SYNTHESIS, CHARACTERIZATION AND CATALYTIC ACTIVITY STUDIES OF OPTICALLY ACTIVE PYRAZOLES

A DISSERTATION

Submitted in partial fulfillment of the requirements for the award of the degree of

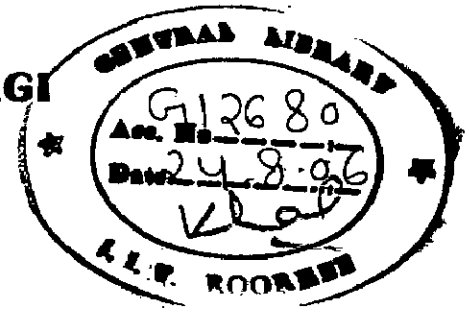
MASTER OF TECHNOLOGY

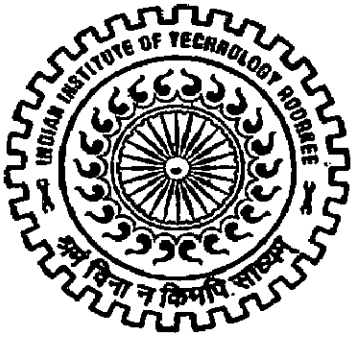
in

ADVANCED CHEMICAL ANALYSIS

By

NIDHI TYAGI





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JUNE, 2006

CANDIDATE'S DECLARATION

I hereby certify the work which is being presented in thesis entitled *"**Synthesis, characterization and catalytic activity studies of optically active pyrazoles**"* in partial fulfillment of the requirement for the award of the degree of master of technology submitted in the **Department of Chemistry, IIT Roorkee,** is an authentic record of my own work carried out during a period from July 2005 to June 2006 under the guidance and supervision of **Dr. A. K. Singh**, Professor, Department of Chemistry, IIT Roorkee, Roorkee and **Dr. Udai P. Singh,** Associate Professor, Department of Chemistry, IIT Roorkee, Roorkee.

The matter embodied in this thesis has not been submitted by me for the award of any other degree.

Nidhi Tyagi

Date: 30-06-06. **(Nidhi Tyagi)**

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

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(Nidhi Tyagi)

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ABSTRACT

The optically active pyrazoles (+)-3(5)(cyclohexylethylamino)methylpyrazole (3c) and (-)-3(5)-N-(phenylmethylene)benzenaminopyrazole (3f) were prepared by the reaction of diketopiprazine with optically active amine (+)-cyclohexylethylamine and (-)-N-benzylidenebenzenamine respectively. These compounds (3c) and (3f) were characterized by IR, UV, GC-MS and NMR. After complete characterization these optically active pyrazoles were used to prepare sodium salt in a manner analogous to that of $KB(pz)_4$. Sodium borohydride was heated in presence of 4 equivalent of (3c)/(3f) at 220-240 °C until 4 equivalent amount of hydrogen gas was evolved. These tertakis(pyrazolyl)borates {sodiumtetrakis{(+)-3(5)cyclohexylethylaminomethylpyrazo -lyl}borate (3d) and sodiumtetrakis{(-)-3(5)-N-(Phenylmethylene)benzenamino-pyrazolyl}borate (3i)} ligands were used in metal catalyzed enantioselective cyclopropation reaction of styrene with ethyldiazoacetate. The highest enantiomeric exess (ee) obtained was 56% & 65% of compounds (3d) & (3i) respectively for cis isomers and 46% for trans isomers in both compounds. The chemical yield was up to 26-40% & 12-18% for compound (3d) & (3i) respectively.

INTRODUCTION

AND

LITERATURE SURVEY

[1.0] GENERAL INTRODUCTION:

Pyrazoles are an intensively studied family of hetrocycles, which are important subunits in a number of natural products, biologically active compounds and have the ability to serve as versatile chiral bulding blocks [1]. Many pyrazole derivatives exhibit a wide range of biological properties as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial and sediative-hypnotic activities [2]. 1,5-Diarylpyrazole derivatives are important in medicinal and pesticidal chemistry [3]. Recently some 1,5-diarylpyrazole derivatives were reported to have nonnucleoside HIV-1 reverse transcriptase inhibitory activities [4]. Extensive studies have been devoted to the 1,5-diarylpyrazole derivatives including *Celecoxib*, the famous cyclooxygenase-2 inhibitor [5]. β-Pyrazolylalanine isosteric with histidine [6] was first isolated from *citrullus vulgaris*, a watermelon in 1957 [7]. Usually pyrazoles can be prepared from the reaction of hydrazines and 1,3-dicarbonyls. Research on the coordination chemistry of optically active pyrazole derived ligands has been progressed very rapidly after introduction of poly(pyrazolyl)borate (PPB) ligands by Trofimenko in 1966 [8].

