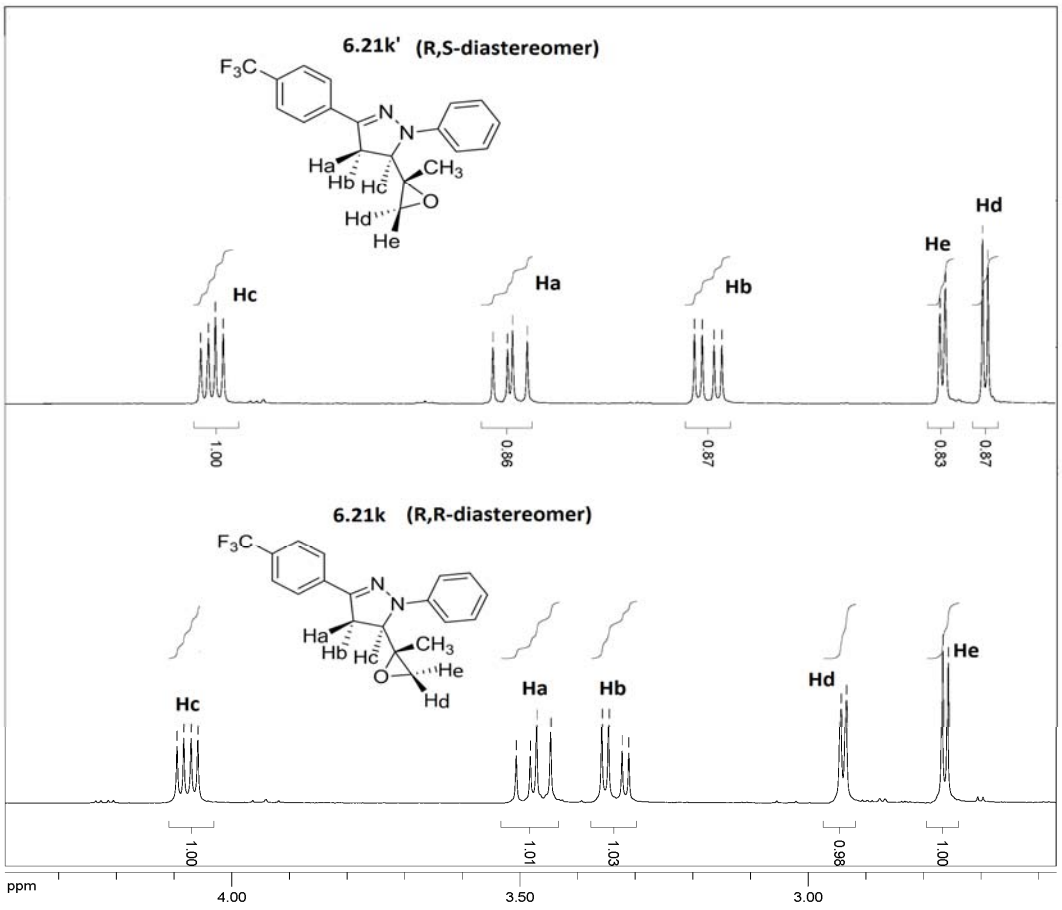
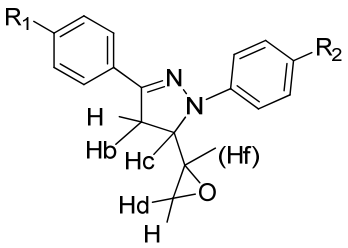


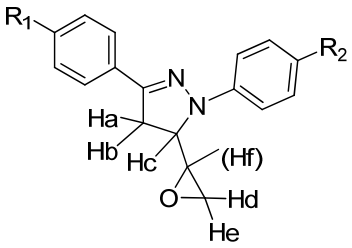
Figure 6.17 Comparison of the important aliphatic proton chemical shifts of separated diastereoisomers **6.21k** and **6.21k'** in partial ^{1}H NMR spectrum

The IR spectra of title compounds **6.21a-u(a'-u')** showed the C=N absorption bands around at 1593-1605 cm^{-1} and C-O-C absorption bands of oxirane rings around at 1100-1180 cm^{-1}. ^{13}C-NMR spectra of all diastereomers showed that the C=N, iminic carbon resonated at around 140-150 ppm and oxirane methinic carbon at around 53-57 ppm.

The nitrilimine cycloaddition reactions with 2-methyl-2-vinyl oxirane yielded *R,R*-diastereomers as major product among the possible two regioisomeric products and it is obviously found that the diastereoselectivity of the reaction is low when the ratio of the diastereoisomers were compared.



6.21



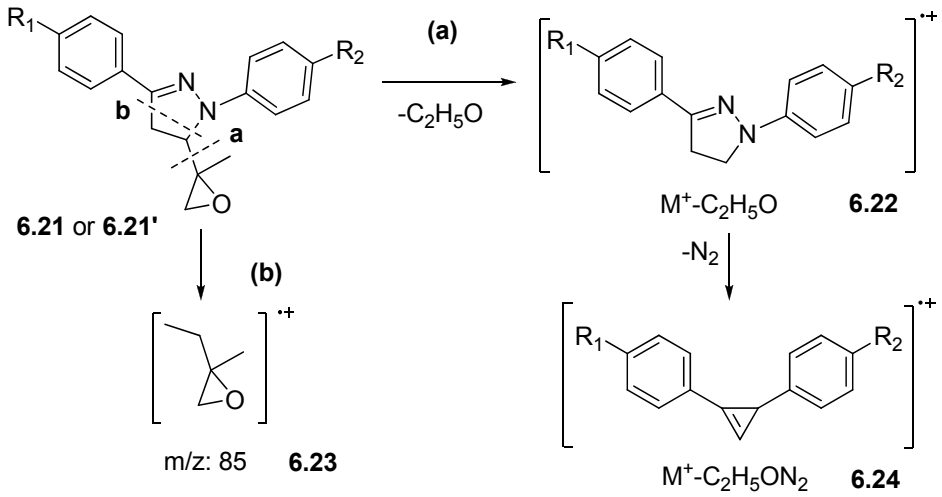
6.21'

Comp.	Ha-Ha' δ (ppm) J(Hz)	Hb-Hb' δ (ppm) J(Hz)	Hc-Hc' δ (ppm) J(Hz)	Hd-Hd' δ (ppm) J(Hz)	He-He' δ (ppm) J(Hz)	Hf-Hf' δ (ppm) J(Hz)
6.21a-a'	3.54-3.65 ,td, 21.8, 12.6	3.39-3.45,dd, 17.6, 5.8 3.23-3.29,dd, 17.2, 6.6	4.04,q, 5.8 4.11,q, 5.6	3.04,d, 4.6 2.78,d, 4.8	2.84, d,4.7 2.86, d,4.7	1.27,s;1.35 ,s
6.21e-e'	3.42-3.54 ,td, 21.7, 11.9	3.27-3.33,dd, 17.6, 5.9 3.11-3.17,dd, 17.2, 6.8	3.91,q, 5.8 3.97,q, 6.8	2.93,d, 4.7 2.68,d, 4.7	2.74, d,4.8 2.76, d,4.8	1.17,s;1.24,s
6.21f-f'	3.55-3.62,dd, 17.7,12.2 3.54-3.62,dd, 17.2,13.0	3.42-3.48,dd, 17.7, 5.9 3.21-3.27,dd, 17.2, 6.7	4.24,q, 5.9 4.16,q, 6.7	3.04,d, 4.4 2.74,d, 4.6	2.87, d,4.6 2.80, d,4.6	1.28,s;1.35 ,s
6.21h-h'	3.41-3.53 ,td, 21.4, 12.5	3.26-3.32,dd, 17.6, 5.9 3.11-3.17,dd, 17.1, 6.8	3.95,q, 6.1 3.90,q, 6.8	2.94,d, 4.7 2.68,d, 4.7	2.77, d,4.7 2.75, d,4.7	1.25,s;1.18 ,s
6.21k-k'	3.44-3.50,dd, 17.6,12.2 3.49-3.55,dd, 17.2,12.8	3.31-3.35,dd, 17.6, 5.8 3.15-3.20,dd, 17.2, 6.8	4.08,q, 5.8 4.05,q, 6.7	2.94,d, 4.7 2.69,d, 4.8	2.75, d,4.7 2.76, d,4.7	1.16,s;1.25 ,s
6.21o-o'	3.42-3.54 ,td, 22.5, 12.8	3.25-3.31,dd, 17.7, 5.8 3.10-3.16,dd, 17.3, 6.7	4.00,q, 5.7 3.90,q, 6.7	2.88,d, 4.7 2.68,d, 4.6	2.74, d,3.2 2.73, d,3.2	1.16,s;1.20 ,s
6.21r-r'	3.48-3.54,dd, 17.6,12.3 3.53-3.59,dd, 17.2,12.9	3.33-3.38,dd, 17.6, 5.7 3.17-3.22,dd, 17.3, 6.7	4.12,q, 9.6 4.05,q, 6.6	2.90,d, 4.6 2.71,d, 4.8	2.76, d,4.6 2.75, d,4.7	1.16,s;1.21 ,s
6.21u-u'	3.48-3.54 ,m	3.30-3.35,dd, 17.7, 4.8 3.15-3.20,dd, 17.4, 5.5	4.10-4.13,dd, 11.8,4.8 3.93-3.96,dd, 12.5, 5.7	2.86,d, 4.6 2.70,d, 4.6	2.74, d,4.6 2.72, d,4.6	1.16,s;1.18 ,s

Table 6.12 ^{1}H NMR chemical shifts and coupling constants for aliphatic protons of diastereomers **6.21a-u** and **6.21a'-u'** in $CDCl_3$

EI and APCI-TOF-MS measurements gave the corresponding molecular ions. For some of the cycloadducts **6.21** or **6.21'**, the base peaks were observed as either 1,3-disubstituted dihydro-1*H*-pyrazole species **6.22** which is formed by the cleavage of oxirane ring from the cycloadducts or

corresponding cyclopropene species **6.24** by the loss of nitrogen from pyrazole species formed and occasionally, base peaks were observed as saturated 2-methyl oxirane species **6.23** by loss of nitrilimine species.



Scheme 6.12 EI or APCI MS spectral fragmentation of title compounds **6.21(6.21')**

6.2. CONCLUSION

In summary, first part of our work includes the preparation of 20 diaryl-substituted hydrazonyl chlorides as precursors of nitrilimines by the chlorination reactions of substituted aromatic aldehyde hydrazones. The hydrazonyl chlorides were characterized by means of IR, ^{1}H and ^{13}C NMR and GC-MS analyses.

In the second part, *C,N*-diaryl subsituted nitrilimines generated *in situ* by the treatment of corresponding diarylsubstituted hydrazonyl chlorides with triethylamine, were reacted with bismaleimides to give rise to the formation of 29 novel dihydrobispyrrolo[3,4-*c*]pyrazole-4,6-diones as single product in excellent yields without needed any chromatographic separation. The structures and relative stereochemistries of biscycloadducts were established

by ^{1}H,^{13}C, COSY, HSQC and NOE NMR spectra and the results were supported by HRMS, IR measurements.

Third part of this work is consisted of Hammett correlation studies in order to examine the effect of *para* substitution on the phenyl ring of biscycloadducts **6.13**, **6.14**, **6.15**, so, the proton NMR chemical shifts of bridge protons and also UV absorption λ_{max} values were plotted against Hammet sigma para constants(σ_p) and excellent correlations have been found and interpreted.

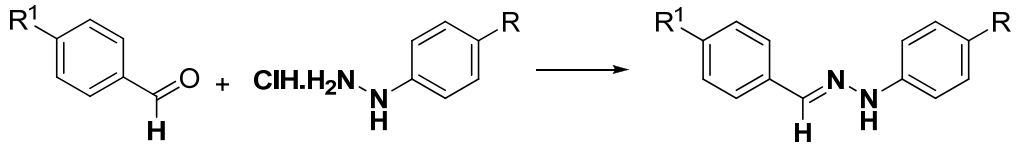
In the fourth part of our research, the nitrilimine cycloaddition reactions with a chiral dipolarophile, *(R)-N*-(1-phenylethyl)maleimide leaded to the formation of 11 novel chiral dihydropyrrolo[3,4-*c*]pyrazole-4,6-dione cycloadducts regioselectively. The structures and stereochemistry of the products were identified by ^{1}H,^{13}C NMR, GC-MS, IR spectra, single crystal X-Ray diffraction and optical rotation measurements.

In the fifth part of our study, to our best knowledge (SciFinder Scholar,Web of Science, Beilstein Crossfire indexes), since no nitrilimine cycloaddition reactions of vinyl oxiranes have been reported, we investigated the reactivity of nitrilimines with 2-methyl-2-vinyloxirane and thus, obtained 6 novel diastereomeric products as single diastereisomers, 5 inseparable diastereomeric mixture of cycloadducts, each containing two diastereomeric products, totally 16 novel heterocyclic products were isolated in moderate to good yields and their stereochemistries were established by ^{1}H,^{13}C, COSY, HSQC NMR, IR spectra, X-ray single crystal diffraction and HRMS measurements.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on BRUKER and VARIAN spectrometers (300, 400 and 500 MHz for proton and 75,100, 125 MHz for carbon) and all chemical shifts are reported in ppm downfield from TMS. IR spectra were recorded on a SHIMADZU FTIR-8400S instruments (KBr pellet or Na-glasses). MALDI-Mass spectra were run on Bruker FTMS 4.7T BioAPEX II instrument and also high resolution mass spectra of the compounds were measured on a Bruker FTMS 4.7T BioAPEX II mass spectrometer. GC-MS spectra were run on Agilent 6890 GC System 5973 MSD instrument. Elemental analyses were performed on Eurovector EA 3000 instrument. The ultraviolet spectra were recorded in 1,2-dichloroethane and THF on a Hitachi U-2900 spectrophotometer at room temperature. Optical rotations of chiral molecules were measured by Rudolph Research Analytical Autopol I Automatic Polarimeter. Single-Crystal X-Ray Diffraction measurements were run on Enraf-Nonius CAD-4 Diffractometer. Chromatotron™ Centrifugal Thin-Layer Chromatograph System were used for isolation of final products. Melting points were determined on a MELTEMP apparatus and uncorrected. TLC was done using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate, phosphomolybdic acid and iodine were used for visualization of the TLC spots.

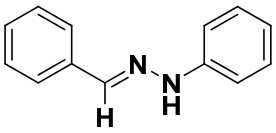
General procedure for the preparation of hydrazones (6.3 a-u)



6.1 **6.2** **6.3**

To a well-stirred solution of phenylhydrazine hydrochloride **6.2** (1.44 g, 10.0 mmol, 10 eq.) in 10 mL of water, solution of **6.1** (10.0 mmol,10 eq.) in 10 mL EtOH was added dropwise and resulting precipitate was stirred for 1 h at room temperature. Finally, the suspension was filtrated to give corresponding hydrazone **6.3** and excess reagents were washed with water (2x50 mL) and EtOH (25 mL), respectively. Finally, powder hydrazone was completely dried under high-vacuum for several hours.

***C,N*-Diphenylhydrazone (6.3a)**

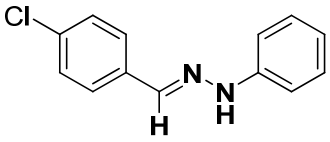


White powder. (1.90 g, 97%).

IR (KBr): $\tilde{\nu}$ = 3311 (N-H), 3026 (Arom. C-H), 1602, 1593, 1494, 1261, 1136, 1066, 929, 756, 690 cm^{-1}.

GC-MS (70 eV): (*m/z*, %) = 196 (100) $[M]^+$, 92(70), 77(30), 65(50), 51(20).

***C*-(4-Chlorophenyl)-*N*-phenyl hydrazone (6.3b)**

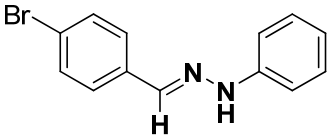


Creamy-white powder. (2.05 g, 89%).

IR (KBr): $\tilde{\nu}$ = 3311 (N-H), 3053 (Arom. C-H), 1599, 1585, 1487, 1299, 1134, 1082, 748, 692 cm^{-1}.

GC-MS (70 eV): (*m/z*, %) = 230 (100) $[M]^+$, 92(80), 75(15), 65(50), 51(10).

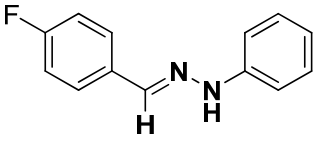
***C*-(4-Bromophenyl)-*N*-phenyl hydrazone (6.3c)**



Light yellow crystals. (2.58 g, 94%).

IR (KBr): $\tilde{\nu}$ = 3304 (N-H), 3051 (Arom. C-H), 1593, 1566, 1512, 1255, 1138, 1070, 904, 821, 756, 696 cm^{-1}.

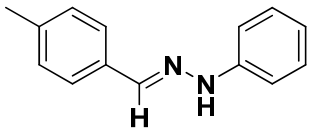
***C*-(4-Fluorophenyl)-*N*-phenyl hydrazone (6.3d)**



White powder. (1.85 g, 87%).

IR (KBr): $\tilde{\nu}$ = 3311 (N-H), 3068 (Arom. C-H), 1600, 1504, 1444, 1263, 1234, 1136, 1091, 837, 752, 692 cm^{-1}.

***C*-(4-Methylphenyl)-*N*-phenyl hydrazone (6.3e)**

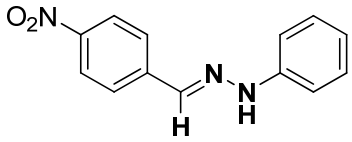


White powder. (1.82 g, 87%).

IR (KBr): $\tilde{\nu}$ = 3309 (N-H), 3010 (Arom. C-H), 1595, 1500, 1492, 1259, 1130, 815, 748, 692 cm^{-1}.

GC-MS (70 eV): (*m/z*, %) = 210 (100) $[M]^+$, 118(15), 92(50), 65(50), 51(10).

***C*-(4-Nitrophenyl)-*N*-phenyl hydrazone (6.3f)**

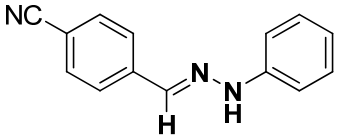


Red powder. (2.31 g, 96%).

IR (KBr): $\tilde{\nu}$ = 3302 (N-H), 3053 (Arom. C-H), 1595, 1556, 1496, 1327, 1273, 1166, 1107, 916, 752, 694 cm^{-1}.

GC-MS (70 eV): (*m/z*, %) = 241 (80) $[M]^+$, 92(100), 75(15), 65(60), 51(10), 39 (15).

***C*-(4-Cyanophenyl)-*N*-phenyl hydrazone (6.3g)**

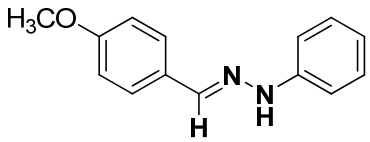


Yellow powder. (2.10 g, 95%).

IR (KBr): $\tilde{\nu}$ = 3277 (N-H), 3036 (Arom. C-H), 2220 (CΞN), 1602, 1577, 1494, 1261, 1157, 835, 750, 690 cm^{-1}.

GC-MS (70 eV): (*m/z*, %) = 221 (100) $[M]^+$, 92(100), 65(50), 51(15), 39 (15).

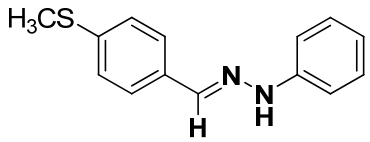
***C*-(4-Methoxyphenyl)-*N*-phenyl hydrazone (6.3h)**



White crystals. (3.15 g, 93%).

IR (KBr): $\tilde{\nu}$ = 3313 (N-H), 3053 (Arom. C-H), 2835, 1597, 1508, 1296, 1246, 1128, 1028, 821, 748, 694 cm^{-1}.

***C*-(4-Thiomethylphenyl)-*N*-phenyl hydrazone (6.3i)**

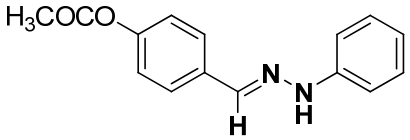


Yellow-pink powder. (2.30 g, 95%).

IR (KBr): $\tilde{\nu}$ = 3294 (N-H), 3032 (Arom. C-H), 2914, 1602, 1595, 1491, 1263, 1132, 810, 748, 692 cm^{-1}.

GC-MS (70 eV): (*m/z*, %) = 242 (100) $[M]^+$, 93(40), 77 (20), 65(30), 51(10), 39 (10).

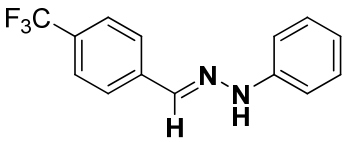
***C*-(4-Acetoxyphenyl)-*N*-phenyl hydrazone (6.3j)**



White powder. (2.40 g, 95%).

IR (KBr): $\tilde{\nu}$ = 3308 (N-H), 3057 (Arom. C-H), 1745 (C=O), 1602, 1570, 1494, 1266, 1230, 1193, 1066, 927, 748, 696 cm^{-1}.

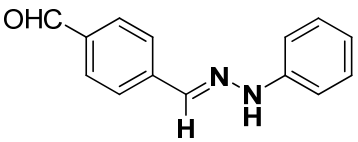
***C*-(4-Trifluoromethylphenyl)-*N*-phenyl hydrazone (6.3k)**



White powder. (2.48 g, 94%).

IR (KBr): $\tilde{\nu}$ = 3292 (N-H), 3032 (Arom. C-H), 1595, 1523, 1508, 1489, 1329, 1257, 1101, 1066, 835, 752, 692 cm^{-1}.

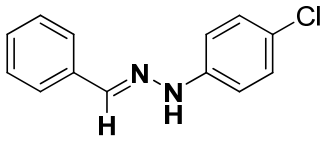
***C*-(4-formylphenyl)-*N*-phenyl hydrazone (6.3l)**



Yellow powder. (2.15 g, 85%).

IR (KBr): $\tilde{\nu}$ = 3296 (N-H), 3053 (Arom. C-H), 1681 (H-C=O), 1600, 1579, 1541, 1494, 1257, 1136, 914, 750, 692 cm^{-1}.

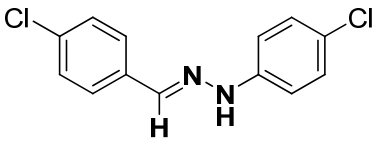
***C*-Phenyl-*N*-(4-chlorophenyl) hydrazone (6.3m)**



White-yellow powder. (0.84 g, 73%).

IR (KBr): $\tilde{\nu}$ = 3317 (N-H), 3057 (arom. CH), 2986, 1602, 1593, 1514, 1487, 1257, 1136, 813, 758, 692 cm^{-1}.

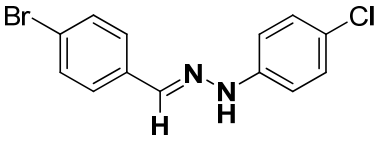
***C*-(4-Chlorophenyl)-*N*-(4-chlorophenyl) hydrazone (6.3n)**



Light brown-orange powder. (1.18 g, 91%).

IR (KBr): $\tilde{\nu}$ = 3296 (N-H), 2963, 2831, 1597, 1585, 1521, 1506, 1489, 1238, 1093, 1030, 835, 806 cm^{-1}.

***C*-(4-Bromophenyl)-*N*-(4-chlorophenyl) hydrazone (6.3o)**

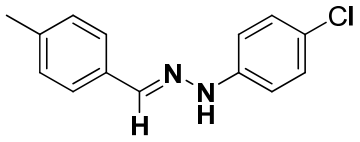


Light brown powder. (1.35 g, 88%).

IR (KBr): $\tilde{\nu}$ = 3308 (N-H), 3063 (arom. CH), 2962, 1599, 1593, 1508, 1487, 1253, 1089, 825 cm^{-1}.

GC-MS (70 eV): (*m/z*, %) = 310 (100) $[M]^+$, 125(70), 99(25), 75(15).

***C*-(4-Methylphenyl)-*N*-(4-chlorophenyl) hydrazone (6.3p)**

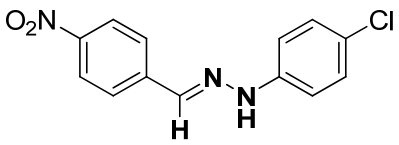


Light orange powder. (1.07 g, 88%).

IR (KBr): $\tilde{\nu}$ = 3317 (N-H), 3032 (arom. CH), 2916, 1599, 1500, 1508, 1406, 1253, 1091, 827 cm^{-1}.

GC-MS (70 eV): (*m/z*, %) = 244 (100) $[M]^+$, 126(50), 91(20), 65(10).

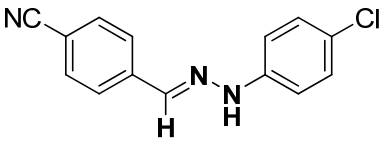
***C*-(4-Nitrophenyl)-*N*-(4-chlorophenyl) hydrazone (6.3r)**



Red crystalline powder. (1.24 g, 90%).

IR (KBr): $\tilde{\nu}$ = 3288 (N-H), 3047 (arom. CH), 1593, 1566, 1508, 1485, 1330, 1261, 1107, 819 cm^{-1}.

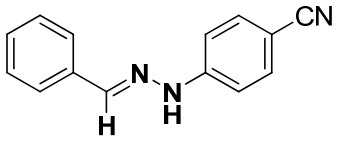
***C*-(4-Cyanophenyl)-*N*-(4-chlorophenyl) hydrazone (6.3s)**



Yellow crystalline powder. (1.04 g, 48%).

IR (KBr): $\tilde{\nu}$ = 3304 (N-H), 2222 (C≡N), 1602, 1573, 1521, 1485, 1330, 1261, 1157, 823 cm^{-1}.

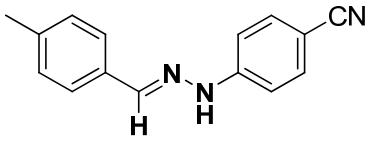
***C*-Phenyl-*N*-(4-cyanophenyl) hydrazone (6.3t)**



Pale pink powder. (0.84 g, 76%).

IR (KBr): $\tilde{\nu}$ = 3294 (N-H), 3069 (arom. CH), 2212 (CΞN), 1608, 1529, 1496, 1271, 1170, 933, 831 cm^{-1}.

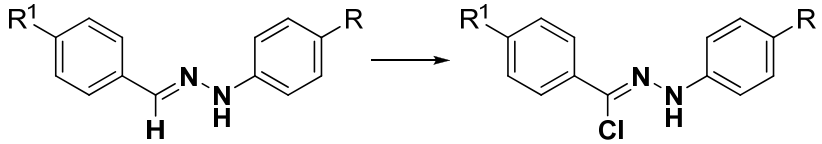
***C*-(4-Methylphenyl)-*N*-(4-cyanophenyl) hydrazone (6.3u)**



Pale orange crystals. (1.09 g, 93%).

IR (KBr): $\tilde{\nu}$ = 3252 (N-H), 3020 (arom. CH), 2214 (CΞN), 1608, 1597, 1535, 1273, 1174, 1136, 839, 810 cm^{-1}.

General procedure for the preparation of hydrazonyl chlorides (6.4 a-u)

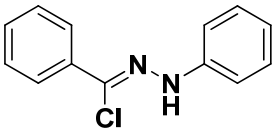


6.3 **6.4**

N-Chlorosuccinimide (10 mmol,1.33 g) was dissolved in CH_2Cl_2 (70 mL) and stirred at 0˚C. Dimethyl sulfide (18 mmol, 1.12 g) was added at 0˚C and a white precipitate that formed almost immediately was allowed to stir for 10 min 0˚C. The reaction mixture was cooled to -40˚C and a solution of

corresponding hydrazone **6.3** (6 mmol) was added to it. The progress of reaction was monitored by TLC (1-2 h) and reaction mixture was allowed to warm to 0˚C over 1h and finally, quenched with cold water. All CH_2Cl_2 was rotaevaporated to precipitate hydrazonyl chloride **6.4** in water and it was collected by filtration and dried under high-vacuum. Finally, hydrazonyl chloride **6.4** was recrystallized from CH_2Cl_2-pet. ether for purification.

***C,N*-Diphenyl hydrazonyl chloride (6.4a)**



Yellow powder. (1.00 g, 90%). M.p. 128-130˚C. R_f: 0.85 (ethyl acetate-n-hexane; 1:3).

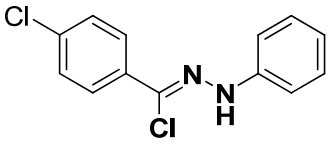
IR (KBr): $\tilde{\nu}$ = 3306 (N-H), 3051(Arom. C-H), 1600 (C=N), 1572, 1502, 1257, 1136, 1168, 943, 756, 684 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.08 (s, 1H), 7.96-7.98 (d, *J*=9.6 Hz, 2H), 7.41-7.47 (m, 3H), 7.34-7.37 (t, *J*=8.5 Hz, 2H), 7.21-7.23 (d, *J*=9.5 Hz, 2H), 6.97-7.00 (t, *J*=7.3 Hz ,1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=143.4, 134.5, 129.4, 129.2, 128.4, 126.4, 124.7, 121.2, 113.4.

GC-MS (70 eV): (*m/z*, %) = 194 (100) $[M]^+$-HCl, 167(15), 77(20), 51(10), 39(5).

***C*-(4-Chlorophenyl)-*N*-phenyl hydrazonyl chloride (6.4b)**



Orange-red powder. (1.93 g, 83%). M.p. 143-145˚C. R_f: 0.85 (ethyl acetate-n-hexane; 1:3).

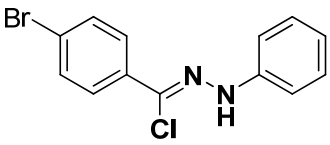
IR (KBr): $\tilde{\nu}$ = 3309 (N-H), 1600 (C=N), 1575, 1485, 1226, 1151, 1093, 941, 827,756, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.06 (s, 1H), 7.87-7.89 (d, *J*=8.7 Hz, 2H), 7.39-7.41 (d, *J*=8.7 Hz, 2H), 7.33-7.36 (t, *J*=8.4 Hz, 2H), 7.19-7.21 (d, *J*=7.4 Hz, 2H), 6.97-7.00 (t, *J*=7.3 Hz ,1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=143.1, 135.1, 133.0, 129.4, 128.6, 127.5, 123.5, 121.4, 113.5.

GC-MS (70 eV): (*m/z*, %) = 228 (100) $[M]^+$-HCl, 166(20), 65(40), 75(20), 63(10).

***C*-(4-Bromophenyl)-*N*-phenyl hydrazonyl chloride (6.4c)**



Light brown powder. (2.11 g, 75%). M.p. 146-148˚C. R_f: 0.85 (ethyl acetate-n-hexane; 1:3).

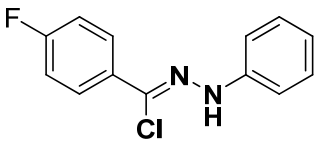
IR (KBr): $\tilde{\nu}$ = 3309 (N-H), 1600 (C=N), 1573, 1504, 1483, 1230, 1151, 1070, 941, 825, 756, 678 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.07 (s, 1H), 7.80-7.82 (d, *J*=8.7 Hz, 2H), 7.55-7.57 (d, *J*=8.7 Hz, 2H), 7.34-7.36 (t, *J*=8.4 Hz, 2H), 7.19-7.20 (d, *J*=7.6 Hz, 2H), 6.97-7.00 (t, *J*=7.3 Hz ,1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=143.1, 133.4, 131.6, 129.4, 127.7, 123.5, 123.4, 121.4, 113.5, 113.4.

GC-MS (70 eV): (*m/z*, %) = 272 (100) $[M]^+$-HCl, 192(15), 166(15), 137(10), 83(10).

_C_-(4-Fluorophenyl)-_N_-phenyl hydrazonyl chloride (6.4d)



Brown crystals. (1.84 g, 88%). M.p. 117-119˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:4).

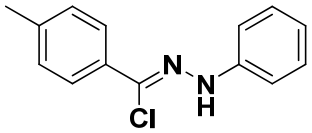
IR (KBr): $\tilde{\nu}$ = 3309 (N-H), 3051(Arom. C-H), 1595 (C=N), 1577, 1508, 1236, 1149, 1136, 941, 833, 754, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.02 (s, 1H), 7.92-7.95 (m, 2H), 7.33-7.36 (t, *J*=7.5 Hz, 2H), 7.19-7.21 (d, *J*=7.6 Hz, 2H), 7.11-7.14 (t, *J*=8.6 Hz ,2H), 6.97-7.00 (t, *J*=7.3 Hz ,1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=164.3, 162.3, 143.3, 130.6, 129.4, 128.2, 128.3, 123.6, 121.2, 115.5, 115.4, 113.4.

GC-MS (70 eV): (*m/z*, %) = 248 (50) $[M]^+$, 212 (80) $[M]^+$-HCl, 91(100), 65(30).

***C*-(4-Methylphenyl)-*N*-phenyl hydrazonyl chloride (6.4e)**



Light yellow crystals. (1.51 g, 90%). M.p. 134-135˚C. R_f: 0.80 (ethyl acetate-n-hexane; 1:3).

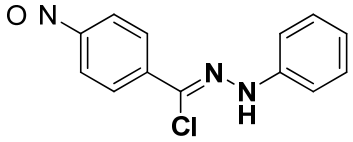
IR (KBr): $\tilde{\nu}$ = 3313 (N-H), 3030(Arom. C-H), 1602 (C=N), 1581, 1500, 1433, 1265, 1134, 941, 813, 756, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.91 (s, 1H), 7.72-7.74 (d, *J*=8.3 Hz, 2H), 7.21-7.24 (t, *J*=7.5 Hz, 2H), 7.08-7.13 (q, *J*=8.0 Hz, 4H), 6.83-6.86 (t, *J*=7.3 Hz ,1H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=143.5, 139.4, 131.8, 129.4, 129.1, 126.4, 124.9, 121.0, 113.4, 21.3 (-CH_3).

GC-MS (70 eV): (*m/z*, %) = 208 (100) $[M]^+$-HCl, 178(10), 91(15), 65(15), 39(10).

***C*-(4-Nitrophenyl)-*N*-phenyl hydrazonyl chloride (6.4f)**



Orange powder. (1.35 g, 91%). M.p. 151-153˚C. R_f: 0.85 (ethyl acetate-n-hexane; 1:2).

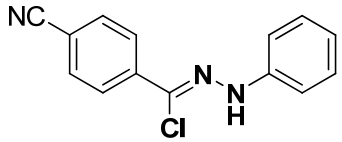
IR (KBr): $\tilde{\nu}$ = 3319 (N-H), 3074(Arom. C-H), 1602 (C=N), 1550, 1508, 1360, 1166, 949, 852, 742, 684 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.2-8.15 (m, 3H), 7.96-7.98 (d, *J*=7.0 Hz, 2H), 7.25-7.28 (dd, *J*=8.6, 1.2 Hz, 2H), 7.10-7.13 (d, *J*=8.2 Hz, 2H), 6.93-6.96 (d, *J*=7.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 148.5, 143.2, 141.0, 130.3, 127.5, 124.5, 123.0, 122.8, 114.5.

GC-MS (70 eV): (*m/z*, %) = 239 (100) $[M]^+$-HCl, 209(25), 166(25), 91(10), 63(15).

***C*-(4-Cyanophenyl)-*N*-phenyl hydrazonyl chloride (6.4g)**



Yellow powder. (1.40 g, 60%). M.p. 145-146˚C. R_f: 0.60 (ethyl acetate-n-hexane; 1:1).

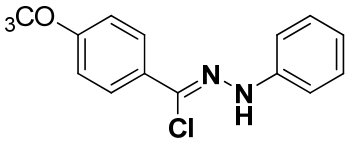
IR (KBr): $\tilde{\nu}$ = 3311 (N-H), 3075(Arom. C-H), 1602 (C=N), 1560, 1496, 1232, 1165, 945, 746, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.23 (s, 1H), 8.02-8.04 (d, *J*=8.6 Hz, 2H), 7.69-7.71(d, *J*=8.6 Hz, 2H), 7.35-7.38 (t, *J*=7.4 Hz, 2H), 7.21-7.23 (d, *J*=7.6 Hz, 2H), 7.01-7.04 (t, *J*=7.3 Hz,1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=142.5, 138.4, 132.2, 129.5, 126.5, 122.4, 122.1, 118.6, 113.7, 112.1.

GC-MS (70 eV): (*m/z*, %) = 219 (100) $[M]^+$-HCl, 132(10), 102(5), 63(5), 51(5).

***C*-(4-Methoxyphenyl)-*N*-phenyl hydrazonyl chloride (6.4h)**



Brown powder. (2.67 g, 76%). M.p. 109-111˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:3).

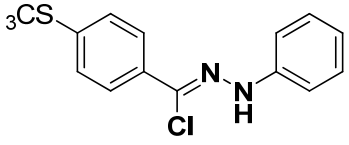
IR (KBr): $\tilde{\nu}$ = 3315 (N-H), 3051(Arom. C-H), 2837, 1602 (C=N), 1504, 1435, 1259, 1172, 1111, 941, 827, 754, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.97 (s, 1H), 7.87-7.89 (d, *J*=8.9 Hz, 2H), 7.53 (d, *J*=4.1 Hz, 1H), 7.32-7.34 (t, *J*=7.0 Hz, 2H), 7.18-7.19 (d, *J*=7.6 Hz, 2H), 6.94-6.96 (m,4H), 3.87(s,3H)(-OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 160.6, 143.6, 129.3, 127.9, 127.2, 124.7, 120.8, 113.8, 113.3, 55.4.

GC-MS (70 eV): (*m/z*, %) = 224 (100) $[M]^+$-HCl, 209(50), 181(20), 152(15), 112(10), 77(5), 63(5).

***C*-(4-Thiomethylphenyl)-*N*-phenyl hydrazonyl chloride (6.4i)**



Yellow-green powder. (2.10 g, 81%). M.p. 132-133˚C. R_f: 0.80 (ethyl acetate-n-hexane; 1:3).

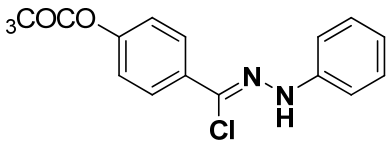
IR (KBr): $\tilde{\nu}$ = 3313 (N-H), 3053 (Arom. C-H), 2918, 1600 (C=N), 1506, 1435, 1269, 1139, 939, 819, 754, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.03 (s, 1H), 7.84-7.86 (d, *J*=8.6 Hz, 2H), 7.33-7.35 (t, *J*=7.5 Hz, 2H), 7.27-7.29 (d, *J*=8.6 Hz, 2H), 7.19-7.20 (d, *J*=7.6 Hz, 2H), 6.95-6.98 (t, *J*=7.3 Hz, 1H), 2.54(s,3H)(-SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 143.3, 140.3, 131.1, 129.4, 126.7, 125.8, 124.4, 121.1, 113.4, 15.4.

GC-MS (70 eV): (*m/z*, %) = 240 (100) $[M]^+$-HCl, 225(60), 192(15), 120(10), 63(5).

***C*-(4-Acetoxyphenyl)-*N*-phenyl hydrazonyl chloride (6.4j)**



Light brown powder. (2.17 g, 80%). M.p. 123-125˚C. R_f: 0.80 (ethyl acetate-n-hexane; 1:3).

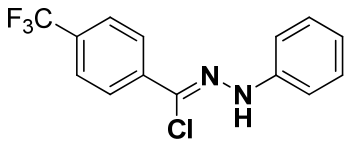
IR (KBr): $\tilde{\nu}$ = 3317 (N-H), 3051(Arom. C-H), 1755 (C=O), 1585 (C=N), 1498, 1220, 1168, 1138, 943, 758, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.94 (s, 1H), 7.83-7.86 (d, *J*=8.8 Hz, 2H), 7.21-7.25 (t, *J*=8.5 Hz, 2H), 7.05-7.10 (m, 4H), 6.85-6.88(t, *J*=7.3 Hz, 1H), 2.24(s,3H)(-$COCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 169.2(C=O), 151.3, 143.2, 132.1, 129.4, 127.5, 123.7, 121.6, 121.2, 113.4, 21.1(-$COCH_3$).

GC-MS (70 eV): (*m/z*, %) = 252 (10) $[M]^+$-HCl, 210(100), 181(10), 152(10), 127(5), 63(5).

_C_-(4-Trifluoromethylphenyl)-_N_-phenyl hydrazonyl chloride (6.4k)



Yellow powder. (1.27 g, 45%). M.p. 124-126˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:4).

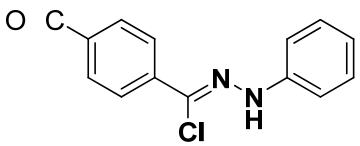
IR (KBr): $\tilde{\nu}$ = 3309 (N-H), 3055(Arom. C-H), 1602 (C=N), 1573, 1504, 1408, 1330, 1230, 1136, 1168,1128, 947, 842, 756, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.16 (s, 1H), 8.04-8.05 (d, *J*=8.2 Hz, 2H), 7.67-7.69 (d, *J*=8.3 Hz, 2H), 7.35-7.38 (t, *J*=8.3 Hz, 2H), 7.21-7.23 (d, *J*=7.6 Hz, 2H), 7.00-7.03 (t, *J*=7.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=142.8, 137.7, 129.5, 126.4, 125.4, 125.4, 125.3, 123.0, 121.7, 113.6.

GC-MS (70 eV): (*m/z*, %) = 298 (50) $[M]^+$, 262(20) $[M]^+$-HCl, 91(100), 65(25).

_C_-(4-formylphenyl)-_N_-phenyl hydrazonyl chloride (6.4l)



Yellow powder. (1.0 g, 50%). M.p. 166-168˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:2).

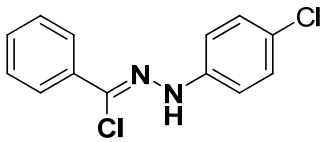
IR (KBr): $\tilde{\nu}$ = 3331 (N-H), 3051(Arom. C-H), 1691 (HC=O), 1600 (C=N), 1572, 1498, 1271, 1151, 1114, 939, 837,746, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 10.0(s, 1H), 8.24 (s, 1H), 8.10-8.13 (t, *J*=9.4 Hz, 2H), 7.97(s, 1H), 7.92-7.94 (d, *J*=8.5 Hz, 1H), 7.34-7.37 (t, *J*=6.8 Hz, 2H), 7.21-7.25 (t, *J*=7.2 Hz, 2H), 6.99-7.01(m,1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 191.5 (HC=O), 143.1, 134.9, 129.4, 126.2, 124.0, 121.9, 121.4, 113.7, 113.5.

GC-MS (70 eV): (*m/z*, %) = 222 (100) $[M]^+$-HCl, 193(20), 164(10), 110(5), 77(5).

_C_-Phenyl-_N_-(4-chlorophenyl) hydrazonyl chloride (6.4m)



Orange powder. (0.79 g, 82%). M.p. 108-109˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:2).

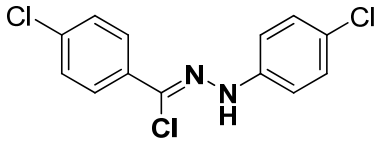
IR (KBr): $\tilde{\nu}$ = 3315 (N-H), 3034(Arom. C-H), 1597 (C=N), 1566, 1500, 1234, 1138, 1097, 945, 825, 761, 675 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.05 (s, 1H), 7.93-7.95 (dd, *J*=8.3, 1.6 Hz, 2H), 7.41-7.44 (m, 3H), 7.28-7.30 (d, *J*=8.8 Hz, 2H), 7.13-7.15 (d, *J*=8.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=142.0, 134.2, 129.4, 129.3, 128.4, 126.4, 125.8, 125.5, 114.6.

GC-MS (70 eV): (*m/z*, %) = 228 (100) $[M]^+$-HCl, 192(10), 166(10), 77(10).

***C*-(4-Chlorophenyl)-*N*-(4-chlorophenyl) hydrazonyl chloride (6.4n)**



Light orange powder. (1.06 g, 83%). M.p. 144-145˚C. R_f: 0.80 (ethyl acetate-n-hexane; 1:2).

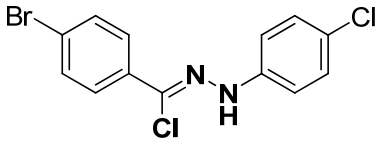
IR (KBr): $\tilde{\nu}$ = 3329 (N-H), 3057(Arom. C-H), 1593 (C=N), 1579, 1502, 1487, 1238, 1156, 1091, 947, 825, 713, 611 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.04 (s, 1H), 7.85-7.87 (d, *J*=8.8 Hz, 2H), 7.39-7.41 (d, *J*=8.8 Hz, 2H), 7.28-7.30 (d, *J*=8.6 Hz, 2H), 7.11-7.13 (d, *J*=8.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=141.7, 135.4, 132.7, 129.3, 128.6, 127.5, 126.1, 124.3, 114.6.

GC-MS (70 eV): (*m/z*, %) = 262 (100) $[M]^+$-HCl, 192(10), 163(10), 111(10), 75(10).

***C*-(4-Bromophenyl)-*N*-(4-chlorophenyl) hydrazonyl chloride (6.4o)**



Light orange powder. (1.33 g, 90%). M.p. 148-148˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:2).

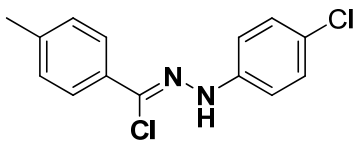
IR (KBr): $\tilde{\nu}$ = 3331 (N-H), 3025(Arom. C-H), 1579 (C=N), 1504, 1483, 1236, 1151, 1089, 939, 821, 700, 605 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.04 (s, 1H), 7.77-7.79 (d, *J*=8.7 Hz, 2H), 7.54-7.56 (d, *J*=8.7 Hz, 2H), 7.27-7.30 (d, *J*=8.8 Hz, 2H), 7.11-7.12 (d, *J*=8.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=141.7, 133.1, 131.6, 129.3, 127.8, 126.1, 124.4, 123.7, 114.6.

GC-MS (70 eV): (*m/z*, %) = 308 (100) $[M]^+$-Cl, 192(20), 163(15), 75(10).

***C*-(4-Methylphenyl)-*N*-(4-chlorophenyl) hydrazonyl chloride (6.4p)**



Red-brown powder. (0.85 g, 71%). M.p. 109-111˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:2).

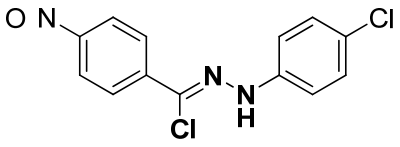
IR (KBr): $\tilde{\nu}$ = 3338 (N-H), 3030(Arom. C-H), 1593 (C=N), 1496, 1402, 1240, 1136, 1087, 941, 817, 705, 623 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.00 (s, 1H), 7.81-7.83 (d, *J*=8.2 Hz, 2H), 7.27-7.29 (d, *J*=8.7 Hz, 2H), 7.23-7.24 (d, *J*=8.0 Hz, 2H), 7.11-7.13 (d, *J*=8.7 Hz, 2H), 2.42 (s,3H)(-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ=142.1, 139.7, 131.5, 129.3, 129.1, 126.4, 125.7, 125.6, 114.5, 21.3(-CH_3).

GC-MS (70 eV): (*m/z*, %)= 242 (100) $[M]^+$-HCl, 178 (10), 152 (10), 91 (10), 65 (10).

_C_-(4-Nitrophenyl)-_N_-(4-chlorophenyl) hydrazonyl chloride (6.4r)



Orange powder. (1.33 g, 96%). M.p. 219-220˚C. R_f: 0.80 (ethyl acetate-n-hexane; 1:2).

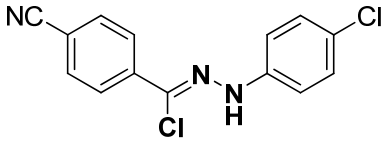
IR (KBr): $\tilde{\nu}$ = 3284 (N-H), 3082 (Arom. C-H), 1599 (C=N), 1560, 1521, 1338, 1238, 1165, 1091, 947, 812, 750, 613 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.29 (s, 1H), 8.26-8.28 (d, *J*=8.8 Hz, 2H), 8.07-8.09 (d, *J*=8.6 Hz, 2H), 7.32-7.34 (d, *J*=8.3 Hz, 2H), 7.16-7.18 (d, *J*=8.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=144.6, 143.4, 141.0, 139.9, 129.5, 126.7, 123.8, 122.9, 115.0.

GC-MS (70 eV): (*m/z*, %)= 273 (100) $[M]^+$-HCl, 243 (20), 192 (30), 164 (20), 82(10), 65 (10).

***C*-(4-Cyanophenyl)-*N*-(4-chlorophenyl) hydrazonyl chloride (6.4s)**



Orange powder. (1.09 g, 94%). M.p. 215-217˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:2).

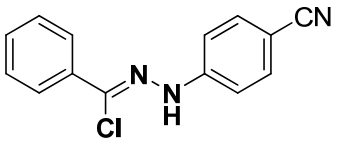
IR (KBr): $\tilde{\nu}$ = 3279 (N-H), 2222 (CΞN), 1600 (C=N), 1570, 1552, 1481, 1238, 1159, 1087, 945, 839, 719, 621 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.21 (s, 1H), 8.02-8.03 (d, *J*=8.4 Hz, 2H), 7.70-7.72 (d, *J*=8.4 Hz, 2H), 7.30-7.32 (d, *J*=8.7 Hz, 2H), 7.14-7.16 (d, *J*=8.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=141.2, 138.2, 132.2, 129.5, 126.8, 126.6, 123.2, 118.5, 114.9, 112.4.

GC-MS (70 eV): (*m/z*, %)= 253 (100) $[M]^+$-HCl, 191 (10), 102 (10), 62 (10).

***C*-Phenyl-*N*-(4-cyanophenyl) hydrazonyl chloride (6.4t)**



Orange powder. (0.85 g, 80%). M.p. 138-140˚C. R_f: 0.75 (ethyl acetate-n-hexane; 1:2).

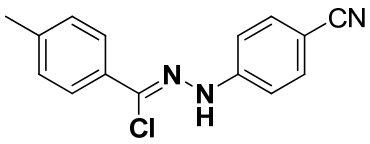
IR (KBr): $\tilde{\nu}$ = 3273 (N-H), 3063 (Arom.CH), 2218 (CΞN), 1606 (C=N), 1518, 1444, 1327, 1271, 1170, 1138, 943, 829, 759, 686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.30 (s, 1H), 7.94-7.96 (m,2H), 7.60-7.61 (d, *J*=8.8 Hz, 2H), 7.45-7.47 (m,3H), 7.23-7.25 (d, *J*=8.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=146.5, 140.2, 133.8, 130.1, 128.6, 128.0, 126.7, 113.5, 110.0, 103.5.

GC-MS (70 eV): (*m/z*, %)= 219 (100) $[M]^+$-HCl, 192 (10), 164 (5), 77 (20), 51 (10).

***C*-(4-Methylphenyl)-*N*-(4-cyanophenyl) hydrazonyl chloride (6.4u)**



Pale red powder. (1.18 g, 95%). M.p. 192-194˚C. R_f: 0.90 (ethyl acetate-n-hexane; 1:2).

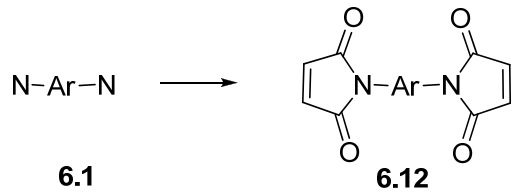
IR (KBr): $\tilde{\nu}$ = 3282 (N-H), 3064 (Arom.CH), 2216 (CΞN), 1602 (C=N), 1510, 1417, 1257, 1172, 1107, 941, 840, 744, 630 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.26 (s, 1H), 7.82-7.84 (d, *J*=8.3 Hz, 2H), 7.59-7.60(d, *J*=8.8 Hz, 2H), 7.21-7.28 (q, *J*=7.9 Hz, 4H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=146.6, 140.5, 133.8, 131.0, 129.3, 128.3, 126.7, 119.6, 113.4, 103.2, 21.3.

GC-MS (70 eV): (*m/z*, %)= 233 (100) $[M]^+$-HCl, 205 (5), 176 (3), 191 (8), 63 (5).

General procedure for the preparation of *N,N'*-(substituted)bis (maleimides) (6.12a-c)

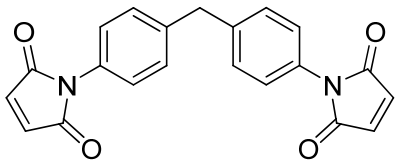


6.1 **6.12**

(Step 1) - A suitable 4,4'-diamine **6.10** (9.4 mmol) was dissolved and stirred in 20 mL of acetone. A solution of maleic anhydride (2.00 g, 20.4 mmol) in 15 mL of acetone was added dropwise over 15 min and stirred at room temperature for 2h. The reaction mixture was poured into 100 mL ice-water to precipitate the yellow product. The precipitate was obtained by filtration and dried under vacuum to yield corresponding 4,4'-bis(maleic acid), which was directly used in next step without further purification (yield: 90-96%).

(Step 2) - 4,4'-bis(maleic acid) (5.0 mmol), anhydrous sodium acetate (0.84 g, 10.2 mmol) and 15 mL (159.3 mmol) acetic anhydride were added into a three-necked flask. The reaction mixture was heated to 90-100˚C for 3h and after cooling to room temperature, reaction mixture was poured into 40 mL of ice-water mixture with stirring for 1h. The precipitate was obtained by suction filtration, washed with water and diethyl ether. The product was dried under vacuum and recrystallized from ethanol to yield corresponding 4,4'-bis(maleimide) **6.12a-c**. (yield: 80-85%).

1,1'-(4,4'-Methylenebis(4,1-phenylene))bismaleimide (6.12a)



Pale yellow powder (84%), R_f: 0.4 (ethyl acetate-n-hexane; 1:2).

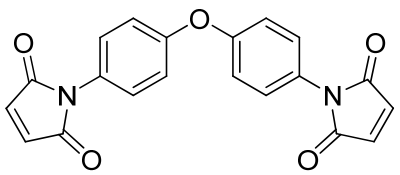
IR (KBr): $\tilde{\nu}$ = 3464, 3105, 3036 (Arom. C-H), 1707 (C=O), 1512, 1394, 1213, 1149, 837, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.29-7.30 (d, *J*=8.4 Hz, 4H), 7.26-7.28 (d, *J*=8.6 Hz, 4H), 6.85 (s, 4H), 4.05 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=170.0, 140.8, 134.6, 130.6, 129.8. 126.6, 41.5.

TOF-MS EI+: (*m/z*, %)= 358 (70) $[M]^+$, 261 (15), 83 (100). HRMS calculated for $C_{21}H_{14}N_2O_4$ 358.0954 found 358.0957.

1,1'-(4,4'-Oxybis(4,1-phenylene))bismaleimide (6.12b)



Yellow powder (85%),M.p. 175-177˚C. R_f: 0.55 (ethyl acetate-n-hexane; 1:2).

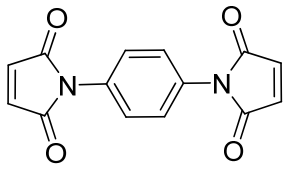
IR (KBr): $\tilde{\nu}$ = 3583, 3097, 3070 (Arom. C-H), 1720 (C=O), 1506 (C-O-C), 1402, 1257, 1155, 827, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.33-7.35 (d, *J*=8.7 Hz, 4H), 7.13-7.15 (d, *J*=8.7 Hz, 4H), 6.88 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=169.5, 156.3, 134.2, 127.7, 126.5. 119.5.

GC-MS (70 eV): (*m/z*, %) = 360 (100) $[M]^+$, 290 (10), 188 (10).

1,1'-(1,4-Phenylene)bismaleimide (6.12c)



Yellow powder (80%), R_f: 0.60 (ethyl acetate-n-hexane; 1:2).

IR (KBr): $\tilde{\nu}$ = 3462, 3105, 3070 (Arom. C-H), 1705 (C=O), 1521, 1392, 1290, 1153, 846, 667 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.81 (s, 2H), 7.40 (s,4H), 6.95 (s, 4H).

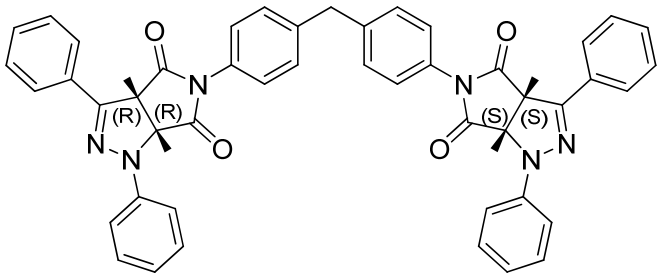
^{13}C NMR (100 MHz, $CDCl_3$): δ=174.5, 139.8, 135.9, 131.9.

TOF-MS EI+: (*m/z*, %)= 268 (100) $[M]^+$, 198 (20), 83 (15). HRMS calculated for $C_{14}H_8N_2O_4$ 268.0484 found 268.0485.

Sythesis of 5,5'-substituted-dihydrobis(pyrrolo[3,4-*c*]pyrazoles) (6.13, 6.14, 6.15)

Typical procedure - Corresponding hydrazonyl chloride **6.4** (1.0 mmol) and bis(maleimide) **6.12 a-c** (0.5 mmol) were dissolved in dry acetonitrile (20 mL). Et_3N (0.404 g, 4 mmol) was added dropwise into the mixture with stirring and after addition is complete, the reaction mixture was stirred at room temperature for 2-4 h. The progress of reaction was monitored by TLC. After the reaction is complete, all CH_3CN was rotaevaporated and the reaction mixture was mixed with 50 mL of water and allowed to dissolve all $Et_3N.HCl$ salt and deposit the crystals of corresponding cycloadduct **6.13**, **6.14** or **6.15**. The powder crystals formed from water was collected by suction filtration and washed with water (2x50 mL), hexane (2x25 mL) and finally, dried under vacuum for 1-2 h.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis(1,3-diphenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione) (6.13a)**



Yellow crystalline solid. (0.190 g, quant.). M.p. 278-280˚C. R_f: 0.75 (ethyl acetate-n-hexane; 1:2).

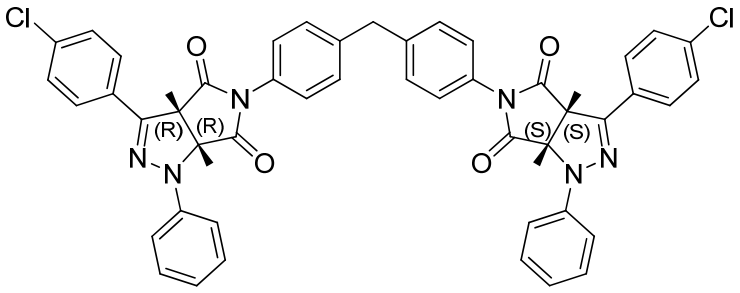
IR (KBr): $\tilde{\nu}$ = 3057 (Arom. C-H), 1720 (C=O),1597 (C=N), 1511, 1494, 1379, 1193, 752, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.05 (d, *J*=8.0 Hz, 4H), 7.58 (d, *J*=8.0 Hz, 4H), 7.51-7.32 (m, 18H), 7.03 (t, *J*=7.2 Hz, 2H), 5.30 (d, *J*=11.0 Hz, 2H), 5.05 (d, *J*=10.9 Hz, 2H), 4.01 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.7 (C=O), 170.8 (C=O), 144.6 (C=N), 142.9, 141.2, 130.3, 129.7, 129.6, 129.5, 129.3, 128.6, 127.2, 126.4, 121.6, 114.5, 65.6 (-CH), 53.5 (-CH), 41.0 ($-CH_2-$).

HRMS calculated for $C_{47}H_{34}N_6O_4$ 746.2985 found ($M+NH_4^+$) 764.2991.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis[3-(4-chlorophenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.13b)**



Yellow-grey crystalline solid. (0.190 g, 92%). M.p. 194-196˚C. R_f : 0.70 (ethyl acetate-n-hexane; 1:2).

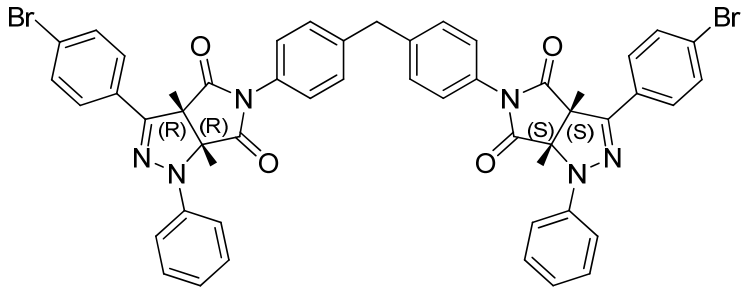
IR (KBr): $\tilde{\nu}$= 3057 (Arom. C-H), 1720 (C=O), 1599 (C=N), 1512, 1492, 1379, 1193, 752,690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.03 (d, *J*=8.0 Hz, 4H), 7.62 (d, *J*=8.0 Hz, 4H), 7.40 (t, *J*=8.1 Hz 8H), 7.22 (s, 8H), 7.03 (t, *J*=7.0 Hz 2H), 5.30 (d, *J*=10.9 Hz, 2H), 4.97 (d, *J*=10.9 Hz, 2H), 4.00 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.7 (C=O), 170.9 (C=O), 144.8 (C=N), 142.0, 141.8, 135.5, 130.0, 129.7, 129.5, 129.4, 129.3, 128.7, 126.7, 121.8, 114.8, 65.8 (-CH), 53.0 (-CH), 41.0 ($-CH_2$).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 814 (100) $[M]^+$, 815 (51) $[MH]^+$, 816 (70) $[M]^+$+2, 817 (30) $[M]^+$+3. HRMS calculated for $C_{47}H_{32}Cl_2N_6O_4$ 814.1862 found 814.1852.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis[3-(4-bromophenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.13c)**



Yellow crystalline solid. (0.230 g, quant.). M.p. 180-182˚C. R_f : 0.77 (ethyl acetate-n-hexane; 1:2).

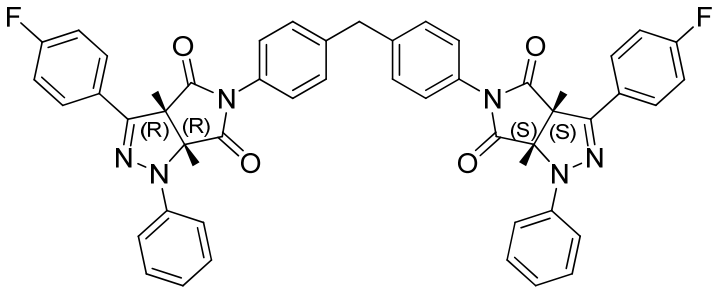
IR (KBr): $\tilde{\nu}$= 3057 (Arom. C-H), 1720 (C=O), 1599 (C=N), 1512, 1498, 1375, 1192, 750, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.98 (d, *J*=8.0 Hz, 4H), 7.64 (d, *J*=9.0 Hz, 4H), 7.58 (d, *J*=9.0 Hz, 4H), 7.38 (t, *J*=7.4 Hz 4H), 7.25-7.19 (q, *J*=8.0 Hz 8H), 7.04 (t, *J*=12.3 Hz 2H), 5.34 (d, *J*=11.1 Hz, 2H), 5.01 (d, *J*=11.0 Hz, 2H), 4.02 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.4 (C=O), 170.6 (C=O), 151.5 (C=N), 144.2, 141.8, 141.3, 131.8, 129.8, 129.4, 129.3, 128.6, 126.3, 121.8, 114.6, 77.2, 65.7 (-CH), 53.4 (-CH), 41.0 (-CH_2-).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 902 (50) $[M]^+$, 904 (100) $[M]^+$+2, 906 (60) $[M]^+$+4. HRMS calculated for $C_{47}H_{32}Br_2N_6O_4$ 902.0852 found 902.0849.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis[3-(4-fluorophenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.13d)**



Orange crystalline solid. (0.210 g, quant.). M.p. 183-185˚C. R_f : 0.77 (ethyl acetate-n-hexane; 1:2).

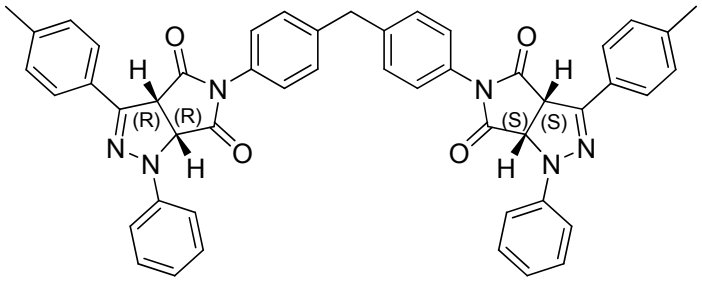
IR (KBr): $\tilde{\nu}$= 3059 (Arom. C-H), 1724 (C=O), 1597 (C=N), 1512, 1492, 1381, 1193, 839, 750, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.10-8.07 (q, *J*=5.4, 2.3 Hz 4H), 7.62 (d, *J*=9.0 Hz, 4H), 7.37 (t, *J*=7.5 Hz 4H), 7.39-7.15 (m, 8H), 7.11 (t, *J*=7.8 Hz, 4H), 7.03 (t, *J*=6.8 Hz, 2H), 5.22 (d, *J*=11.3 Hz, 2H), 4.92 (d, *J*=10.9 Hz, 2H), 3.99 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.7 (C=O), 170.8 (C=O), 165.0 (C=N), 162.5, 144.5, 142.0, 141.3, 133.9, 129.8, 129.2, 129.0, 126.4, 121.7, 115.7, 114.5, 65.7(-CH), 53.6 (-CH), 41.0 ($-CH_2-$).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 782 (100) $[M]^+$, 783 (55) $[MH]^+$.HRMS calculated for $C_{47}H_{32}F_2N_6O_4$ 782.2453 found 782.2441.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis[3-(4-methylphenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.13e)**



Yellow crystalline solid. (0.198 g, quant.). M.p. 180-182˚C. R_f : 0.75 (ethyl acetate-n-hexane; 1:2).

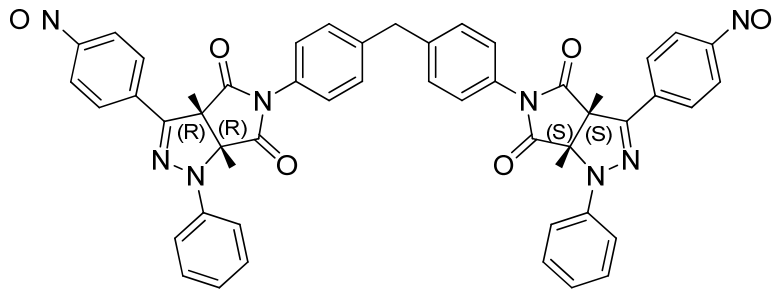
IR (KBr): $\tilde{\nu}$= 3034 (Arom. C-H), 1720 (C=O), 1597 (C=N), 1514, 1498, 1379, 1184, 817, 752, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.00 (d, *J*=8.1 Hz, 4H), 7.64 (d, *J*=7.8 Hz, 4H), 7.37 (t, *J*=7.4 Hz, 6H), 7.28-7.20 (m, 10H), 7.02 (t, *J*=7.3 Hz, 2H), 5.29 (d, *J*=11.0 Hz, 2H), 5.03 (d, *J*=10.9 Hz, 2H), 4.02 (s, 2H), 2.42 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.8 (C=O), 170.8 (C=O), 144.8 (C=N), 143.1, 141.2, 139.8, 129.7, 129.5, 129.3, 129.2, 127.5, 127.2, 126.4, 121.4, 114.5, 65.6 (-CH), 53.6 (-CH), 41.0 (-CH_2-), 21.5 (-CH_3).

HRMS calculated for $C_{49}H_{38}N_6O_4$+NH_4^+ 792.3298 found $C_{49}H_{38}N_6O_4$+NH_4^+ 792.3296.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis[3-(4-nitro phenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.13f)**



Dark orange crystalline solid. (0.215 g, quant.). M.p. 208-210˚C. R_f : 0.5 (ethyl acetate-n-hexane; 1:2).

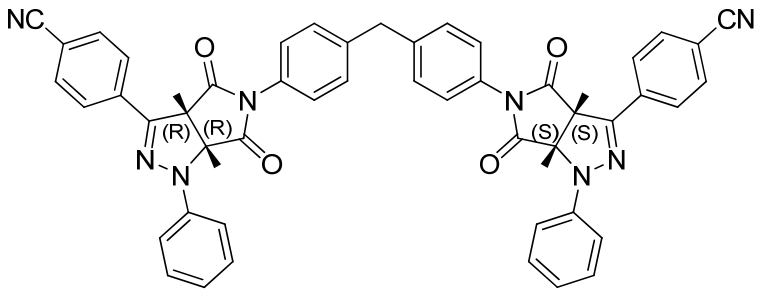
IR (KBr): $\tilde{\nu}$= 3041 (Arom. C-H), 1720 (C=O), 1595 (C=N), 1546, 1512, 1500, 1381, 1193, 850, 750, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.33-8.20 (q, *J*=9.0 Hz, 8H), 7.67 (d, *J*=9.0 Hz, 4H), 7.41 (t, *J*=7.5 Hz, 4H), 7.27-7.20 (m, 8H), 7.09 (t, *J*=7.3 Hz, 2H), 5.47 (d, *J*=11.2 Hz, 2H), 5.08 (d, *J*=11.2 Hz, 2H), 4.03 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=170.9 (C=O), 170.5 (C=O), 147.7 (C=N), 143.3, 141.4, 140.2, 136.5, 129.8, 129.7, 129.4, 127.5, 126.3, 123.9, 122.6, 114.8, 65.7 (-CH), 53.0 (-CH), 45.7(-CH_2-).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 836 (100) $[M]^+$, 837 (70) $[MH]^+$.HRMS calculated for $C_{47}H_{32}N_8O_8$ 836.2343 found 836.2338.

4-[(3a*R,6a*R**)-5-(4-{4-[(3a*S**,6a*S**)-3-(4-Cyanophenyl)-4,6-dioxo-1-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-c]pyrazol-5(1*H*)-yl]benzyl}phenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazol-3-yl]benzonitrile (6.13g)**



Bright yellow crystalline solid. (0.203 g, quant.). M.p. 209-211˚C. R_f : 0.6 (ethyl acetate-n-hexane; 1:2).

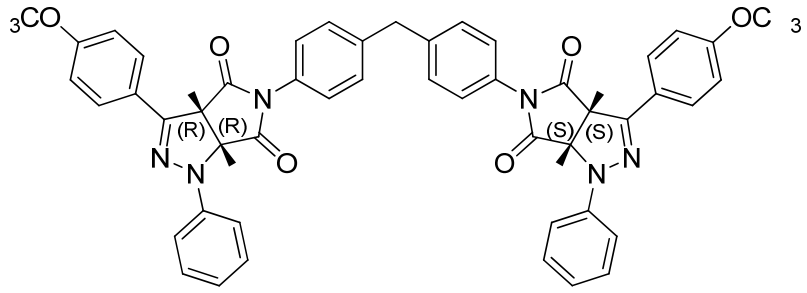
IR (KBr): $\tilde{\nu}$= 3059 (Arom. C-H), 2225 (C≡N), 1720 (C=O), 1597 (C=N), 1512, 1498, 1381, 1193, 842, 752, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.20 (d, *J*=8.4 Hz, 4H), 7.73 (d, *J*=8.5 Hz, 4H), 7.66 (d, *J*=8.5 Hz, 4H), 7.40 (t, *J*=7.3 Hz, 4H), 7.32-7.17 (m, 8H), 7.08 (t, *J*=7.3 Hz, 2H), 5.46 (d, *J*=11.2 Hz, 2H), 5.06 (d, *J*=11.2 Hz, 2H), 4.04 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.2 (C=O), 170.6 (C=O), 143.5 (C=N), 141.4, 140.7, 134.7, 132.3, 129.8, 129.4, 129.3, 127.3, 126.3, 122.4, 118.8, 114.7, 112.2 (C≡N), 65.7 (-CH), 53.1(-CH), 41.0 (-CH_2-).

HRMS calculated for $C_{49}H_{32}N_8O_4+NH_4^+$ 814.2890 found $C_{49}H_{32}N_8O_4+NH_4^+$ 814.2894.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis[3-(4-methoxyphenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.13h)**



Brown crystalline solid. (0.215 g, quant.). M.p. 169-171˚C. R_f : 0.37 (ethyl acetate-n-hexane; 1:2).

IR (KBr): $\tilde{\nu}$= 3057 (Arom. C-H), 1720 (C=O), 1597 (C=N), 1512, 1498, 1379, 1253, 1176, 835, 750, 692 cm^{-1}.

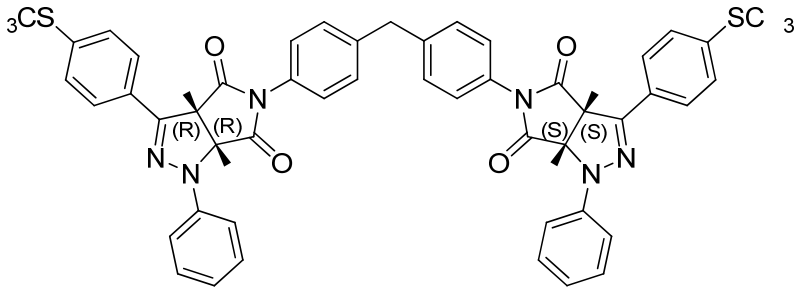
^1H NMR (400 MHz, $CDCl_3$): δ= 8.05 (d, *J*=8.8 Hz, 4H), 7.61 (d, *J*=7.7 Hz, 4H), 7.36 (t, *J*=7.4 Hz, 4H), 7.28-6.70 (m, 14H), 5.20 (d, *J*=10.9 Hz, 2H), 4.93 (d, *J*=10.9 Hz, 2H), 4.02 (s, 2H), 3.86 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.9 (C=O), 170.9 (C=O), 160.8 (C=N), 145.0, 142.9, 141.2, 134.1, 129.7, 129.2, 128.9, 126.4, 123.0, 121.3, 114.4,

114.0, 65.7 (-CH), 55.4 (-O-CH_3), 53.7(-CH), 41.0 (-CH_2-).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 806 (100) $[M]^+$, 807 (55) $[MH]^+$. HRMS calculated for $C_{49}H_{38}N_6O_6$ 806.2853 found 806.2848.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis[3-[4-(methylthio)phenyl]-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.13i)**



Brown crystalline solid. (0.224 g, quant.). M.p. 170-172°C. R_f: 0.50 (ethyl acetate-n-hexane; 1:2).

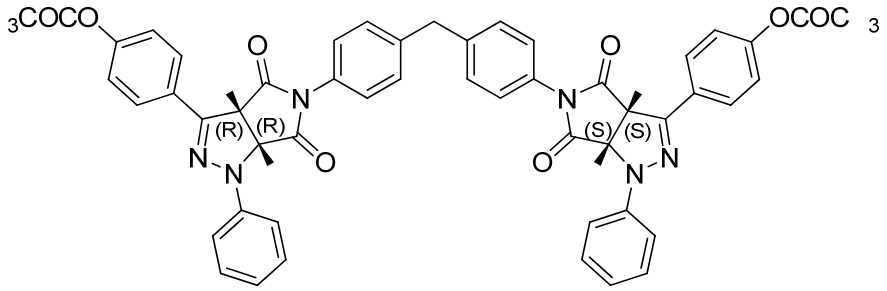
IR (KBr): $\tilde{\nu}$= 3036 (Arom. C-H), 1720 (C=O), 1597 (C=N), 1510, 1492, 1379, 1188, 821, 750, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.98 (d, *J*=8.3 Hz, 4H), 7.62 (d, *J*=8.1 Hz, 4H), 7.36 (t, *J*=7.6 Hz, 4H), 7.30-7.10 (m, 12H), 7.03 (t, *J*=7.2 Hz, 2H), 5.22 (d, *J*=10.9 Hz, 2H), 4.91 (d, *J*=10.9 Hz, 2H), 3.97 (s, 2H), 2.50 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.7 (C=O), 170.8 (C=O), 144.6 (C=N), 142.6, 141.2, 140.8, 129.7, 129.5, 129.2, 127.5, 126.9, 126.4, 125.9, 121.5, 114.5, 65.6 (-CH), 53.5 (-CH), 41.0 (-CH_2-), 15.3 (-S-CH_3).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 838 (100) $[M]^+$, 839 (56) $[MH]^+$. HRMS calculated for $C_{49}H_{38}N_6O_4S_2$ 838.2396 found 838.2397.

4-[(3a*R,6a*R**)-5-(4-{4-[(3a*S**,6a*S**)-3-[4-(Acetyloxy)phenyl]-4,6-dioxo-1-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazol-5(1H)-yl]benzyl}phenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazol-3-yl] phenyl acetate (6.13j)**



Light yellow crystalline solid. (0.203 g, 95%). M.p. 190-192˚C. R_f : 0.75 (ethyl acetate).

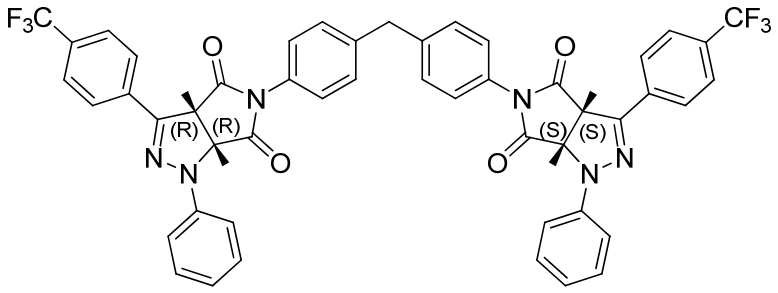
IR (KBr): $\tilde{\nu}$= 3061 (Arom. C-H), 1720 (C=O), 1599 (C=N), 1510, 1498, 1371, 1199, 1166, 848, 752,692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.10 (d, *J*=8.4 Hz, 4H), 7.62 (d, *J*=7.9 Hz, 4H), 7.35 (t, *J*=7.3 Hz, 4H), 7.23-7.10 (m, 12H), 7.05 (t, *J*=7.0 Hz, 2H), 5.25 (d, *J*=11.0 Hz, 2H), 4.90 (d, *J*=10.9 Hz, 2H), 4.00 (s, 2H), 2.34 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.7 (C=O), 170.8 (C=O), 169.3 (C=O), 151.5 (C=N), 144.5, 142.0, 141.3, 129.7, 129.5, 129.2, 128.4, 128.2, 126.4, 121.8, 121.6, 114.5, 65.8 (-CH), 53.5 (-CH), 41.0 ($-CH_2-$), 21.2 ($-CH_3$).

HRMS calculated for $C_{51}H_{38}N_6O_8+NH_4^+$ 880.3095 found $C_{51}H_{38}N_6O_8+NH_4^+$ 880.3094.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Methylenebis(4,1-phenylene)]bis[1-phenyl-3-[4-(trifluoromethyl)phenyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.13k)**



Bright yellow crystalline solid. (0.223 g, quant.). M.p. 185-187˚C. R_f : 0.45 (ethyl acetate-n-hexane; 1:2).

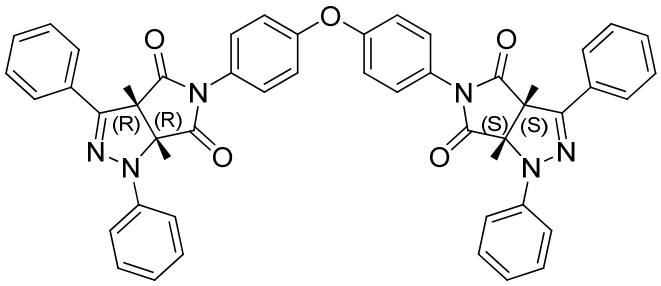
IR (KBr): $\tilde{\nu}$= 3059 (Arom. C-H), 1720 (C=O), 1599 (C=N), 1550, 1517, 1498, 1383, 1166, 1124, 844, 752,692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ= 8.16 (d, *J*=8.1 Hz, 4H), 7.65-7.59 (dd, *J*=8.3, 7.9 Hz, 8H), 7.33 (t, *J*=7.5 Hz, 4H), 7.18 (dd, *J*=8.6, 4.2 Hz, 8H), 6.99 (t, *J*=7.3 Hz, 2H), 5.40 (d, *J*=11.1 Hz, 2H), 5.06 (d, *J*=11.1 Hz, 2H), 3.98 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ=176.8 (C=O), 176.0 (C=O), 149.0 (C=N), 146.8, 146.0, 139.0, 134.6, 134.2, 134.0, 132.0, 131.5, 130.2, 129.8, 126.4, 119.5, 119.3, 71.0 (-CH), 58.5, (-CH), 50.8 (-CH_2-).

HRMS calculated for $C_{49}H_{32}F_6N_6O_4+NH_4^+$ 900.2733 found $C_{49}H_{32}F_6N_6O_4+NH_4^+$ 900.2736.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Oxybis(4,1-phenylene)]bis(1,3-diphenyl-3a, 6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione) (6.14a)**



Yellow-green crystalline solid. (0.177 g, 95%). M.p. 178-180˚C (dec.). R_f : 0.47 (ethyl acetate-n-hexane; 1:2).

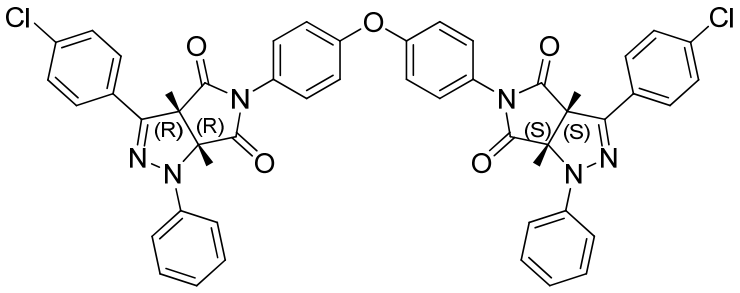
IR (KBr): $\tilde{\nu}$=3061 (Arom. C-H), 1720 (C=O), 1597 (C=N), 1500, 1383, 1244, 1193, 754,690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.89 (d, *J*=7.9 Hz, 4H), 7.42 (d, *J*=8.2 Hz, 4H), 7.30-7.05 (m, 14H), 6.88 (d, *J*=8.0 Hz, 4H), 6.78 (t, *J*=7.0 Hz, 2H), 5.27 (d, *J*=10.8 Hz, 2H), 5.00 (d, *J*=10.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=173.1 (C=O), 172.1 (C=O), 156.7 (C=N), 145.0, 144.5, 131.0, 129.7, 129.5, 129.4, 128.9, 127.8, 127.5, 121.2, 119.6, 114.4, 66.3 (-CH), 54.5 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 748 (100) $[M]^+$, 749 (50) $[MH]^+$. HRMS calculated for $C_{46}H_{32}N_6O_5$ 748.2434 found 748.2430.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Oxybis(4,1-phenylene)]bis[3-(4-chloro phenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.14b)**



Olive-green crystalline solid. (0.206 g, quant.). M.p.167-169˚C (dec.). R_f : 0.56 (ethyl acetate-n-hexane; 1:2).

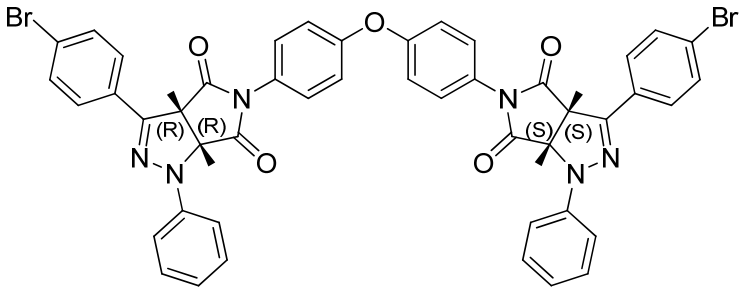
IR (KBr): $\tilde{\nu}$= 3061 (Arom. C-H), 1720 (C=O), 1599 (C=N), 1500, 1381, 1242, 1193, 831, 750,692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.04 (d, *J*=8.1 Hz, 4H), 7.54 (t, *J*=8.6 Hz, 8H), 7.35 (d, *J*=7.9 Hz, 8H), 7.14 (d, *J*=8.3 Hz, 4H), 6.96 (t, *J*=7.0 Hz, 2H), 5.55 (d, *J*=10.9 Hz, 2H), 5.36 (d, *J*=10.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=173.0 (C=O), 172.1 (C=O), 156.7 (C=N), 144.7, 143.4, 134.3, 129.9, 129.5, 129.4, 129.0, 127.8, 121.3, 119.6, 114.5, 66.4 (-CH), 54.4 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 816 (100) $[M]^+$, 818 (70) ($[M]^+$+2), 819 (40) ($[M]^+$+3). HRMS calculated for $C_{46}H_{30}Cl_2N_6O_5$ 816.1655 found 816.1649.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Oxybis(4,1-phenylene)]bis[3-(4-bromo phenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.14c)**



Light brown crystalline solid. (0.226 g, quant.). M.p. 174-176˚C (dec.). R_f : 0.63 (ethyl acetate-n-hexane;1:2).

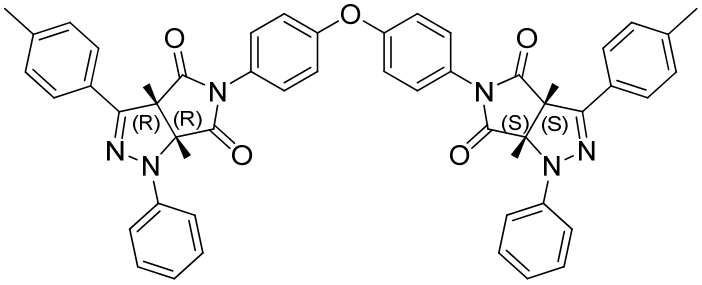
IR (KBr): $\tilde{\nu}$= 3045 (Arom. C-H), 1720 (C=O), 1599 (C=N), 1500, 1381, 1244, 1193, 829, 750, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.96 (d, *J*=8.4 Hz, 4H), 7.68 (d, *J*=8.4 Hz, 4H), 7.52 (d, *J*=8.3 Hz, 4H), 7.31 (t, *J*=8.1 Hz, 8H), 7.10 (d, *J*=8.7 Hz, 4H), 6.92 (t, *J*=7.3 Hz, 2H), 5.55 (d, *J*=11.0 Hz, 2H), 5.35 (d, *J*=10.9 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=173.1 (C=O), 172.1 (C=O), 156.7 (C=N), 145.0, 143.5, 132.1, 130.5, 129.7, 129.5, 129.4, 127.8, 123.5, 121.5, 119.6, 114.5, 66.4 (-CH), 54.5 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 904 (50) $[M]^+$, 906 (100) ($[M]^+$+2), 907 (50) ($[M]^+$+3), 908 (50) ($[M]^+$+4). HRMS calculated for $C_{46}H_{30}Br_2N_6O_5$ 904.0644 found 904.0635.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Oxybis(4,1-phenylene)]bis[3-(4-methyl phenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.14e)**



Bright yellow powder. (0.188 g, 97%). M.p. 173-175˚C (dec.). R_f: 0.56 (ethyl acetate-n-hexane; 1:2).

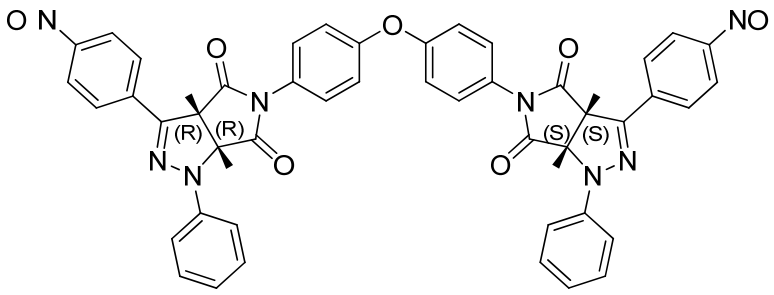
IR (KBr): $\tilde{\nu}$= 3066 (Arom.C-H), 2918 (Aliphatic C-H), 1720 (C=O), 1597 (C=N), 1500, 1381, 1244, 1194, 819, 750, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.90 (d, *J*=7.8 Hz, 4H), 7.50 (d, *J*=8.0 Hz, 4H), 7.40-7.20 (m), 7.14 (d, *J*=8.5 Hz, 4H), 6.91 (t, *J*=7.1 Hz, 2H), 5.50 (d, *J*=10.8 Hz, 2H), 5.34 (d, *J*=10.8 Hz, 2H), 2.42 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2 (C=O), 172.1 (C=O), 156.7 (C=N), 145.2, 144.6, 139.5, 129.5, 129.5, 129.4, 128.3, 127.9, 127.5, 121.0, 119.6, 114.4, 66.3 (-CH), 54.6 (-CH), 21.4 ($-CH_3$).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 776 (100) $[M]^+$, 777 (55) $[MH]^+$. HRMS calculated for $C_{48}H_{36}N_6O_5$ 776.2747 found 776.2746.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Oxybis(4,1-phenylene)]bis[3-(4-nitrophenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.14f)**



Dark orange crystalline solid. (0.210 g, quant.). M.p. 208-210˚C (dec.). R_f : 0.29 (ethyl acetate-n-hexane; 1:2).

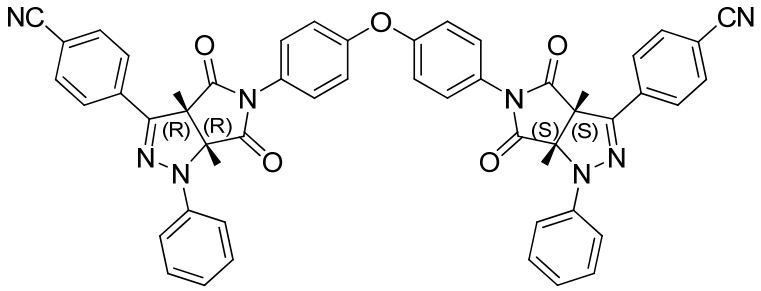
IR (KBr): $\tilde{\nu}$= 3109, 3057 (Arom. C-H), 1720 (C=O), 1595 (C=N), 1546, 1498, 1383, 1340, 1242, 1193, 835, 750, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.32 (d, *J*=8.9 Hz, 4H), 8.22 (d, *J*=8.9 Hz, 4H), 7.58 (d, *J*=7.9 Hz, 4H), 7.40-7.30 (q, *J*=7.50 Hz, 8H), 7.14 (d, *J*=8.8 Hz, 4H), 7.00 (t, *J*=7.2 Hz, 2H), 5.68 (d, *J*=11.1 Hz, 2H), 5.42 (d, *J*=11.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=172.7 (C=O), 172.0 (C=O), 156.7 (C=N), 147.5, 143.9, 142.3, 137.5, 129.6, 129.5, 128.1, 127.8, 124.2, 121.9, 119.5, 114.8, 66.5 (-CH), 54.0 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 838 (100) $[M]^+$, 839 (55) $[MH]^+$. HRMS calculated for $C_{46}H_{30}N_8O_9$ 838.2136 found 838.2133.

4-[(3a*R,6a*R**)-5-(4-{4-[(3a*S**,6a*S**)-3-(4-cyanophenyl)-4,6-dioxo-1-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl]phenoxy}phenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazol-3-yl] benzonitrile (6.14g)**



Bright yellow crystalline solid. (0.190 g, 95%). M.p. 288-290˚C (dec.). R_f : 0.25 (ethyl acetate-n-hexane; 1:2).

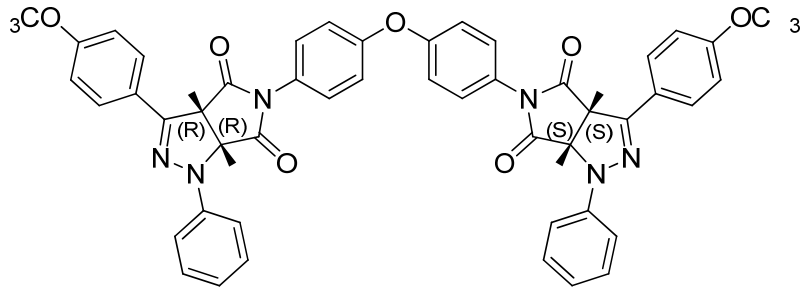
IR (KBr): $\tilde{\nu}$= 3057 (Arom. C-H), 2225 (C≡N), 1722 (C=O), 1599 (C=N), 1500, 1383, 1242, 1193, 839, 750, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.11 (d, *J*=8.4 Hz, 4H), 7.61 (d, *J*=8.3 Hz, 4H), 7.52 (d, *J*=7.9 Hz, 4H), 7.40 (d, *J*=12.8 Hz, 2H), 7.25 (t, *J*=7.5 Hz, 2H), 7.20 (d, *J*=8.8 Hz, 4H), 7.01 (d, *J*=8.9 Hz, 4H), 6.90 (t, *J*=7.1 Hz, 2H), 5.45 (d, *J*=11.1 Hz, 2H), 5.10 (d, *J*=11.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=172.6 (C=O), 171.9 (C=O), 156.7 (C=N), 144.1, 142.4, 135.5, 132.6, 129.4, 129.4, 129.2, 127.8, 121.7, 119.5, 119.1, 114.7, 111.4 (C≡N), 66.4 (-CH), 53.9 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 798 (90) $[M]^+$, 799 (50) $[MH]^+$.HRMS calculated for $C_{48}H_{30}N_8O_5$ 798.2339 found 798.2334.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Oxybis(4,1-phenylene)]bis[3-(4-methoxy phenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.14h)**



Light orange-brown crystalline solid. (0.202 g, quantitative). M.p. 164-166˚C (dec.). R_f : 0.60 (ethyl acetate-n-hexane; 1:3).

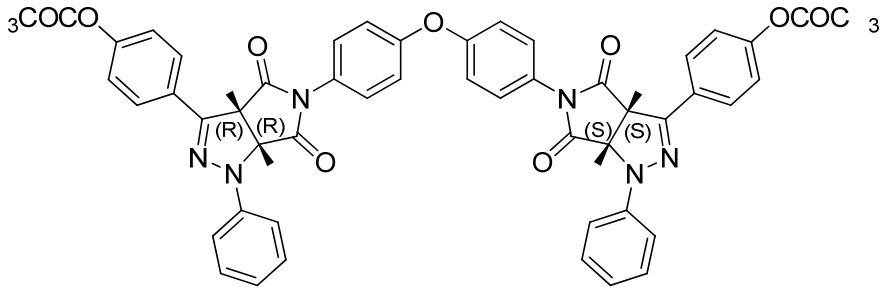
IR (KBr): $\tilde{\nu}$= 3057 (Arom. C-H), 1720 (C=O), 1597 (C=N), 1498, 1381, 1247, 1176, 833, 750, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.02 (d, *J*=8.7 Hz, 4H), 7.58 (t, *J*=7.9 Hz, 4H), 7.30 (t, *J*=7.9 Hz, 4H), 7.25-6.62 (m, 14H), 5.22 (d, *J*=10.8 Hz, 2H), 4.96 (d, *J*=10.8 Hz, 2H), 3.83 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=172.1 (C=O), 171.1 (C=O), 161.0 (C=N), 156.9, 145.1, 143.1, 129.4, 129.0, 128.7, 128.2, 123.1, 121.6, 119.7, 114.6, 114.2, 65.8 (-CH), 55.6 (O-CH_3), 53.8 (-CH).

Anal Calcd for $C_{48}H_{36}N_6O_7$. C, 71.28; H, 4.49; N, 10.39; found C, 70.70; H, 4.69; N, 10.43.

4-[(3a*R,6a*R**)-5-(4-{4-[(3a*S**,6a*S**)-3-[4-(Acetyloxy)phenyl]-4,6-dioxo-1-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl]phenoxy} phenyl)-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*] pyrazol-3-yl]phenyl acetate (6.14j)**



Brown crystalline solid. (0.220 g, quantitative). m.p. 190-192˚C (dec.). R_f : 0.25 (ethyl acetate-n-hexane; 1:3).

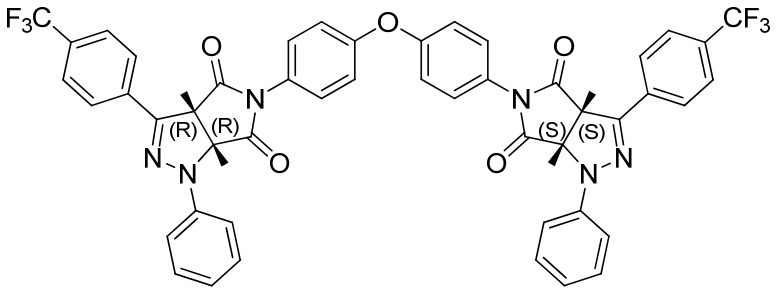
IR (KBr): $\tilde{\nu}$= 3066 (Arom. C-H), 1720 (C=O), 1599 (C=N), 1500, 1371, 1197, 750, 690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ= 8.10 (d, *J*=8.7 Hz, 4H), 7.60 (d, *J*=8.7 Hz, 4H), 7.38 (t, *J*=7.3 Hz, 4H), 7.23-6.85 (m, 14H), 5.26 (d, *J*=11.1 Hz, 2H), 4.95 (d, *J*=10.8 Hz, 2H), 2.30 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.9 (C=O), 171.0 (C=O), 169.5 (C=O), 151.8 (C=N), 144.6, 142.1, 129.5, 128.6, 128.3, 128.2, 126.7, 122.1, 121.9, 119.7, 114.7, 65.9 (-CH), 53.7 (-CH), 21.4 ($COCH_3$).

Anal Calcd for $C_{50}H_{36}N_6O_9$. C, 69.44; H, 4.20; N, 9.72; found C, 69.39; H, 4.48; N, 9.77.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-[Oxybis(4,1-phenylene)]bis[1-phenyl-3-[4-(trifluoromethyl)phenyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.14k)**



Bright yellow crystalline solid. (0.213 g, 96 %). M.p. 184-186˚C (dec.). R_f : 0.62 (ethyl acetate-n-hexane; 1:3).

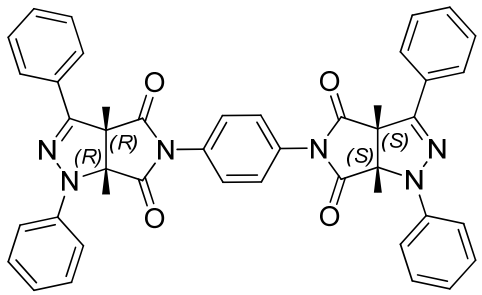
IR (KBr): $\tilde{\nu}$= 3059 (Arom. C-H), 1724 (C=O), 1599 (C=N), 1500, 1384, 1244, 750, 692 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ= 8.20 (d, *J*=8.2 Hz, 4H), 7.69-7.62 (dd, *J*=14.9, 8.4 Hz, 8H), 7.38 (t, *J*=7.6 Hz, 4H), 7.27-7.25 (m, 4H), 7.09-7.02 (m, 6H), 5.40 (d, *J*=11.1 Hz, 2H), 5.07 (d, *J*=11.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.5 (C=O), 170.8 (C=O), 157.0 (C=N), 144.0, 141.3, 133.8, 129.5, 128.1, 128.0, 127.4, 126.6, 125.8, 125.7, 122.4, 119.7, 114.8, 65.8 (-CH), 53.4 (-CH).

Anal Calcd for $C_{48}H_{30}F_6N_6O_5$. C, 65.16; H, 3.42; N, 9.50; found C, 65.30; H, 3.73; N, 9.63.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-(1,4-Phenylene)bis(1,3-diphenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione) (6.15a)**



Light yellow powder. (0.158 g, 96%). M.p. 354-356˚C (dec.). R_f : 0.62 (ethyl acetate-n-hexane; 1:2).

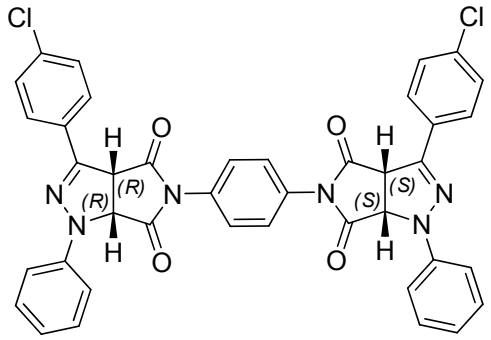
IR (KBr): $\tilde{\nu}$= 3057 (Arom. C-H), 1722 (C=O), 1597 (C=N), 1517, 1498, 1371, 1290, 1195,758,684 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.02 (d, *J*=7.4 Hz, 4H), 7.52 (d, *J*=8.0 Hz, 6H), 7.49-7.38 (m, 8H), 7.33 (t, *J*=7.7 Hz, 4H), 6.94 (t, *J*=7.0 Hz, 2H), 5.52 (d, *J*=10.9 Hz, 2H), 5.35 (d, *J*=10.8 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=172.9 (C=O), 171.9 (C=O), 144.9 (C=N), 144.2, 132.4, 130.9, 129.7, 129.4, 128.8, 128.1, 127.9, 127.5,121.1, 114.4, 66.3 (-CH), 54.5 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 656 (100) $[M]^+$, 657 (45) $[MH]^+$. HRMS calculated for $C_{40}H_{28}N_6O_4$ 656.2172 found 656.2162.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-(1,4-Phenylene)bis[3-(4-chlorophenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.15b)**



Light green crystalline solid. (0.177 g, 98%). M.p. 205-207˚C (dec.). R_f : 0.63 (ethyl acetate-n-hexane; 1:2).

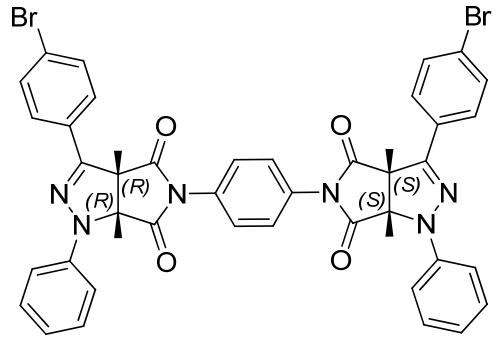
IR (KBr): $\tilde{\nu}$= 3064 (Arom. C-H), 1722 (C=O), 1597 (C=N), 1514, 1492, 1367, 1292, 1190, 831, 752,692 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.04 (d, *J*=6.5 Hz, 4H), 7.84-7.13 (m, 16H), 6.97 (s, 2H), 5.57 (d, *J*=10.1 Hz, 2H), 5.38 (d, *J*=10.2 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=172.9 (C=O), 171.9 (C=O), 144.7 (C=N), 143.3, 134.3, 132.5, 129.9, 129.5, 129.1, 129.0, 128.2, 126.4, 121.3, 114.4, 66.4 (-CH), 54.5 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 724 (100) $[M]^+$, 726 (80) $[M]^+$+2, 727 (35) $[M]^+$+3. HRMS calculated for $C_{40}H_{26}Cl_2N_6O_4$ 724.1393 found 724.1388.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-(1,4-Phenylene)bis[3-(4-bromophenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.15c)**



Light brown crystalline solid. (0.182 g, 90%). M.p. 263-265˚C (dec.). R_f : 0.50 (ethyl acetate-n-hexane; 1:2).

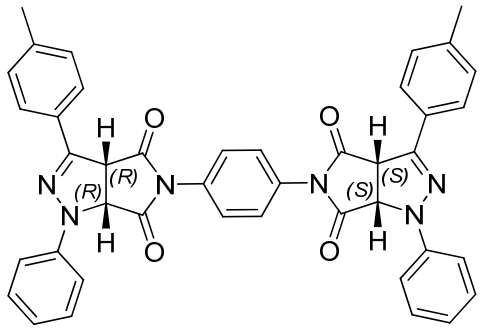
IR (KBr): $\tilde{\nu}$= 3043 (Arom. C-H), 1722 (C=O), 1599 (C=N), 1512, 1492, 1365, 1294, 1176, 827, 750,690 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.85 (d, *J*=8.5 Hz, 4H), 7.54-7.39 (m, 10H), 7.28-7.2.0 (m, 4H), (6.93 (t, *J*=7.2 Hz 4H), 5.26 (d, *J*=11.1 Hz, 2H), 4.94 (d, *J*=11.0 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=172.9 (C=O), 171.9 (C=O), 144.3 (C=N), 142.0, 131.8, 131.5, 129.3, 129.2, 128.5, 126.8, 123.7, 121.8, 114.5, 65.8 (-CH), 53.5 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 812 (50) $[M]^+$, 814 (100) $[M]^+$+2, 816 (50) $[M]^+$+4. HRMS calculated for $C_{40}H_{26}Br_2N_6O_4$ 812.0382 found 812.0379.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-(1,4-Phenylene)bis[3-(4-methylphenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.15e)**



Creamy-white powder. (0.165 g, 96%). M.p. 338-340˚C (dec.). R_f: 0.69 (ethyl acetate-n-hexane; 1:2).

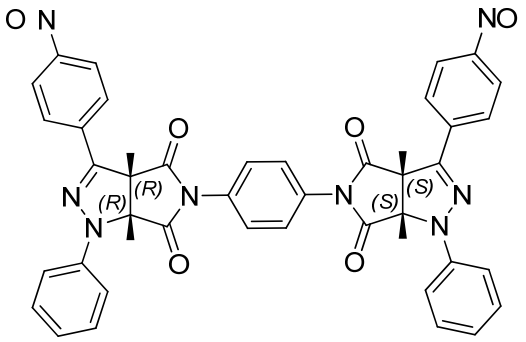
IR (KBr): $\tilde{\nu}$= 3066 (Arom. C-H), 2941 (aliphatic C-H), 1724 (C=O), 1595 (C=N), 1514, 1498, 1371, 1288, 1195, 819, 754, 692 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.86 (d, *J*=8.1 Hz, 4H), 7.49 (d, *J*=7.9 Hz, 4H), 7.42 (s, 4H), 7.24 (t, *J*=7.5 Hz, 4H), 7.15 (d, *J*=8.1 Hz, 4H), 6.88 (t, *J*=7.2 Hz, 2H), 5.30 (d, *J*=10.9 Hz, 2H), 5.06 (d, *J*=10.9 Hz, 2H), 2.30 (s, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=173.0 (C=O), 171.9 (C=O), 145.1 (C=N), 144.5, 139.5, 132.5, 129.6, 129.5, 129.4, 128.2, 127.5, 121.0, 114.3, 66.3 (-CH), 54.6 (-CH), 21.4 (-CH_3).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 684 (100) $[M]^+$, 685 (50) $[MH]^+$.HRMS calculated for $C_{42}H_{32}N_6O_4$ 684.2485 found 684.2478.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-(1,4-Phenylene)bis[3-(4-nitrophenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.15f)**



Orange powder. (0.185 g, 99 %). M.p. 307-309˚C (dec.). R_f: 0.43 (ethyl acetate-n-hexane; 1:2).