He described the synthesis and the application of poly(pyrazolyl)borate (PPB), in extraordinarily wide range of chemistry, from modeling of active site of metalloenzymes through analytical chemistry and organic synthesis to catalysis and material science [9]. One of the outstanding characteristic of poly(pyrazolyl)borate complexes is their high stability. The fundamental feature in all poly(pyrazolyl)borate complexes are uninegative chelating ligands having six member ring with general structure $RR'B(\mu\text{-}pz)_2M(L)_n$

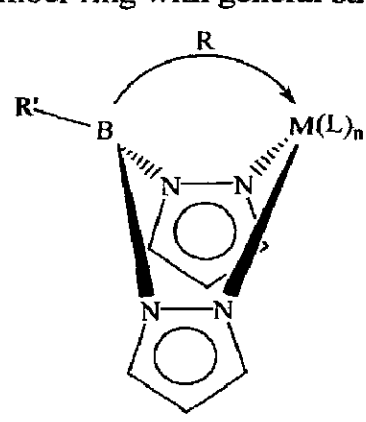
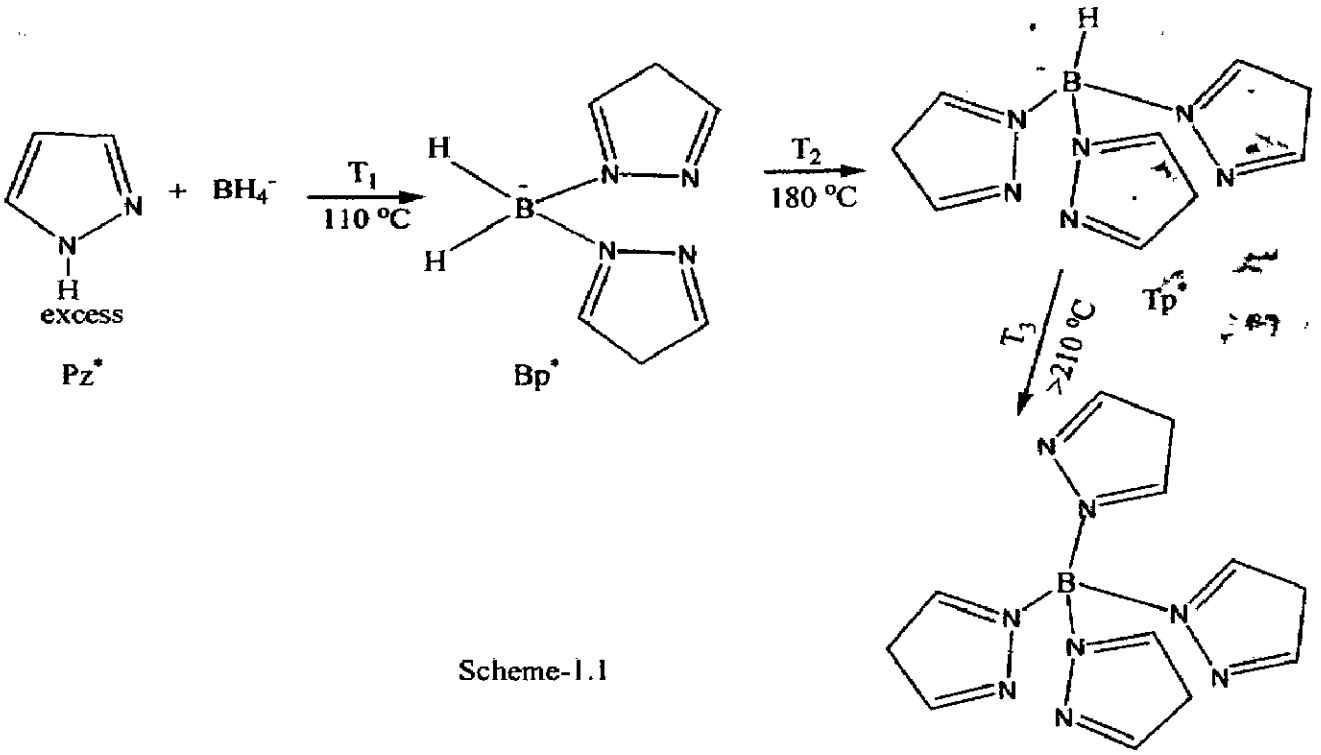


Fig-1.1

(Fig-1.1), where R′ is non-coordinating substitutent, pz is 1-pyrazolyl groups (n = 0, 1 or 2) [10]. In Fig-1.1, R and R' are different, the pseudo equatorial R' is pointing away from the metal but the pseudo axial R (may be another pyrazolyl ring) is directed towards the metal and may bond to it. Due to this property (pyrazolyl)borates also termed as "*scorpionates*". Chiral chelating ligands are considered important for transition metal catalyzed enantioselective reactions. Generally C_2-symmtric catalysts are successful but in some cases lack of C_2-symmtry leads to additional stereo electronic effects that improves enantioselectivity. This effect attained by using heterodonating ligand (nitrogen or sulphur ligands). Mostly chiral pyrazoles are derived from derivatives of natural monoterphenes (+)-3-carene [11]. In literature lot of optically active pyrazoles have been reported e.g. (7(R)-isopropyl-4(R)-methyl-4,5,6,7-tetrahydroindazolyl)pyrazole, 7(S)-tert-butyl-4(R)-methyl-4,5,6,7-tetrahydroindazolyl)pyrazole [12], (±)-5-isopropeny-3-methyl-1-(2-methoxyphenyl)-1,4,5,6-tetrahydrocyclopentapyrazole, (±)-2-(5-isoprppyl-3-methyl-5,6-dihydro-4H-cyclopentapyrazol-1-yl)ethanol, (±)-5-isopropeny-3-methyl-1-(2-pyridyl)-1,4,5,6-tetrahydrocyclopentapyrazole, (±)-5-isopropeny-3-methyl-1-(2,6-dimethyl-4-pyrimidyl)-1,4,5,6-tetrahydrocyclopentapyrazole [13], (-)-3(5)-methyl-1-phenylethylaminoethylpyrazole [14, 15], hydrotris(3-mesitylpyrazole), hydrotris(5-mesitylpyrazole) [16], 2-(pyrazol-1-yl)pyridines, 2,6-bis(pyrazolyl)pyridine, 6,6′-bis(pyrazolyl)-2,2′-bipyridine [17], (R)-2-(1-pyrazolyl)-1-phenylethanol, (R)-2-(1-pyrazolyl)-1-(pentafluorophenyl)ethanol, (R)-2-(1-imidazolyl)-1-phenylethanol, (R)-2-(1-2-methyl-1-imidazolyl)-1-phenylethanol [18], tris{(4S,7R)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl}phosphineoxide [19], 1,3,4-triethoxy-4-(1-phenyl-1H-4-pyrazolyl)-(2R,3S,4R)-butan-2-ol [20], 3,4-diphenyl-5-methylpyrazole [21], 1,3,5,7-tetramethylpyrazabole [22], 3,4-dimethyl-1,5-diphenylpyrazole [23], 3-(pentaflouroethyl)pyrazole, 3-(heptaflouropropyl)pyrazole [24] etc.

By using different substituted pyrazole molecule, different type of optically active (pyrazolyl)borate salt can be prepared by heating optically active pyrazole with alkali metal borohydride maintaining temperature around 110 °, 180 ° and > 210 °C respectively to give di-, tri-, and tetra(pyrazolyl)borate salt (Scheme-1.1).



Scheme-1.1

The use of tripod nitrogen ligand as tris(pyrazolyl)borate (Tp) ion are very effective in forming a number of complexes because of their high stability [25]. Although poly (pyrazolyl)borates have been compared with β–diketones, when bidentate $[R_2B(pz)_2]$ and cyclopentadiene (Cp), when tridentate $[RB(pz)_3]$ as shown in Fig-1.2, but structurally

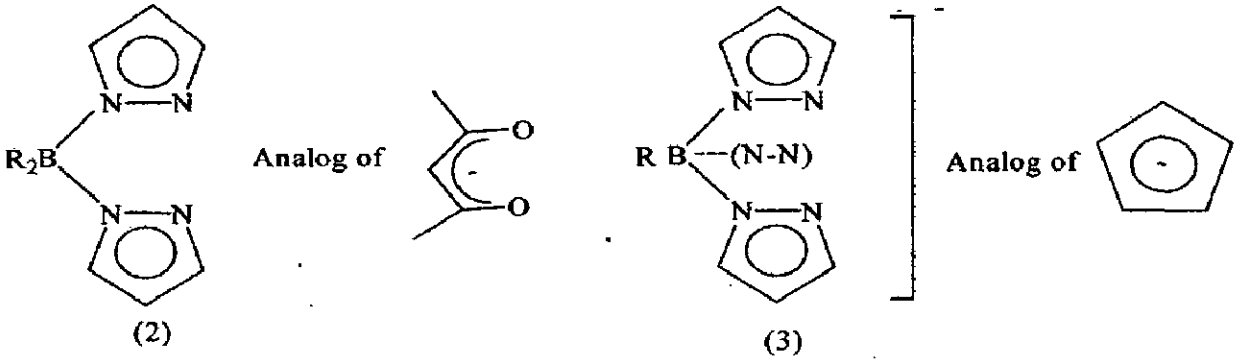
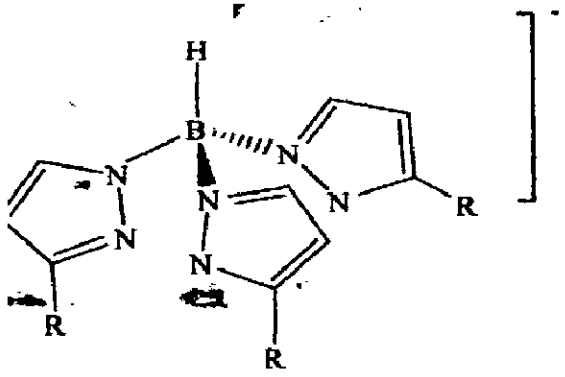


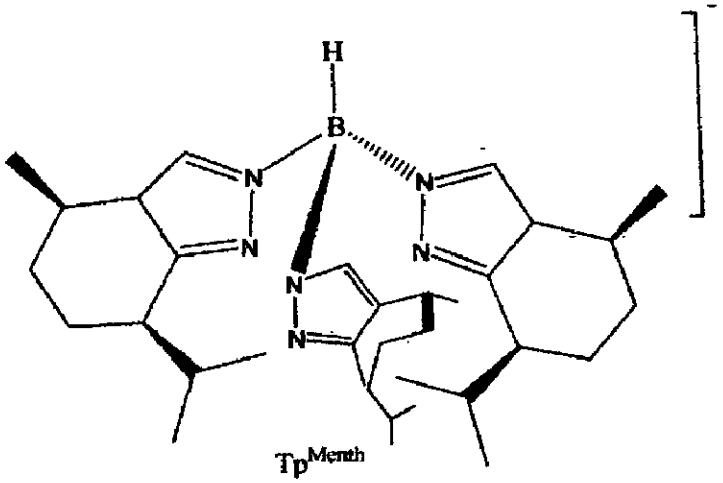
Fig-1.2

similar tris(pyrazolyl)borates (Tp) are more stable than cyclopentadiene (Cp) compounds [26, 27] because only one substituent can be placed on C_5H_5 ($-C_5R_5$) to yield a derivative ligand with retention of the original ligand symmetry, there are 15 ways of placing from one to ten identical substituent on the parent $HB(pz)_3^-$ ligand and still maintain its original