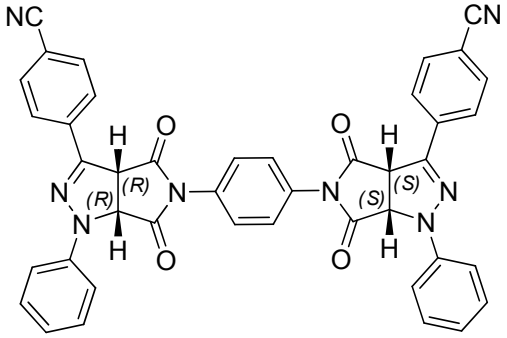
IR (KBr): $\tilde{\nu}$= 3074 (Arom. C-H), 1724 (C=O), 1595 (C=N), 1515, 1500, 1340, 1292, 1192, 850, 750, 690 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.29 (d, *J*=8.0 Hz, 4H), 8.21 (d, *J*=8.3 Hz, 4H), 7.56 (d, *J*=7.4 Hz, 4H), 7.44 (s, 4H), 7.35 (t, *J*=7.6 Hz, 4H), 7.00 (t, *J*=6.6 Hz, 2H), 5.70 (d, *J*=10.9 Hz, 2H), 5.40 (d, *J*=11.0 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=173.0 (C=O), 171.8 (C=O), 147.8 (C=N), 144.3, 142.2, 137.4, 132.2, 129.6, 128.2, 128.0, 124.2, 122.0, 114.7, 66.3 (-CH), 53.9 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 746 (100) $[M]^+$, 747 (50) $[MH]^+$. HRMS calculated for $C_{40}H_{26}N_8O_8$ 746.1874 found 746.1869.

4-((3a*R,6a*R**)-5-{4-[(3a*S**,6a*S**)-3-(4-Cyanophenyl)-4,6-dioxo-1-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl]phenyl}-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazol-3-yl)benzonitrile (6.15g)**



Yellow powder. (0.168 g, 95%). M.p. 361-363˚C (dec.). R_f: 0.37 (ethyl acetate-n-hexane; 1:2).

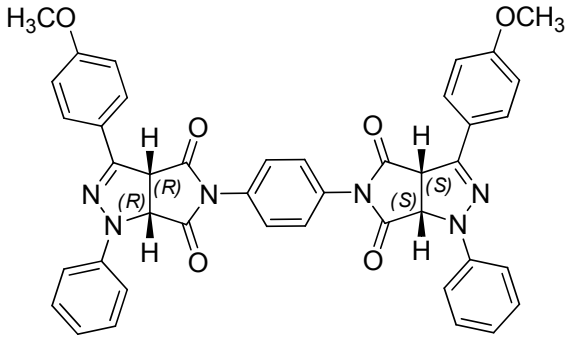
IR (KBr): $\tilde{\nu}$= 3063 (Arom. C-H), 2225 (C≡N), 1724 (C=O), 1597 (C=N), 1514, 1498, 1367, 1255, 1190, 837, 754, 690 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.02 (d, *J*=8.3 Hz, 4H), 7.77 (d, *J*=8.2 Hz, 4H), 7.40 (d, *J*=7.8 Hz, 4H), 7.23 (t, *J*=7.4 Hz, 4H), 6.86 (t, *J*=7.1 Hz, 2H), 5.51 (d, *J*=11.4 Hz, 2H), 5.22 (d, *J*=10.9 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=172.9 (C=O), 171.9 (C=O), 144.7 (C=N), 143.3, 134.3, 132.5, 129.9, 129.5, 129.1, 129.0, 128.2, 126.4, 121.3, 114.4 (C≡N), 66.4 (-CH), 54.5 (-CH).

MALDI-MS (pos.mode, DCTB): (*m/z*, %)= 706 (100) $[M]^+$, 707 (50) $[MH]^+$. HRMS calculated for $C_{42}H_{26}N_8O_4$ 706.2077 found 706.2078.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-(1,4-Phenylene)bis[3-(4-methoxyphenyl)-1-phenyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.15h)**



Light orange-brown crystalline solid. (0.165 g, 92%). m.p. 173-175˚C (dec.). R_f : 0.25 (ethyl acetate-n-hexane; 1:3).

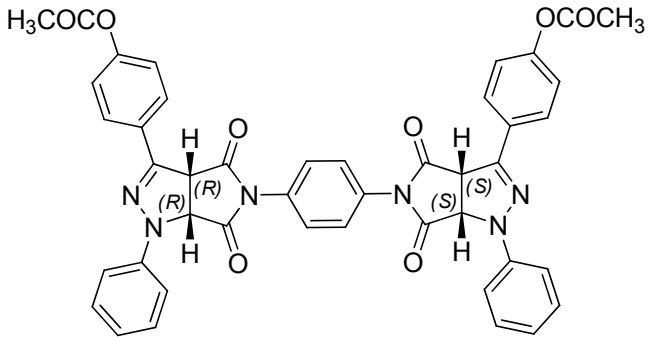
IR (KBr): $\tilde{\nu}$= 3057 (Arom. C-H), 1724 (C=O),1597 (C=N), 1514, 1498, 1367, 1176, 835, 752, 692 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 7.95 (d, *J*=8.2 Hz, 4H), 7.67-6.80 (m, 18H), 5.44 (d, *J*=11.5 Hz, 2H), 5.32 (d, *J*=10.8 Hz, 2H), 3.79 (s, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=172.6 (C=O), 172.1 (C=O), 160.9 (C=N), 145.5, 144.6, 129.7, 129.4, 128.7, 128.5, 123.6, 121.0, 119.5, 114.8, 114.6, 114.4, 66.5 (-CH), 56.0 (O-CH_3), 55.1 (-CH).

Anal Calcd for $C_{42}H_{32}N_6O_6$. C, 70.38; H, 4.50; N, 11.73; found C, 70.11; H, 4.75; N, 11.49.

4-((3a*R,6a*R**)-5-{4-[(3a*S**,6a*S**)-3-[4-(Acetyloxy)phenyl]-4,6-dioxo-1-phenyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*c*]pyrazol-5(1*H*)-yl]phenyl}-4,6-dioxo-1-phenyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazol-3-yl)phenyl acetate (6.15j)**



Light brown crystalline solid. (0.195 g, quant.). m.p. 216-218˚C (dec.). R_f: 0.25 (ethyl acetate-n-hexane; 1:3).

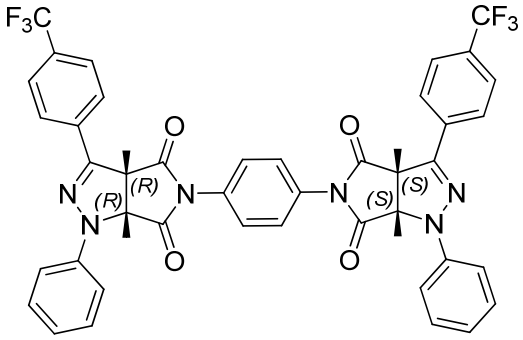
IR (KBr): $\tilde{\nu}$= 3066 (Arom. C-H), 1722 (C=O), 1599 (C=N), 1514, 1498, 1369, 1199, 752,692 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 8.05 (d, *J*=8.7 Hz, 4H), 7.52 (d, *J*=8.4 Hz, 4H), 7.45 (s, 6H), 7.35 (t, *J*=7.3 Hz, 4H), 7.26 (d, *J*=8.7 Hz, 4H), 6.95 (t, *J*=7.3 Hz,2H), 5.54 (d, *J*=11.1 Hz, 2H), 5.37 (d, *J*=11.1 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=173.3 (C=O), 172.3 (C=O), 151.8 (C=N), 145.1, 143.9, 129.7, 128.9, 128.5, 122.7, 121.4, 114.5, 66.4 (-CH), 54.7 (-CH), 21.5 ($COCH_3$).

Anal Calcd for $C_{44}H_{32}N_6O_8$. C, 68.39; H, 4.17; N, 10.88; found C, 68.23; H, 4.61; N, 10.75.

(3a*R,6a*R**,3a'*S**,6a'*S**)-5,5'-(1,4-Phenylene)bis[1-phenyl-3-[4-(trifluoro methyl)phenyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione] (6.15k)**



Bright yellow crystalline solid. (0.181 g, 91 %). M.p. 293-295˚C (dec.). R_f : 0.62 (ethyl acetate-n-hexane; 1:3).

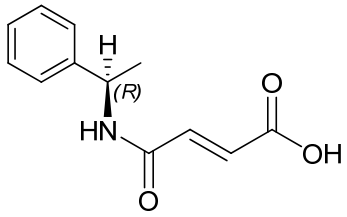
IR (KBr): $\tilde{\nu}$=3063 (Arom. C-H), 1724 (C=O), 1599 (C=N), 1514, 1498, 1327, 1170, 840,750, 690 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 8.20 (d, *J*=8.2 Hz, 4H), 7.84 (d, *J*=8.2 Hz, 4H), 7.54 (d, *J*=8.2 Hz, 4H), 7.45 (s, 4H), 7.37 (t, *J*=8.2 Hz, 4H), 6.99 (t, *J*=8.2 Hz, 2H), 5.63 (d, *J*=11.4 Hz, 2H), 5.43 (d, *J*=11.1 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=173.0 (C=O), 172.2 (C=O), 144.5 (C=N), 143.1, 135.2, 132.7, 129.8, 128.5, 128.1, 126.7, 126.1, 121.8, 114.7, 66.6 (-CH), 54.5 (-CH).

Anal Calcd for $C_{42}H_{26}F_6N_6O_4$. C, 63.64; H, 3.31; N, 10.60; found C, 63.17; H, 3.74; N, 10.67.

(*R,E*)-4-oxo-4-(1-phenylethylamino)but-2-enoic acid (6.17)

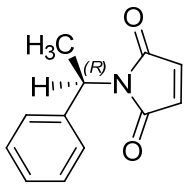


Procedure1 — (*R*)-*N*-(1-phenylethyl)amine **6.16** (2.42 g, 20.0 mmol) is dissolved and stirred in 25 mL of acetone. A solution of maleic anhydride **3.4** (4.10 g, 42.0 mmol) in 25 mL of acetone is added dropwise over 15 min and resulting yellow solution is stirred at room temperature for 4h. The reaction mixture is poured into 50 mL ice-water to precipitate the white product. The precipitate is isolated by filtration and dried under vacuum to yield (*R,E*)-4-oxo-4-(1-phenylethylamino)but-2-enoic acid **6.17**, which was used in the next step without purification.

White powder. (3.21 g, 73%). R_f: 0.14 (ethyl acetate-n-hexane; 1:2).

IR (KBr): $\tilde{\nu}$ = 3226 (N-H), 3053 (Arom. C-H), 2980 (Aliph. C-H), 1712 (C=O), 1639, 1529, 1309, 1141, 1128, 854, 696 cm^{-1}.

(*R*)-*N*-(1-phenylethyl)maleimide (6.18)



Procedure2 — (*R,E*)-4-oxo-4-(1-phenylethylamino)but-2-enoic acid **6.17**(14.6 mmol), anhydrous sodium acetate (1.43 g, 17.5 mmol) and 45 g (438 mmol)

acetic anhydride are added into a three-necked flask. Yellow reaction mixture is heated to 95-100˚C for 3h and after cooling to room temperature, brown reaction mixture is poured into 40 mL of ice-water mixture with stirring for 1h. The reaction mixture is extracted with ethyl acetate (3x25 mL) and collected ethyl acetate layers are dried over Na_2SO_4. Finally, all solvent is rotaevaporated and resulting orange oil is dried under vacuum. (*R*)-*N*-(1-phenylethyl)maleimide **6.18** is purified and isolated with CC (hexane:EtOAc-3:1).

Light yellow oil. (1.6 g, 54%). $[\alpha]_{589}^{21^{o}C}$ = +88.7° (c= 0.01 g/mL, l=10 cm, $CHCl_3$). R_f: 0.57 (ethyl acetate-n-hexane; 1:2).

IR (KBr): $\tilde{\nu}$ = 3099 (Arom. C-H), 2982, 2941 (Aliph. C-H), 1703 (C=O), 1587, 1496, 1452, 1384, 1361, 1168, 827, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.44 (d, *J*=7.2 Hz, 2H), 7.35 (t, *J*=7.0 Hz, 2H), 7.30 (d, *J*=8.1 Hz, 1H), 6.65 (s, 2H), 5.38 (q, *J*=7.3 Hz, 1H), 1.85 (d, *J*=7.4 Hz ,3H).

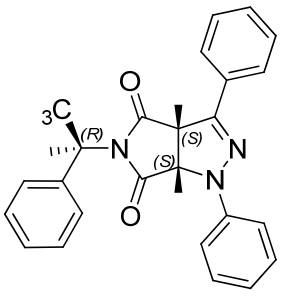
^{13}C NMR (100 MHz, $CDCl_3$): δ=171.0, 140.6, 134.4, 128.9, 128.1, 127.6, 50.0, 18.0 (-CH_3).

GC-MS (70 eV): (*m/z*, %) = 201 (100) $[M]^+$, 182(28), 158(20), 104(30), 77(28), 51(10).

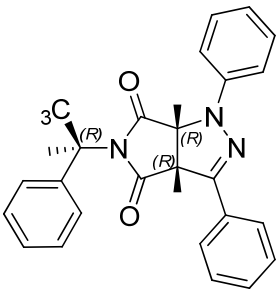
Synthesis of chiral 1,3-disubstituted-5-((*R*)-1-phenylethyl)-1,6a-dihydro pyrrolo [3,4-*c*]pyrazole-4,6(3a*H*,5*H*)-diones (6.19a-k)

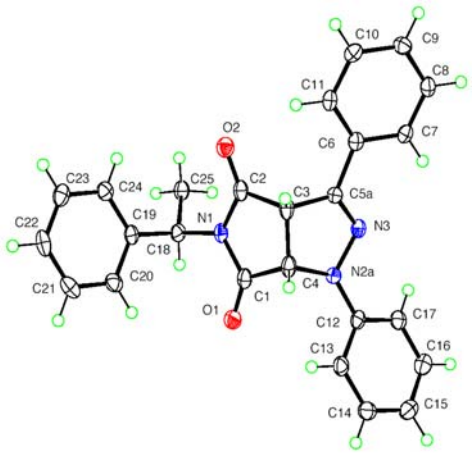
General procedure - Corresponding hydrazonyl chloride **6.4** (0.5 mmol) and maleimide **6.18** (0.5 mmol) were dissolved in dry acetonitrile (20 mL). Et_3N (0.202 g, 2 mmol) was added dropwise into the mixture with stirring and after addition is completed, the reaction mixture was stirred at room temperature for 2-4 h. The progress of reaction was monitored by TLC. After the reaction is complete, all CH_3CN was rotaevaporated and the reaction mixture was mixed with 50 mL of water and allowed to dissolve all Et_3N.HCl salt . The precipitated crude cycloadduct was collected by suction filtration and washed with water (50 mL), hexane (25 mL) respectively, and dried under vacuo for 1-2 h. Finally, chiral cycloadducts **6.19** were purified with Chromatotron (Centrifugal Thin-Layer Chromatograph) using n-hexane-ethyl acetate as eluant and recrystallized from appropriate solvent mixtures indicated.

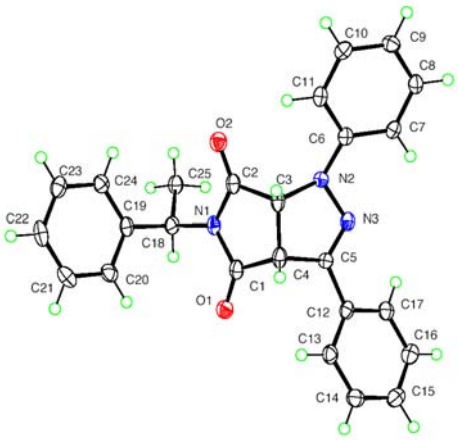
(3a*S*,6a*S*)-1,3-Diphenyl-5-[(1*R*)-1-phenylethyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (6.19a) and (3a*R*,6a*R*)-1,3-diphenyl-5-[(1*R*)-1-phenylethyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (6.19a'). Inseparable isomers. Detected by X-Ray Diffraction.



and







6.19a **6.19a'**

Colorless plate crystals (obtained by slow evaporation in acetone). (100 mg, 51%). $[\alpha]_{589}^{21^{o}C}$ = +80.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 150-152˚C (acetone). R_f: 0.75 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3483, 3059, 2926 (C-H), 1710 (C=O),1597 (C=N), 1494, 1386, 1346, 1222, 1192, 754, 696 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.98 (t, *J*=6.9 Hz, 2H), 7.43-7.50 (m, 5H), 7.24-7.36 (m, 7H), 6.95 (q, *J*=7.3 Hz, 1H), 5.42 (dd, *J*=10.8, 3.3 Hz, 1H), 5.30 (q, *J*=7.2 Hz, 1H), 5.24 (dd, *J*=10.8,1.7 Hz, 1H), 1.70 (t, *J*=4.2 Hz, 3H).

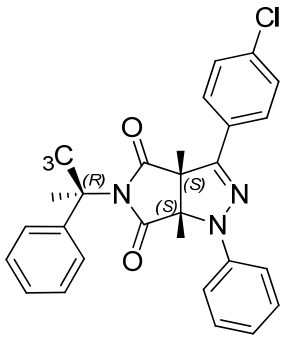
^{13}C NMR (100 MHz, DMSO-d_6): δ=173.8(C=O), 172.8 (C=O), 145.0 (C=N), 144.5, 139.8, 131.0, 129.5, 128.9, 128.9, 128.8,127.9,127.5,127.0, 121.0, 114.4, 66.0(-CH), 54.0 (-CH), 50.3 (-CH), 16.8 (-CH_3).

MS (70 eV): (*m/z*, %)= 395 (100) $[M]^+$, 291 (65), 247 (40), 219 (25), 105 (20), 77 (20). Anal Calcd for $C_{25}H_{21}N_3O_2$. C, 75.93; H, 5.35; N, 10.63; O, 8.09; found C, 75.41; H, 5.20; N, 10.61.

Crystal data

$C_{25}H_{21}N_3O_2$, M_r = 395.45, Monoclinic, $P2_1$, Hall symbol:P 2yb *a* = 9.276 (2) Å, *b* = 8.853 (2) Å, *c* = 12.248 (3) Å, *V* = 979.2 (4) $Å^3$, *Z* = 2, F_{000}=416, *Dx* = 1.341 Mg m^{-3}, *Dm* not measured, Cu Kα radiation, λ = 1.54178 Å, Cell parameters from 7851 reflections, θ = 5.0– 68.3°, μ = 0.69 mm^{-1}, T = 90 K, Fragment, Colorless, 0.19 × 0.17 × 0.16 mm.

(3a*S*,6a*S*)-3-(4-Chlorophenyl)-1-phenyl-5-[(1*R*)-1-phenylethyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (6.19b)



Light yellow needle crystals (from DCM-hexane). (181 mg, 84%). $[\alpha]_{589}^{21^\circ C}$ = +70.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 189-191˚C (dichloromethane-n-hexane). R_f : 0.76 (ethyl acetate-n-hexane; 1:2).

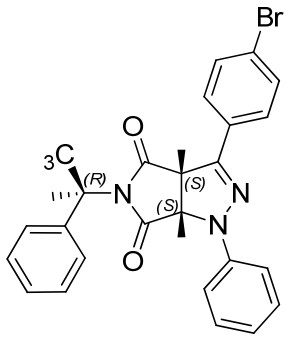
IR (KBr): v = 3470, 3090, 2939 (C-H), 1705 (C=O),1597 (C=N), 1492, 1379, 1356, 1220, 1193, 831, 750, 696 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.01 (d, *J*=8.0 Hz, 2H), 7.58 (d, *J*=6.7 Hz, 2H), 7.19-7.48 (m, 9H), 7.02 (t, *J*=6.5,1H), 5.44 (t, *J*=7.0, 1H), 5.01 (dd, *J*=35.7, 10.9 Hz, 1H), 4.70(dd, *J*=22.1, 10.9 Hz, 1H), 1.80 (t, *J*=7.2, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=171.5 (C=O), 170.5 (C=O),144.5 (C=N), 142.3, 142.1, 139.0,135.4, 129.3, 128.9, 128.8,128.6, 128.3,127.6, 121.7, 114.4, 65.3(-CH), 53.1 (-CH), 51.5 (-CH), 16.3 (-CH_3).

MS (70 eV): (*m/z*, %)= 429 (100) $[M]^+$, 325 (82), 281 (35), 253 (29), 105 (35), 77 (29). Anal Calcd for $C_{25}H_{20}ClN_3O_2$. C, 69.85; H, 4.69; N, 9.77; found C, 68.40; H, 4.65; N, 9.41.

(3a*S*,6a*S*)-3-(4-Bromophenyl)-1-phenyl-5-[(1*R*)-1-phenylethyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (6.19c)



Light yellow crystals. (170 mg, 72%). $[\alpha]_{589}^{21^oC}$ = +60.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 146-148˚C (acetone). R_f : 0.76 (ethyl acetate-n-hexane; 1:2).

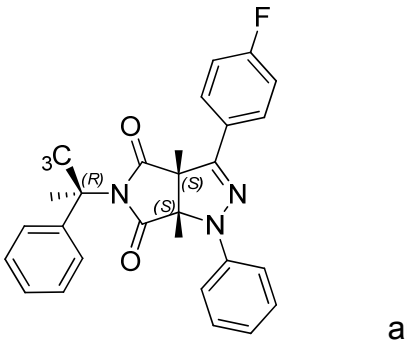
IR (KBr): v = 3471, 3032, 2939 (C-H), 1708 (C=O), 1599 (C=N), 1573, 1491, 1379, 1356, 1193, 750, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.93 (d, *J*=8.5 Hz, 2H), 7.57 (q, *J*=4.0 Hz, 4H), 7.46 (t, *J*=6.4 Hz 2H), 7.28-7.39 (m, 5H), 7.02 (t, *J*=7.2 Hz, 1H), 5.43 (t, *J*=7.0 Hz, 1H), 5.01 (dd, *J*=34.8, 11.0 Hz, 1H), 4.70(dd, *J*=22.9, 10.9 Hz, 1H), 1.81 (t, *J*=7.3 Hz, 3H).

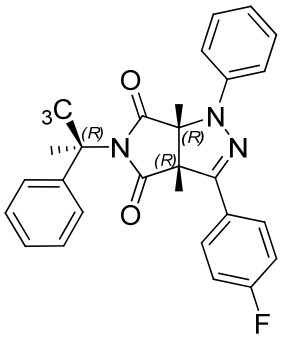
^{13}C NMR (100 MHz,$CDCl_3$): δ=172.3 (C=O), 171.5 (C=O),144.3 (C=N), 141.8, 138.7, 131.7, 129.4, 129.2, 128.6, 128.5, 128.2, 127.6, 123.7, 121.7, 114.4, 65.3(-CH), 53.1 (-CH), 51.5 (-CH), 16.3 ($-CH_3$).

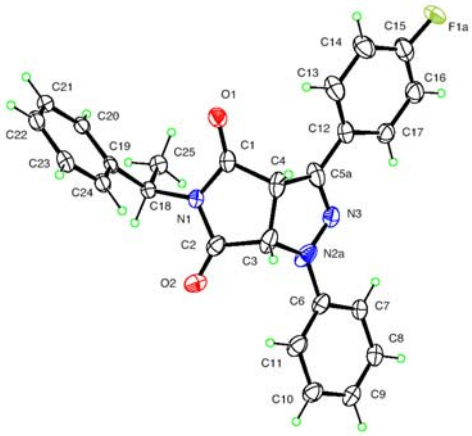
MS (70 eV): (*m/z*, %)= 473 (100) $[M]^+$, 369 (74), 327 (32), 299 (29), 247 (15), 105 (53), 77 (47). Anal Calcd for $C_{25}H_{20}BrN_3O_2$. C, 63.30; H, 4.25; N, 8.86; found C, 63.09; H, 4.37; N, 8.53.

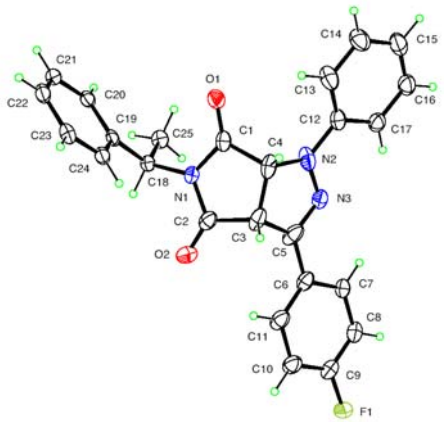
(3a*S*,6a*S*)-3-(4-fluorophenyl)-1-phenyl-5-((*R*)-1-phenylethyl)-1,6a-dihydro pyrrolo[3,4-*c*]pyrazole-4,6(3a*H*,5*H*)-dione (6.19d) (3a*R*,6a*R*)-3-(4-fluorophenyl)-1-phenyl-5-((*R*)-1-phenylethyl)-1,6a-dihydropyrrolo[3,4-*c*] pyrazole-4,6(3a*H*,5*H*)-dione (6.19d') and Inseparable isomers. Detected by X-Ray Diffraction.



and







6.19d **6.19d'**

White crystals (from DCM-pentane). (175 mg, 85%). $[\alpha]_{589}^{21^{\circ}C}$ = +60.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 205-206˚C (dichloromethane-n-pentane). R_f : 0.75 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3481, 3061, 2980 (C-H), 2941, 1708 (C=O),1597 (C=N), 1498, 1379, 1356, 1224, 1193, 1128, 750, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.07 (t, *J*=3.1 Hz, 2H), 7.58 (d, *J*=7.2 Hz, 2H), 7.47 (t, *J*=6.8 Hz, 2H), 7.28-7.37 (m, 5H), 7.13-7.22 (m, 2H), 7.02 (t, *J*=7.0 Hz, 1H), 5.44 (quintet, *J*=7.4 Hz, 1H), 5.01 (dd, *J*=34.6, 10.9 Hz, 1H), 4.70 (dd, *J*=20.9, 10.9 Hz, 1H), 1.83 (t, *J*=7.1 Hz, 3H).

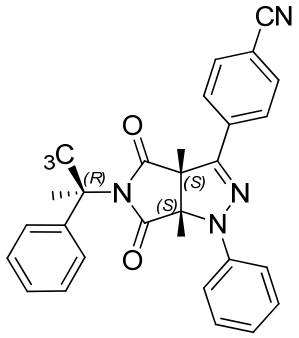
^{13}C NMR (100 MHz, $CDCl_3$): δ=172.5 (C=O), 171.5 (C=O),144.6 (C=N), 142.0, 138.7, 129.2, 129.1,129.0, 128.6, 128.2, 127.6, 121.5, 115.8, 115.6,114.4, 65.4(-CH), 53.3 (-CH), 51.5 (-CH), 16.3 ($-CH_3$).

MS (70 eV): (*m/z*, %)= 413 (100) $[M]^+$, 309 (78), 265 (35),105 (29), 70 (21).Anal Calcd for $C_{25}H_{20}FN_3O_2$. C, 72.63; H, 4.88; N, 10.16; found C, 73.43; H, 4.93; N, 10.23.

Crystal data

$C_{25}H_{20}FN_3O_2$, M_r = 413.44, Orthorhombic, $P2_12_12_1$, *a* = 5.6997 (5) Å, *b* = 18.2380 (15) Å, *c* = 19.330 (2) Å, *V* = 2009.4 (3) $Å^3$, *Z* = 4, F_{000}=864, *Dx* = 1.367 Mg m^{-3}, *Dm* not measured, Cu Kα radiation, λ = 1.54178 Å, Cell parameters from 8954 reflections, θ = 2.3– 68.2°, μ = 0.77 mm^{-1}, T = 90 K, Fragment, Colorless, 0.24 × 0.20 × 0.20 mm.

4-{(3a*S*,6a*S*)-4,6-Dioxo-1-phenyl-5-[(1*R*)-1-phenylethyl]-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazol-3-yl}benzonitrile (6.19g)



Yellow powder. (194 mg, 92%). $[\alpha]_{589}^{21^{o}C}$ = +68.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 207-209˚C. R_f: 0.7 (ethyl acetate-n-hexane; 1:2).

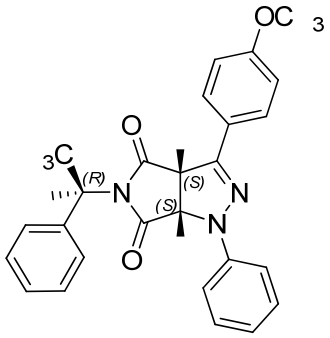
IR (KBr): v = 3398, 3059, 2941 (C-H), 2225 (C≡N), 1712 (C=O),1597 (C=N), 1496, 1384, 1356, 1220, 1193, 750, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.15 (d, *J*=7.1 Hz, 2H), 7.70 (d, *J*=8.1 Hz, 2H), 7.60 (d, *J*=5.7 Hz, 2H), 7.45 (t, *J*=6.5, 2H), 7.30-7.41 (m, 5H), 7.06 (t, *J*=7.2,1H), 5.44 (quintet, *J*=6.7 Hz,1H), 5.15 (dd, *J*=32.2, 11.1 Hz, 1H), 4.76 (dd, *J*=20.1, 11.1 Hz, 1H), 1.81 (t, *J*=7.0, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=171.9 (C=O), 171.3 (C=O),143.5 (C=N), 140.7, 138.5, 134.7, 132.3, 129.3, 128.7, 128.3, 127.6, 127.2, 122.3, 118.8, 114.6,112.1,65.4(-CH), 52.7 (-CH), 51.6 (-CH), 16.4 ($-CH_3$).

MS (70 eV):(*m/z*,%)= 420 (100) $[M]^+$, 316 (78), 272 (25), 244 (16), 105 (33), 70 (38). Anal Calcd for $C_{26}H_{20}N_4O_2$. C, 74.27; H, 4.79; N, 13.33; O, 7.61; found C, 74.23; H, 4.79; N, 12.89.

(3a*S*,6a*S*)-3-(4-Methoxyphenyl)-1-phenyl-5-[(1*R*)-1-phenylethyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (6.19h)



Light yellow needles (from DCM-hexane). (209 mg, 97%). $[\alpha]_{589}^{21^{o}C}$ = +40.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p.135-137˚C (dichloromethane-n-hexane). R_f : 0.75 (ethyl acetate-n-hexane; 1:2).

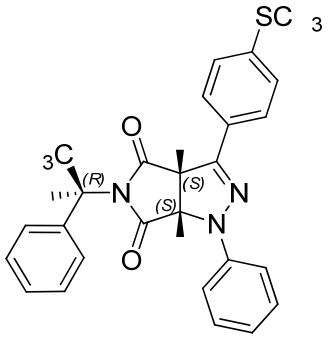
IR (KBr): v = 3487, 3056, 2935 (C-H), 2837, 1708 (C=O),1597 (C=N), 1496, 1379, 1356, 1253, 1176, 835, 750, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.01 (t, *J*=6.3 Hz, 1H), 7.59 (d, *J*=7.3 Hz, 2H), 7.46 (q, *J*=7.6 Hz, 2H), 7.20-7.35 (m, 5H), 6.98 (d, *J*=8.0 Hz, 3H), 6.64 (s, 1H), 5.37 (quintet, *J*=7.4 Hz, 1H), 4.95 (dd, *J*=33.4,10.7 Hz, 1H), 4.75 (dd, *J*=24.1, 10.7 Hz, 1H), 3.80 (s, 3H), 1.81 (t, *J*=7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=172.7 (C=O), 171.7 (C=O), 160.8, 145.0 (C=N), 142.9, 134.0, 129.2, 128.8, 128.5, 128.1, 127.7, 127.2, 123.1, 121.2, 114.3, 65.3 (-CH,3aC), 55.4 (OCH_3), 53.4 (-CH), 51.4 (-CH), 16.4 ($-CH_3$).

MS (70 eV): (*m/z*, %)= 201(100) $[M]^{+}$-$C_{16}H_5N$-N=C-$C_6H_4OCH_3$, 158 (25), 104 (40), 77 (40), 51 (15). Anal Calcd for $C_{26}H_{23}N_3O_3$. C, 73.39; H, 5.45; N, 9.88; found C, 72.21; H, 5.27; N, 9.50.

(3a*S*,6a*S*)-3-[4-(Methylthio)phenyl]-1-phenyl-5-[(1*R*)-1-phenylethyl]-3a, 6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (6.19i)



Light yellow crystals (from DCM-pentane). (200 mg, 91%). $[\alpha]_{589}^{21^{o}C}$ = +44.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 82-84˚C(dichloromethane-n-pentane). R_f : 0.80 (ethyl acetate-n-hexane; 1:2).

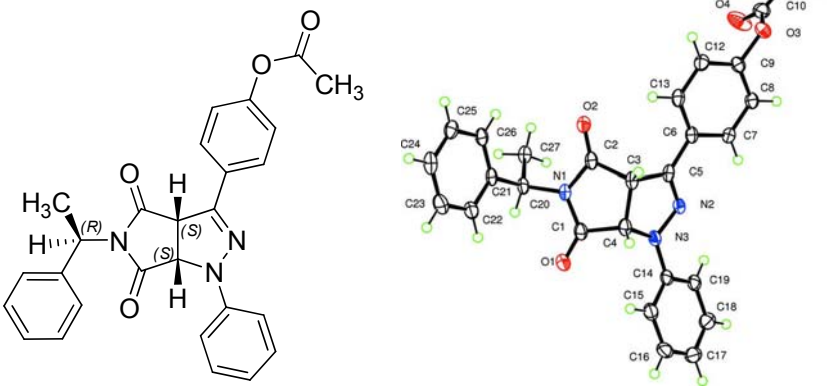
IR (KBr): v = 3483, 30565, 2980, 2920 (C-H), 1708 (C=O),1597 (C=N), 1494, 1388, 1356, 1226, 1093, 750, 696 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.95-7.99 (m, 2H), 7.58 (q, *J*=4.0 Hz, 2H), 7.46 (t, *J*=6.5 Hz, 2H), 7.28-7.38 (m, 7H), 7.01 (t, *J*=7.2 Hz, 1H), 5.43 (quintet, *J*=7.3 Hz, 1H), 4.98 (dd, *J*=32.7, 10.9 Hz, 1H), 4.75 (dd, *J*=24.4, 10.9 Hz, 1H), 2.53 (s, 3H), 1.80 (t, *J*=7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=172.5 (C=O), 171.6 (C=O), 144.6 (C=N), 142.6, 140.7, 134.0, 129.2, 128.6, 128.2, 127.6, 127.4, 127.2, 125.8,121.4,114.3, 65.2(-CH,3aC), 53.2 (-CH), 51.4 (-CH), 16.4 ($-CH_3$), 15.3 ($-SCH_3$).

MS (70 eV): (*m/z*, %)= 441 (100) $[M]^+$, 337 (65), 295 (22), 266 (45), 250 (33), 105 (22), 70 (15). Anal Calcd for $C_{26}H_{23}N_3O_2S$. C, 70.72; H, 5.25; N, 9.52; S, 7.26; found C, 70.13; H, 5.22; N, 9.00.

4-{(3a*S*,6a*S*)-4,6-Dioxo-1-phenyl-5-[(1*R*)-1-phenylethyl]-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazol-3-yl}phenyl acetate (6.19j)



Yellow needle crystals (from DCM-hexane-acetone) . (160 mg, 71%). $[\alpha]_{589}^{21^{o}C}$ = +79.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 86-88˚C (dichloromethane-n-hexane-acetone). R_f : 0.60 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3412, 3063, 2937 (C-H), 1757(C=O), 1710(C=O), 1599 (C=N), 1498, 1452, 1357, 1197, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.10 (q, *J*=3.8 Hz, 2H), 7.58 (t, *J*=7.6 Hz, 2H), 7.47 (t, *J*=7.2 Hz, 2H), 7.24-7.36 (m, 5H), 7.18 (q, *J*=4.6 Hz, 2H), 7.01 (t, *J*=7.3 Hz, 1H), 5.44 (t, *J*=7.1 Hz, 1H), 4.95 (dd, *J*=51.1, 10.9 Hz, 1H), 4.70 (dd, *J*=21.5,11.0 Hz, 1H), 2.35 (s, 3H) 1.80 (t, *J*=6.8 Hz, 3H).

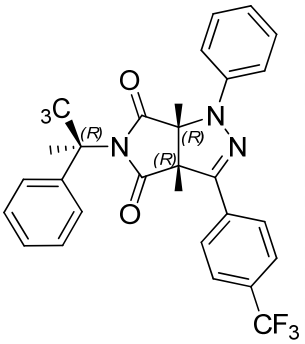
^{13}C NMR (100 MHz,$CDCl_3$): δ=172.4 (C=O), 171.5 (C=O), 169.4 (C=O),151.5 (C=N), 144.5, 142.0, 138.7, 129.2, 128.9, 128.6, 128.3, 128.2, 127.6,121.8, 121.5, 114.4, 65.4 (-CH), 53.3 (-CH), 51.4 (-CH), 21.1(-CH_3), 16.4 (-CH_3).

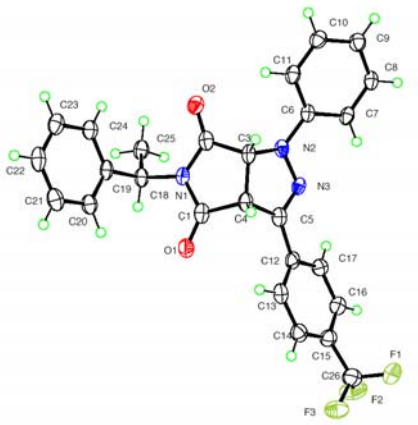
MS (70 eV): (*m/z*, %)= 453 (100) $[M]^+$, 411 (65), 307 (100), 236 (50), 207 (10), 105 (33), 70 (10). Anal Calcd for $C_{27}H_{23}N_3O_4$. C, 71.51; H, 5.11; N, 9.27; found C, 71.63; H, 5.11; N, 9.25.

Crystal data

$C_{27}H_{23}N_3O_4$, M_r = 453.48, Monoclinic, $P2_1$, Hall symbol:P 2yb *a* = 9.1391 (5) Å, *b* = 8.7465 (5) Å, *c* = 14.442 (1) Å, *V* = 1121.17 (12) $Å^3$, *Z* = 2, F_{000}=476, *Dx* = 1.343 Mg m^{-3}, *Dm* not measured, Cu Kα radiation, λ = 1.54178 Å, Cell parameters from 7860 reflections, θ = 3.2– 68.3°, μ = 0.75 mm^{-1}, T = 90 K, Fragment, Yellow, 0.30 × 0.25 × 0.19 mm.

(3a*R*,6a*R*)-1-Phenyl-5-[(1*R*)-1-phenylethyl]-3-[4-(trifluoromethyl)phenyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (6.19k')





Light green crystals (from acetic acid). (161 mg, 70%). $[\alpha]_{589}^{21^{\circ}C}$ = +12.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 174-176˚C (acetic acid). R_f: 0.68 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3452, 3064, 2941 (C-H), 1708 (C=O),1599 (C=N), 1500, 1327, 1193, 1166, 1068, 844, 750, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.17 (q, *J*=3.8 Hz, 2H), 7.70 (t, *J*=4.7 Hz, 2H), 7.61 (t, *J*=7.6 Hz, 2H), 7.47 (t, *J*=6.5 Hz, 2H), 7.28-7.41 (m, 5H), 7.05 (t, *J*=7.0 Hz, 1H), 5.44 (quintet, *J*=7.0 Hz, 1H), 5.08 (dd, *J*=29.8, 11.0 Hz, 1H), 4.76 (dd, *J*=23.2, 11.0 Hz, 1H), 1.82 (t, *J*=7.3 Hz, 3H).

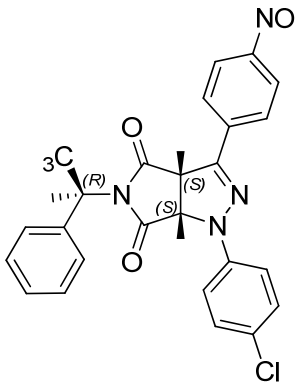
^{13}C NMR (100 MHz,$CDCl_3$): δ=172.1(C=O), 171.4 (C=O),143.9 (C=N), 141.2, 138.6, 133.8, 130.9, 129.3, 128.6, 128.3, 127.6, 127.1, 125.5 (-CF_3), 122.6, 121.9, 114.5 (CF_3), 65.3 (-CH,3aC), 52.9 (-CH_3CH), 51.6 (-CH,6aC), 16.4 (-CH_3).

MS (70 eV): (*m/z*, %)= 463 (100) $[M]^+$, 359 (80), 315 (30), 269 (10), 105 (40), 70 (43).Anal Calcd for $C_{26}H_{20}F_3N_3O_2$. C, 67.38; H, 4.35; N, 9.07; found C, 66.45; H, 4.50; N, 8.74.

Crystal data

$C_{26}H_{20}F_3N_3O_2$, M_r = 463.45, Orthorhombic, $P2_12_12_1$, Hall symbol:P 2ac 2ab *a* = 8.7982 (15) Å, *b* = 9.3064 (15) Å, *c* = 25.992 (4) Å, *V* = 2128.2 (6) Å^3, *Z* = 4, F_{000}=960, *Dx* = 1.446 Mg m^{-3}, *Dm* not measured, Cu Kα radiation, λ = 1.54178 Å, Cell parameters from 3807 reflections, θ = 3.4– 65.8^o, μ = 0.93 mm^{-1}, T = 90 K, Lath, Colorless, 0.30 × 0.18 × 0.03 mm.

(3a*S*,6a*S*)-1-(4-Chlorophenyl)-3-(4-nitrophenyl)-5-[(1*R*)-1-phenylethyl]-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (6.19r)



Orange powder. (210 mg, 88%). $[\alpha]_{589}^{21^{o}C}$ = +53.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 242-244˚C. R_f : 0.62 (ethyl acetate-n-hexane; 1:2).

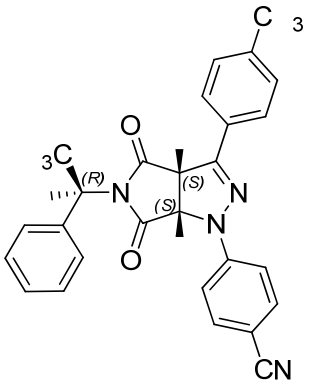
IR (KBr): v = 3475, 3057, 2935 (C-H), 1708 (C=O),1593 (C=N), 1550, 1492, 1392, 1334, 1222, 1195, 852, 690 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.32 (q, *J*=4.5 Hz, 2H), 8.20 (t, *J*=7.6, 2H), 7.53 (t, *J*=8.8, 2H), 7.42 (q,*J*=4.5 Hz, 2H), 7.24-7.29 (m, 5H), 5.57 (t, *J*=9.7 Hz,1H), 5.28-5.34 (td, *J*=10.8, 3.3 Hz, 2H), 1.69 (t, *J*=6.5 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ=173.5 (C=O), 172.5 (C=O), 147.5 (C=N), 143.0, 142.5,139.7,137.0, 129.4, 128.9, 128.2, 128.0, 127.1, 125.6, 124.2,116.3, 65.9 (-CH), 53.8 (-CH), 50.6 (-CH), 16.8 ($-CH_3$).

MS (70 eV): (*m/z*, %)= 395 (100) $[M]^{+}$-NO_2Cl, 291 (70), 247 (40), 218 (25), 105 (20), 70 (10). Anal Calcd for $C_{25}H_{19}ClN_4O_4$. C, 63.23; H, 4.03; N, 11.80; found C, 62.45; H, 4.10; N, 11.46.

4-[(3a*S*,6a*S*)-3-(4-Methylphenyl)-4,6-dioxo-5-[(1*R*)-1-phenylethyl]-4,5,6, 6a-tetrahydropyrrolo[3,4-*c*]pyrazol-1(3a*H*)-yl]benzonitrile (6.19u)



White needle crystals (from EtOH-Hexane-Acetone-DCM). (213 mg, 96%). $[\alpha]_{589}^{21^{o}C}$ = +80.0° (c= 0.01 g/mL, l=10 cm, acetone). M.p. 234-236˚C (ethanol-n-hexane-acetone-dichloromethane). R_f: 0.58 (ethyl acetate-n-hexane; 1:2). IR (KBr): v= 3470, 3032, 2980, 2941 (C-H), 2218 (C≡N), 1712 (C=O),1602 (C=N), 1508, 1390, 1186, 829, 696 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.96 (dd,*J*=3.5, 4.6 Hz, 2H), 7.60 (s, 4H), 7.44 (t, *J*=6.9, 2H), 7.26-7.36 (m, 5H), 5.42 (quintet, *J*=5.8 Hz, 1H), 5.10 (dd, *J*=29.7, 10.7 Hz, 1H), 4.86 (dd, *J*=23.2, 10.7 Hz, 1H), 2.41 (s, 3H), 1.80 (t, *J*= 5.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 172.5 (C=O), 171.5 (C=O), 147.5 (C=N), 146.0, 142.0, 139.0, 133.5, 129.5, 128.7,127.6, 127.5, 127.4, 120.0,114.2, 103.0, 64.5(-CH), 54.0(-CH), 51.5 (-CH), 22.0 (-CH_3), 16.0 (-CH_3).

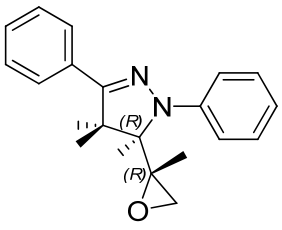
MS (70 eV): (*m/z*, %)= 434 (100) $[M]^+$, 330 (78), 286 (53), 105 (46), 70 (23).Anal Calcd for $C_{27}H_{22}N_4O_2$. 0.25 H_2O C, 73.92; H, 5.10; N, 12.77; found C, 73.28; H, 5.44; N, 12.05.

Synthesis of (*R*)-5-((*R*) or (*R*)-5-((*S*)-2-methyloxiran-2-yl)-1,3-disubstituted - 4,5-dihydro-1*H*-pyrazole (6.21a-u (a'-u'))

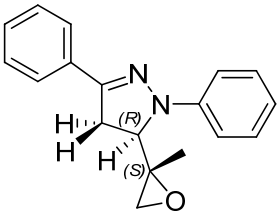
Typical procedure - Corresponding hydrazonyl chloride **6.4** (0.5 mmol) and Et_3N (4 mmol) were dissolved in dry dichloromethane (20 mL) and stirred for 30 min. Then, isoprene monoxide **6.20** (1.5 mmol) was added dropwise into the mixture and reaction mixture was stirred at room temperature under N_2 atmosphere. The progress of reaction was monitored by TLC (20-96 h). After the reaction is complete, all DCM was rotaevaporated and the reaction mixture was mixed and stirred with water (30 mL) to dissolve all Et_3N.HCl salt and extracted by DCM (2x20 mL), dried over $MgSO_4$ and solvent was removed. Finally, the cycloadducts **6.21** were isolated by Column Chromatography (EtOAc: Hexane) as either single isomer or mixture of isomers.

(*R*)-5-((*R*)-2-methyloxiran-2-yl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole (6.21a) and (*R*)-5-((*S*)-2-methyloxiran-2-yl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole (6.21a'). Two inseparable diastereomers.

(Assigned diastereomeric ratio by ^{1}H-NMR spectra - 5*R*,2*R*-diasteromer/ 5*R*,2*S*-diasteromer = 1.16:1.00)



and



Orange oily solid. (110 mg, 92 %). Melting range: 82-87˚C. R_f: 0.55-0.45 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3057, 2983 (C-H), 2926, 1600 (C=N), 1552, 1500, 1394, 1323, 1124, 883, 758,750 cm^{-1}.

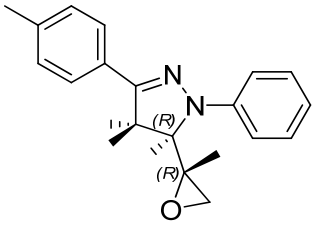
^1H NMR (400 MHz, $CDCl_3$): δ= 7.76 (t, *J*=7.3 Hz, 4H), 7.40-7.45 (m,4H), 7.30-7.38 (m, 8H), 7.22 (d, *J*=7.7 Hz, 2H), 6.87-6.91(t, *J*=7.2 Hz, 2H), 4.04-4.04-4.09 (q, *J*=5.8 Hz,1H), 4.11-4.15 (q, *J*=5.6 Hz,1H), 3.54-3.65 (td, *J*=21.8, 12.6 Hz, 2H), 3.39-3.45 (dd, *J*=17.6, 5.8 Hz, 1H), 3.23-3.29 (dd, *J*=17.2, 6.6 Hz, 1H), 3.04 (d, *J*=4.6 Hz, 1H), 2.86-2.87 (d, *J*=4.7 Hz, 1H), 2.84-2.85 (d, *J*=4.7 Hz, 1H), 2.78(d, *J*=4.8 Hz, 1H), 1.35 (s,3H) (-CH_3 of 5*R*,2*S*-diastereomer), 1.27 (s,3H) (-CH_3 of 5*R*,2*R*-diastereomer).

^{13}C NMR (100 MHz, $CDCl_3$): δ=150.0, 148.3, 147.3, 145.7, 137.4, 132.8, 129.5, 129.5, 129.2, 129.1, 129.0, 128.9, 126.2, 126.1, 119.9, 119.8, 114.0, 113.8, 65.8, 64.7, 59.5, 58.6, 56.7,52.8, 37.8, 37.6, 17.1 (-CH_3 of 5*R*,2*S*-diastereomer), 16.6 (-CH_3 of 5*R*,2*R*-diastereomer).

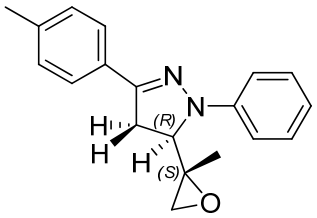
TOF-MS EI+: (*m/z*, %)= 278 (15) $[M]^+$, 221 (50), 176 (20), 105 (90), 85 (100). HRMS calculated for $C_{18}H_{18}N_2O$ 278.1419 found 278.1417.

(*R*)-5-((*R*)-2-methyloxiran-2-yl)-1-phenyl-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazole (6.21e) and (*R*)-5-((*S*)-2-methyloxiran-2-yl)-1-phenyl-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazole (6.21e'). Two inseparable diastereomers.

(Assigned diastereomeric ratio by ^1H-NMR spectra - 5*R*,2*R*-diasteromer/ 5*R*,2*S*-diasteromer = 1.57:1.00)



and



White crystals. (117 mg, 80%). Melting range: 92-98˚C. R_f : 0.50-0.45 (ethyl acetate-n-hexane; 1:4).

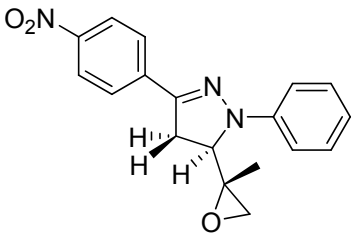
IR (KBr): v = 3036, 2922 (C-H), 2852, 1597 (C=N), 1500, 1390, 1325, 1124, 815, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.56 (t, *J*=8.5 Hz, 4H), 7.18-7.24 (m,6H), 7.13-7.09 (m, 5H), 6.78 (t, *J*=6.8 Hz, 2H), 3.97-4.01 (q, J=5.8 Hz, 1H), 3.91-3.96 (q, *J*=6.8 Hz, 1H), 3.42-3.54 (td, *J*=21.7, 11.9 Hz, 2H), 3.27-3.33 (dd, *J*=17.6, 5.9 Hz, 1H), 3.11-3.17 (dd, *J*=17.2, 6.8 Hz, 1H), 2.93 (d, *J*=4.7 Hz, 1H), 2.76 (d, *J*=4.8 Hz, 1H), 2.74 (d, *J*=4.8 Hz, 1H), 2.68 (d, *J*=4.7 Hz, 1H), 2.31(s,3H) (-CH_3 of 5*R*,2*S*-diastereomer), 2.30 (s,3H) (-CH_3 of 5*R*,2*R*-diastereomer), 1.24 (s,3H) (-CH_3 of 5*R*,2*S*-diastereomer), 1.17 (s,3H) (-CH_3 of 5*R*, 2*R*-diastereomer).

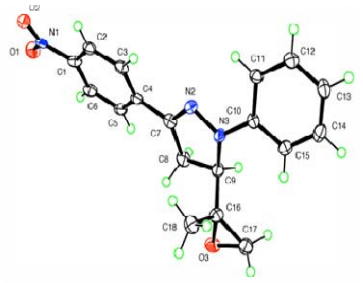
^{13}C NMR (100 MHz, $CDCl_3$): δ= 156.0, 155.7, 150.0, 148.5, 147.5, 146.3, 145.9, 145.7, 139.4, 130.0, 129.7, 129.6, 129.5, 129.5, 126.2, 126.1, 119.8, 119.7, 114.0, 113.7, 65.8, 64.7, 59.5, 58.6, 56.7, 52.8, 37.9, 37.7, 21.8(-CH_3), 17.1 (-CH_3 of 5*R*,2*S*-diastereomer), 16.6 (-CH_3 of 5*R*,2*R*-diastereomer).

TOF-MS EI+: (*m/z*, %)= 292 (30) $[M]^+$, 272 (15), 235 (100), 77 (20). HRMS calculated for $C_{19}H_{20}N_2O_3$ 292.1576 found 292.1578.

(*R*)-5-((*R*)-2-methyloxiran-2-yl)-3-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (6.21f) and (*R*)-5-((S)-2-methyloxiran-2-yl)-3-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole(6.21f'). Two separated diastereomers.



6.21f



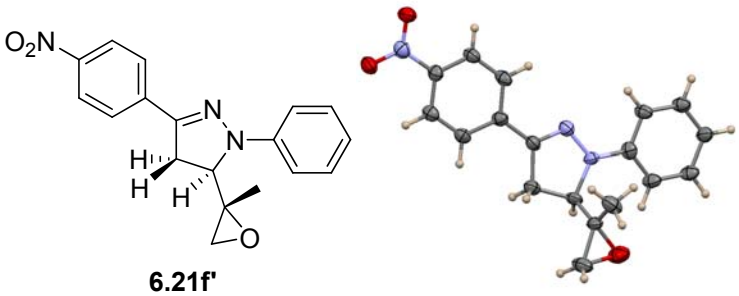
Light orange crystals (from Diisopropylphenylether-acetone). (30 mg, 20%). M.p. 155-157˚C. R_f : 0.75 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3047, 2924 (C-H), 2850, 1593 (C=N), 1552, 1500, 1340, 1107, 846, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.27 (d, *J*=9.0 Hz, 2H), 7.86 (d, *J*=9.0, 2H), 7.34 (t, *J*=7.3, 2H), 7.22-7.25 (dd, *J*=8.8, 1.1 Hz, 2H), 6.96 (t, *J*=7.4 Hz, 1H), 4.24 (q, *J*=5.9 Hz,1H), 3.55-3.62 (dd, *J*=17.7, 12.2 Hz, 1H), 3.42-3.48 (dd, *J*=17.7, 5.9 Hz, 1H), 3.04 (d, *J*= 4.4 Hz, 1H), 2.87 (d, *J*=4.6 Hz, 1H), 1.25 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=143.9, 142.0, 140.6, 135.3, 126.1, 122.4, 120.8, 117.5, 110.8, 62.3, 54.7, 53.0, 33.4, 12.9.

TOF-MS EI+: (*m/z*, %)= 323 (35) $[M]^+$, 266 (90), 235 (95), 83 (100). HRMS calculated for $C_{18}H_{17}N_3O_3$ 323.1270 found 323.1276.



6.21f'

Dark orange crystals (from Diisopropylphenylether-acetone). (25 mg, 20%). M.p.152-154˚C. R_f : 0.62 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3059, 2926 (C-H), 2854, 1593 (C=N), 1552, 1502, 1340, 1107, 846, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.20 (d, *J*=8.8 Hz, 2H), 7.78 (d, *J*=8.8, 2H), 7.32-7. (d, *J*=4.2, 4H), 6.91 (p, *J*=4.3 Hz, 1H), 4.16 (q, *J*=6.7 Hz,1H), 3.54-3.62 (dd, *J*=17.2, 13.0 Hz, 1H), 3.21-3.27 (dd, *J*=17.2, 6.7 Hz, 1H), 2.80 (d, *J*=4.6 Hz, 1H), 2.74 (d, *J*=4.6 Hz, 1H), 1.28 (s, 3H).

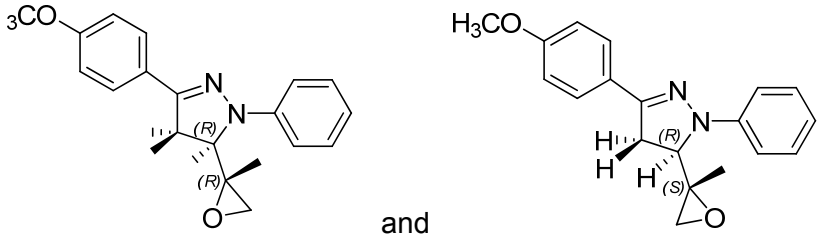
^{13}C NMR (100 MHz, $CDCl_3$): δ=143.2, 140.6, 140.3, 135.0, 125.6, 122.2, 120.4, 117.2, 110.2, 62.2, 56.2, 48.8, 34.2, 13.1.

TOF-MS EI+: (*m/z*, %)= 323 (5) $[M]^+$, 289 (20), 273 (40), 235 (100), 83 (100). HRMS calculated for $C_{18}H_{17}N_3O_3$ 323.1270 found 323.1269.

(*R*)-3-(4-methoxyphenyl)-5-((*R*)-2-methyloxiran-2-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (6.21h) and (*R*)-3-(4-methoxyphenyl)-5-((*S*)-2-methyloxiran-2-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (6.21h').

As a mixture of two inseparable diastereomers.

(Assigned diastereomeric ratio by ^{1}H-NMR spectra - 5*R*,2*R*-diasteromer/ 5*R*,2*S*-diasteromer = 1.33:1.00)



and

Brown oil. (75 mg, 65%). R_f : 0.75-0.65 (ethyl acetate-n-hexane; 1:2).

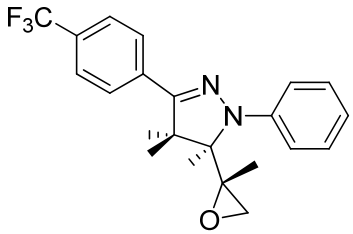
IR (KBr): v = 3049, 2931 (C-H), 2837, 1597 (C=N), 1500, 1390, 1251, 1172, 833, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.61 (t, *J*=9.0 Hz, 4H), 7.18-7.23 (m,6H), 7.10-7.08 (d, *J*=7.7 Hz, 2H), 6.77-6.87 (m, 6H), 3.95-3.99 (q, J=6.1 Hz, 1H), 3.90-3.95 (q, *J*=6.8 Hz, 1H), 3.78 (s,3H) (-OCH_3 of 5*R*,2*S*-diastereomer), 3.77 (s,3H) (-OCH_3 of 5*R*,2*R*-diastereomer), 3.41-3.53 (td, *J*=21.4, 12.5 Hz, 2H), 3.26-3.32 (dd, *J*=17.6, 5.9 Hz, 1H), 3.11-3.17 (dd, *J*=17.1, 6.8 Hz, 1H), 2.94 (d, *J*=4.7 Hz, 1H), 2.77 (d,4.7 Hz, 1H), 2.75 (d,4.7 Hz, 1H), 2.68 (d, *J*=4.7 Hz, 1H), 1.25 (s,3H) (-CH_3 of 5*R*,2*S*-diastereomer), 1.18 (s,3H) (-CH_3 of 5*R*,2*R*-diastereomer).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 161.0, 160.6, 151.1, 150.0, 146.0, 142.3, 142.1, 139.9, 132.8, 129.5, 129.3, 128.5, 127.7, 127.6, 125.0, 119.5, 114.5, 114.4, 113.9, 113.7, 65.7, 64.7, 56.7 (-OCH_3 of 5*R*,2*S*-diastereomer), 55.8 (-OCH_3 of 5*R*,2*R*-diastereomer), 52.9, 48.6, 38.0, 34.7, 17.2 (-CH_3 of 5*R*,2*S*-diastereomer), 16.7 (-CH_3 of 5*R*,2*R*-diastereomer).

TOF-MS EI+: (*m/z*, %)= 308 (55) $[M]^+$, 251 (100), 235 (80), 207 (50). HRMS calculated for $C_{19}H_{20}N_2O_2$ 308.1525 found 308.1522.

(*R*)-5-((*R*)-2-methyloxiran-2-yl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole (6.21k) and (*R*)-5-((*S*)-2-methyloxiran-2-yl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole (6.21k'). Two separated diastereomers.



6.21k

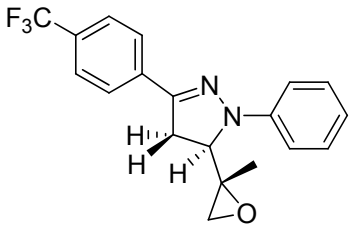
Light green powder. (50 mg, 44%). M.p. 118-120˚C. R_f : 0.44 (ethyl acetate-n-hexane; 1:4).

IR (KBr): v = 3055, 2928 (C-H), 2848, 1599 (C=N), 1498, 1325, 1122, 1066, 840, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.75 (d, *J*=8.1 Hz, 2H), 7.57 (d, *J*=8.3, 2H), 7.24 (t, *J*=7.4, 2H), 7.12 (d, *J*=8.7 Hz, 2H), 6.83 (t, *J*=7.2 Hz, 1H), 4.08 (q, *J*=5.8 Hz,1H), 3.44-3.50 (dd, *J*=17.6, 12.2 Hz, 1H), 3.31-3.35 (dd, *J*=17.6, 5.8 Hz, 1H), 2.94 (d, *J*=4.7 Hz, 1H), 2.75 (d, *J*=4.7 Hz, 1H), 1.16 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=146.1, 144.5, 135.7, 129.2, 125.7, 125.5, 125.5, 120.1, 113.8, 64.6, 58.0, 56.4, 36.9, 16.1.

TOF-MS AP+: (*m/z*, %)= 347 (100) $[MH]^+$, 348 (25) $[MH]^+$, 318 (15), 289 (15). HRMS calculated for $C_{19}H_{18}N_2OF_3$ 347.1371 found 347.1375.



6.21k'

Light green oil. (45 mg, 40%). R_f : 0.33 (ethyl acetate-n-hexane; 1:4).

IR (KBr): v = 3061, 2928 (C-H), 2854, 1593 (C=N), 1599, 1500, 1325, 1124, 1066, 842, 750 cm^{-1}.

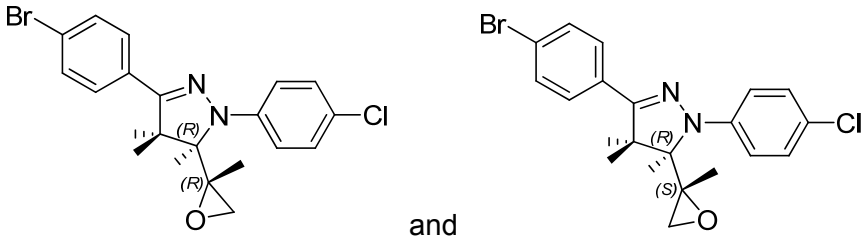
^1H NMR (400 MHz, $CDCl_3$): δ= 7.73 (d, *J*=8.1 Hz, 2H), 7.56 (d, *J*=8.2, 2H), 7.24 (d, *J*=4.1, 4H), 6.82-6.85 (p, *J*=4.3, 1H), 4.05 (q, *J*=6.7 Hz,1H), 3.49-3.55 (dd, *J*=17.2, 12.8 Hz, 1H), 3.15-3.20 (dd, *J*=17.2, 6.8 Hz, 1H), 2.76 (d, *J*=4.7 Hz, 1H), 2.69 (d, *J*=4.7 Hz, 1H), 1.25 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=145.1, 144.7, 135.8, 129.2, 125.7, 125.5, 125.5, 125.4, 120.0, 113.6, 65.6, 58.9, 52.4, 37.0, 16.7.

TOF-MS AP+: (*m/z*, %)= 347 (100) $[MH]^+$, 348 (25) $[MH]^+$. HRMS calculated for $C_{19}H_{18}N_2OF_3$ 347.1371 found 347.1371.

(*R*)-3-(4-Bromophenyl)-1-(4-chlorophenyl)-5-((*R*)-2-methyloxiran-2-yl)-4,5-dihydro-1*H*-pyrazole (6.21o) and (*R*)-3-(4-bromophenyl)-1-(4-chlorophenyl)-5-((*S*)-2-methyloxiran-2-yl)-4,5-dihydro-1*H*-pyrazole (6.21o'). Two inseparable diastereomers.

(Assigned diastereomeric ratio by ^1H-NMR spectra - 5*R*,2*S*-diasteromer / 5*R*,2*R*-diastereomer = 1.35:1.00)



White crystals. (108 mg, 95%). Melting range: 126-128˚C. R_f : 0.40-0.30 (ethyl acetate-n-hexane; 1:2).

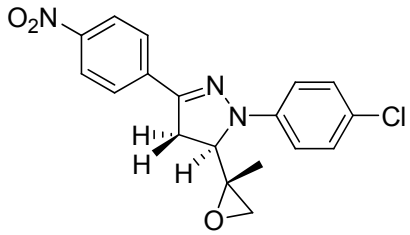
IR (KBr): v = 3049, 2922 (C-H), 2850, 1597 (C=N), 1490, 1386, 1093, 1006, 821 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.43-7.50 (m, 8H), 7.17 (d, *J*=6.0 Hz, 8H), 7.02 (d, *J*=8.9 Hz, 2H), 4.00-4.04 (q, *J*=5.7 Hz, 1H), 3.90-3.95 (q, *J*=6.7 Hz, 1H), 3.42-3.54 (td, *J*=22.5, 12.8 Hz, 2H), 3.25-3.31 (dd, *J*=17.7, 5.8 Hz, 1H), 3.10-3.16 (dd, *J*=17.3, 6.7 Hz, 1H), 2.88 (d, *J*=4.7 Hz, 1H), 2.74 (d, *J*=3.2 Hz, 1H), 2.73 (d, *J*=3.2 Hz, 1H), 2.68(d, *J*=4.6 Hz, 1H), 1.20 (s,3H) (-CH_3 of 5*R*,2*S*-diastereomer), 1.16 (s,3H) (-CH_3 of 5*R*,2*R*-diastereomer).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 147.7, 146.6, 143.9, 143.8, 143.6, 132.2, 132.2, 129.5, 129.4, 127.7, 127.7, 127.6, 124.9, 124.9, 115.2, 115.0, 66.2, 64.7, 59.3, 58.3, 56.1, 52.6, 37.8, 37.6, 16.8 (-CH_3 of 5*R*,2*S*-diastereomer), 16.7 (-CH_3 of 5*R*,2*R*-diastereomer).

TOF-MS AP+: (*m/z*, %)= 391 (80) $[M]^+$, 393 (100) $[M]^+$+2. HRMS calculated for $C_{18}H_{17}N_2OClBr$ 391.0213 found 391.0216.

(*R*)-1-(4-chlorophenyl)-5-((*R*)-2-methyloxiran-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole (6.21r) and (*R*)-1-(4-chlorophenyl)-5-((*S*)-2-methyloxiran-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole (6.21r'). Two separated diastereomers.



6.21r

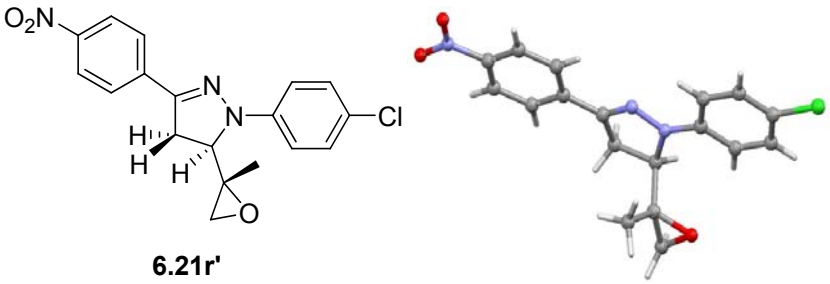
Light orange crystals. (40 mg, 24%). M.p. 195-197˚C. R_f : 0.60 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3109, 3039, 2912 (C-H), 2848, 1593 (C=N), 1496, 1342, 1109, 819, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 8.18 (d, *J*=9.0 Hz, 2H), 7.77 (d, *J*=9.0, 2H), 7.20 (d, *J*=9.0 Hz, 2H), 7.07 (d, *J*=9.0 Hz, 2H), 4.12-4.16 (q, *J*=9.6 Hz,1H), 3.48-3.54 (dd, *J*=17.6, 12.3 Hz, 1H), 3.33-3.38 (dd, *J*=17.6, 5.7 Hz, 1H), 2.90 (d, *J*=4.6 Hz, 1H), 2.76 (d, *J*=4.6 Hz, 1H), 1.16 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=147.3, 145.7, 142.5, 138.2, 129.2, 126.0, 124.1, 115.1, 64.6, 57.7, 55.9, 36.8, 16.3.

TOF-MS EI+: (*m/z*, %)= 357 (25) $[M]^+$, 327 (30), 300 (60), 269 (100). HRMS calculated for $C_{18}H_{16}N_3O_3Cl$ 357.0880 found 357.0876.



6.21r'

Orange-red crystals. (60 mg, 35%). M.p. 189-191˚C. R_f : 0.45 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3064, 2924 (C-H), 2856, 1593 (C=N), 1491, 1338,1323, 1141, 1097, 848, 821, 748 cm^{-1}.

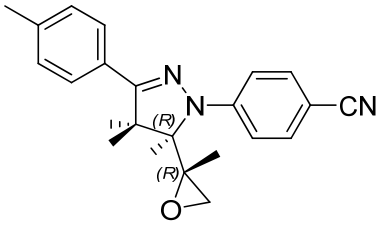
^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.16 (d, *J*=8.9 Hz, 2H), 7.74 (d, *J*=9.0, 2H), 7.21 (d, *J*=1.3, 4H), 4.05 (q, *J*=6.6 Hz,1H), 3.53-3.59 (dd, *J*=17.2, 12.9 Hz, 1H), 3.17-3.22 (dd, *J*=17.3, 6.7 Hz, 1H), 2.75 (d, *J*=4.6 Hz, 1H), 2.71 (d, *J*=4.6 Hz, 1H), 1.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ=147.2, 144.6, 142.6, 138.3, 129.2, 125.9, 124.0, 115.0, 110.2, 66.1, 58.8, 52.2, 37.0, 29.7, 16.4.

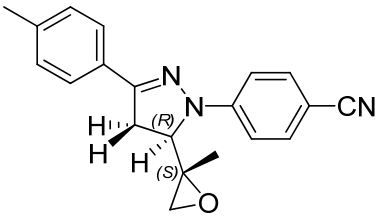
TOF-MS EI+: (*m/z*, %)= 357 (25) $[M]^+$, 327 (40), 300 (60), 270 (100). HRMS calculated for $C_{18}H_{16}N_3O_3Cl$ 357.0880 found 357.0877.

4-((*R*)-5-((*R*)-2-methyloxiran-2-yl)-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl) benzonitrile (6.21u) and 4-((*R*)-5-((*S*)-2-methyloxiran-2-yl)-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)benzonitrile (6.21u'). Two inseparable diastereomers.

(Assigned diastereomeric ratio by ^{1}H-NMR spectra - 5*R*,2*R*-diasteromer/ 5*R*,2*S*-diasteromer = 1.28:1.00)



and



Brown powder. (75 mg, 65%). Melting range: 137-145˚C. R_f : 0.22-0.11 (ethyl acetate-n-hexane; 1:2).

IR (KBr): v = 3049, 2922 (C-H), 2860, 2214 (CΞN), 1605 (C=N), 1510, 1398, 1332, 1174, 827 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.56 (t, *J*=8.7 Hz, 4H), 7.46 (t, *J*=9.0 Hz, 4H), (7.27 (d, *J*=9.0 Hz, 3H), 7.15-7.17 (m, 5H), 7.08 (d, *J*=8.9 Hz, 2H), 4.10-4.13 (dd, *J*=11.8, 4.8 Hz, 1H), 4.02-4.07 (q, *J*=7.2 Hz, 1H), 3.93-3.96 (dd, *J*=12.5, 5.7 Hz, 2H), 3.48-3.59 (m, 4H), 3.30-3.35 (dd, *J*=17.7, 4.8 Hz, 1H), 3.15-3.20 (dd, *J*=17.4, 5.5 Hz, 1H), 2.86 (d, *J*= 4.6 Hz, 1H), 2.74 (d, *J*=4.6 Hz, 1H), 2.72 (d, *J*=4.6 Hz, 1H), 2.70 (d, *J*=4.6 Hz, 1H), 2.32 (s, 6H), 1.18 (s,3H) (-CH_3 of 5*R*,2*S*-diastereomer), 1.16 (s,3H) (-CH_3 of 5*R*,2*R*-diastereomer).

^{13}C NMR (100 MHz, $CDCl_3$): δ=150.9, 149.8, 147.7, 147.6, 139.9, 133.5, 133.4, 129.5, 129.4, 128.9, 128.7, 126.2, 126.1, 113.2, 113.0, 100.8, 65.2, 62.9, 58.8, 57.7, 55.0, 51.8, 37.9, 37.6, 21.4 (-CH_3), 16.5 (-CH_3 of 5*R*,2*S*-diastereomer), 15.8 (-CH_3 of 5*R*,2*R*-diastereomer).

TOF-MS AP+: (*m/z*, %)= 318 (100) $[M]^+$, 359 (30) $[M]^+$+K. HRMS calculated for $C_{20}H_{20}N_3O$ 318.1606 found 318.1620.