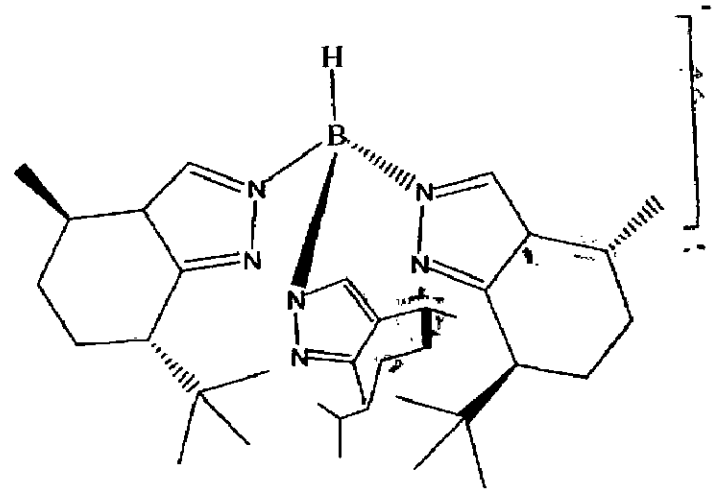
C_{3v}-symmetry. Continuing interest in organometallic stereochemistry and asymmetric catalysis leads to a steady increase in the study of optically active organometallic complexes. Most of the chiral complexes described with asymmetric metal atom contains cyclopentadienyl (Cp) ligand, few with poly(pyrazolyl)borates are also available [28]. A substituent in the position of a tris(pyrazolyl)borate (Tp) has the most telling effect on the coordination chemistry. Combined with the pronounced steric effects of substituents at 3-position of pyrazolyl rings on the properties of resulting metal complexes [29] has lead to target novel optically active variants of generalized structure-A in Fig-1.3 for synthetic studies [30, 12] this is because the 3-substituent is closed to the coordinated metal ion, and it define the size of the cavity harboring the metal by cone and wedge angle or by some



Structure-A



Tp^{Menth}



$Tp^{Mementh}$

Fig-1.3

other means. The effect of a 3-substituent is dominant than 4- or 5- substitution. The 4-substituent on the pyrazolyl ring is remote from both coordinated metal and boron atom, because of little steric consequence. However the 4-substituent may influence the electron density of the ligand through electron donation or withdrawal. It is considered that the incorporation of pyrazole unit into certain chiral molecule provides new chiral ligands, since the potential utility of pyrazoles as efficient coordinating ligand is well established in inorganic chemistry. The C_3-symmetric array of stereogenic centers in structure-A is designed to afford an unusual chiral fence about a coordinated metal ion that may induce interesting and potentially useful stereoselective metal-mediated reactive [31]. In addition this ligand system admits greater stabilization influence upon the metal center [32], often resulting in air stable compounds [33]. For example, bis[hydrotris(3,5-dimethyl-1-pyrazolyl)borate] complexes of manganese (II), copper (II) and zinc (II) have been reported [34]. An important impetus in this chemistry was the introduction of alkyl substitution of the pyrazolyl ring at 3 (and 5) position(s) to prevent a formation of an inert sandwich type compounds such as L_2M. The tetrakis(pyrazolyl)borates mainly tridentate as $B(pz)_4$ (= pzTp) and $B(3\text{-}Mepz)_4$ (= pzTpMe) [35] were reported.

The poly(pyrazolyl)borate are versatile proligands useful for the preparation of a wide range of complexes of metal ion through out the periodic table as the steric and electronic properties of these ligands are easily modified by changing either the number of pyrazolyl ring or by substituents thereon at the boron center. The tris(pyrazolyl)borate

(Tp) ligands have become increasingly popular in synthetic inorganic ... chemistry [36], where they resemble the imadazol coordination in models for active site of metallo-enzymes [37], metallo-proteins such as oxy-hemocyanin [38], copper containing mono-oxygenaes [39], and blue copper proteins [40]. Particularly, the geometry as well as strong electron donating property of alkyl substituted hydrotris(pyrazolyl)borates are useful for the synthesis of small molecule models. Trofimenko initiated the investigation into the use of poly(1-pyrazolyl)borates to model histidine donors, several of which act as biomimetic compounds [41], tris(1-pyrazolyl)borates have been used to structurally mimic the three histidine residue in the preparation of hemerythin analogue [42] as well as model methane monooxygenase [43]. Poly(1-pyrazolyl)alkane (PPA) ligands afford several advantages in the synthesis of iron complexes containing N-donor ligands poly(1-pyrazolyl)alkane (PPA) ligands are neutral and have appropriated mimics of naturally occurring histidine residue in metalloenzymes. In addition the boron bounded hydrides of the poly(pyrazolyl)borate are known to be reactive and the interaction of the B-H residue with the metal center have been reported [44].

These tris(pyrazolyl)borate (Tp) ligands have been employed for modeling the active site of blue copper and non-heme iron proteins, the zinc center of carbonicanhydrase, molybdopterin enzymes and polymaganese site of the photosystem - II oxygen-evolving center [45-51]. There are fewer examples of iron (II) complexes containing bidentate(pyrazolyl)borate ligands [52, 53] with tris(pyrazolyl)borate (TPB) such as $[Fe(TPB)_2]$ and $[Fe(dmTPB)_2]$, {tris(3,5-dimethyl-1-pyrazolylborate = dmTPB}, iron (II) complexes containing only one tridentate PPB ligands bound to metal center have been reported e.g. $[Fe(TPB)(CO)_2(C_3F_4)]$ and complexes with optically active PPB ligands [54]. Organotin (IV) poly(pyrazolyl)borates have been studied for their potential biological activity [55] as antimutagenic activity [56]. Pyrazolylborate-zinchydroxide complexes showed a comparable activity to *β-Lactamase* activity as antibiotics [57]. Large number of copper complexes with sterically tris(pyrazolyl)hydroborate ligand are available in literature and used as synthetic analoge for cuproprotein active site [58]. The most effective model to data for the oxygen transport protein hemocynin (Hc) [59] utilizes the ligand tris[1-(3,5-diisopropylpyrazolyl)]hydroborate (Tp^{ipr2}), which forms a peroxo-dicopper (II) complexes with spectroscopic and physicochemical properties that are