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APPENDICES

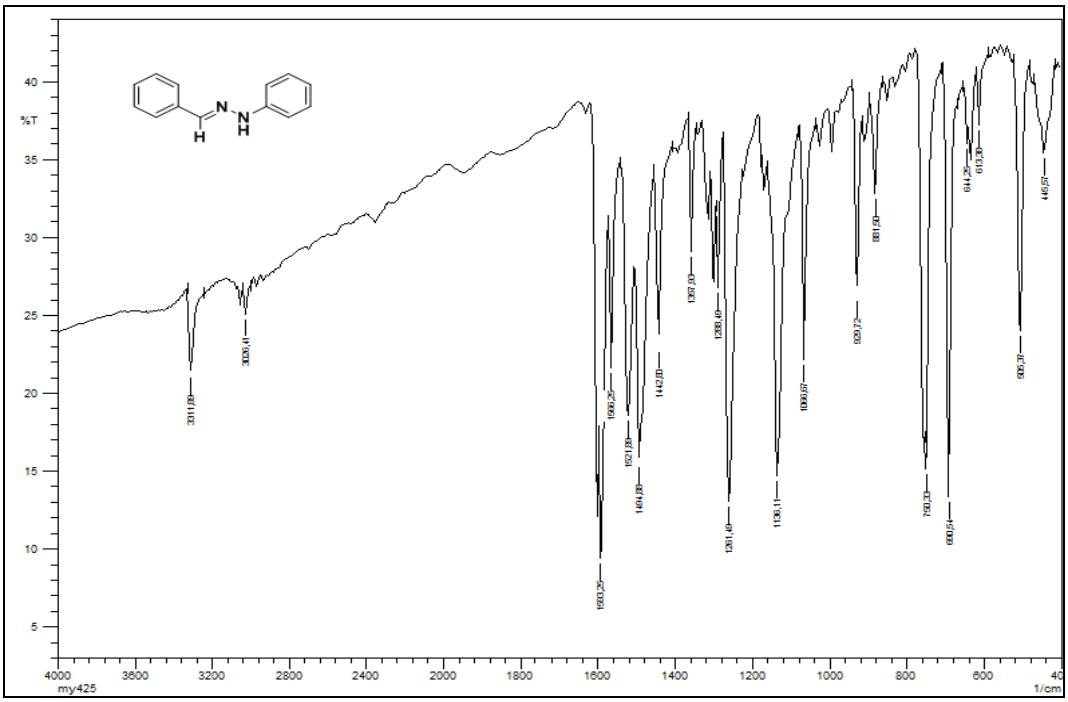

Figure 7.1 Representative IR spectrum of compounds **6.3**

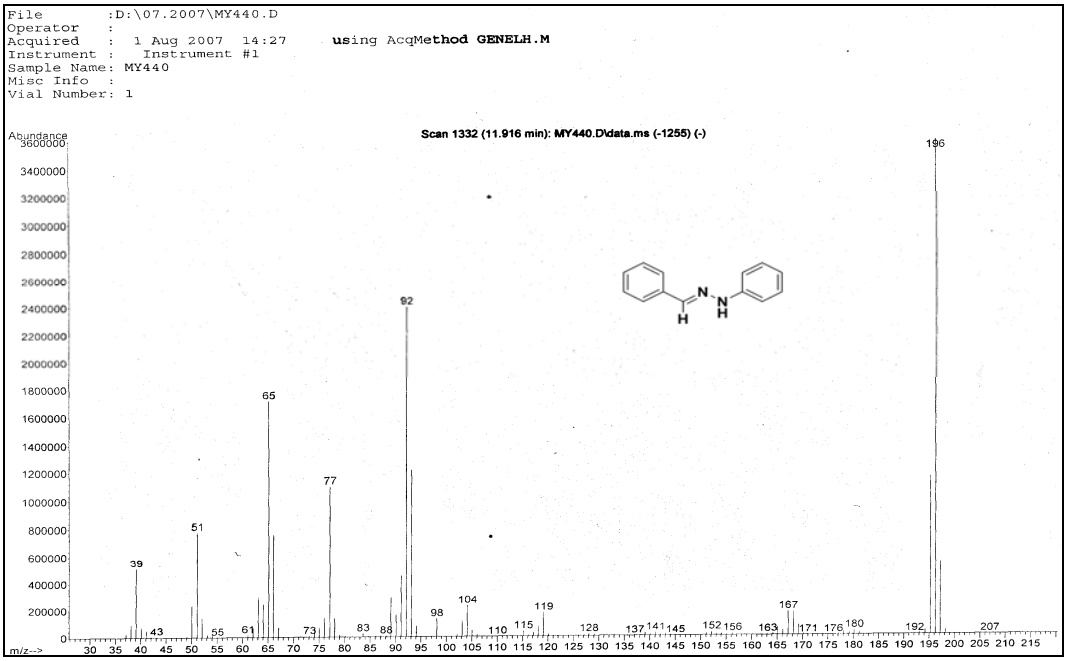

Figure 7.2 Representative Mass spectrum of compounds **6.3**

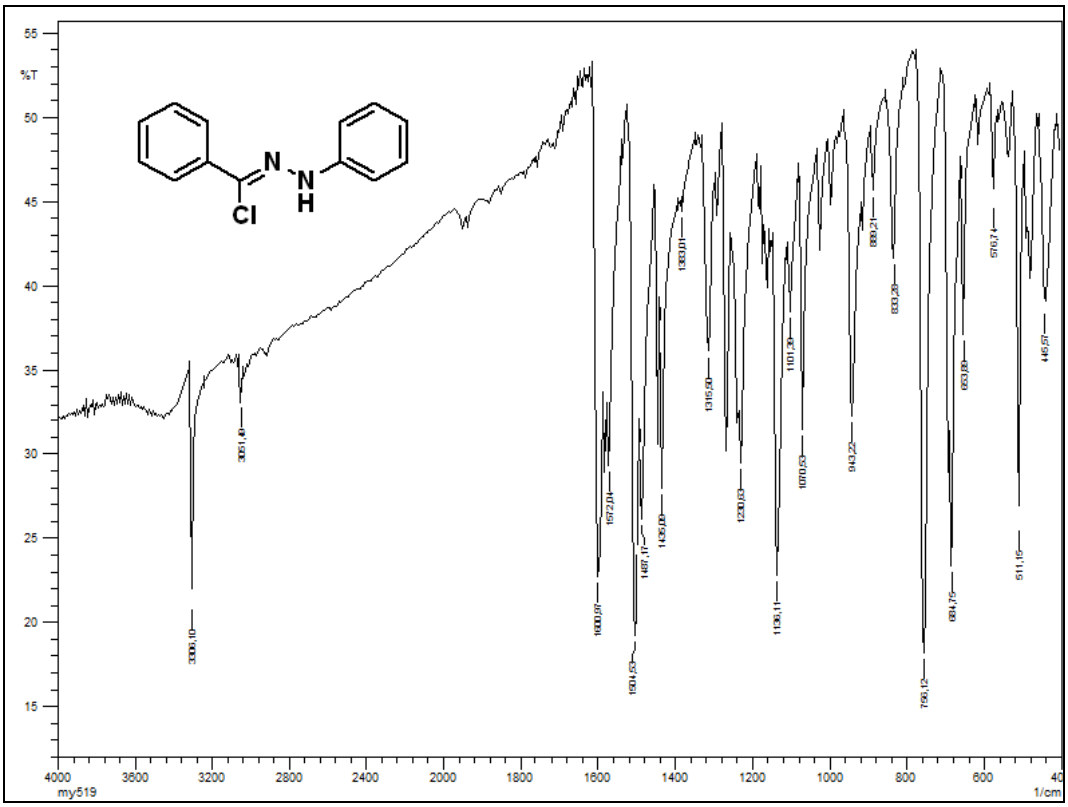

Figure 7.3 Representative IR spectrum of compounds **6.4**

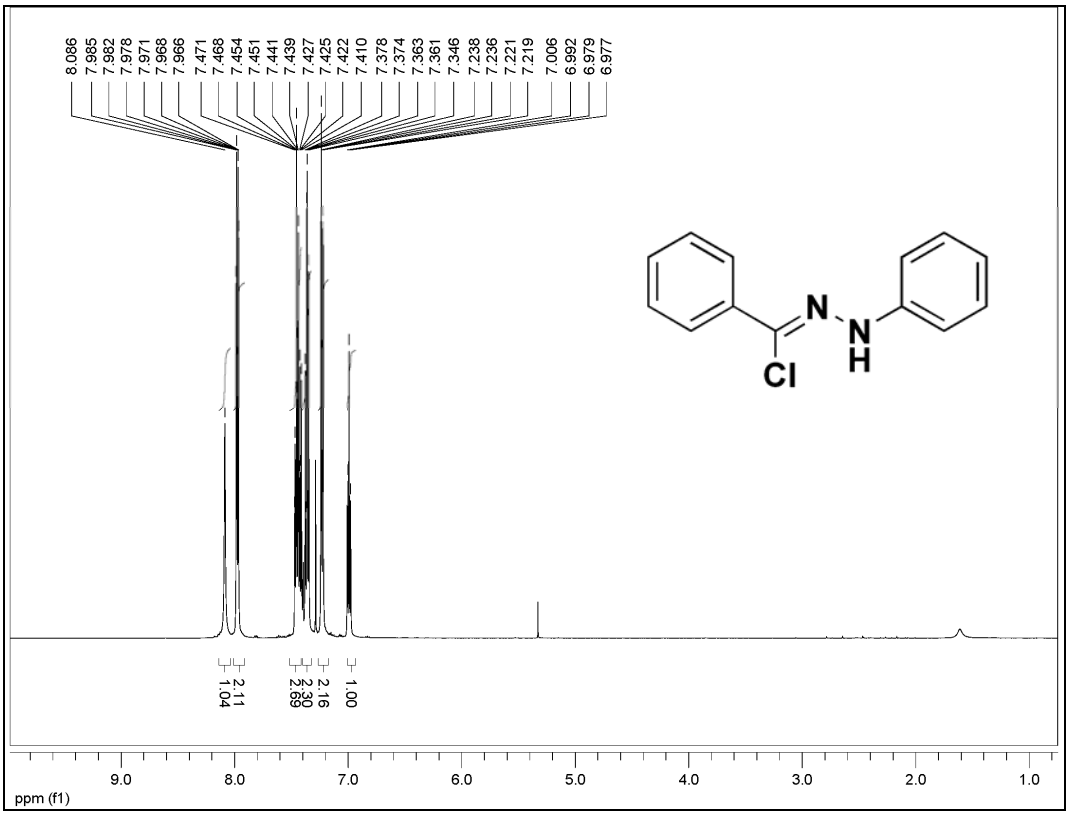

Figure 7.4 Representative ^{1}H-NMR spectrum of compounds **6.4** in $CDCl_3$

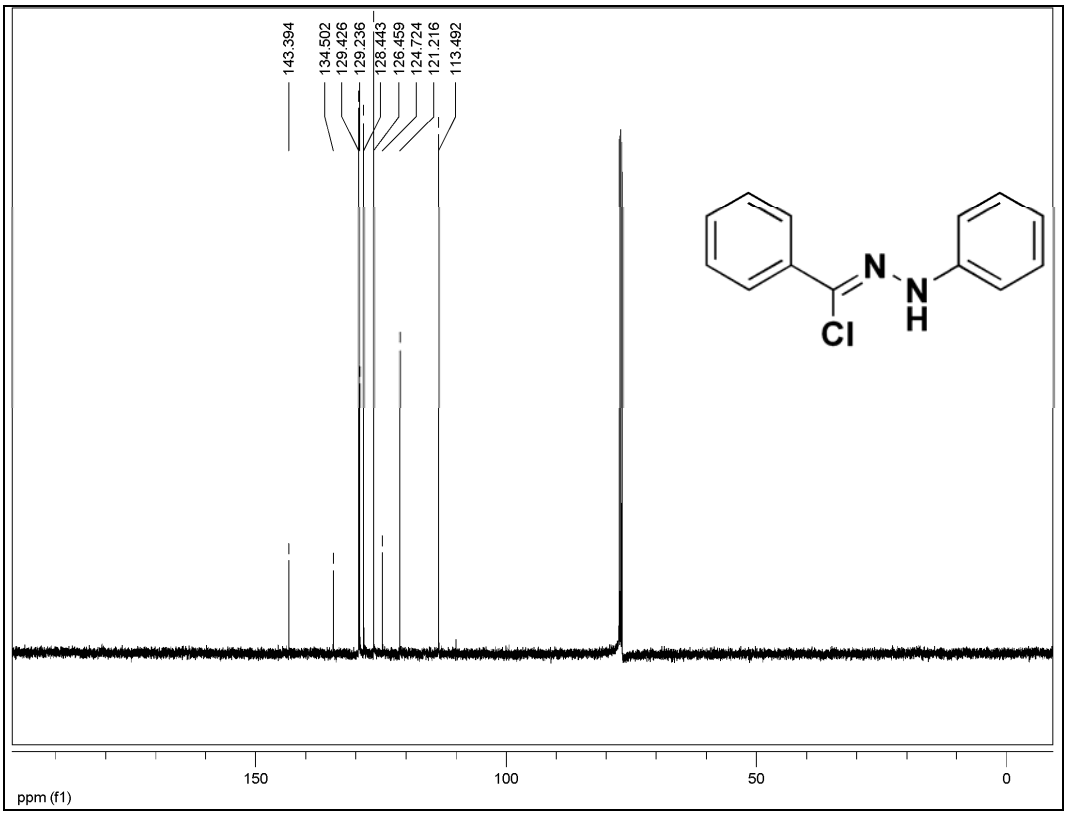

Figure 7.5 Representative ^{13}C-NMR spectrum of compounds **6.4** in $CDCl_3$

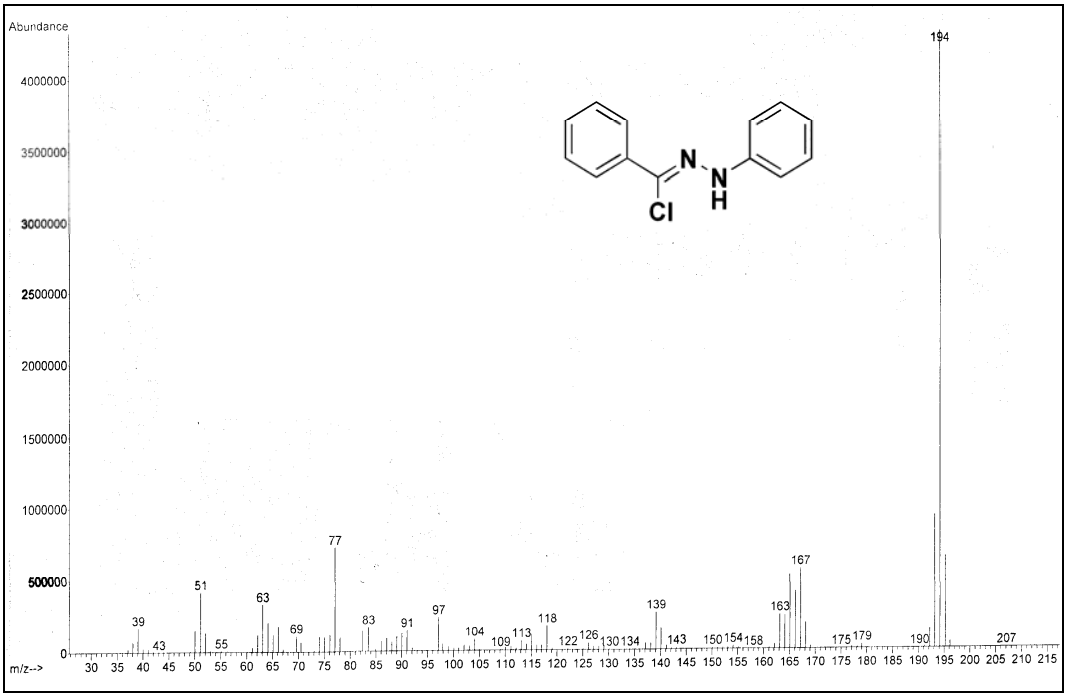

Figure 7.6 Representative Mass spectrum of compounds **6.4**

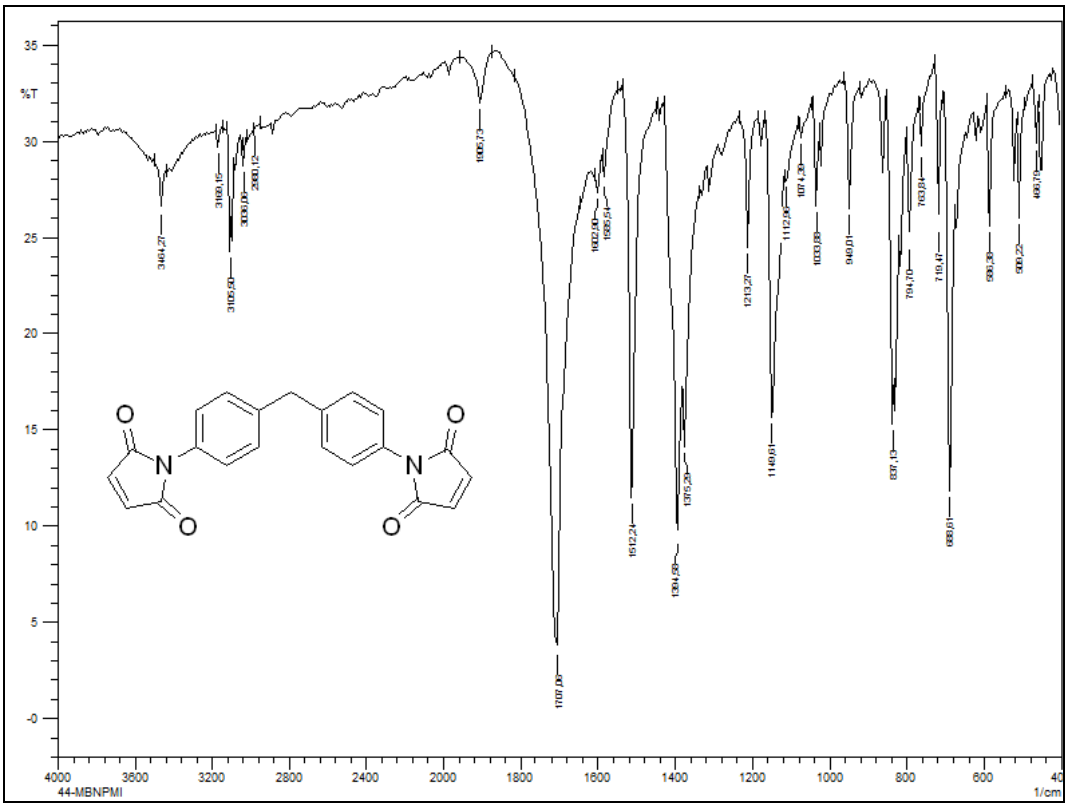

Figure 7.7 IR spectrum of compound **6.12a**

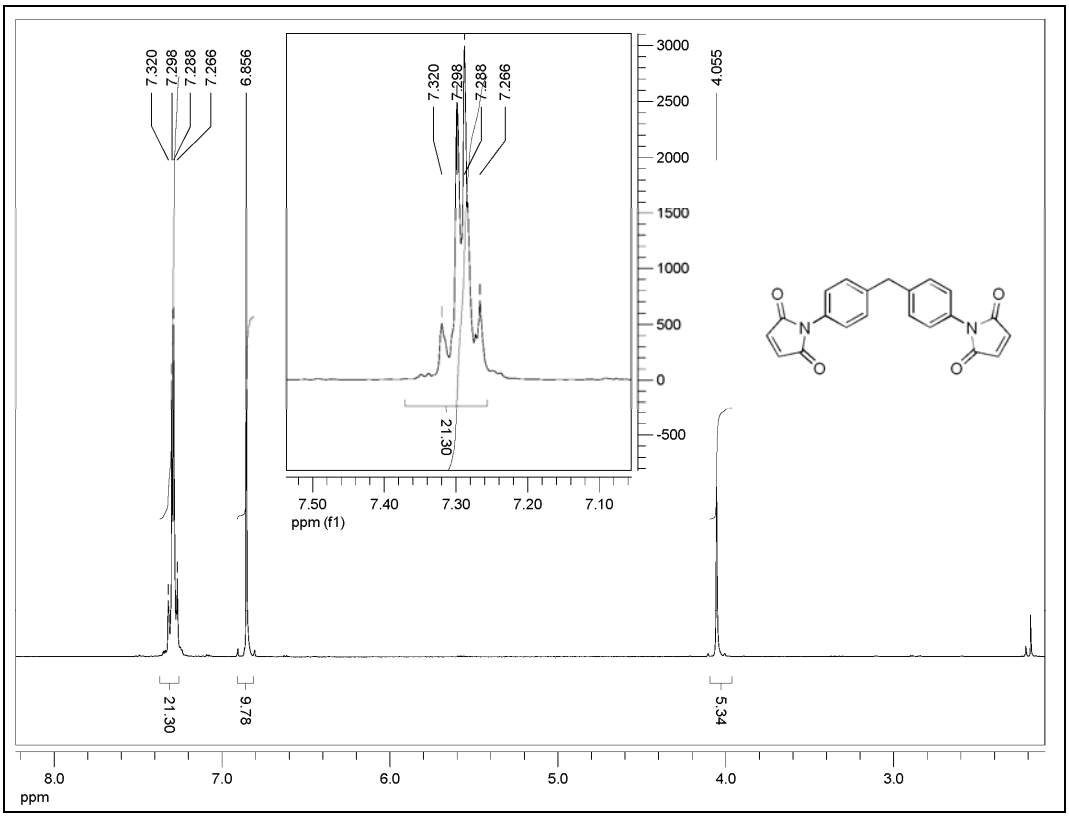

Figure 7.8 ^{1}H-NMR spectrum of compound **6.12a** in $CDCl_3$

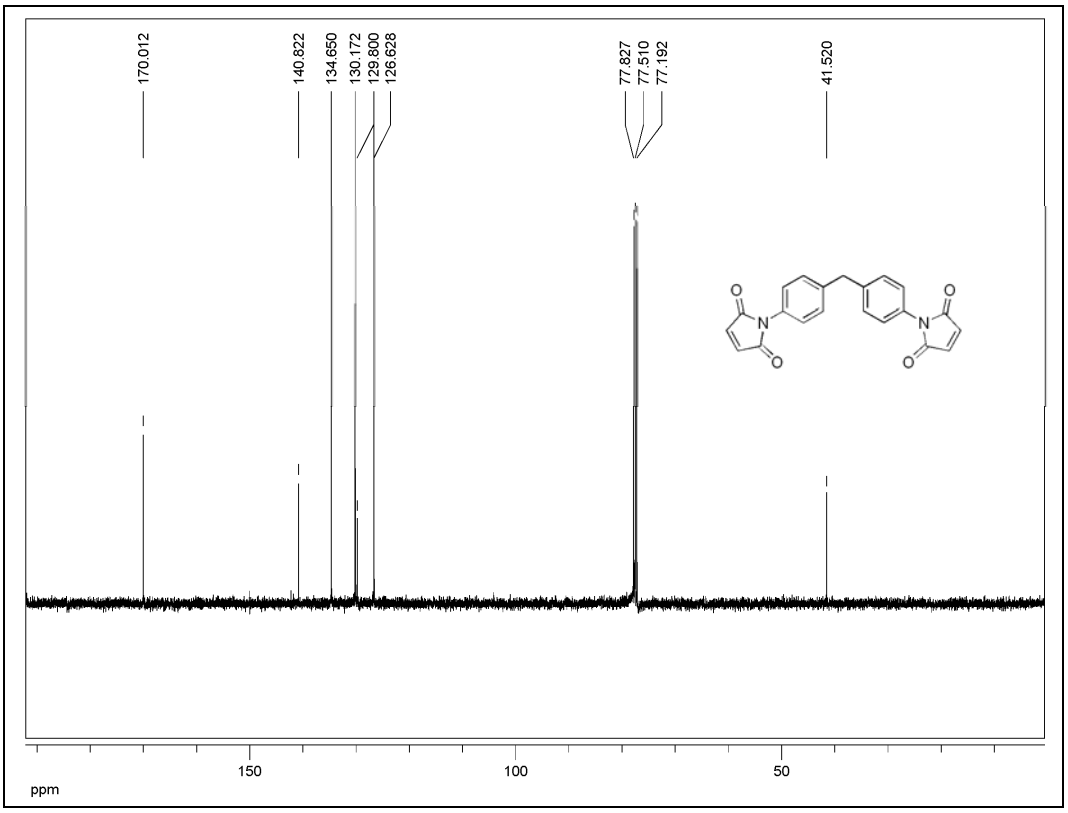

Figure 7.9 ^{13}C-NMR spectrum of compound **6.12a** in $CDCl_3$

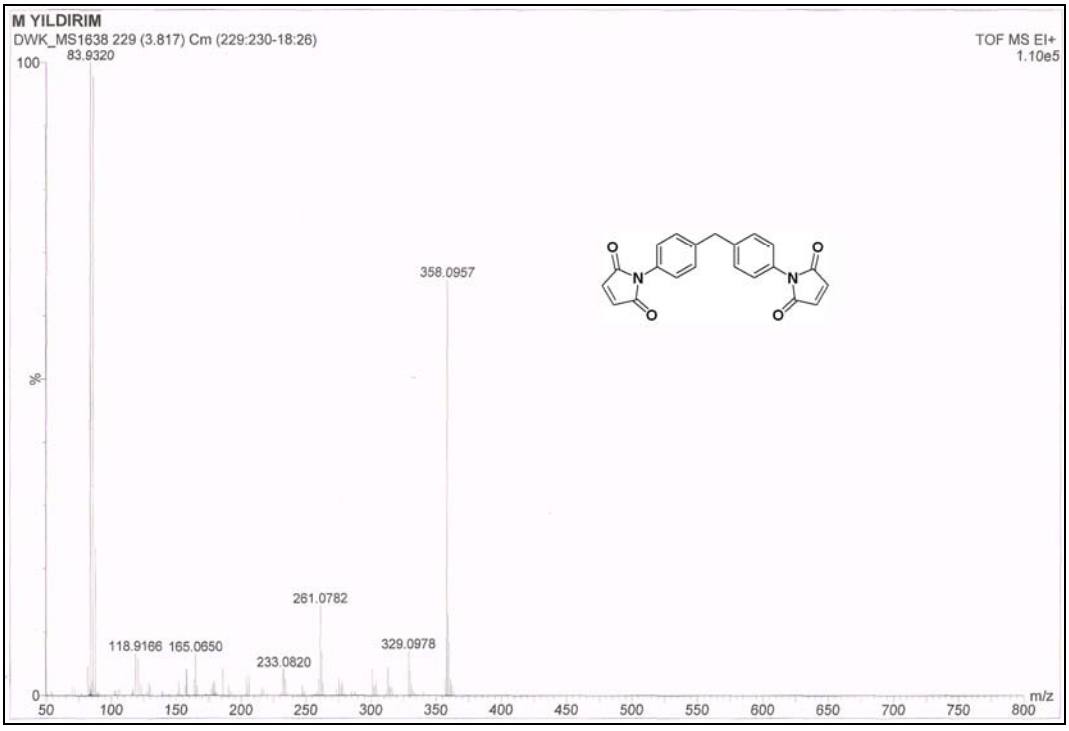

Figure 7.10 Mass spectrum of compound **6.12a**

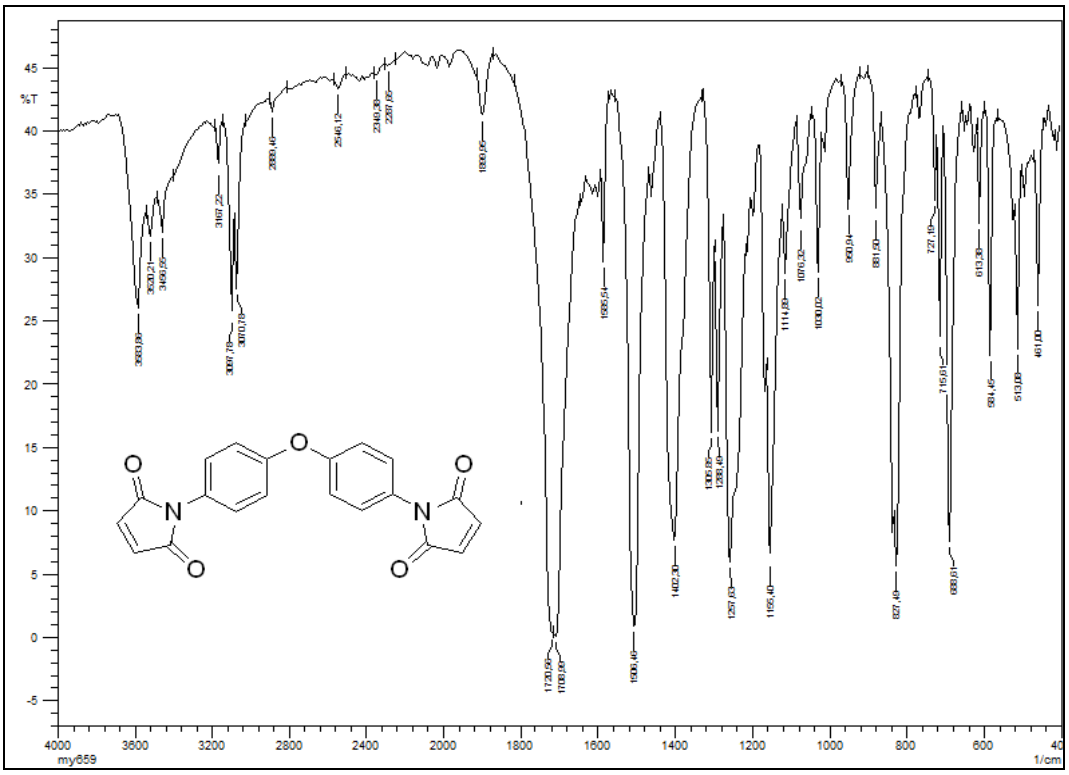

Figure 7.11 IR spectrum of compound **6.12b**

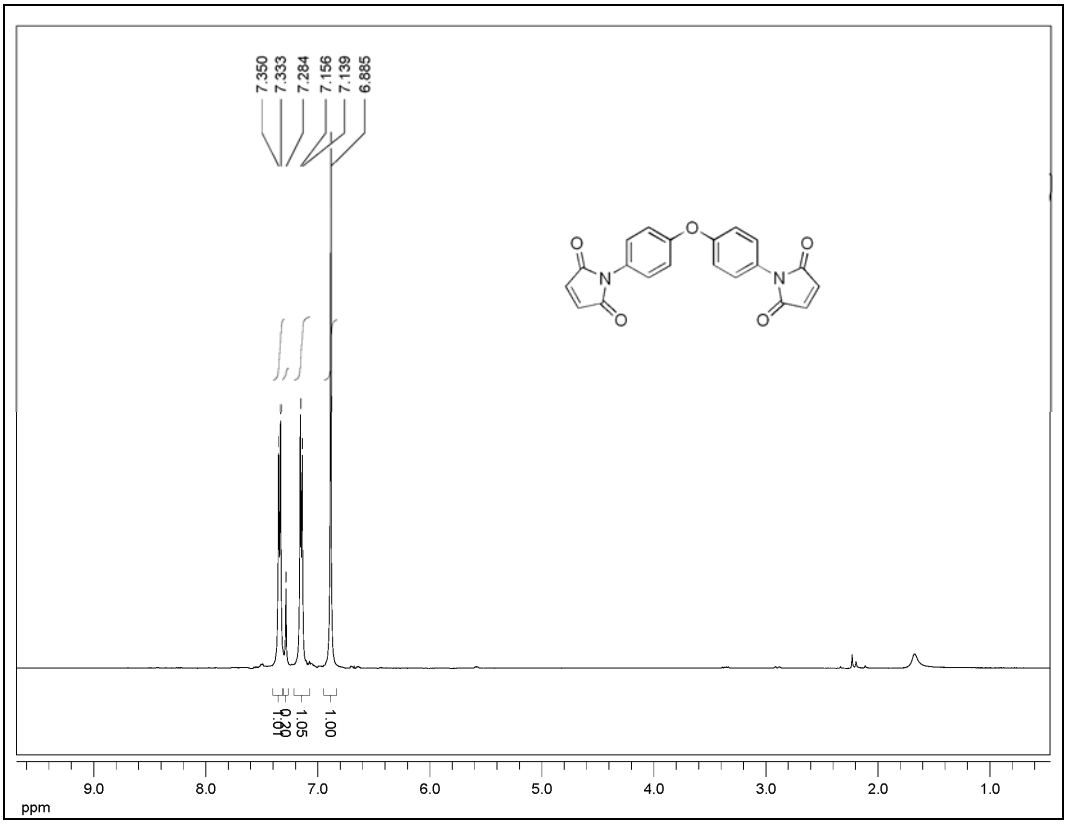

Figure 7.12 ^{1}H-NMR spectrum of compound **6.12b** in $CDCl_3$

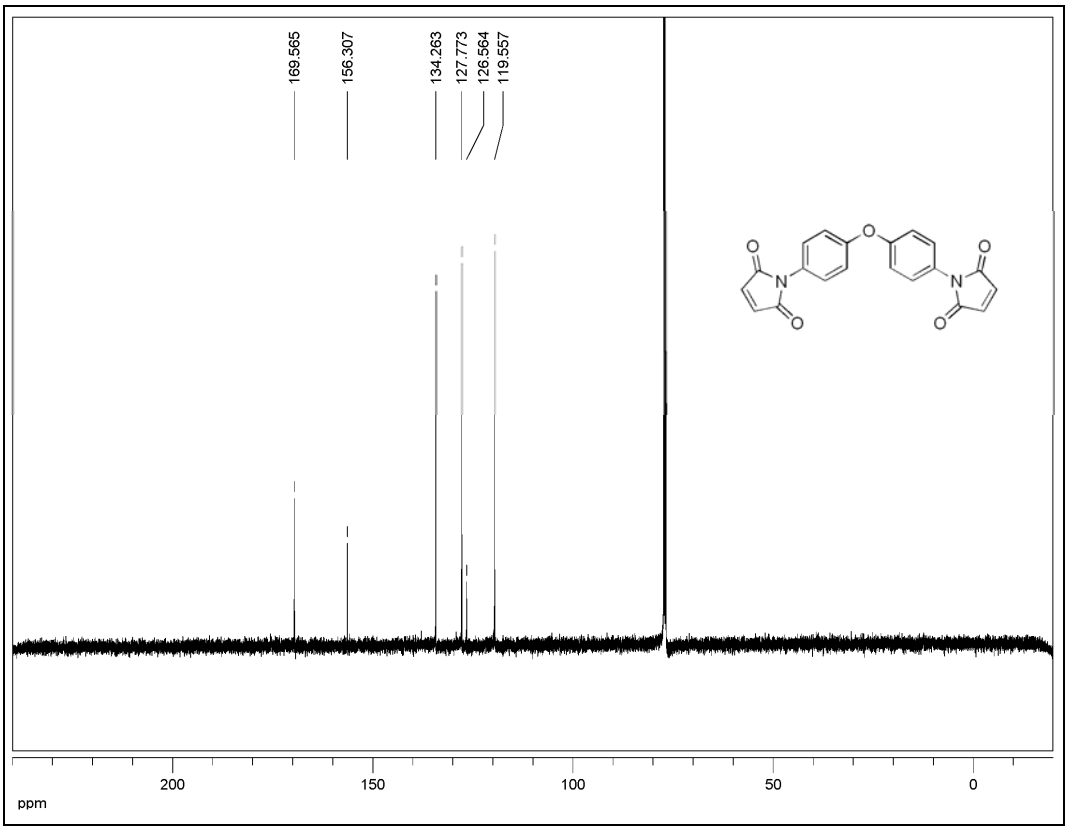

Figure 7.13 ^{13}C-NMR spectrum of compound **6.12b** in $CDCl_3$

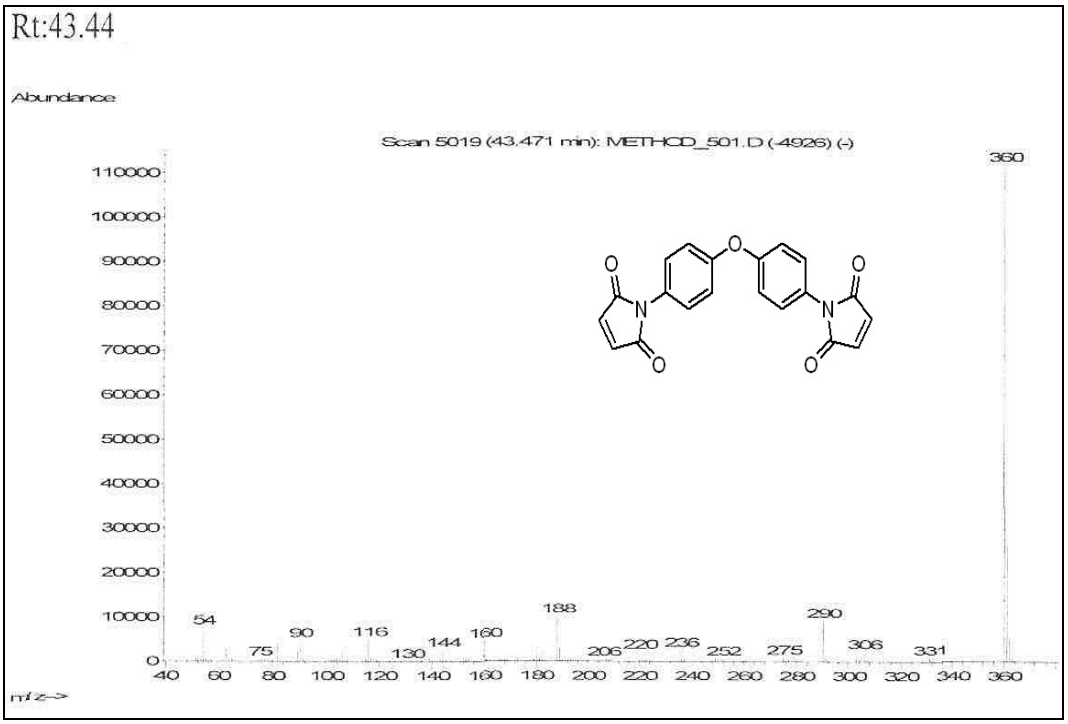

Figure 7.14 Mass spectrum of compound **6.12b**

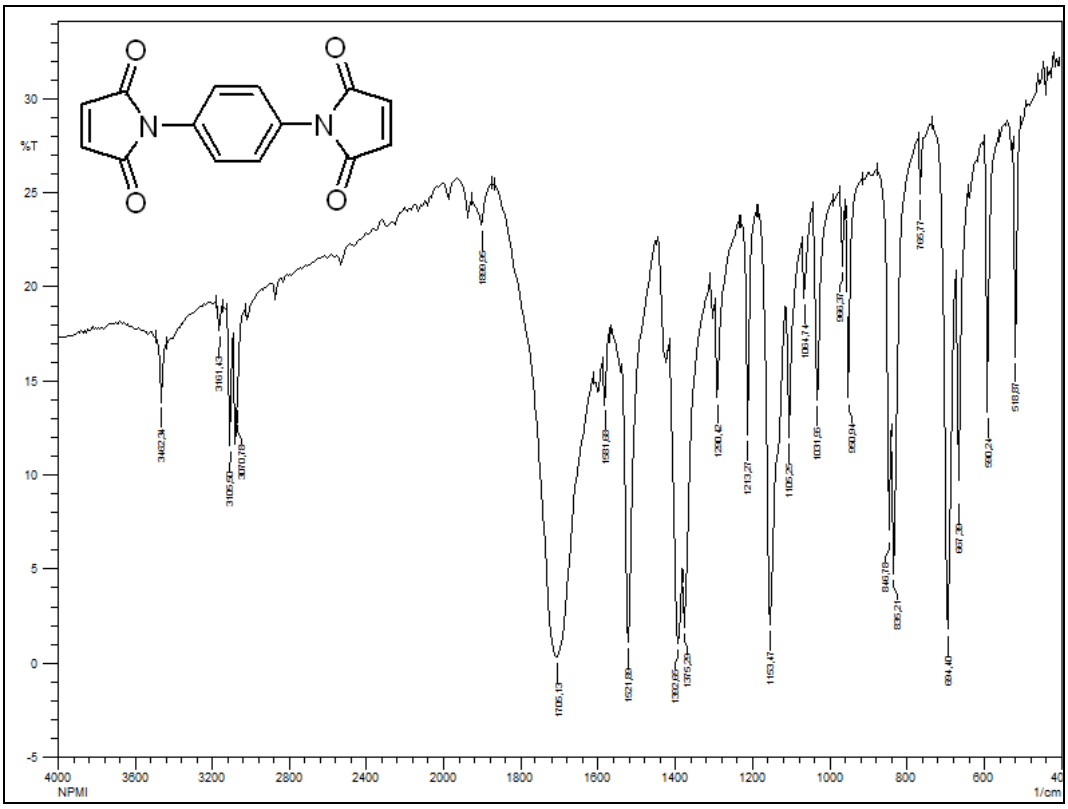

Figure 7.15 IR spectrum of compound **6.12c**

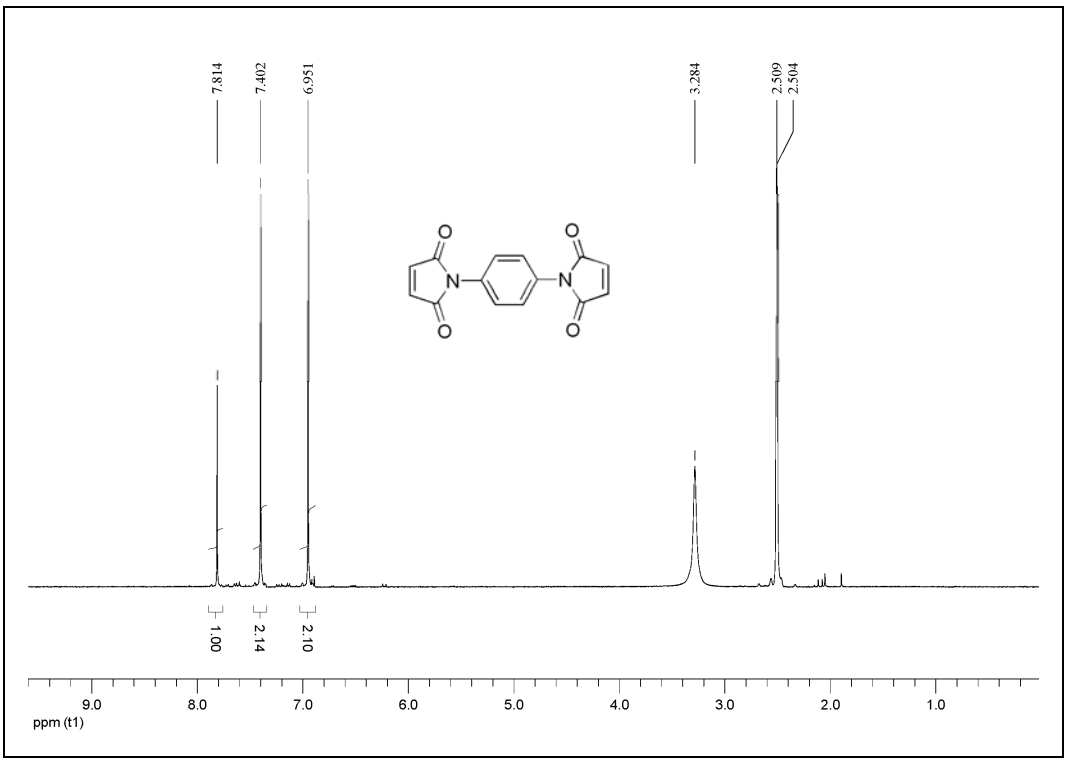

Figure 7.16 ^{1}H-NMR spectrum of compound **6.12c** in $CDCl_3$-DMSO-d_6

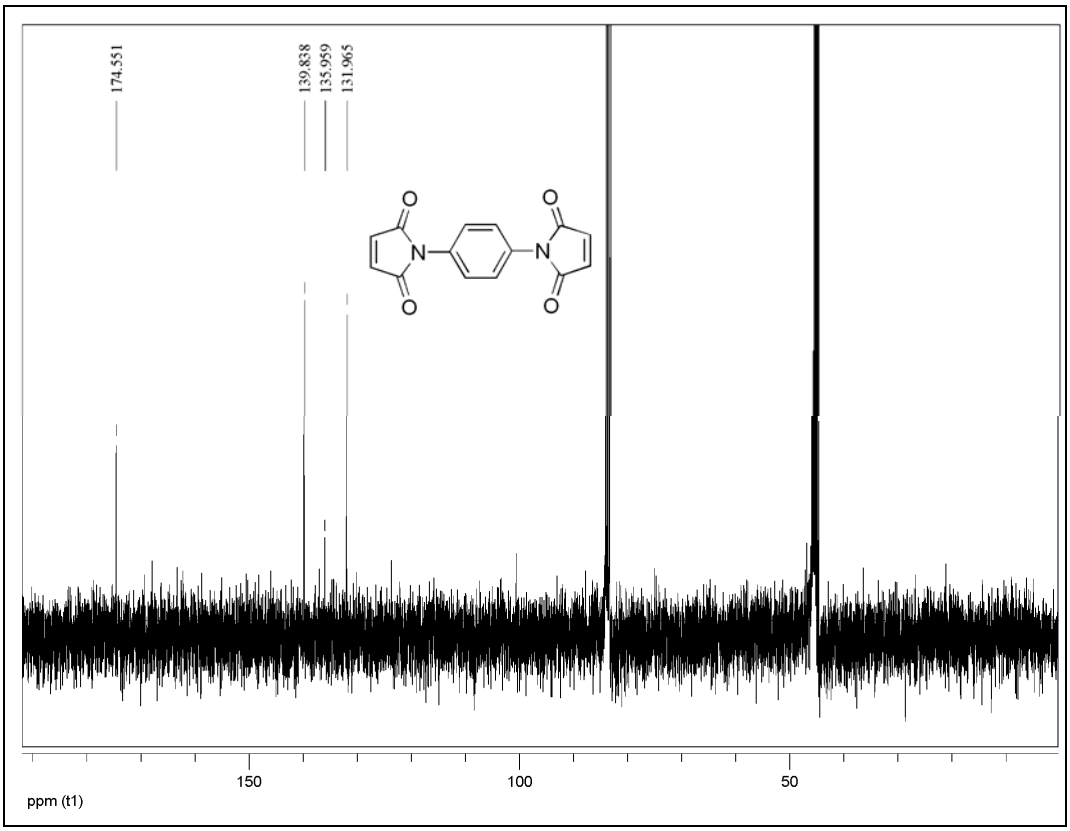

Figure 7. 17 ^{13}C-NMR spectrum of compound **6.12c** in $CDCl_3$-DMSO-d_6

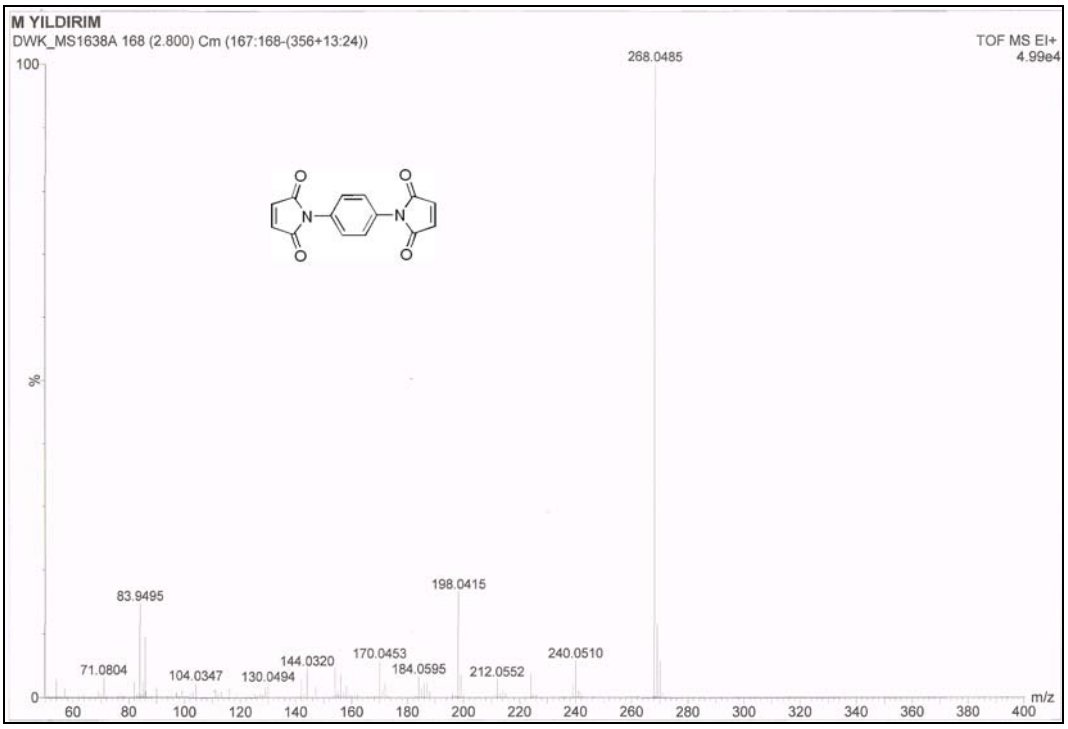

Figure 7. 18 Mass spectrum of compound **6.12c**

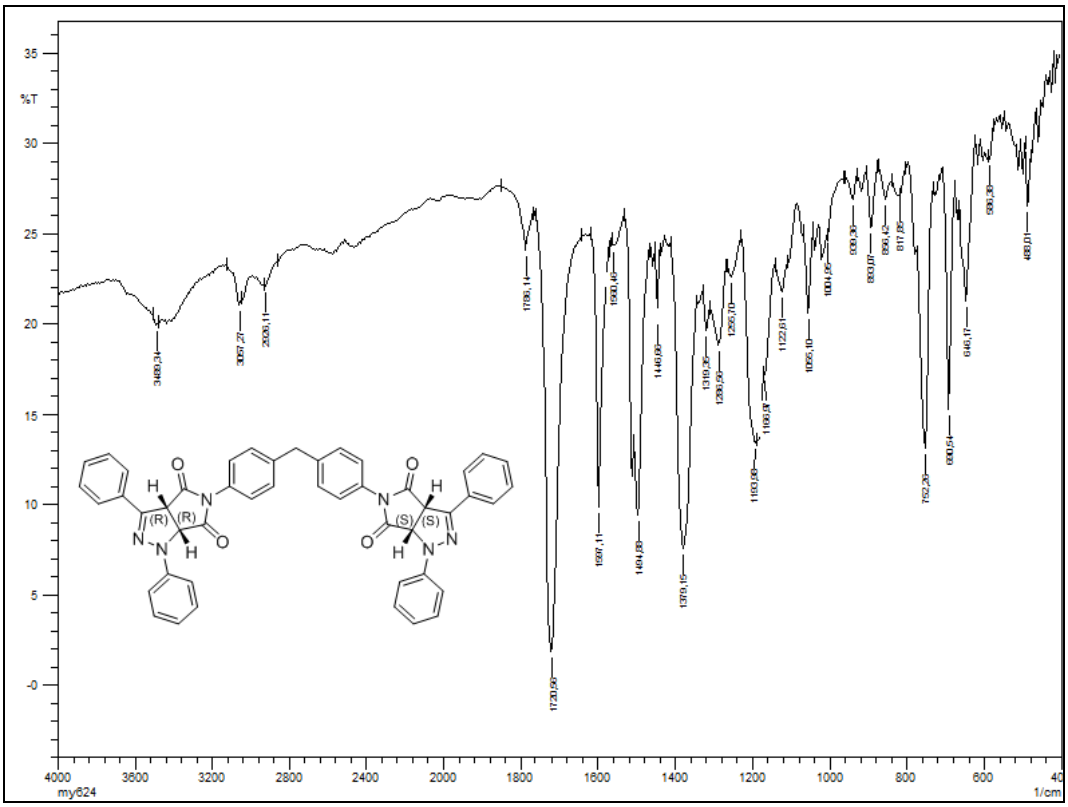

Figure 7.19 IR spectrum of compound **6.13a**

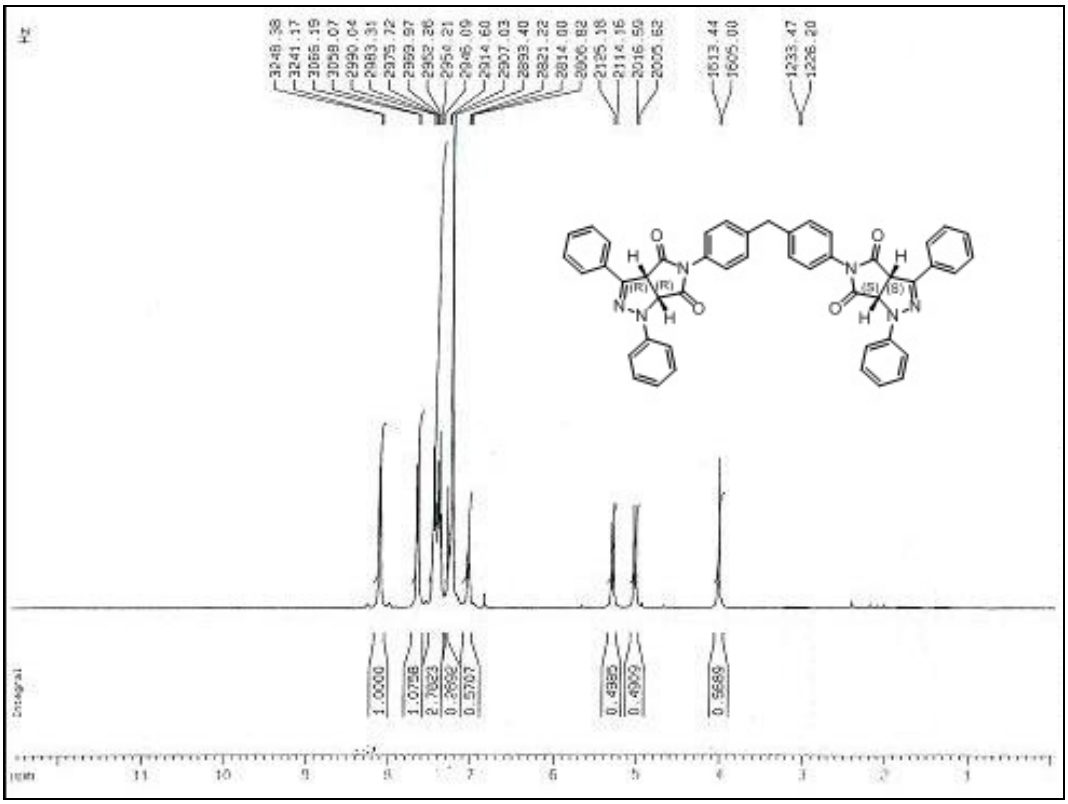

Figure 7.20 ^{1}H-NMR spectrum of compound **6.13a** in $CDCl_3$

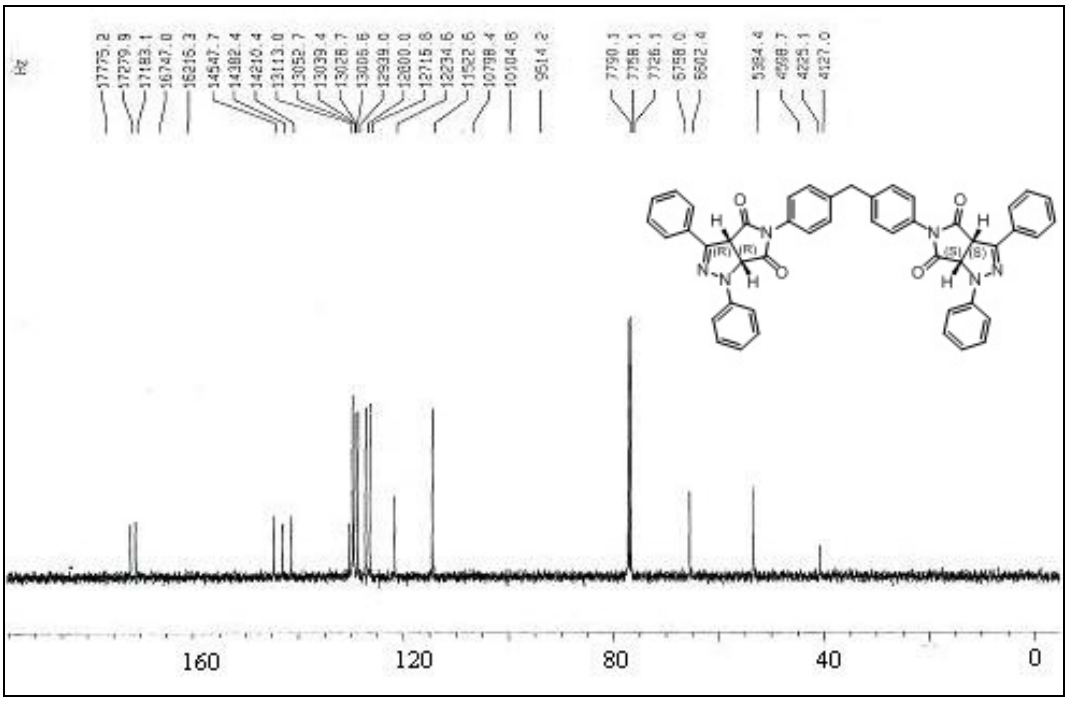

Figure 7.21 ^{13}C-NMR spectrum of compound **6.13a** in $CDCl_3$

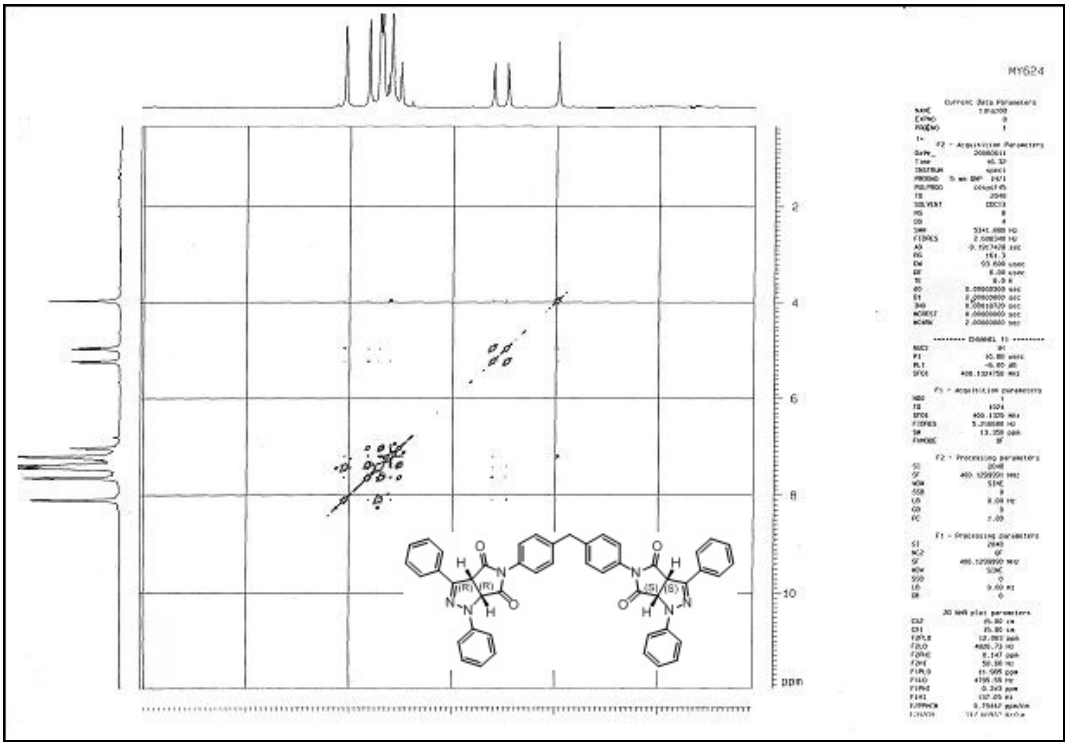

Figure 7.22 COSY-NMR spectrum of compound **6.13a** in $CDCl_3$

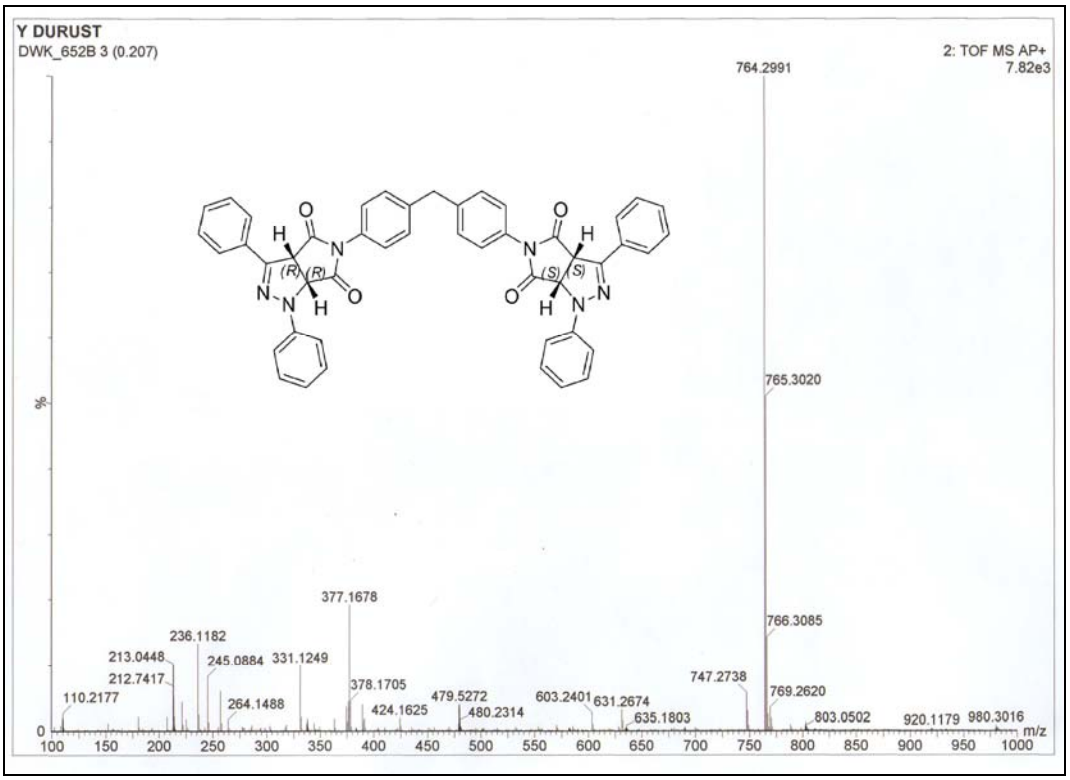

Figure 7.23 Mass spectrum of compound **6.13a**

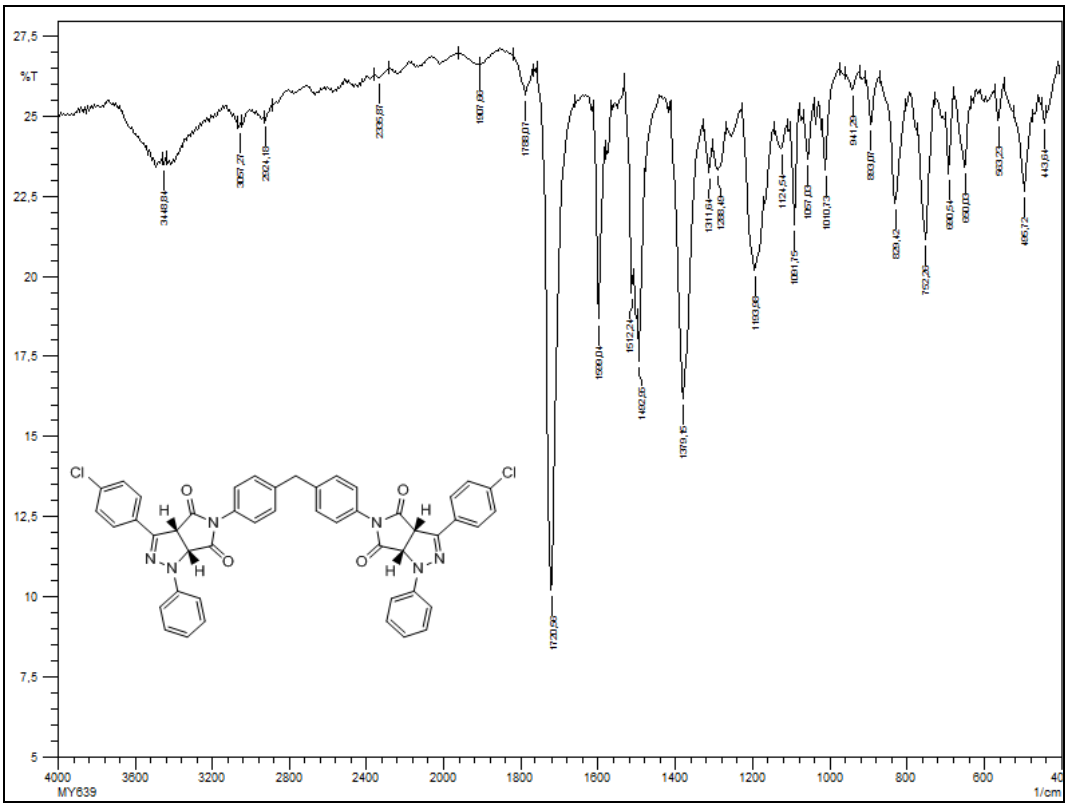

Figure 7.24 IR spectrum of compound **6.13b**

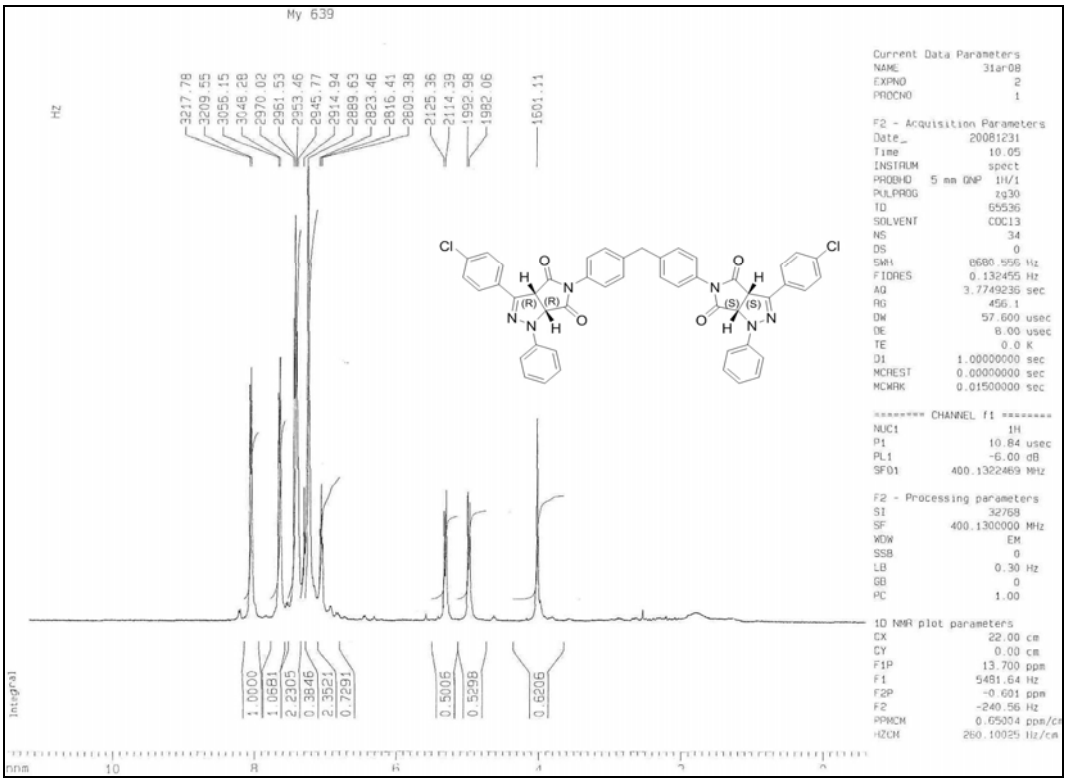

Figure 7.25 ^{1}H-NMR spectrum of compound **6.13b** in $CDCl_3$

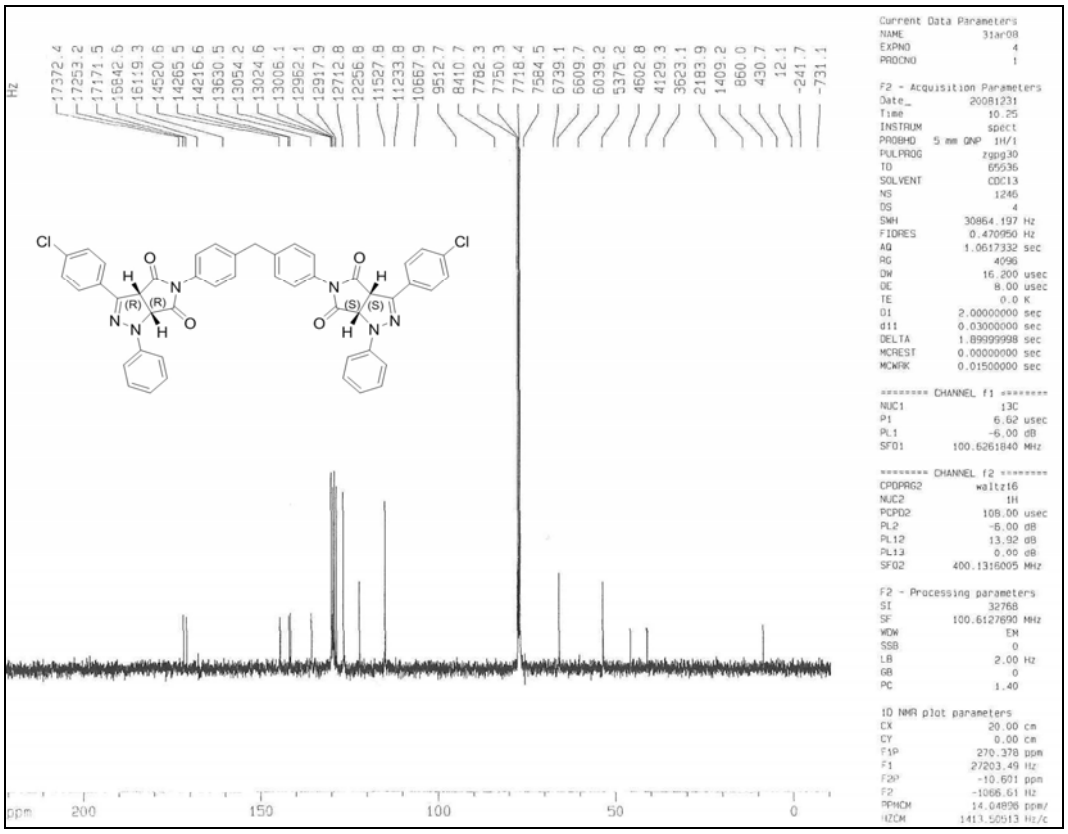

Figure 7.26 ^{13}C-NMR spectrum of compound **6.13b** in $CDCl_3$

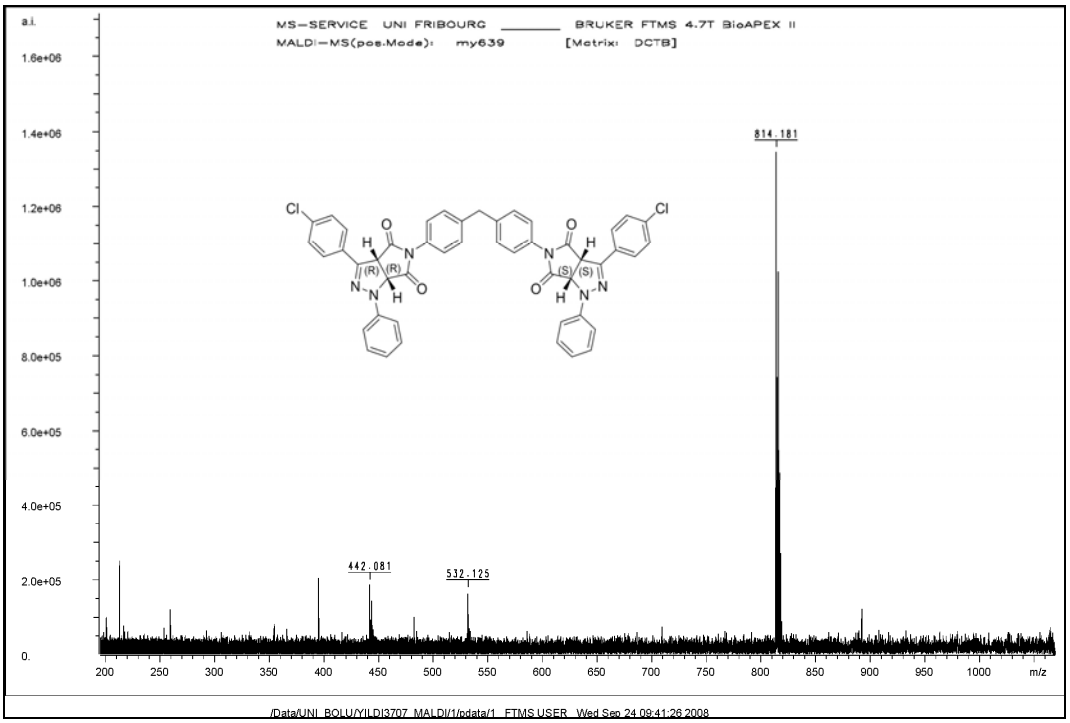

Figure 7.27 Mass spectrum of compound **6.13b**

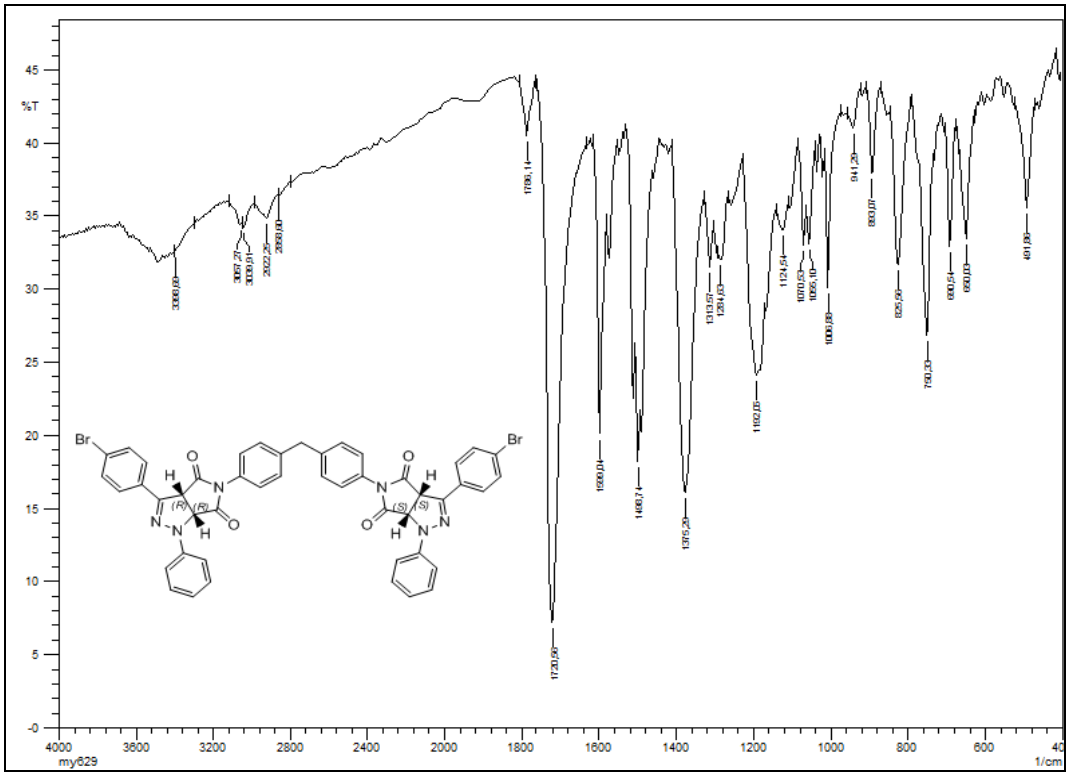

Figure 7.28 IR spectrum of compound **6.13c**

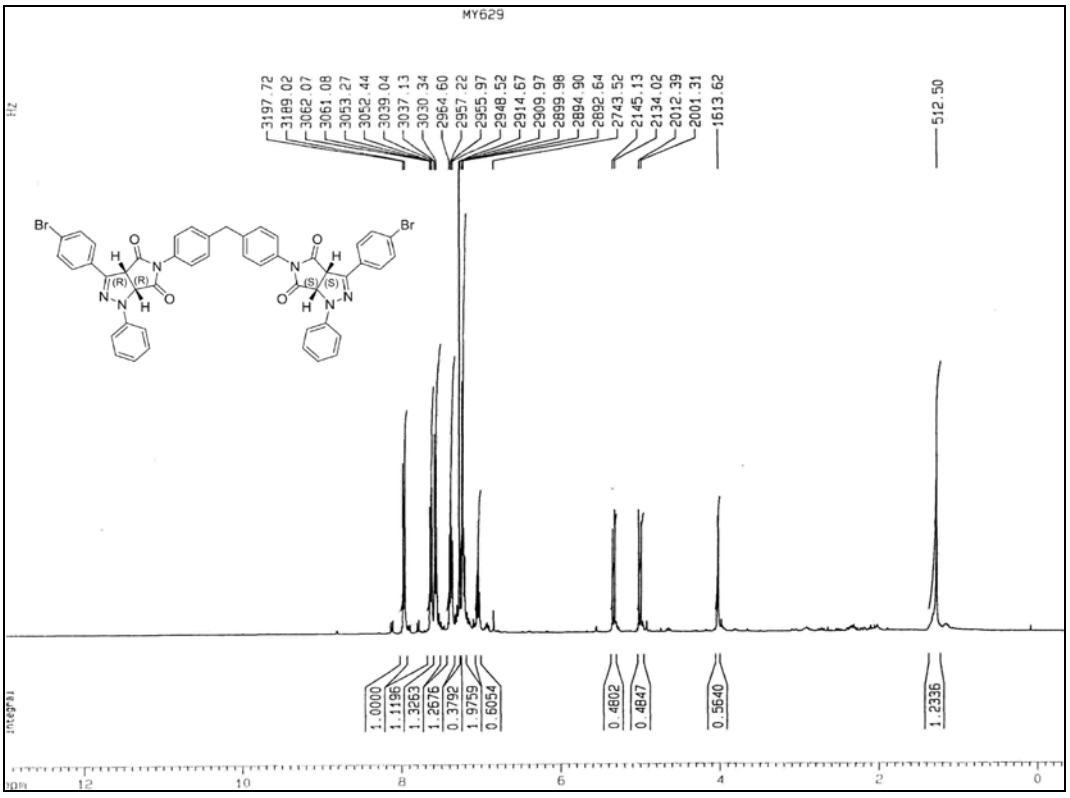

Figure 7.29 ^{1}H-NMR spectrum of compound **6.13c** in $CDCl_3$

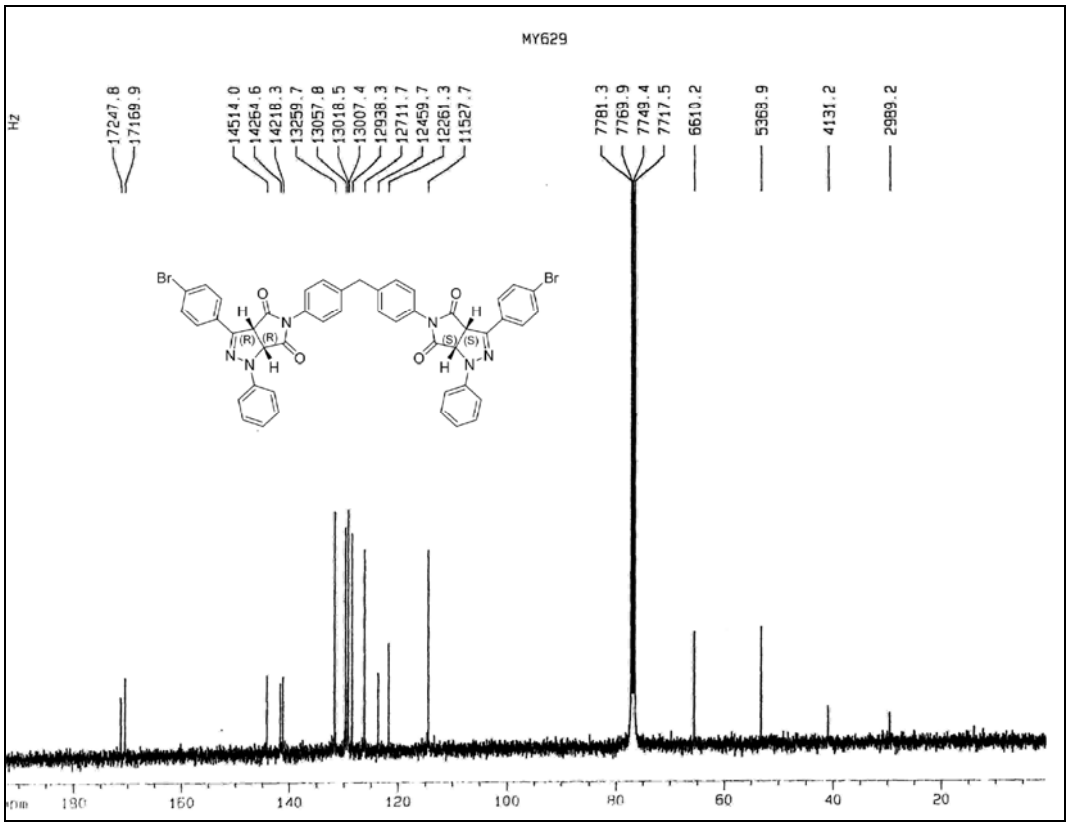

Figure 7.30 ^{13}C-NMR spectrum of compound **6.13c** in $CDCl_3$

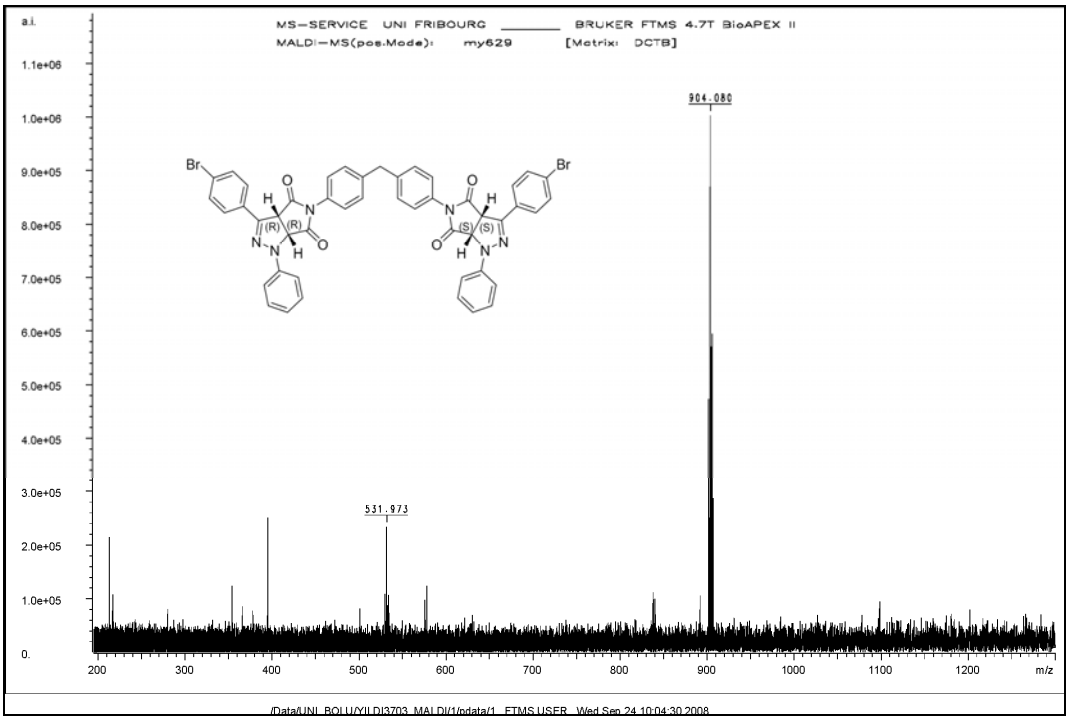

Figure 7.31 Mass spectrum of compound **6.13c**

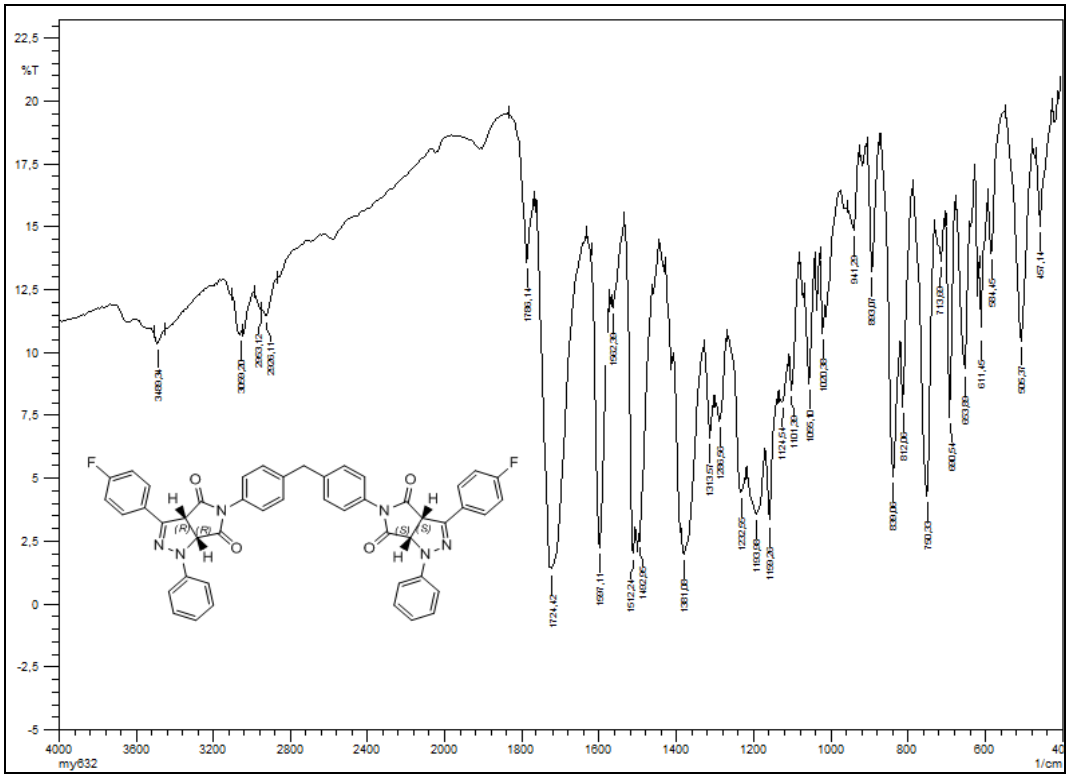

Figure 7. 32 IR spectrum of compound **6.13d**

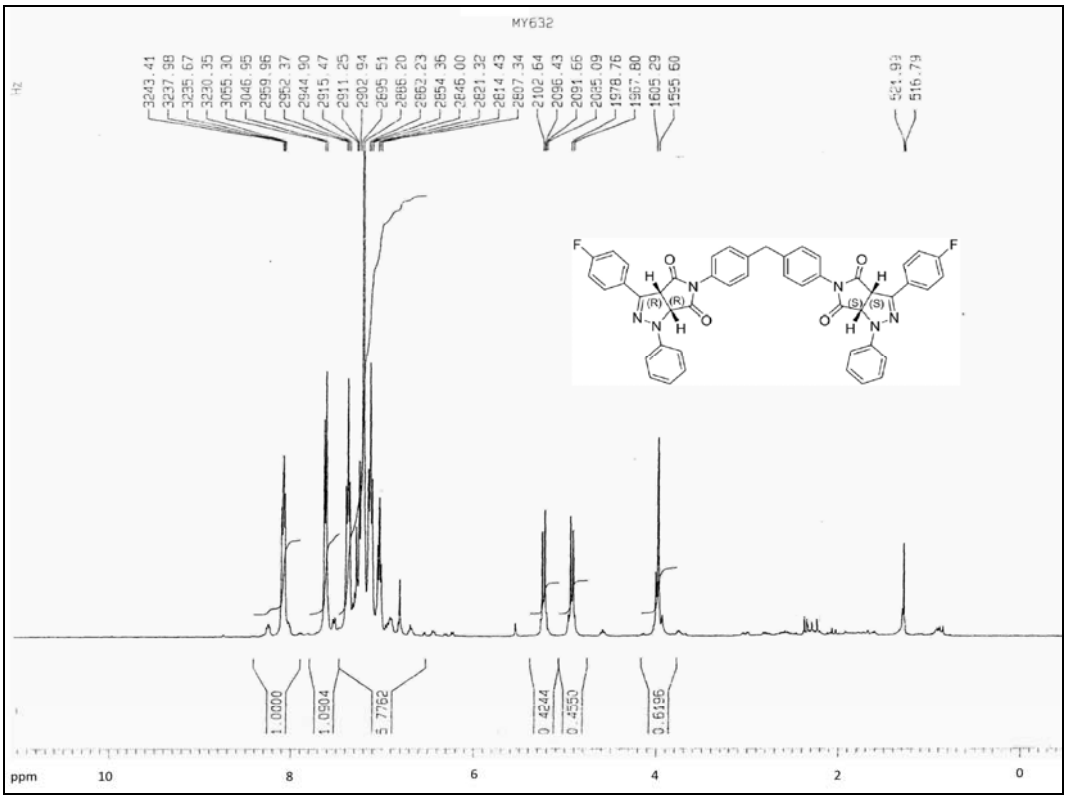

Figure 7.33 ^{1}H-NMR spectrum of compound **6.13d** in $CDCl_3$

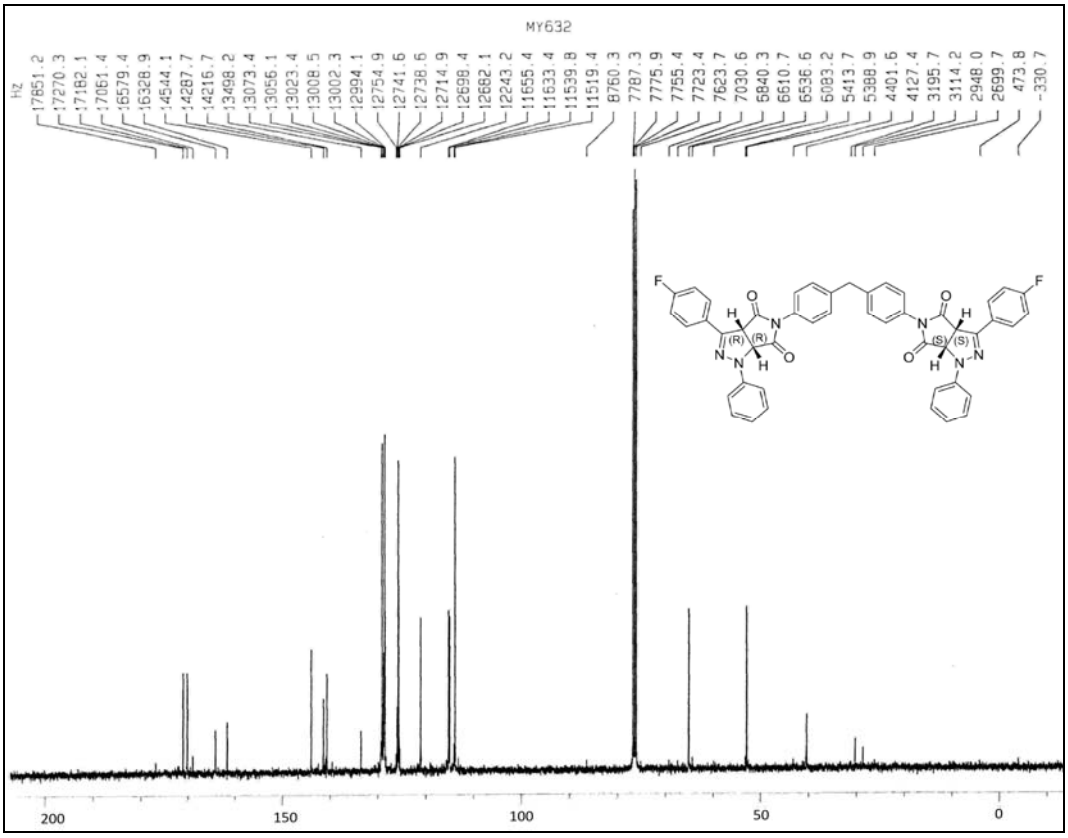

Figure 7. 34 ^{13}C-NMR spectrum of compound **6.13d** in $CDCl_3$

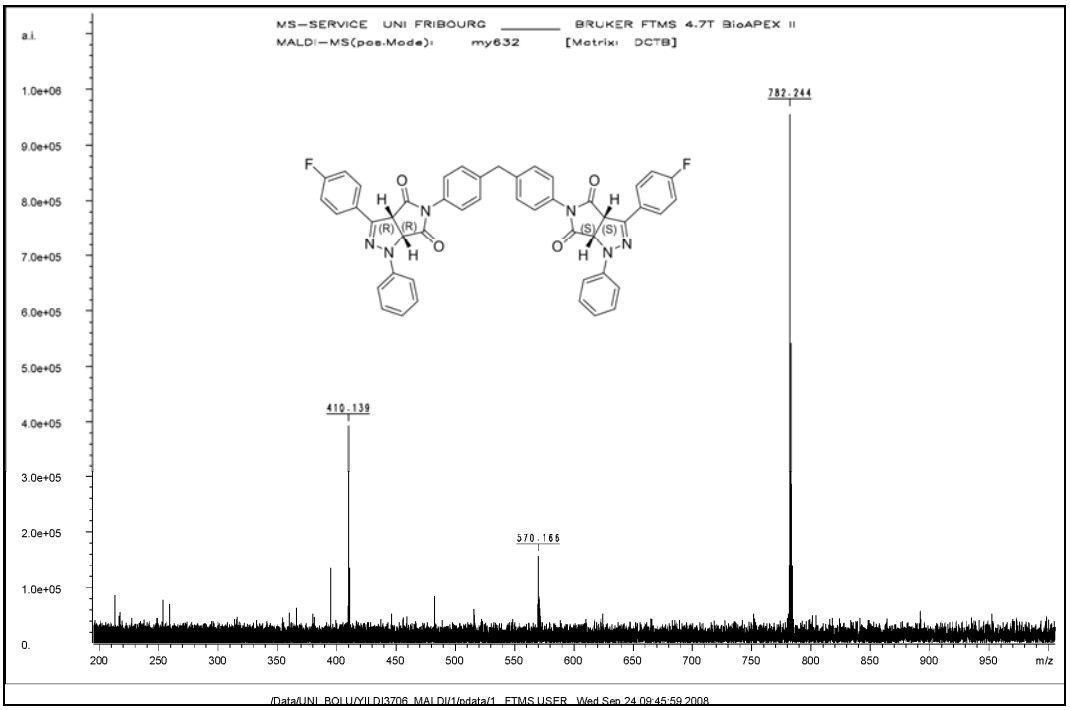

Figure 7.35 Mass spectrum of compound **6.13d**