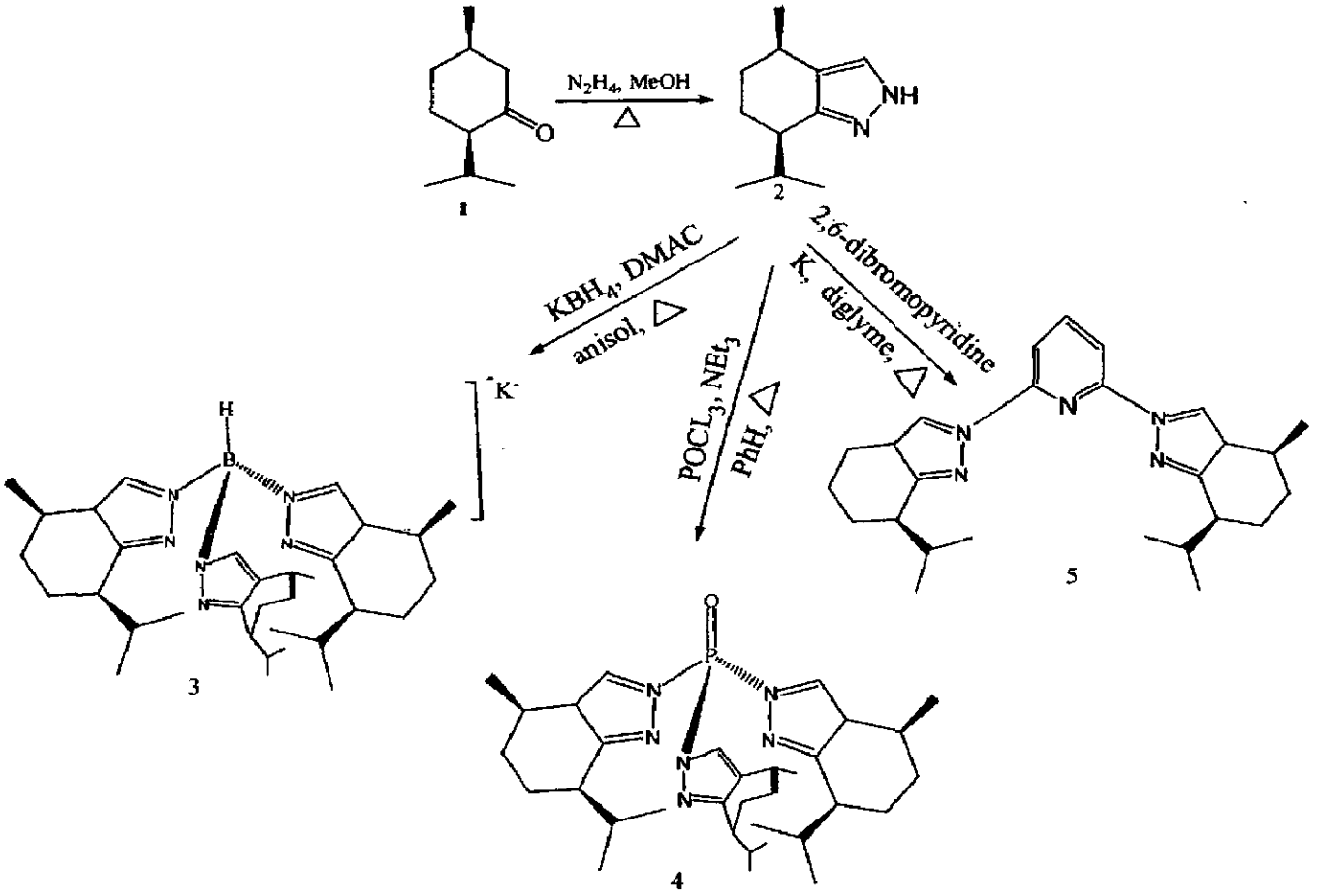
strikingly similar to the protein [46]. Coppper (I) carbonyl complexes with tris(pyrazolyl)borates (Tp) ligands were reported in which tunable steric and/or electronic effects were evident at the 3 and/or 5 position of the pyrazole ring. Typical examples include $[Cu(HB(3,5\text{-}(CF_3)_2\text{-}pz)_3)(CO)]$ [60], $[Cu(HB(3,5\text{-}i\text{-}pr)_2pz)_3)(CO)]$ [40] and $[Cu(CO)(HC(3\text{-}(t\text{-}Bu)pz)_3)]PF_6$ [61]. A series of metal varied $[ML(SC_6F_6)]$ model complexes (where L = hydrotris(3,5-diisopropyl-1)pyrazolyl)borate and (M = Mn, Fe, Co, Ni, Cu and Zn) related to blue copper protein have been studied [62]. Numerous of existing pyrazoles permit the construction of many unsymmetrical bis(pyrazolyl)borates, chiral tripod bis(pyrazolyl)borates [63] and chiral tris(pyrazolyl)borates.