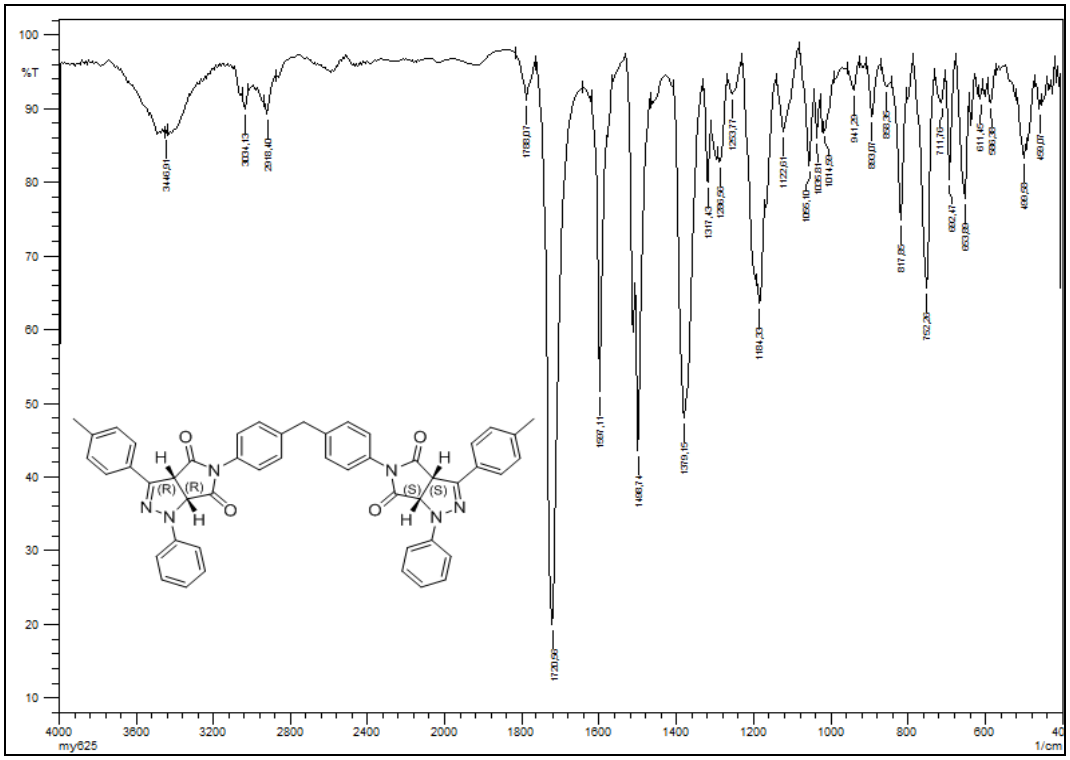

Figure 7.36 IR spectrum of compound **6.13e**

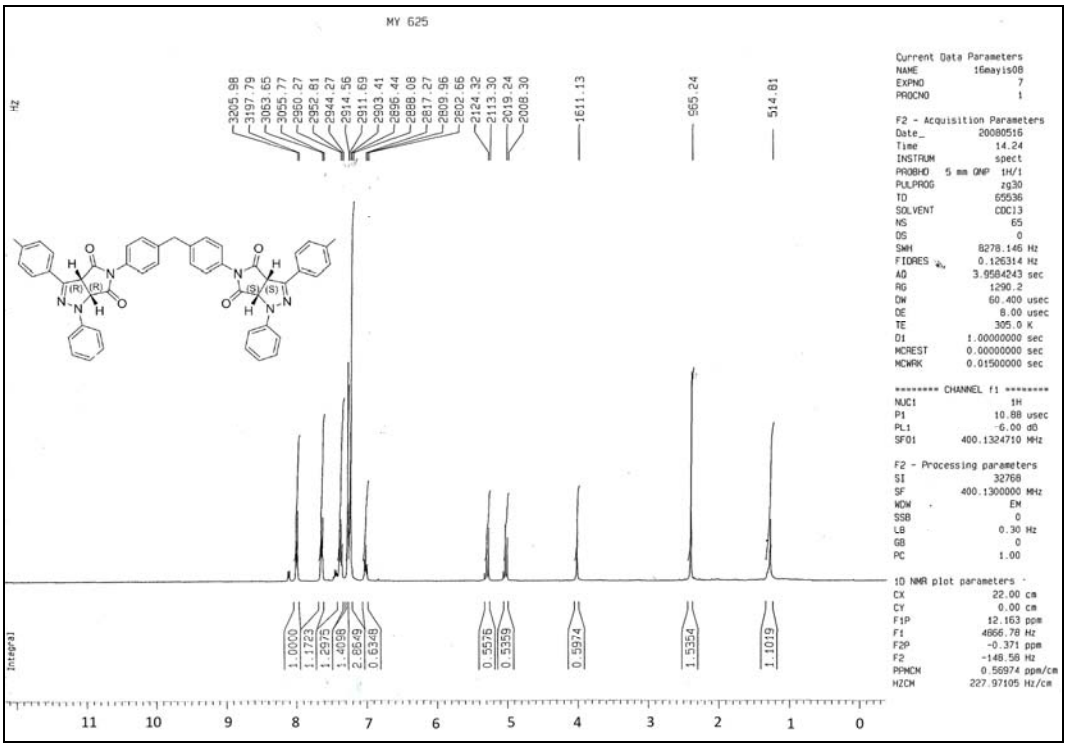

Figure 7.37 ^{1}H-NMR spectrum of compound **6.13e** in $CDCl_3$

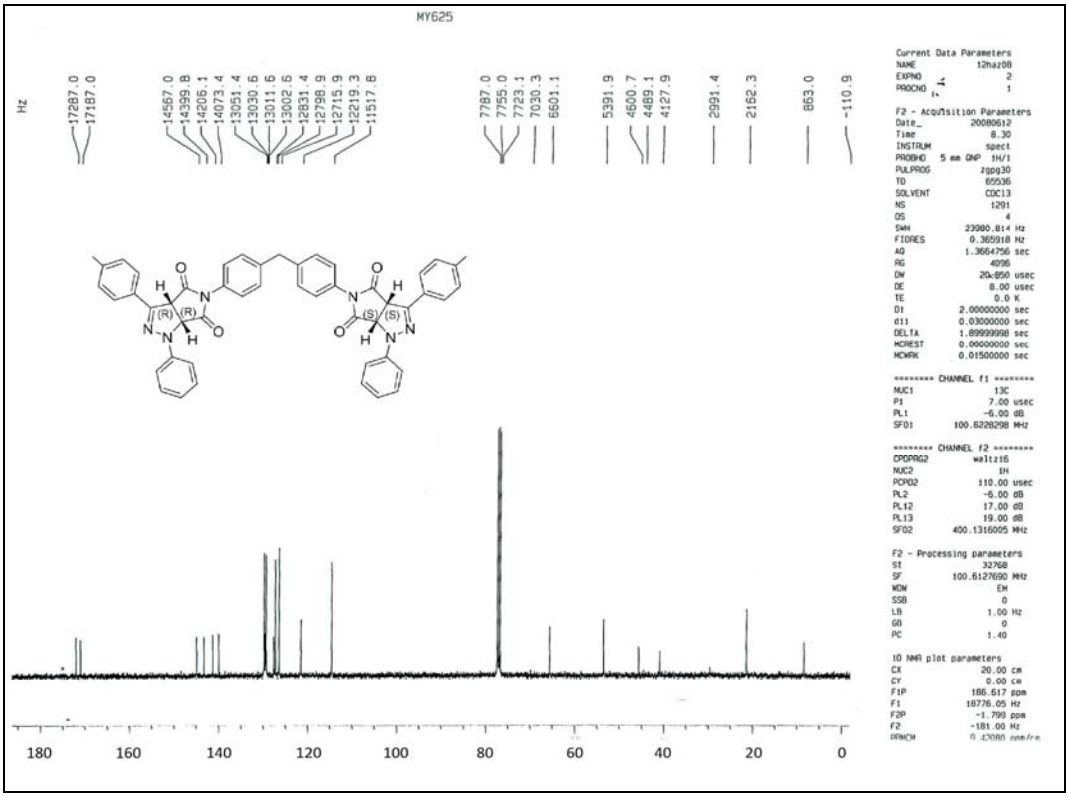

Figure 7.38 ^{13}C-NMR spectrum of compound **6.13e** in $CDCl_3$

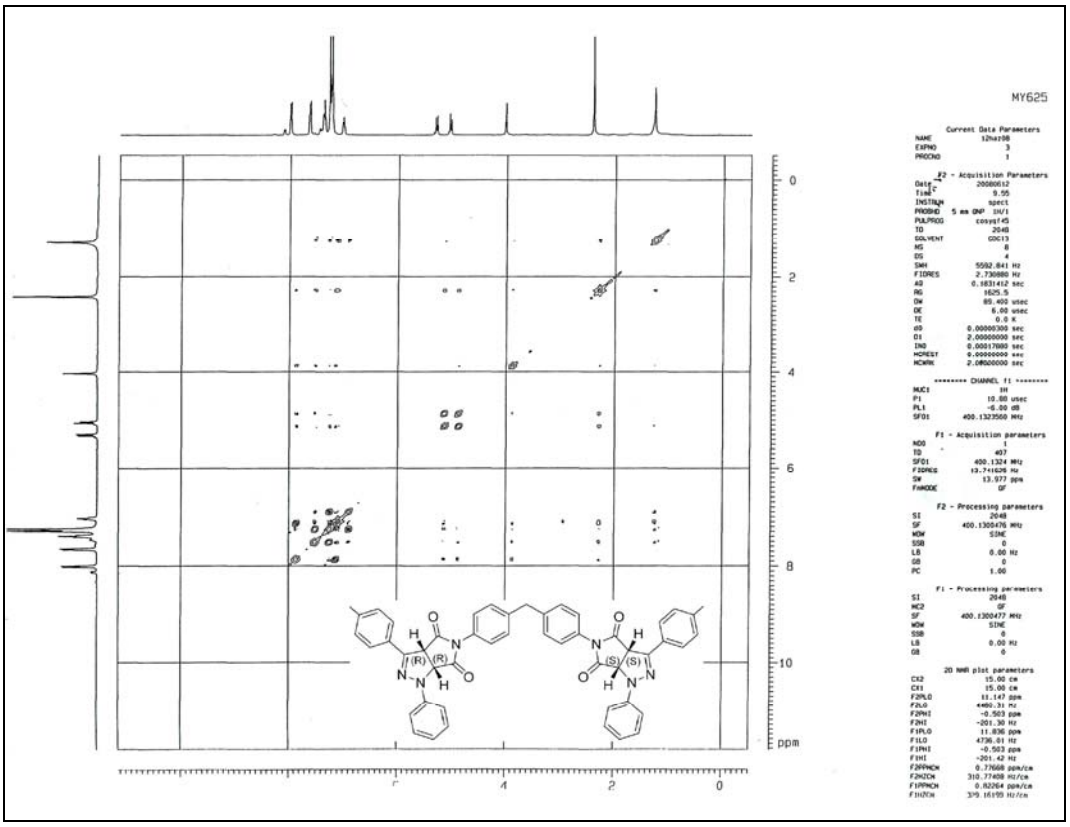

Figure 7.39 COSY-NMR spectrum of compound **6.13e** in $CDCl_3$

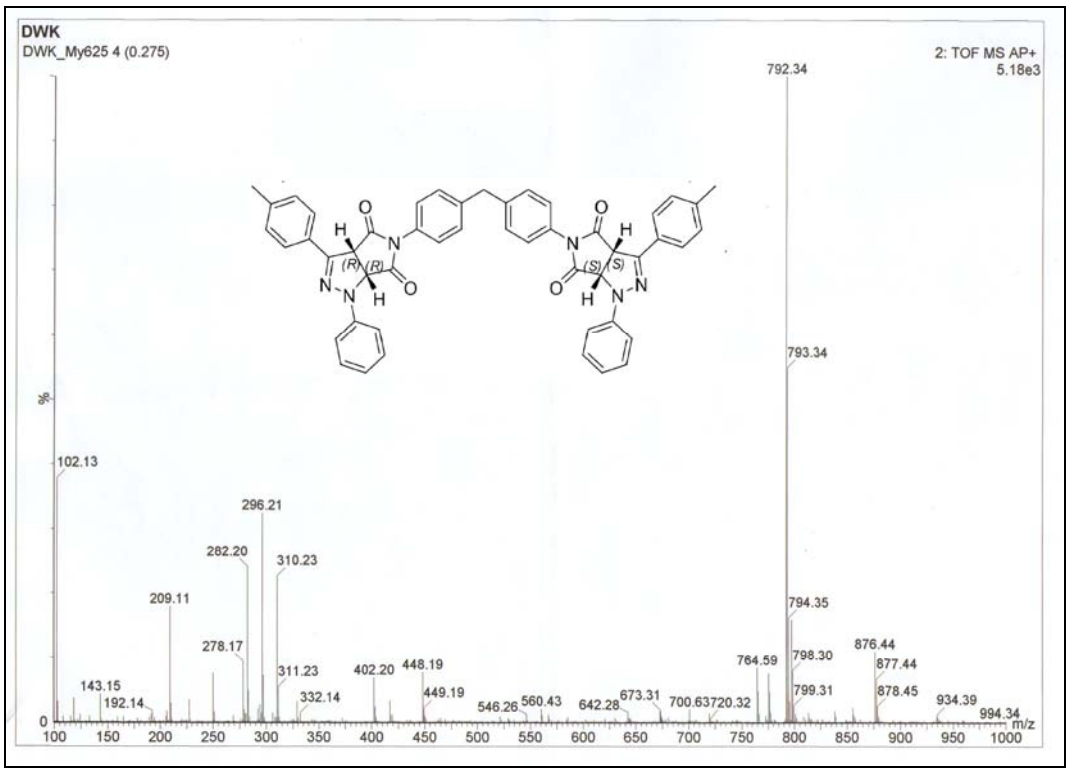

Figure 7.40 Mass spectrum of compound **6.13e**

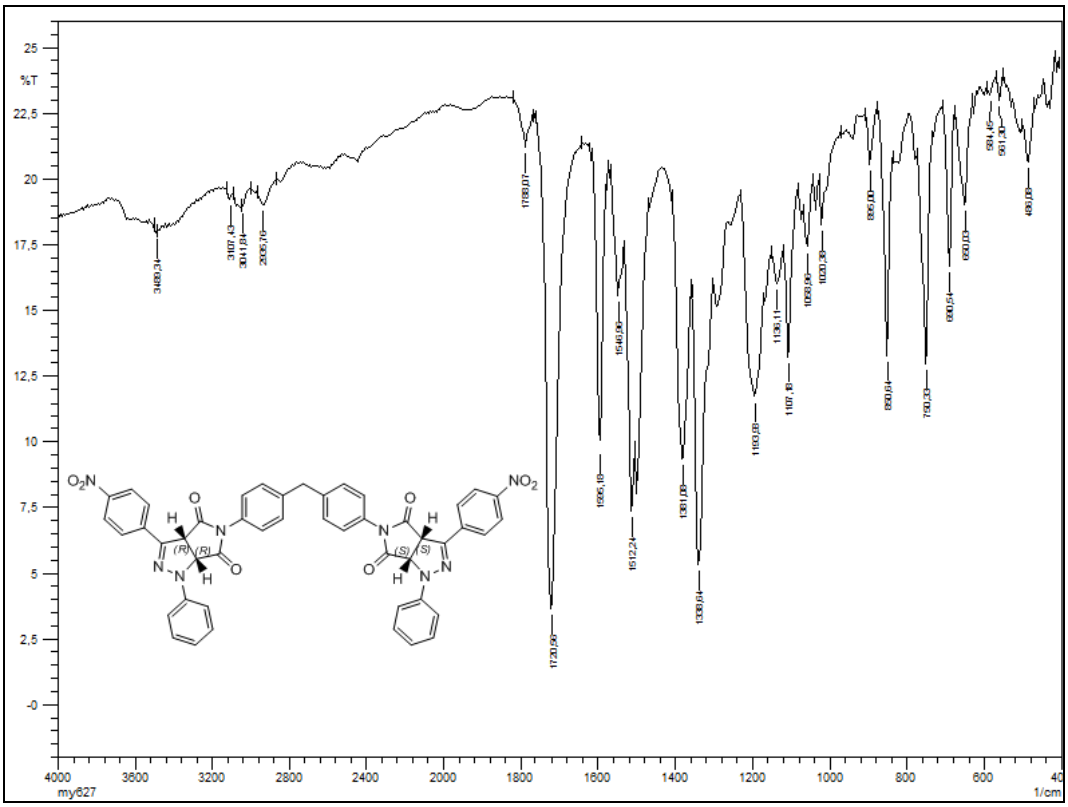

Figure 7.41 IR spectrum of compound **6.13f**

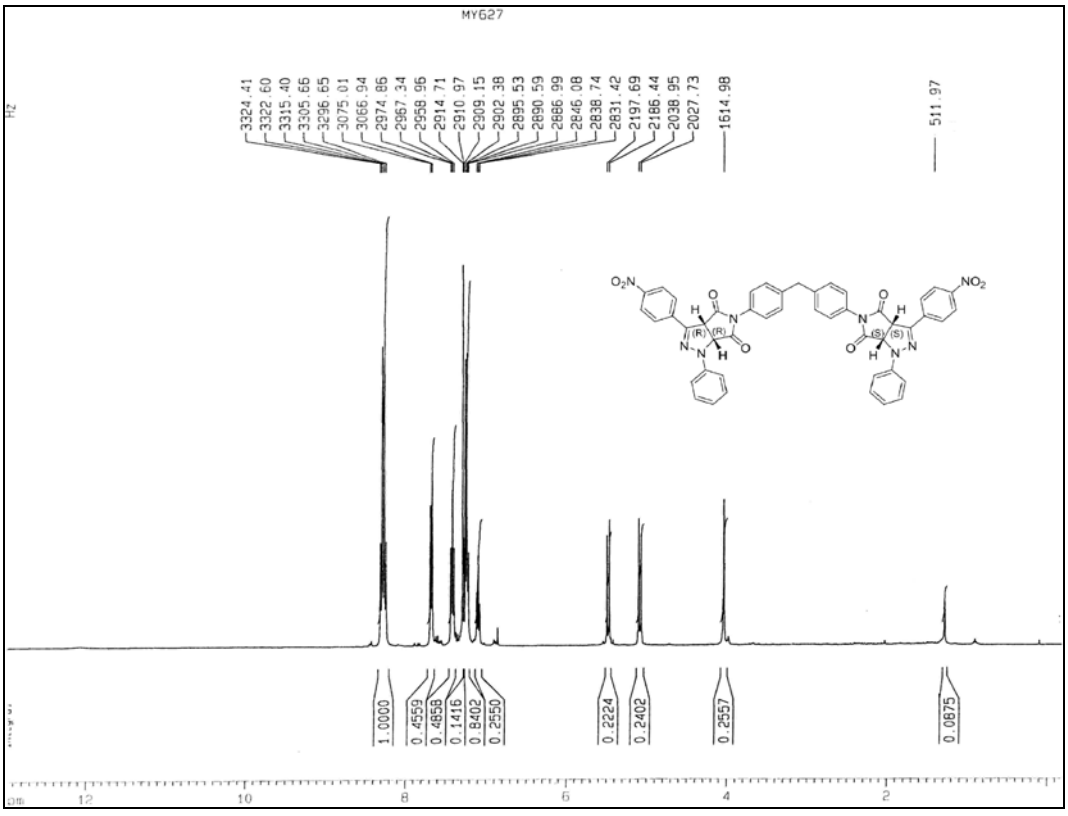

Figure 7.42 ^{1}H-NMR spectrum of compound **6.13f** in $CDCl_3$

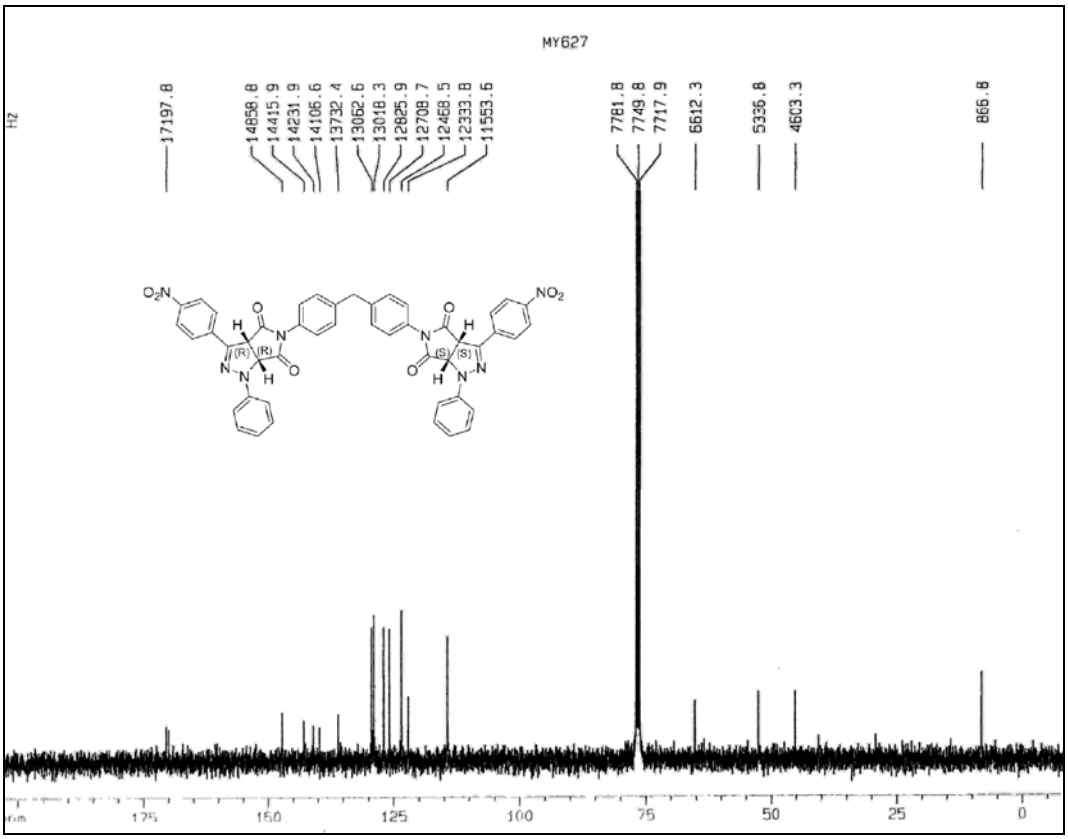

Figure 7.43 ^{13}C-NMR spectrum of compound **6.13f** in $CDCl_3$

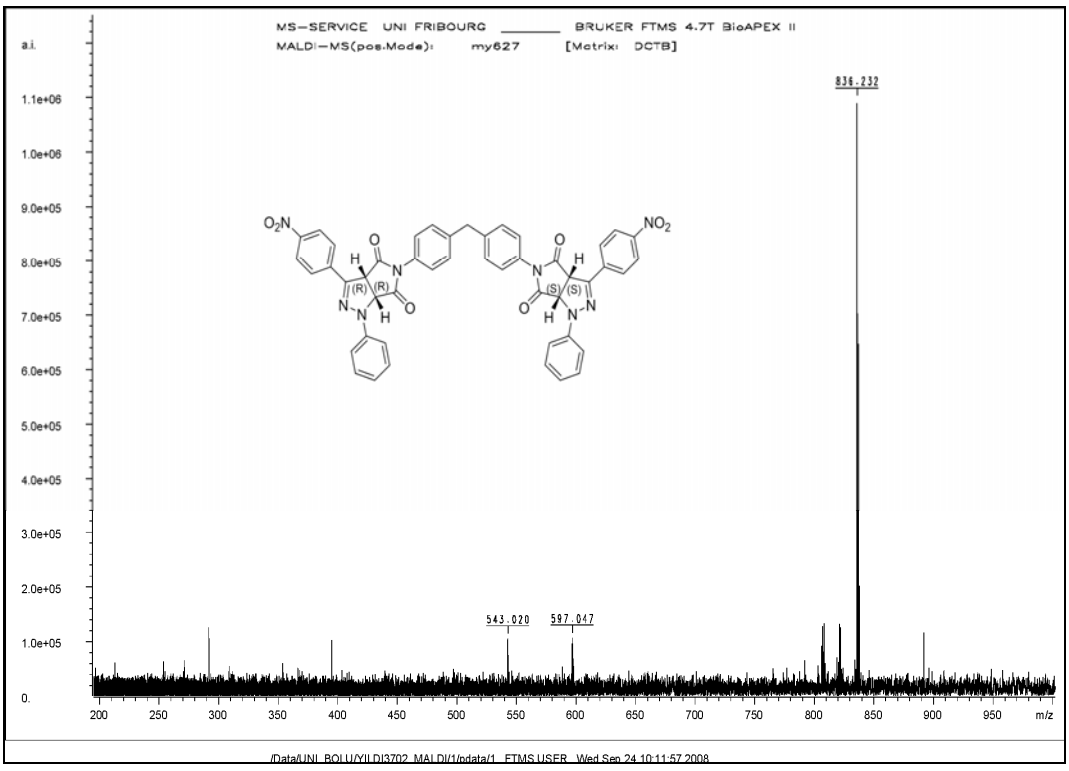

Figure 7.44 Mass spectrum of compound **6.13f**

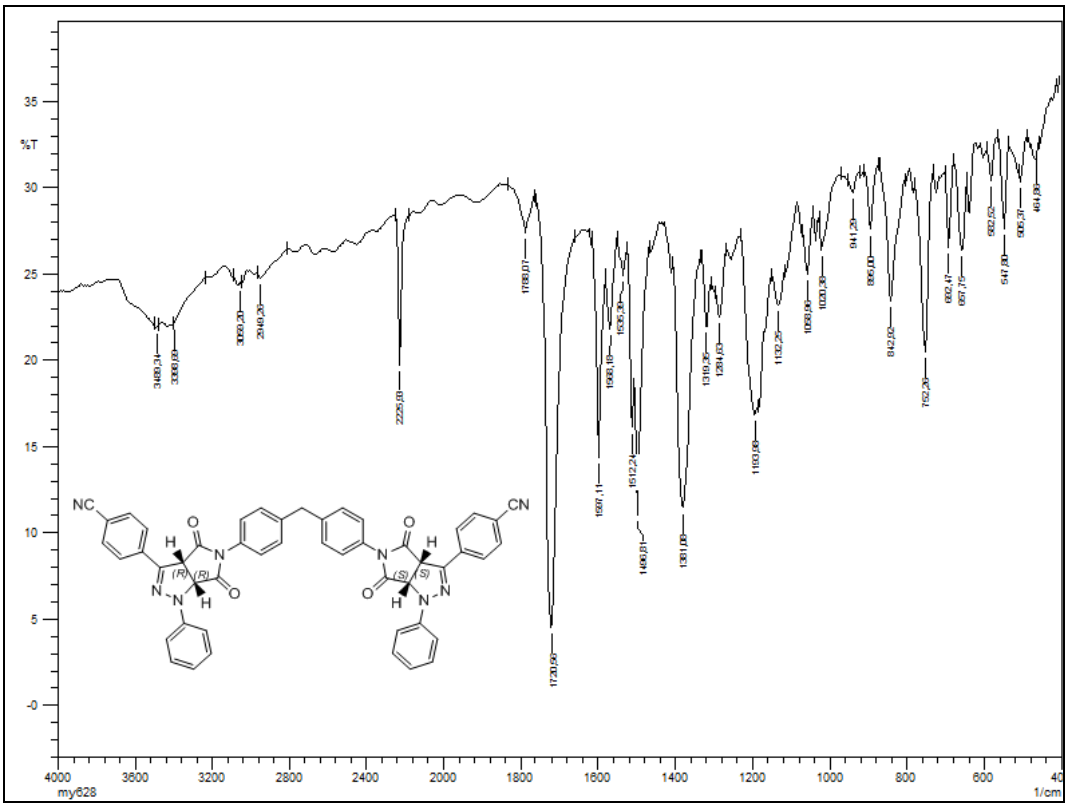

Figure 7.45 IR spectrum of compound **6.13g**

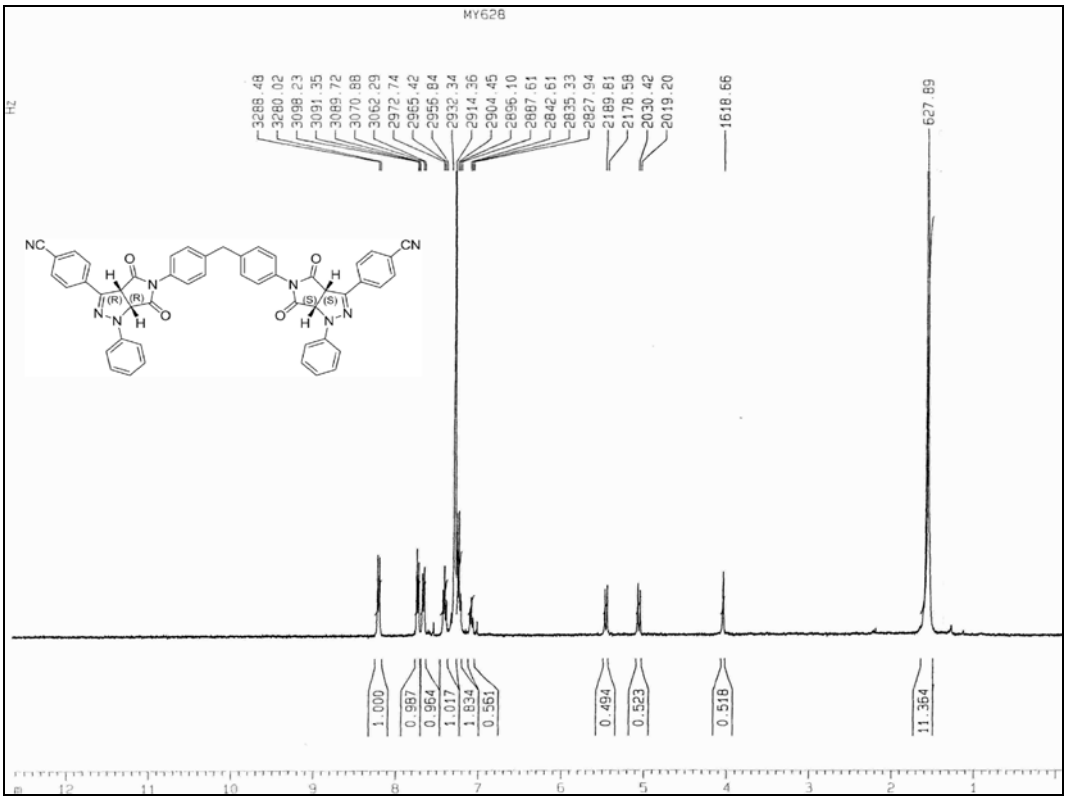

Figure 7.46 ^{1}H-NMR spectrum of compound **6.13g** in $CDCl_3$

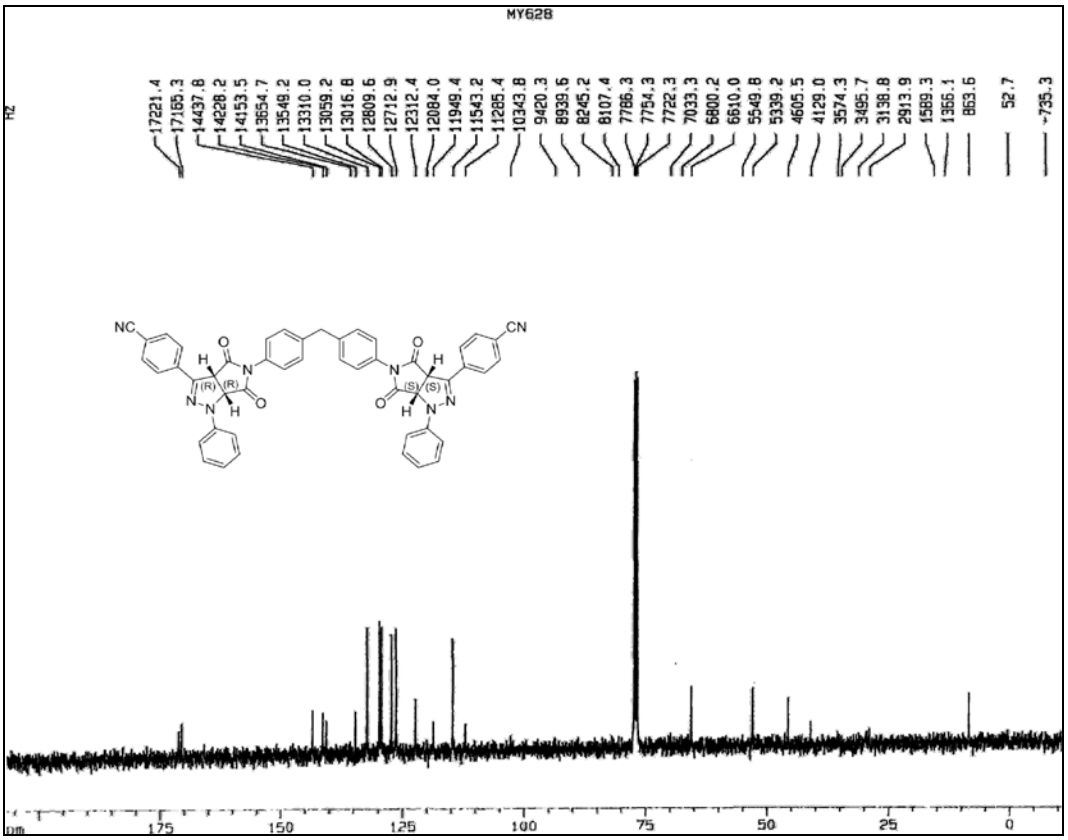

Figure 7.47 ^{13}C-NMR spectrum of compound **6.13g** in $CDCl_3$

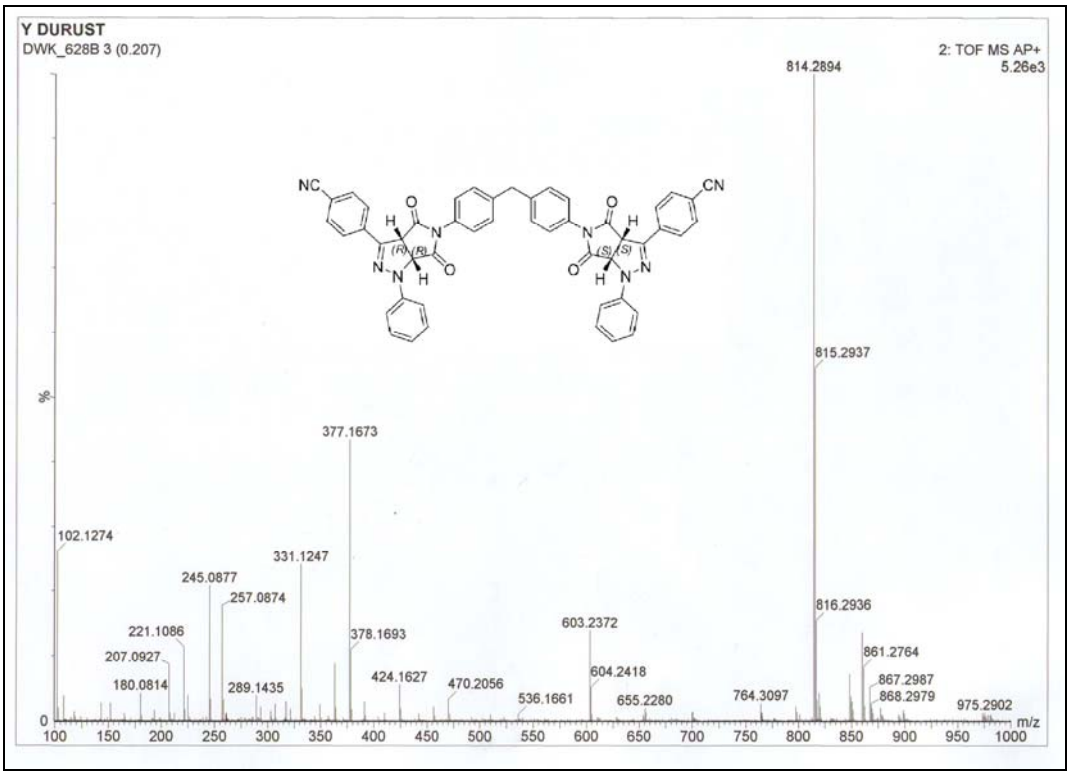

Figure 7.48 Mass spectrum of compound **6.13g**

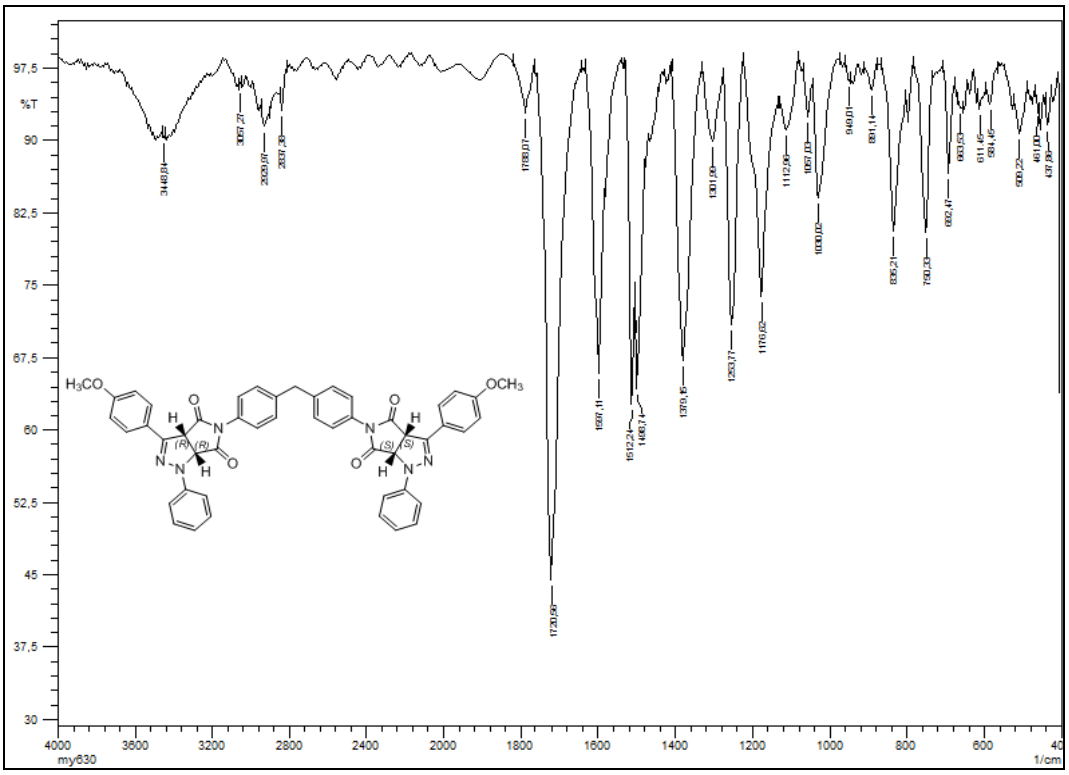

Figure 7.49 IR spectrum of compound **6.13h**

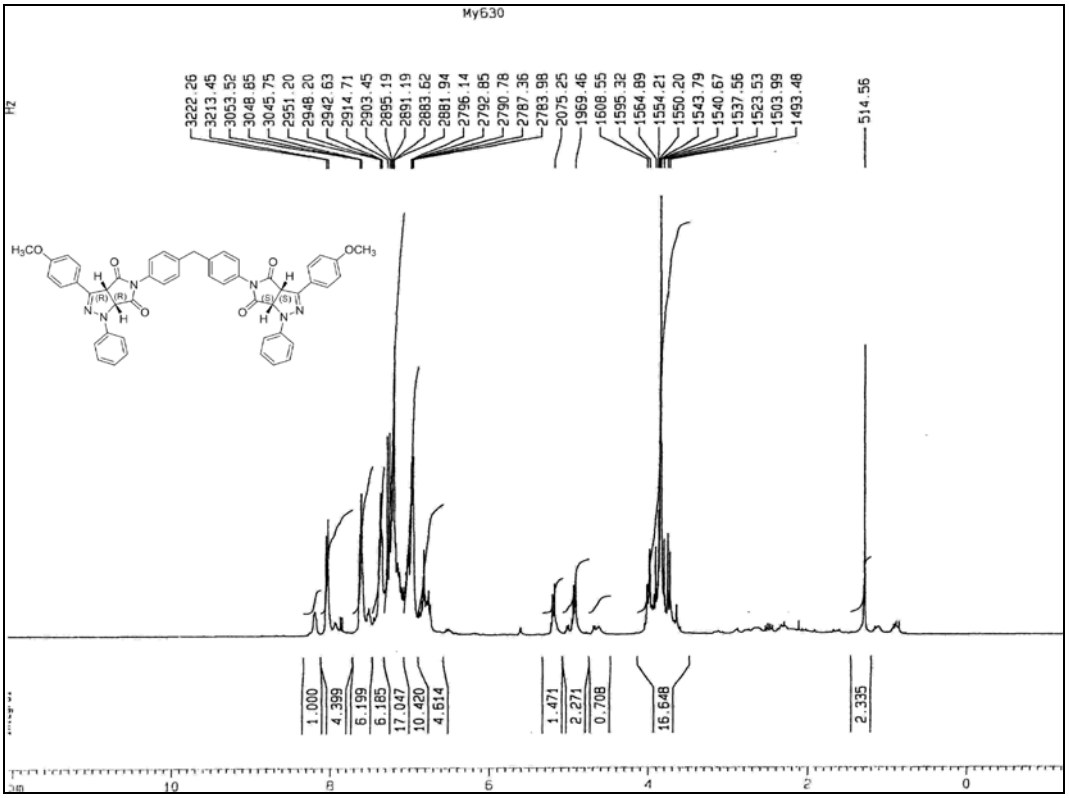

Figure 7.50 ^{1}H-NMR spectrum of compound **6.13h** in $CDCl_3$

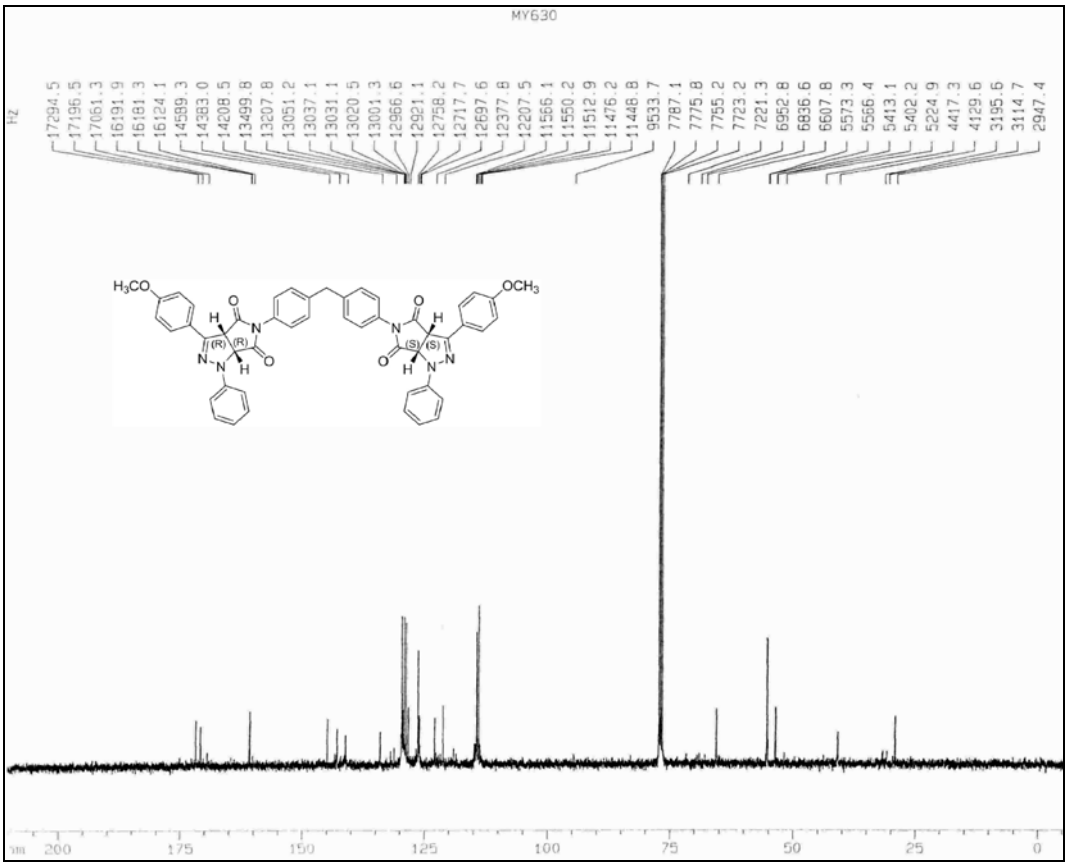

Figure 7.51 ^{13}C-NMR spectrum of compound **6.13h** in $CDCl_3$

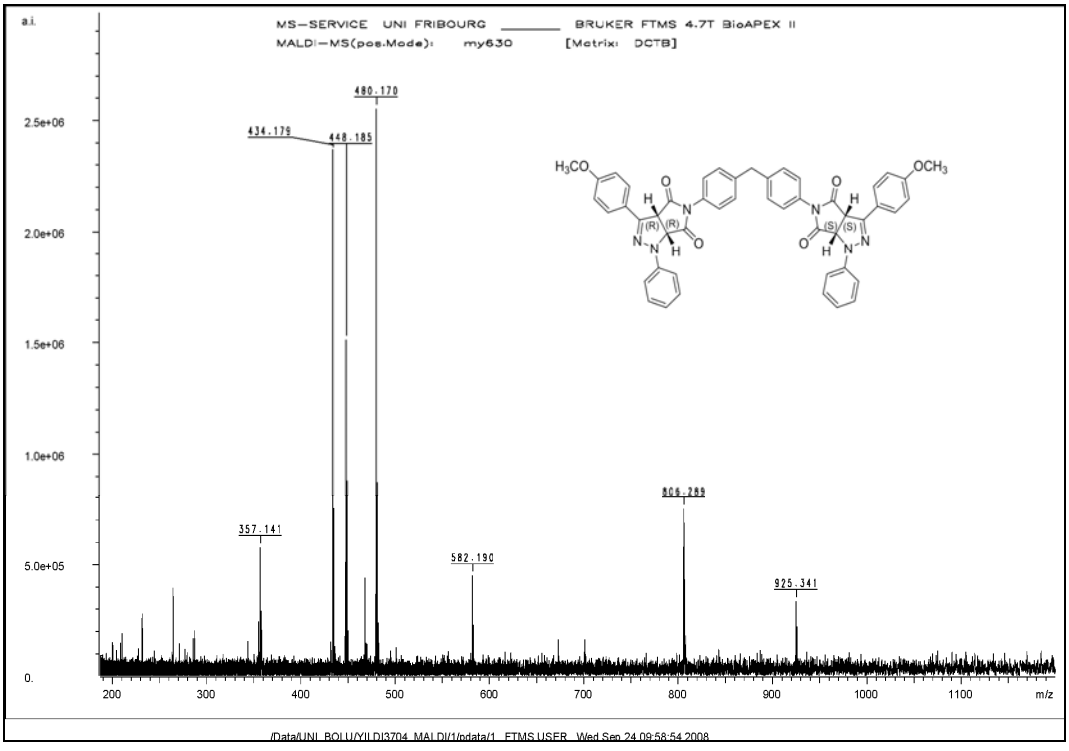

Figure 7.52 Mass spectrum of compound **6.13h**

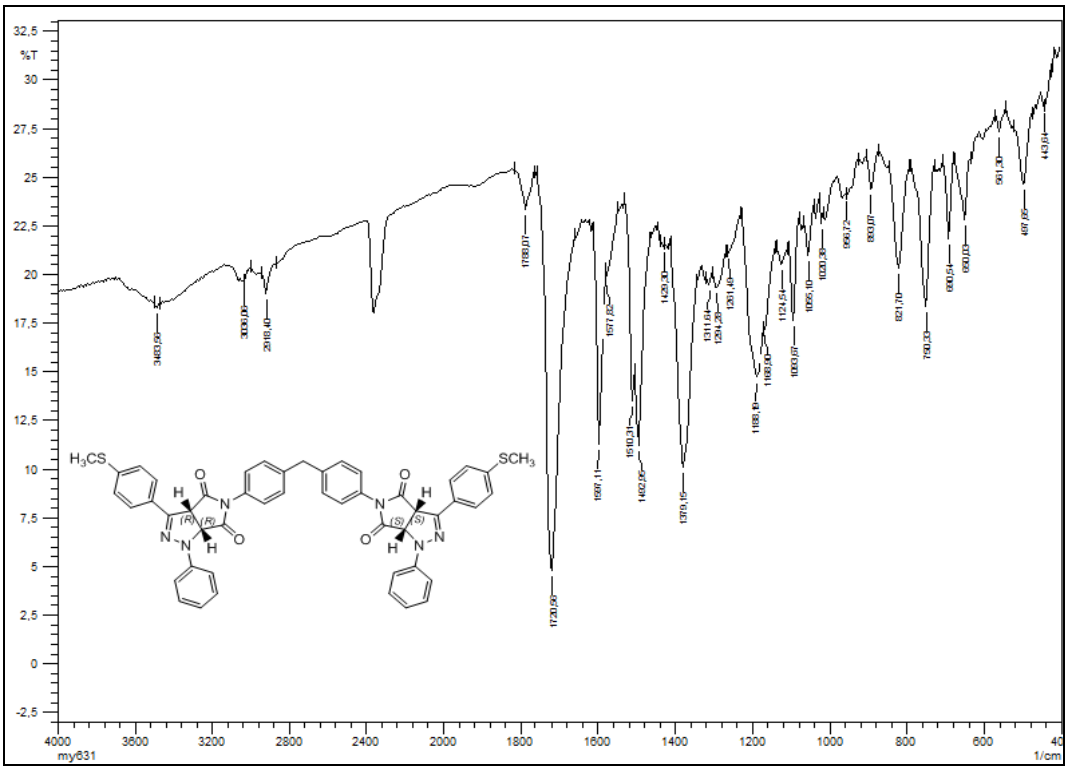

Figure 7.53 IR spectrum of compound **6.13i**

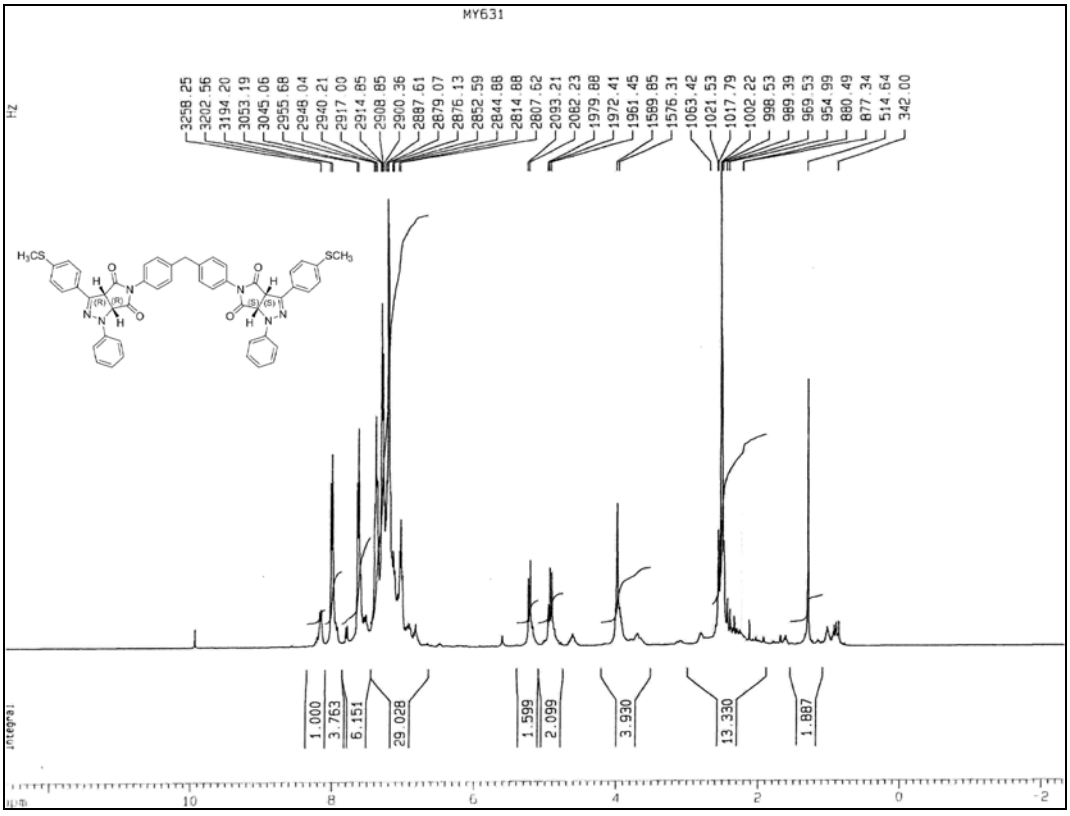

Figure 7.54 ^{1}H-NMR spectrum of compound **6.13i** in $CDCl_3$

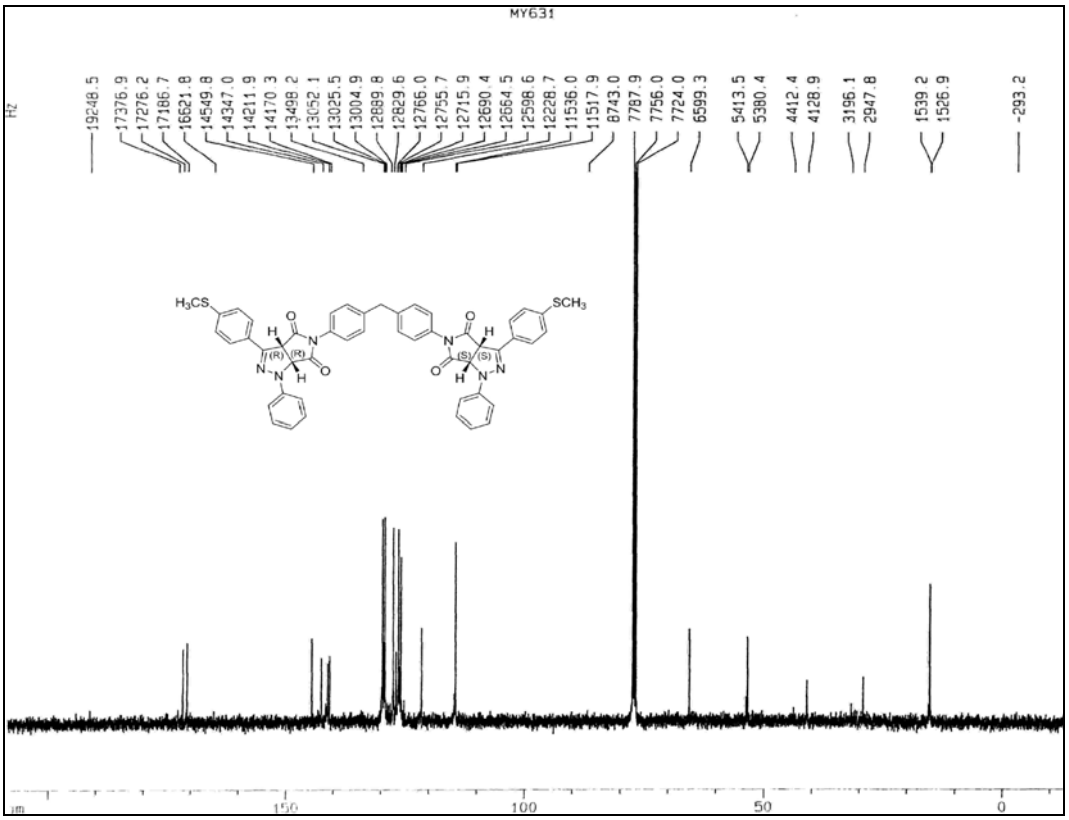

Figure 7.55 ^{13}C-NMR spectrum of compound **6.13i** in $CDCl_3$

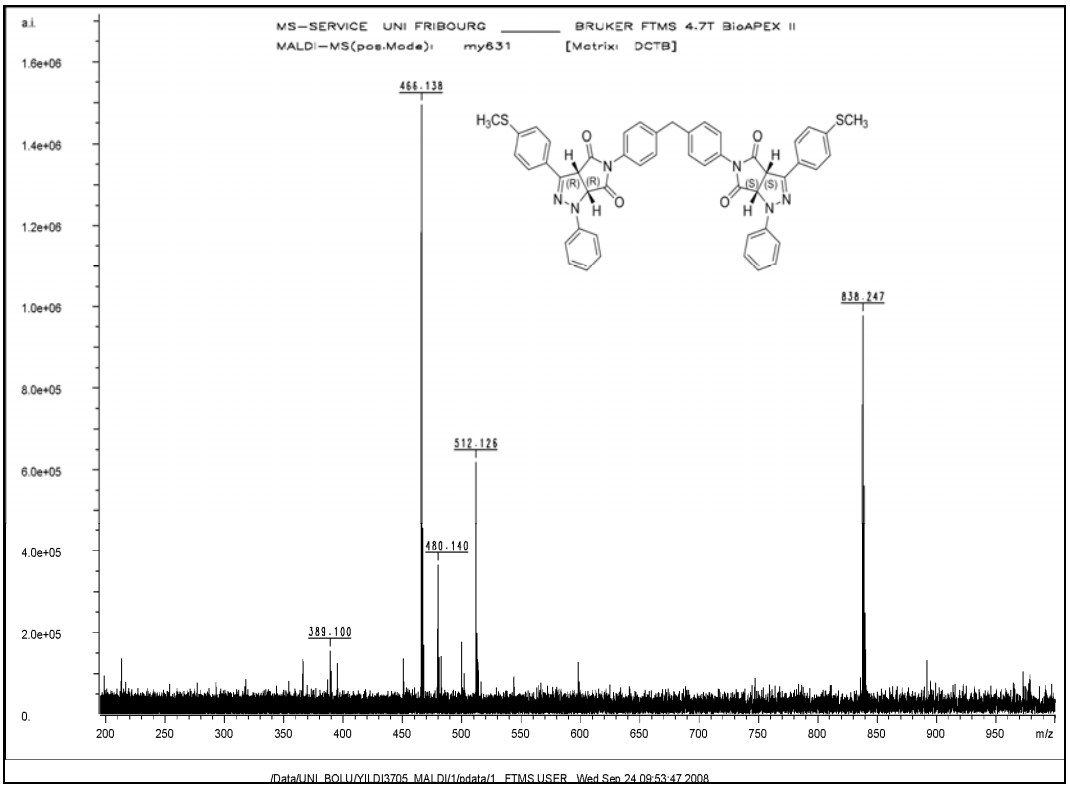

Figure 7.56 Mass spectrum of compound **6.13i**

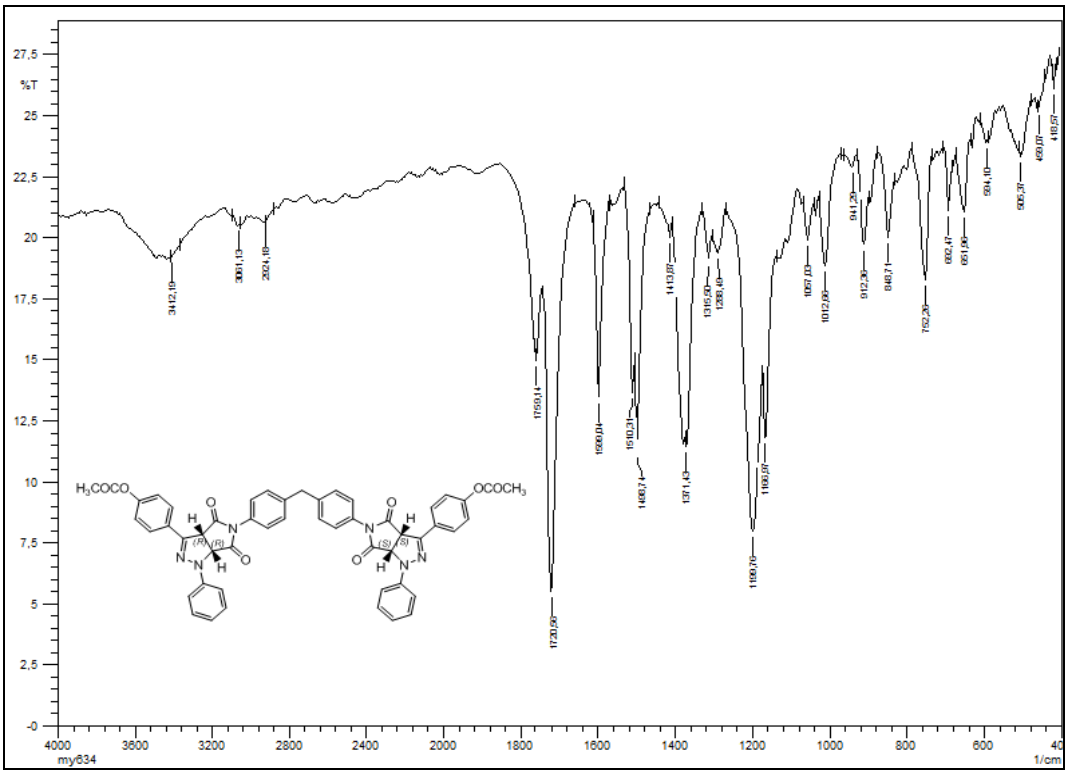

Figure 7.57 IR spectrum of compound **6.13j**

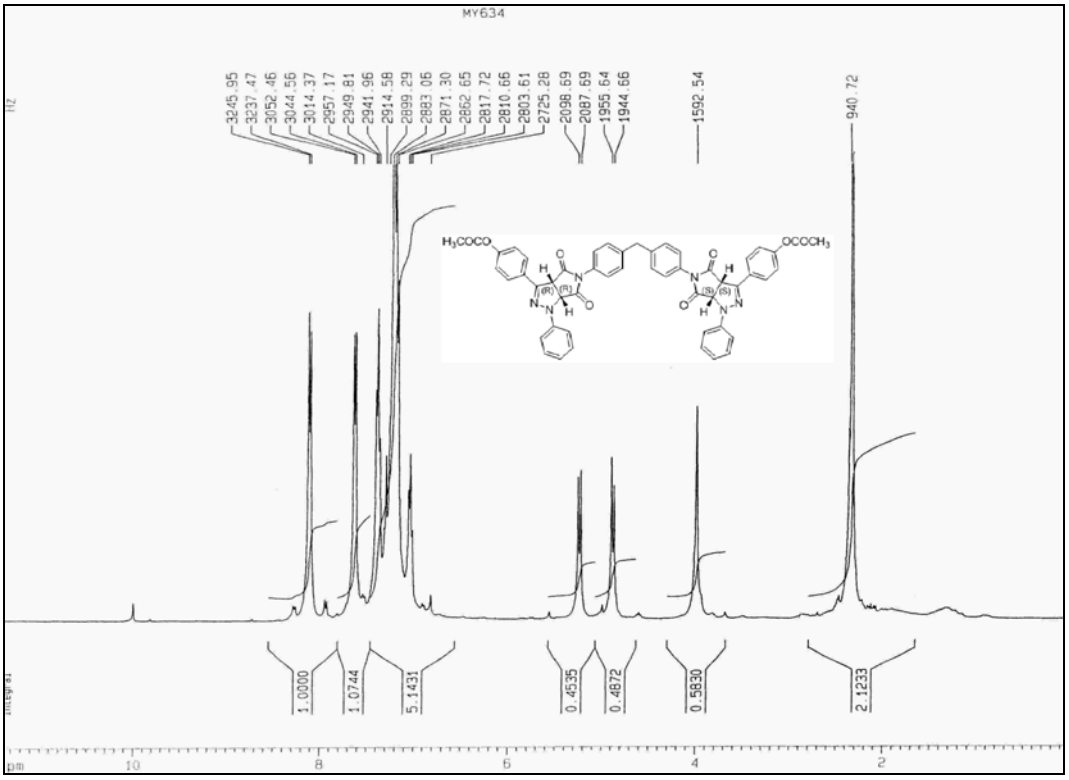

Figure 7.58 ^{1}H-NMR spectrum of compound **6.13j** in $CDCl_3$

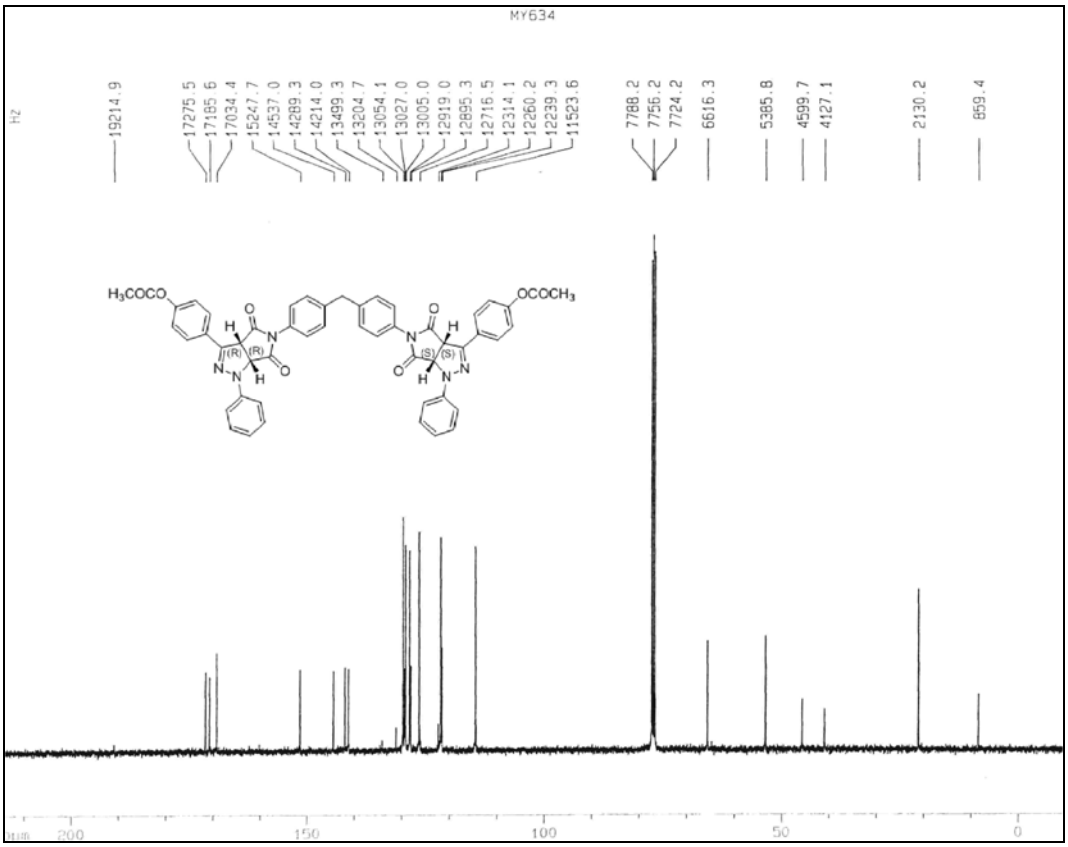

Figure 7.59 ^{13}C-NMR spectrum of compound **6.13j** in $CDCl_3$

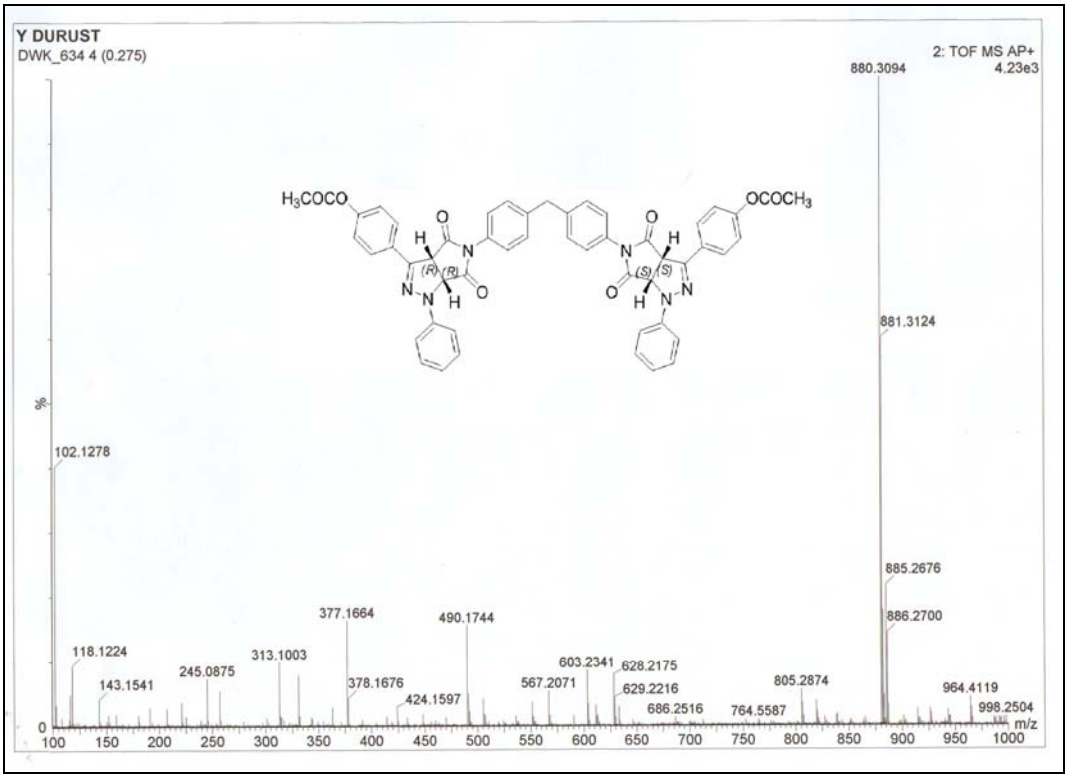

Figure 7.60 Mass spectrum of compound **6.13j**

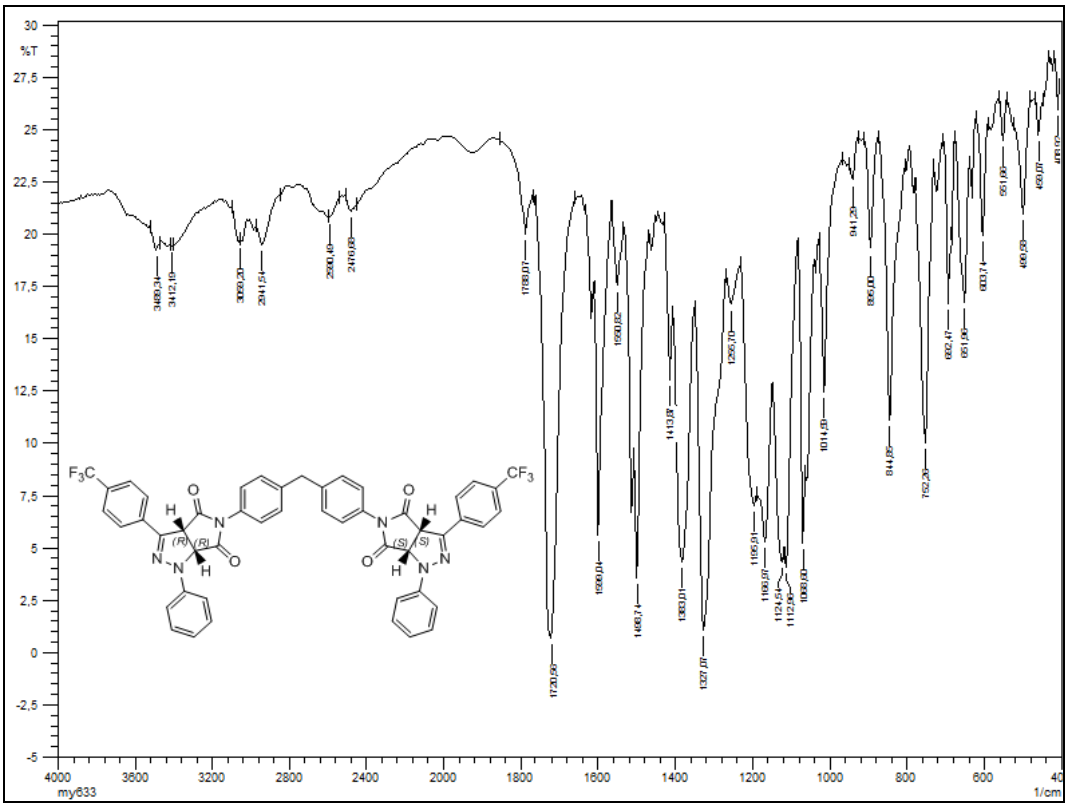

Figure 7.61 IR spectrum of compound **6.13k**

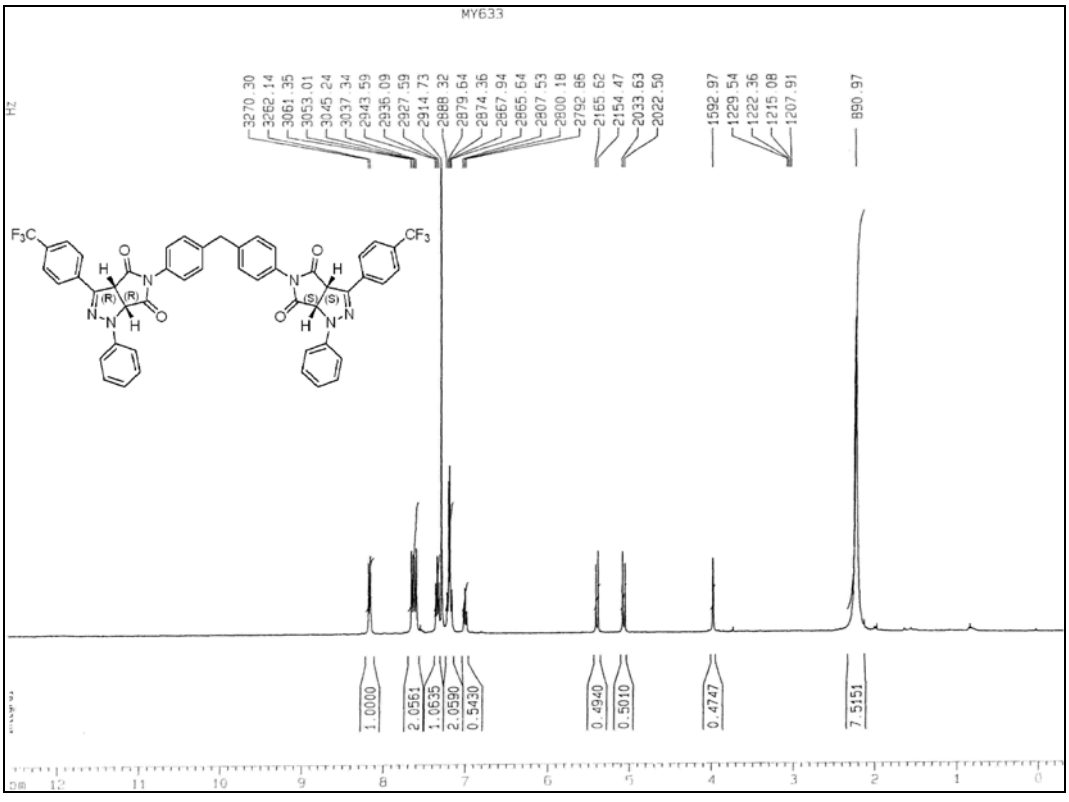

Figure 7.62 ^{1}H-NMR spectrum of compound **6.13k** in $CDCl_3$-DMSO-d_6

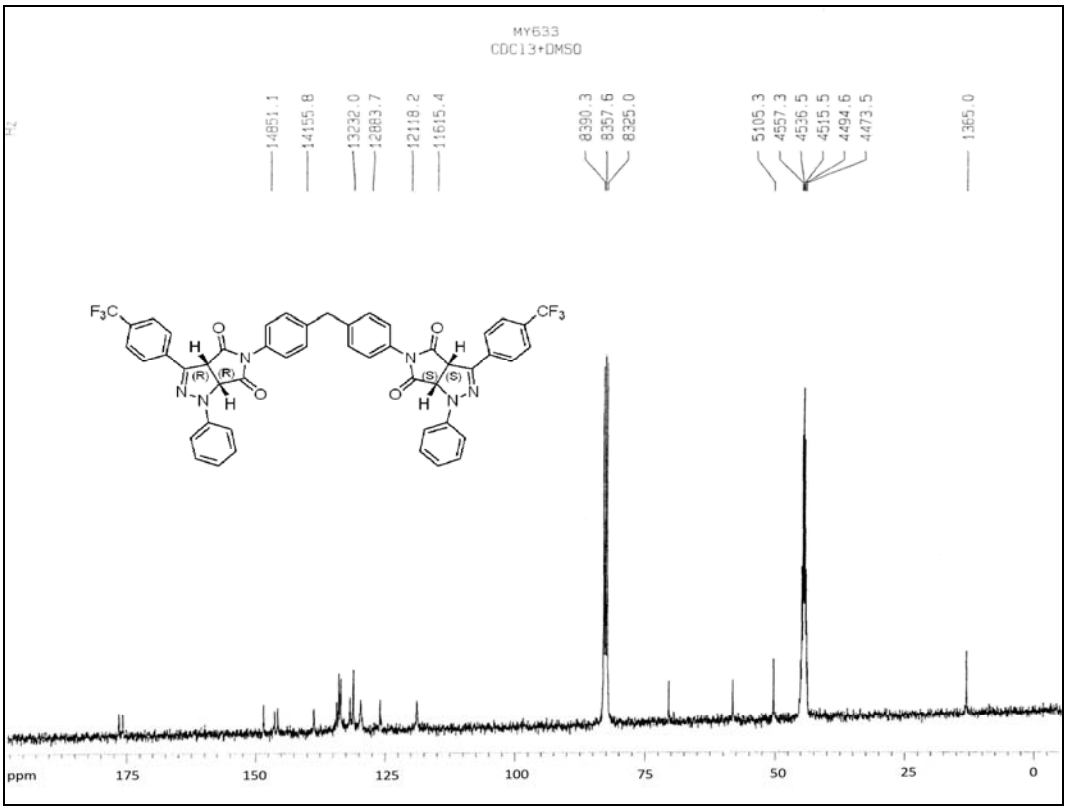

Figure 7.63 ^{13}C-NMR spectrum of compound **6.13k** in $CDCl_3$-DMSO-d_6

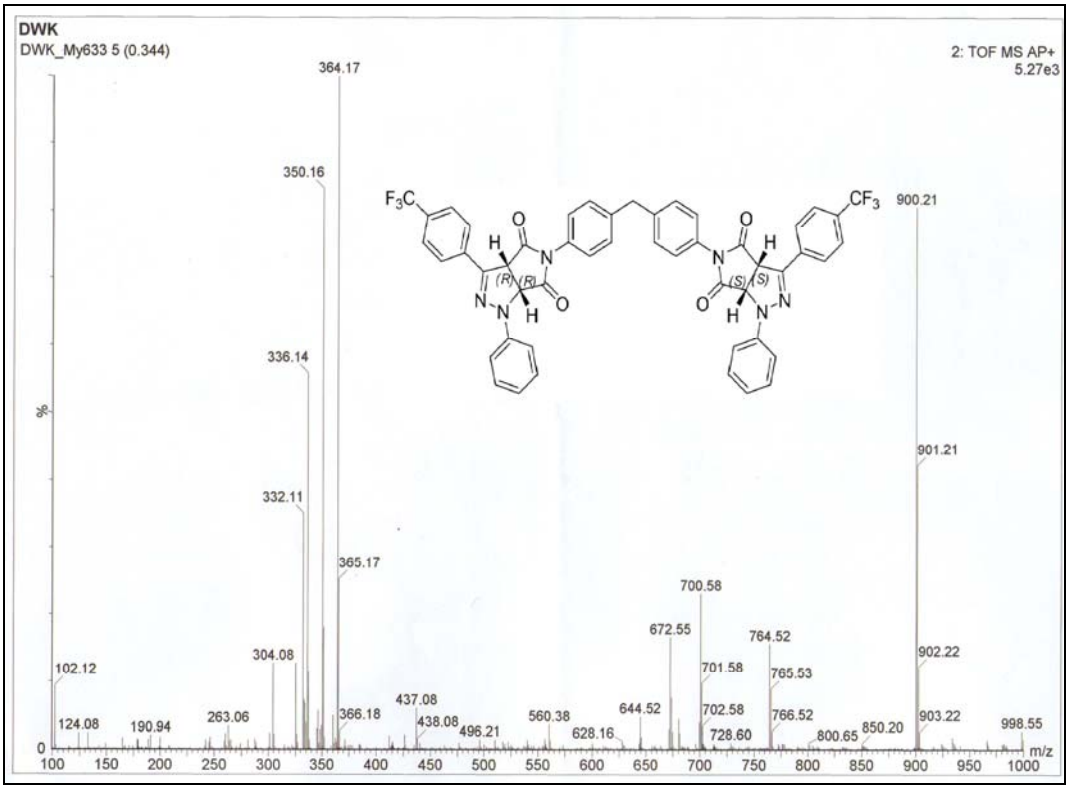

Figure 7.64 Mass spectrum of compound **6.13k**

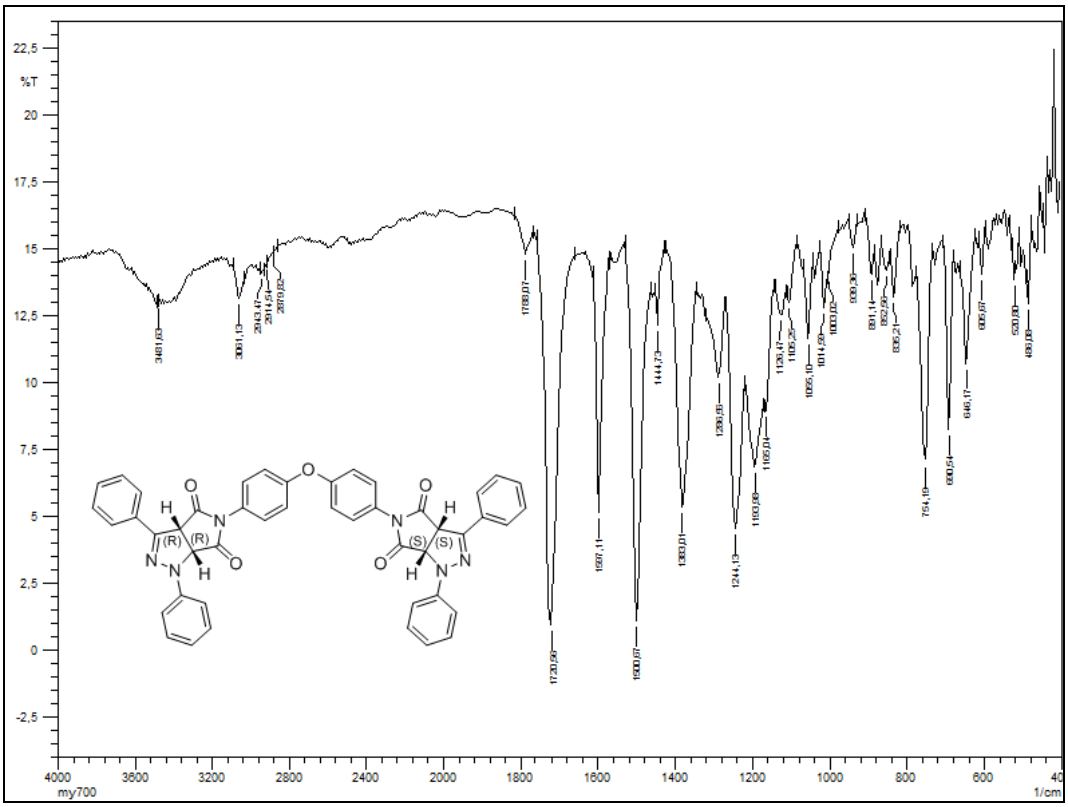

Figure 7.65 IR spectrum of compound **6.14a**

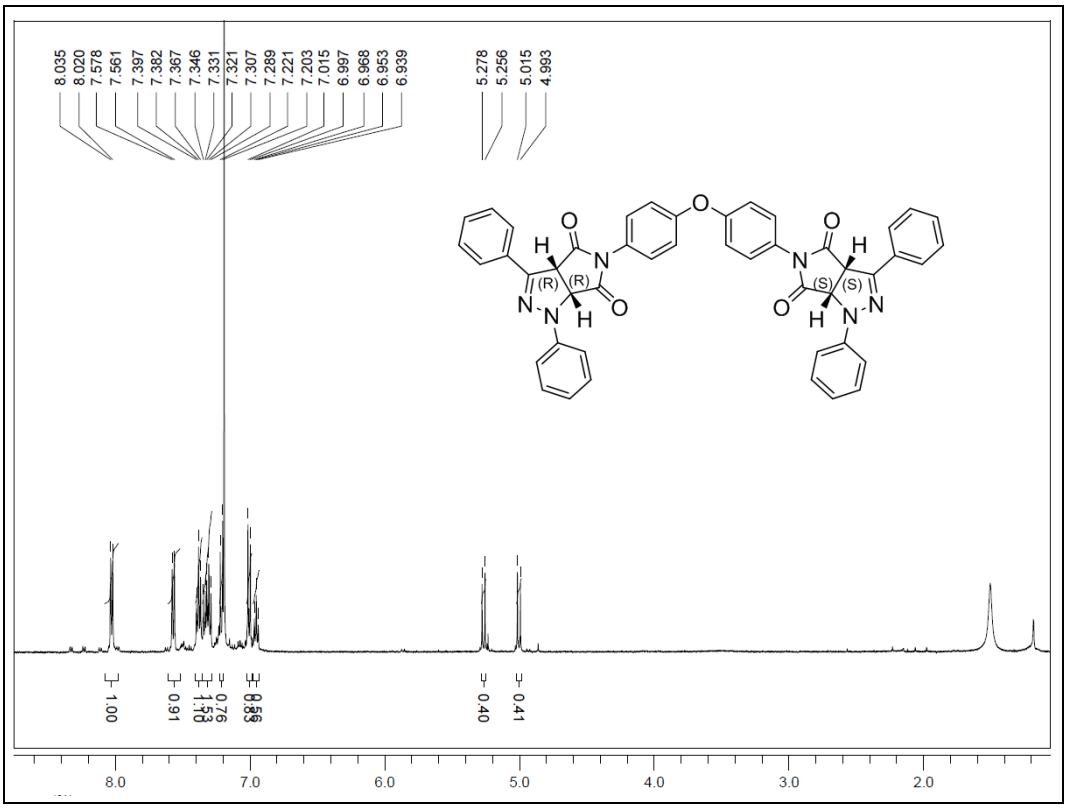

Figure 7.66 ^{1}H-NMR spectrum of compound **6.14a** in $CDCl_3$

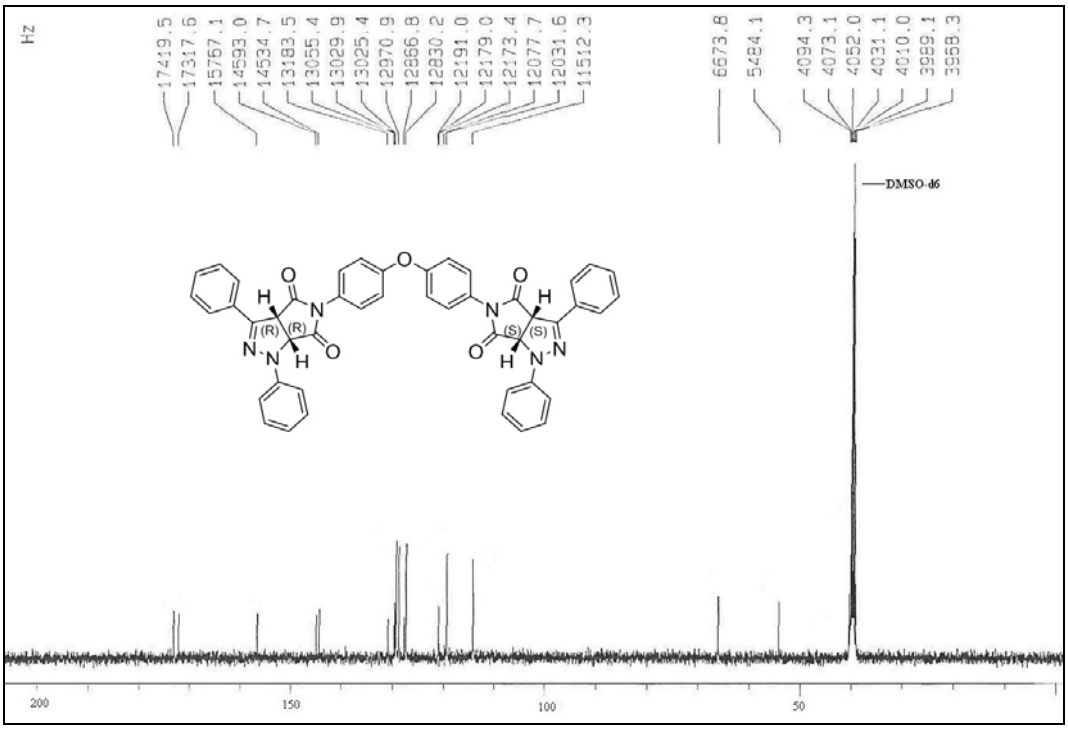

Figure 7.67 ^{13}C-NMR spectrum of compound **6.14a** in DMSO-d_6

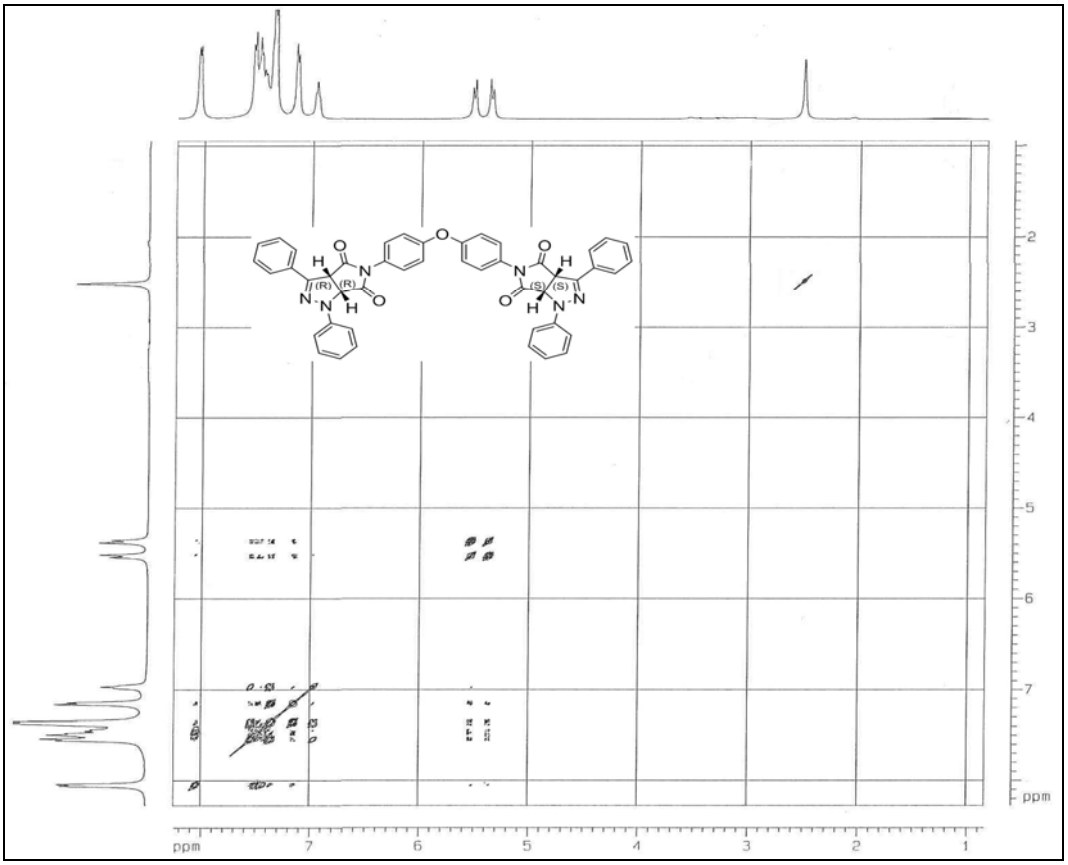

Figure 7.68 COSY-NMR spectrum of compound **6.14a** in DMSO-d_6

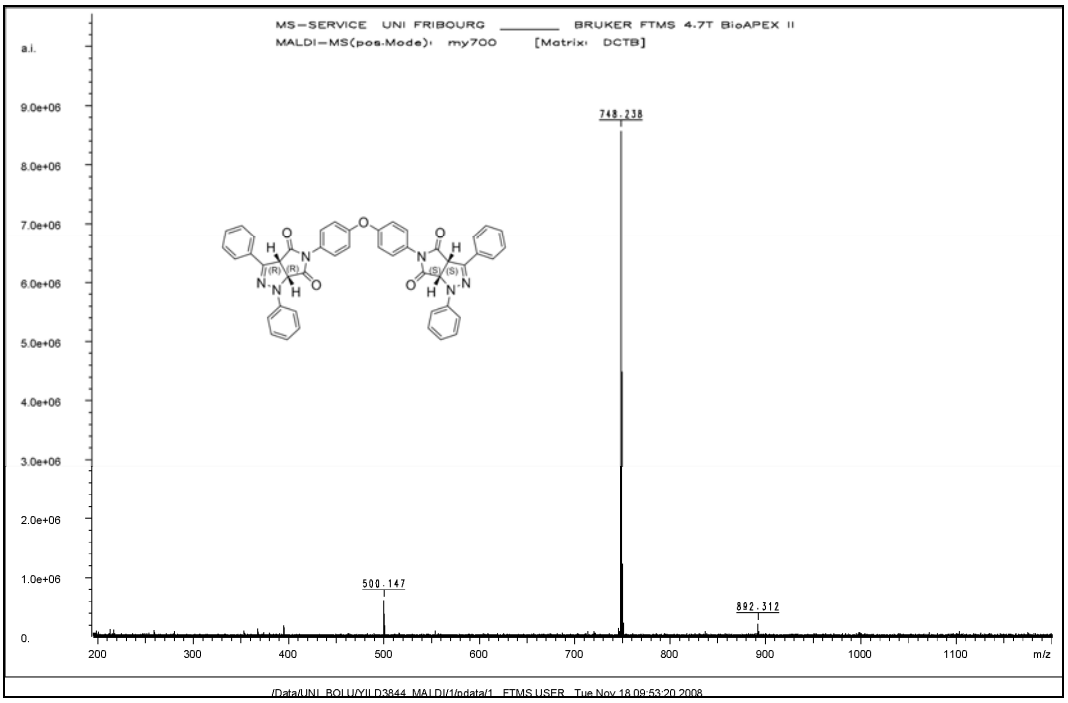

Figure 7.69 Mass spectrum of compound **6.14a**

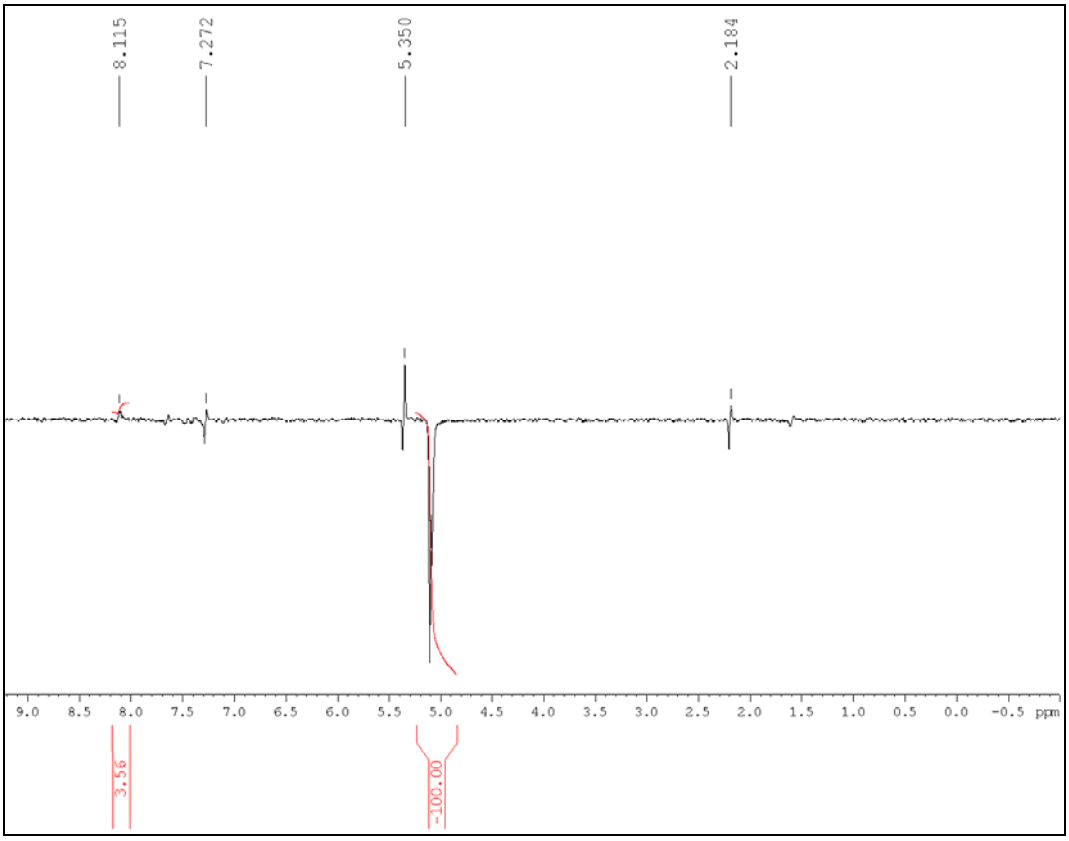

Figure 7.70 NOE experiment for proton 3a-H(3a'-H) of compound **6.14a** in $CDCl_3$

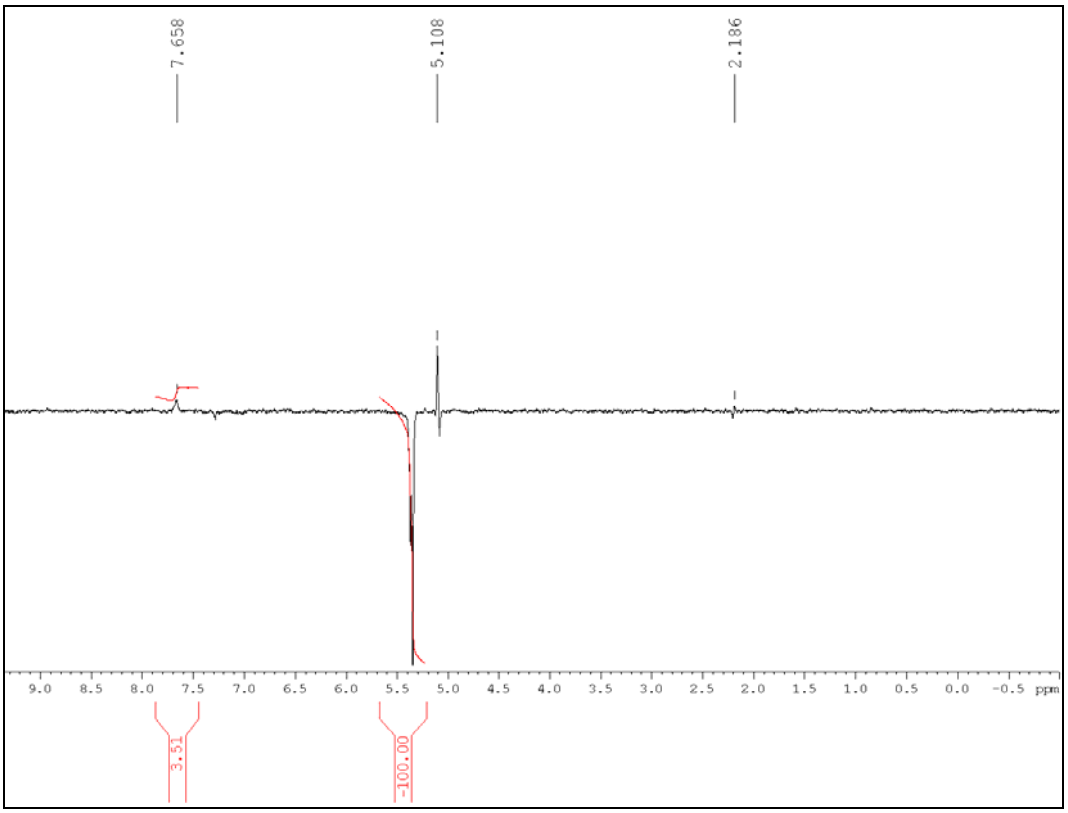

Figure 7.71 NOE experiment for proton 6a-H(6a'-H) of compound **6.14a** in $CDCl_3$