Other achiral ligands of this type are well known and use of their complexes in enantioselective cyclopropanation and epoxidation have been studied. The enantioselective cyclopropanation of olefins with diazoacetates catalyzed by copper complexes bearing chiral ligands, initiated by Nozaki et. al. which is one of the most useful reactions in the synthesis of optically active cyclopropanes [64]. Several chiral nitrogen based ligands in combination with Cu and Rh complexes in asymmetric cyclopropanation have been reported [65]. Poly(pyrazolyl)borate ligand is employed to induce a significant degree of asymmetry in cyclopropanation reaction. Tolman and co-workers have been reported a series of hydrotris(pyrazolyl)borate-Cu complexes, where the pyrazole ring provides chirality. Bis(pyrazolyl)borate-Cu complexes have also been employed as precatalyst. The possibility of tailoring the pyrazolyl borates in addition to the great stability of their complexes led to attempt the synthesis of optically active poly(pyrazolyl)borates, since chiral ligands are excessesively designed for asymmetric catalytic reaction.

In this report attempt has been made to synthesize some optically active pyrazoles, their borates salt for catalytic activity study in cyclopropanation reaction of olifens with diazoacetates.

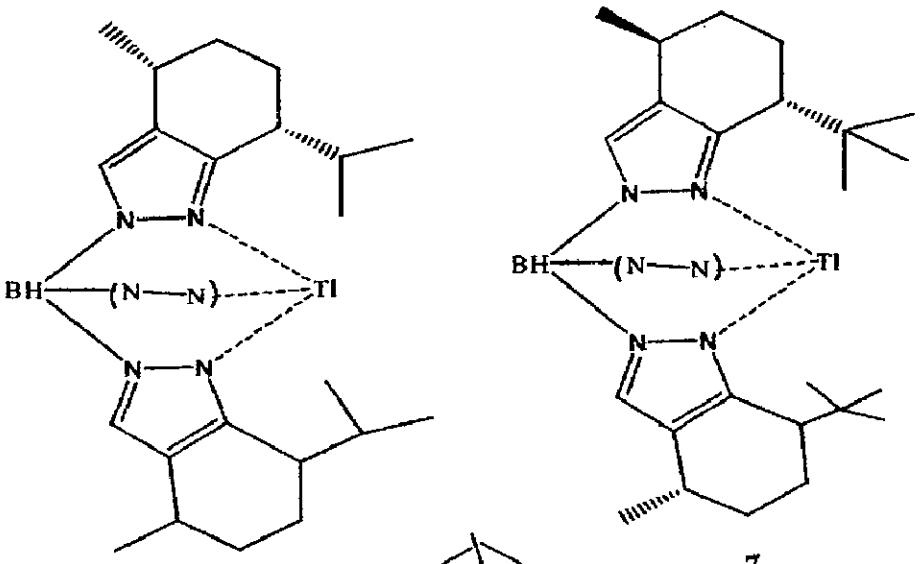
[1.1] LITERATURE SURVEY ON PYRAZOLYLBORATES COMPLEXES:

LeCloux et. al. reported multigram-scale synthesis of optically active and C_3-symmetric tris(pyrazolyl)hydroborate and tris(pyrazolyl)phosphineoxide ligands with Tl (I): tris(pyrazolyl)hydroborate {Tl[HB(pz^*)$_3$]} [pz^* = 7(R)-isopropyl-4(R)-methyl-4,5,6,7-tetrahydroindazolyl (Menthpz) and 7(S)-tert-butyl-4(R)-methyl-4,5,6,7-tetrahydroindazolyl (Mementhpz)] and tris(pyrazolyl)phosphine oxide [OP(pz^*)$_3$] {pz^* = (4S,7R)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl (Camphpz), ligands of potential utility for stereo selective metal-mediated organic transformations, the assignment of their ^{1}H and ^{13}C NMR spectra using COSY and HETCOR methods and representative X-ray crystal structures that define their absorbance configurations and steric properties. The crystal structures of OP(Camphpz)$_3$, Tl[HB(Menthpz)$_3$] (TlTp^{Menth}) and Tl[HB(Mementhpz)$_3$] (TlTp^{Mementh}) were determined [12]. They also prepared complexes of type Tp^{Menth}M(II)Cl {M (II) = Zn (II), Ni (II), Co (II), Cu (II), Mn (II), Fe (II)}, Tp^{Mementh}Zn(II)Cl, Tp^{Menth}M(II)(NO_3) {M (II) = Cu (II), Ni (II)}, Tp^{Menth}M(II)(OAc) {M (II) = Cu (II), Ni (II)}, Tp^{Menth}Rh(I)(CO)$_2$, Tp^{Menth}Ti(IV)Cl_3, and Tp^{Menth*}Ti(IV)Cl_3, where Tp^{Menth*} is an isomerized version of Tp^{Menth} in which one pyrazolyl group is attached to B via the more rather than less hindered N atom. Metal ion geometries were pseudo-octahedral 4-coordinate for (Tp^{Menth}MCl and Tp^{Mementh}ZnCl), distorted square-pyramidal 5-coordinate for [Tp^{Menth}M(OAc) and Tp^{Menth}M(NO_3)] and octahedral 6-coordinated for (Tp^{Menth}$TiCl_3$ and Tp^{Menth*}$TiCl_3$). IR and NMR data indicated that Tp^{Menth}Rh(CO)$_2$ exists as a mixture of 4- and 5-coordinate isomers. LeCloux et. al. also synthesized and suggested that the chiral Tp ligands have effective steric properties similar to those of achiral variants with 3-t-Bu or 3-i-Pr substituents on the pyrazolyl rings [66]. Brunner et. al. reported the synthesis of optically active tetrakis(pyrazolyl)borate for enantioselective cyclopropanation reaction [14]. LeCloux and Tolman prepared different types of optically active pyrazole and as outlined in Scheme-1.1.1 by formylation commercially available (2S,5R)-methone and then heated with hydrazine.