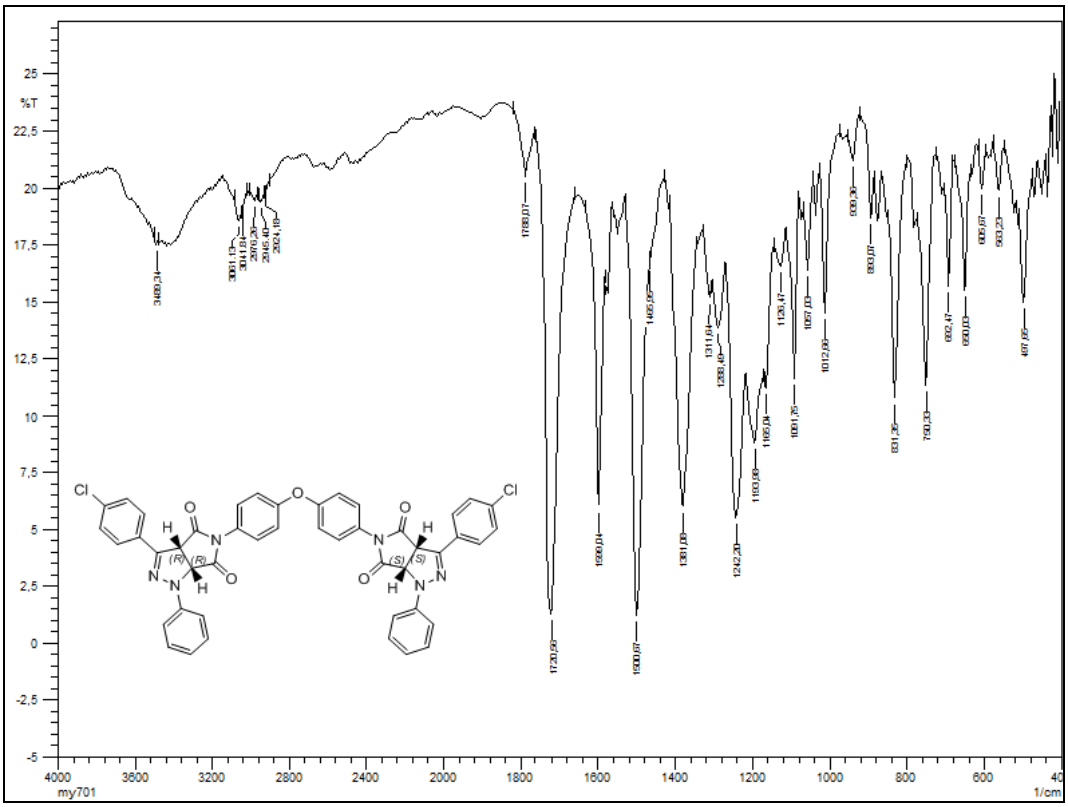

Figure 7.72 IR spectrum of compound **6.14b**

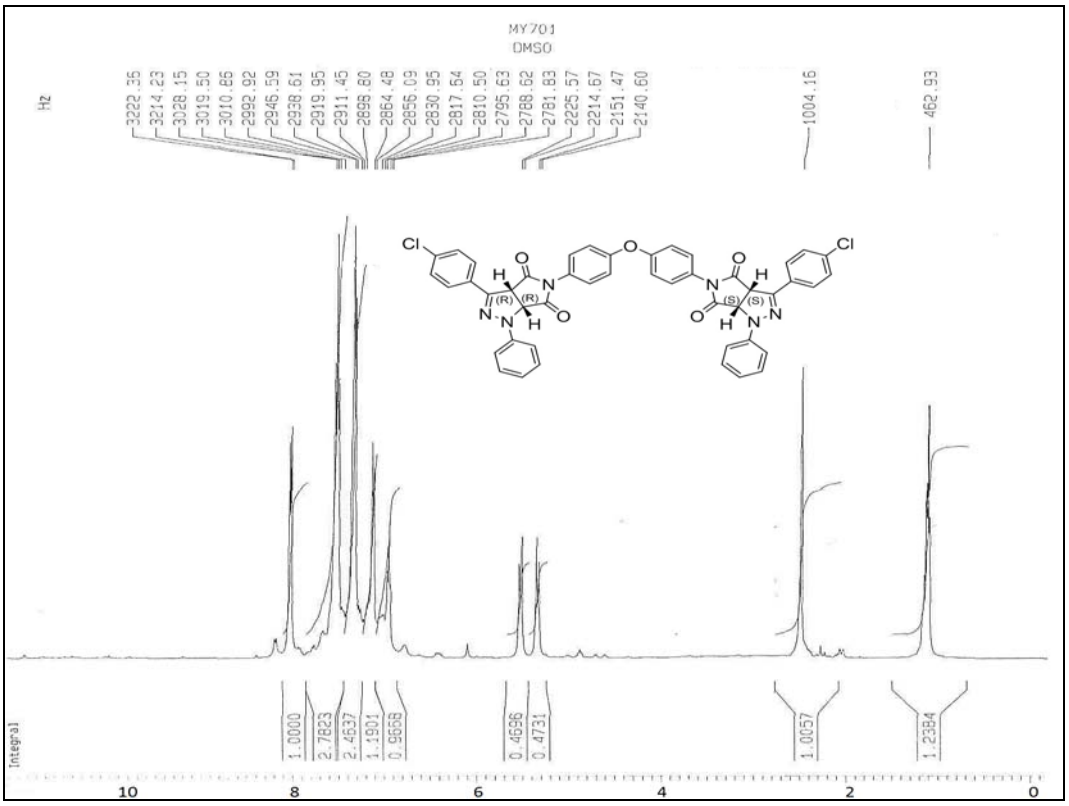

Figure 7.73 ^{1}H-NMR spectrum of compound **6.14b** in DMSO-d_6

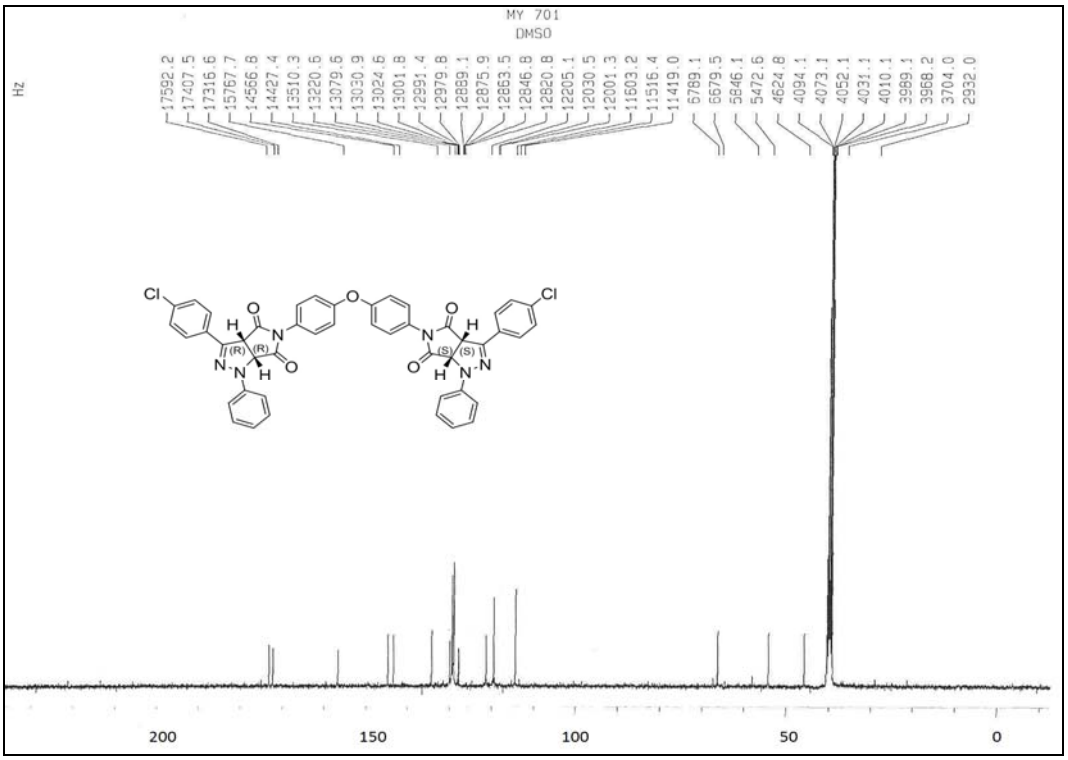

Figure 7.74 ^{13}C-NMR spectrum of compound **6.14b** in DMSO-d_6

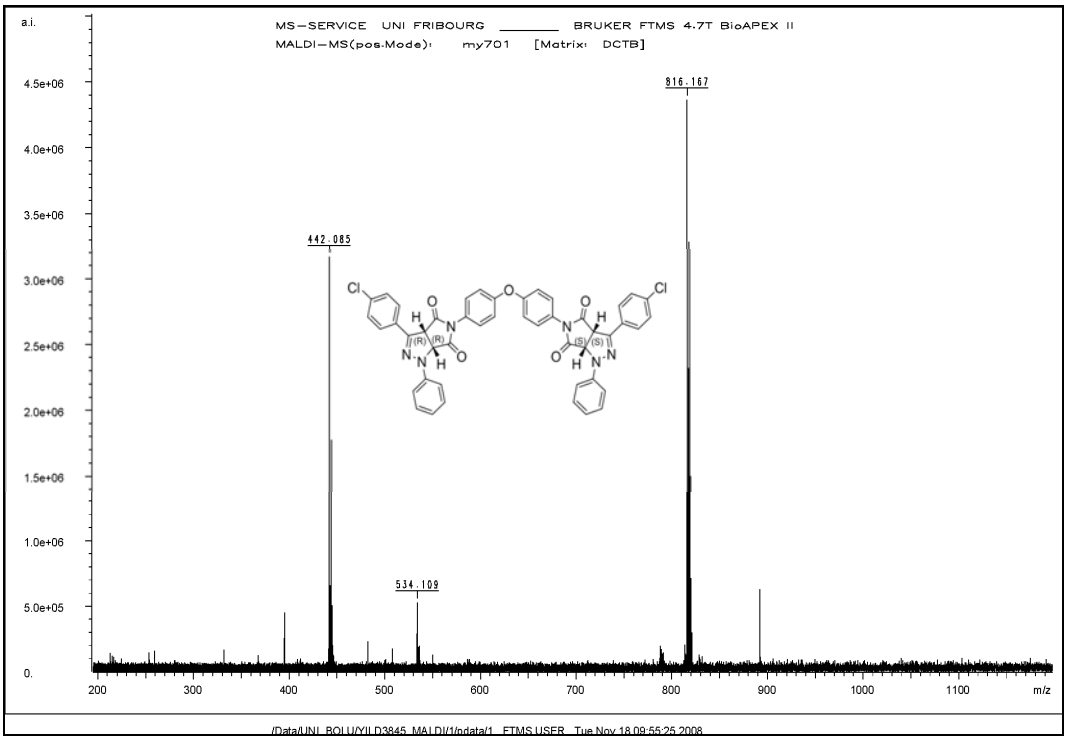

Figure 7. 75 Mass spectrum of compound **6.14b**

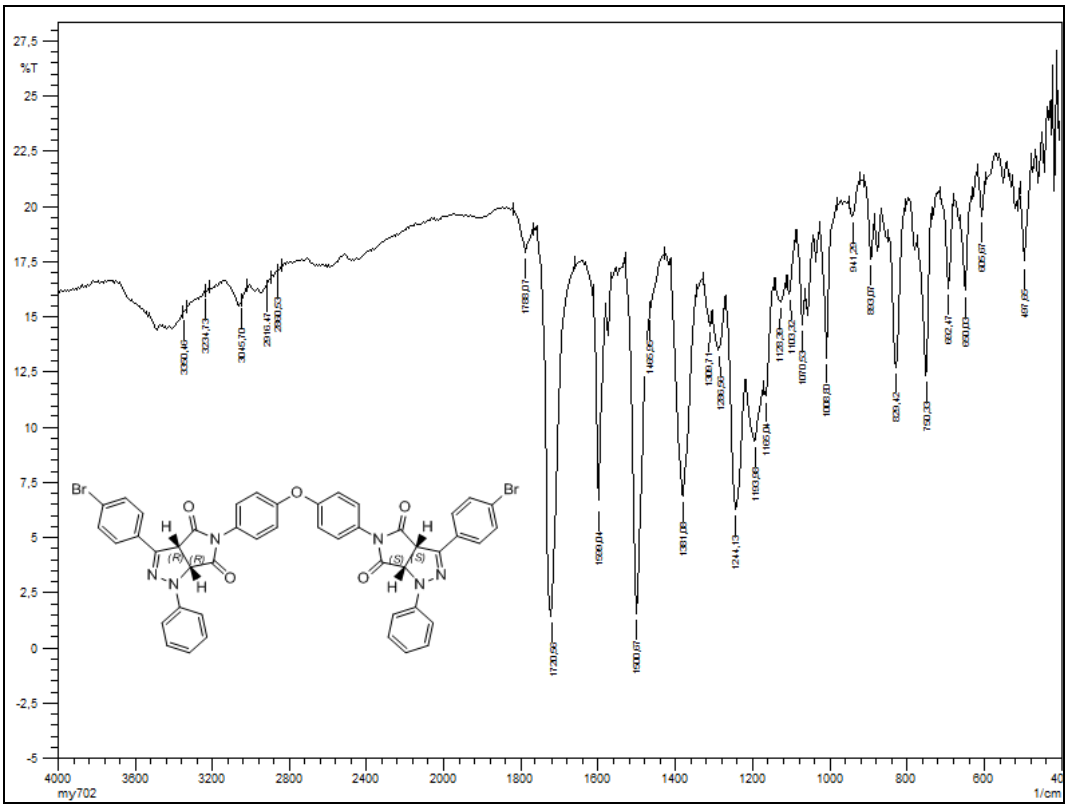

Figure 7.76 IR spectrum of compound **6.14c**

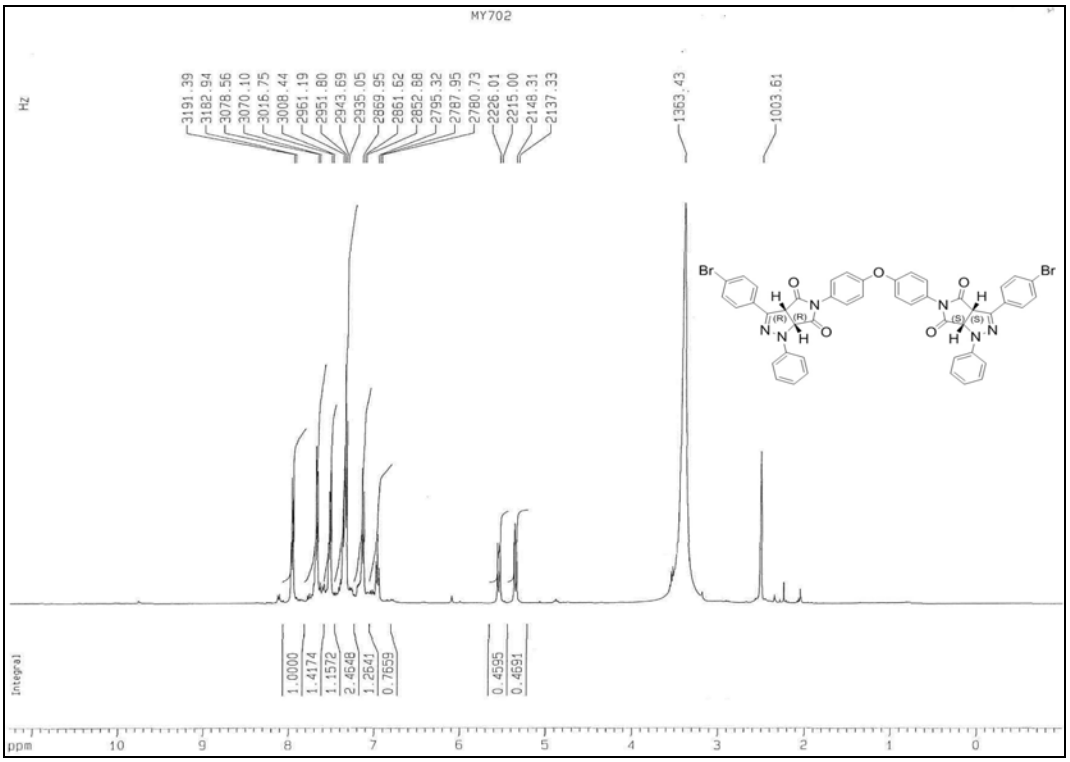

Figure 7.77 ^{1}H-NMR spectrum of compound **6.14c** in DMSO-d_6

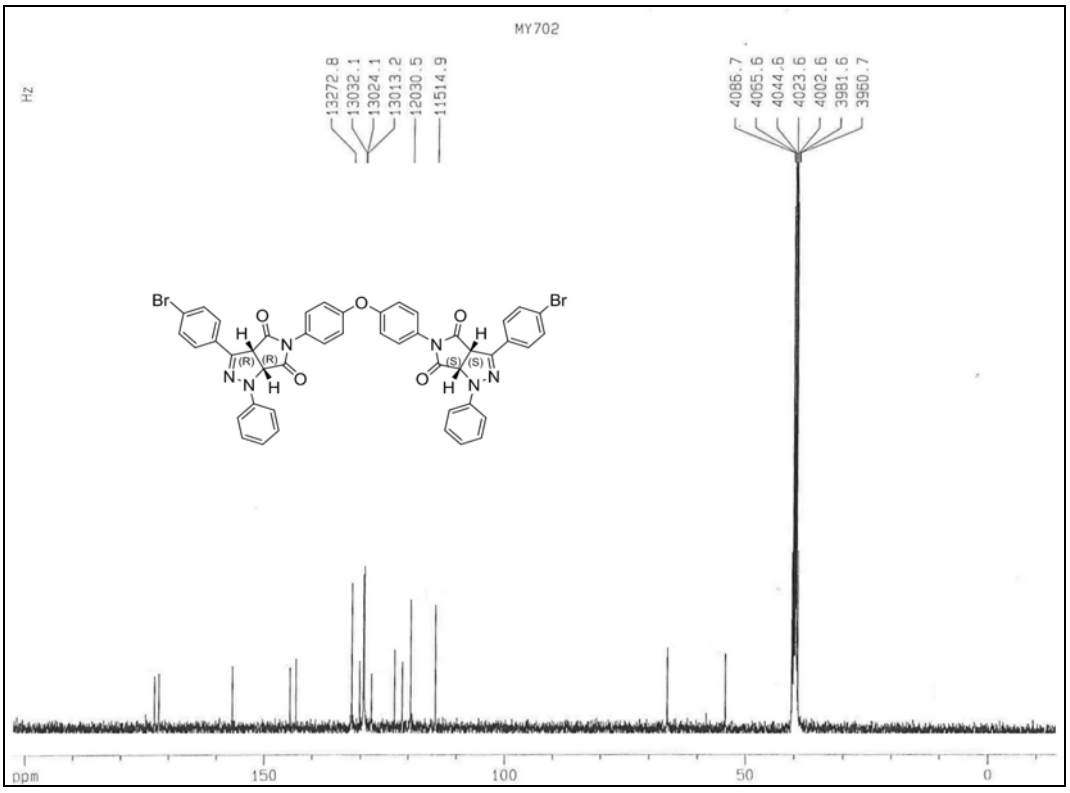

Figure 7.78 ^{13}C-NMR spectrum of compound **6.14c** in DMSO-d_6

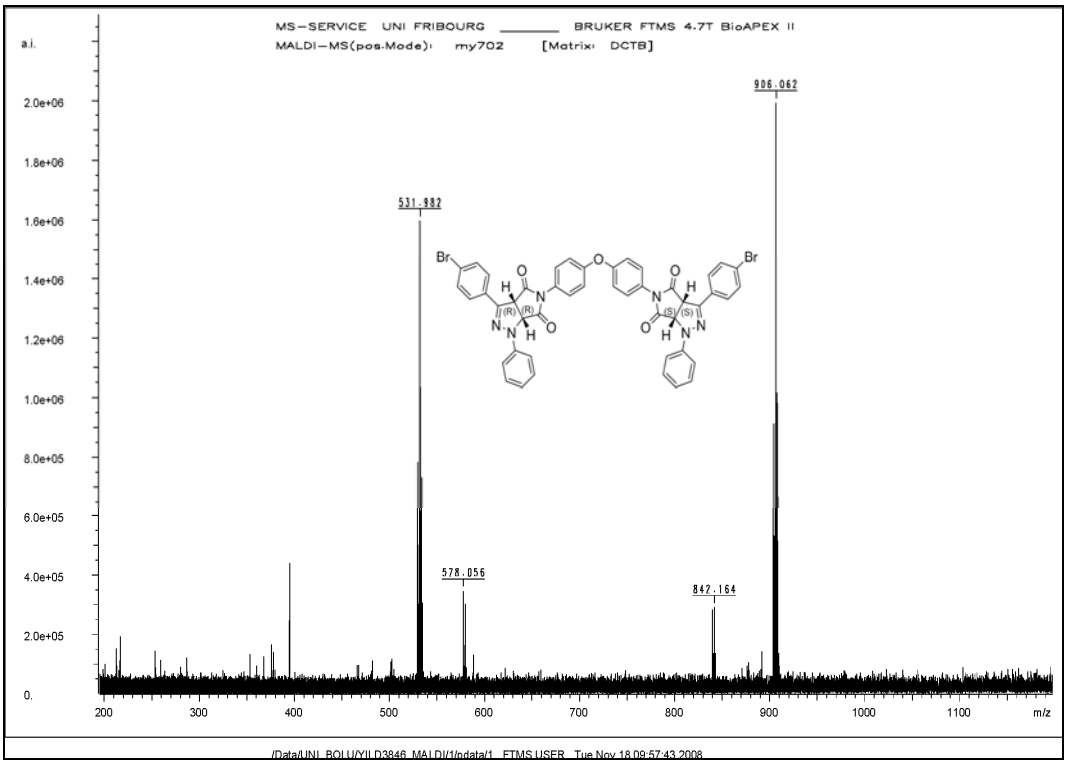

Figure 7.79 Mass spectrum of compound **6.14c**

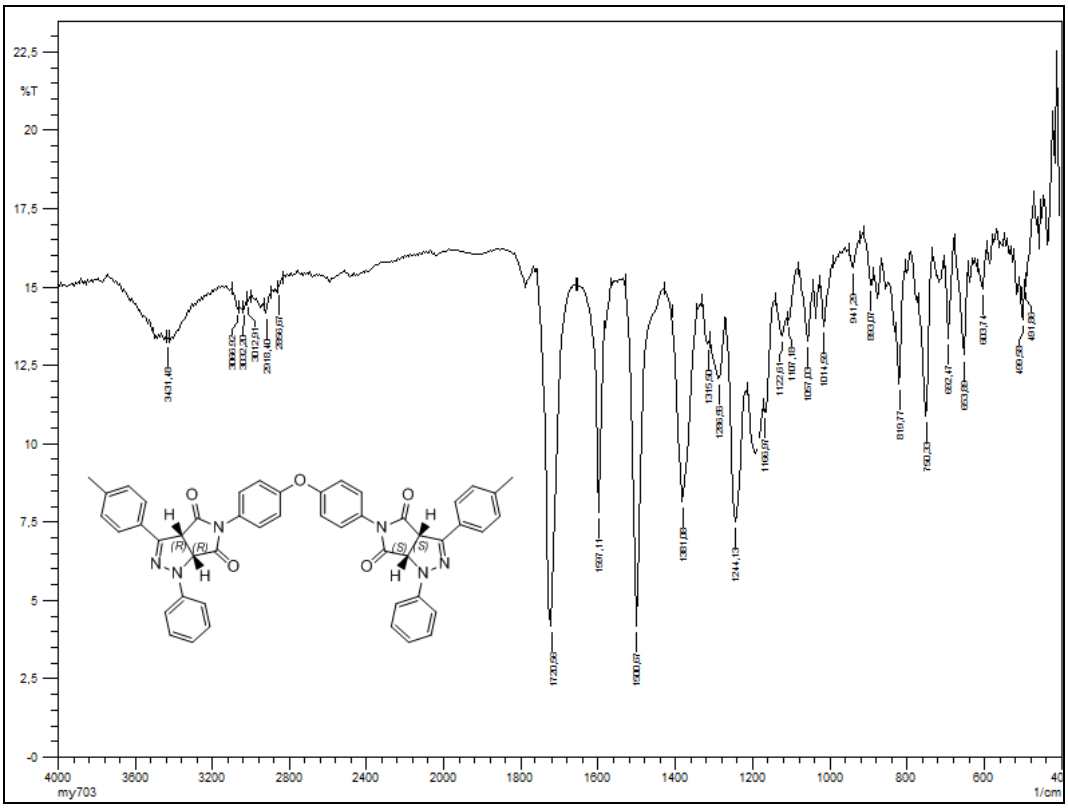

Figure 7.80 IR spectrum of compound **6.14e**

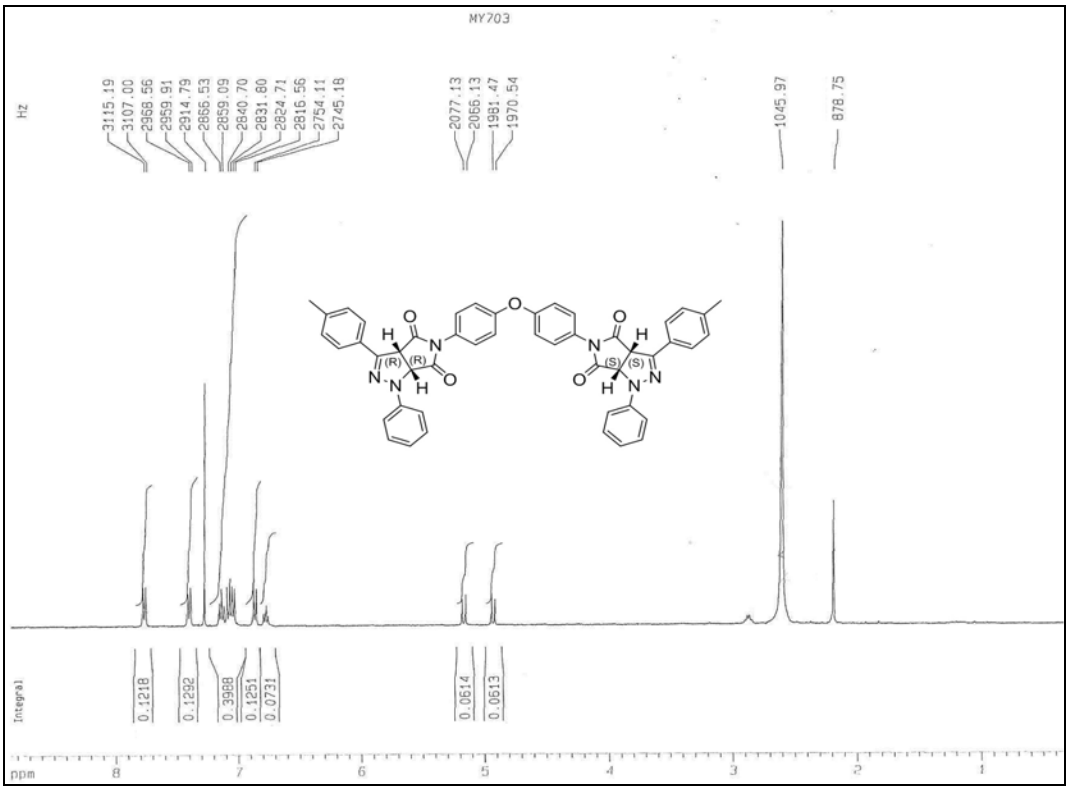

Figure 7.81 ^{1}H-NMR spectrum of compound **6.14e** in DMSO-d_6

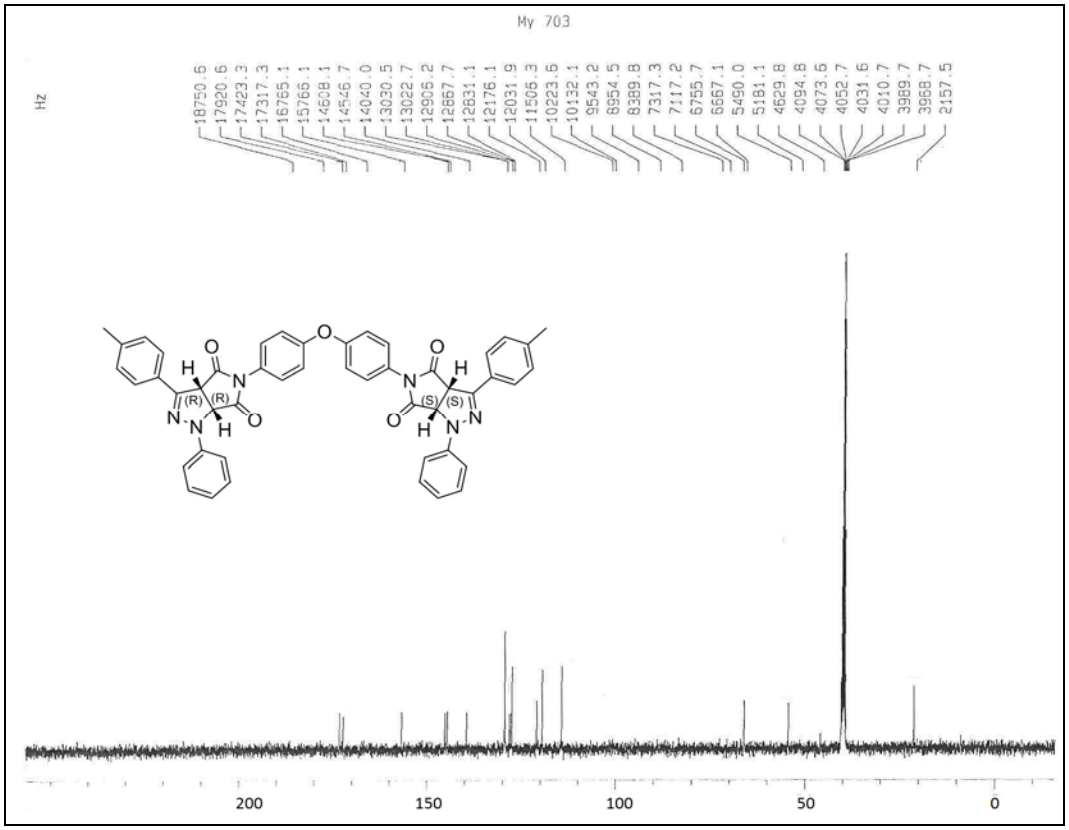

Figure 7.82 ^{13}C-NMR spectrum of compound **6.14e** in DMSO-d_6

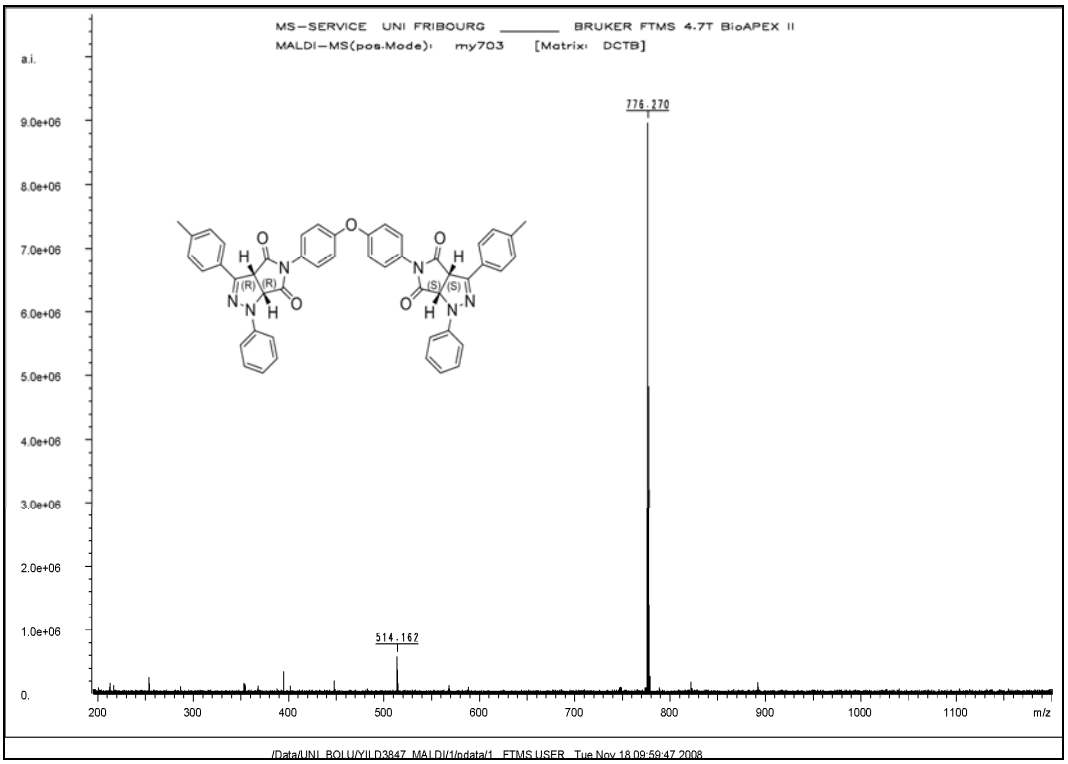

Figure 7.83 Mass spectrum of compound **6.14e**

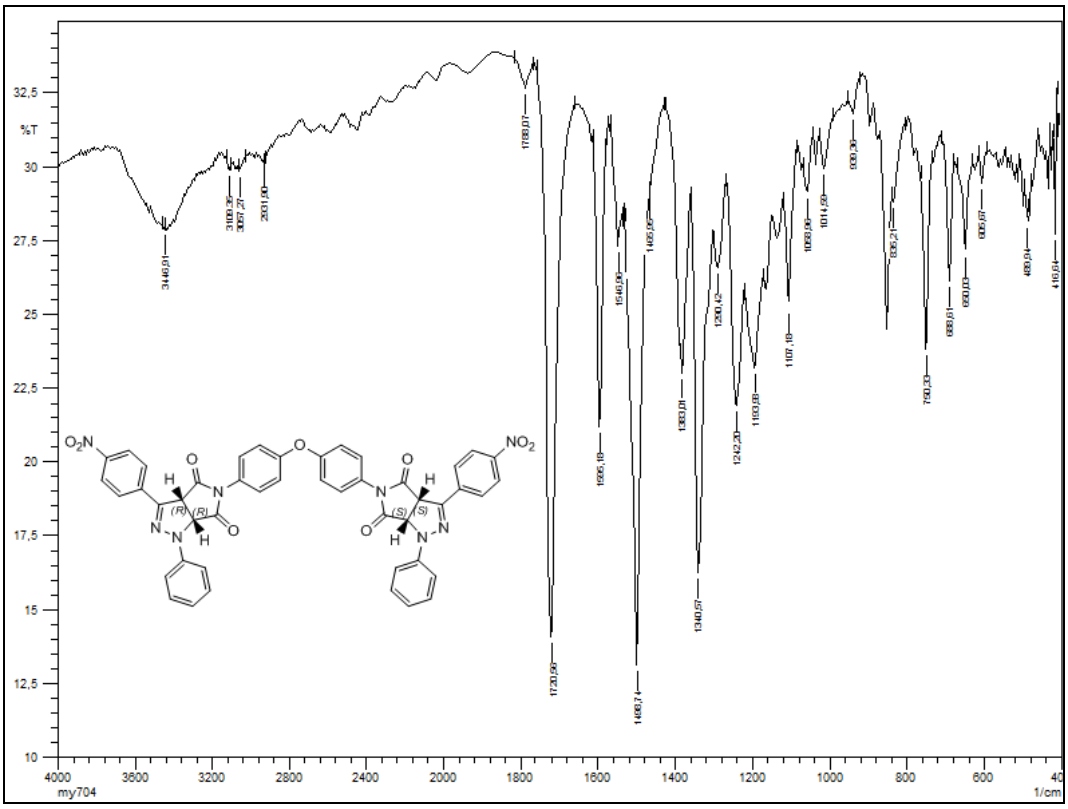

Figure 7.84 IR spectrum of compound **6.14f**

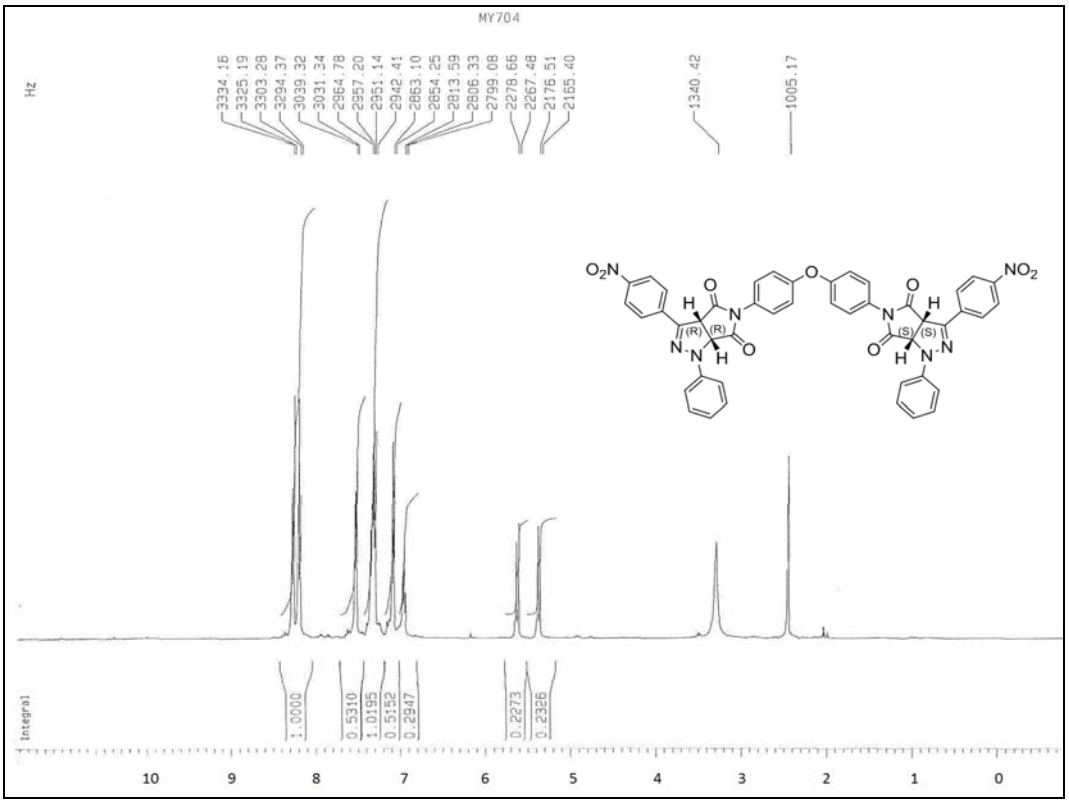

Figure 7.85 ^{1}H-NMR spectrum of compound **6.14f** in DMSO-d_6

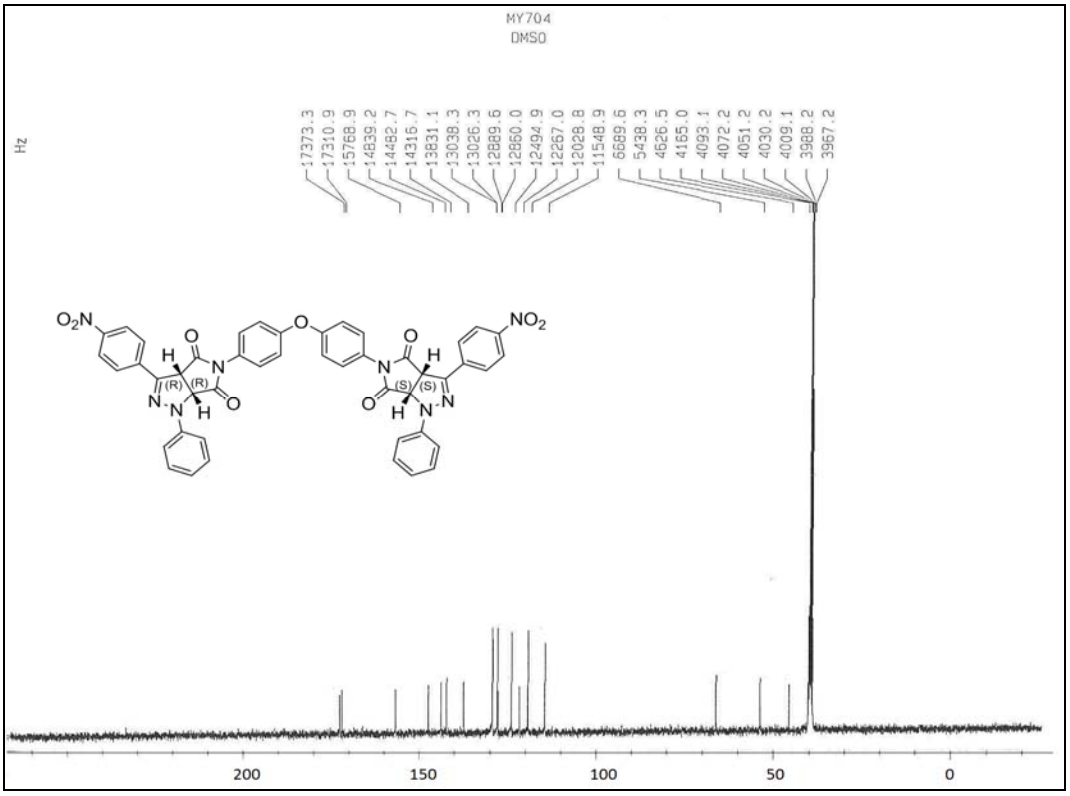

Figure 7.86 ^{13}C-NMR spectrum of compound **6.14f** in DMSO-d_6

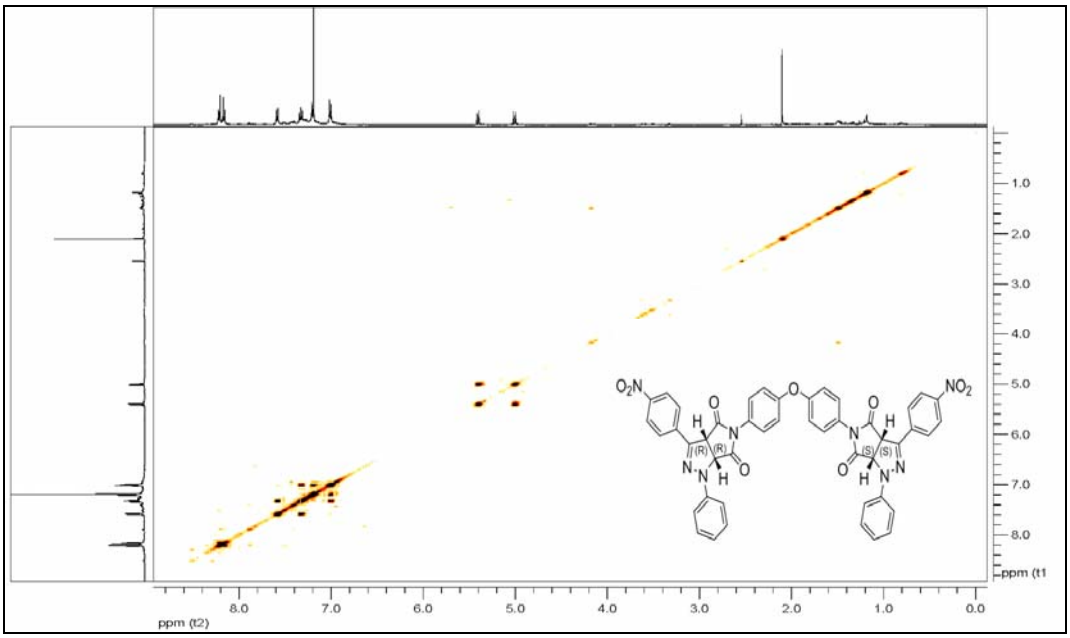

Figure 7.87 COSY-NMR spectrum of compound **6.14f** in DMSO-d_6

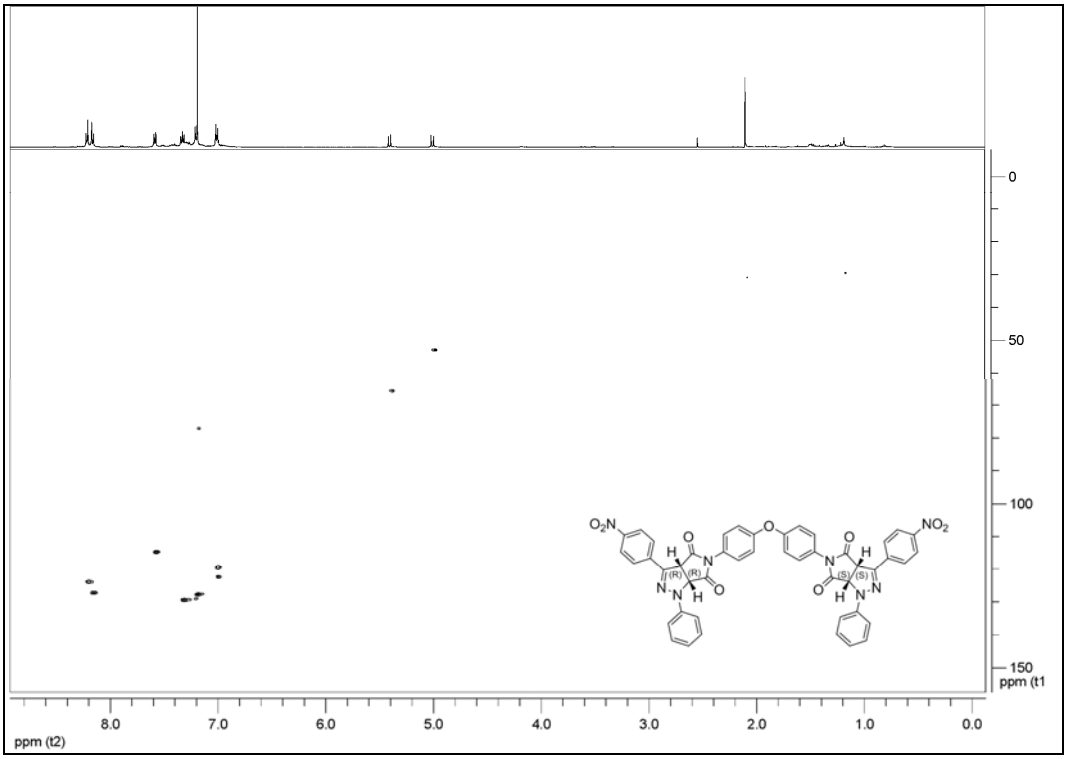

Figure 7.88 HSQC-NMR spectrum of compound **6.14f** in DMSO-d_6

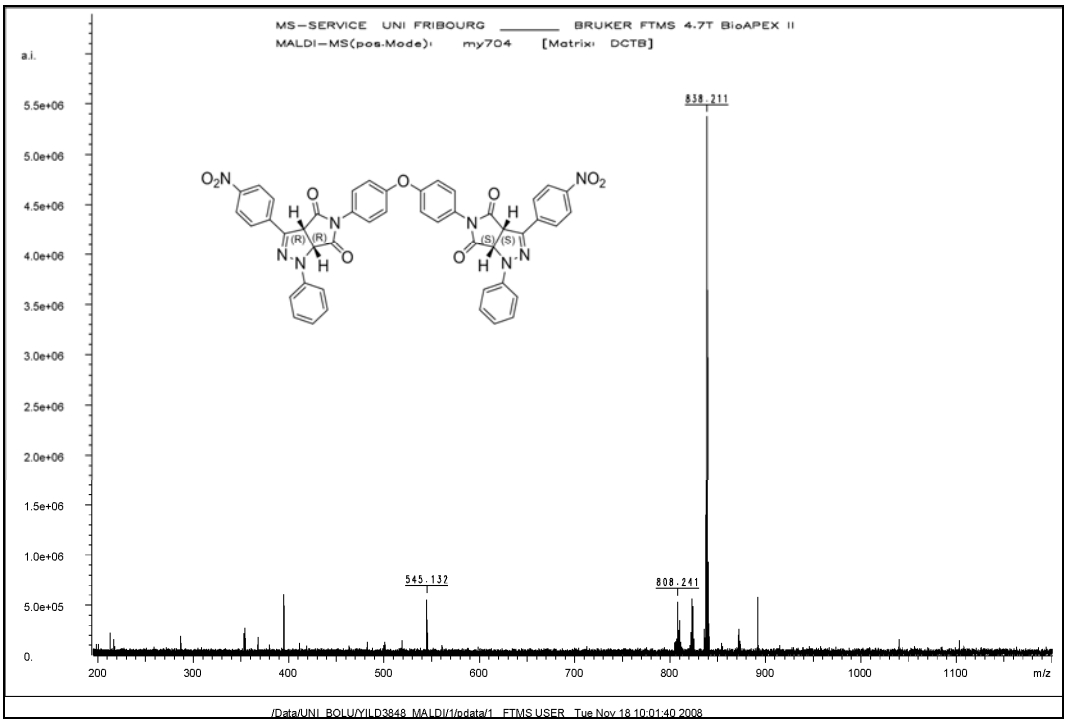

Figure 7.89 Mass spectrum of compound **6.14f**

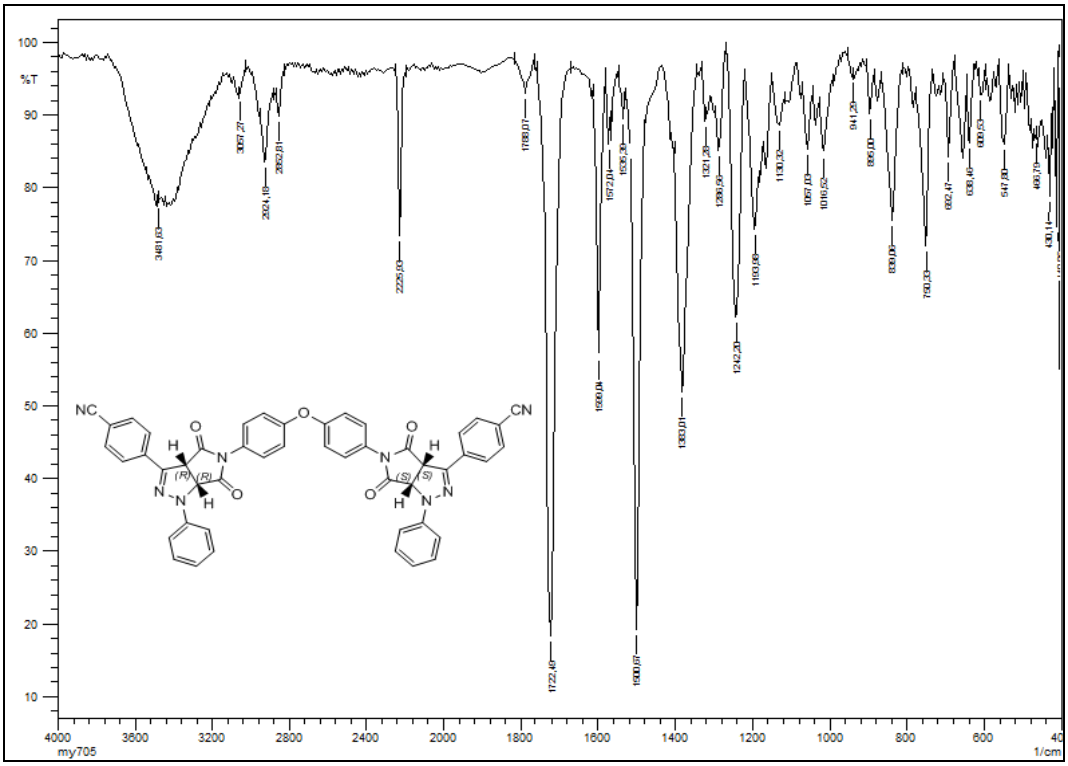

Figure 7.90 IR spectrum of compound **6.14g**

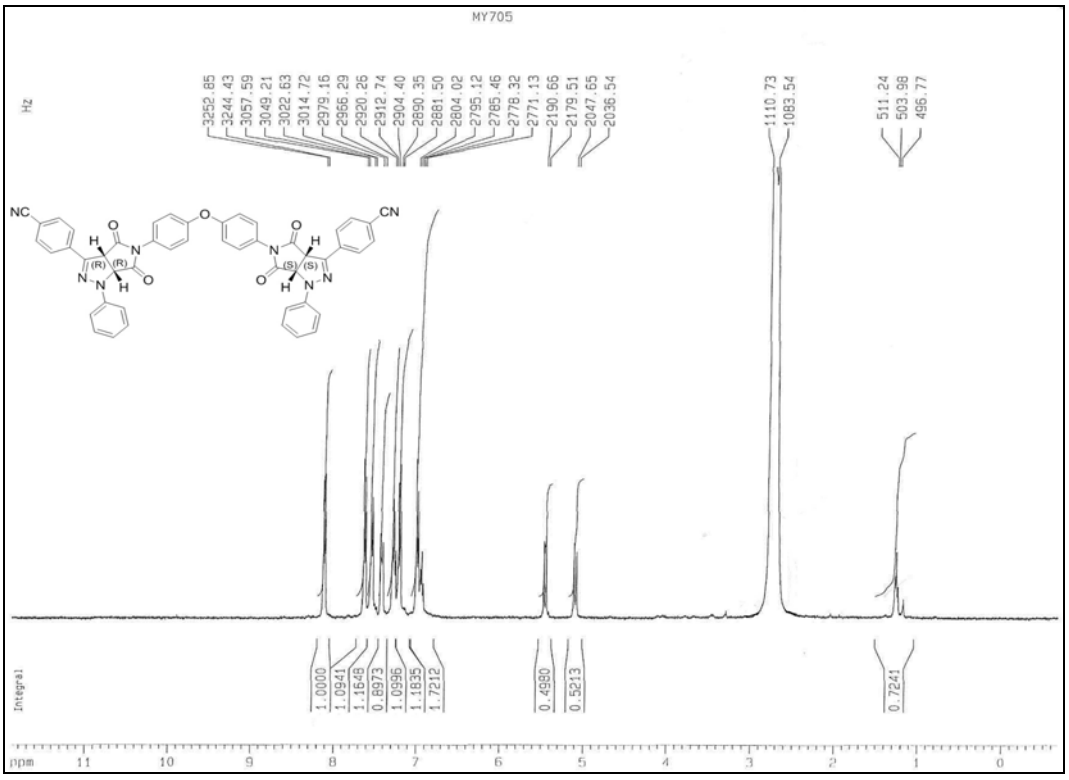

Figure 7.91 ^{1}H-NMR spectrum of compound **6.14g** in $CDCl_3$-DMSO-d_6

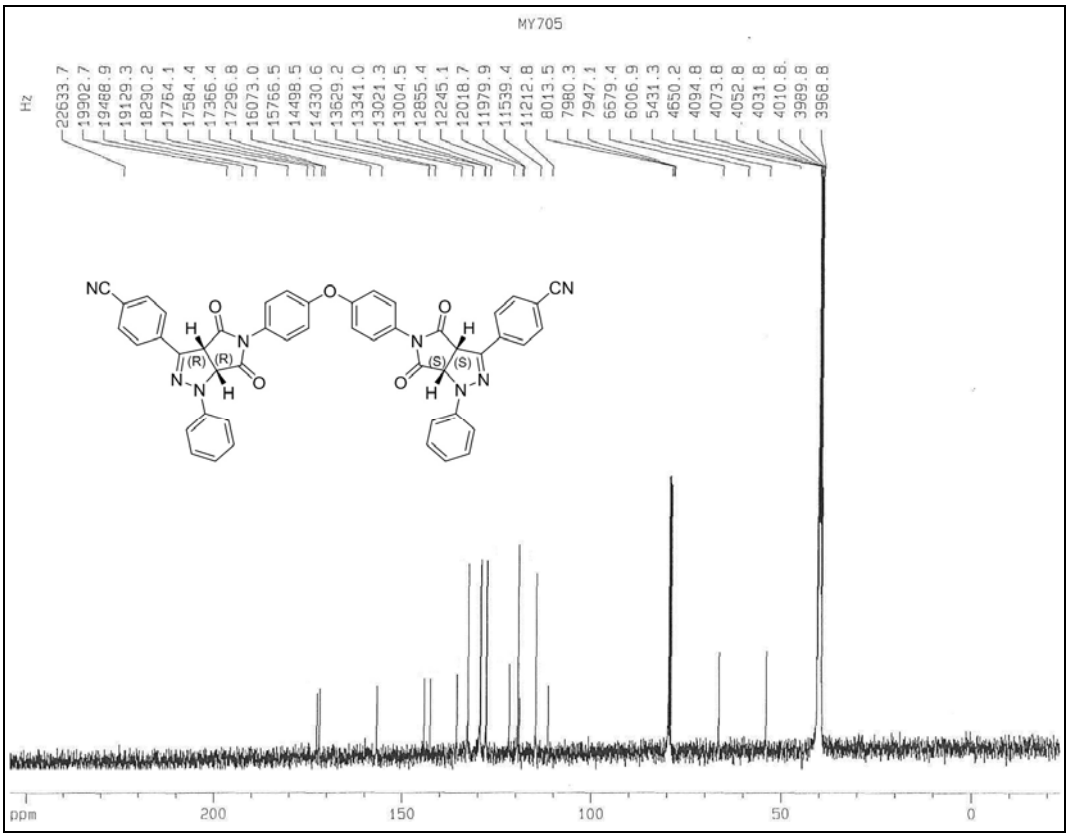

Figure 7.92 ^{13}C-NMR spectrum of compound **6.14g** in $CDCl_3$-DMSO-d_6

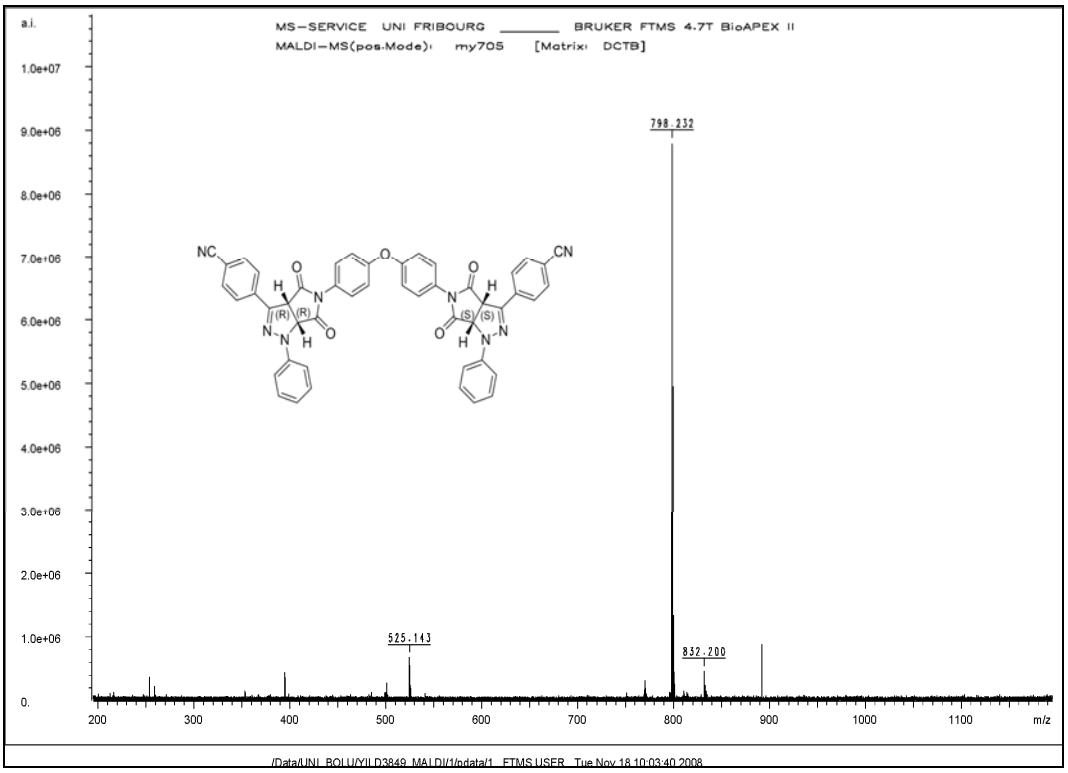

Figure 7.93 Mass spectrum of compound **6.14g**

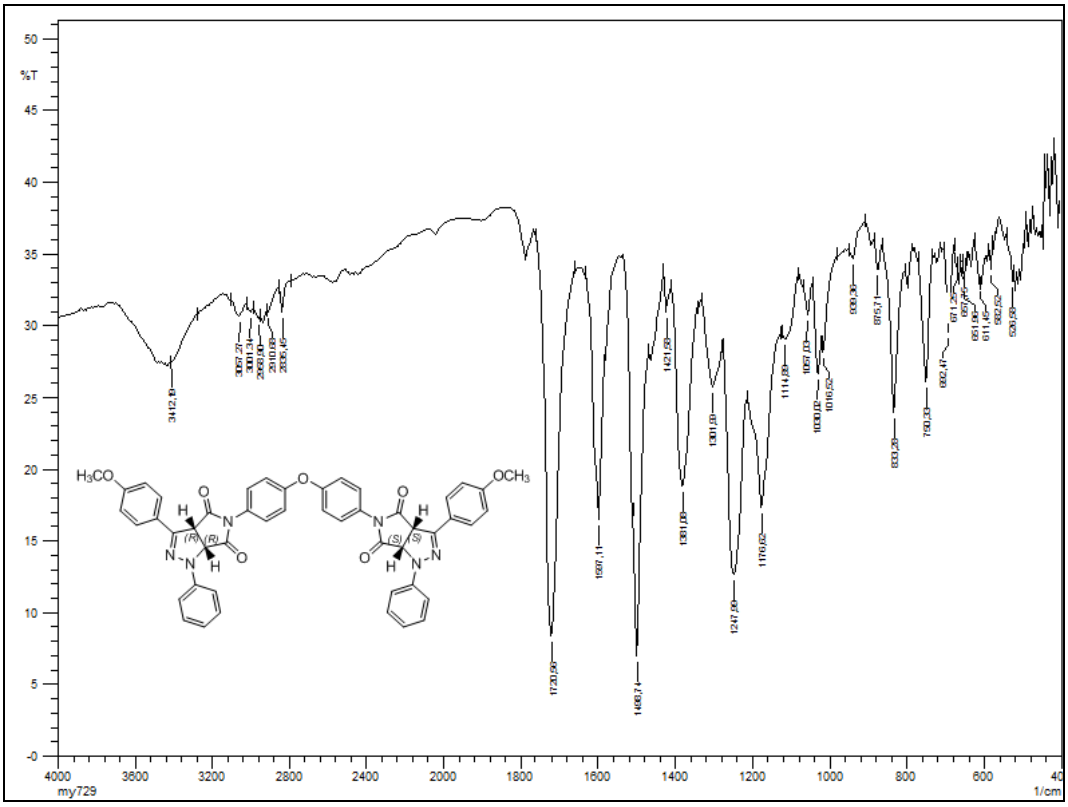

Figure 7.94 IR spectrum of compound **6.14h**

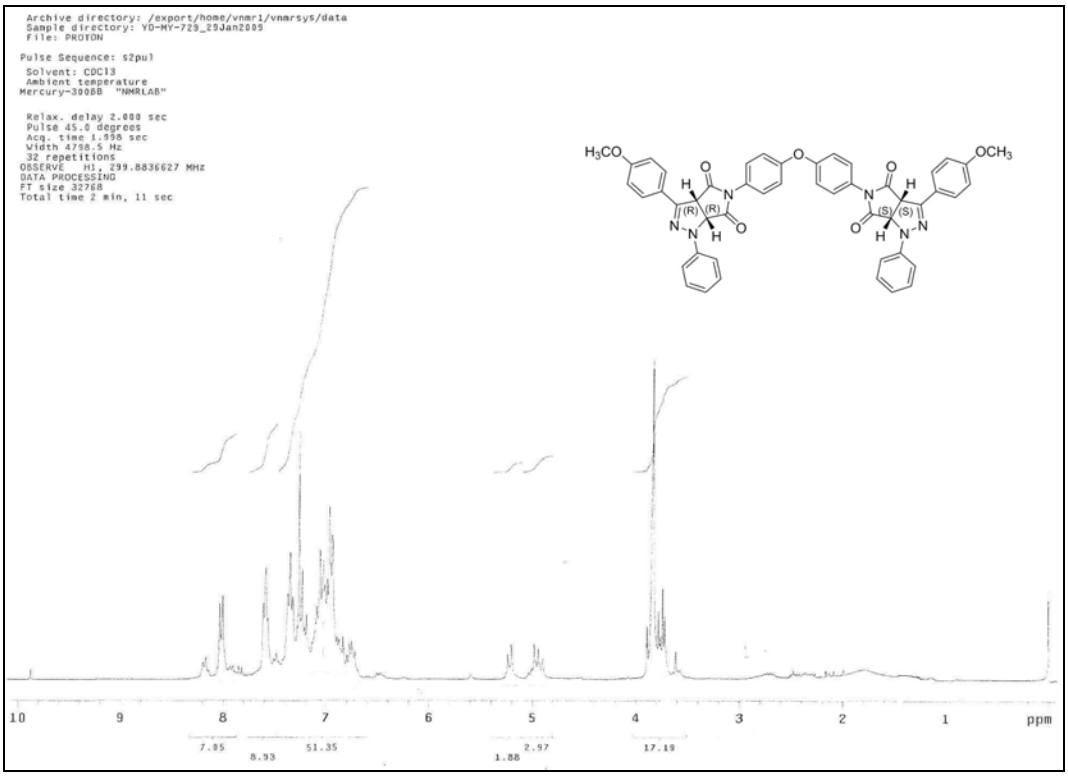

Figure 7.95 ^{1}H-NMR spectrum of compound **6.14h** in $CDCl_3$

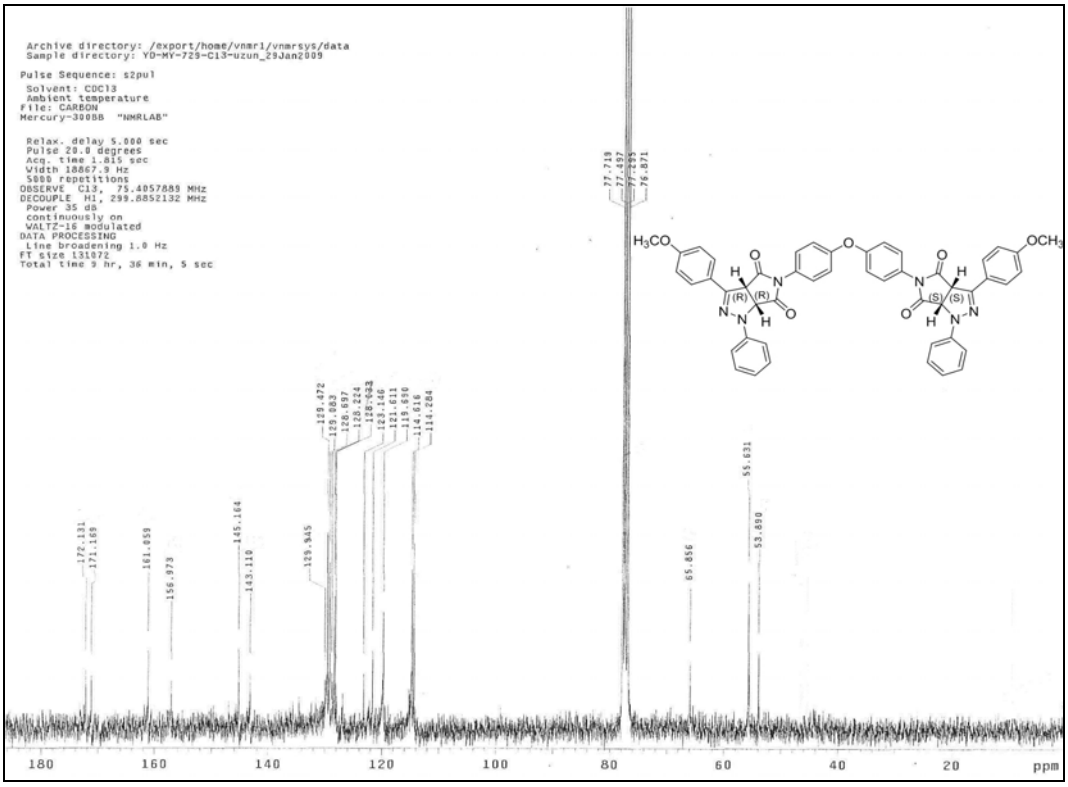

Figure 7.96 ^{13}C-NMR spectrum of compound **6.14h** in $CDCl_3$

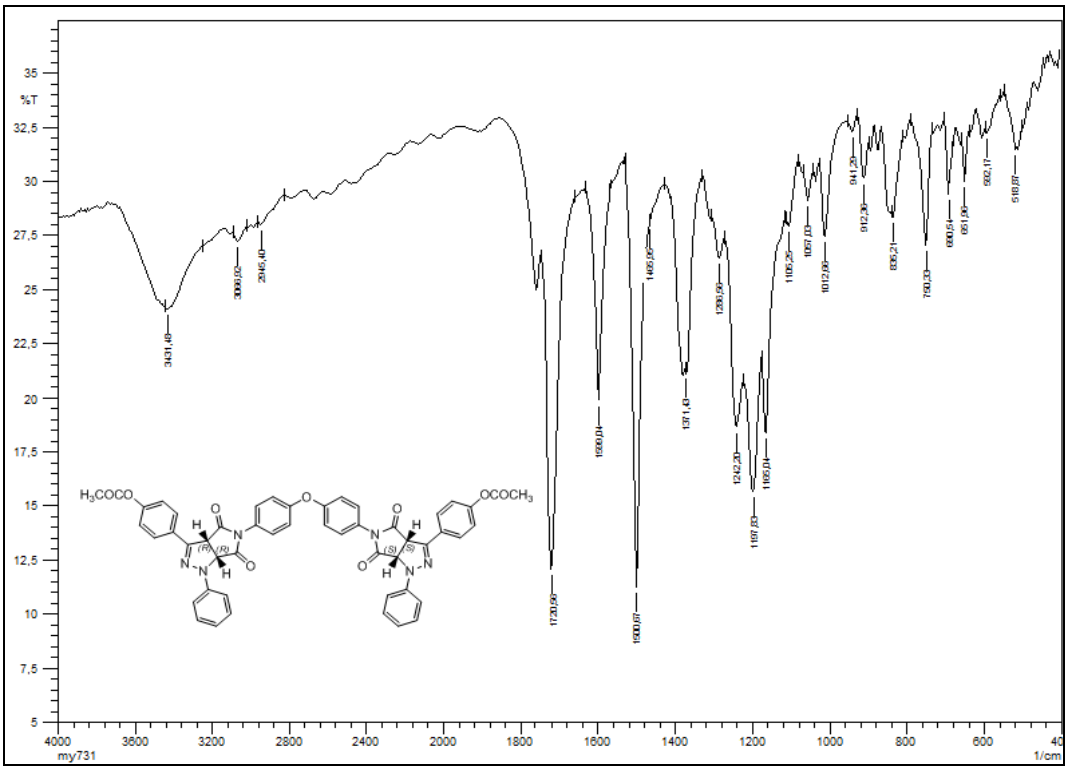

Figure 7.97 IR spectrum of compound **6.14j**

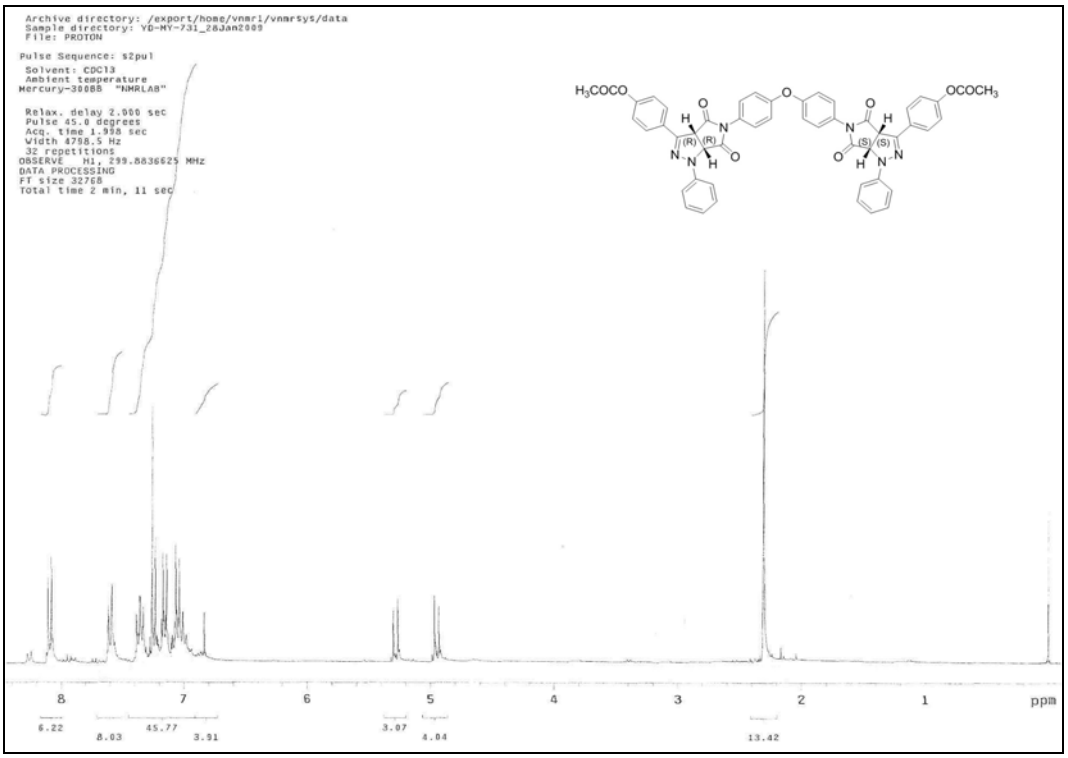

Figure 7.98 ^{1}H-NMR spectrum of compound **6.14j** in $CDCl_3$

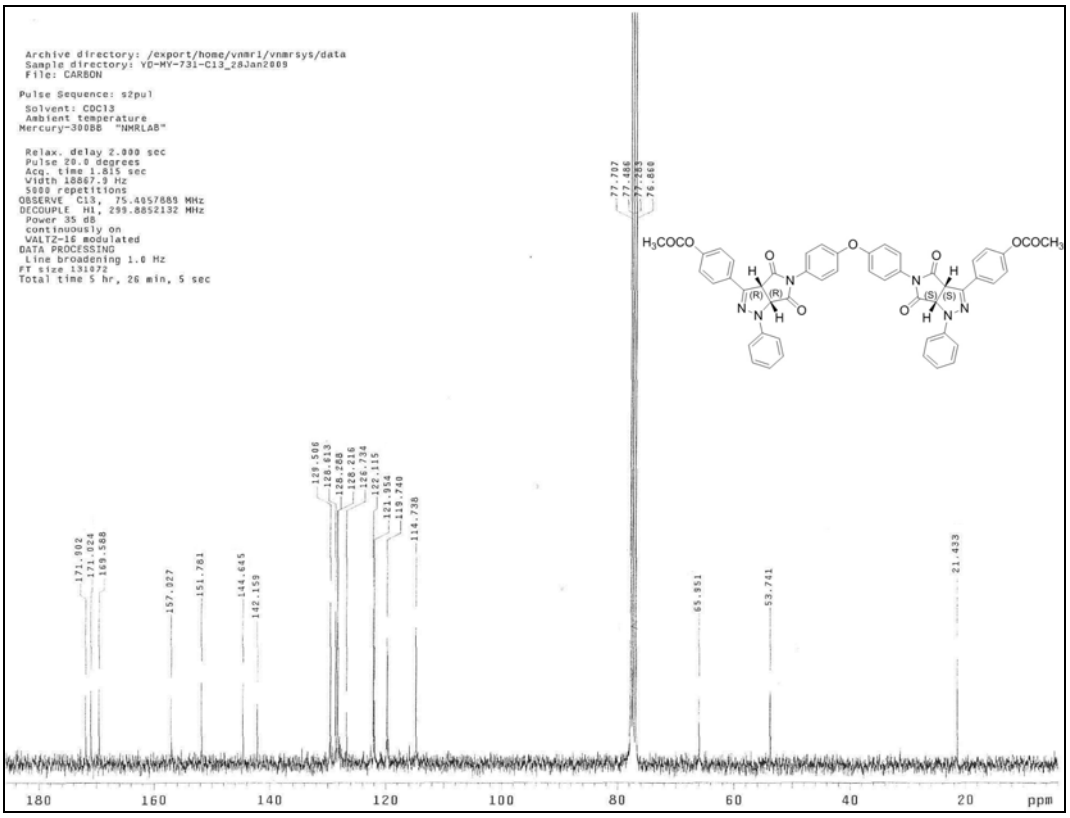

Figure 7.99 ^{13}C-NMR spectrum of compound **6.14j** in $CDCl_3$

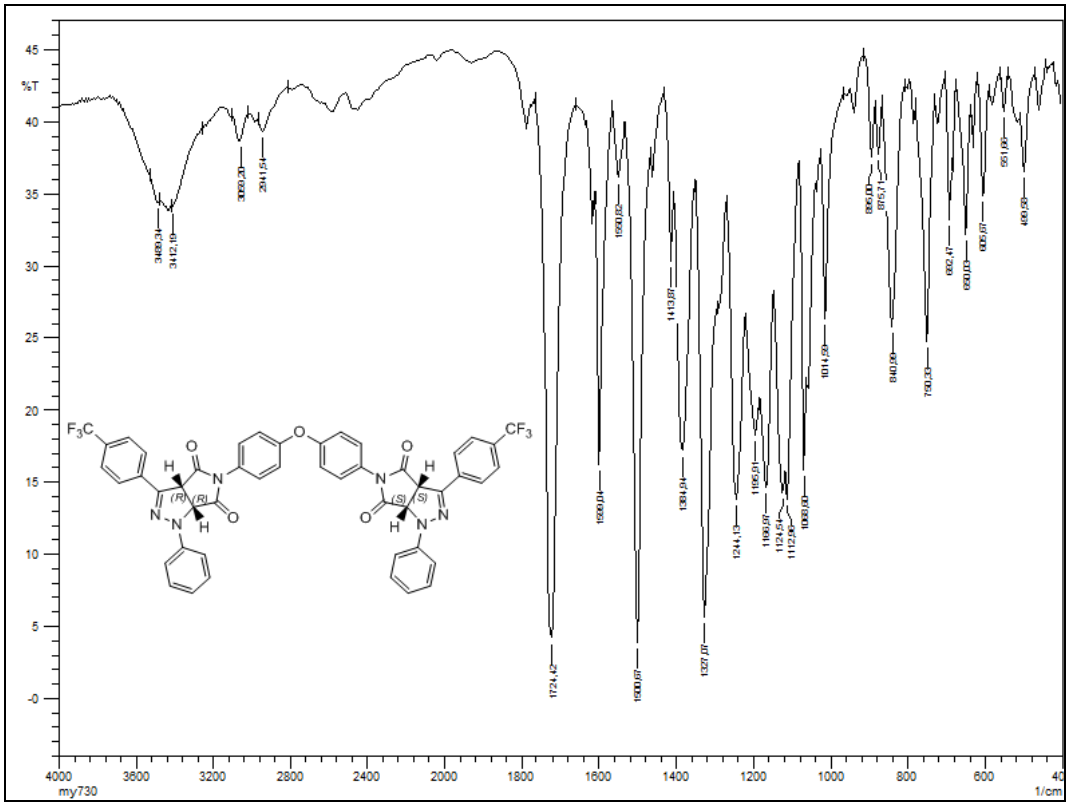

Figure 7.100 IR spectrum of compound **6.14k**

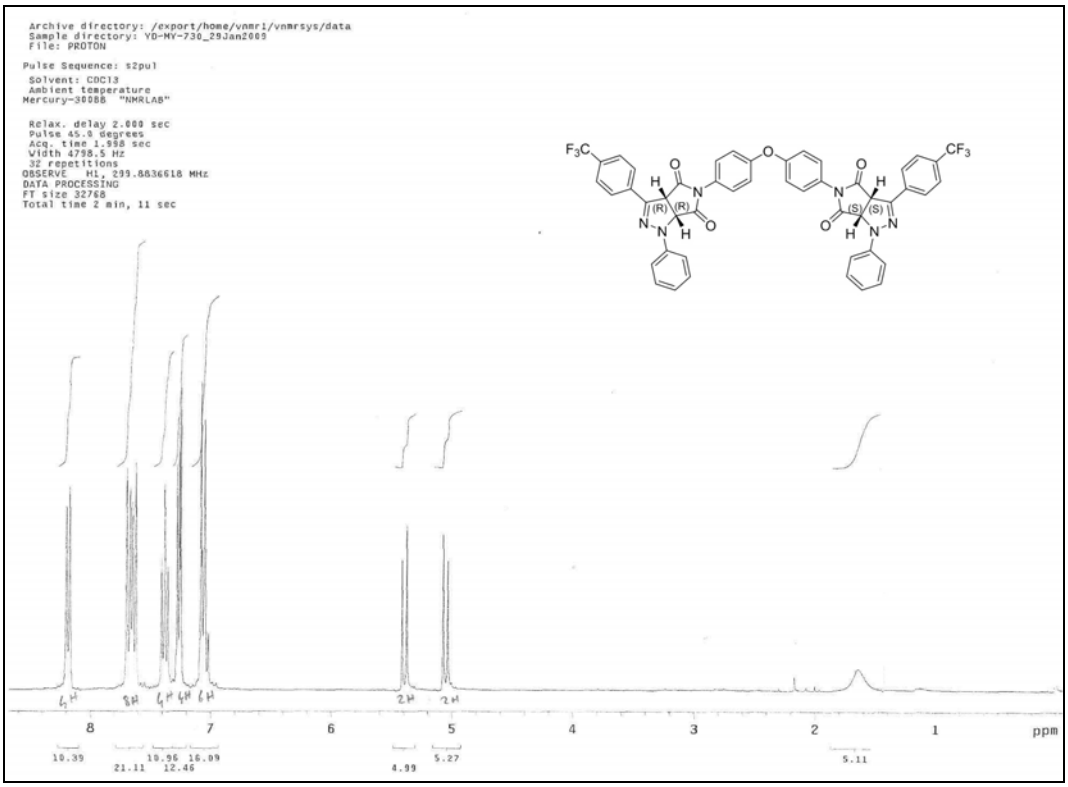

Figure 7.101 ^{1}H-NMR spectrum of compound **6.14k** in $CDCl_3$

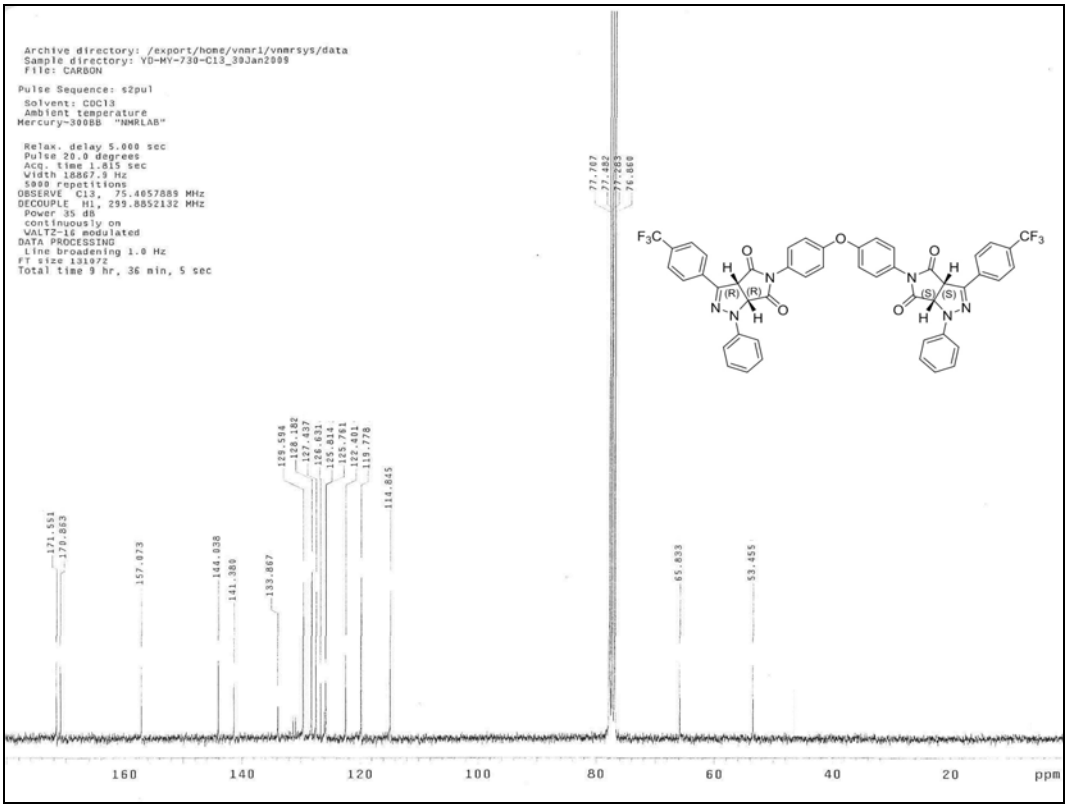

Figure 7.102 ^{13}C-NMR spectrum of compound **6.14k** in $CDCl_3$

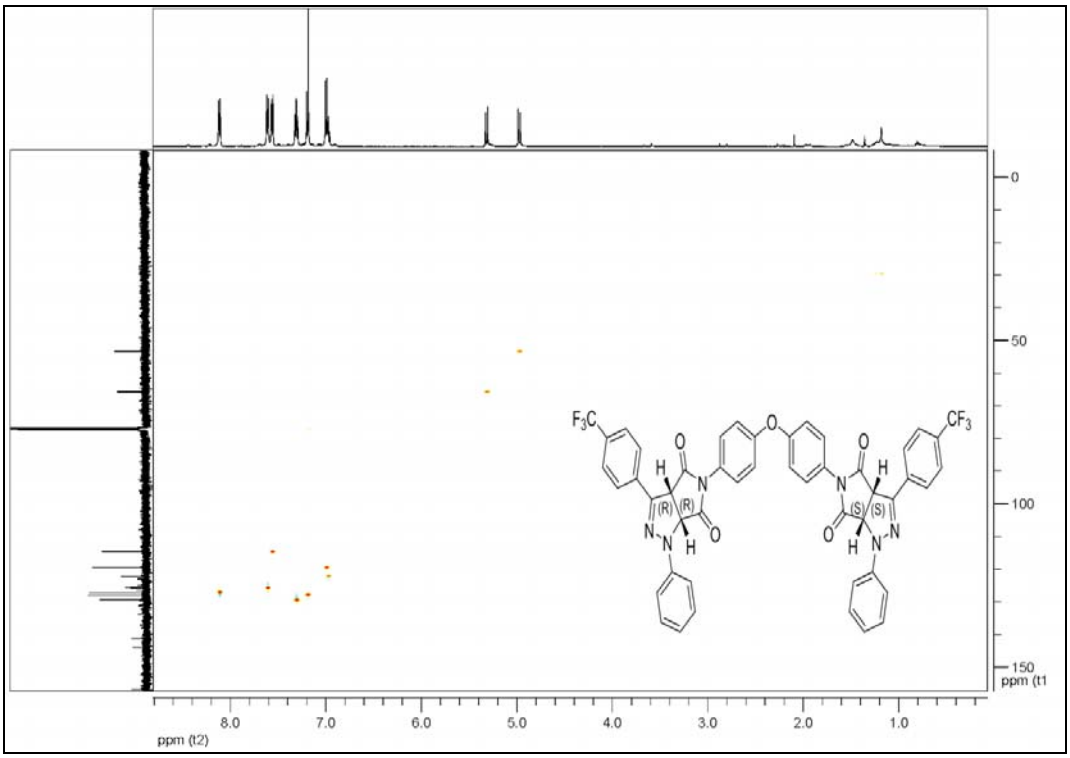

Figure 7.103 HSQC-NMR spectrum of compound **6.14k** in $CDCl_3$

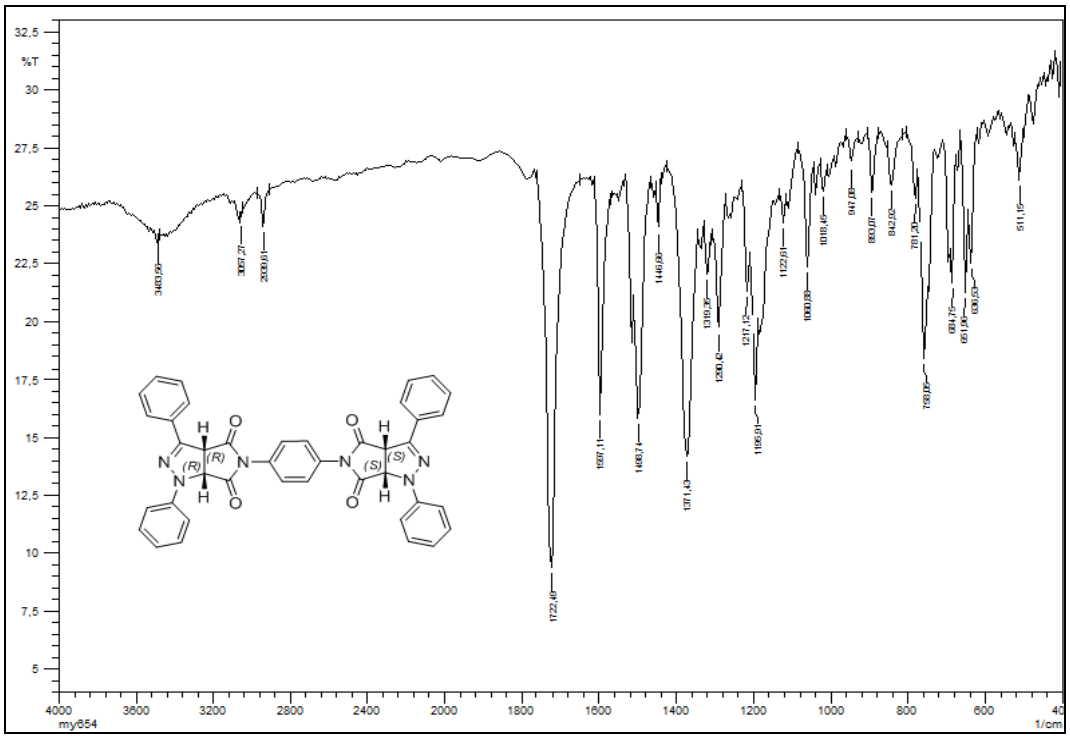

Figure 7.104 IR spectrum of compound **6.15a**

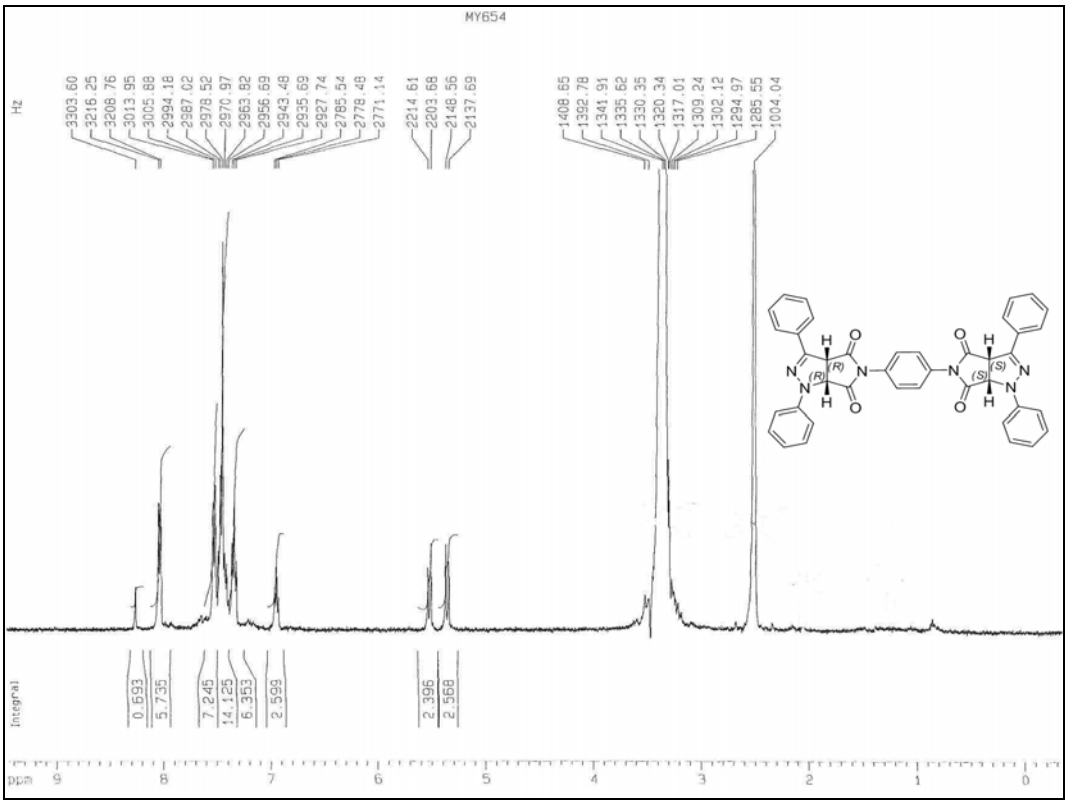

Figure 7.105 ^{1}H-NMR spectrum of compound **6.15a** in DMSO-d_6

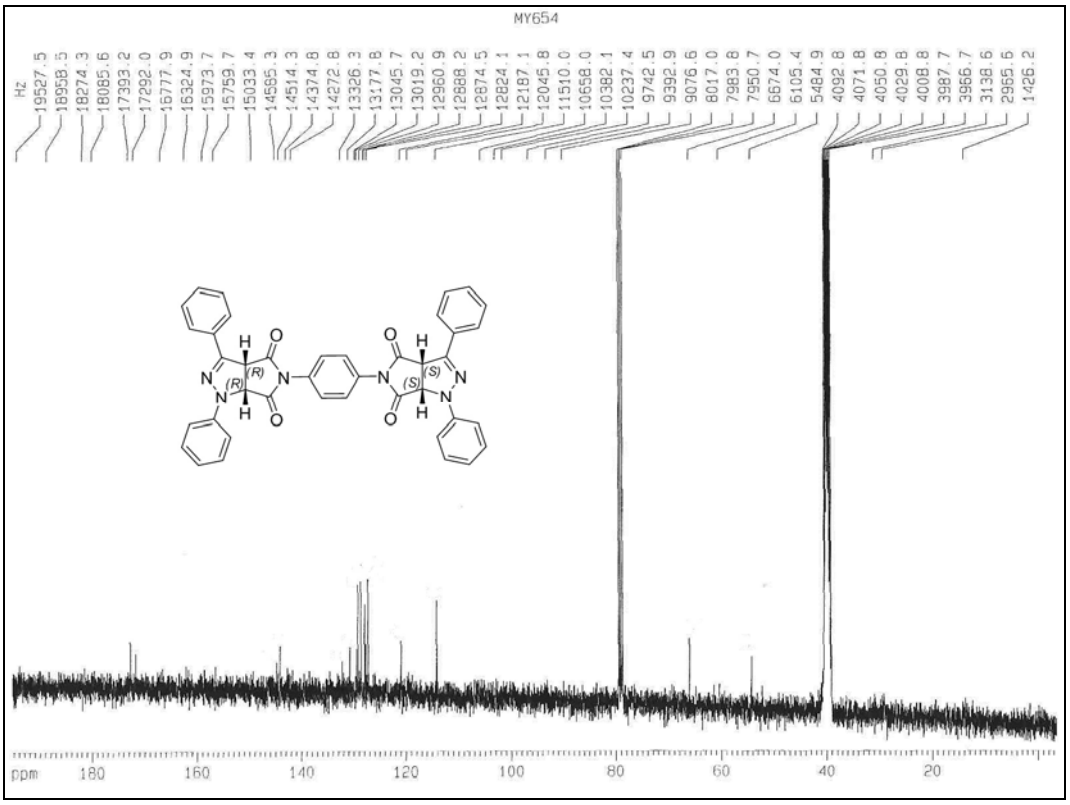

Figure 7.106 ^{13}C-NMR spectrum of compound **6.15a** in DMSO-d_6

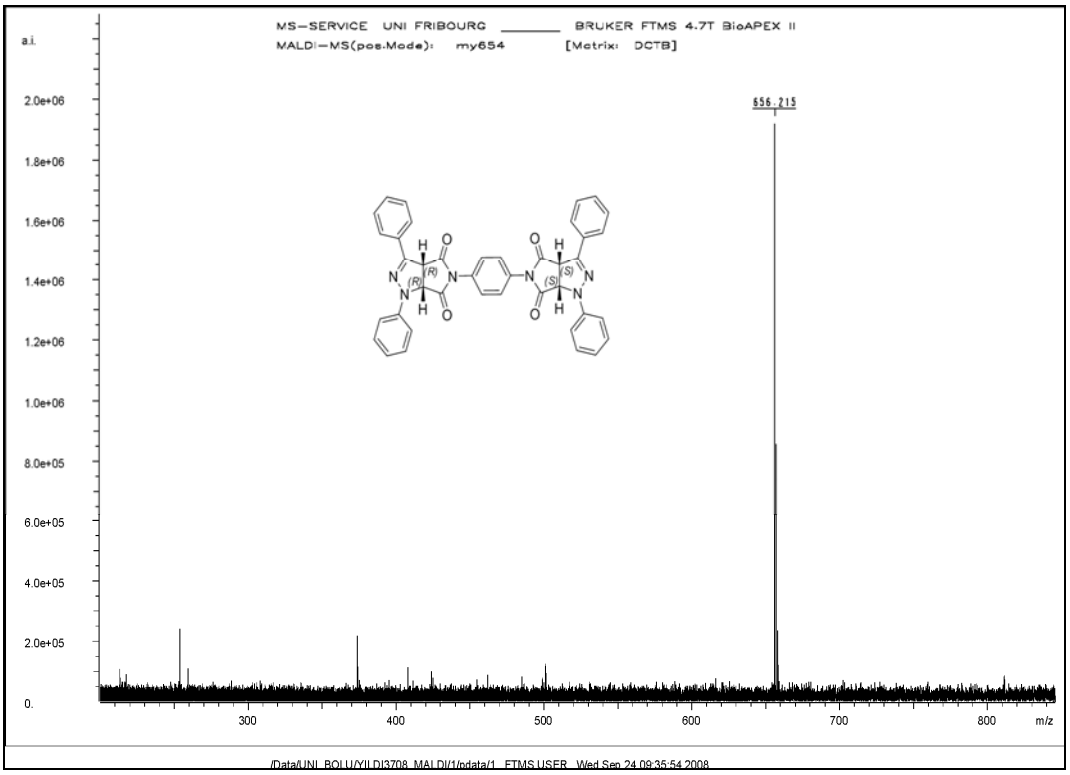

Figure 7.107 Mass spectrum of compound **6.15a**

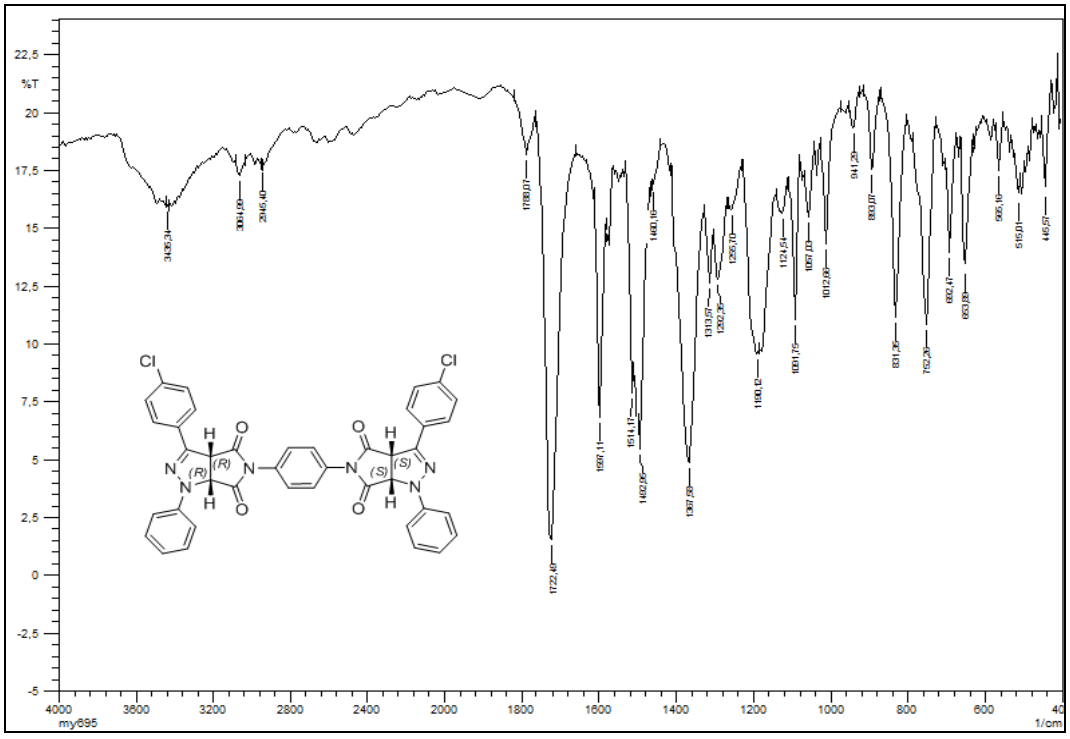

Figure 7.108 IR spectrum of compound **6.15b**

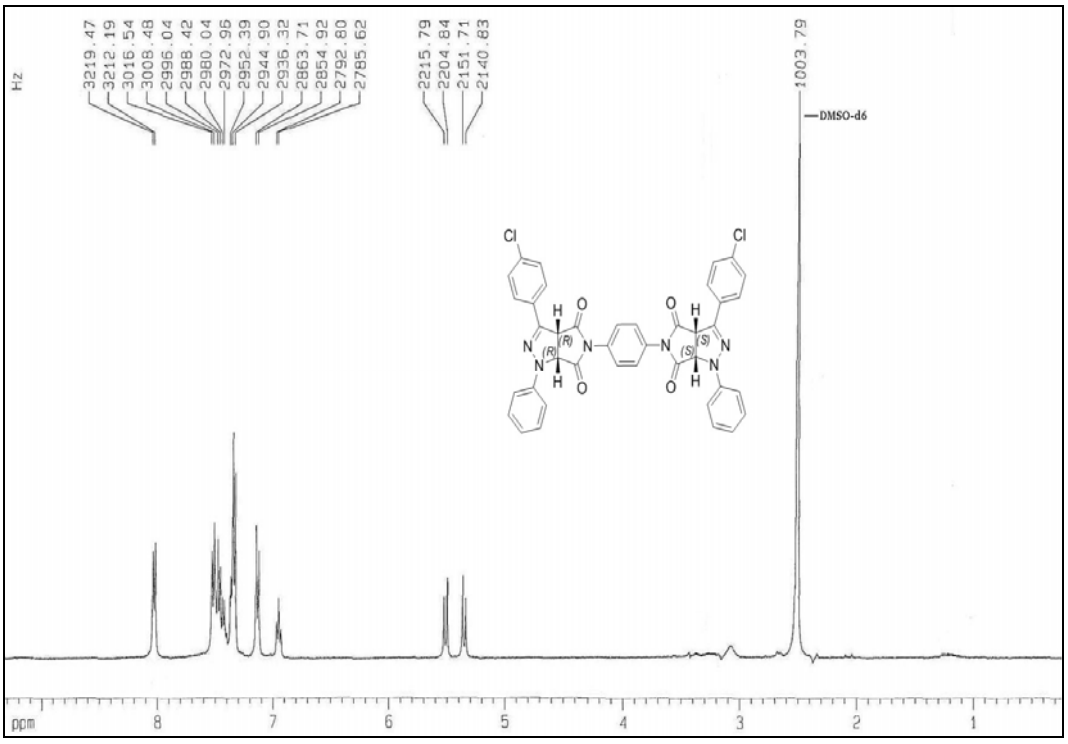

Figure 7.109 ^{1}H-NMR spectrum of compound **6.15b** in DMSO-d_6

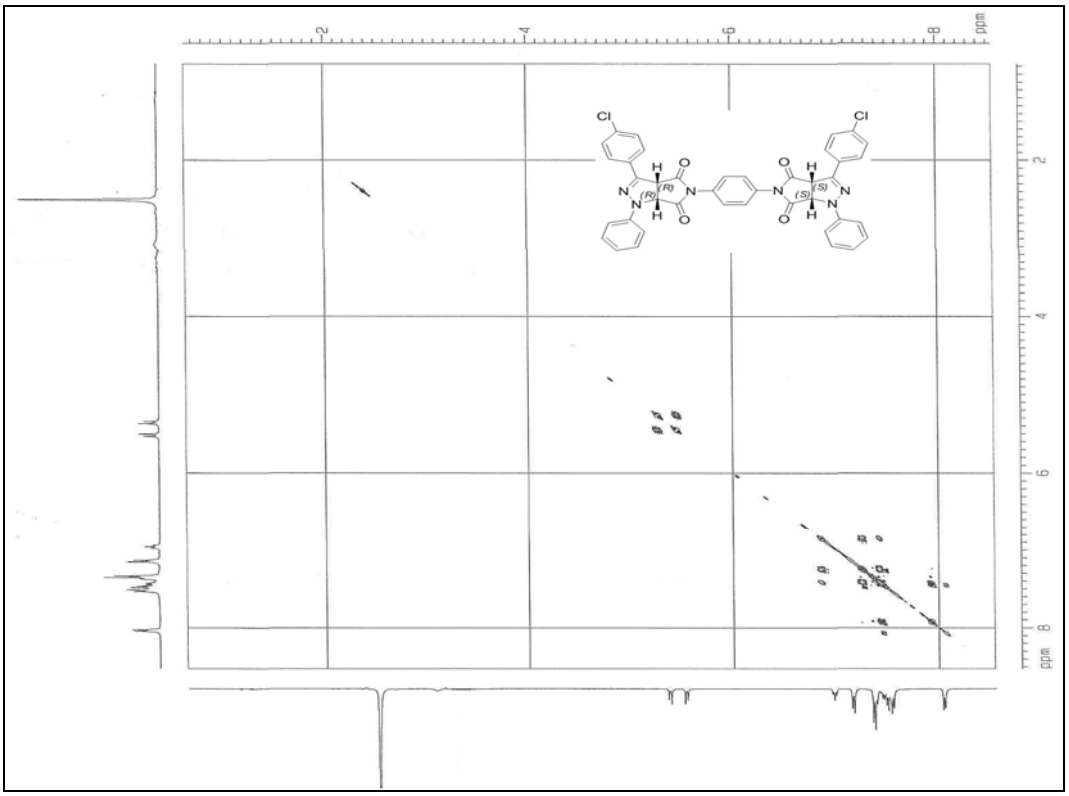

Figure 7.110 COSY-NMR spectrum of compound **6.15b** in DMSO-d_6

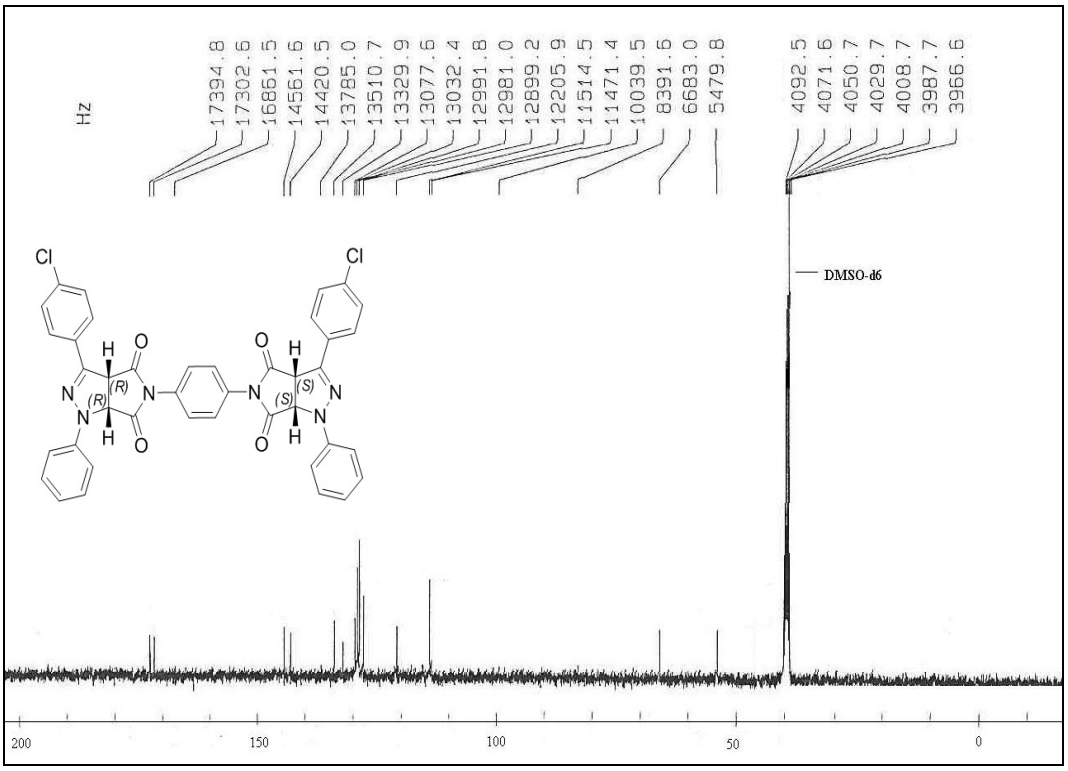

Figure 7.111 ^{13}C-NMR spectrum of compound **6.15b** in DMSO-d_6

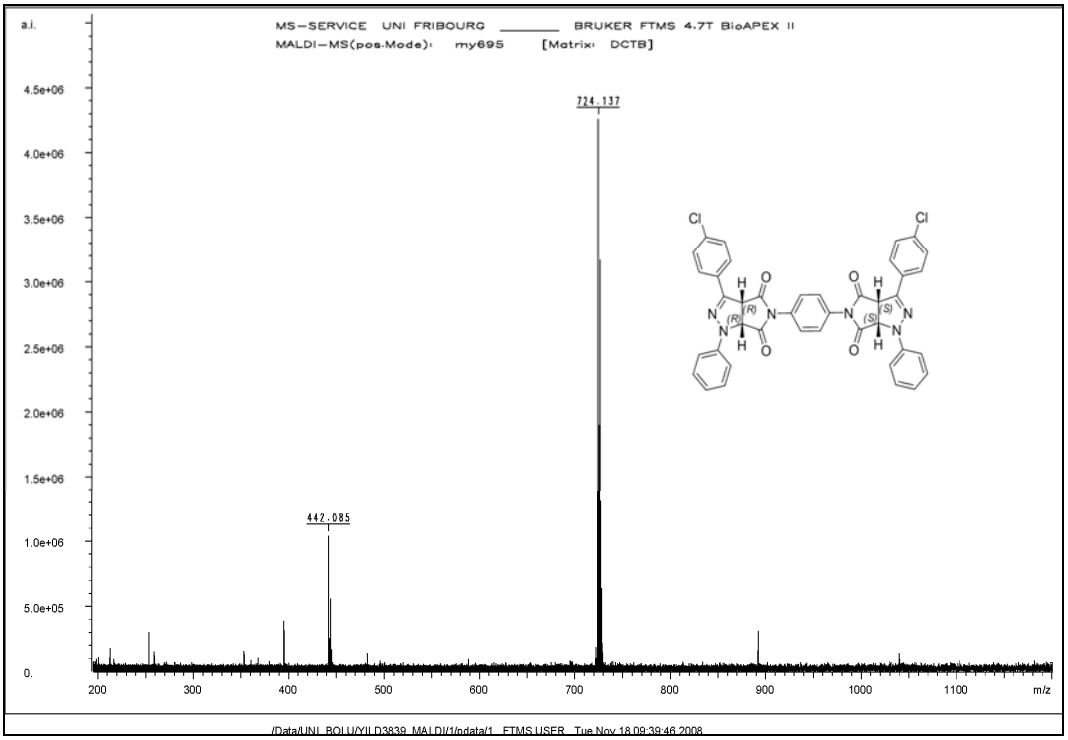

Figure 7.112 Mass spectrum of compound **6.15b**

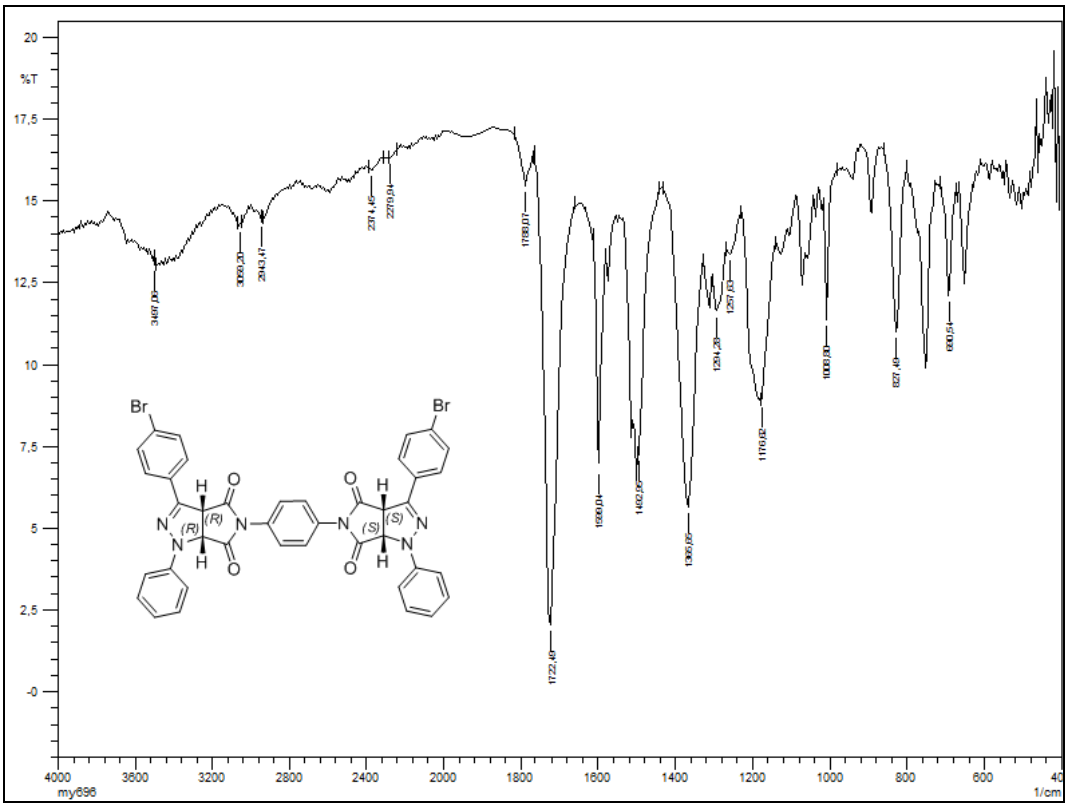

Figure 7.113 IR spectrum of compound **6.15c**

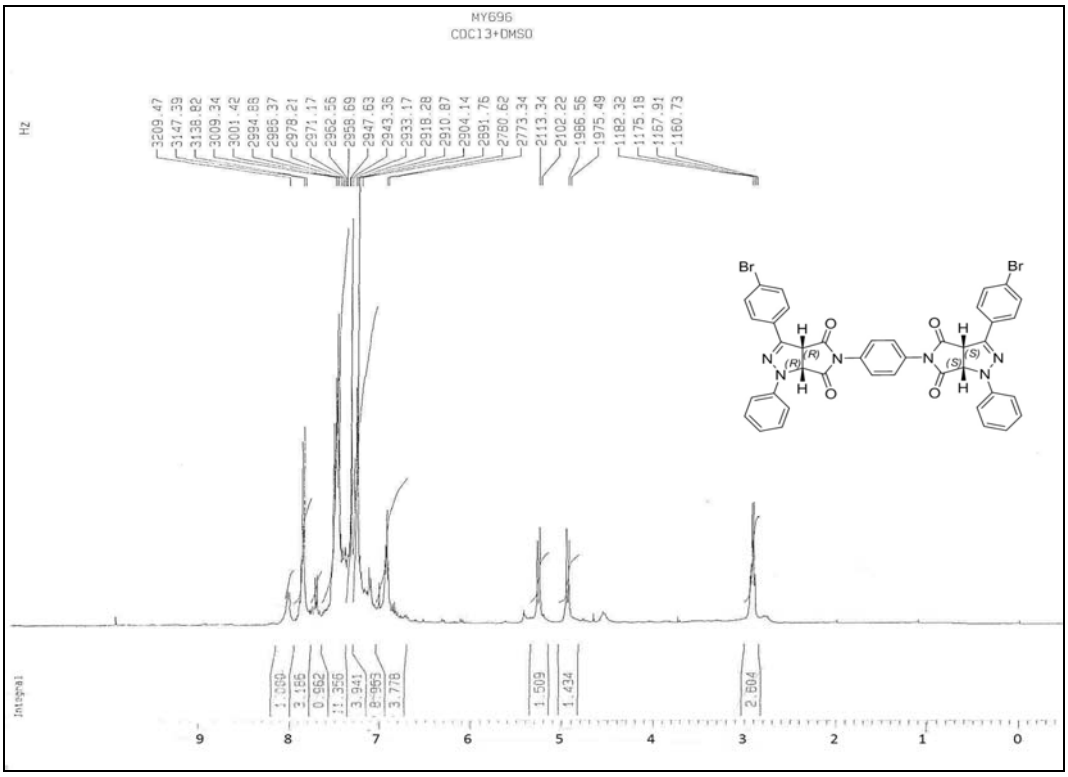

Figure 7.114 ^{1}H-NMR spectrum of compound **6.15c** in $CDCl_3$

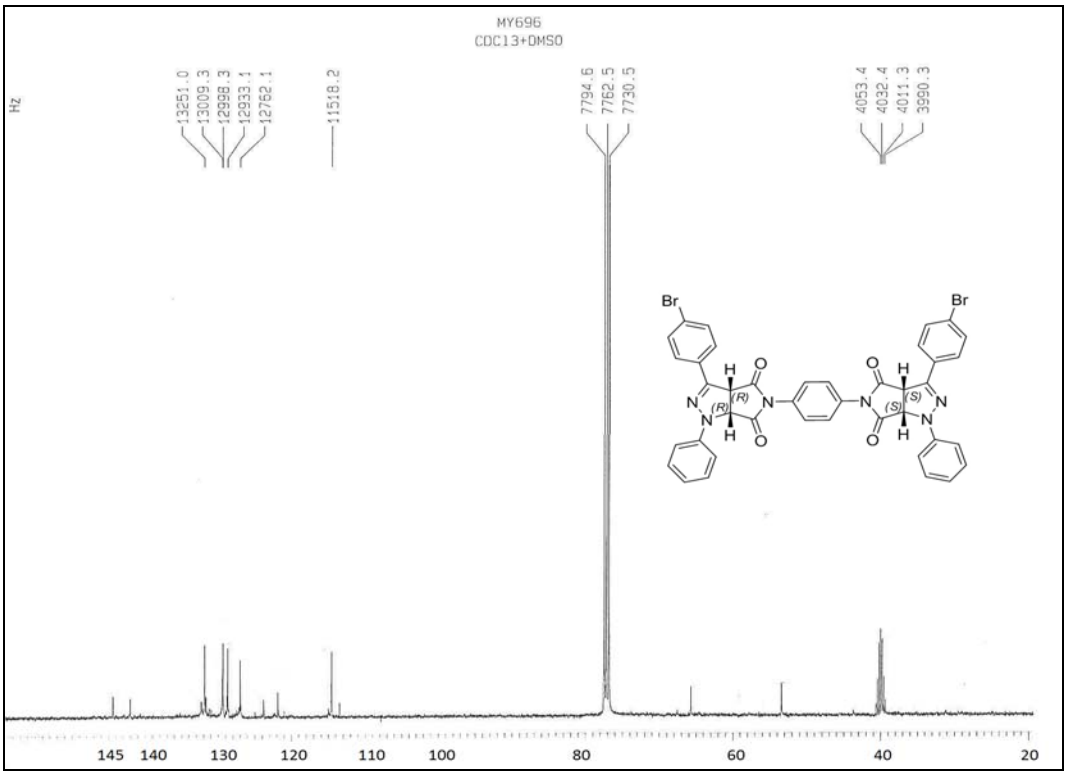

Figure 7.115 ^{13}C-NMR spectrum of compound **6.15c** in $CDCl_3$

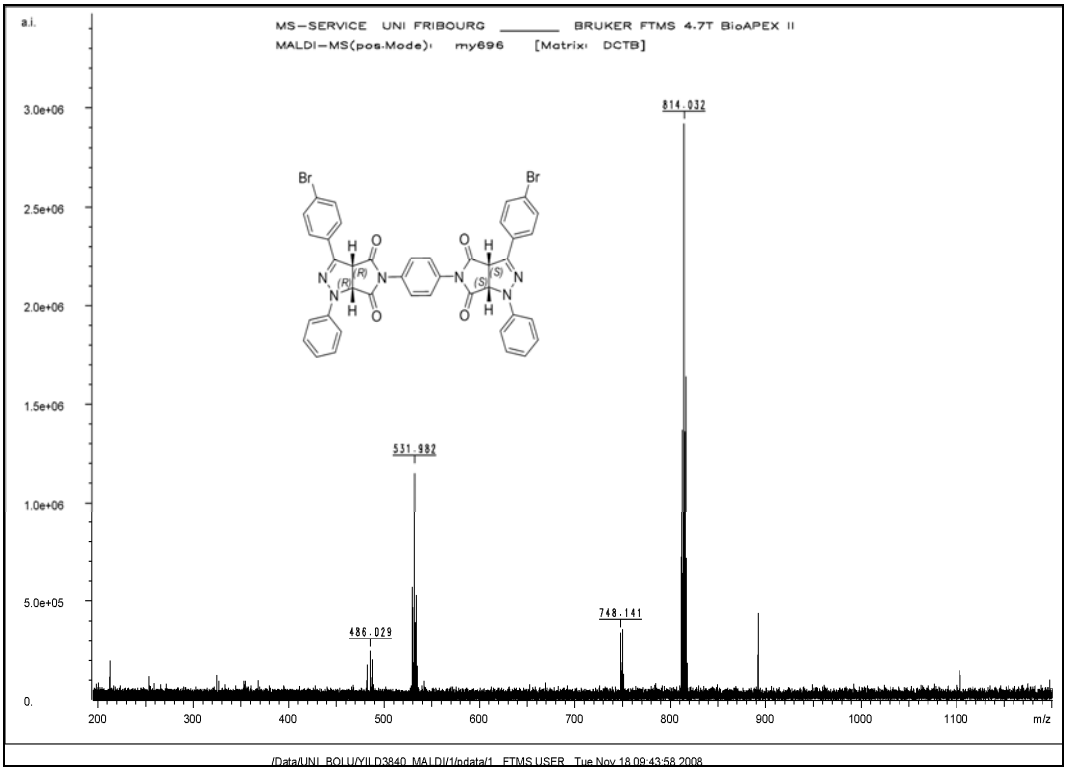

Figure 7.116 Mass spectrum of compound **6.15c**

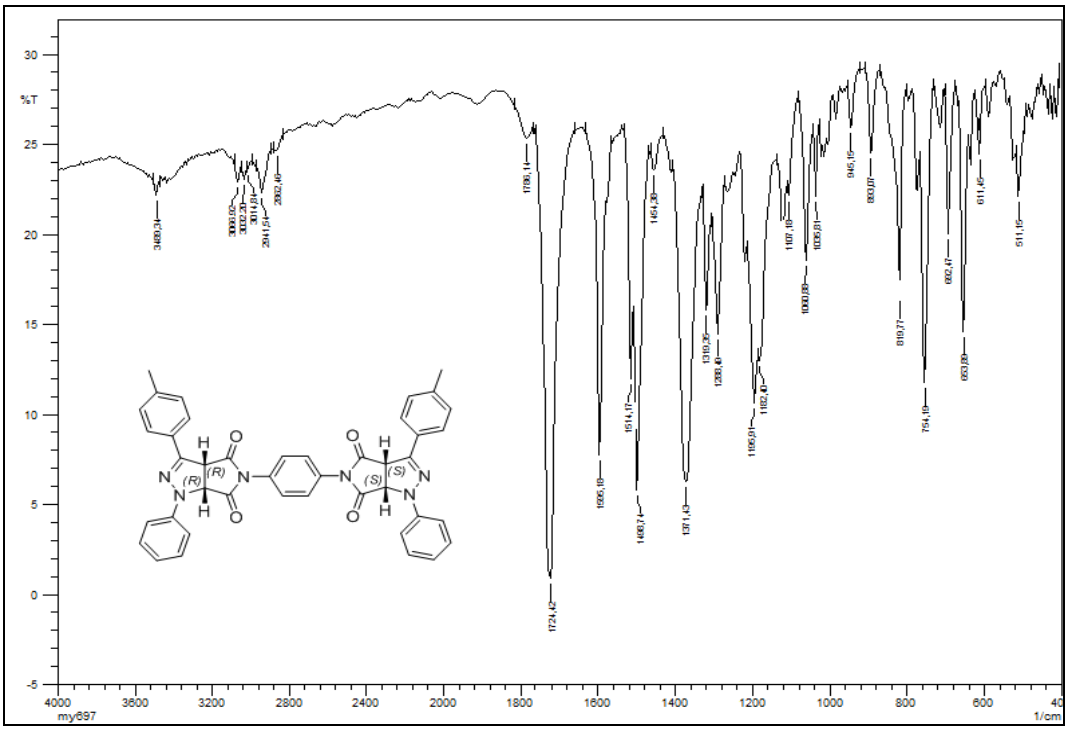

Figure 7.117 IR spectrum of compound **6.15e**

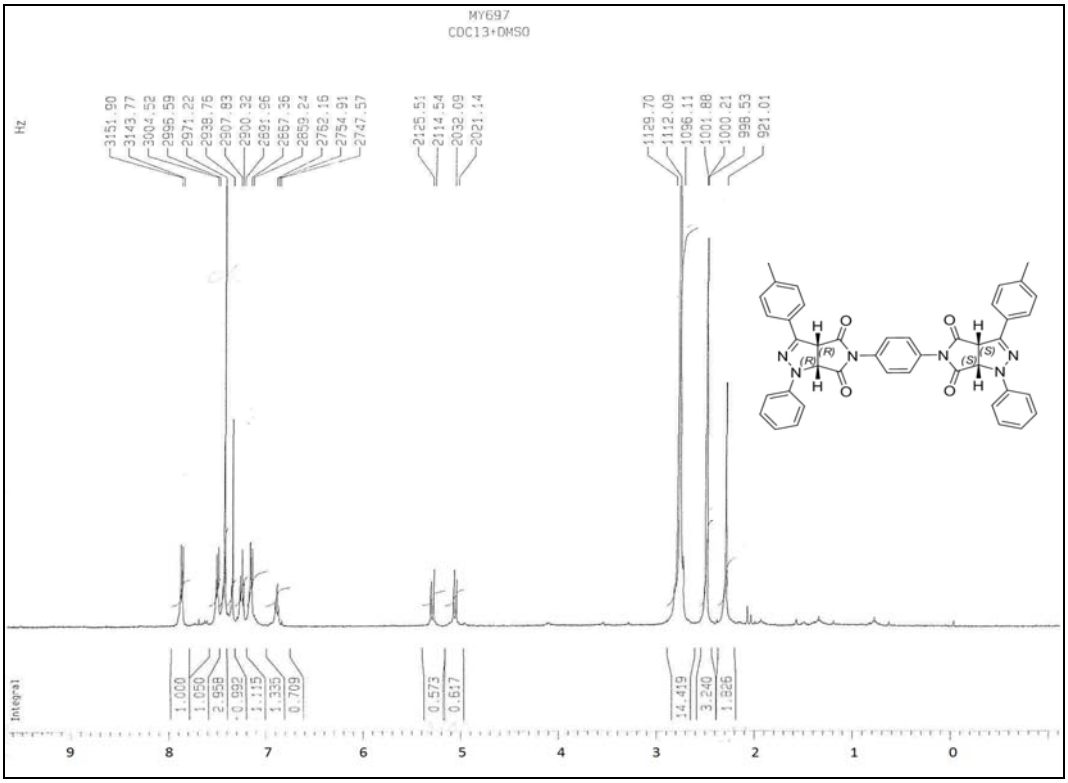

Figure 7.118 ^{1}H-NMR spectrum of compound **6.15e** in DMSO-d_6

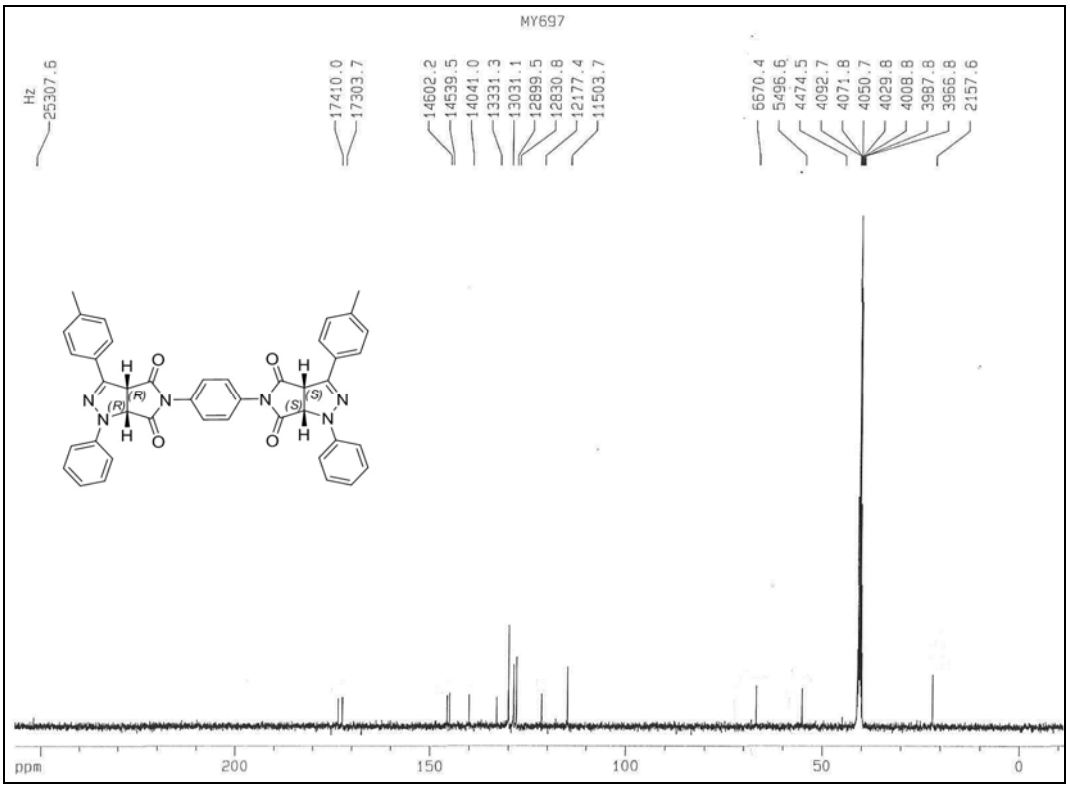

Figure 7.119 ^{13}C-NMR spectrum of compound **6.15e** in DMSO-d_6

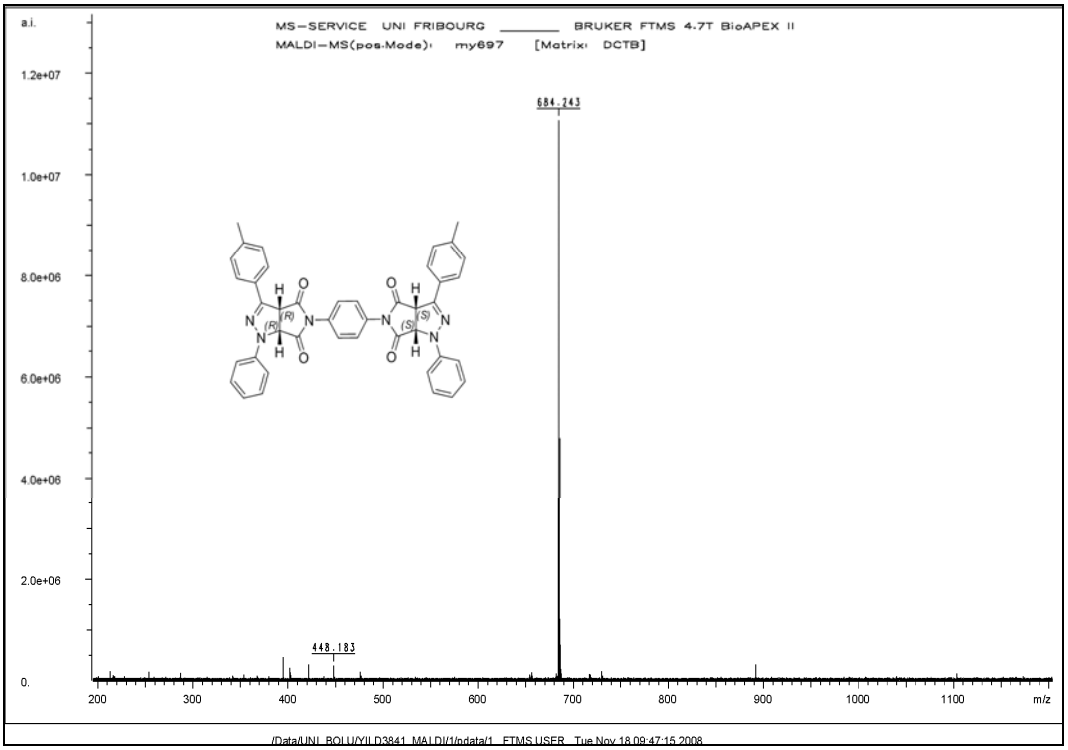

Figure 7.120 Mass spectrum of compound **6.15e**

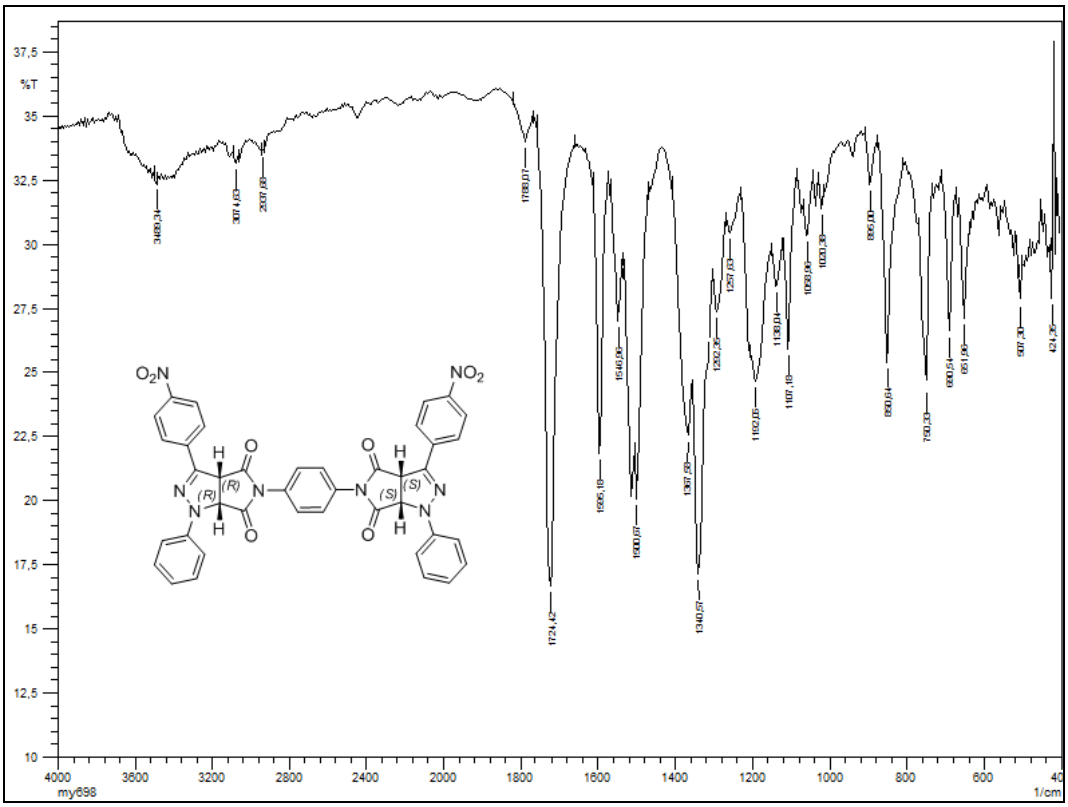

Figure 7.121 IR spectrum of compound **6.15f**

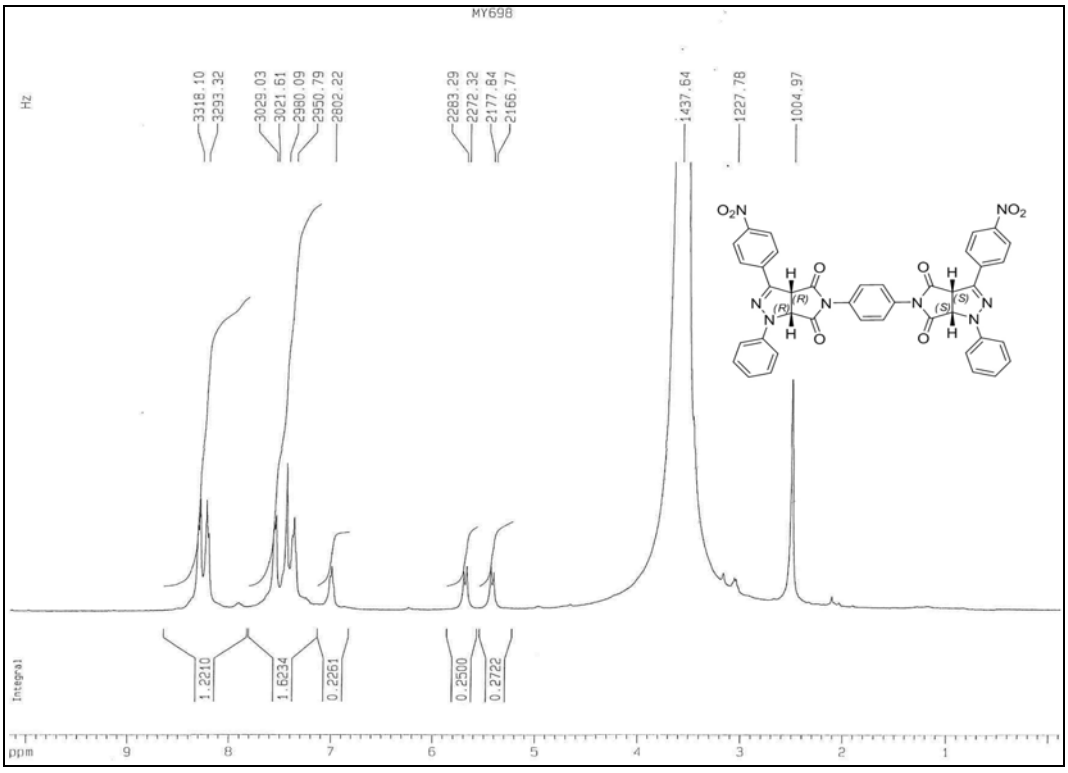

Figure 7.122 ^{1}H-NMR spectrum of compound **6.15f** in DMSO-d_6

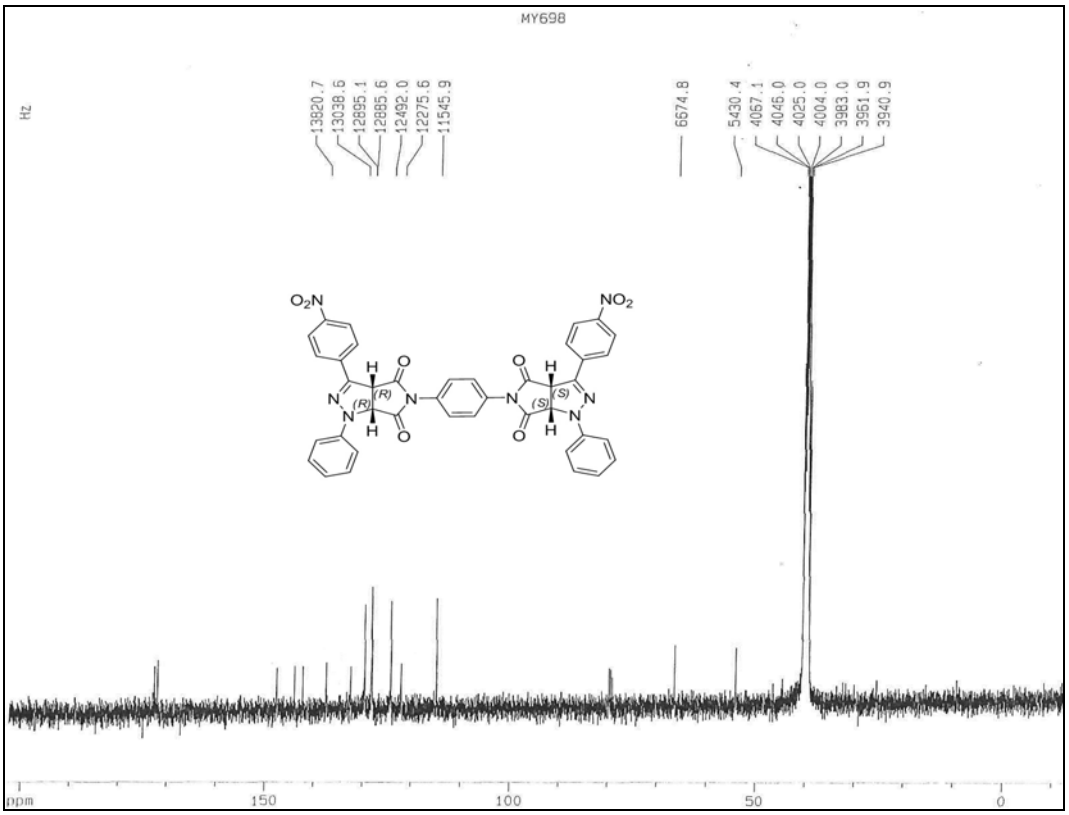

Figure 7.123 ^{13}C-NMR spectrum of compound **6.15f** in DMSO-d_6

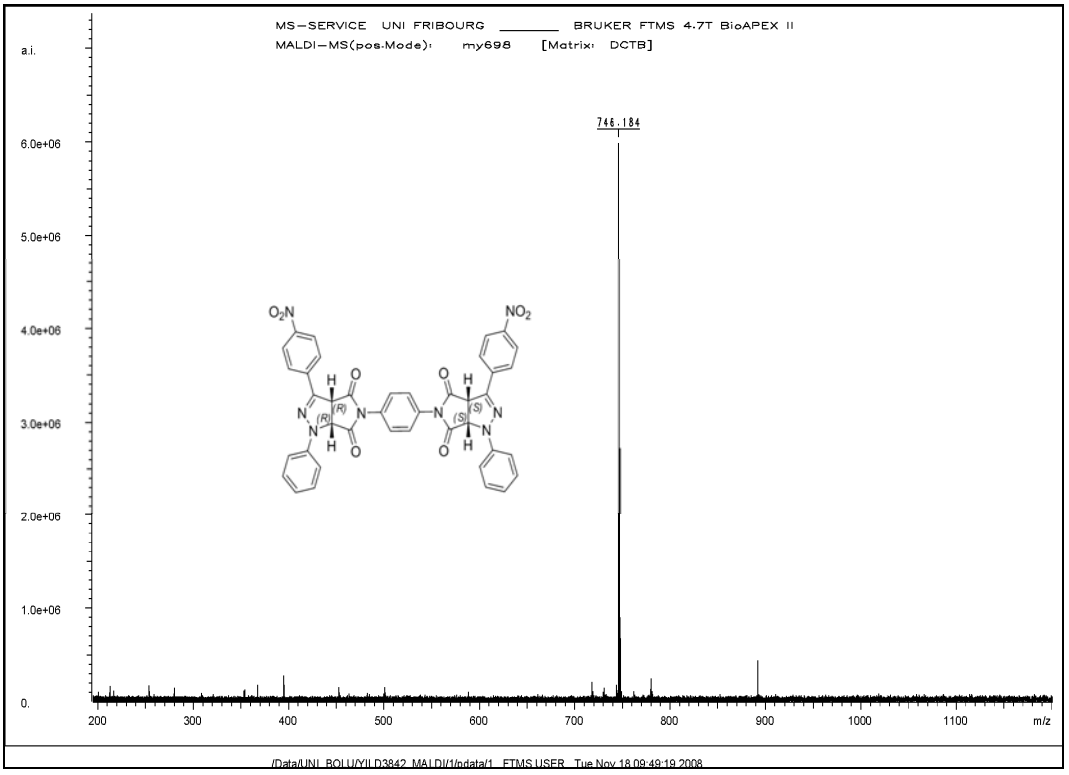

Figure 7.124 Mass spectrum of compound **6.15f**

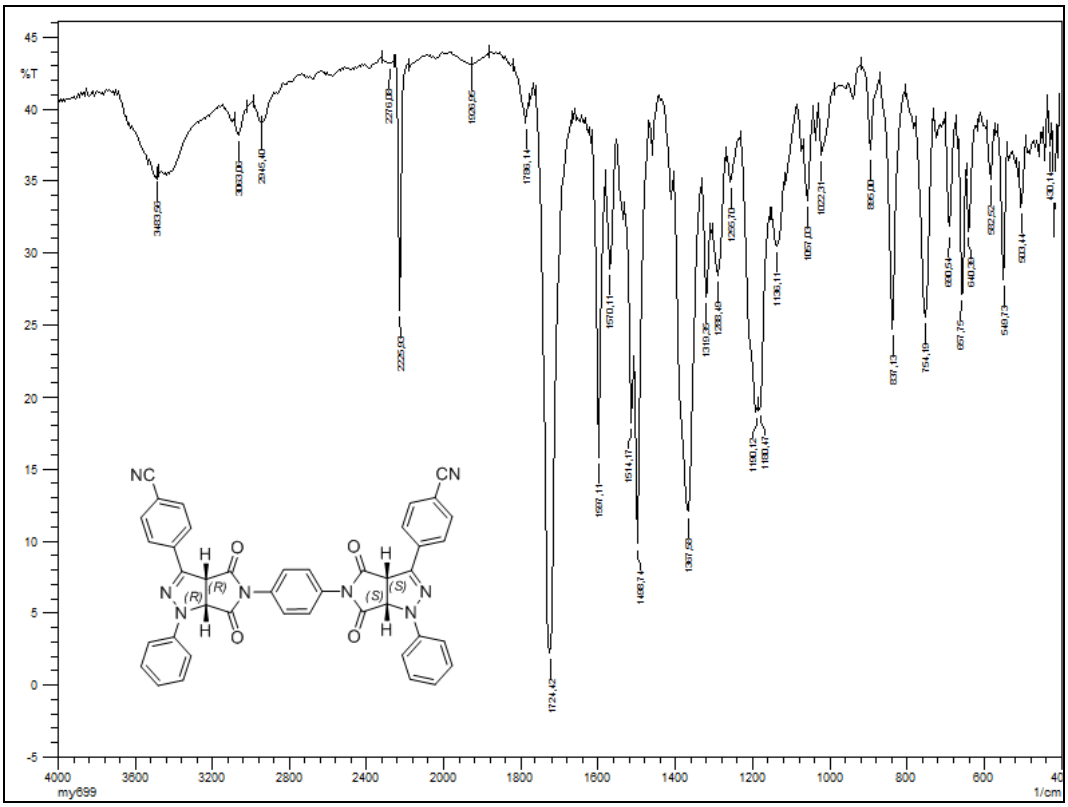

Figure 7.125 IR spectrum of compound **6.15g**

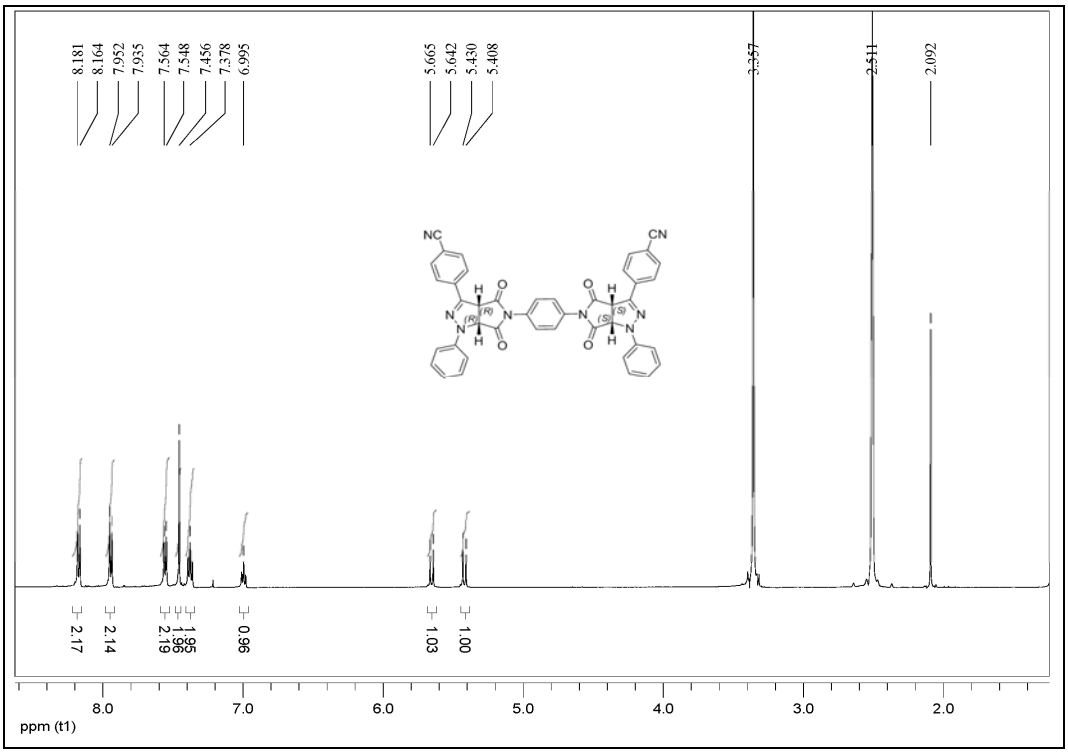

Figure 7.126 ^{1}H-NMR spectrum of compound **6.15g** in DMSO-d_6

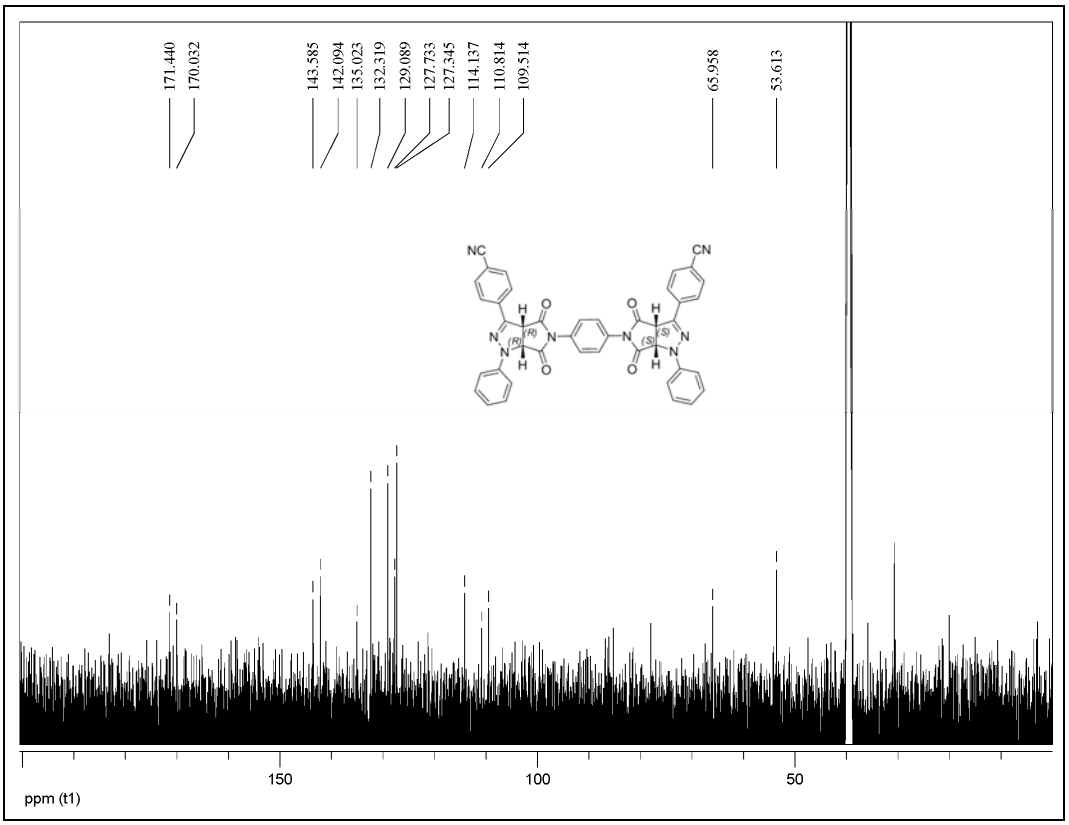

Figure 7.127 ^{13}C-NMR spectrum of compound **6.15g** in DMSO-d_6

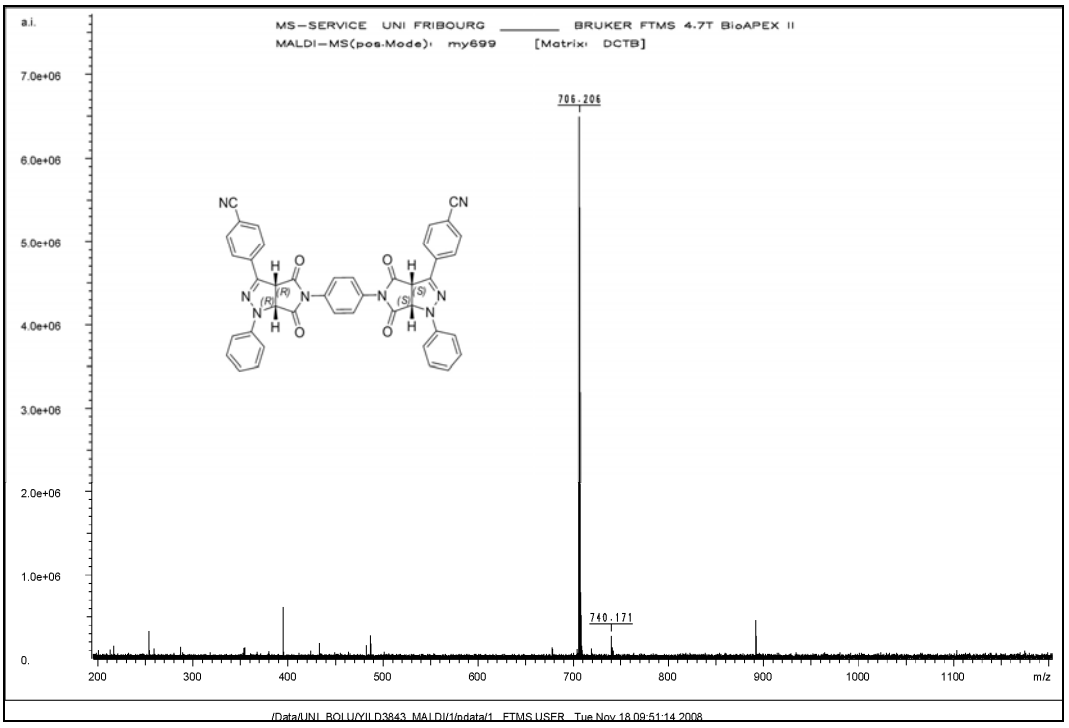

Figure 7.128 Mass spectrum of compound **6.15g**

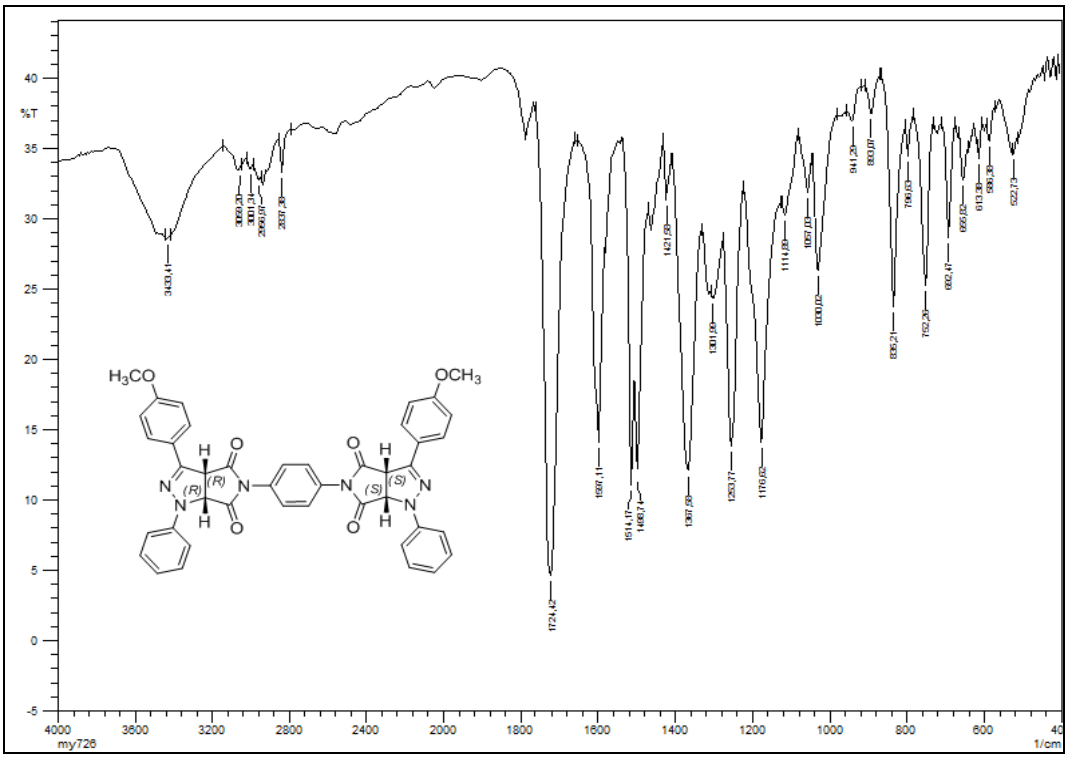

Figure 7.129 IR spectrum of compound **6.15h**

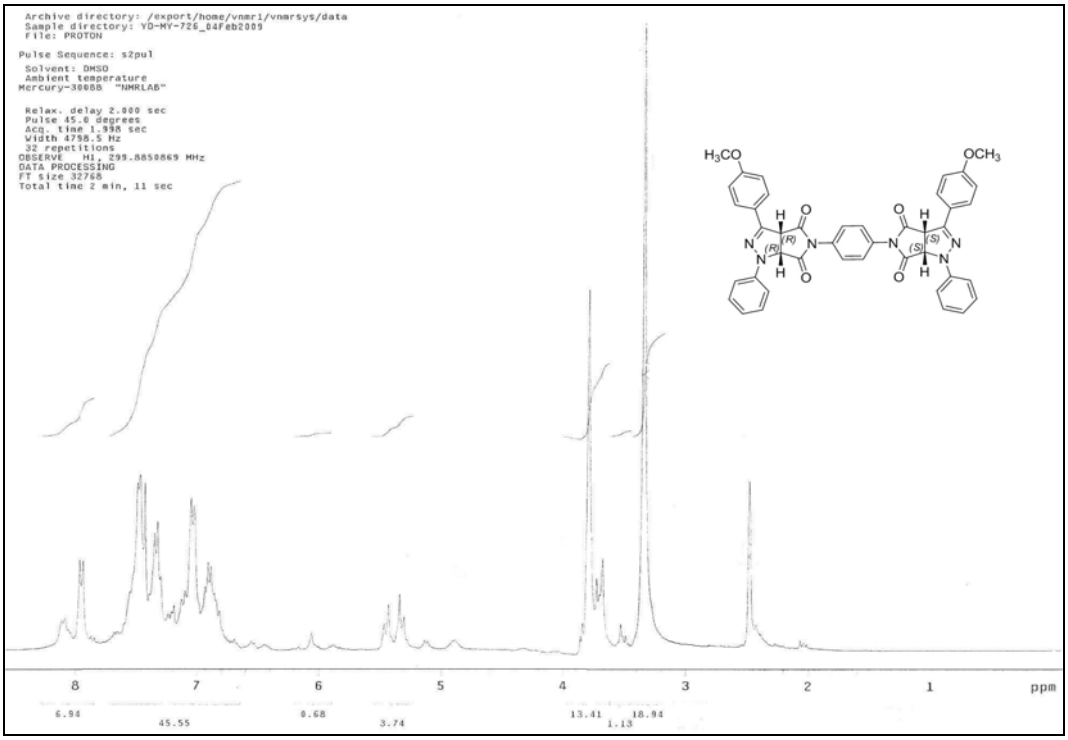

Figure 7.130 ^{1}H-NMR spectrum of compound **6.15h** in DMSO-d_6

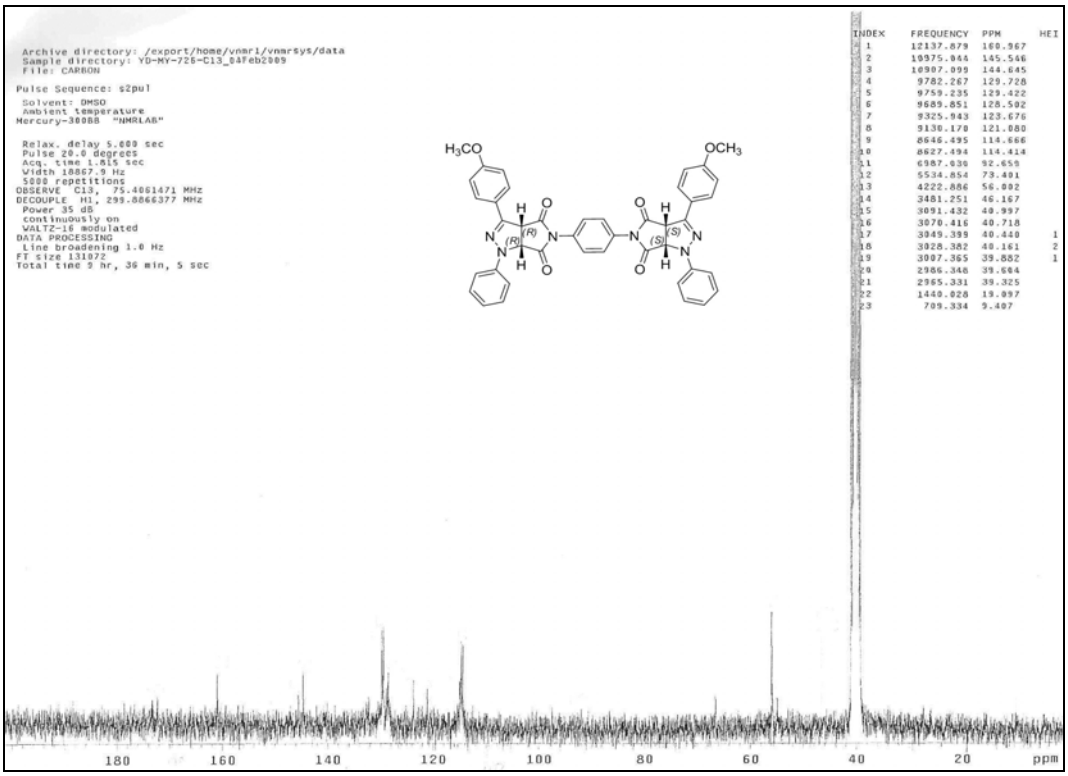

Figure 7.131 ^{13}C-NMR spectrum of compound **6.15h** in DMSO-d_6

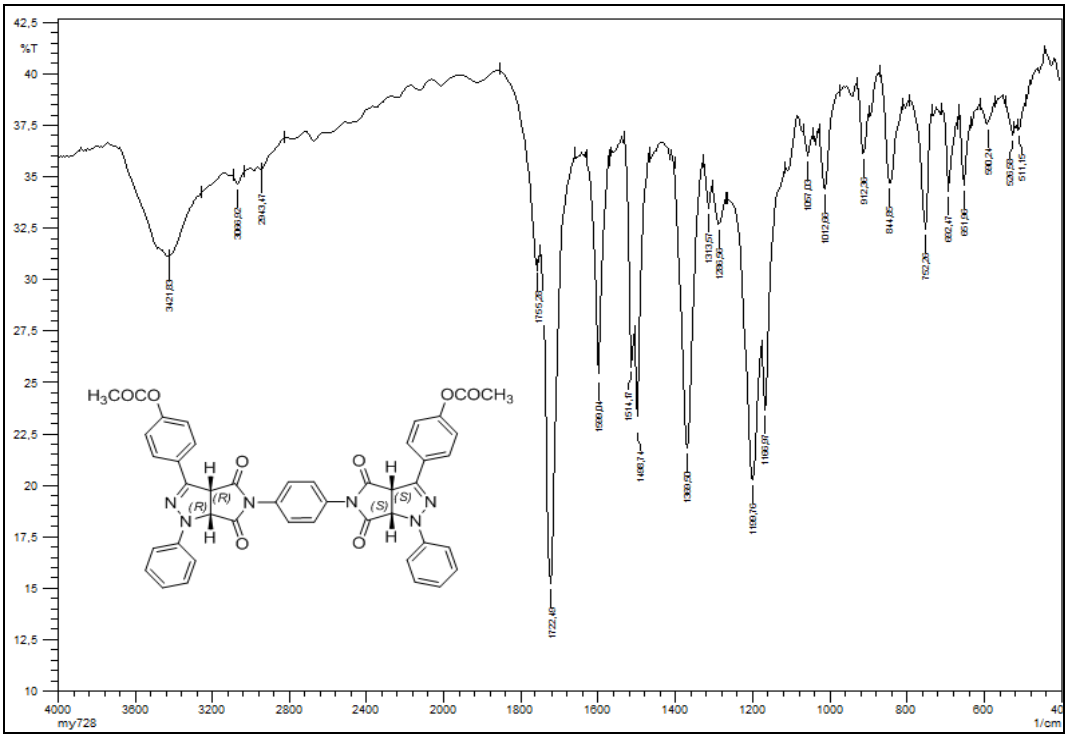

Figure 7.132 IR spectrum of compound **6.15j**

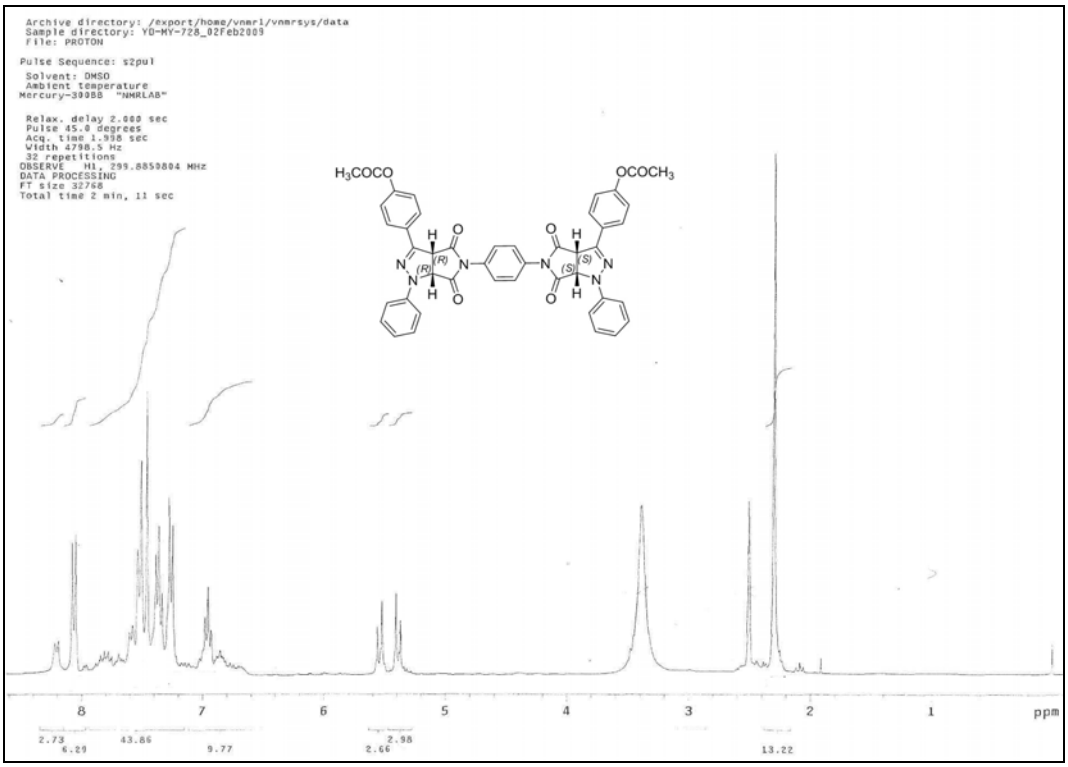

Figure 7.133 ^{1}H-NMR spectrum of compound **6.15j** in DMSO-d_6

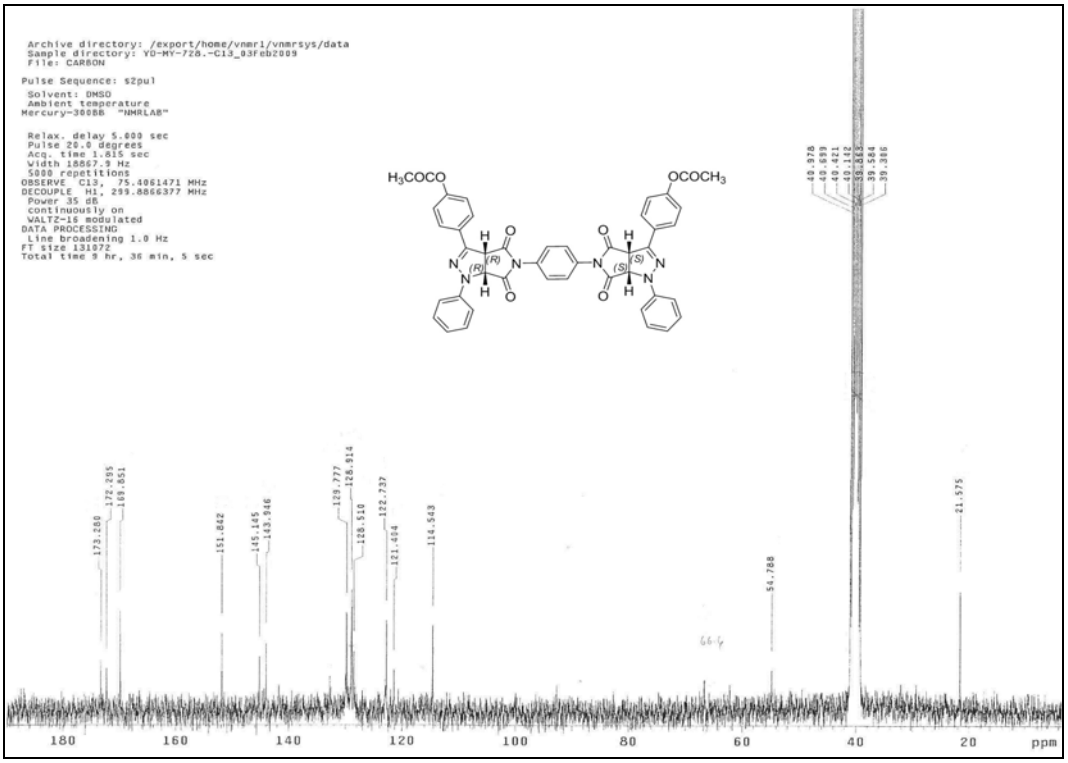

Figure 7.134 ^{13}C-NMR spectrum of compound **6.15j** in DMSO-d_6

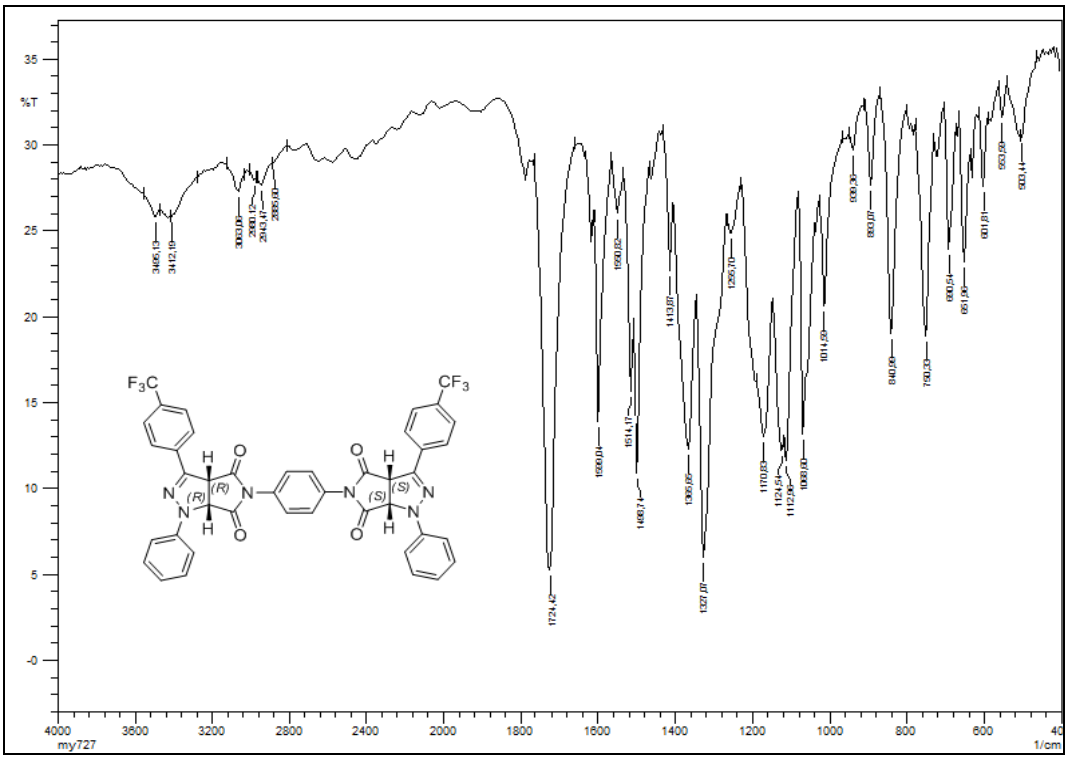

Figure 7.135 IR spectrum of compound **6.15k**

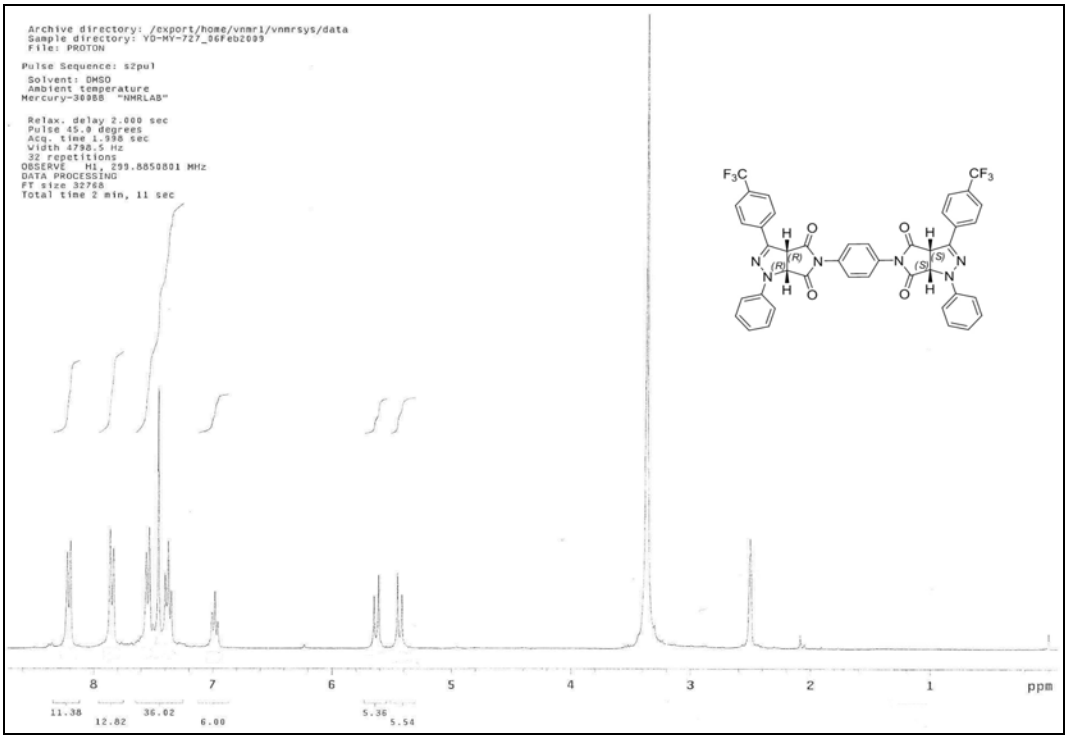

Figure 7.136 ^{1}H-NMR spectrum of compound **6.15k** in DMSO-d_6

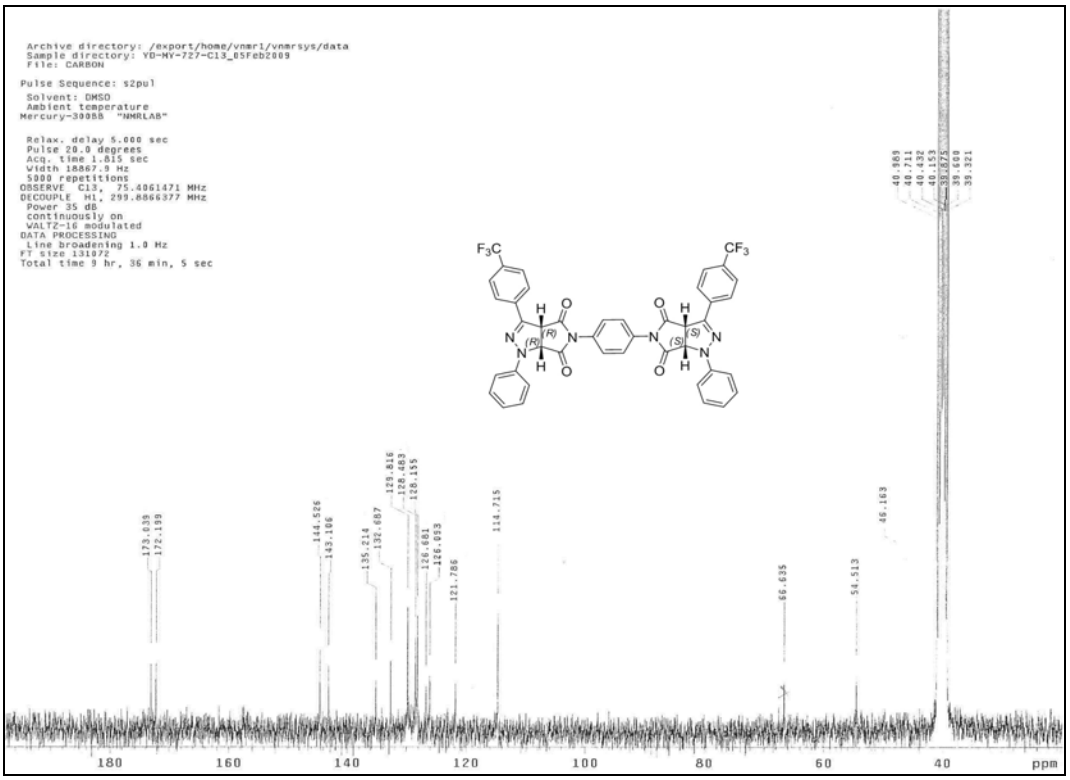

Figure 7.137 ^{13}C-NMR spectrum of compound **6.15k** in DMSO-d_6

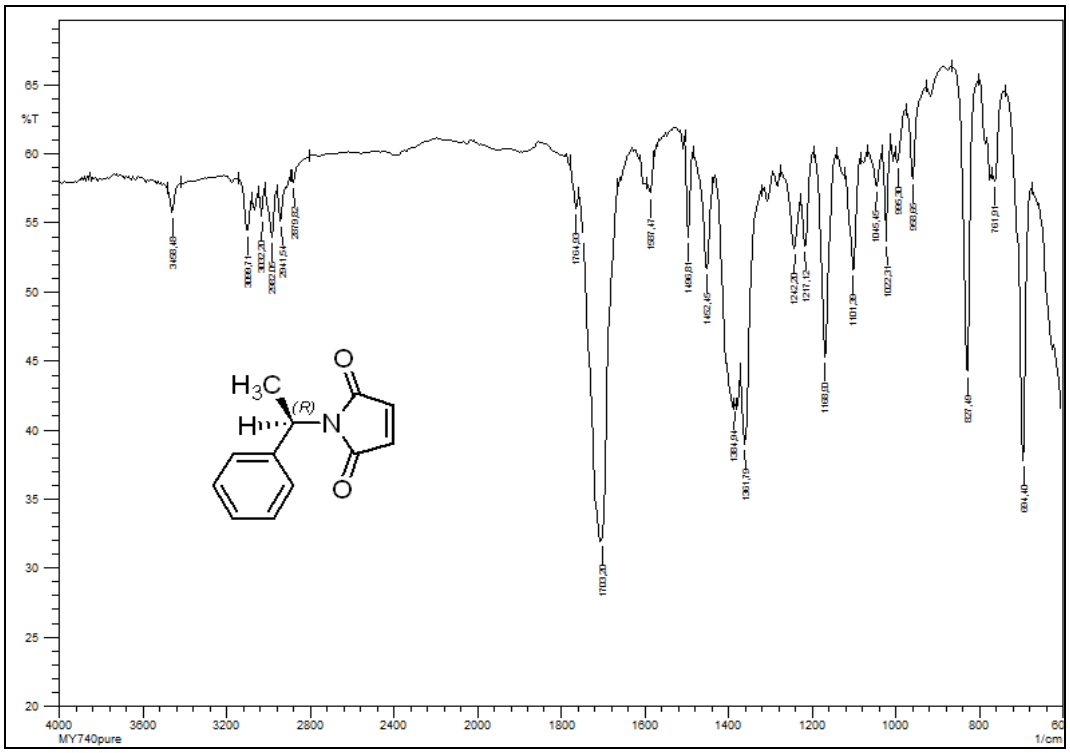

Figure 7.138 IR spectrum of compound **6.18**

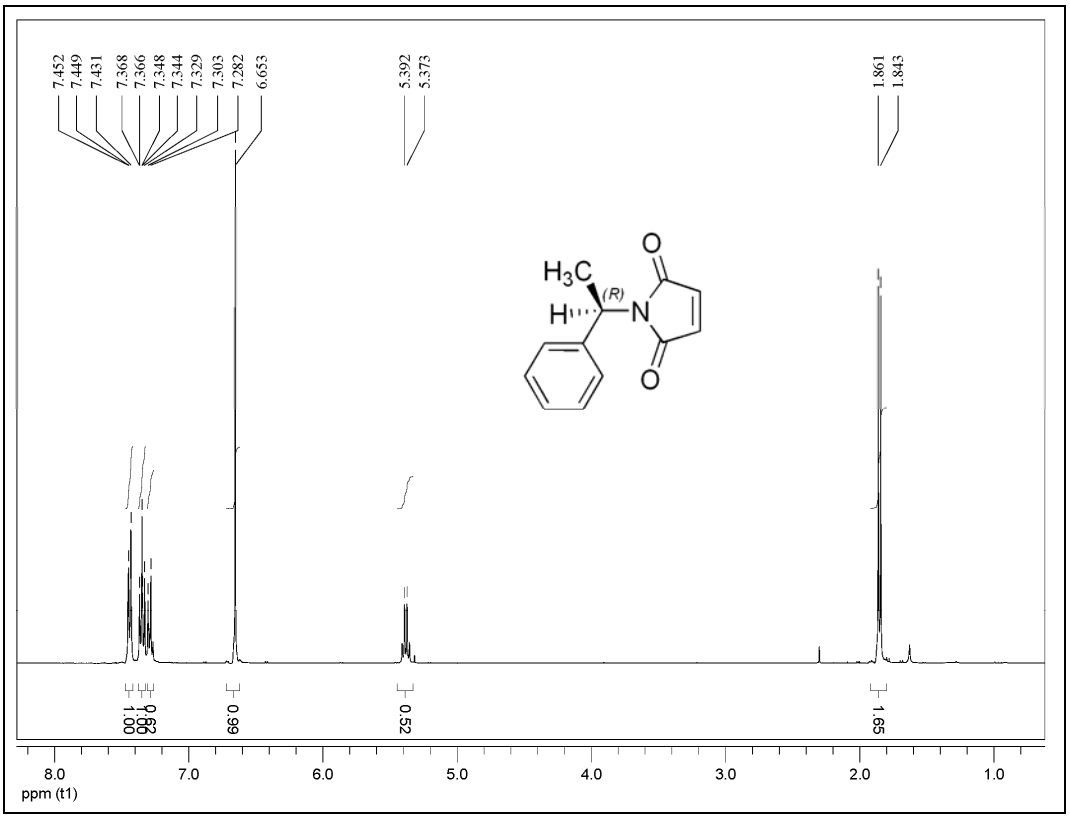

Figure 7.139 ^{1}H-NMR spectrum of compound **6.18** in $CDCl_3$

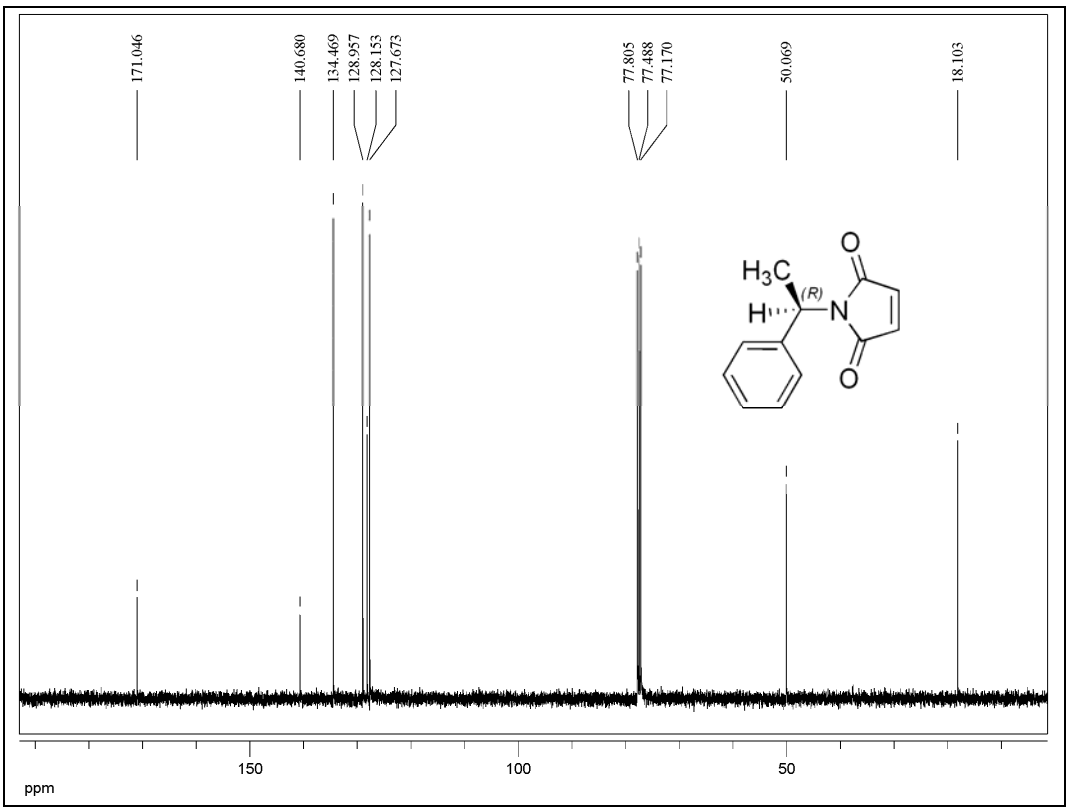

Figure 7.140 ^{13}C-NMR spectrum of compound **6.18** in $CDCl_3$

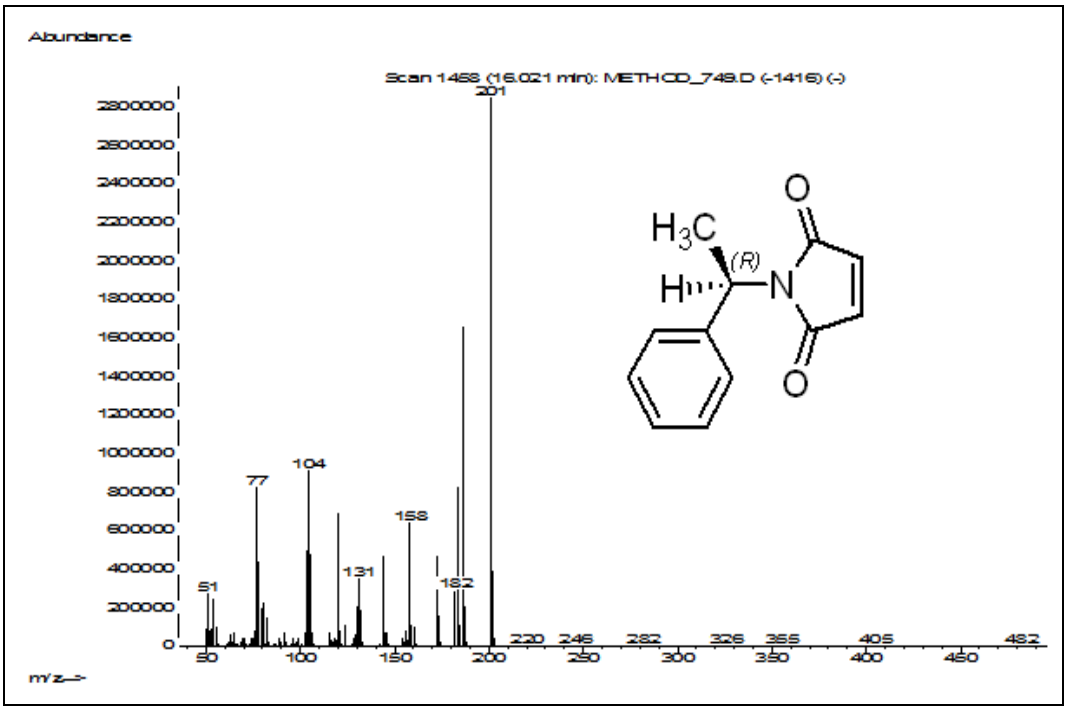

Figure 7.141 Mass spectrum of compound **6.18**

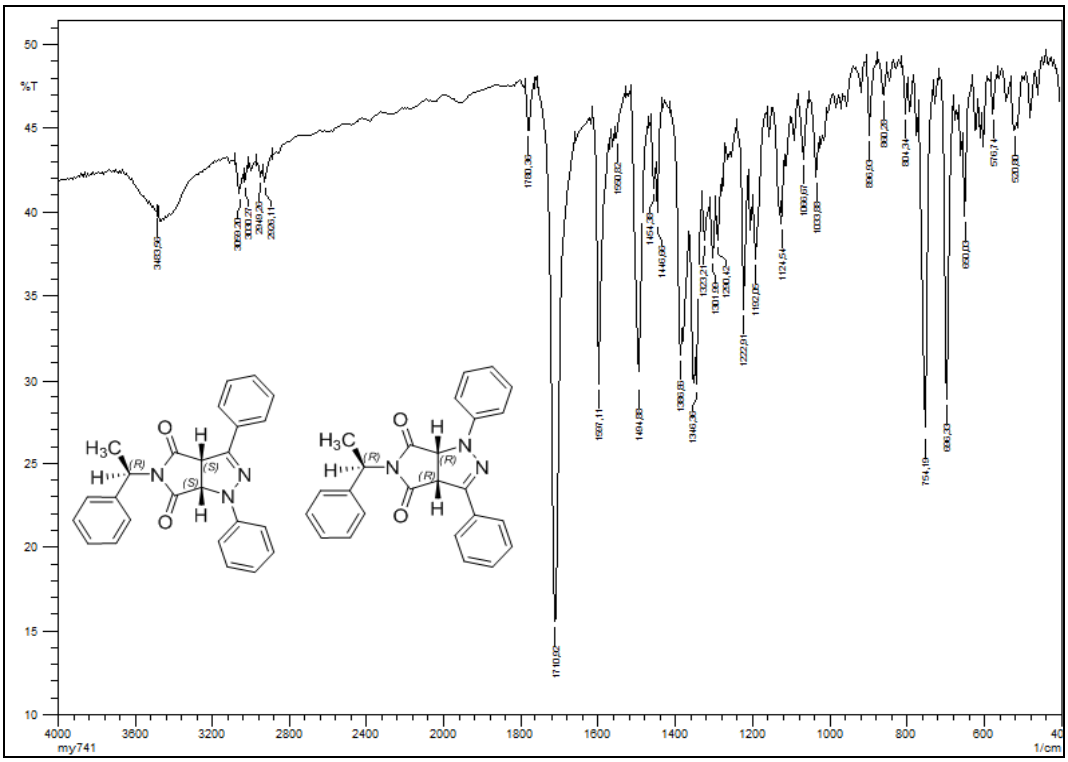

Figure 7.142 IR spectrum of compound **6.19a-a'**

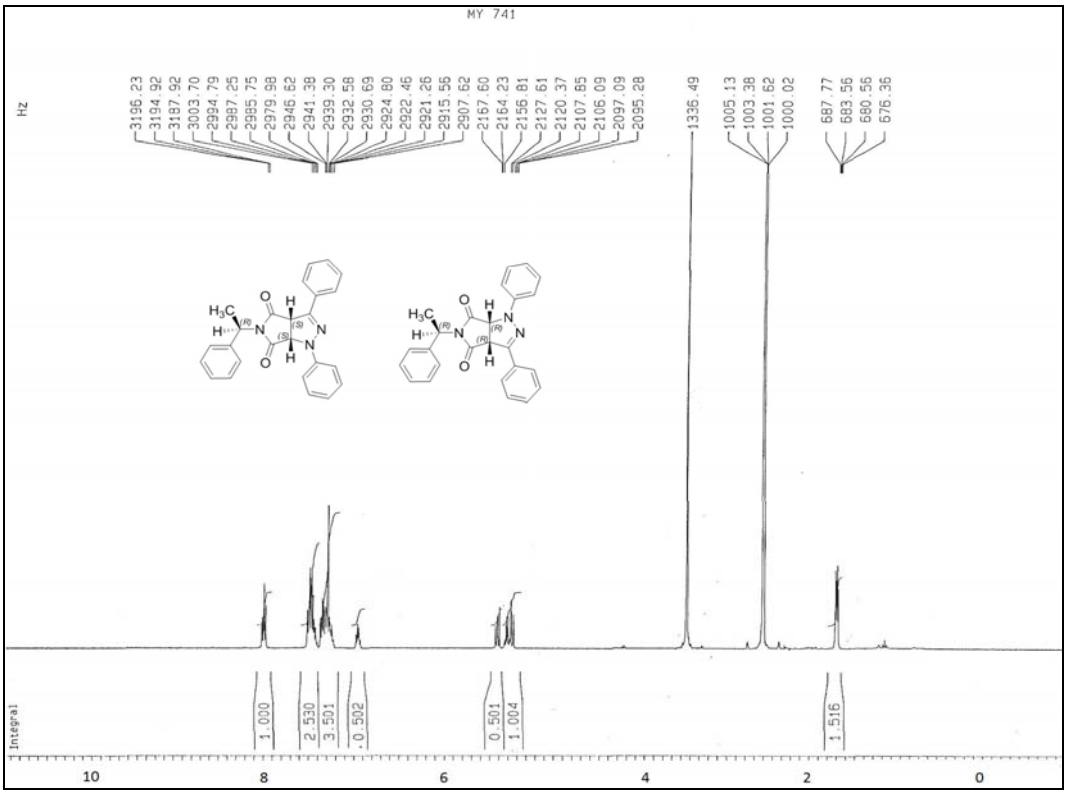

Figure 7.143 ^{1}H-NMR spectrum of compound **6.19a-a'** in DMSO-d_6

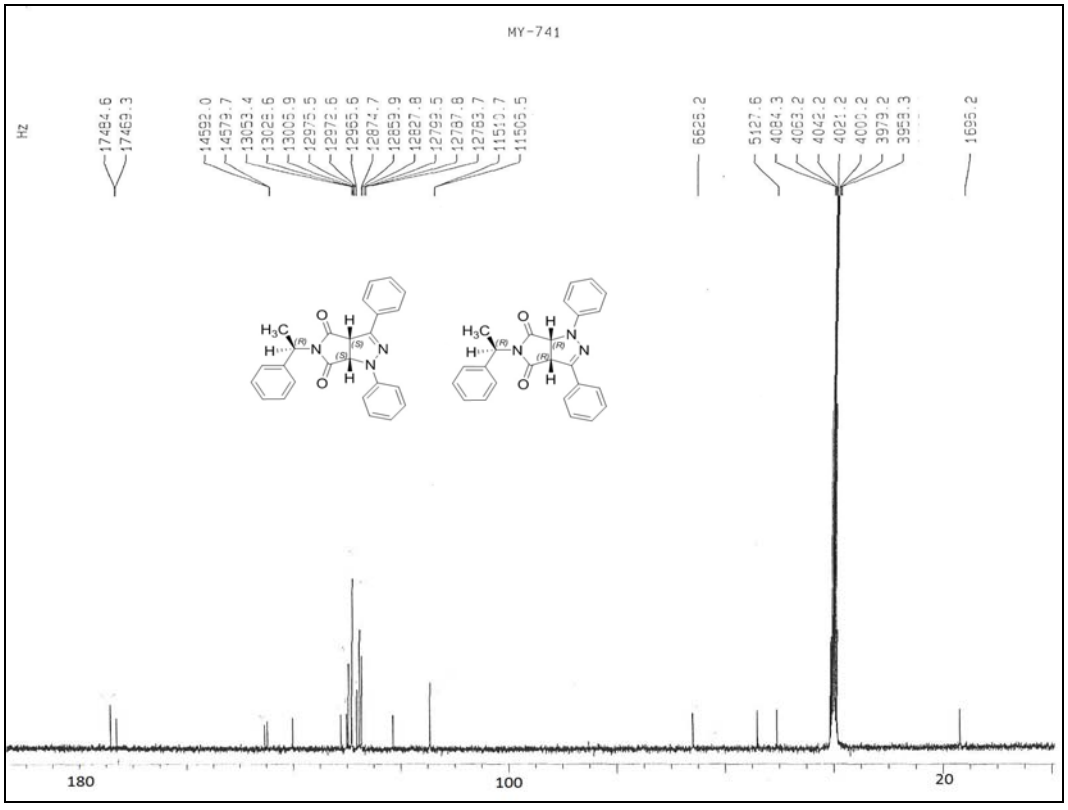

Figure 7.144 ^{13}C-NMR spectrum of compound **6.19a-a'** in DMSO-d_6

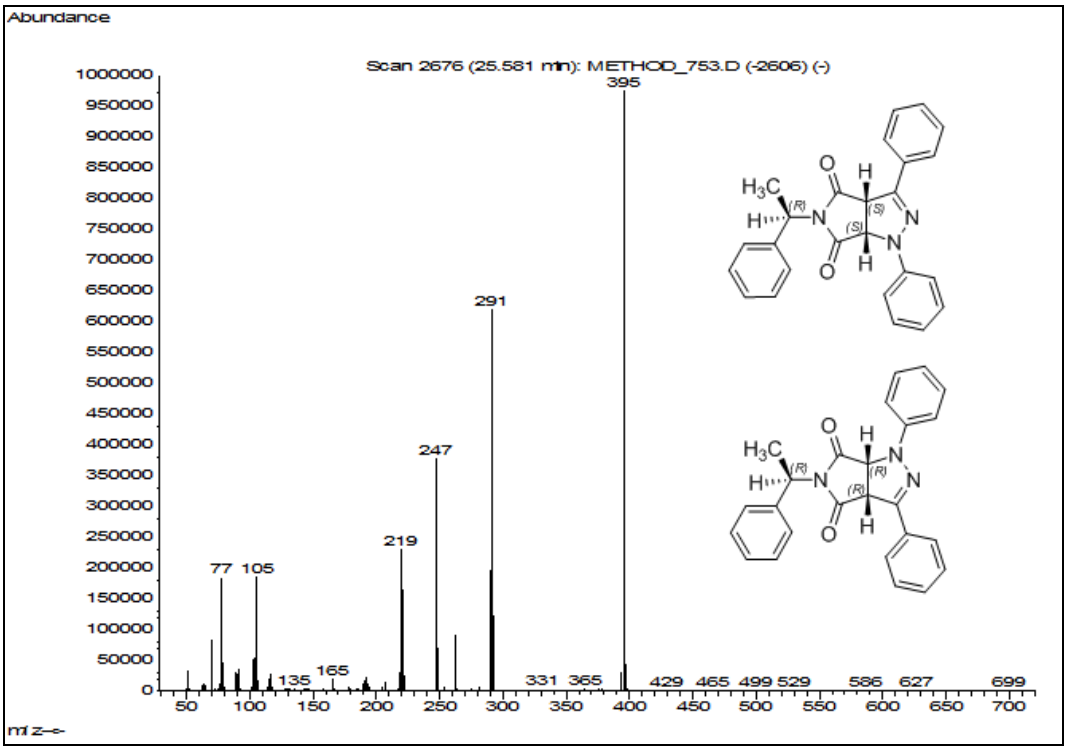

Figure 7.145 Mass spectrum of compound **6.19a-a'**

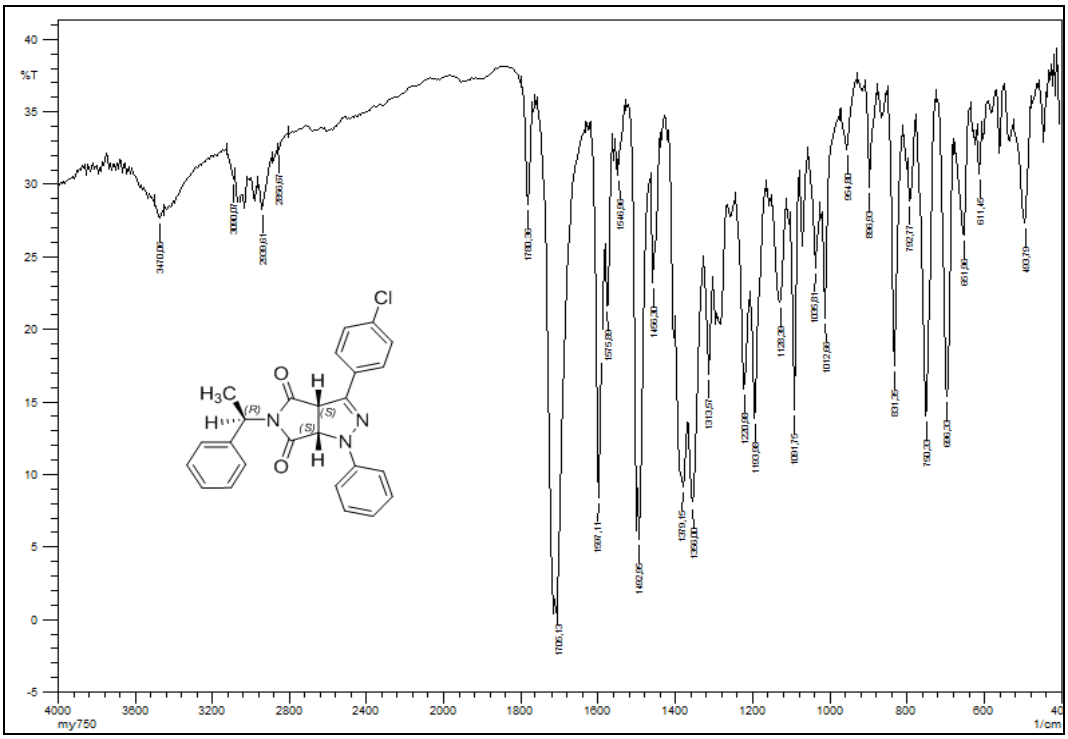

Figure 7.146 IR spectrum of compound **6.19b**

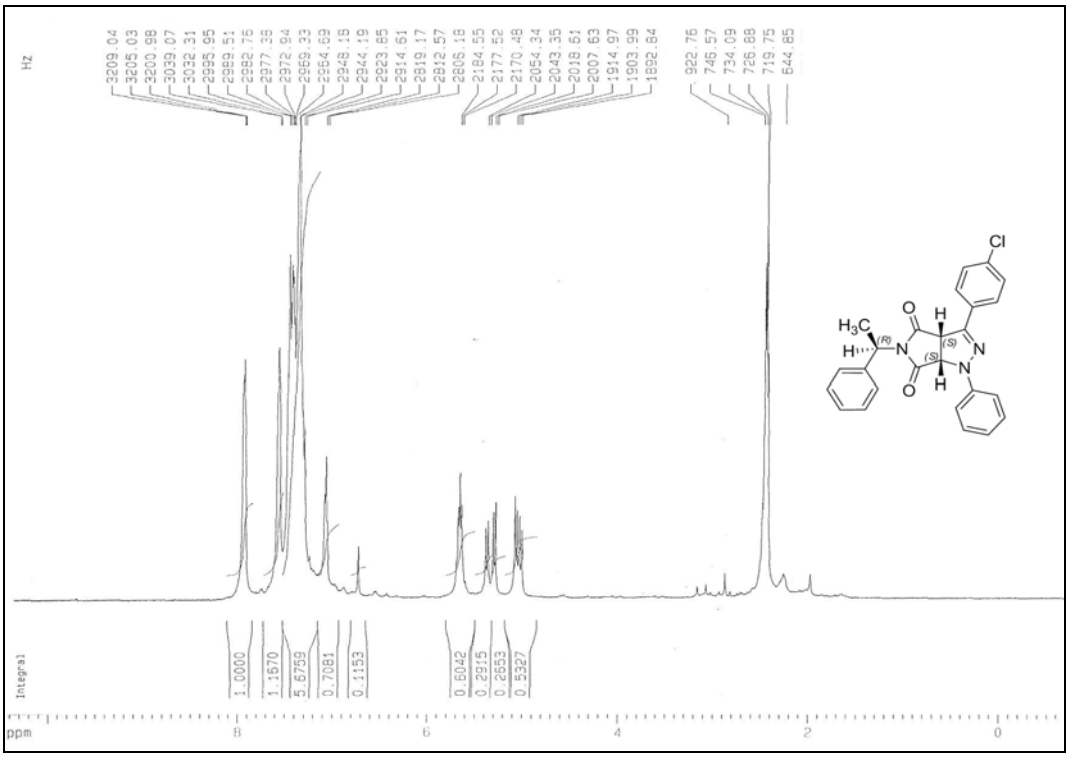

Figure 7.147 ^{1}H-NMR spectrum of compound **6.19b** in $CDCl_3$

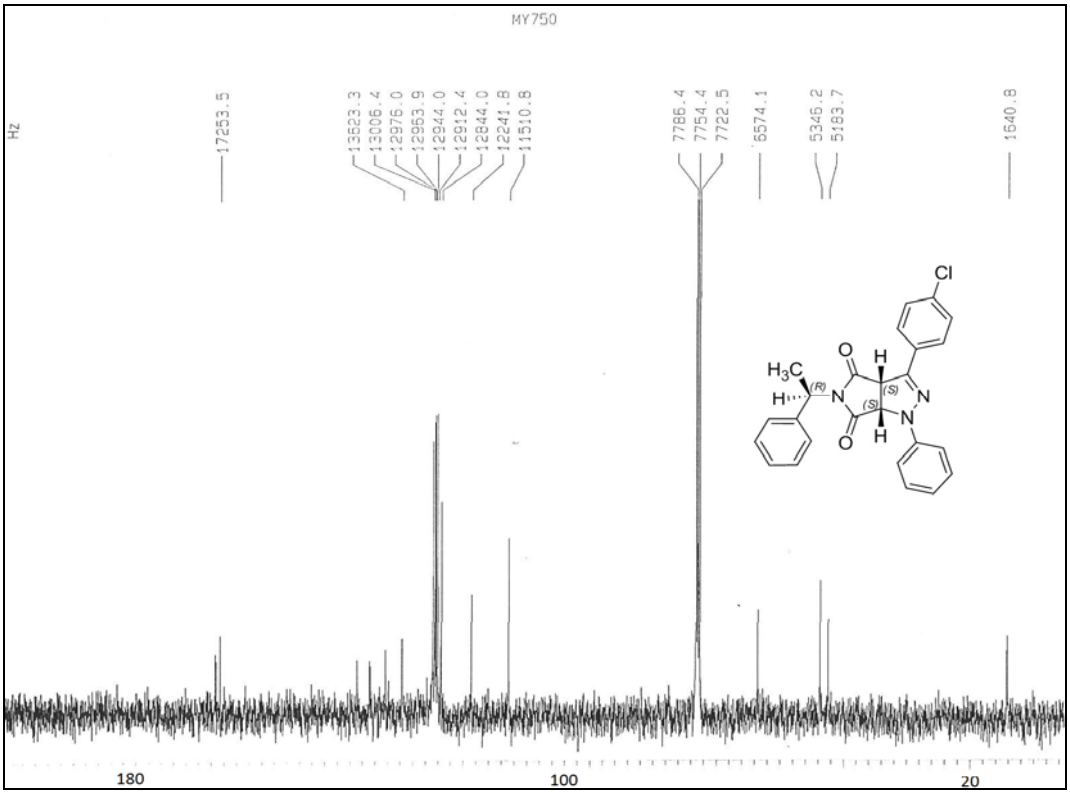

Figure 7.148 ^{13}C-NMR spectrum of compound **6.19b** in $CDCl_3$

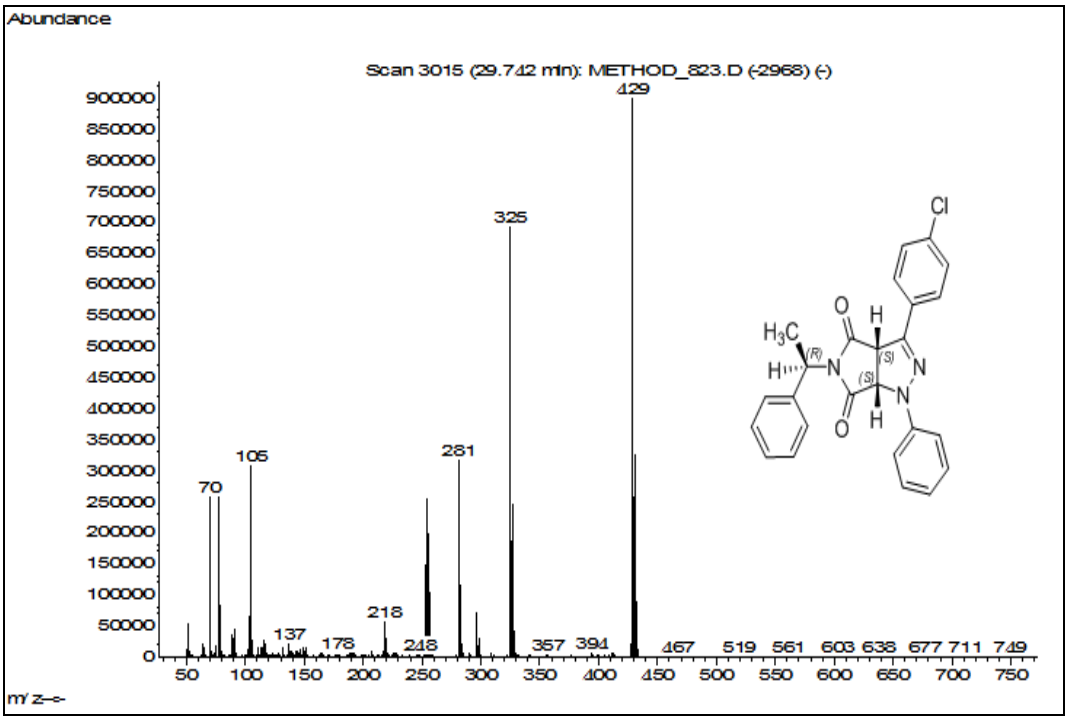

Figure 7.149 Mass spectrum of compound **6.19b**

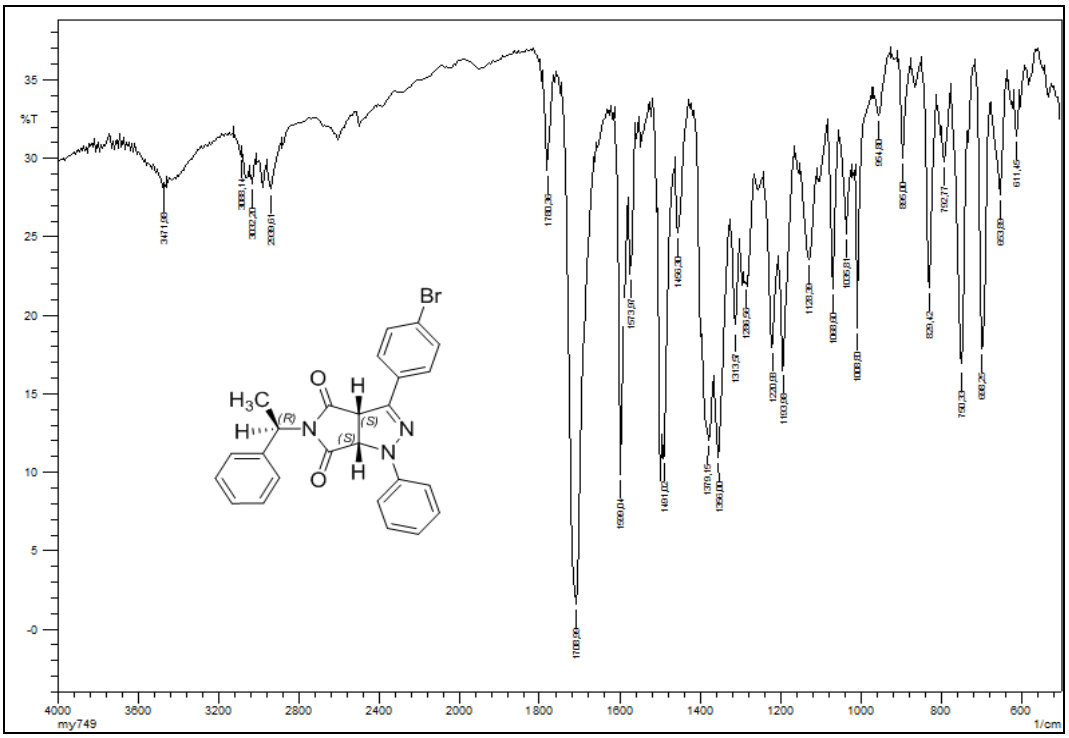

Figure 7.150 IR spectrum of compound **6.19c**

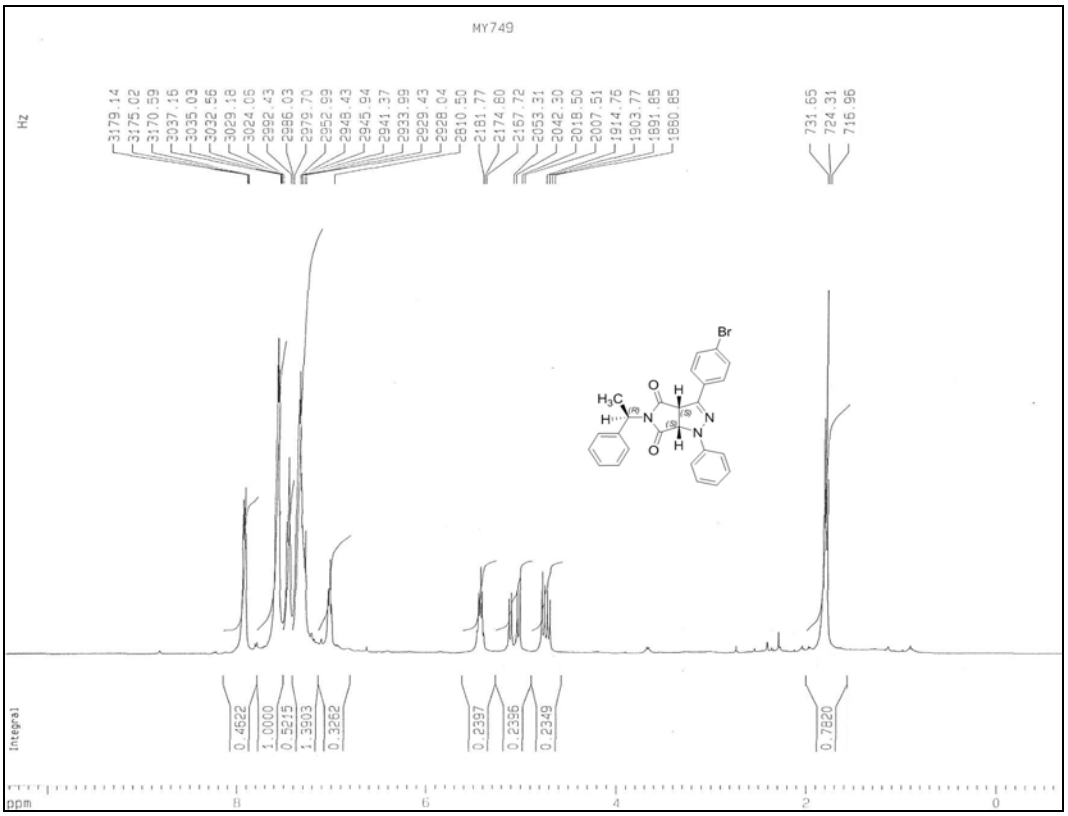

Figure 7.151 ^{1}H-NMR spectrum of compound **6.19c** in $CDCl_3$

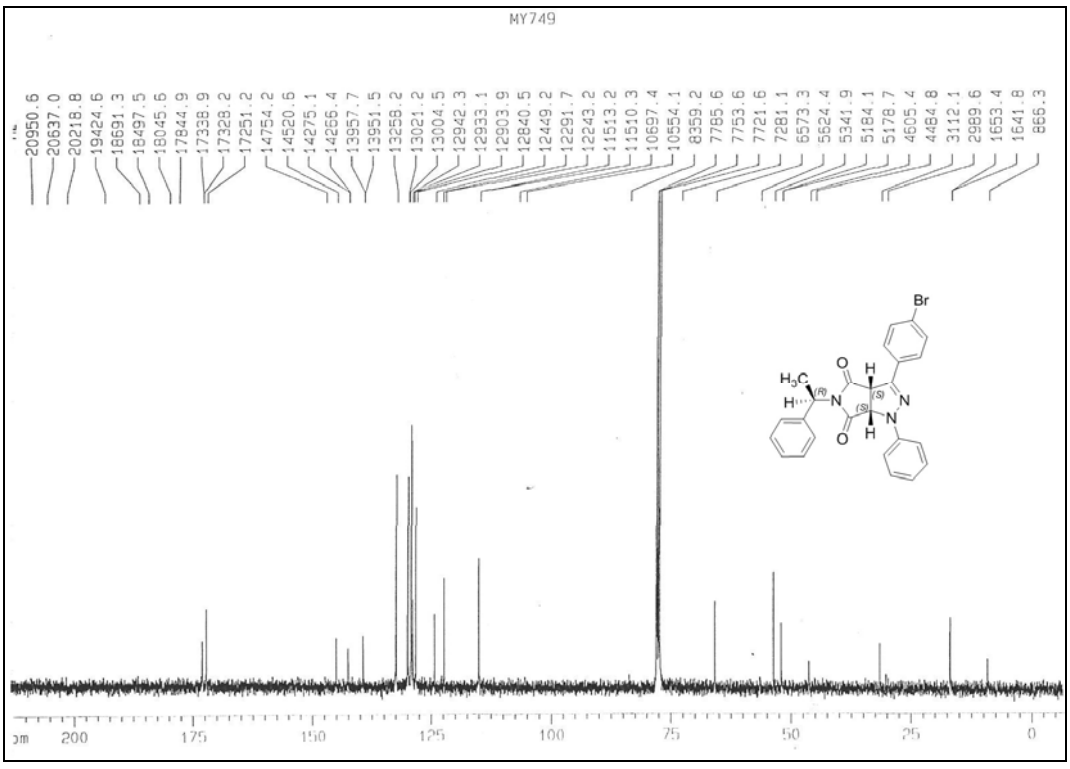

Figure 7.152 ^{13}C-NMR spectrum of compound **6.19c** in $CDCl_3$

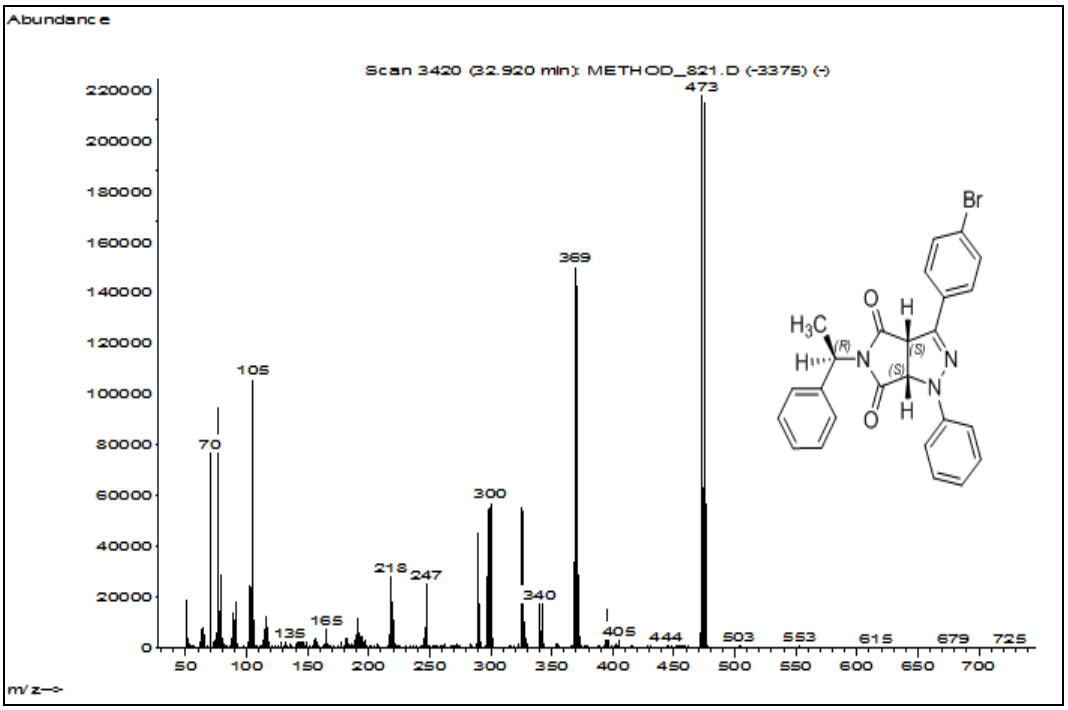

Figure 7.153 Mass spectrum of compound **6.19c**

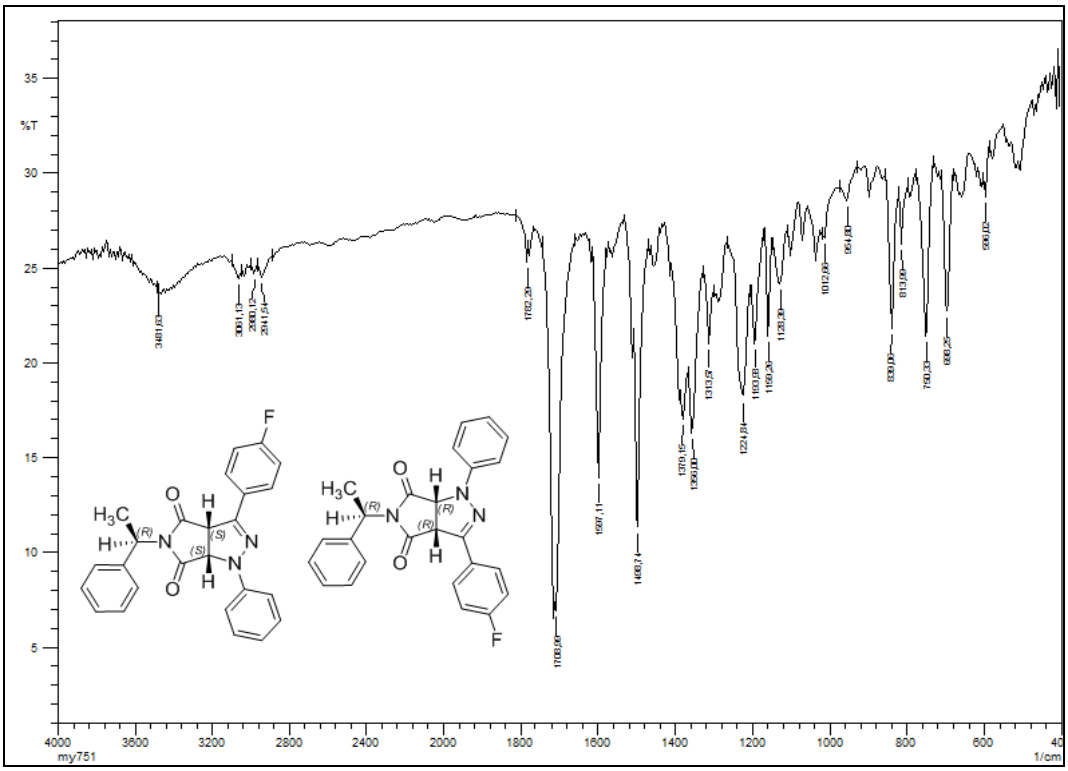

Figure 7.154 IR spectrum of compounds **6.19d-d'**

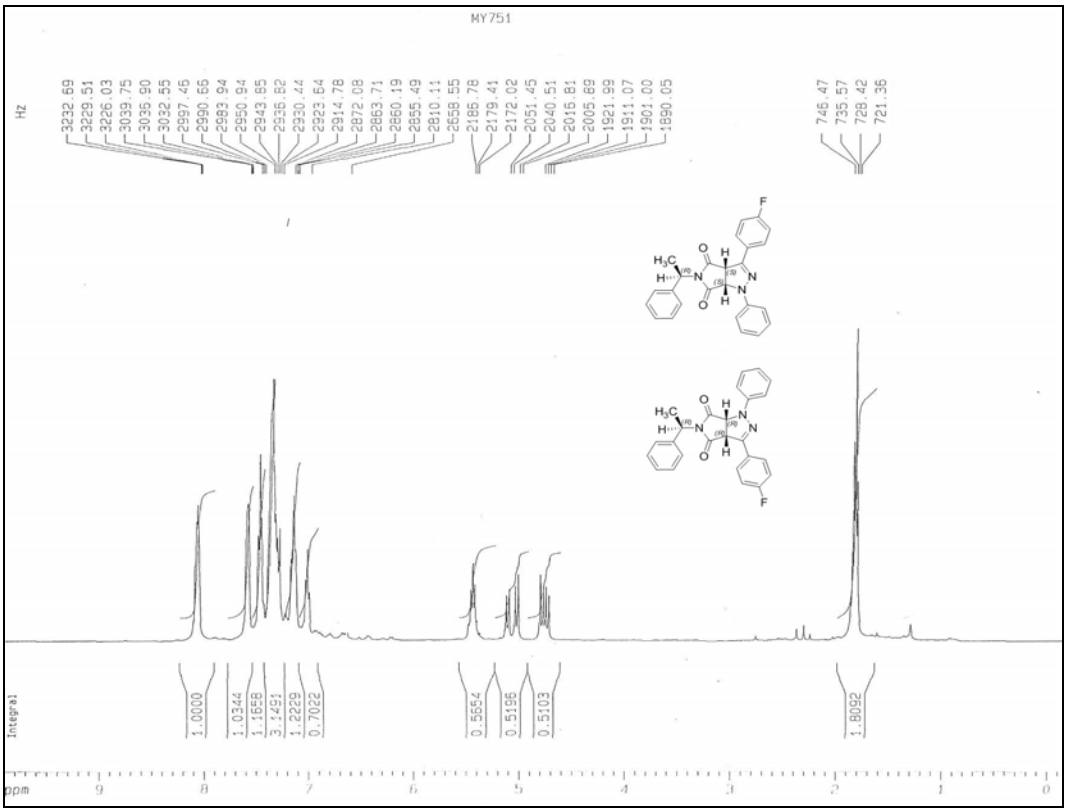

Figure 7.155 ^{1}H-NMR spectrum of compounds **6.19d-d'** in $CDCl_3$

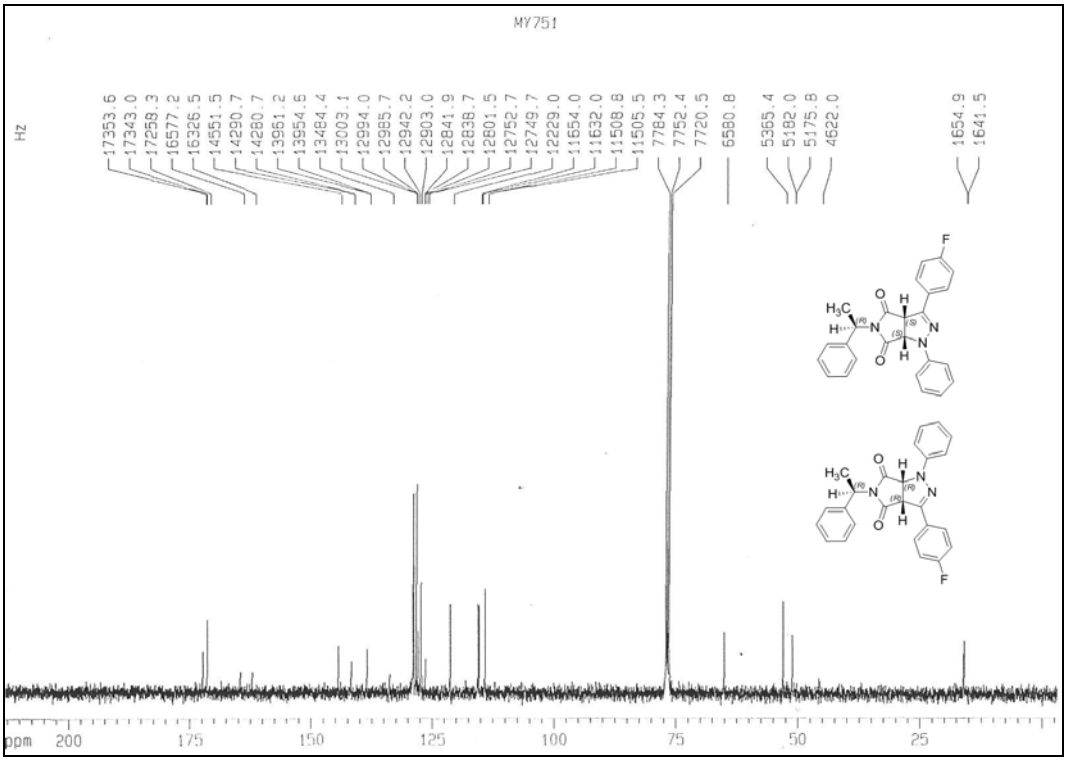

Figure 7.156 ^{13}C-NMR spectrum of compounds **6.19d-d'** in $CDCl_3$

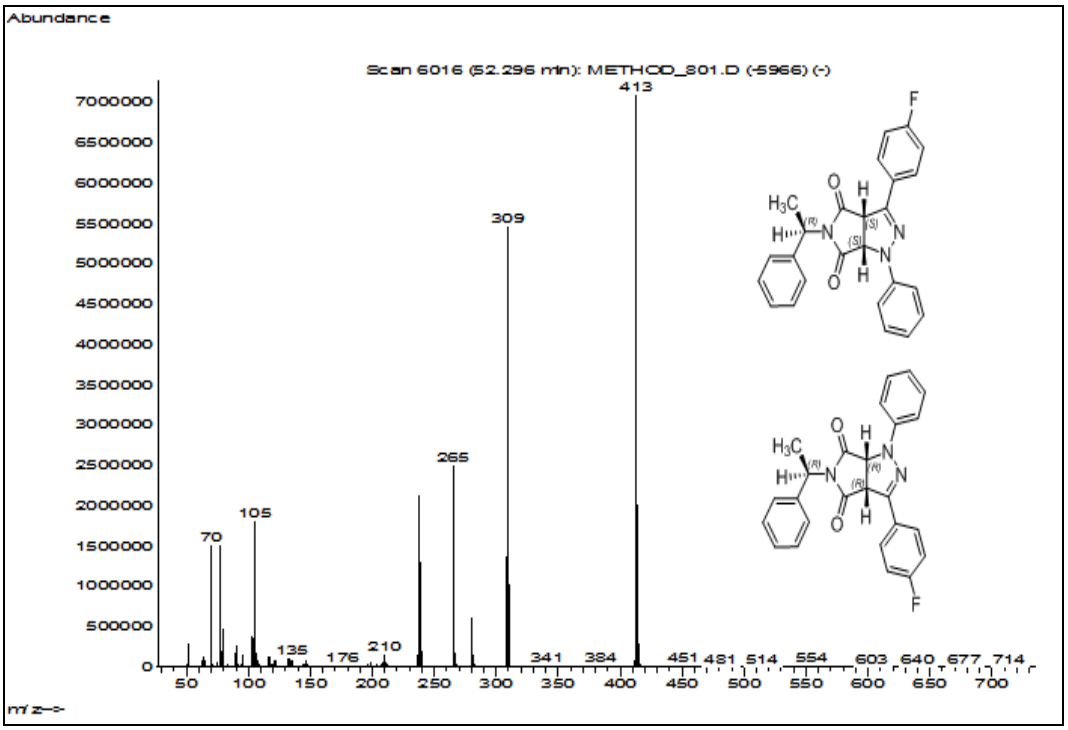

Figure 7.157 Mass spectrum of compounds **6.19d-d'**

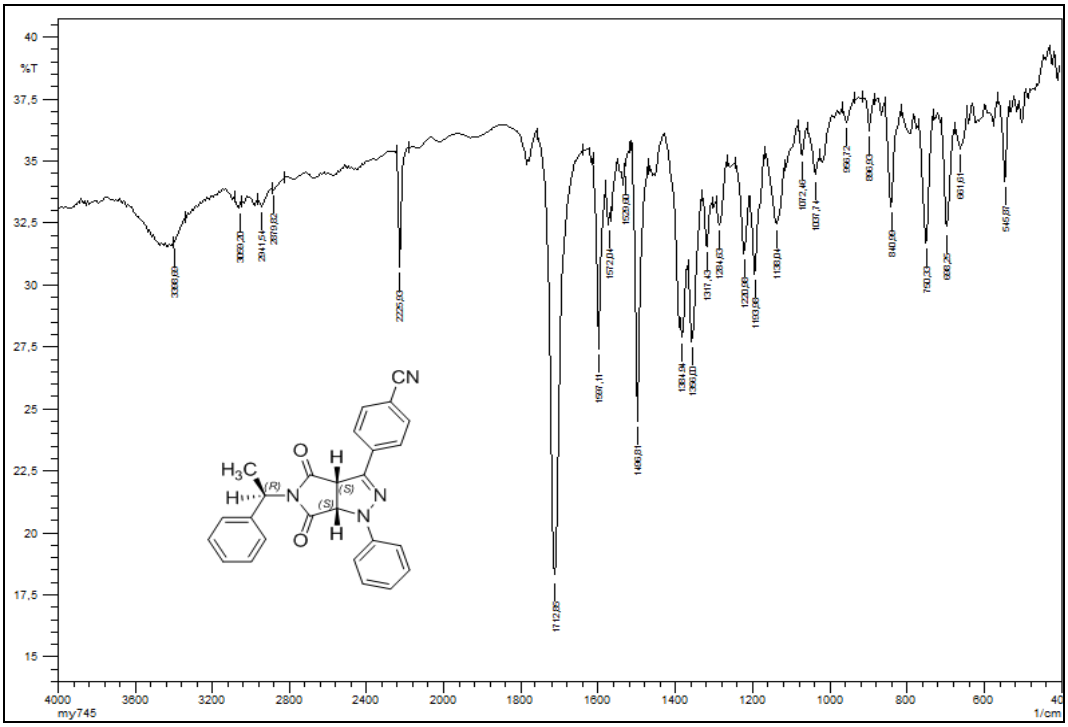

Figure 7.158 IR spectrum of compound **6.19g**

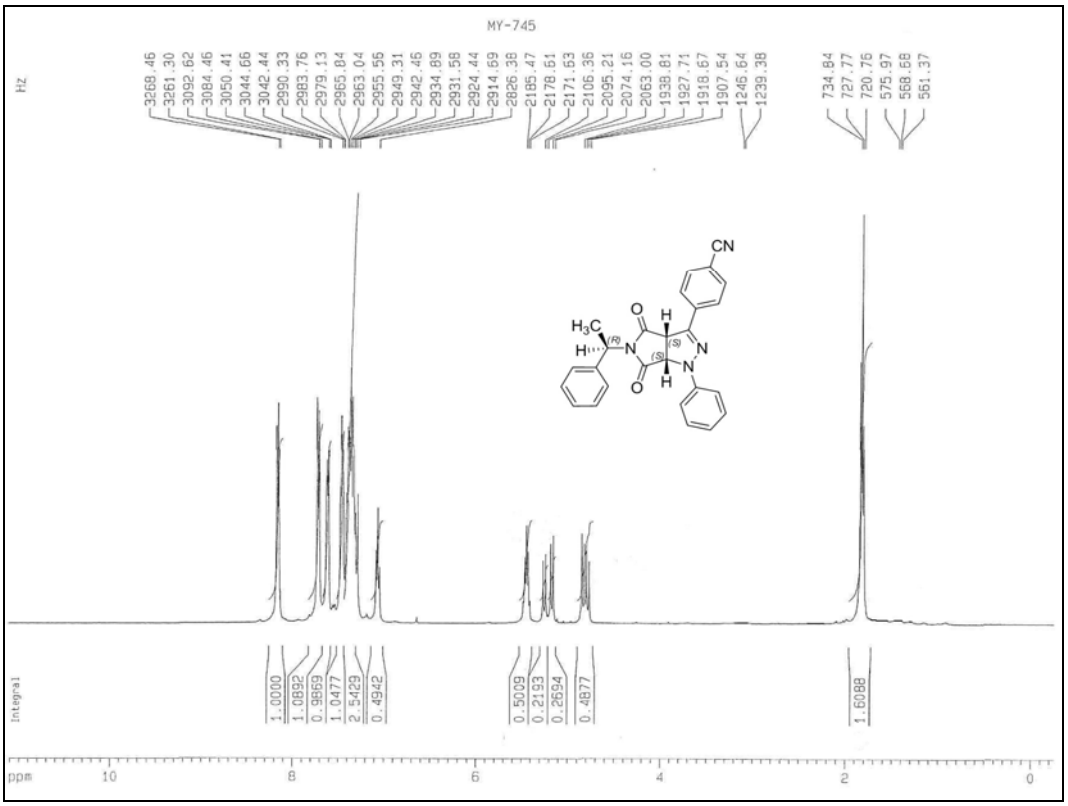

Figure 7.159 ^{1}H-NMR spectrum of compound **6.19g** in $CDCl_3$

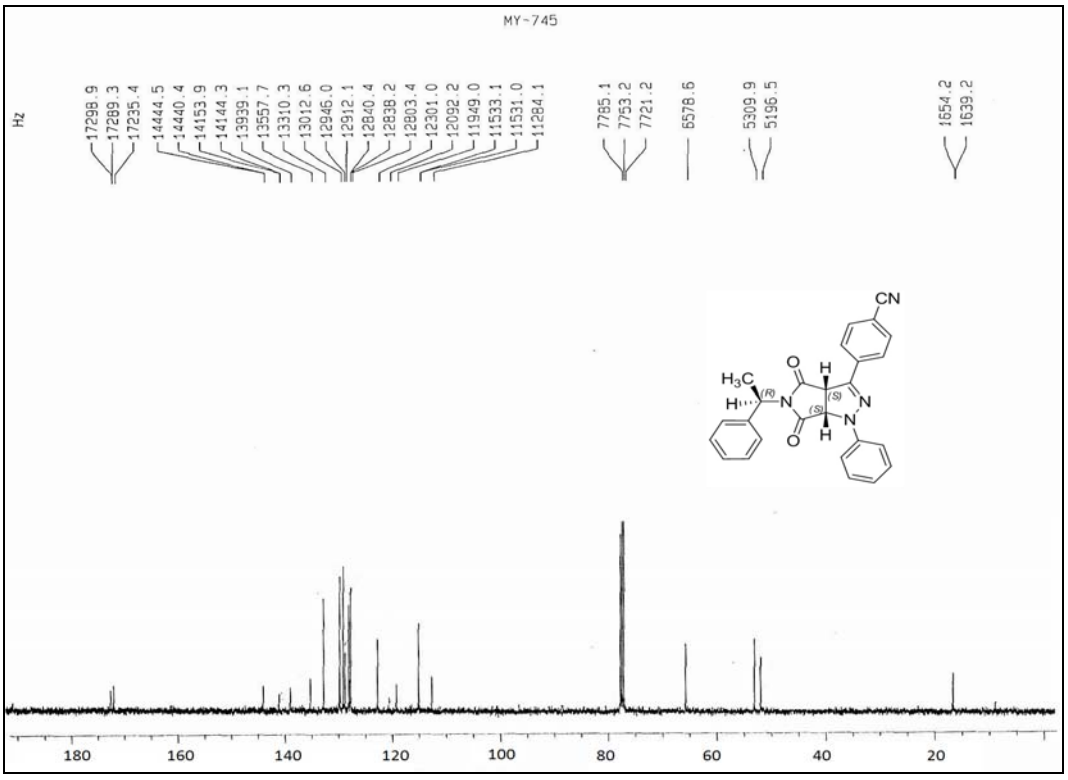

Figure 7.160 ^{13}C-NMR spectrum of compound **6.19g** in $CDCl_3$

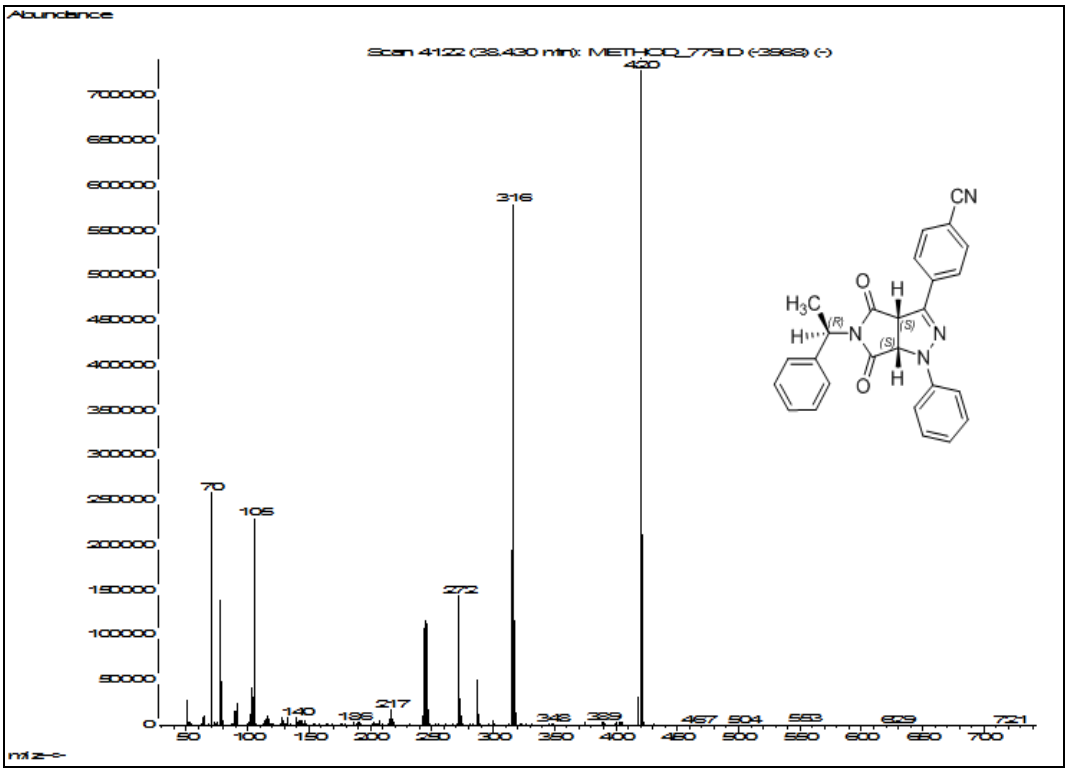

Figure 7.161 Mass spectrum of compound **6.19g**

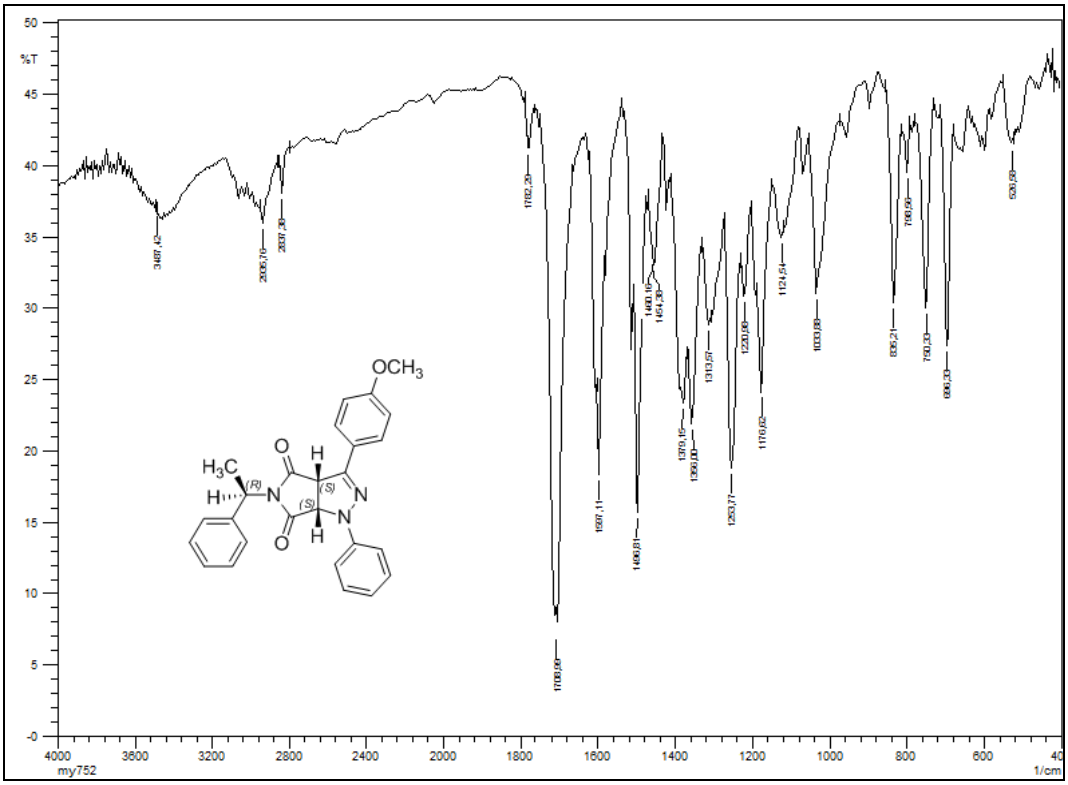

Figure 7.162 IR spectrum of compound **6.19h**

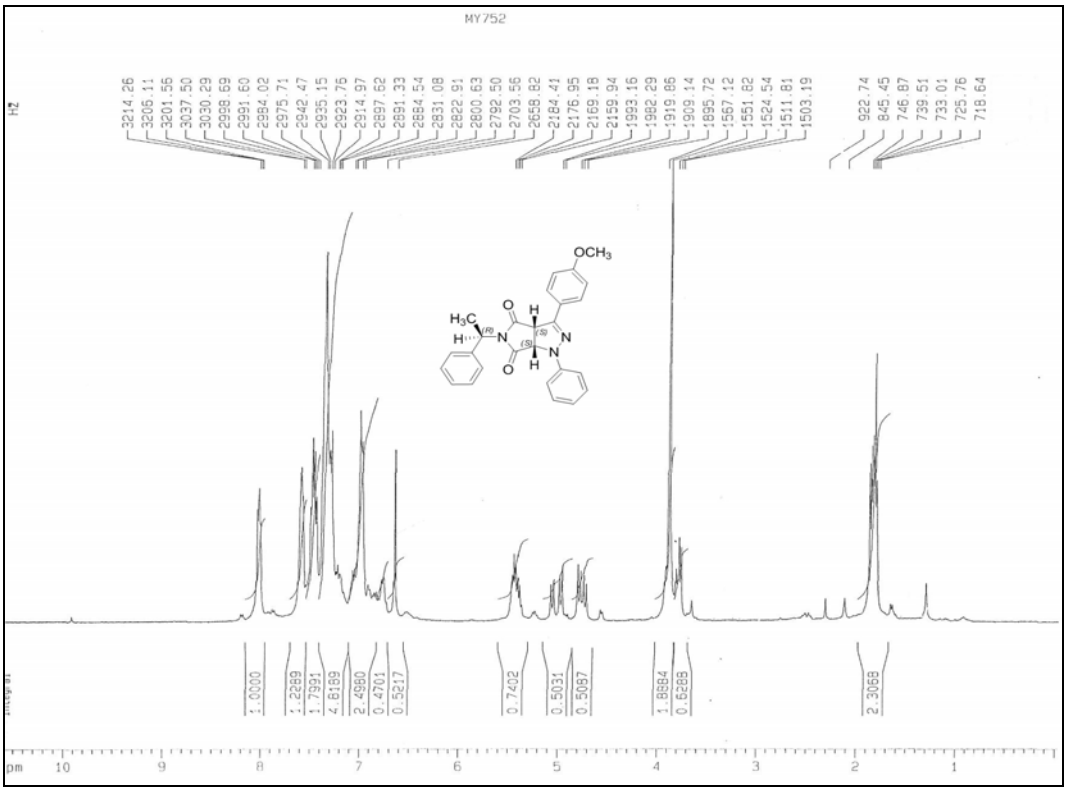

Figure 7.163 ^{1}H-NMR spectrum of compound **6.19h** in $CDCl_3$

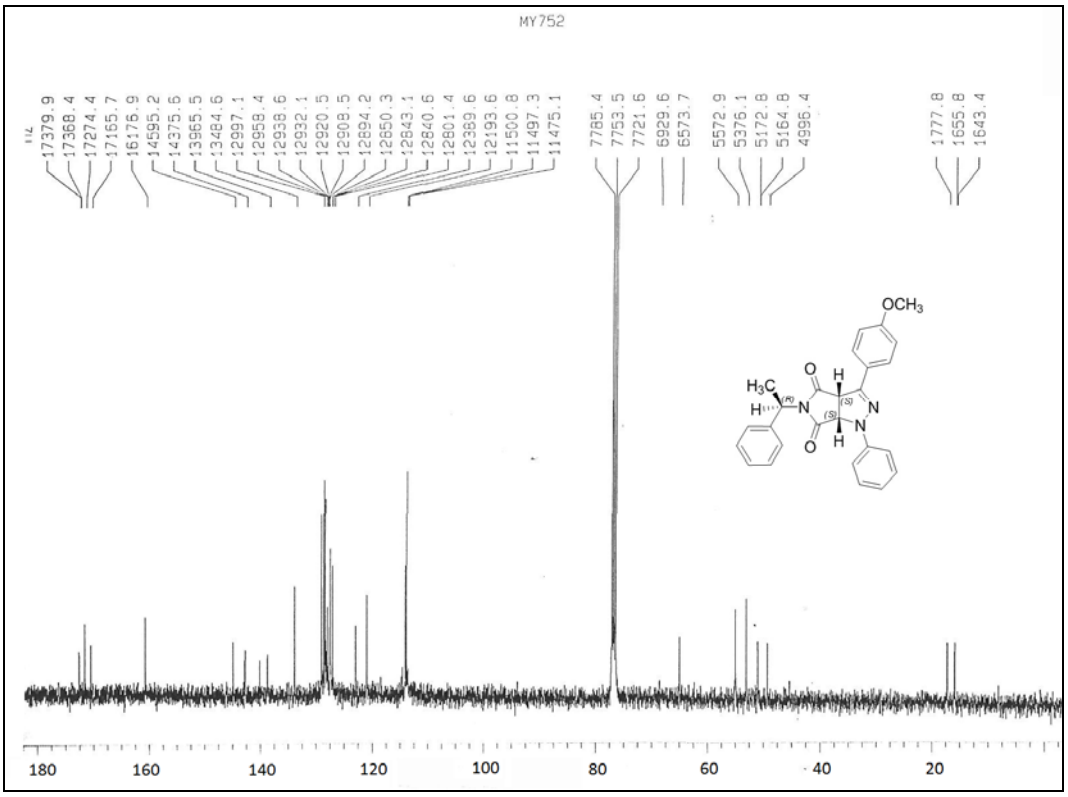

Figure 7.164 ^{13}C-NMR spectrum of compound **6.19h** in $CDCl_3$

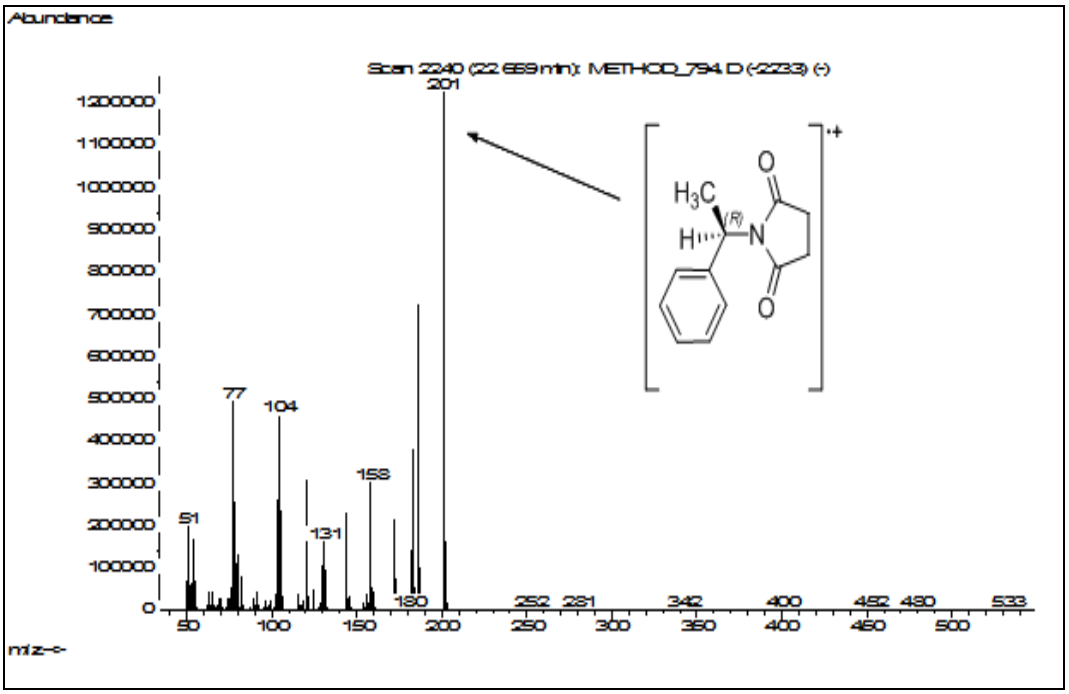

Figure 7.165 Mass spectrum of compound **6.19h**

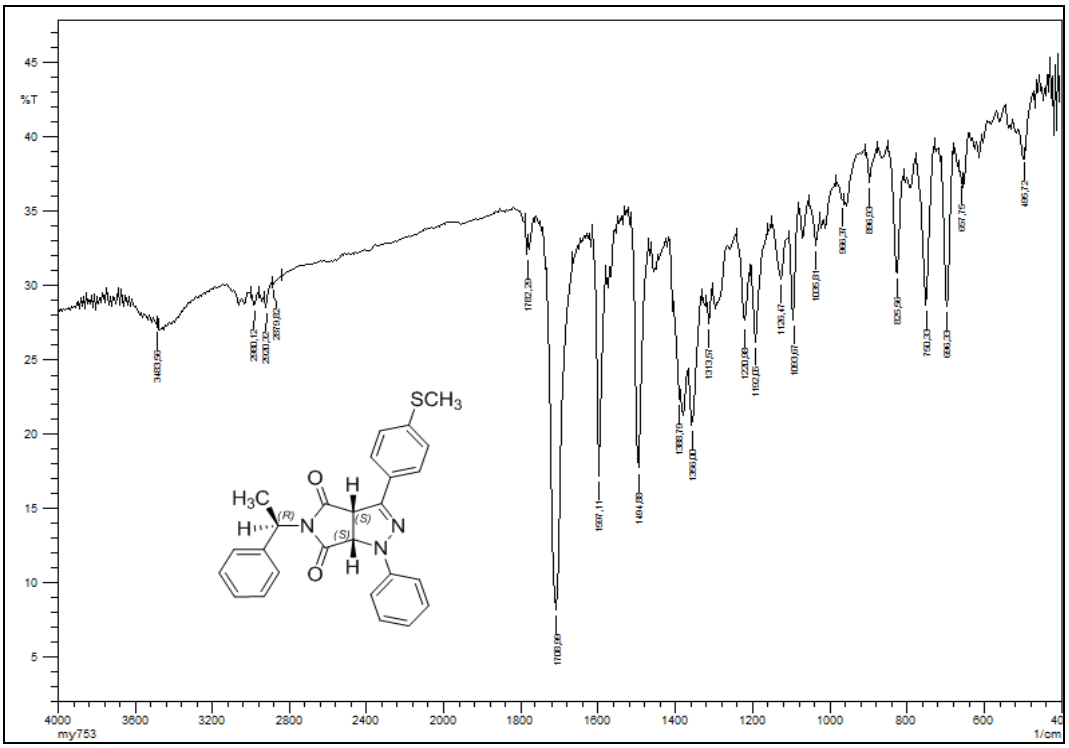

Figure 7.166 IR spectrum of compound **6.19i**

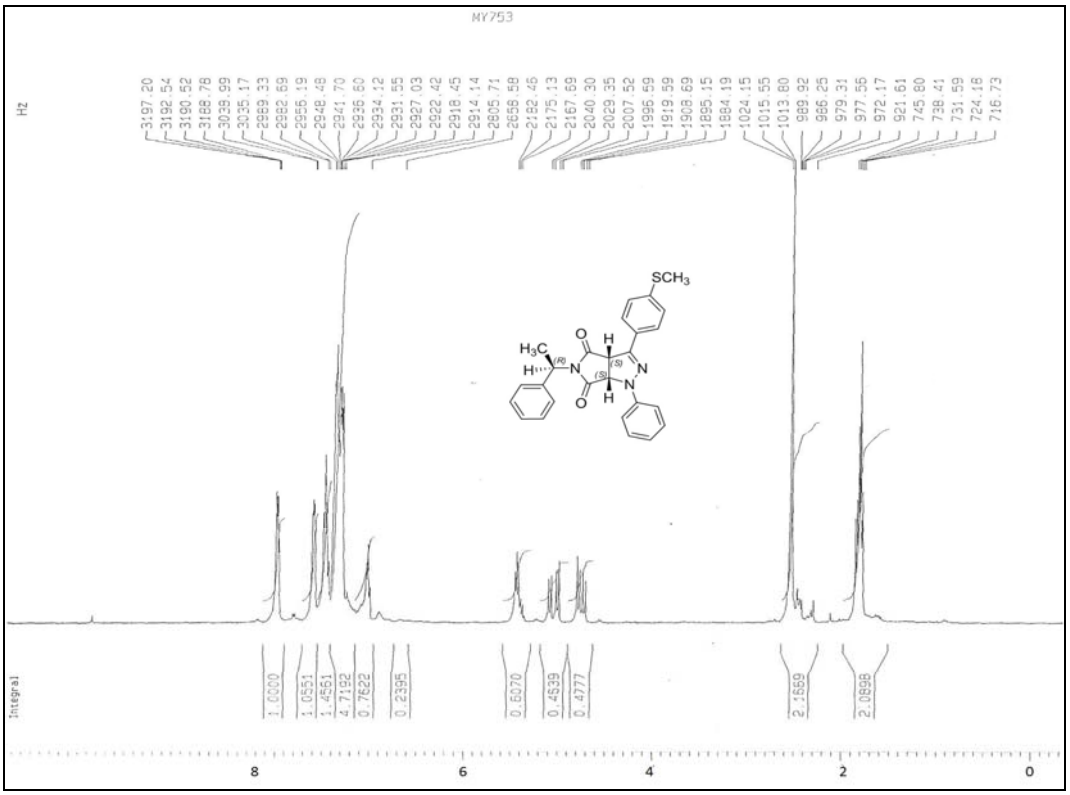

Figure 7.167 ^{1}H-NMR spectrum of compound **6.19i** in $CDCl_3$

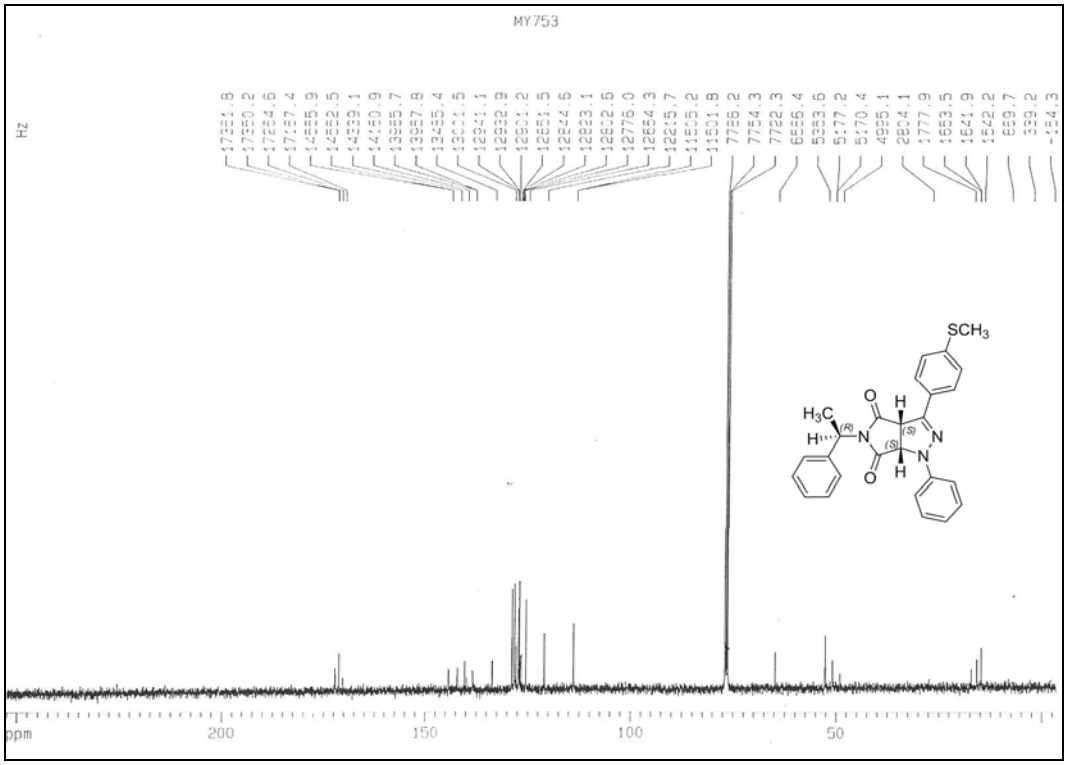

Figure 7.168 ^{13}C-NMR spectrum of compound **6.19i** in $CDCl_3$

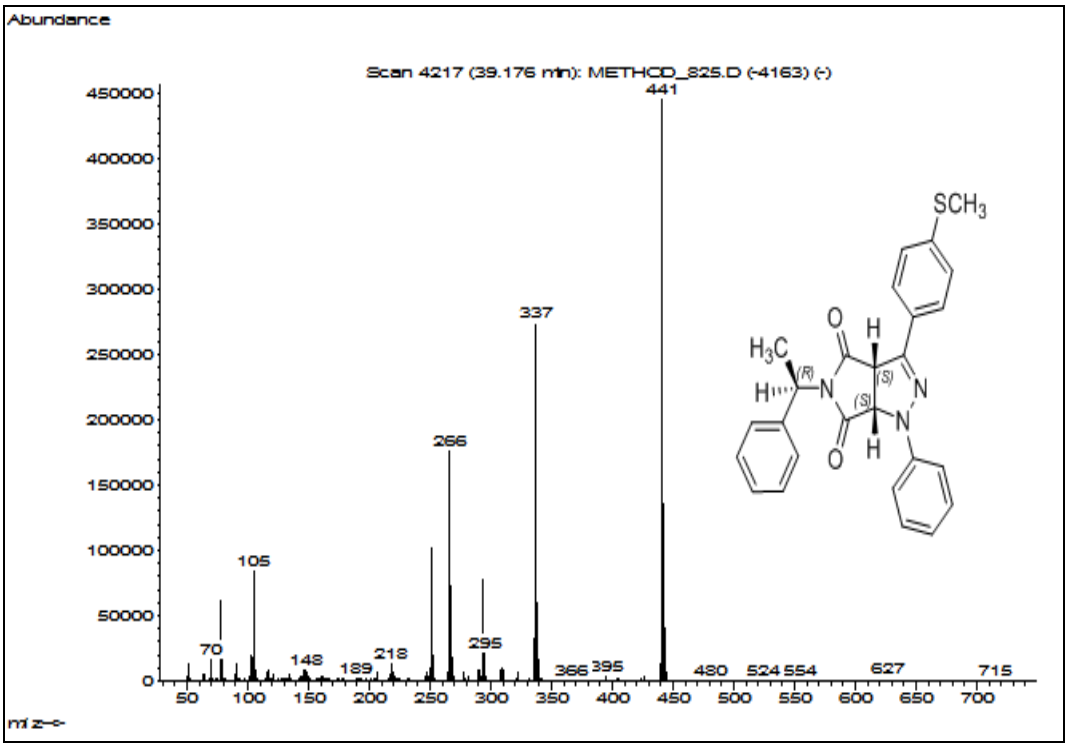

Figure 7.169 Mass spectrum of compound **6.19i**

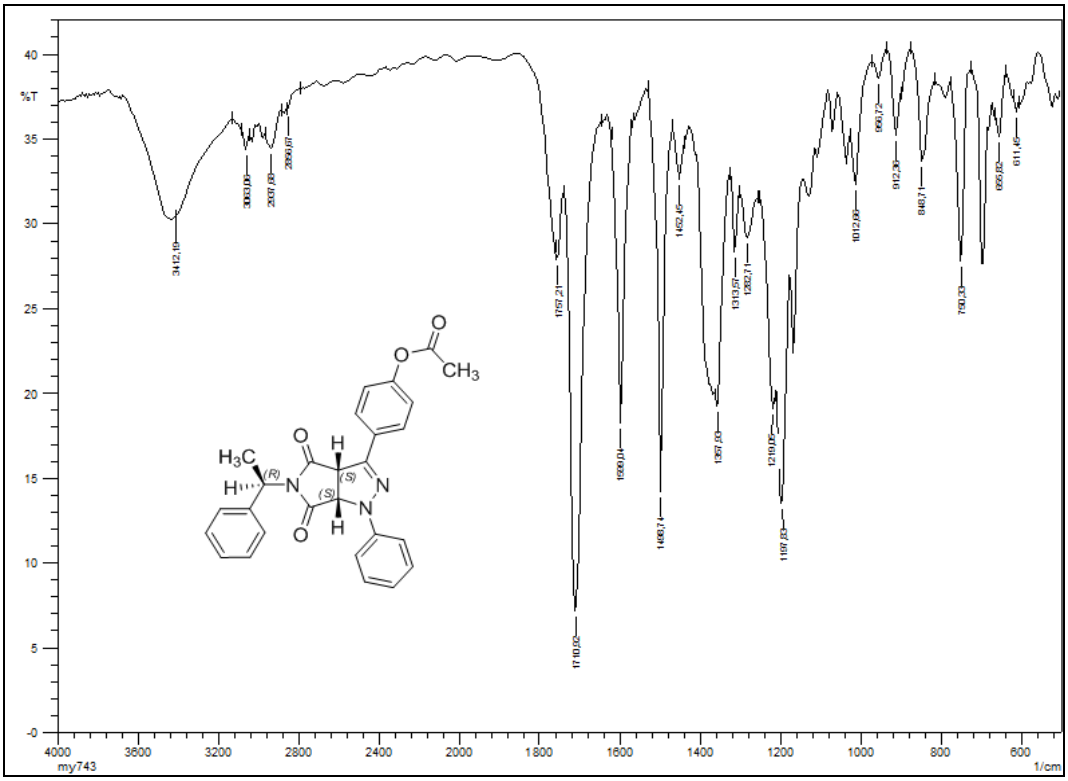

Figure 7.170 IR spectrum of compound **6.19j**

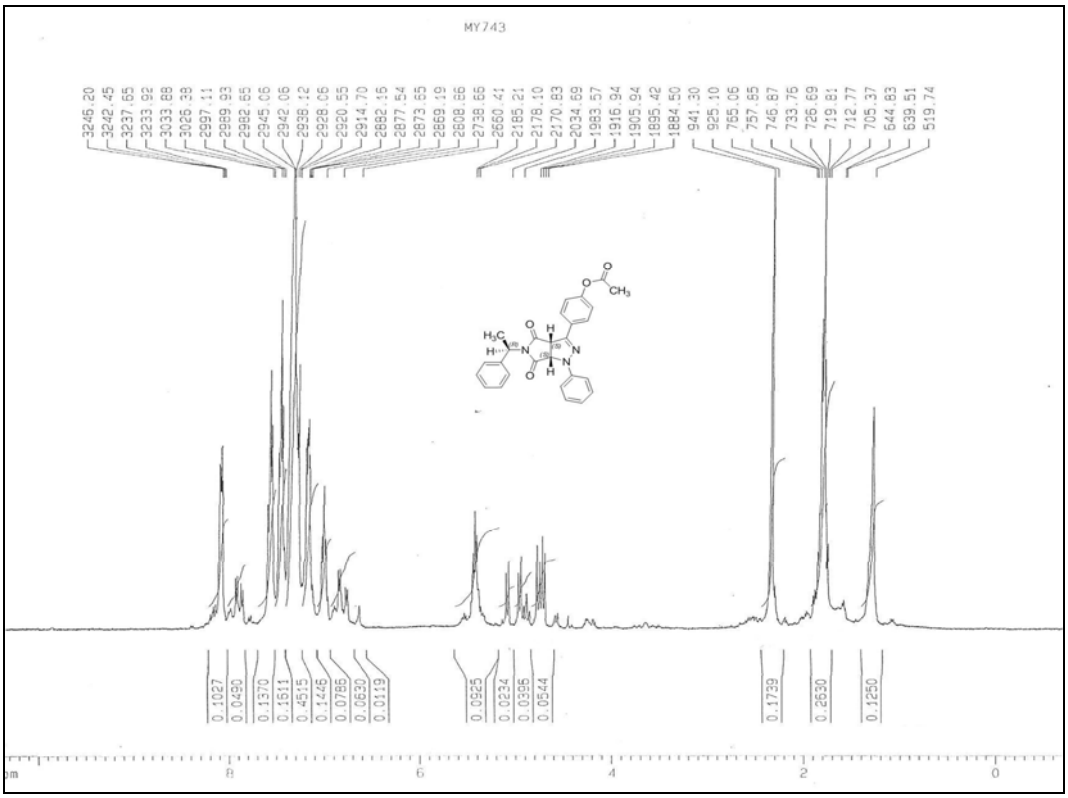