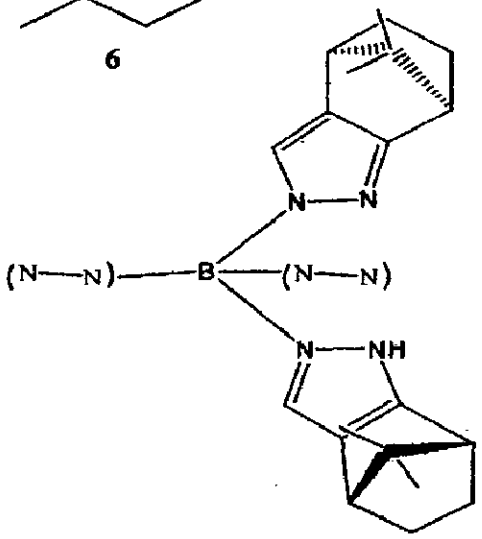
Scheme-1.1.1

They suggested that the propensity of Tp ligands strongly coordinated to a wide range of metal ions coupled with the demonstrated steric effects of pyrazolyl ring substituents suggests that chiral Tp's and derived metal complexes would be promising reagents for enantioselective metal-centered molecular recognition or catalysis of organic transformations **6** was synthesized from (2S,5R)-menthone, **7** from (R)-(+)-pulegone and **8** from (1R)-(+)-camphor. The potassium salt of the pyrazole used to make **7** was reacted with 2,6-dibromopyridine to give **5**.



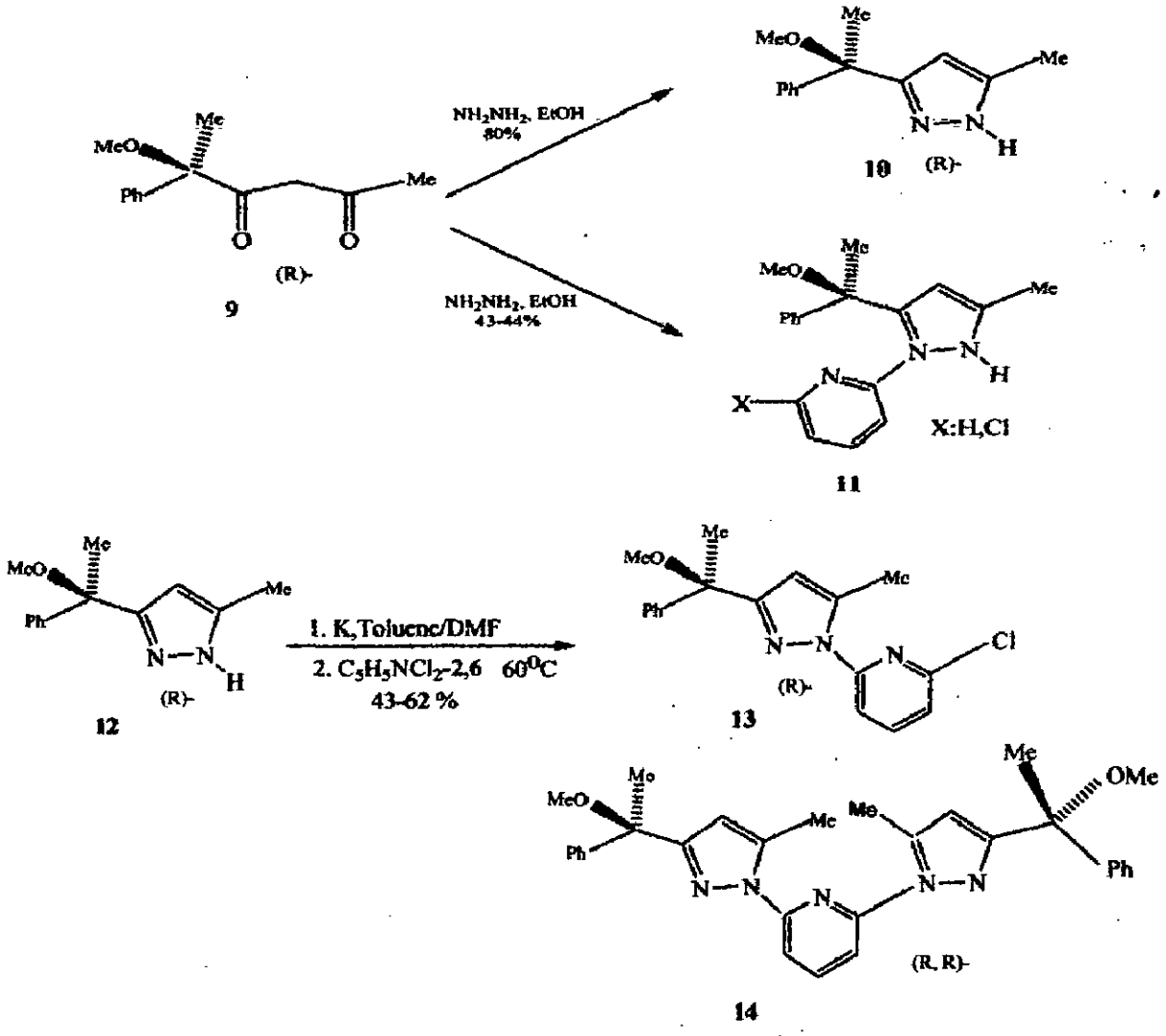
6

7



8

Regioselective synthesis of optically active 2-(pyrazol-1-yl)pyridines with adjacent quaternary carbon sterocenter having chiral N,N-donating ligands using resolved O-methylether of atrolactic acid as a source of the adjacent quaternary carbon sterocenter were reported by Kowalczyk and different regioisomers were formed selectively in the reaction of 2-hydrazinopyridine with the chiral 1,3-diketone and in the nucleophilic substitution of 2-choloropyridine with potassium salt of chiral pyrazole. The second route gave 2-(pyrazol-1-yl)pyridines with stereogenic center neighboring the coordinating nitrogen in the pyrazole ring. Also new C_2-symmetric chiral ligands based on 2,6-bis (pyrazolyl)pyridine and 6,6′-bis(pyrazolyl)-2,2′-bipyridine structures (Scheme-1.1.2) have been reported [17].