Figure 7.171 ^{1}H-NMR spectrum of compound **6.19j** in $CDCl_3$

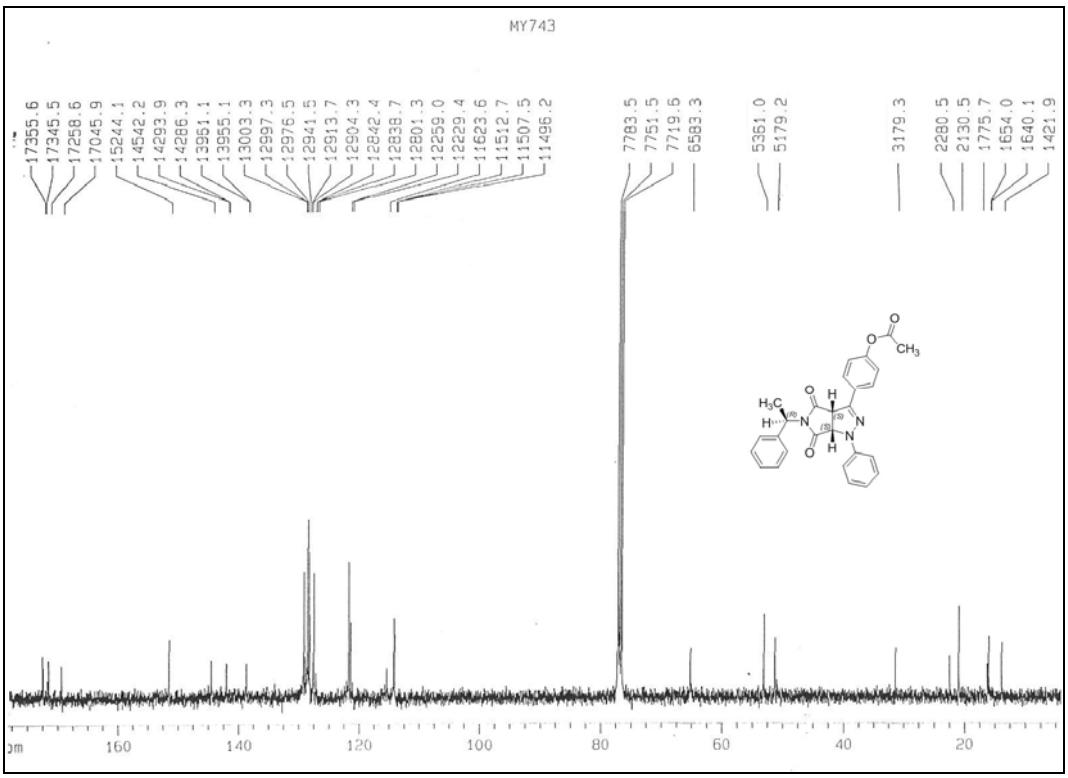

Figure 7.172 ^{13}C-NMR spectrum of compound **6.19j** in $CDCl_3$

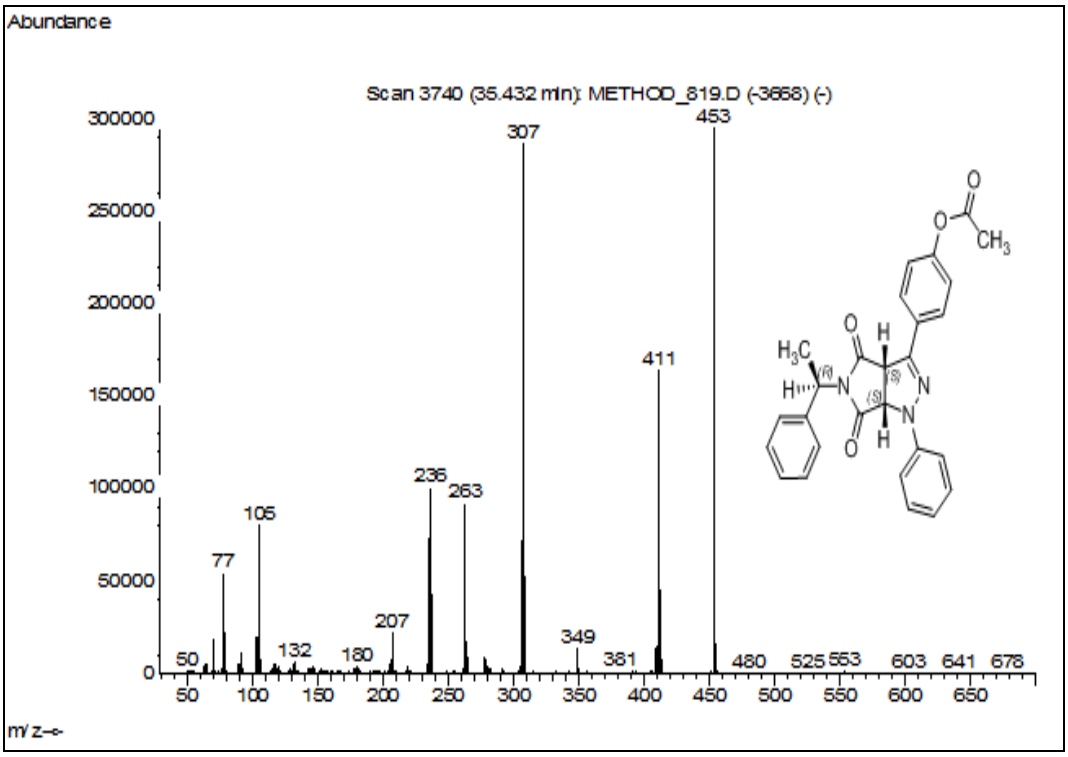

Figure 7.173 Mass spectrum of compound **6.19j**

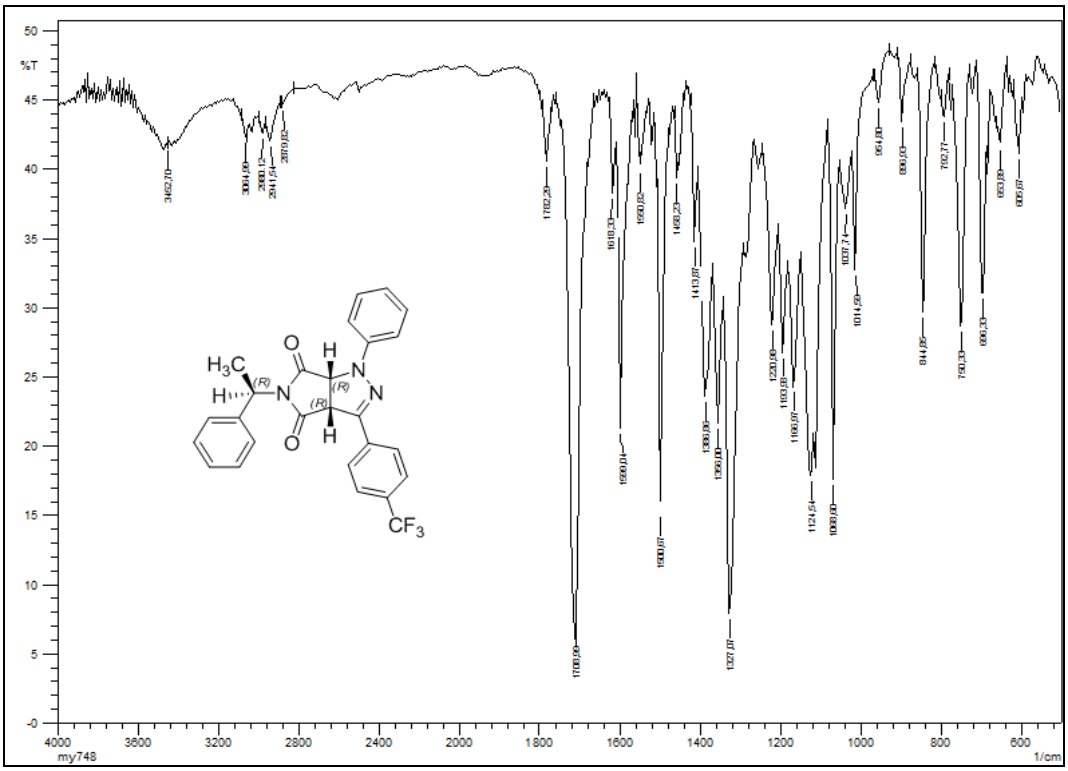

Figure 7.174 IR spectrum of compound **6.19k'**

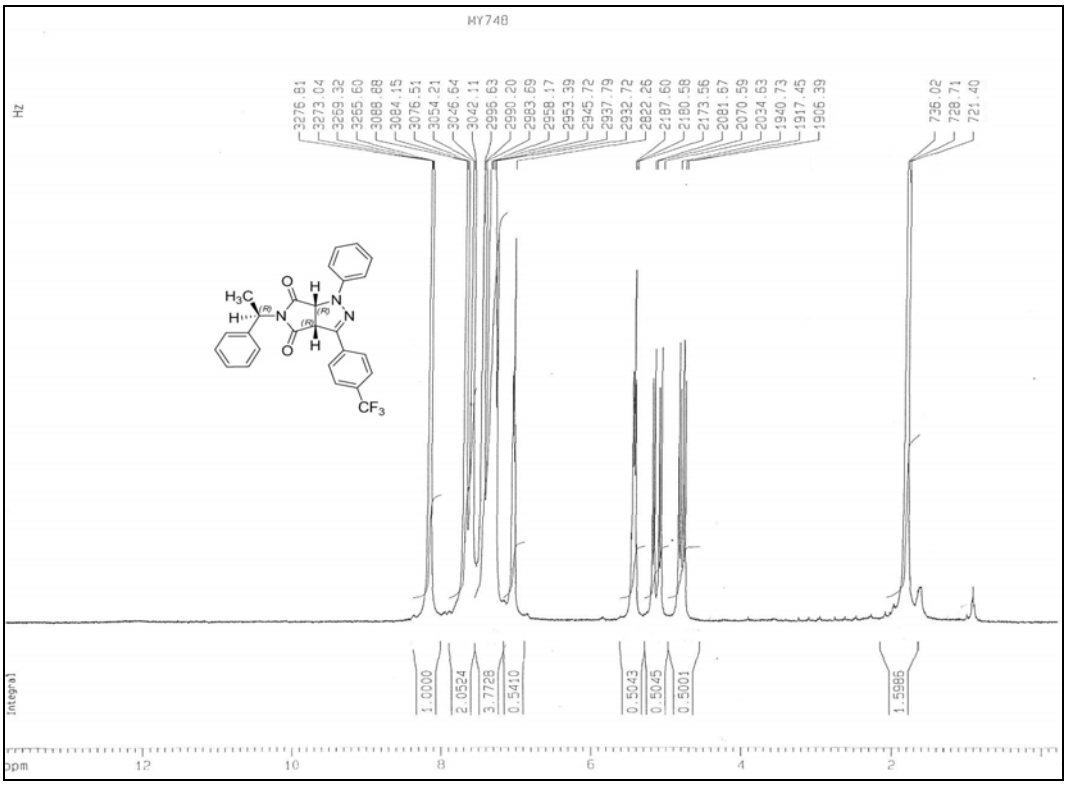

Figure 7.175 ^{1}H-NMR spectrum of compound **6.19k'** in $CDCl_3$

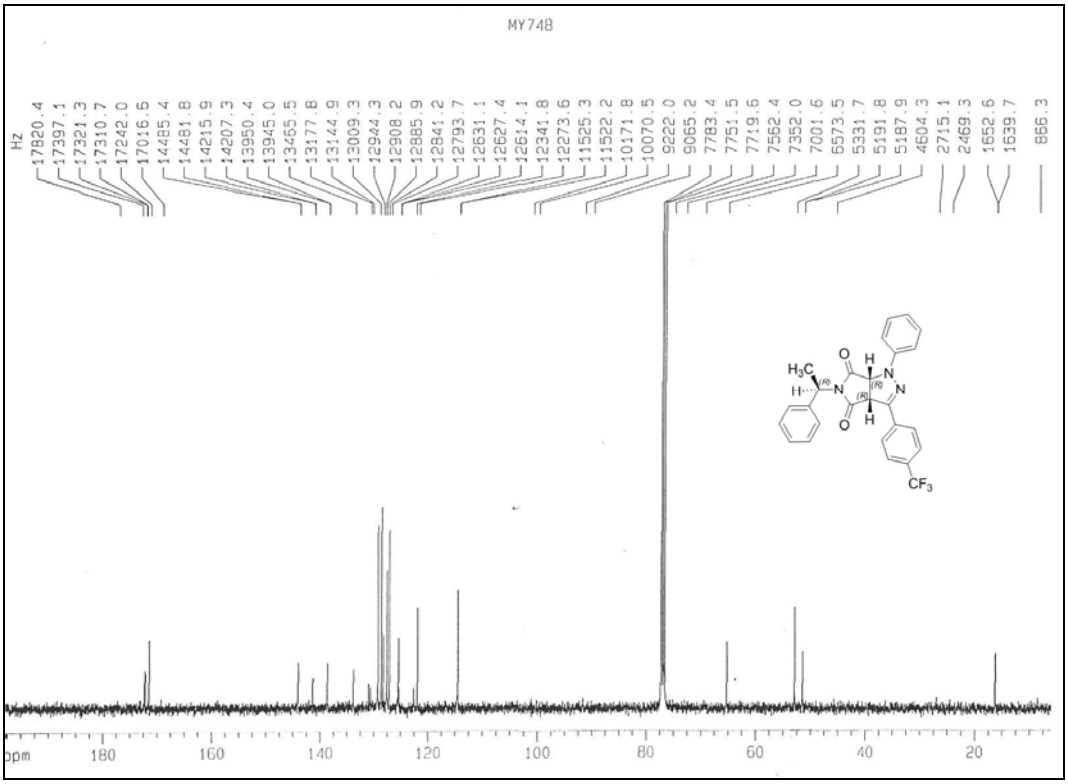

Figure 7.176 ^{13}C-NMR spectrum of compound **6.19k'** in $CDCl_3$

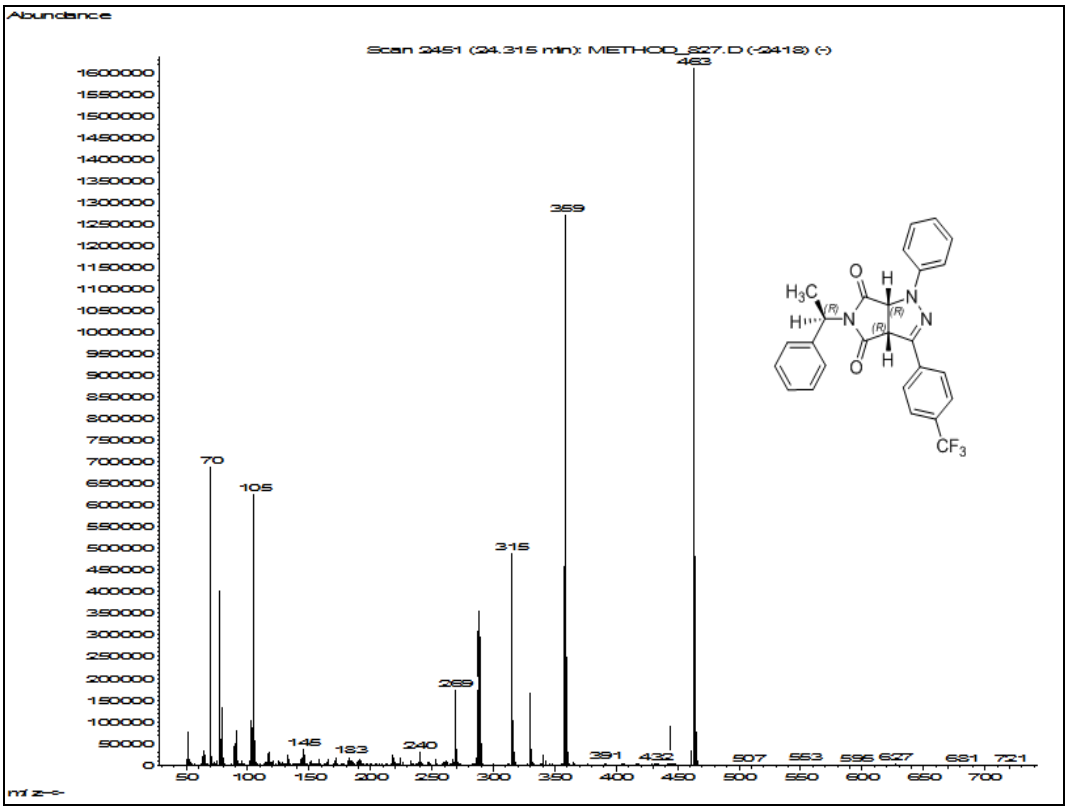

Figure 7.177 Mass spectrum of compound **6.19k'**

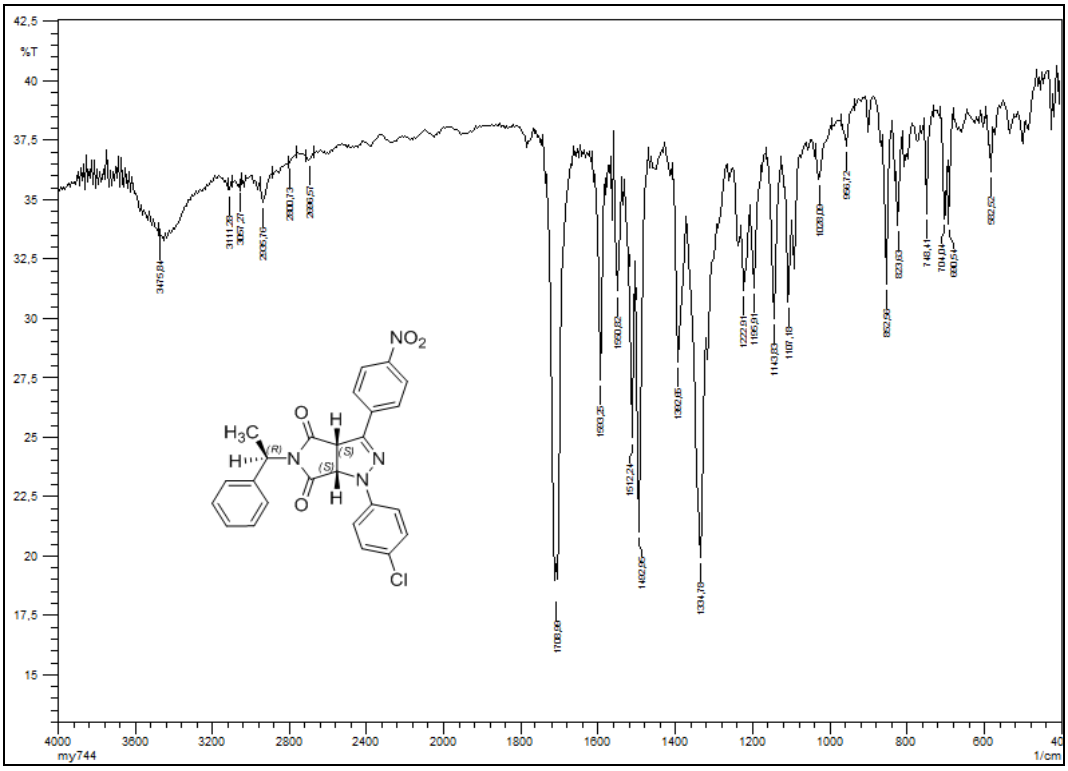

Figure 7.178 IR spectrum of compound **6.19r**

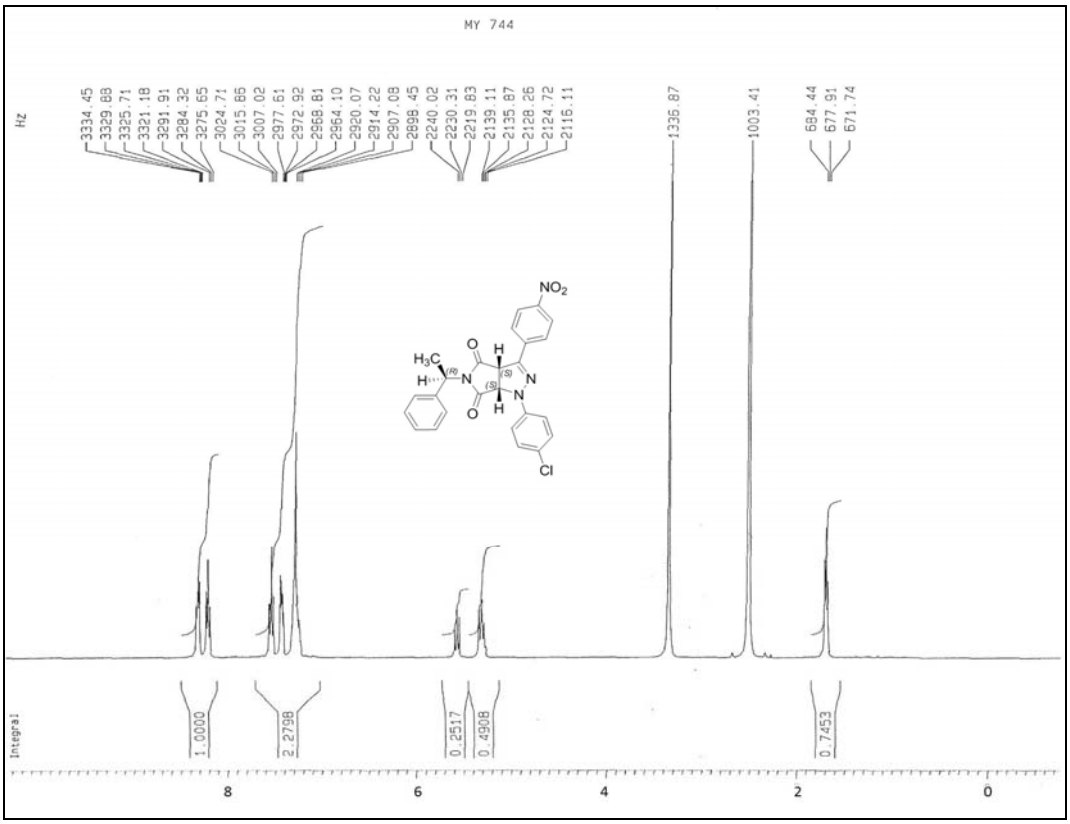

Figure 7.179 ^{1}H-NMR spectrum of compound **6.19r** in DMSO-d_6

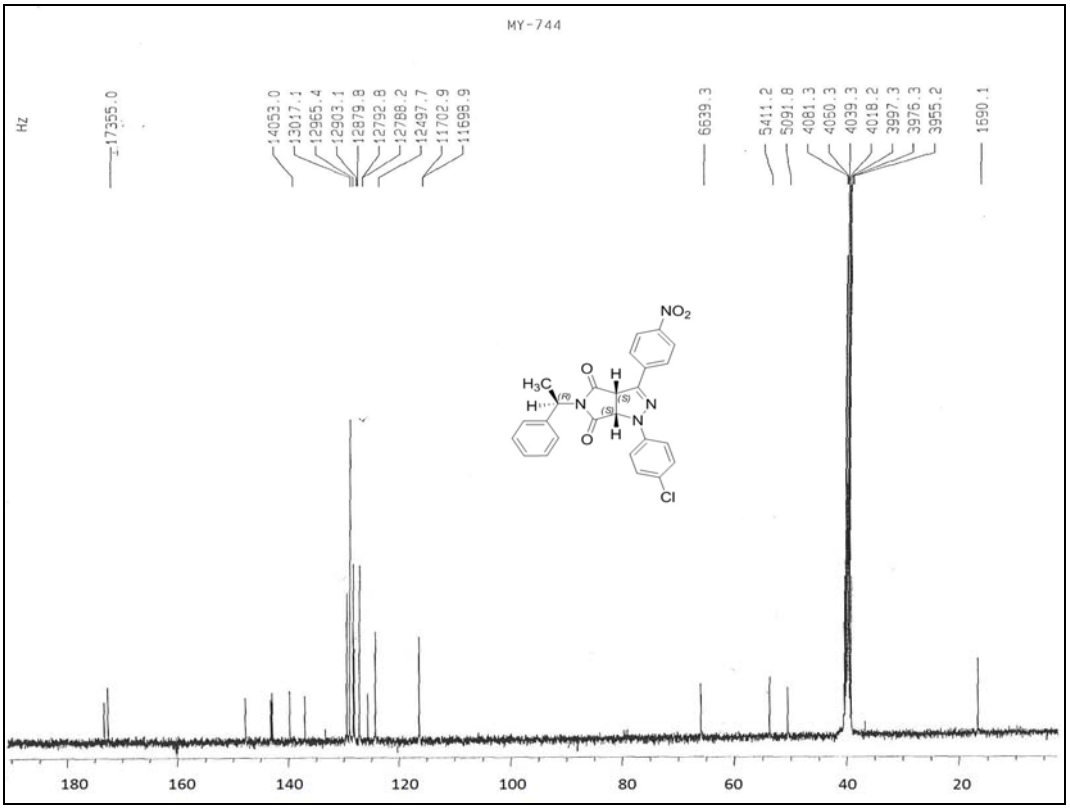

Figure 7.180 ^{13}C-NMR spectrum of compound **6.19r** in DMSO-d_6

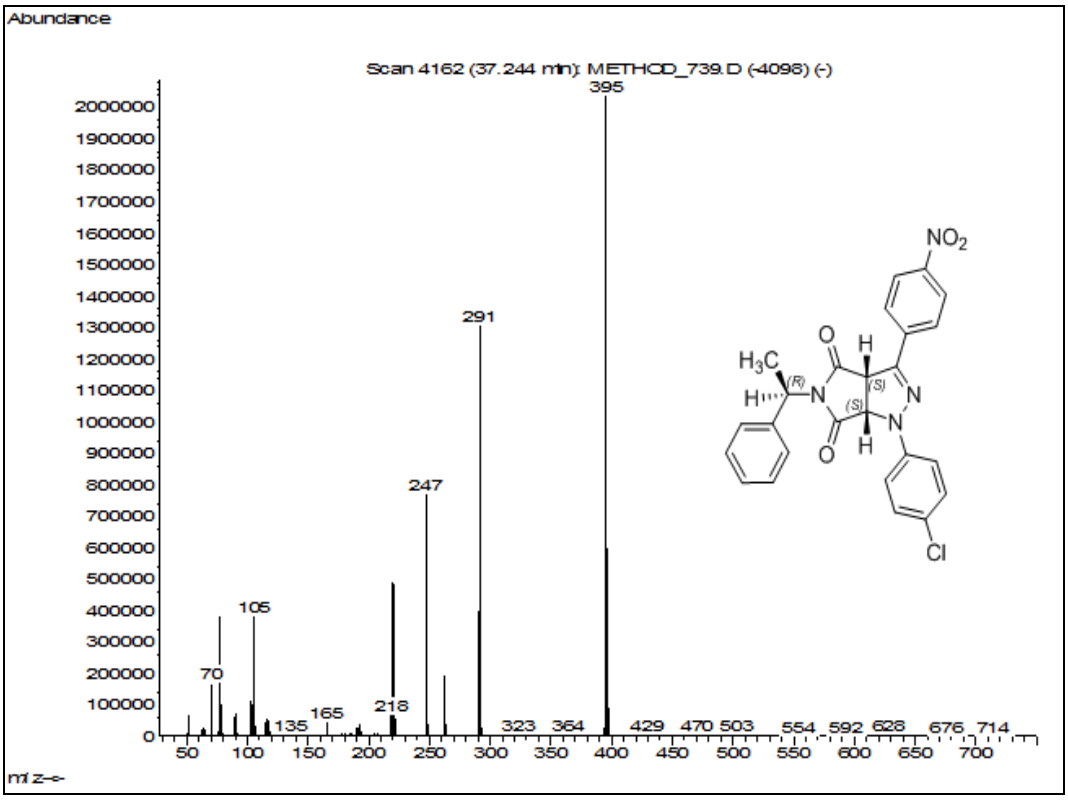

Figure 7.181 Mass spectrum of compound **6.19r**

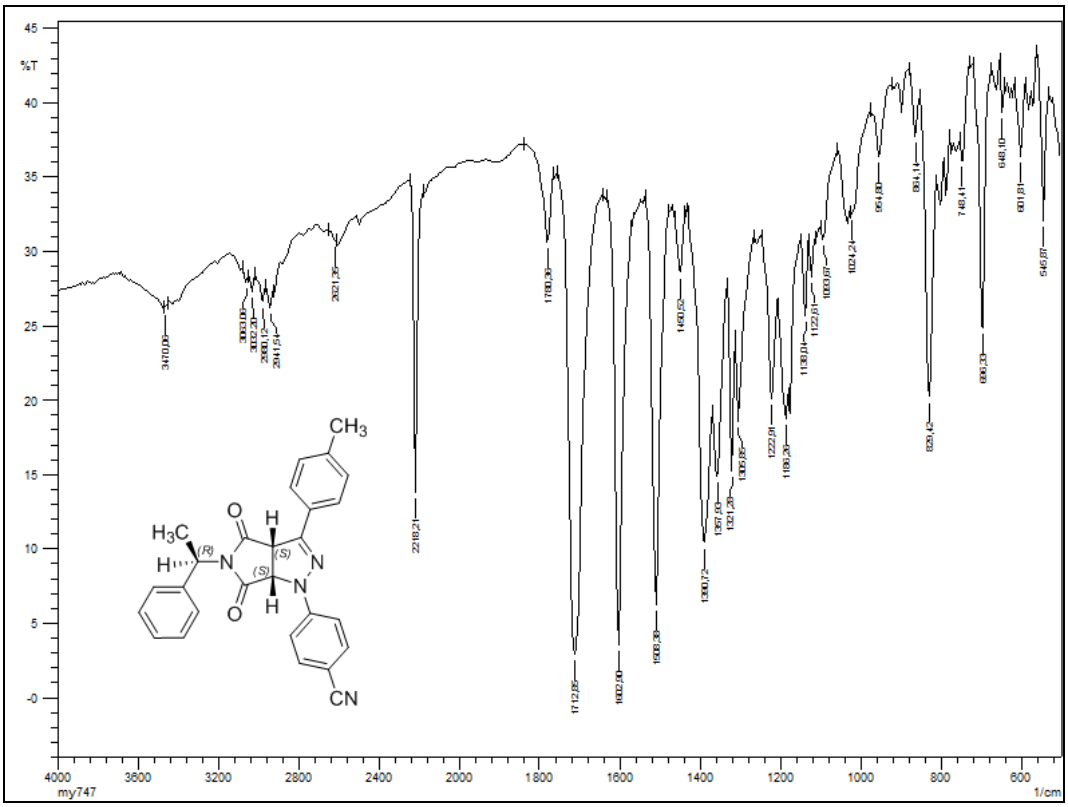

Figure 7.182 IR spectrum of compound **6.19u**

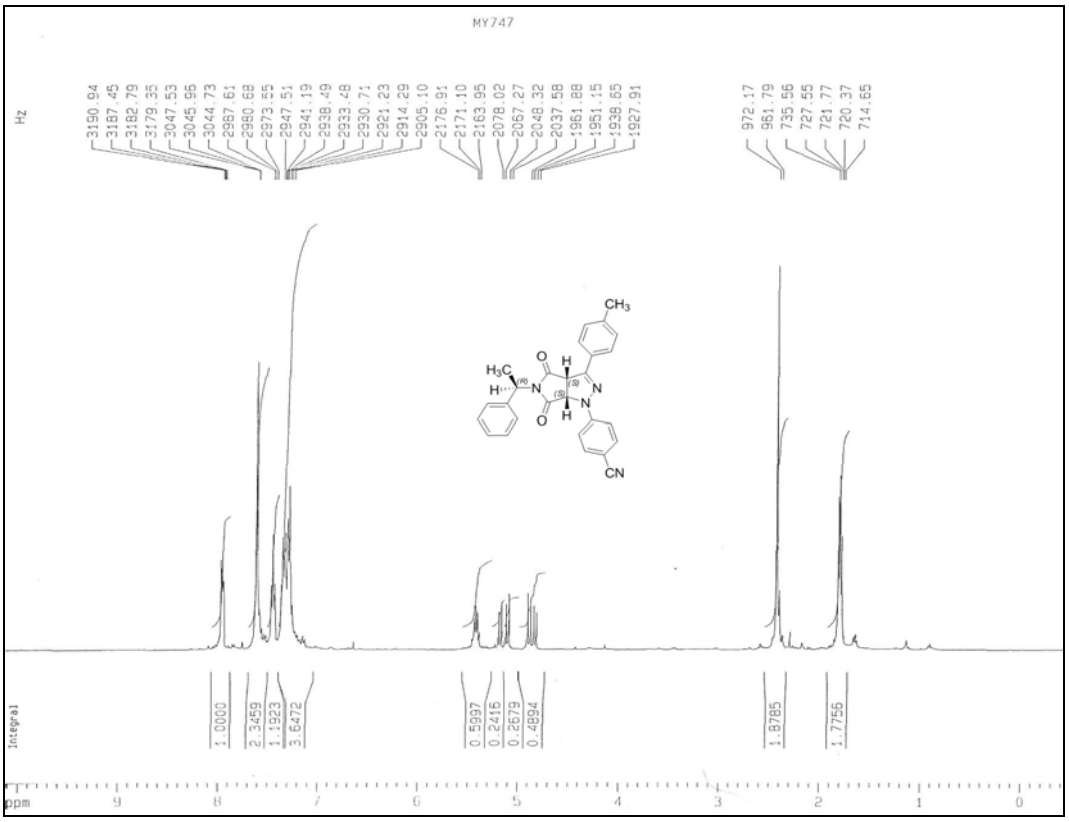

Figure 7.183 ^{1}H-NMR spectrum of compound **6.19u** in $CDCl_3$

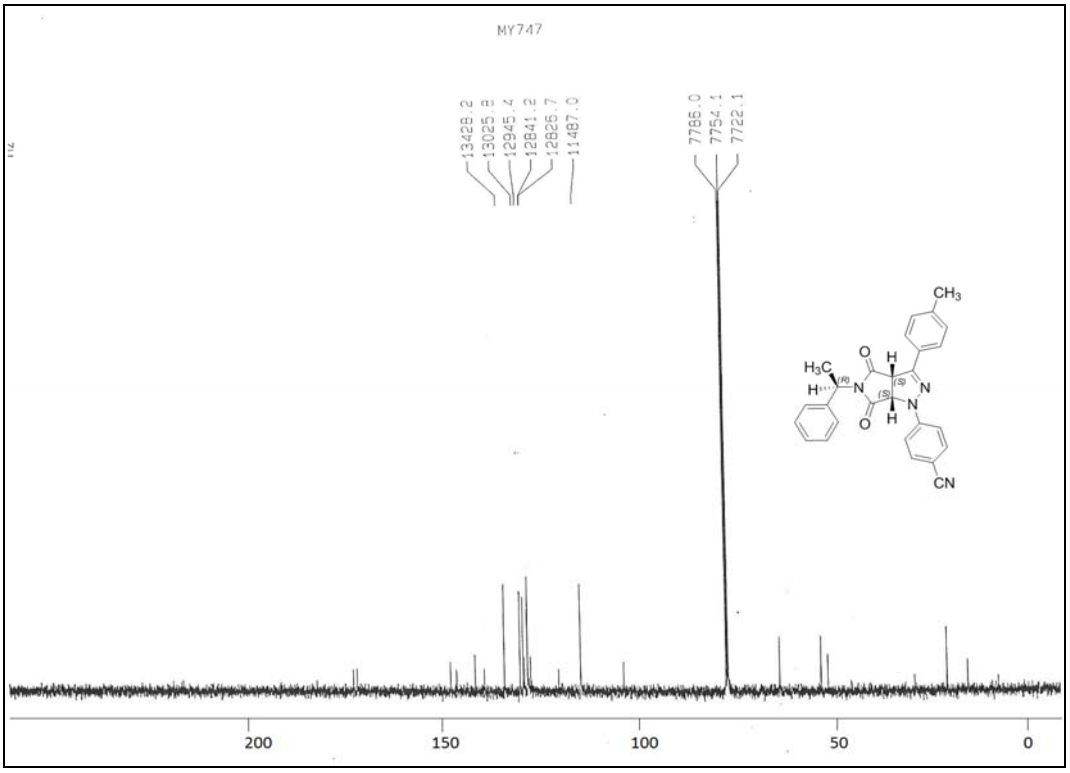

Figure 7.184 ^{13}C-NMR spectrum of compound **6.19u** in $CDCl_3$

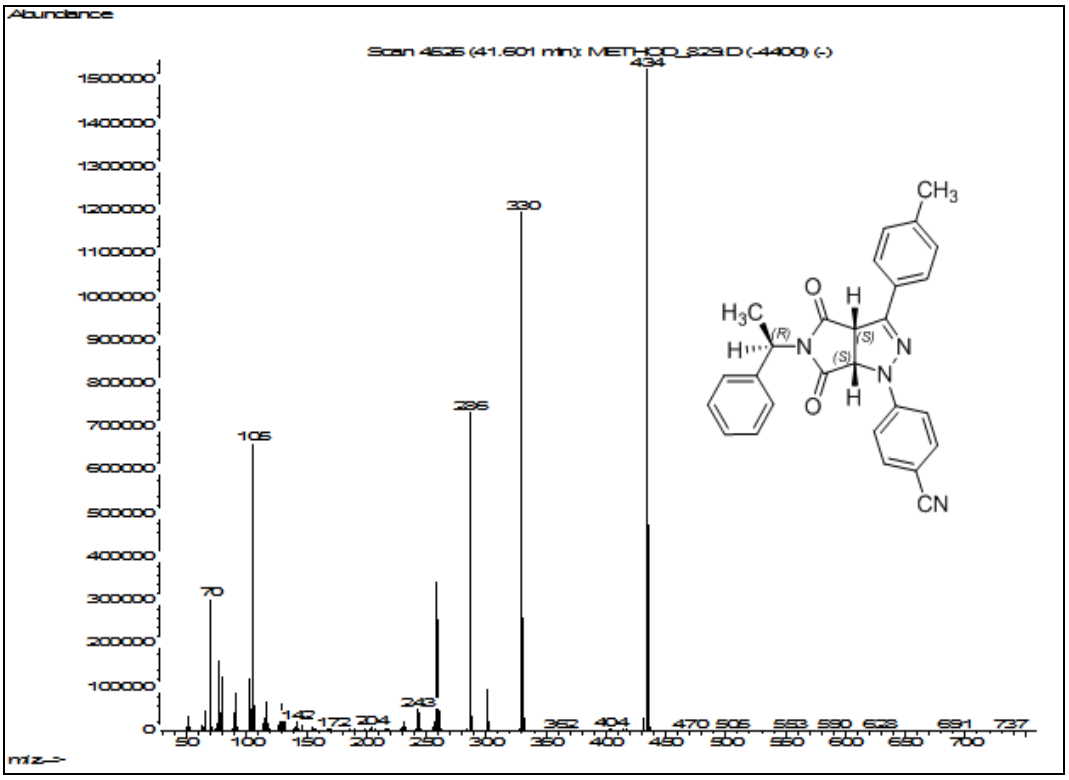

Figure 7.185 Mass spectrum of compound **6.19u**

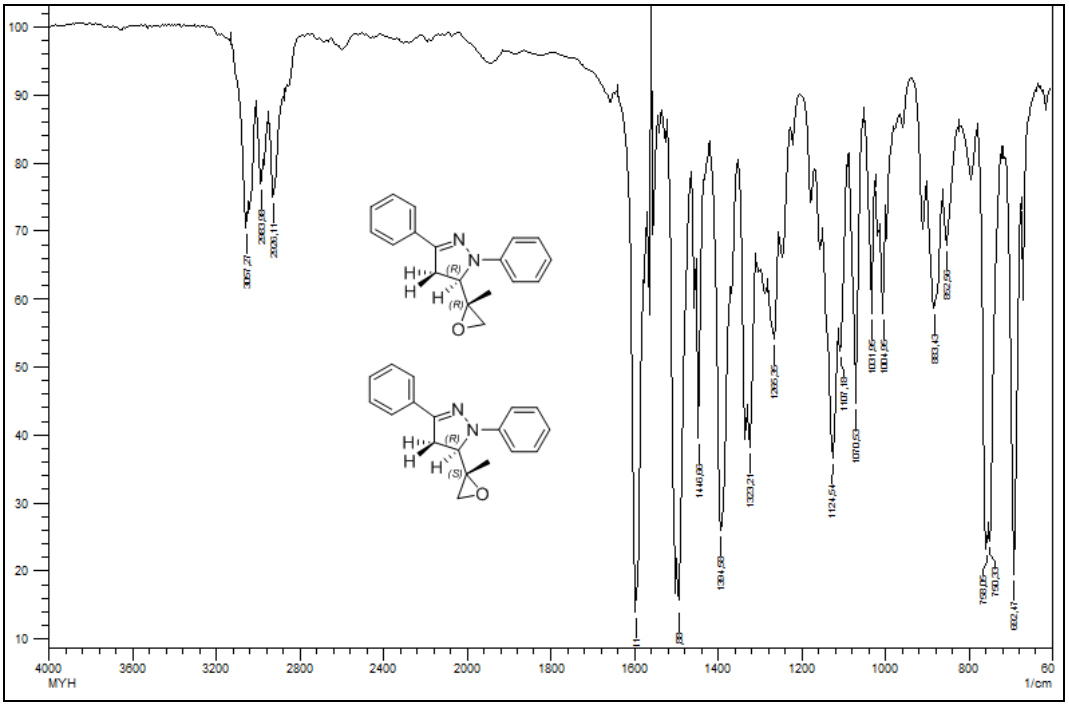

Figure 7.186 IR spectrum of compounds **6.21a-a'**

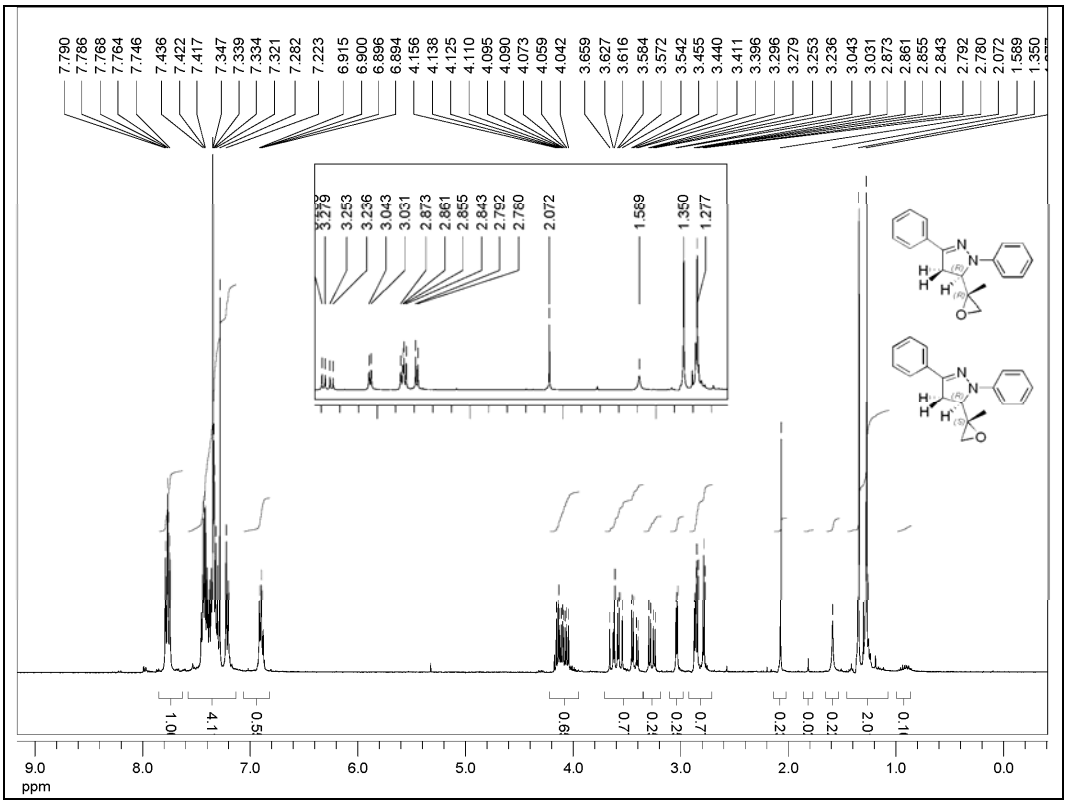

Figure 7.187 ^{1}H-NMR spectrum of compounds **6.21a-a'** in $CDCl_3$

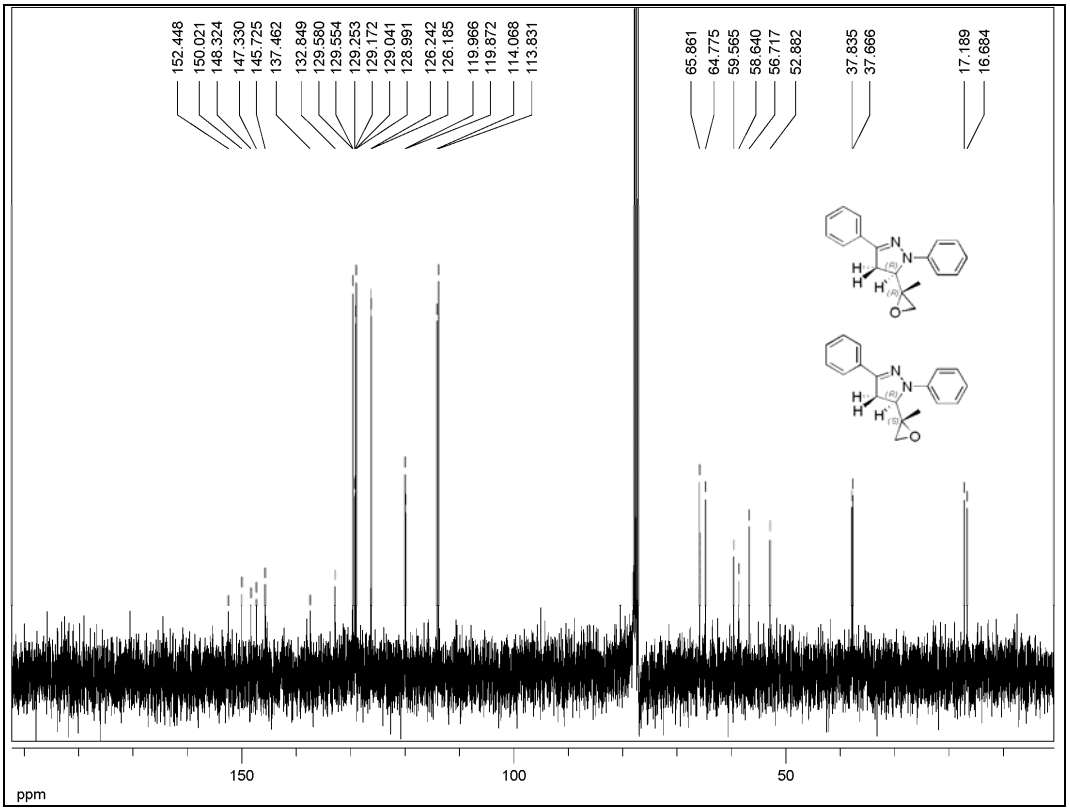

Figure 7.188 ^{13}C-NMR spectrum of compounds **6.21a-a'** in $CDCl_3$

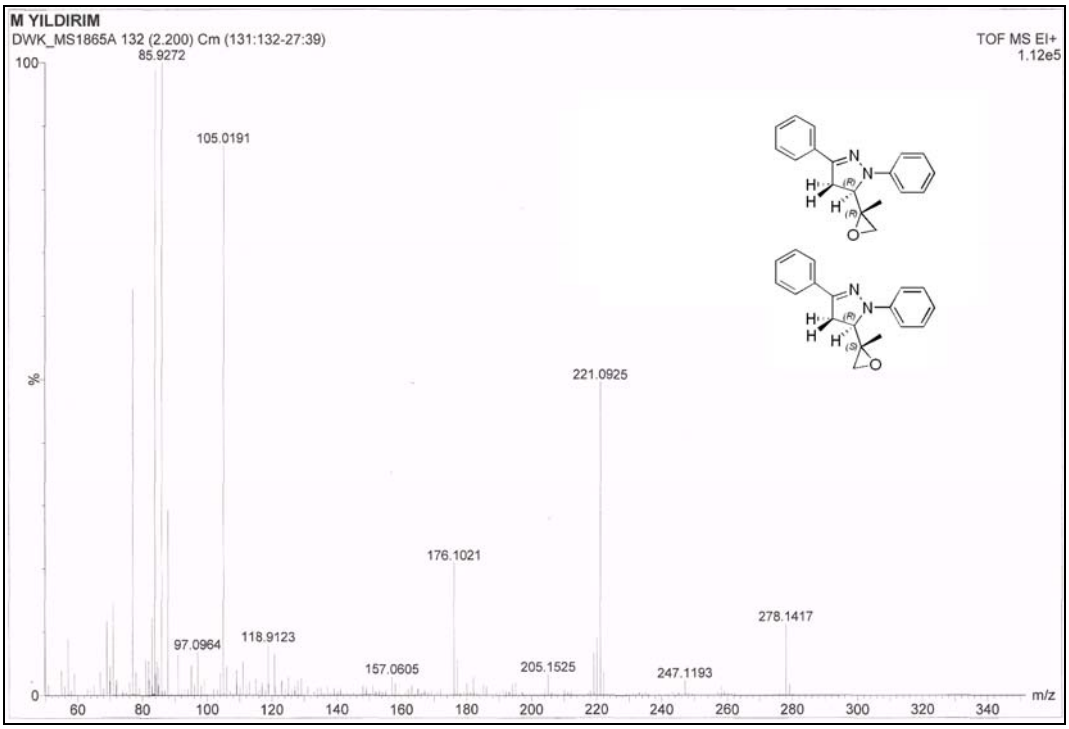

Figure 7.189 Mass spectrum of compounds **6.21a-a'**

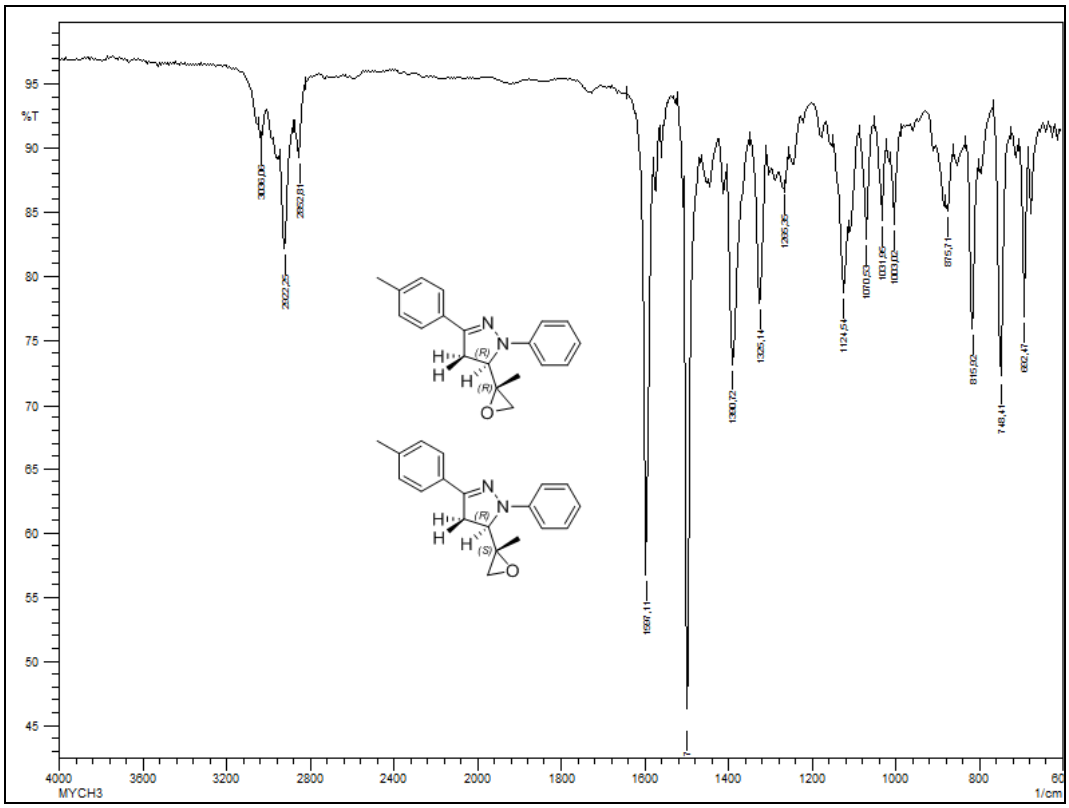

Figure 7.190 IR spectrum of compounds **6.21e-e'**

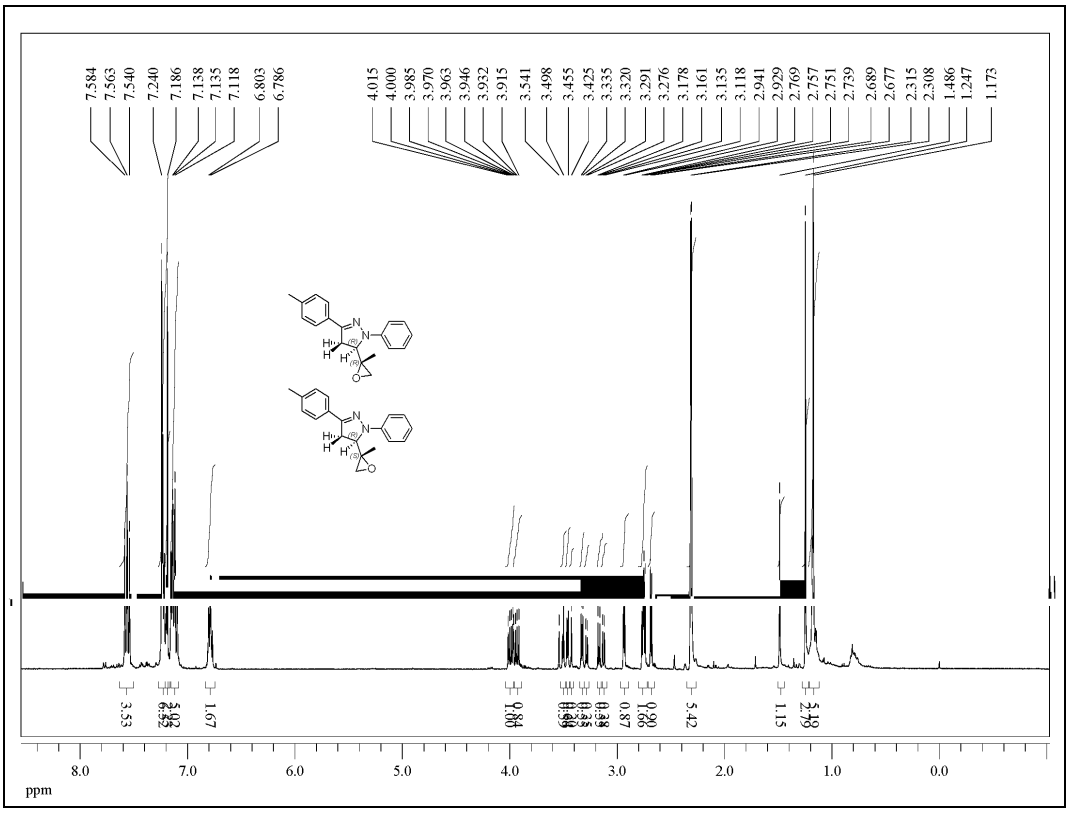

Figure 7.191 ^{1}H-NMR spectrum of compounds **6.21e-e'** in $CDCl_3$

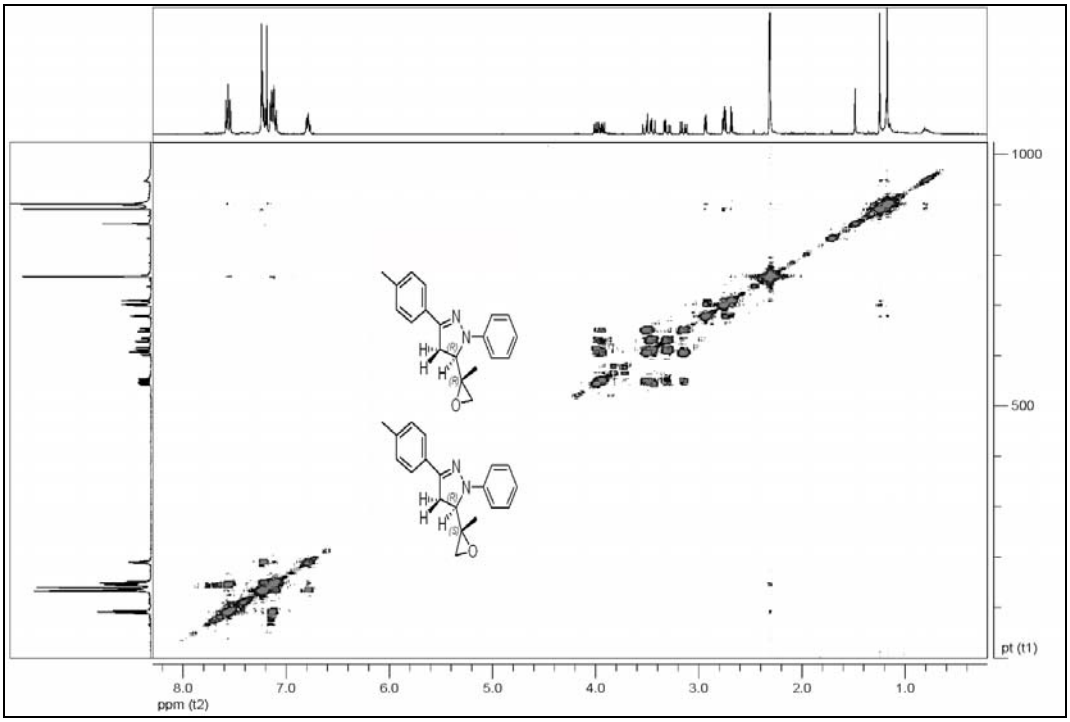

Figure 7.192 COSY-NMR spectrum of compounds **6.21e-e'** in $CDCl_3$

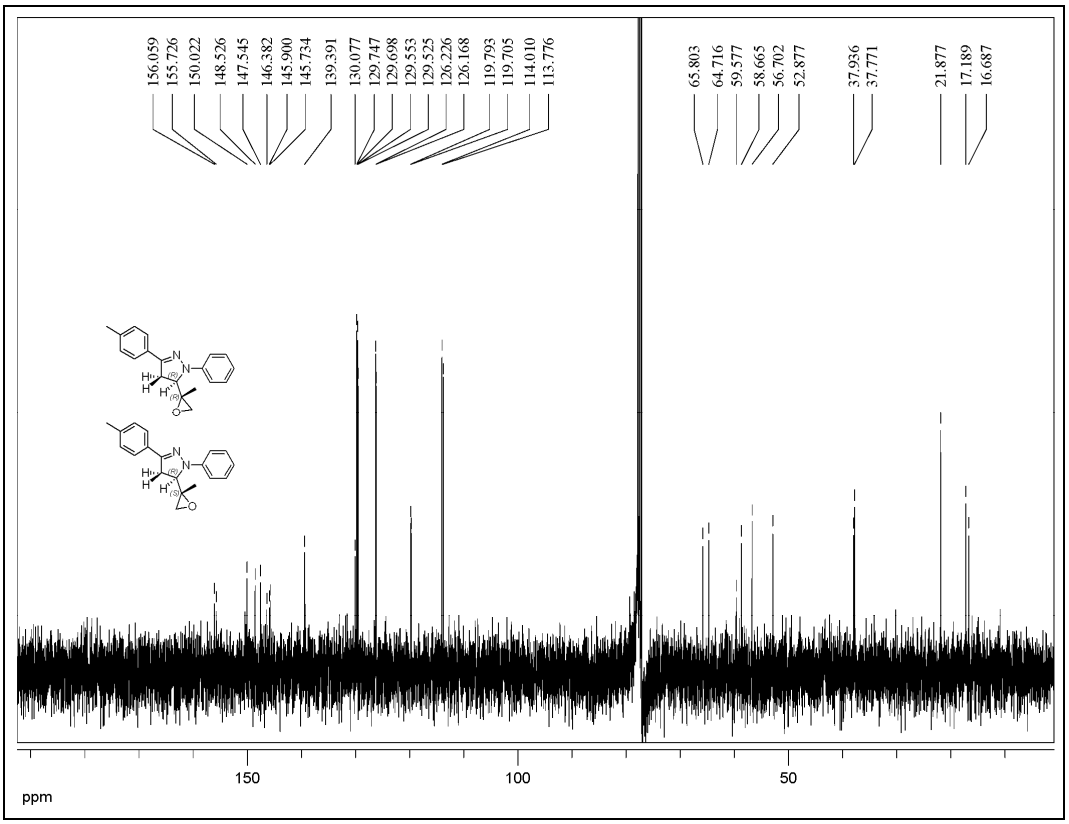

Figure 7.193 ^{13}C-NMR spectrum of compounds **6.21e-e'** in $CDCl_3$

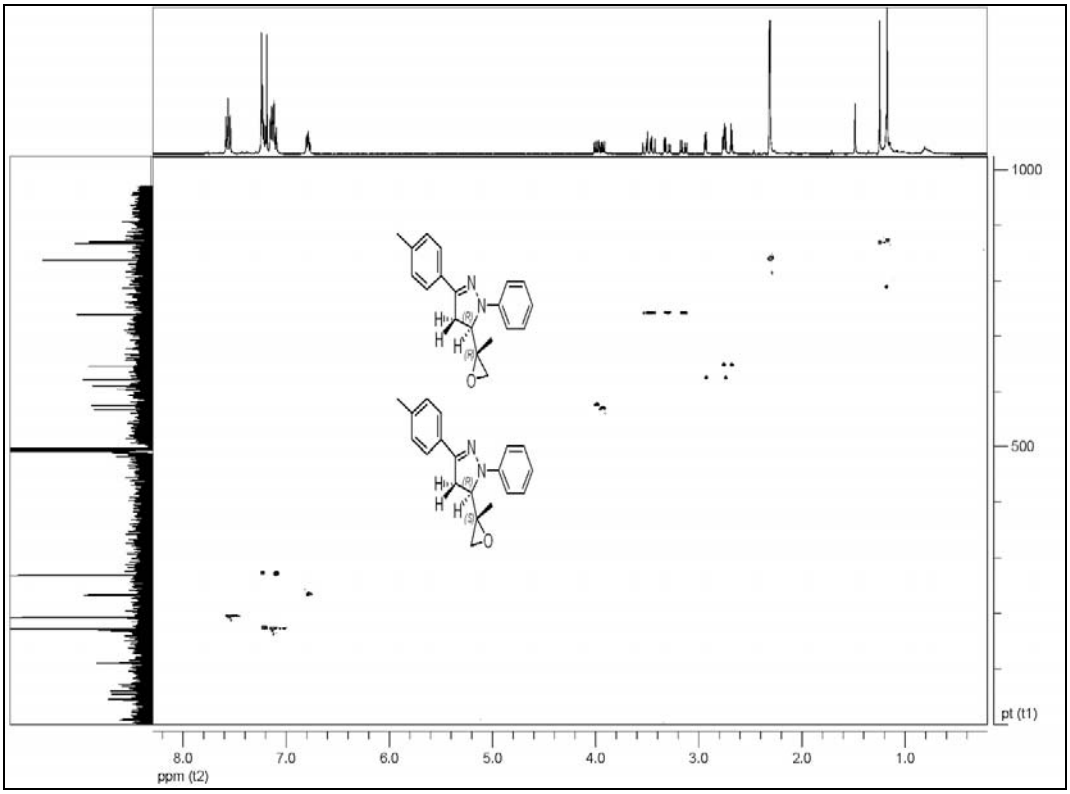

Figure 7.194 HSQC-NMR spectrum of compounds **6.21e-e'** in $CDCl_3$

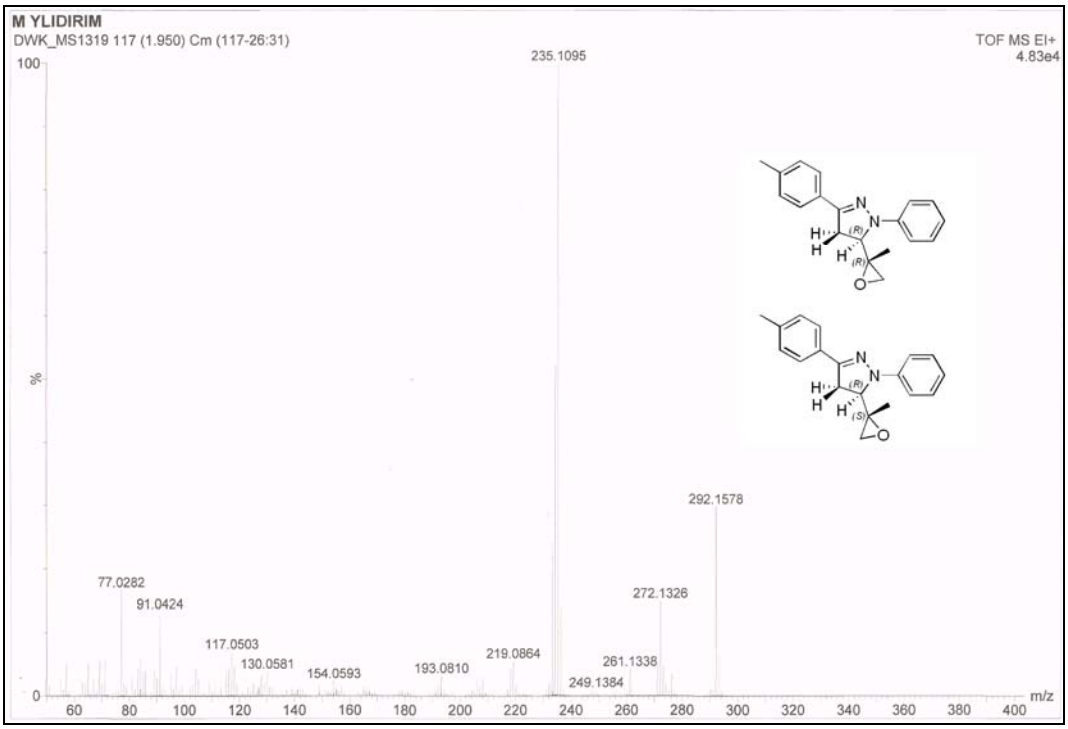

Figure 7.195 Mass spectrum of compounds **6.21e-e'**

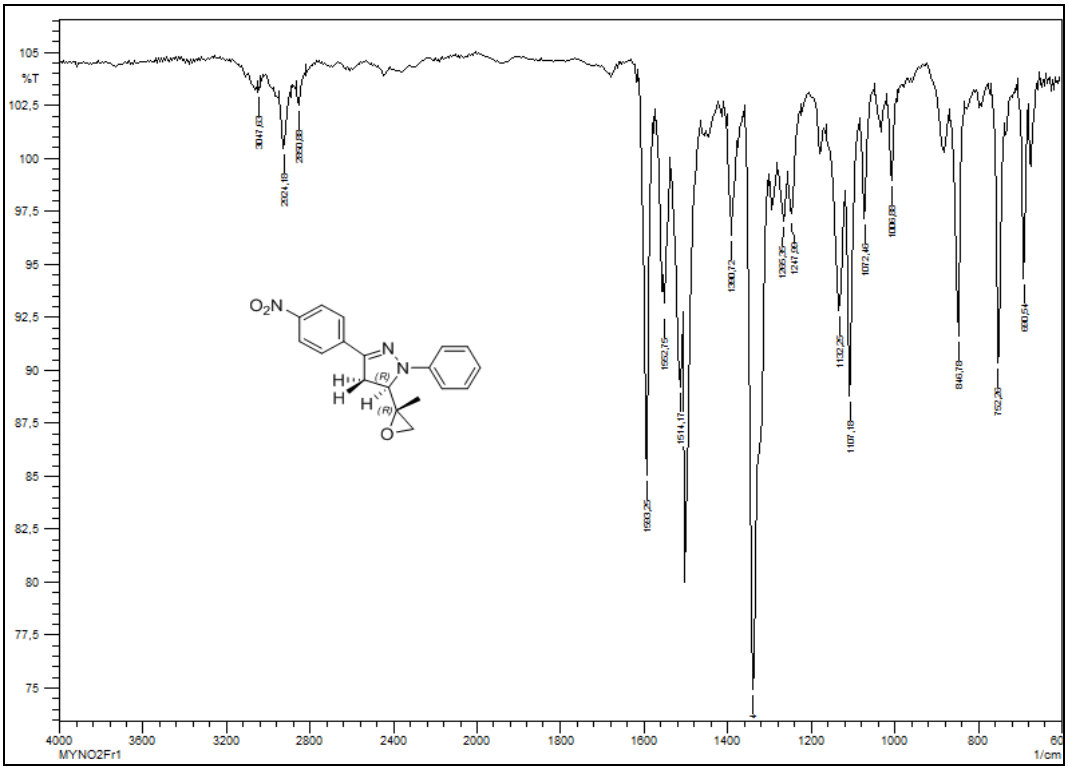

Figure 7.196 IR spectrum of compound **6.21f**

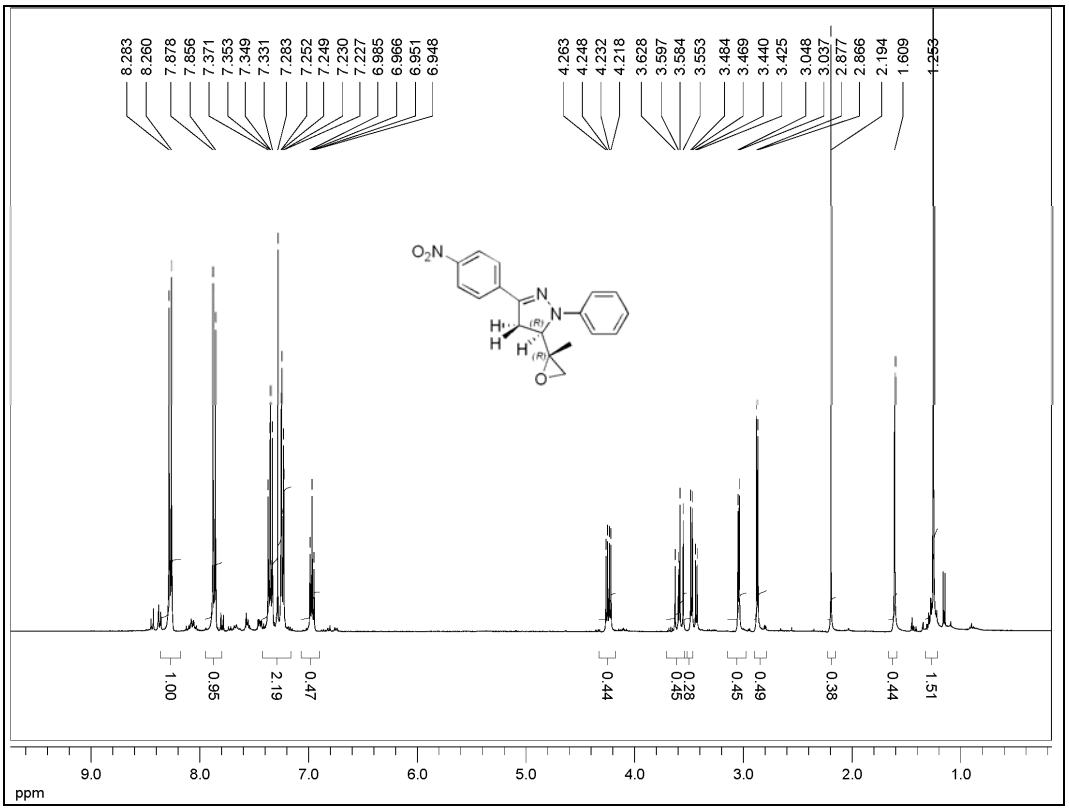

Figure 7.197 ^{1}H-NMR spectrum of compound **6.21f** in $CDCl_3$

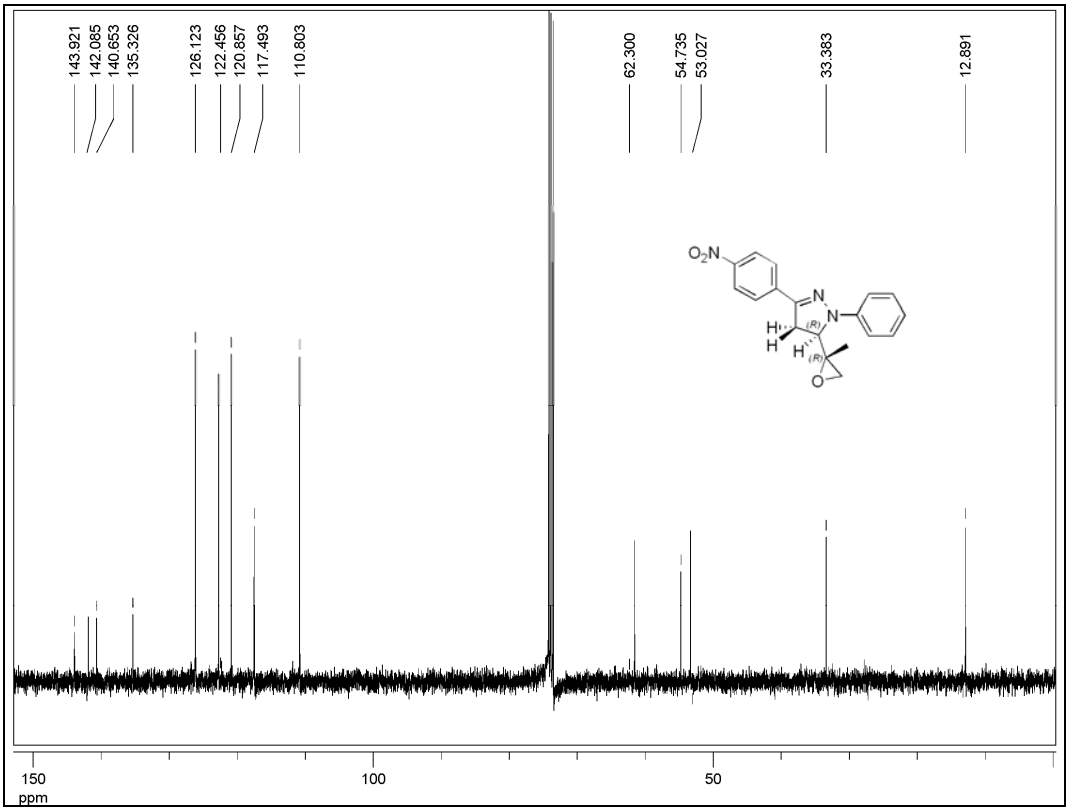

Figure 7.198 ^{13}C-NMR spectrum of compound **6.21f** in $CDCl_3$

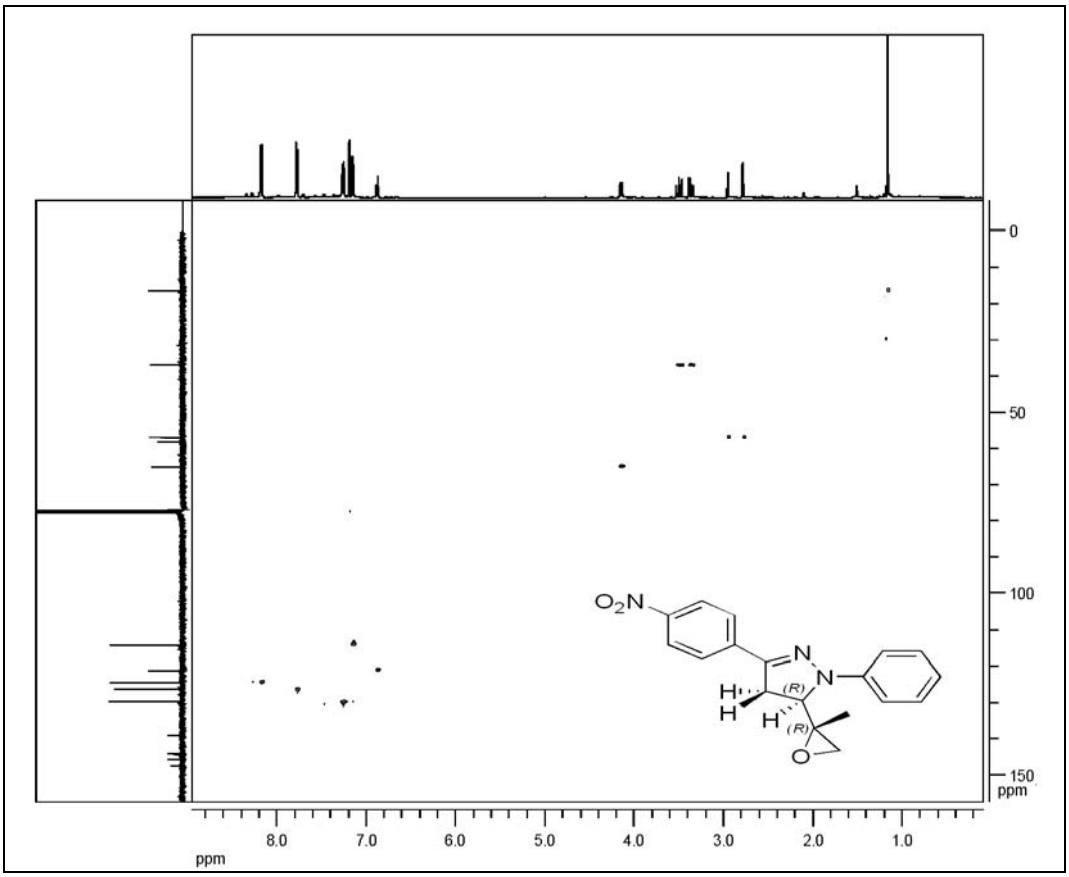

Figure 7.199 HSQC-NMR spectrum of compound **6.21f** in $CDCl_3$

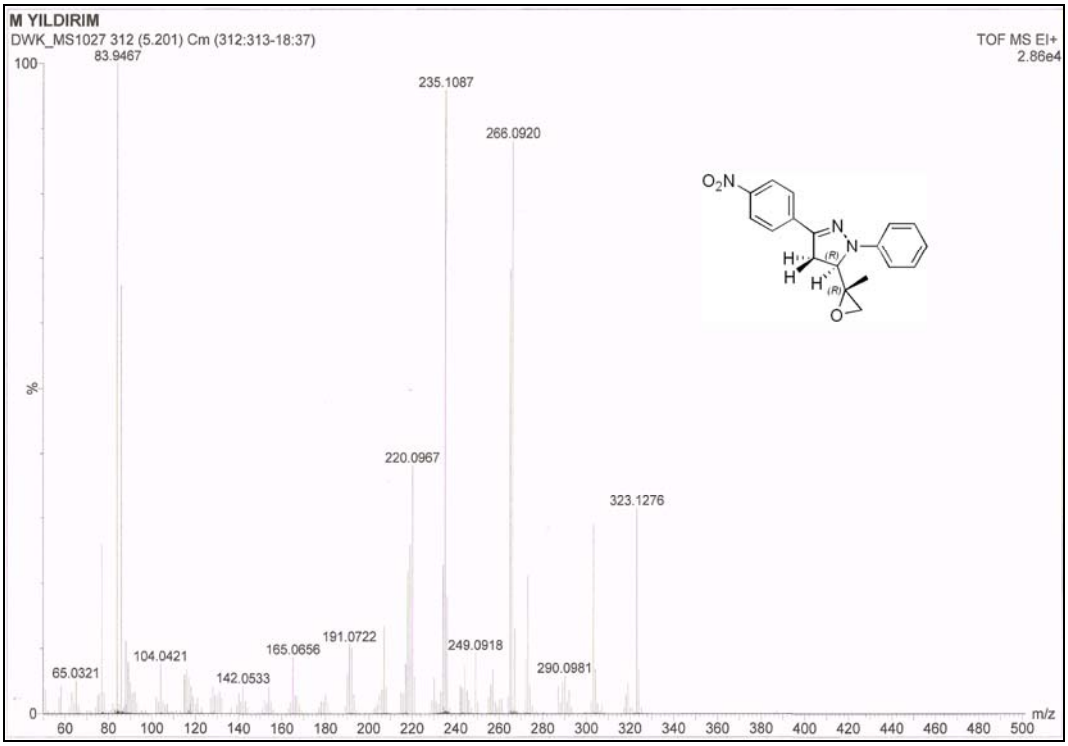

Figure 7.200 Mass spectrum of compound **6.21f**

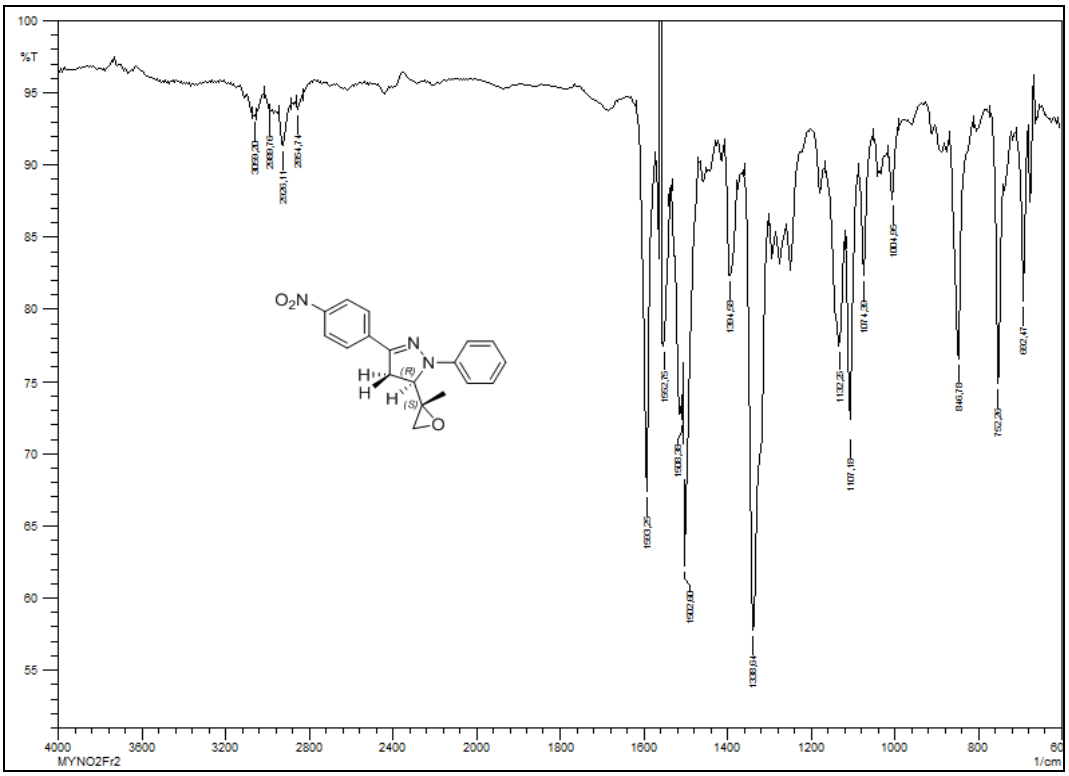

Figure 7.201 IR spectrum of compound **6.21f'**

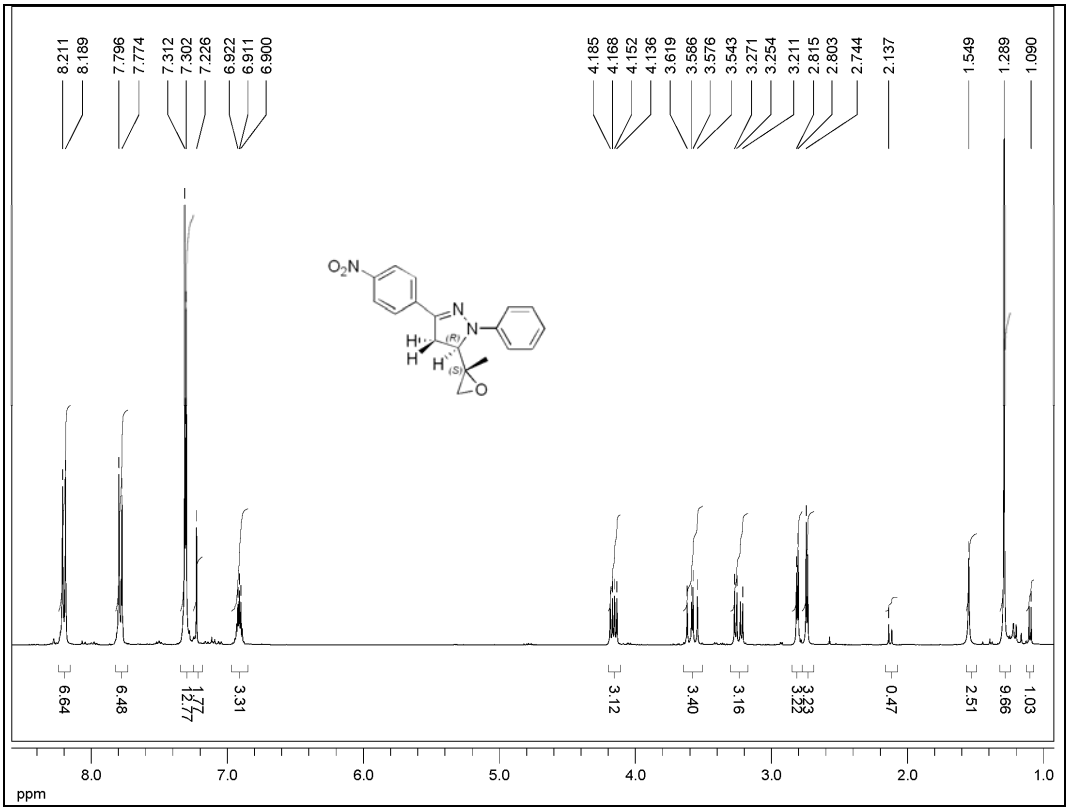

Figure 7.202 ^{1}H-NMR spectrum of compound **6.21f'** in $CDCl_3$

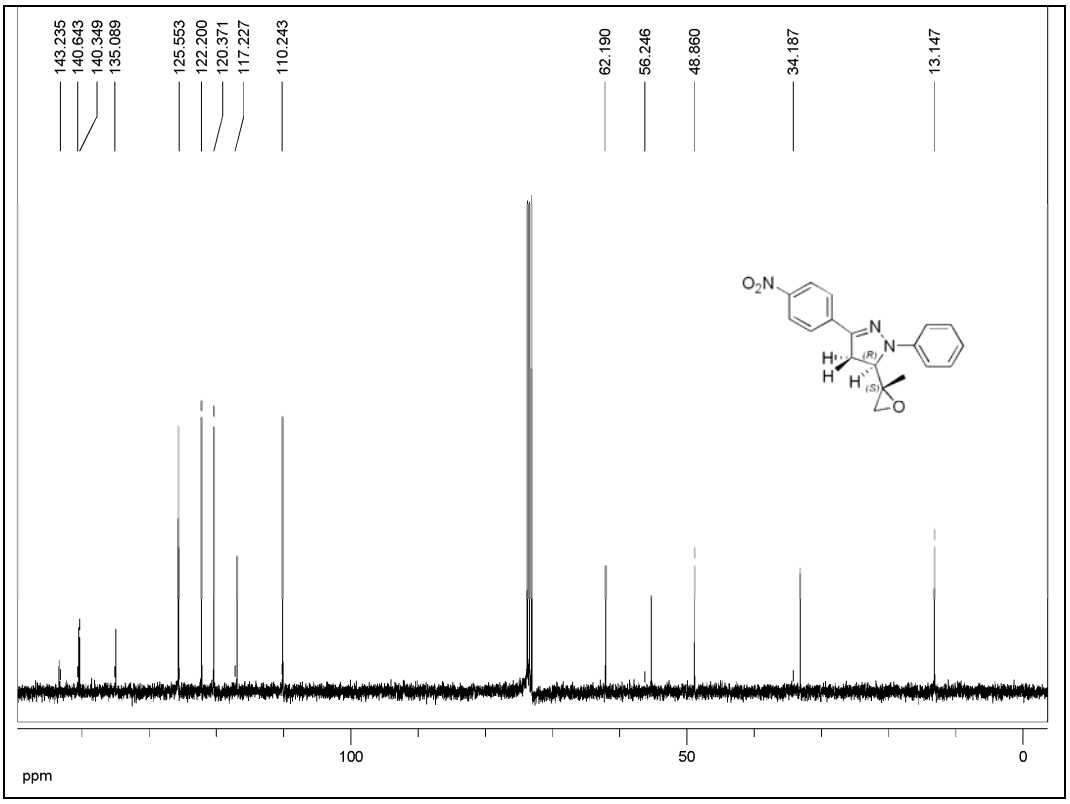

Figure 7.203 ^{13}C-NMR spectrum of compound **6.21f'** in $CDCl_3$

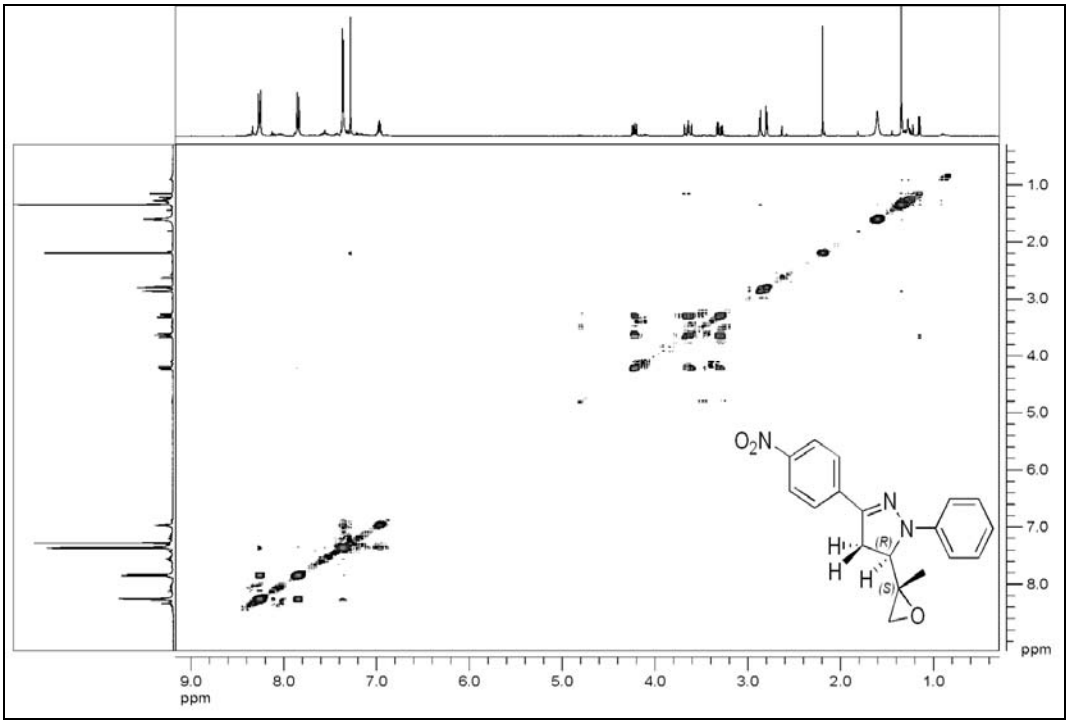

Figure 7.204 COSY-NMR spectrum of compound **6.21f'** in $CDCl_3$

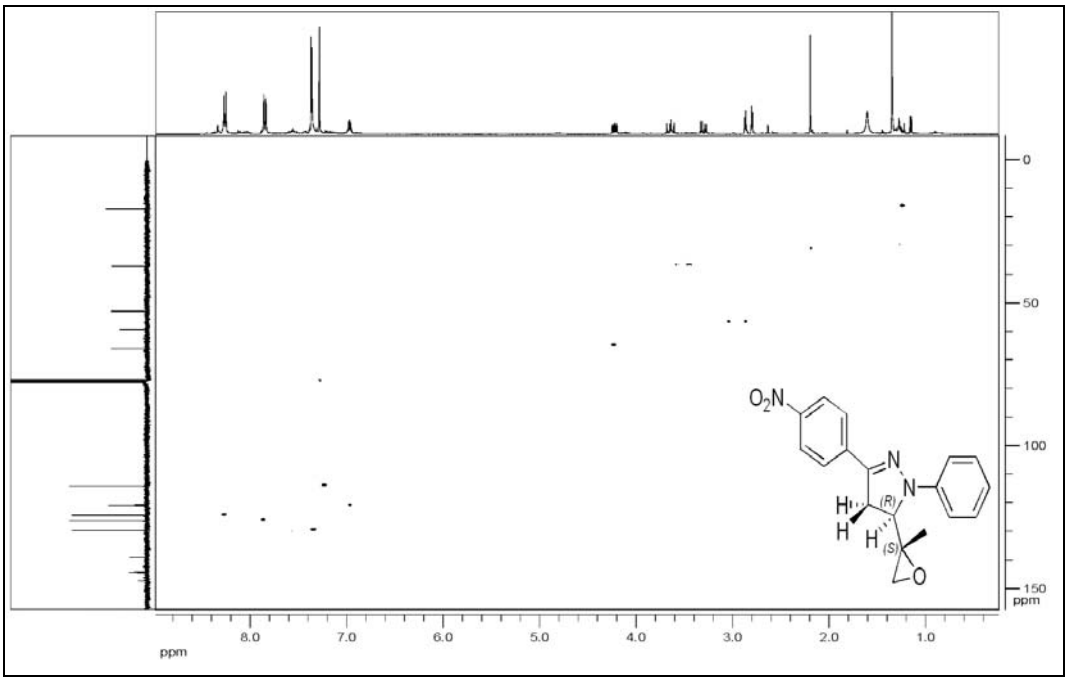

Figure 7.205 HSQC-NMR spectrum of compound **6.21f'** in $CDCl_3$

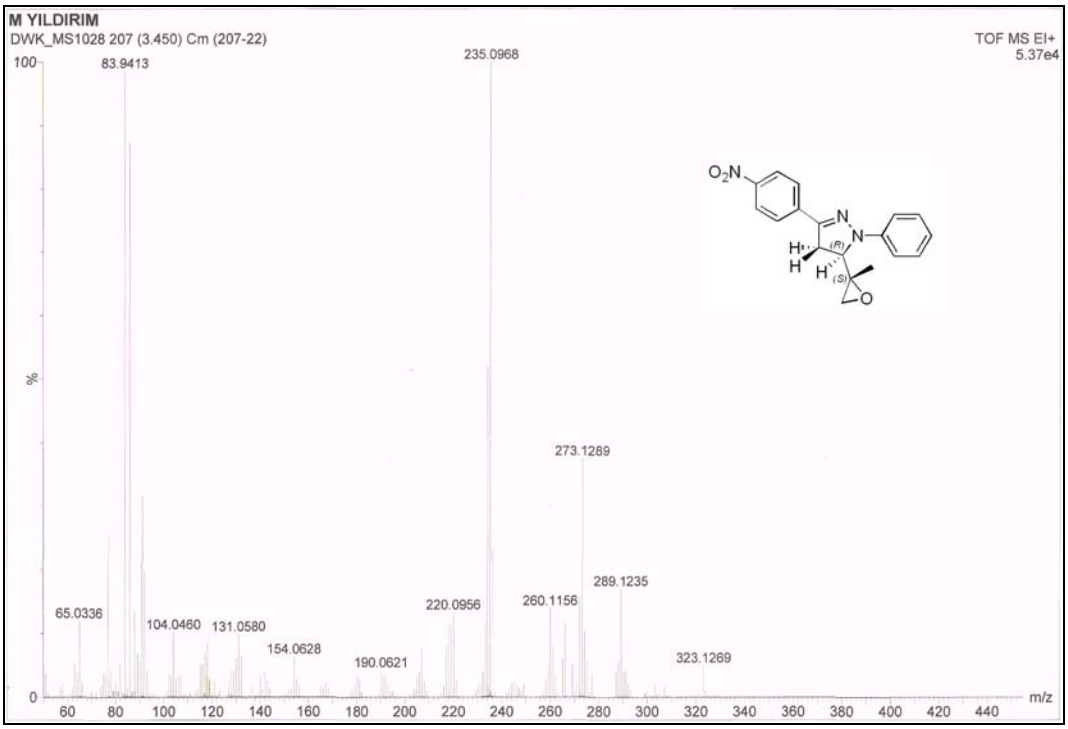

Figure 7.206 Mass spectrum of compound **6.21f'**

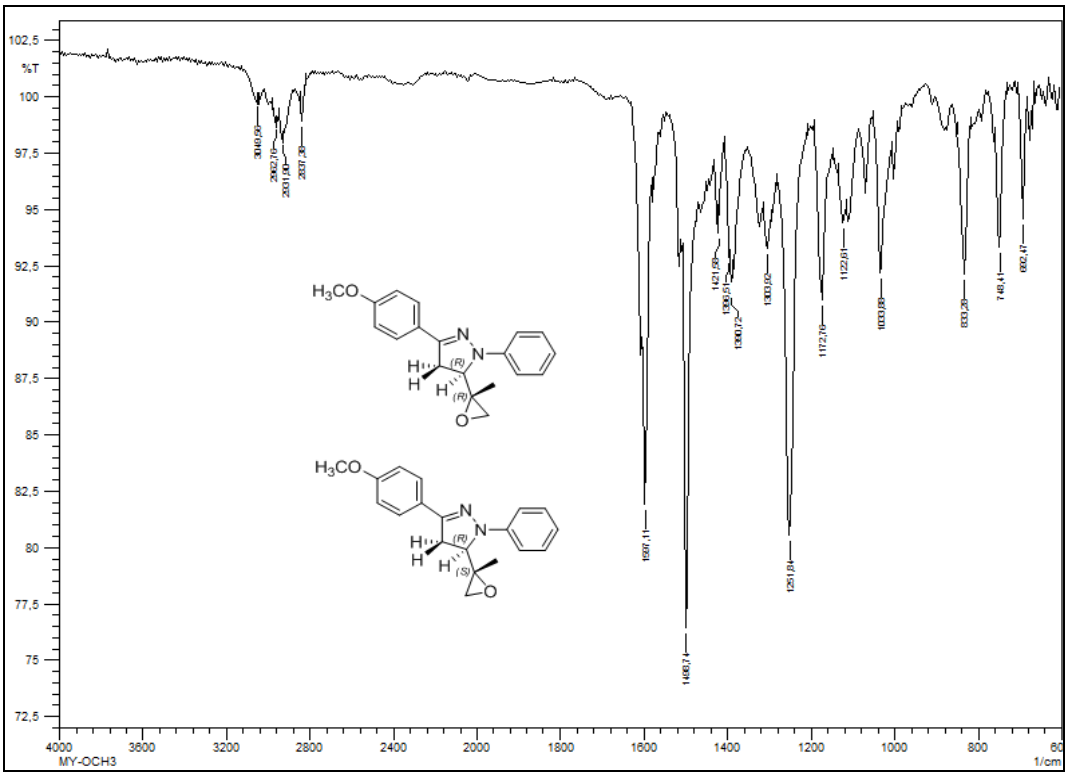

Figure 7.207 IR spectrum of compounds **6.21h-h'**

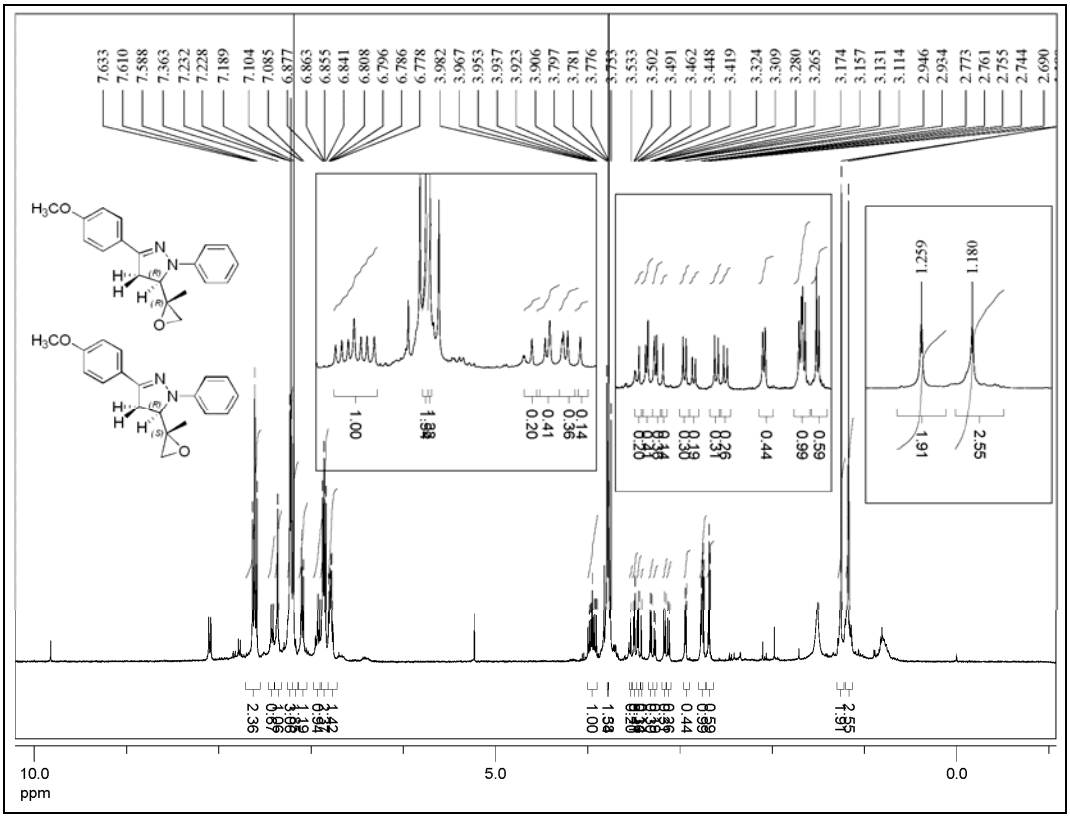

Figure 7.208 ^{1}H-NMR spectrum of compounds **6.21h-h'** in $CDCl_3$

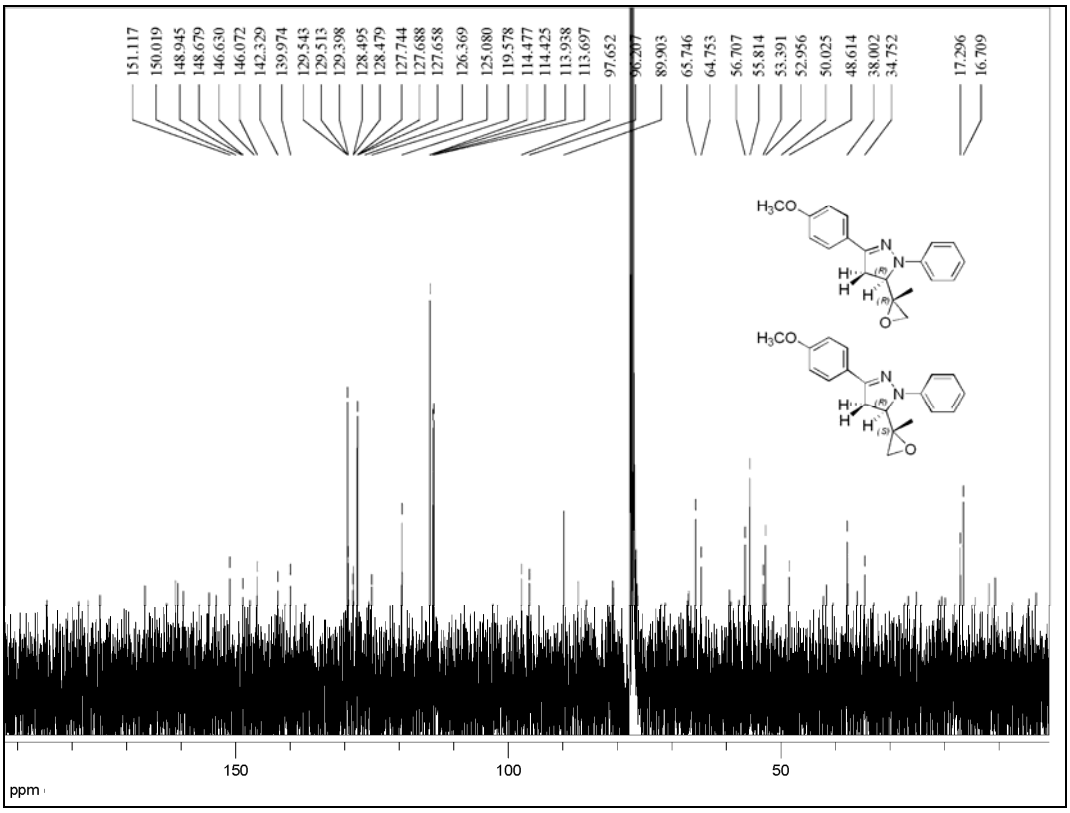

Figure 7.209 ^{13}C-NMR spectrum of compounds **6.21h-h'** in $CDCl_3$

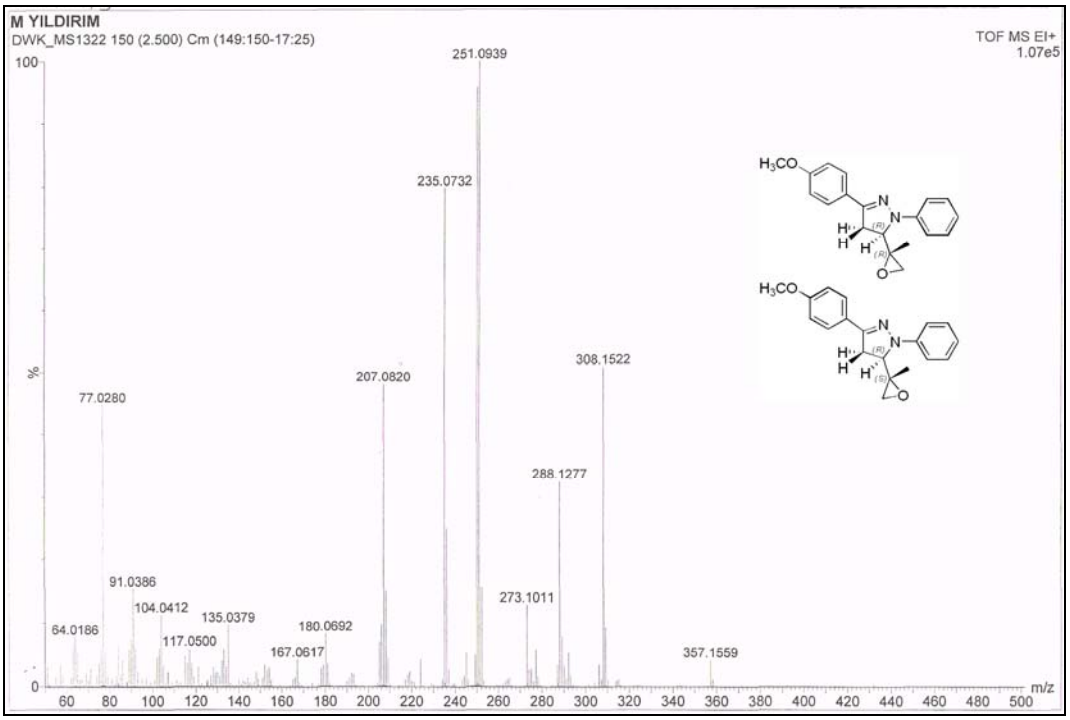

Figure 7.210 Mass spectrum of compounds **6.21h-h'**

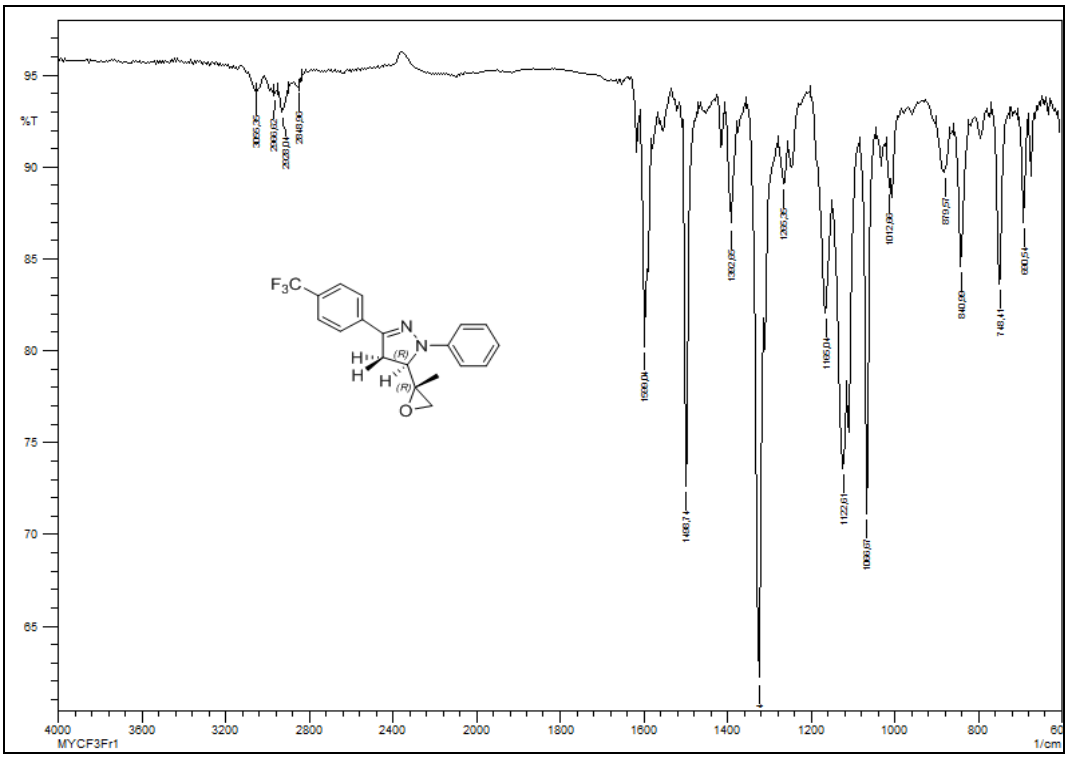

Figure 7.211 IR spectrum of compound **6.21k**

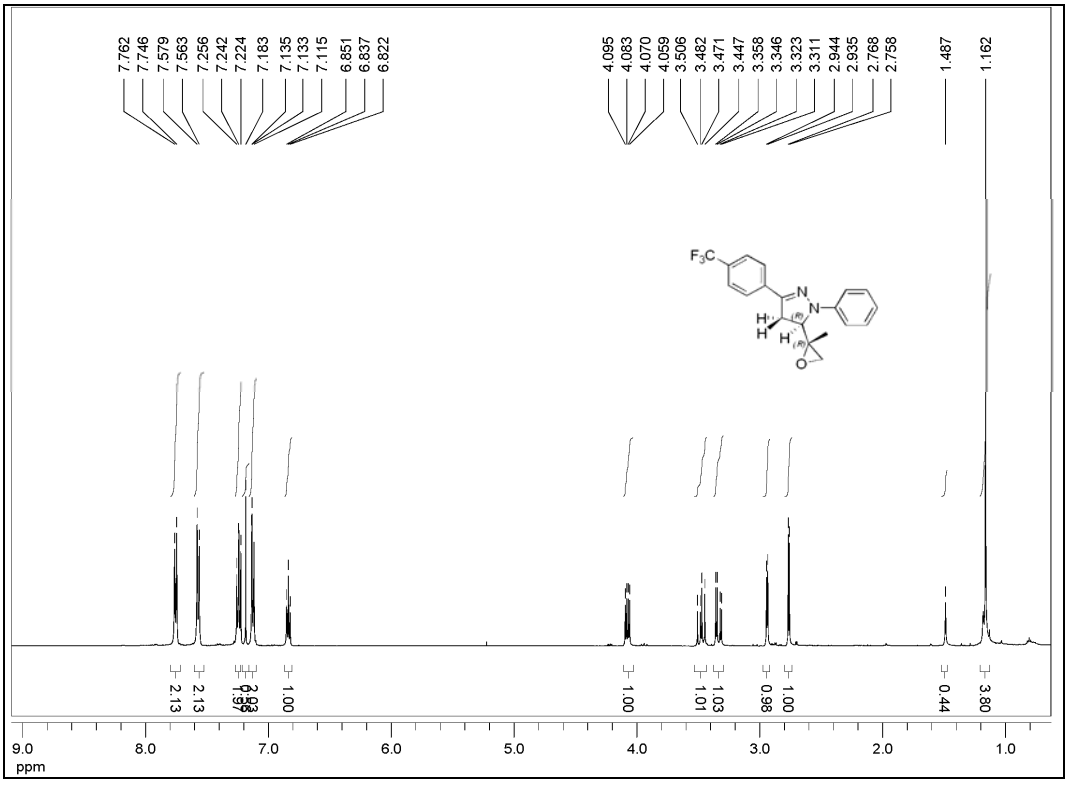

Figure 7.212 ^{1}H-NMR spectrum of compound **6.21k** in $CDCl_3$

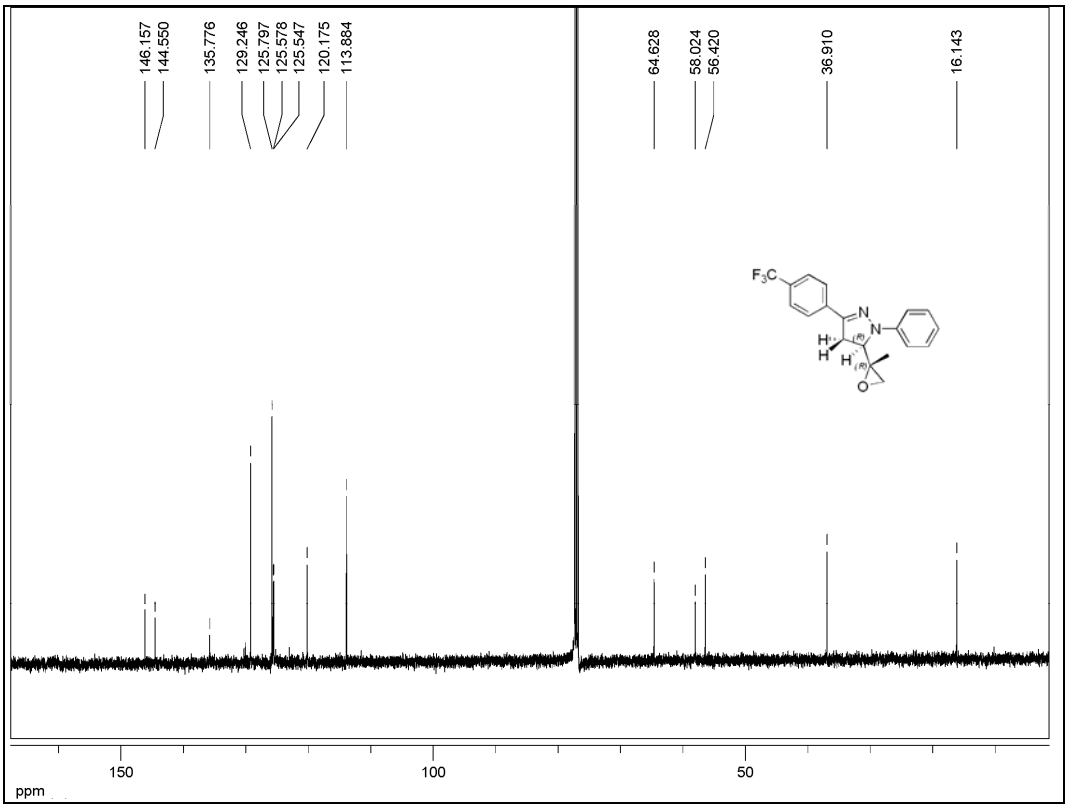

Figure 7.213 ^{13}C-NMR spectrum of compound **6.21k** in $CDCl_3$

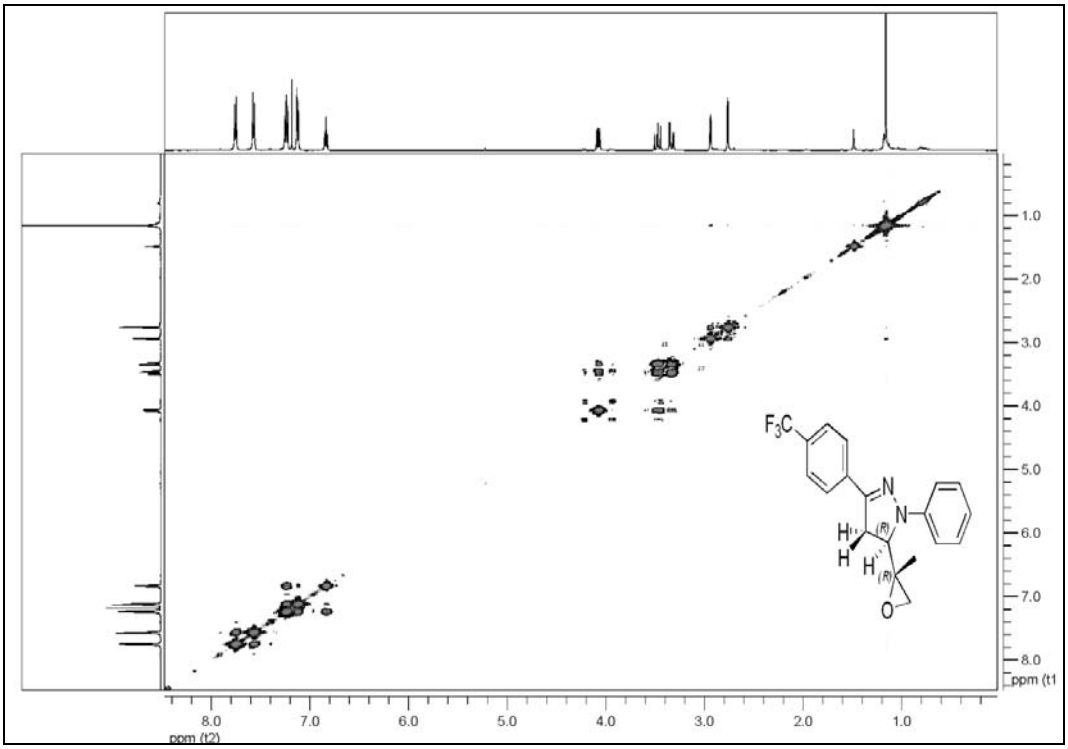

Figure 7.214 COSY-NMR spectrum of compound **6.21k** in $CDCl_3$

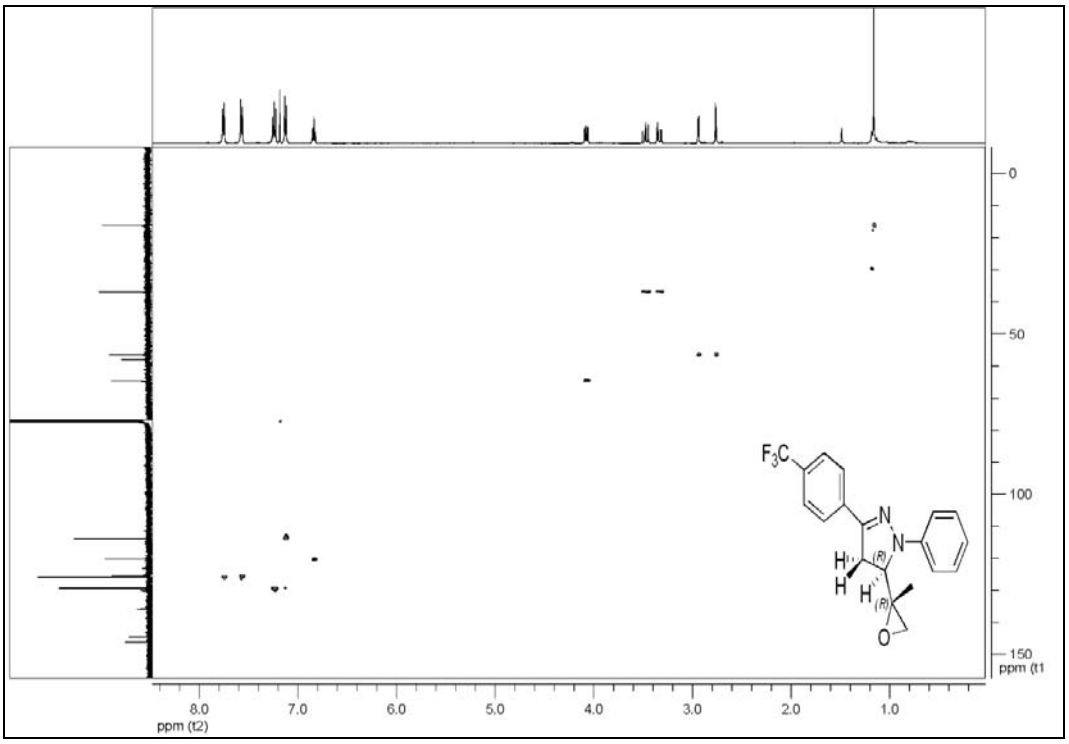

Figure 7.215 HSQC-NMR spectrum of compound **6.21k** in $CDCl_3$

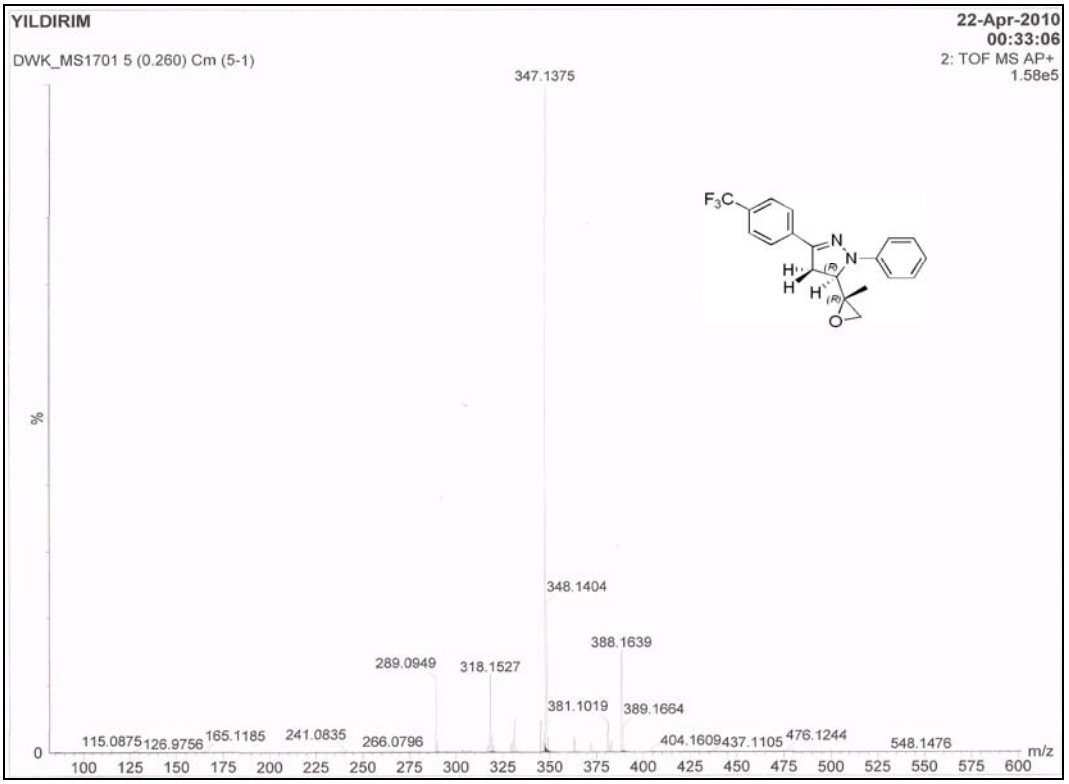

Figure 7.216 Mass spectrum of compound **6.21k**

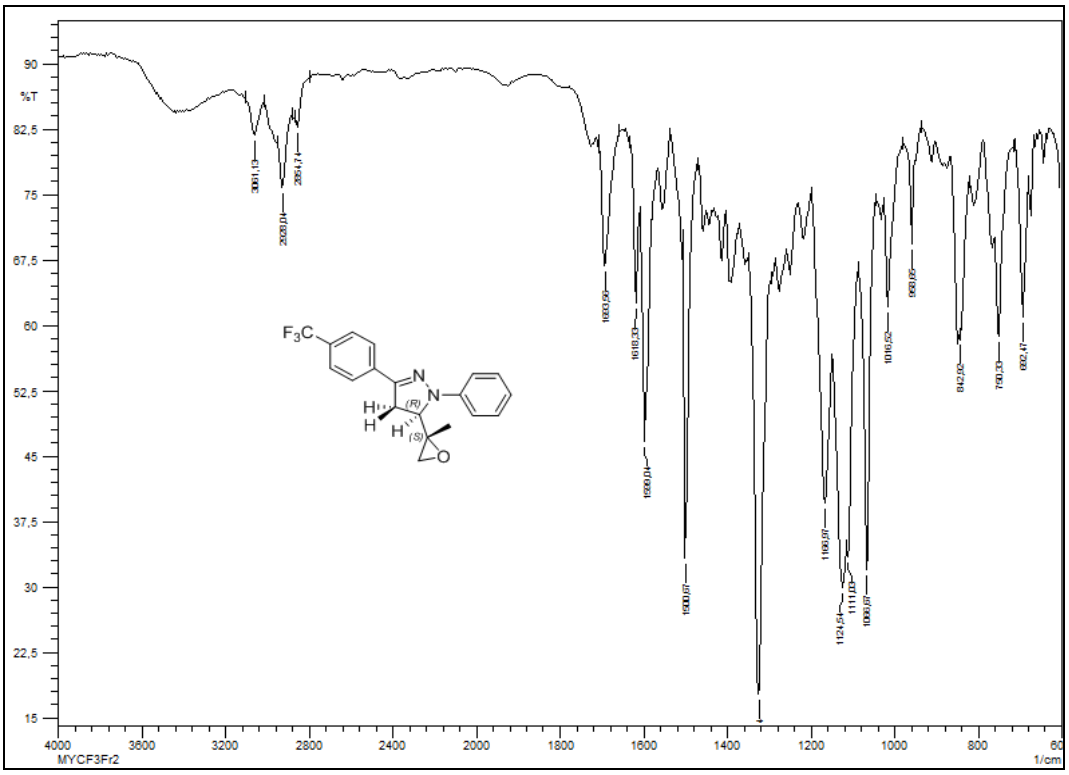

Figure 7.217 IR spectrum of compound **6.21k'**

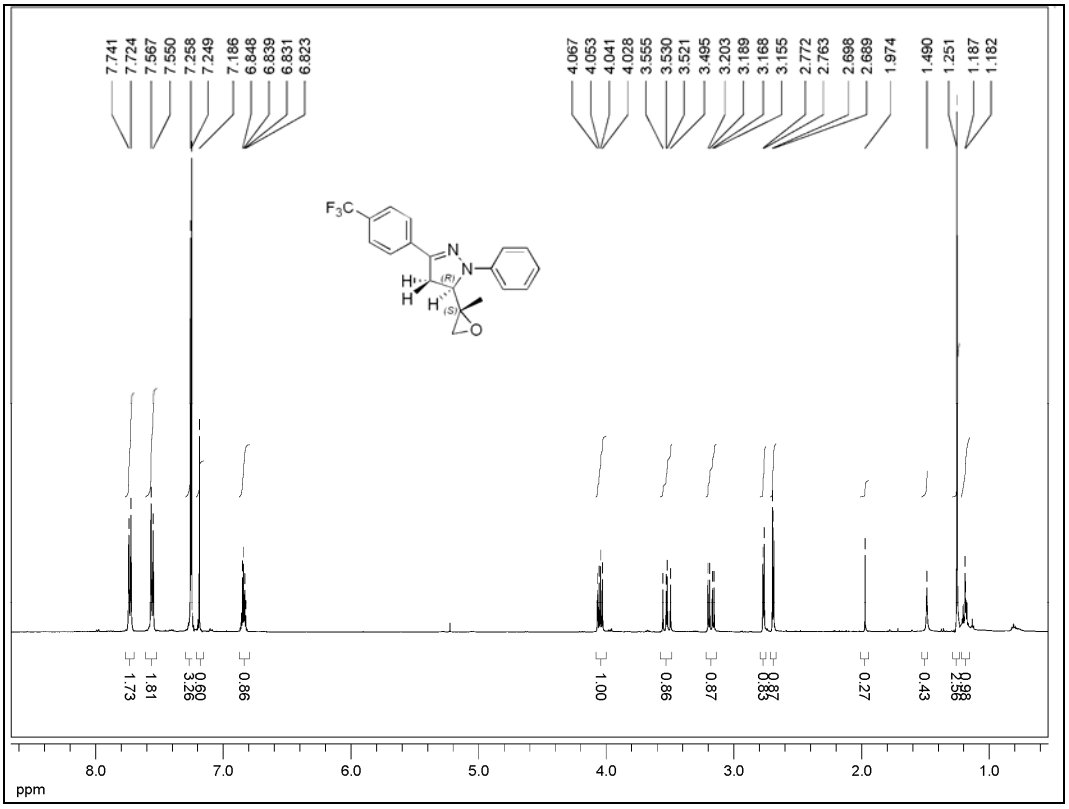

Figure 7.218 ^{1}H-NMR spectrum of compound **6.21k'** in $CDCl_3$

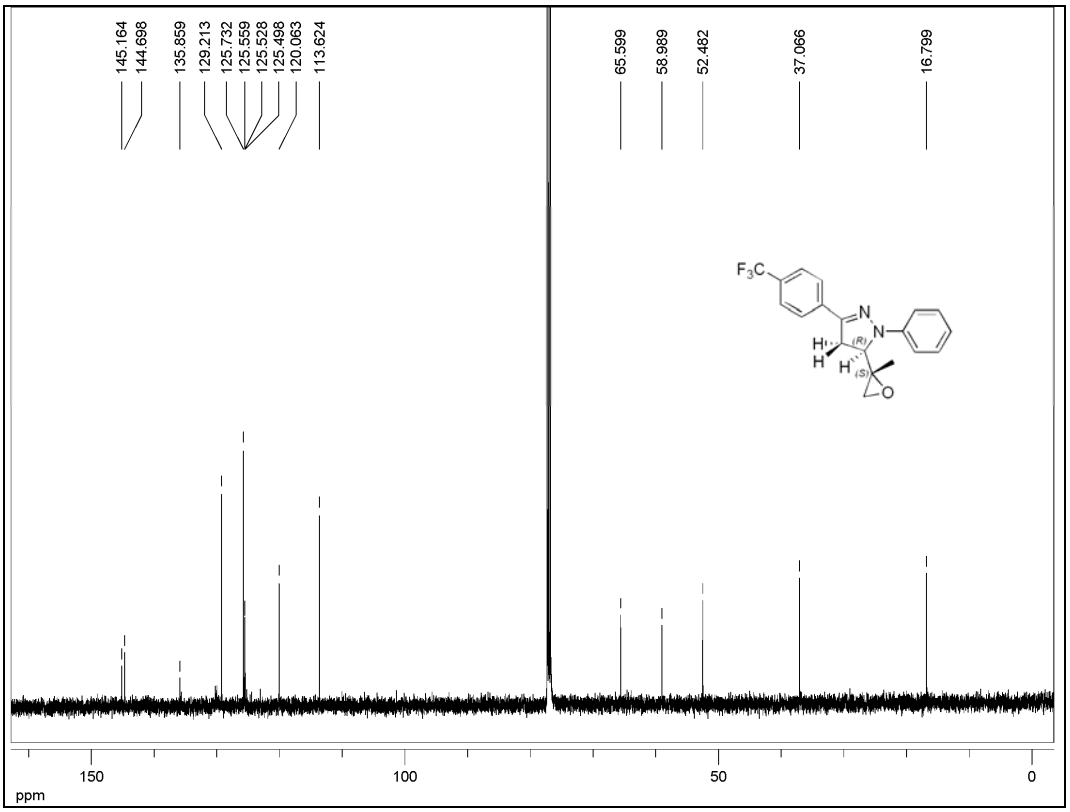

Figure 7.219 ^{13}C-NMR spectrum of compound **6.21k'** in $CDCl_3$

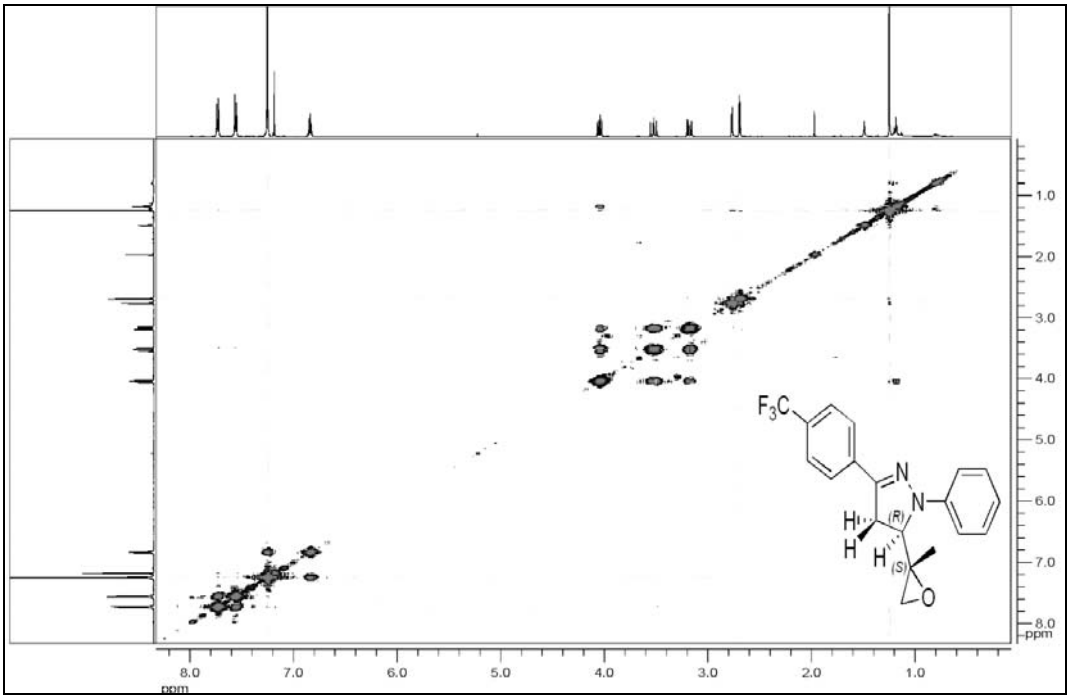

Figure 7.220 COSY-NMR spectrum of compound **6.21k'** in $CDCl_3$

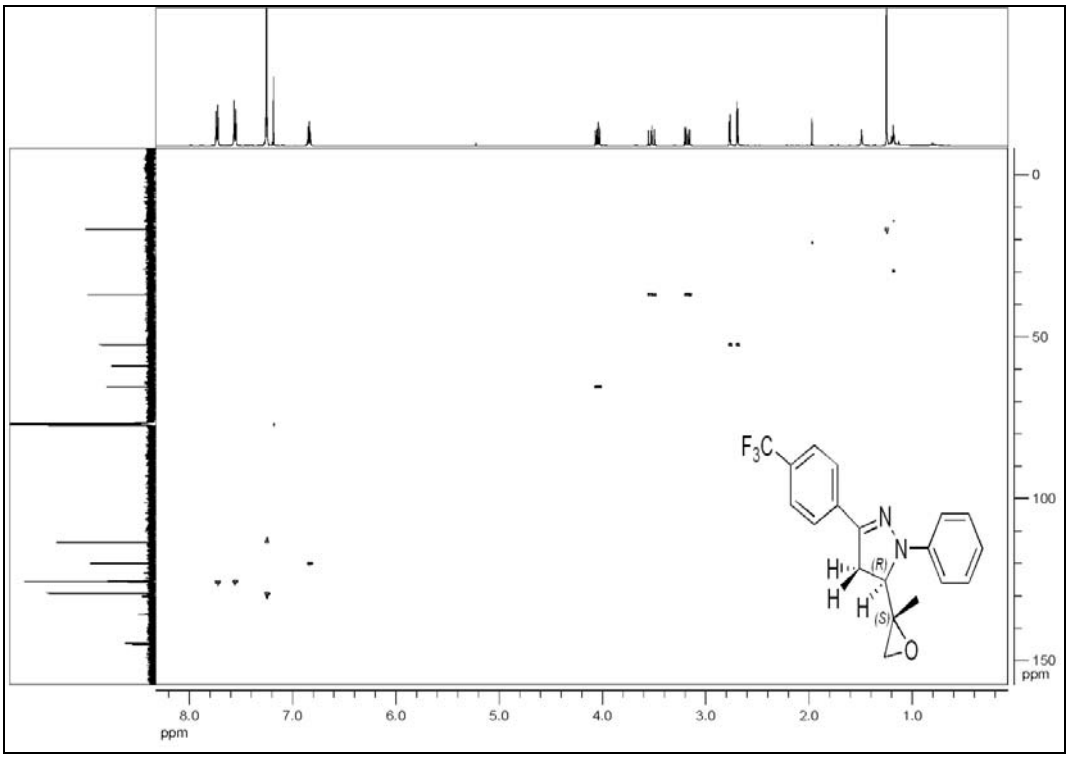

Figure 7.221 HSQC-NMR spectrum of compound **6.21k'** in $CDCl_3$

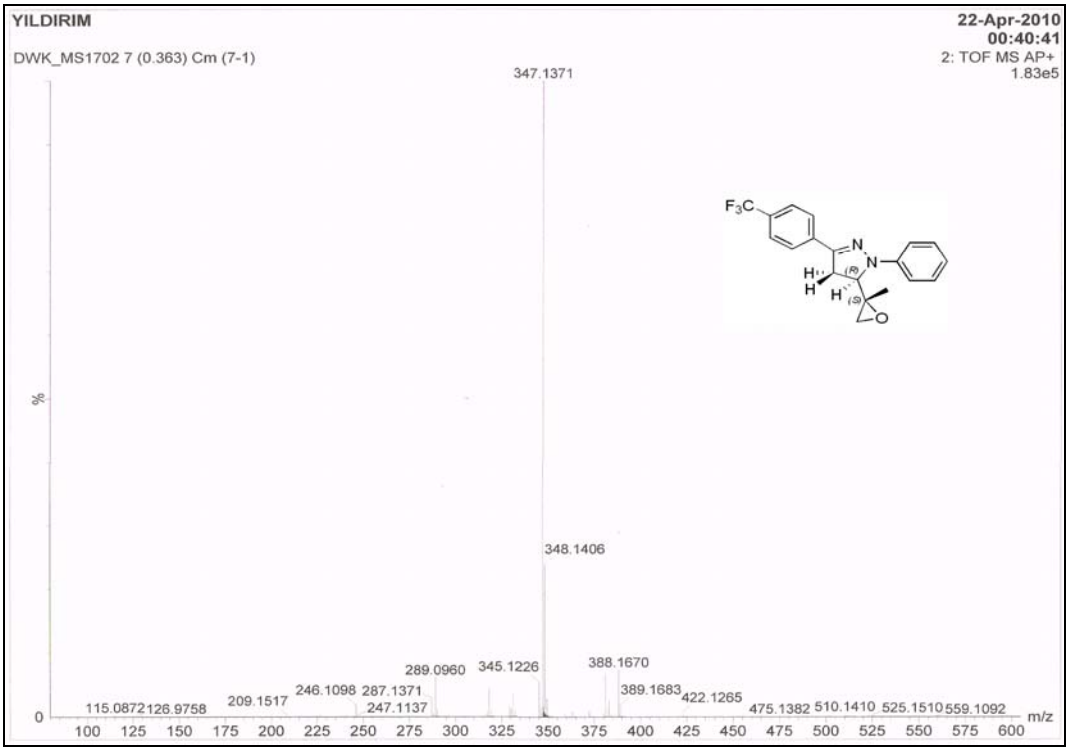

Figure 7.222 Mass spectrum of compound **6.21k'**

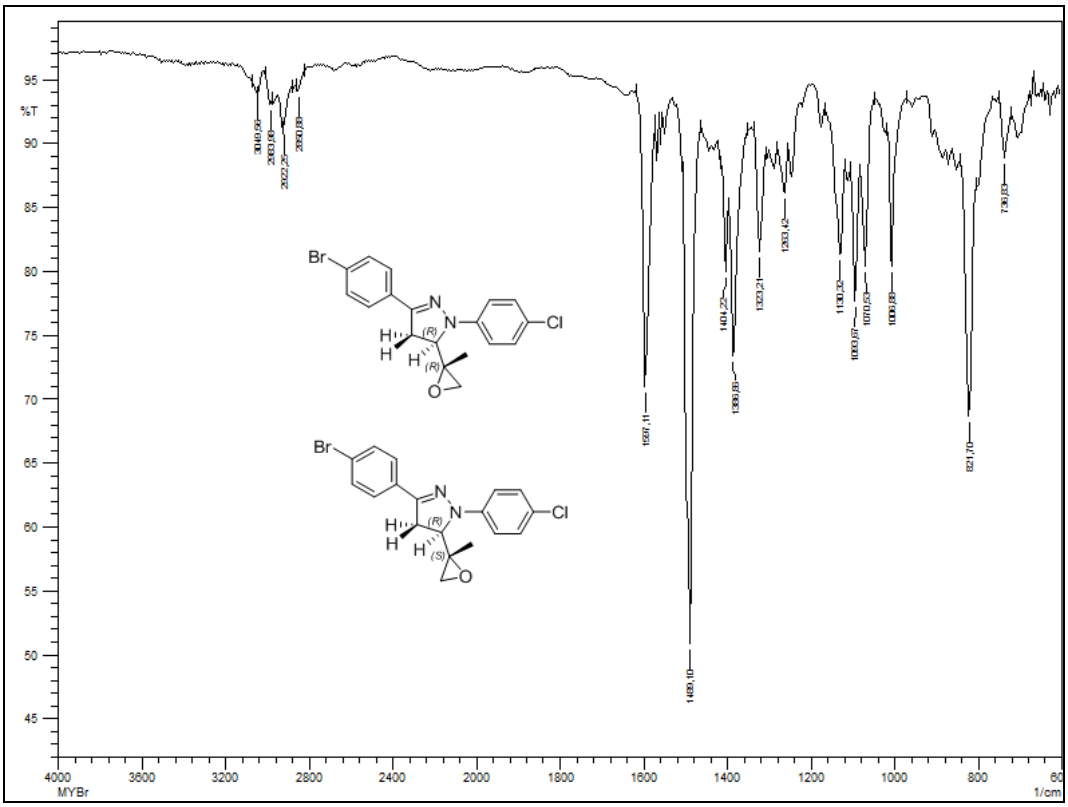

Figure 7.223 IR spectrum of compounds **6.21o-o'**

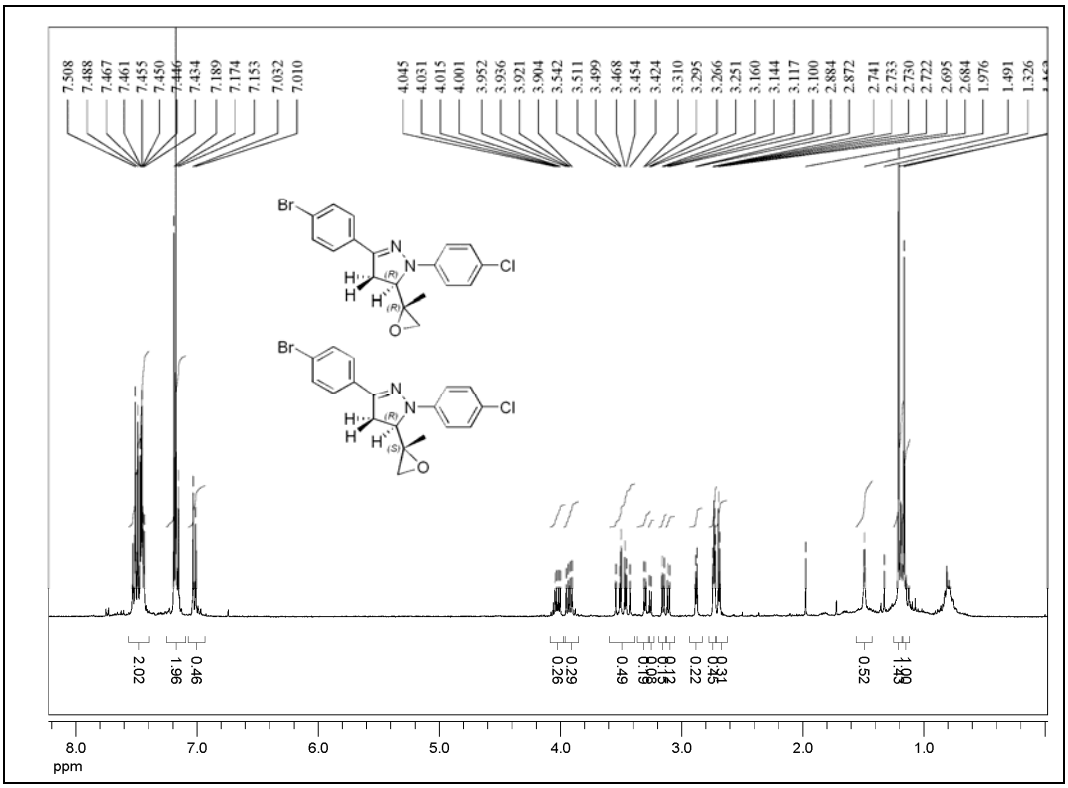

Figure 7.224 ^{1}H-NMR spectrum of compounds **6.21o-o'** in $CDCl_3$

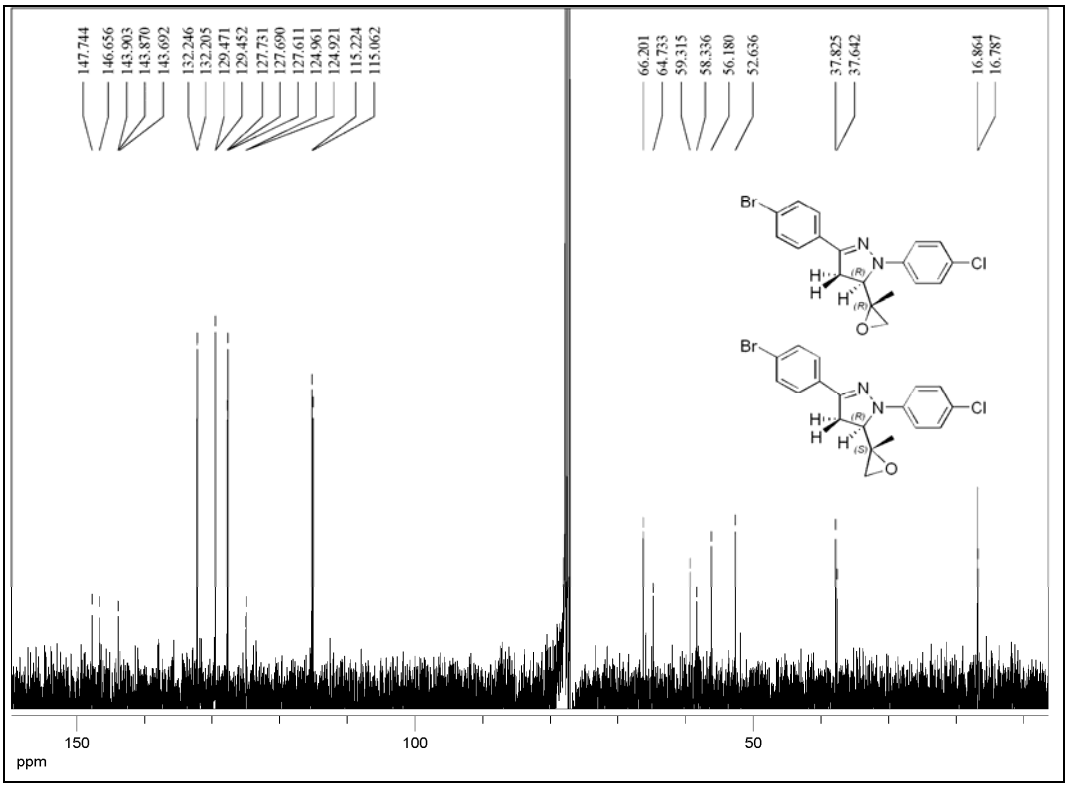

Figure 7.225 ^{13}C-NMR spectrum of compounds **6.21o-o'** in $CDCl_3$

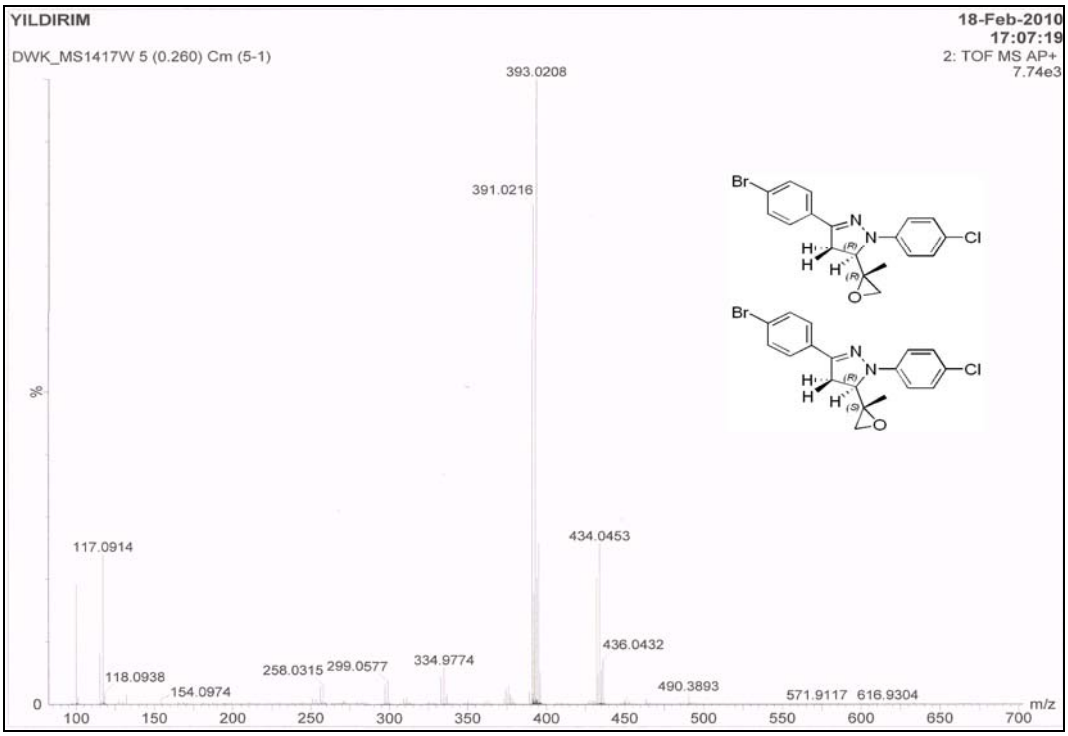

Figure 7.226 Mass spectrum of compounds **6.21o-o'**

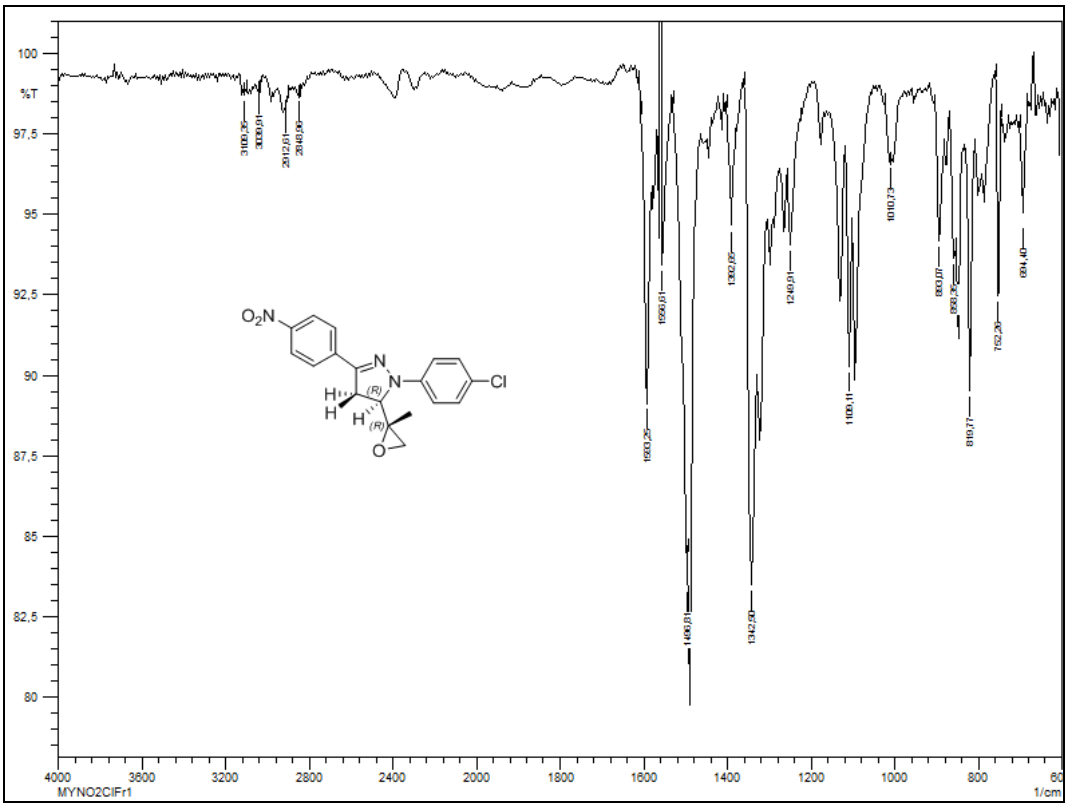

Figure 7.227 IR spectrum of compound **6.21r**

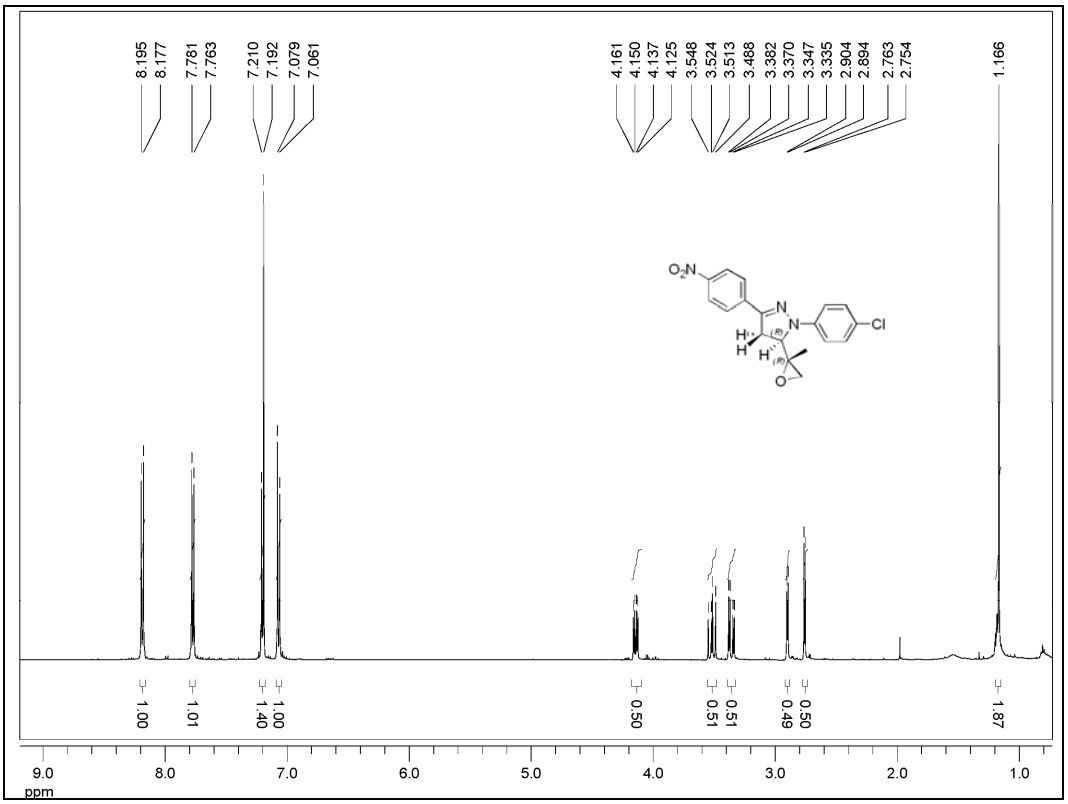

Figure 7.228 ^{1}H-NMR spectrum of compound **6.21r** in $CDCl_3$

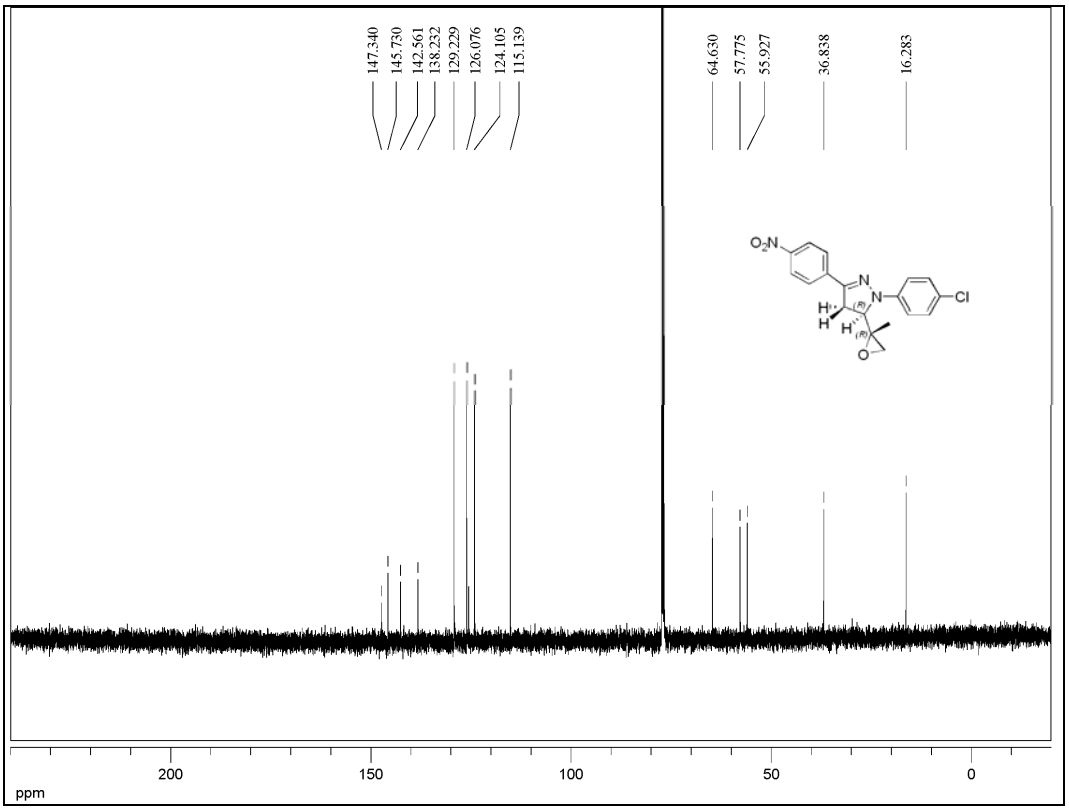

Figure 7.229 ^{13}C-NMR spectrum of compound **6.21r** in $CDCl_3$

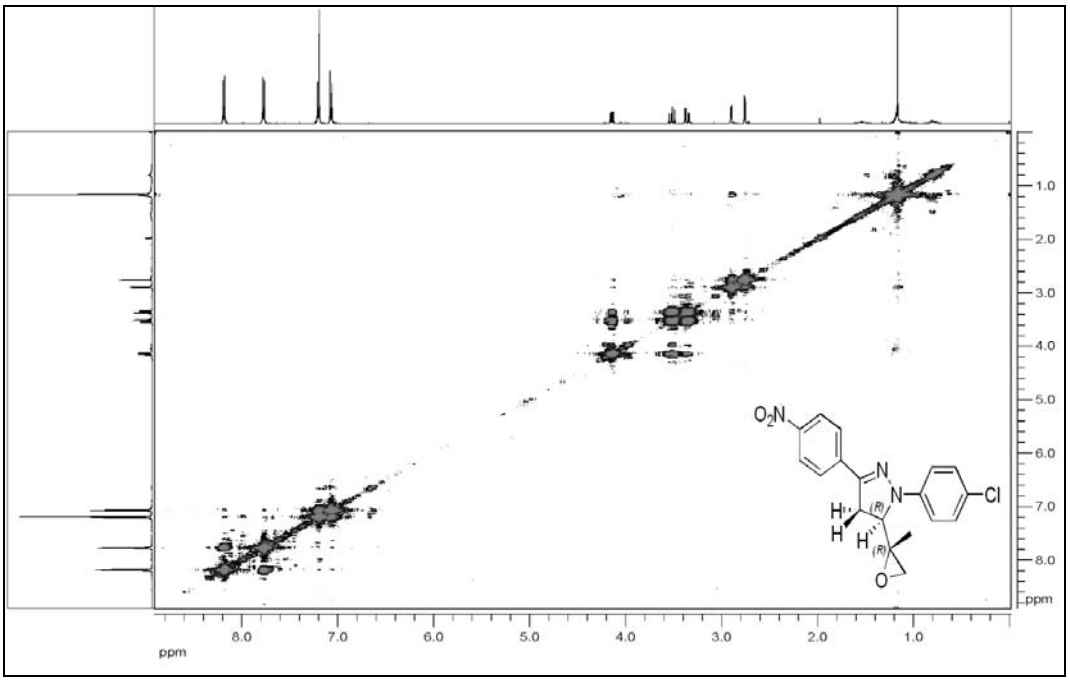

Figure 7.230 COSY-NMR spectrum of compound **6.21r** in $CDCl_3$

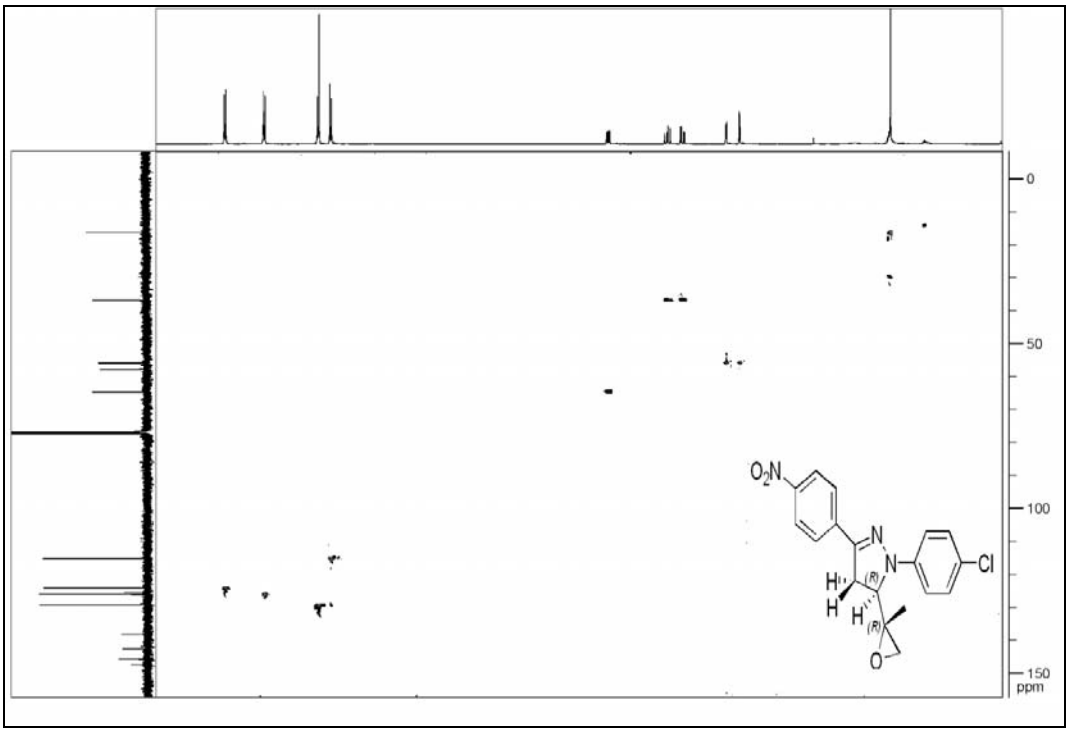

Figure 7.231 HSQC-NMR spectrum of compound **6.21r** in $CDCl_3$

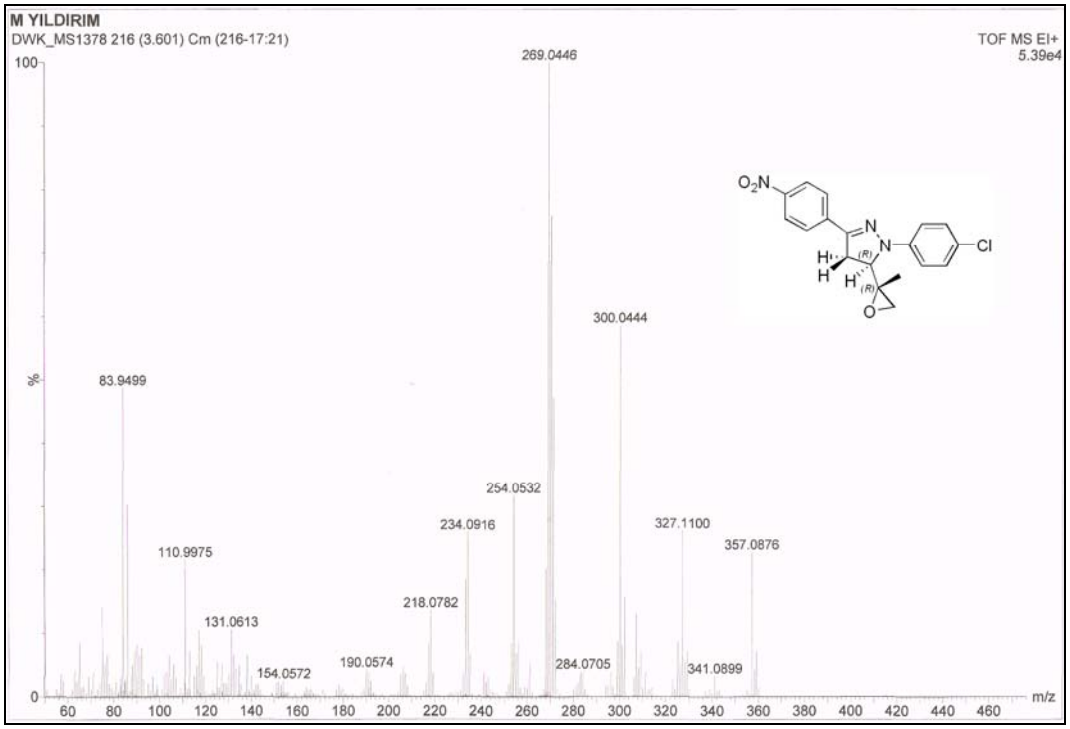

Figure 7.232 Mass spectrum of compound **6.21r**

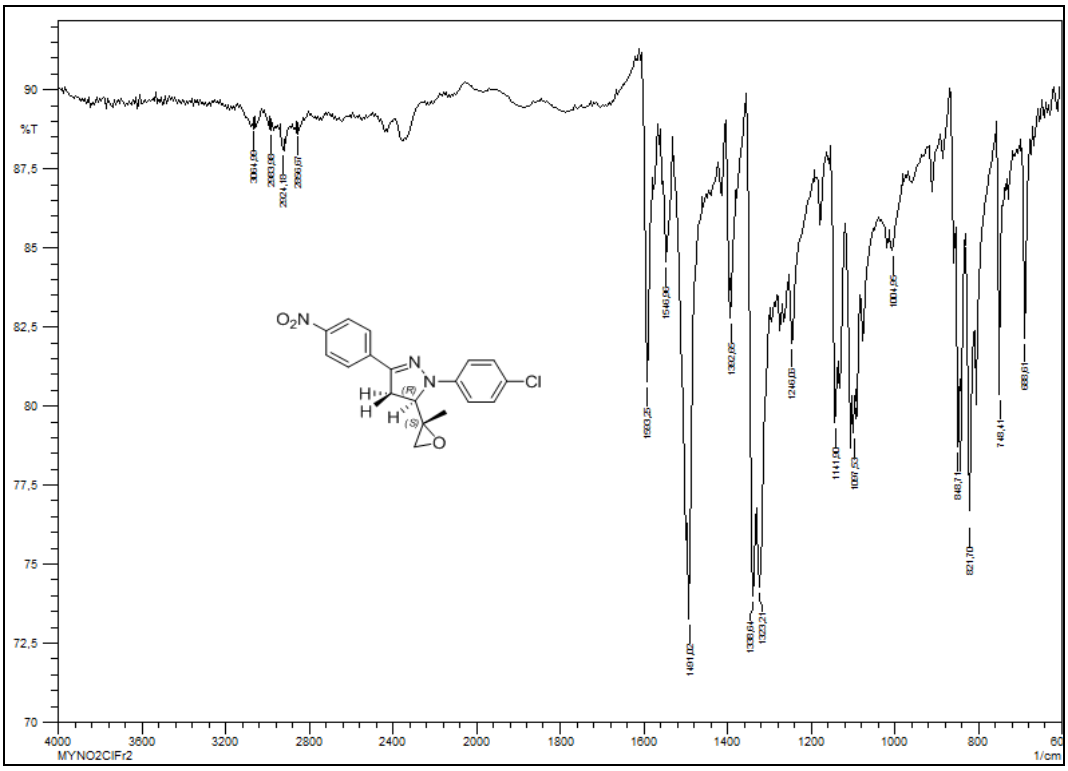

Figure 7.233 IR spectrum of compound **6.21r'**

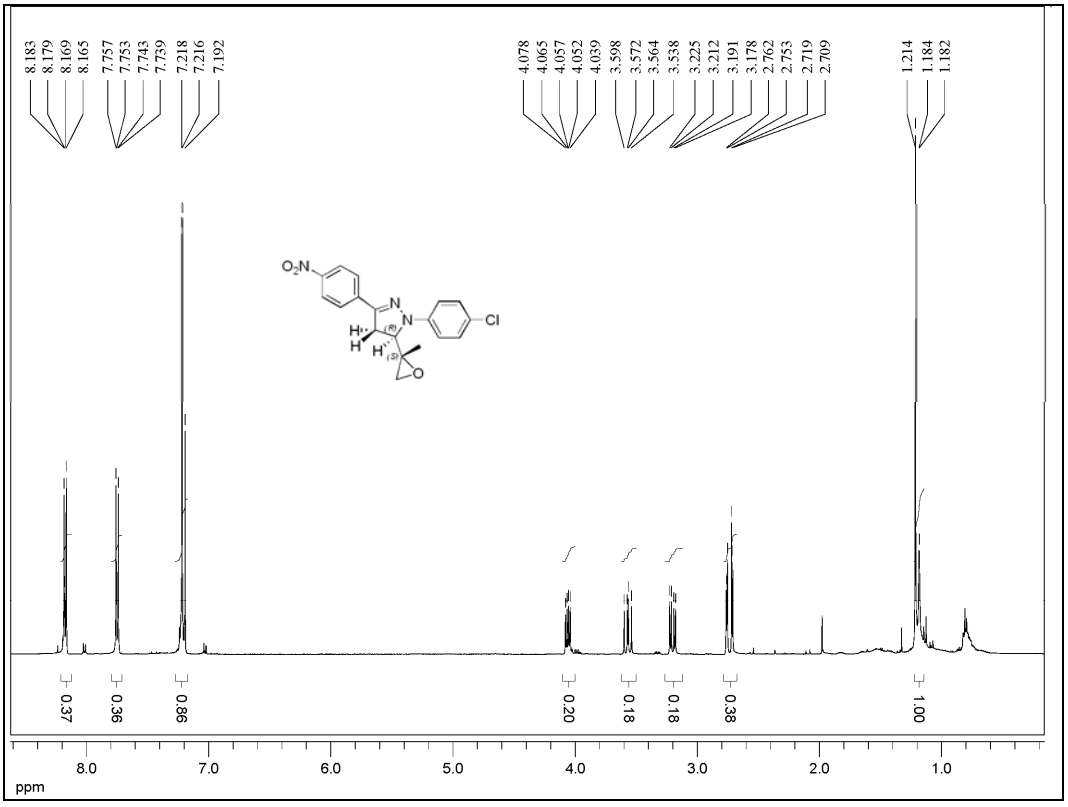

Figure 7.234 ^{1}H-NMR spectrum of compound **6.21r'** in $CDCl_3$

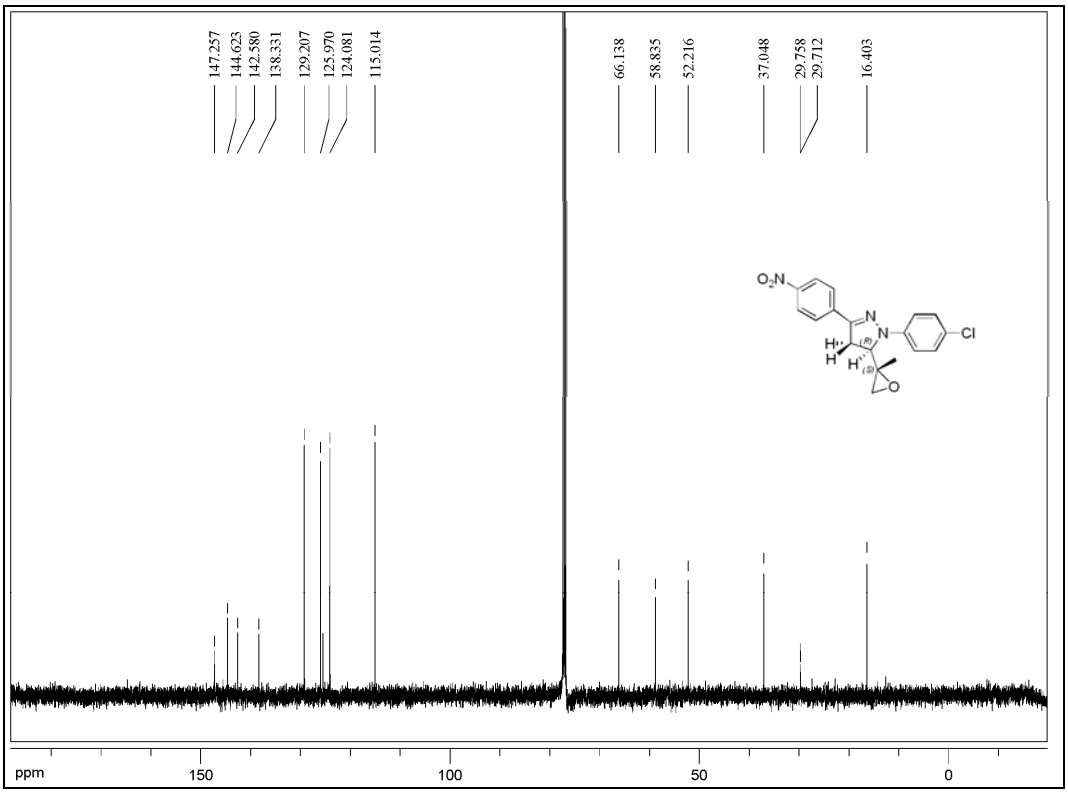

Figure 7.235 ^{13}C-NMR spectrum of compound **6.21r'** in $CDCl_3$

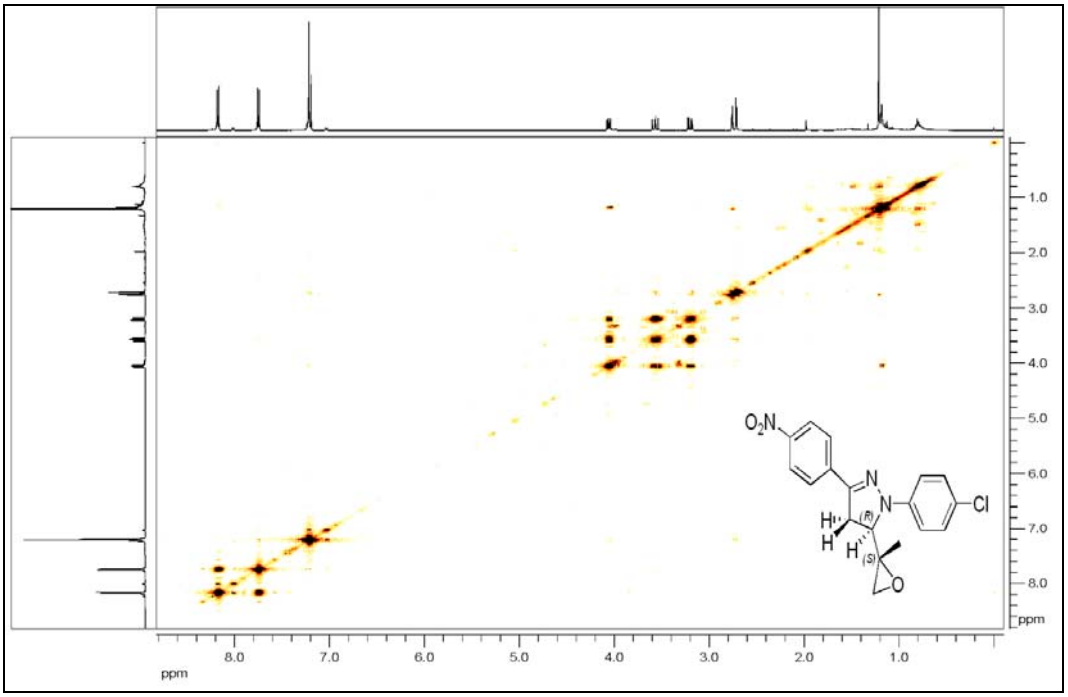

Figure 7.236 COSY-NMR spectrum of compound **6.21r'** in $CDCl_3$

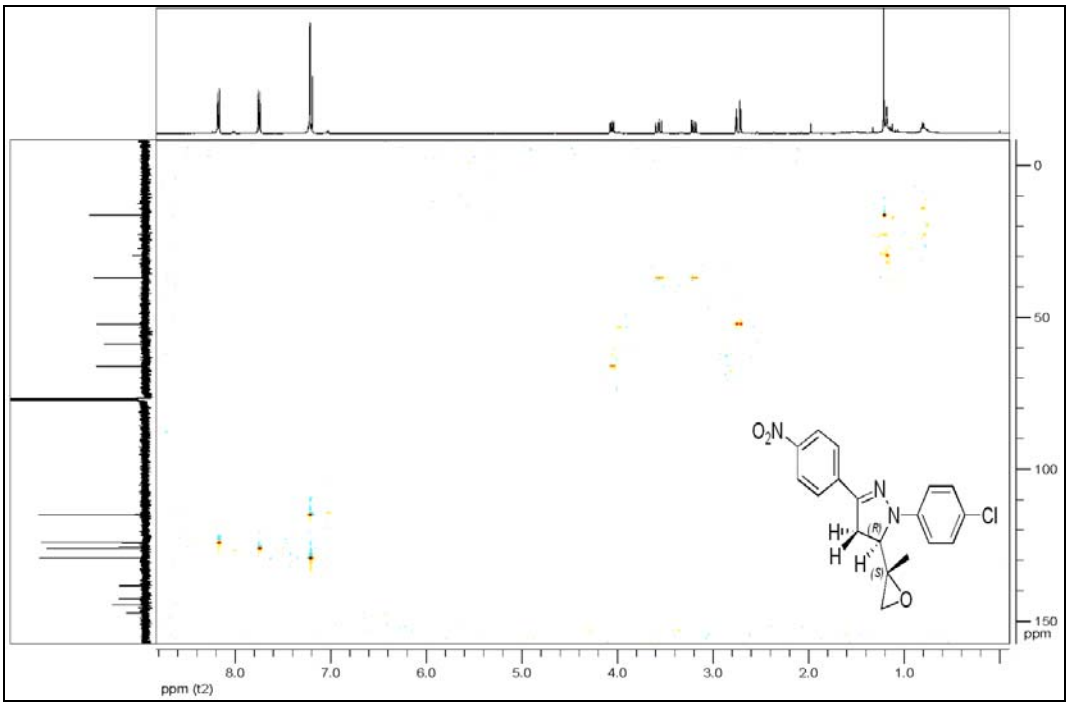

Figure 7.237 HSQC-NMR spectrum of compound **6.21r'** in $CDCl_3$

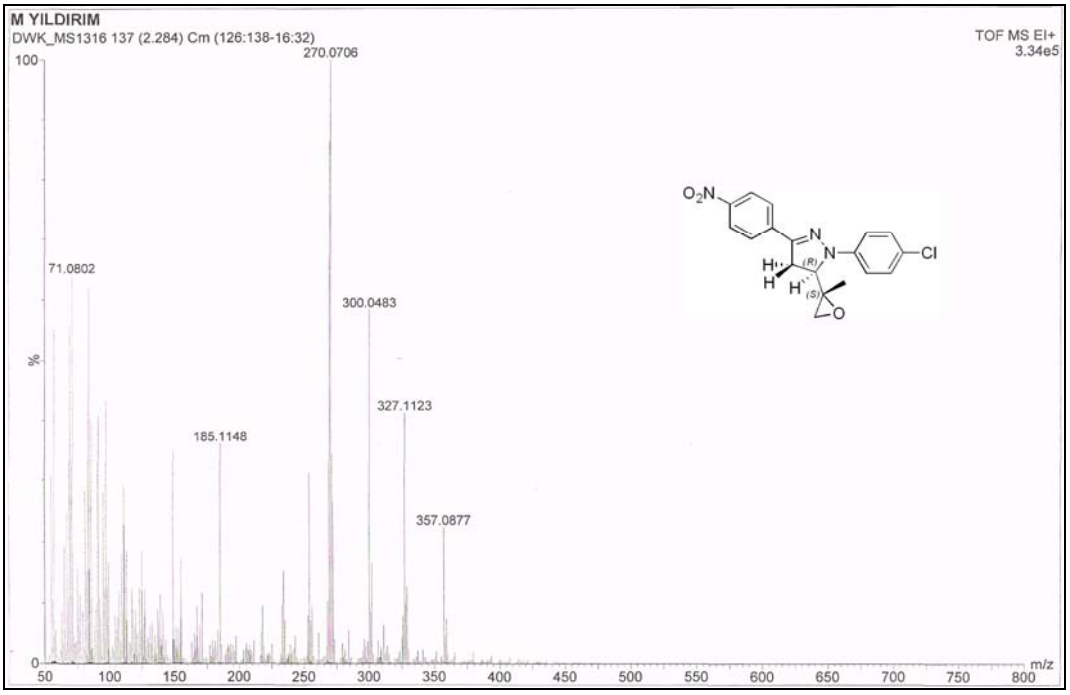

Figure 7.238 Mass spectrum of compound **6.21r'**

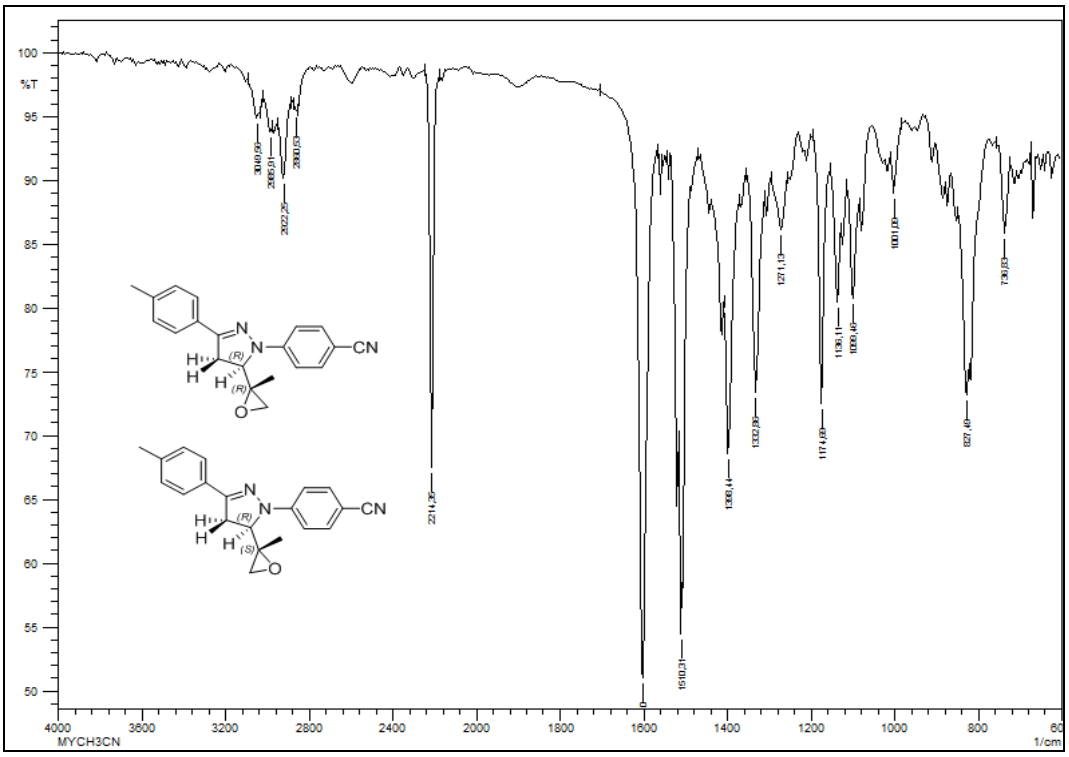

Figure 7.239 IR spectrum of compounds **6.21u-u'**

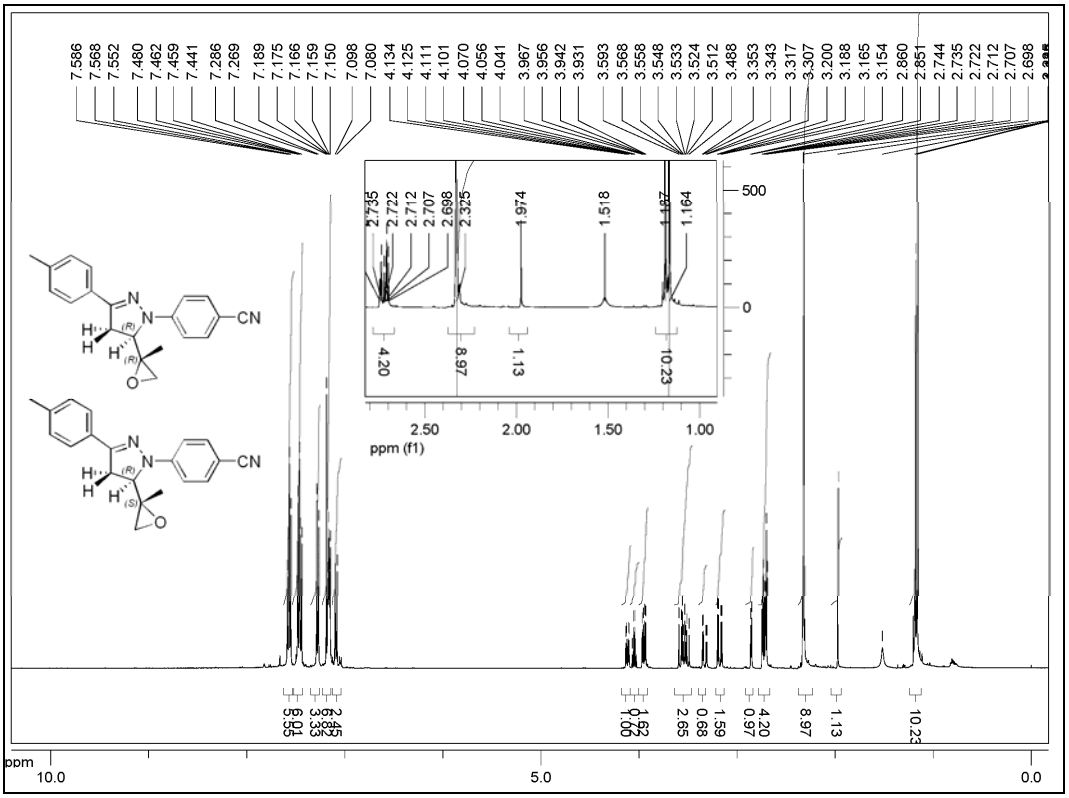

Figure 7.240 ^{1}H-NMR spectrum of compounds **6.21u-u'** in $CDCl_3$

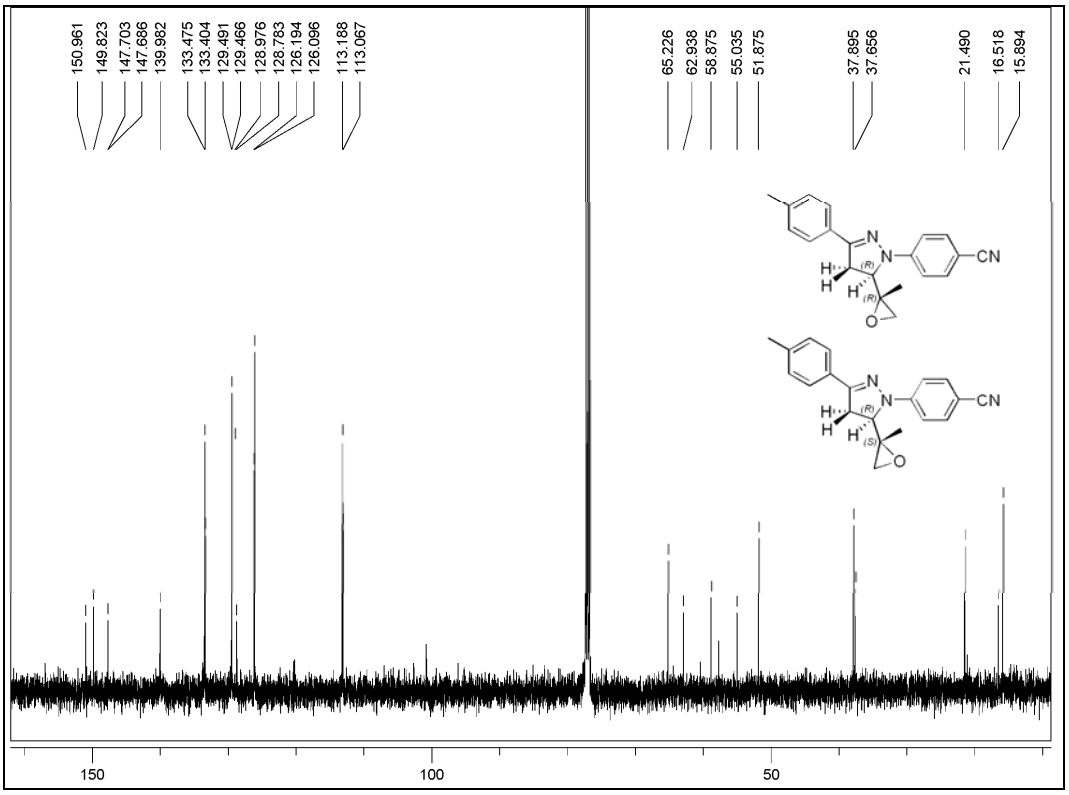

Figure 7.241 ^{13}C-NMR spectrum of compounds **6.21u-u'** in $CDCl_3$

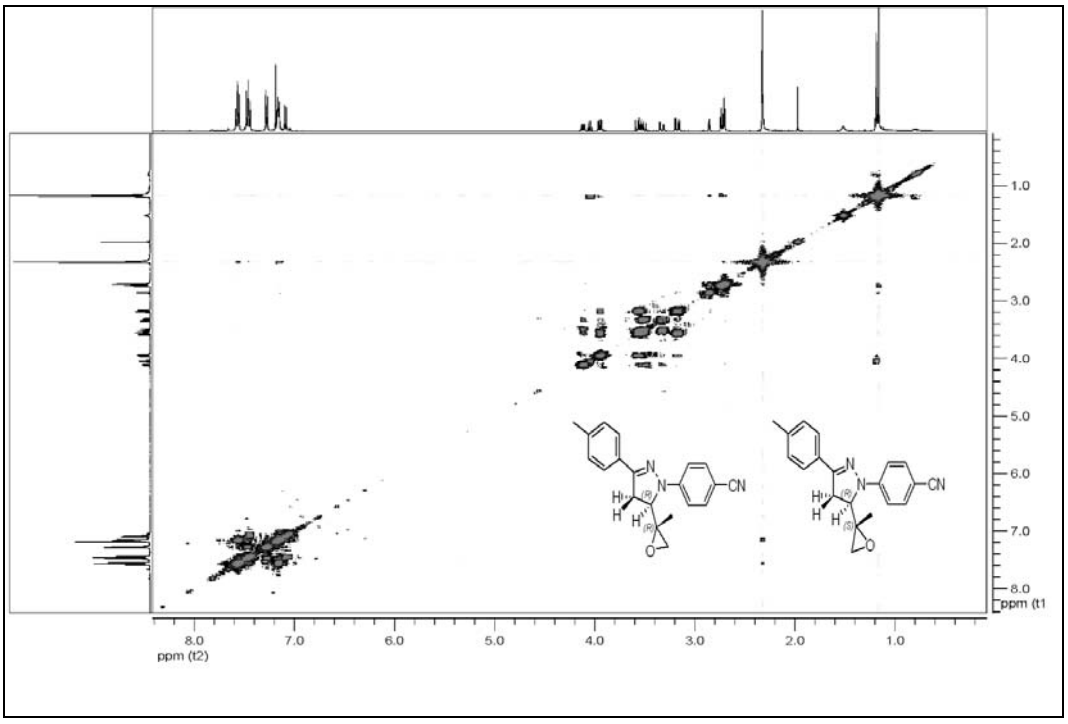

Figure 7.242 COSY-NMR spectrum of compounds **6.21u-u'** in $CDCl_3$

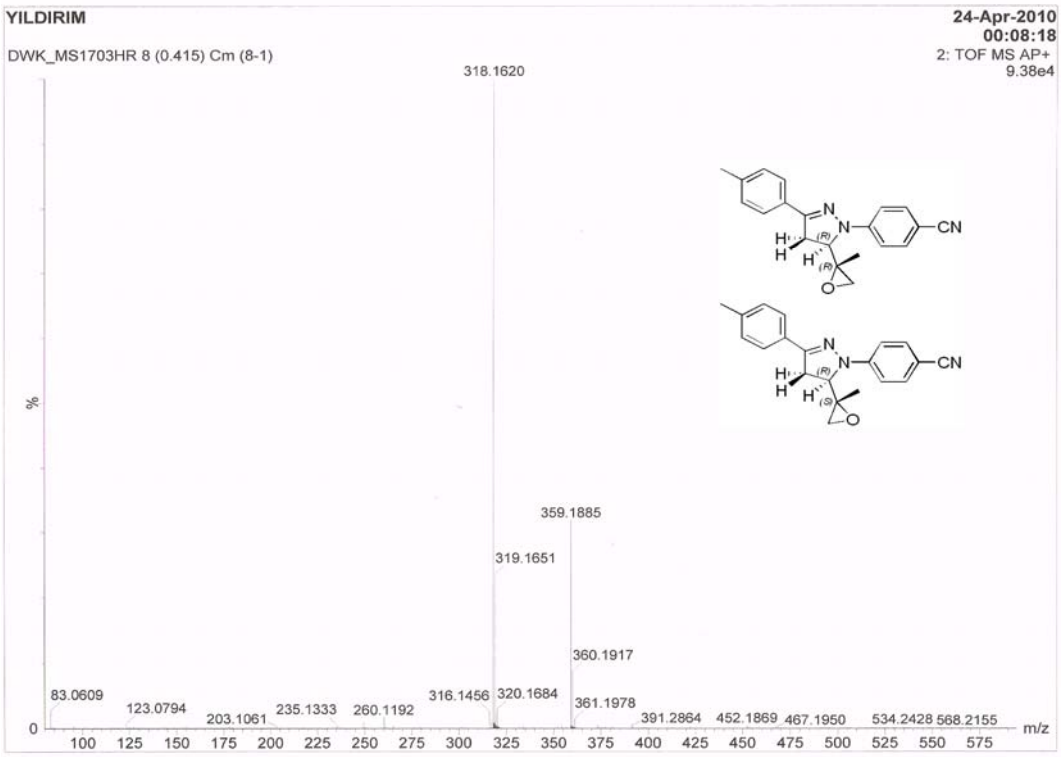

Figure 7.243 Mass spectrum of compounds **6.21u-u'**

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Abant İzzet Baysal University	2001-2004	M.Sc.	Aug, 2004
Abant İzzet Baysal University	2004-2010	Ph.D.	July, 2010

Publications

1- Yasar Durust, Muhammet Yıldırım, Asli Aycan. An Efficient One-Pot Synthesis of 5-Amino Substituted 1,2,4-Thia(oxa)diazoles, *J.Chem.Res,* 4, 235-239, 2008.

2- M.Yıldırım, E.Sen, O.Kulkoyluoglu. Modelling of the Water Quality of Büyüksu Stream,Bolu,Turkey, *Water Environ. Res.*, 81, 325, 2009.

3- C. F. Fronczek, Y. Dürüst, M. Yildirim and F. R. Fronczek. (3a*R*,6a*R*)-1-phenyl-5-[(*R*)-1-phenylethyl]-3-[4-(trifluoromethyl)phenyl]-1,6a-dihydropyrrolo [3,4-*c*]pyrazole-4,6(3a*H*,5*H*)-dione, *Acta Cryst.,*E65,12,o3196-o319,2009.

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5- Yaşar Dürüst, Muhammet Yıldırım. Synthesis, UV-VIS Spectra and Hammett Correlation of Some Novel Dihydro Bispyrrolo[3,4-*c*]Pyrazoles *Monatsh Chem,*141, (in press), 8, 2010.

Communications to national scientific meetings

1- M.Yıldırım, E.Şen, Surface water quality modelling studies on Büyüksu(Bolu) Stream**.** *XVIII.National Chemistry Congress*, p.102. 5-9 July, 2004, Kafkas University, Kars, TURKEY.

2- M.Yıldırım, Y.Dürüst, A.Aycan, One pot synthesis of some new 5-amino substituted thiadiazole and oxadiazole derivatives using thiourea compounds. *XX. National Chemistry Congress.* OKP-14. 4-8 September, 2006, Erciyes University, Kayseri,TURKEY.

3- M.Yıldırım, Y.Dürüst. 1,3-Dipolar Cycloaddition Reactions of *C,N*-Nitrilimines with isoprene Monoxide. *24. National Chemistry Congress,* OP010, 29 Haziran-2 Temmuz, 2010, Zonguldak Karaelmas University, Zonguldak,TURKEY.

4- M.Yıldırım, Y.Dürüst. 1,3-Dipolar Cycloaddition of Nitrilimines with Chiral Maleimides: Synthesis of Optical Active (3a*S*,6a*S*)- and (3a*R*,6a*R*)-[3,4-*c*] Pyrazol-4,6-Dione(s). *24. National Chemistry Congress,* OP011, 29 Haziran-2 Temmuz, 2010, Zonguldak Karaelmas University, Zonguldak,TURKEY.

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1- M.Yıldırım, Y.Dürüst, A.Aycan. A convenient route to the synthesis of 5-amino substituted thia(oxa)diazole. *2nd. EuChems Chemistry Congress.* No: 11828. 16-20 September, 2008, Torino, ITALY.

2- M.Yıldırım, Y.Dürüst. An Efficient Synthesis of Partially Saturated Pyrrolo[3,4-*c*] pyrazoles via Nitrilimine-Bismaleimide Cycloaddition. *10th*

Annual - Florida Heterocyclic and Synthetic Conference. No:17. 8-11 March, 2009, University of Florida, Gainesville, Florida, USA.

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