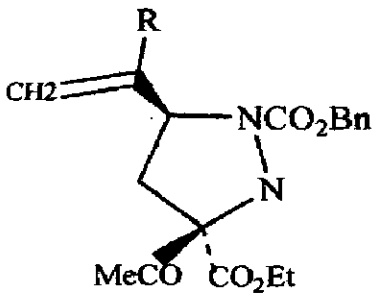


Scheme-1.1.2

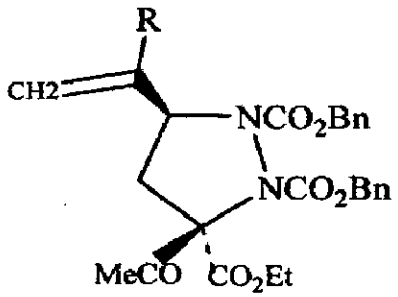
New chiral pyrazoles, cis(4R,7R)-4-methyl-7-isopropyl-3-phenyl, trans(4R,7R)-4-methyl-7-isopropyl, cis(4R,7R)-4-methyl-7-isopropyl-7-methyl, and trans(4R,7R)-4-isopropyl-7-methyl-4,5,6,7-tetrahydro-1-H-indazole were structurally characterized by ^{1}H NMR spectroscopy and gives useful effects for a chiral catalyst or a chiral auxiliary [67]. Optically pure complexes with 3-fold rotational symmetry can improve enantioselectivity in catalytic reactions. In investigation of this premise, a novel C_3-symmetric copper complexes of tris(pyrazolyl)hydoborate ligands with phenyl substitutents enclosing the bound metal ion were developed. Monomeric and dimeric copper complexes were discovered [68].

Shengming et. al. reported the construction of optically active pyrazolidine derivatives, **15** and **16** [R = (un) substituted Ph, CH: $CHCO_2Me$, CH: CHBu, 2-thienyl]

have been constructed by the Cu= and Pd- catalyzed asymmetric one pot tandem addition cyclization reaction of 2-(2′,3′-dimethyl)-β-petoester CH_2:C:$CHCH_2CH(COMe)CO_2Et$, organic iodides RI and dibenzylazodicarboxylate. They also suggested that the absolute configuration of the final products depends on the structure of ligand (S,S)-PhBox or (R,R)-PhBox [69].

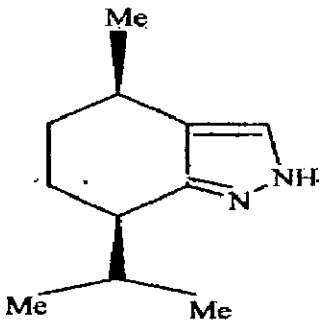


15



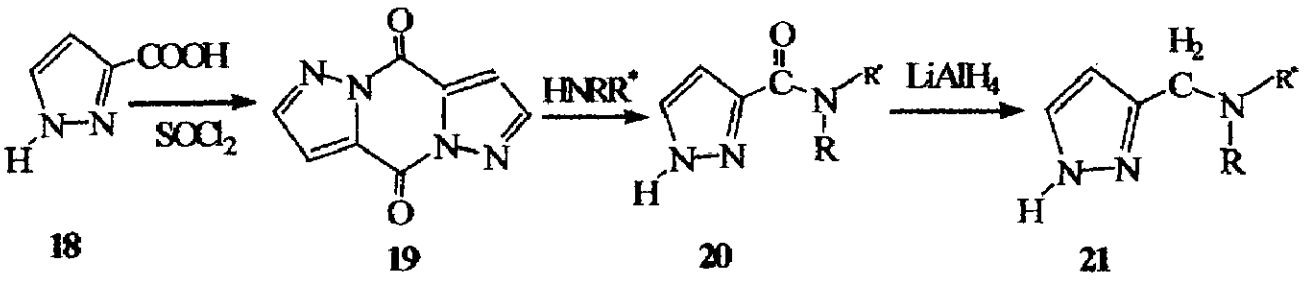
16

Bovens et. al. reported the preparation of optically active pyrazole 4R-methyl-7R-isopropyl-4,5,6,7-tetrahydroindazole **17** prepared from (-)-methanone, then used for the preparation of the ligand bis(4R-methyl-7R-isopropyl-4,5,6,7-tetrahydro-indazolyl)methane (a), bis(4R-methyl-7R-isopropyl-4,5,6,7-tetrahydro-N_1,N_2-indazolyl)methane (b), and bis(4R-methyl-7R-isopropyl-4,5,6,7-tetrahydro-N_1-indazolyl)methane (c). Their complexes with Pd, $[Pd(\eta^3\text{-}C_3H_5)(LL)PP_6]$ (LL = a, b and c) were also used as catalyst precursor for the reaction of rac-(E)-1,3-diphenyl-3-acetoxy-1-propene with dimethylmalonate, when ligand (b) was used methyl-2-carbomethoxy-3,5-diphenyl-4-enoate obtained in 84% ee [70].



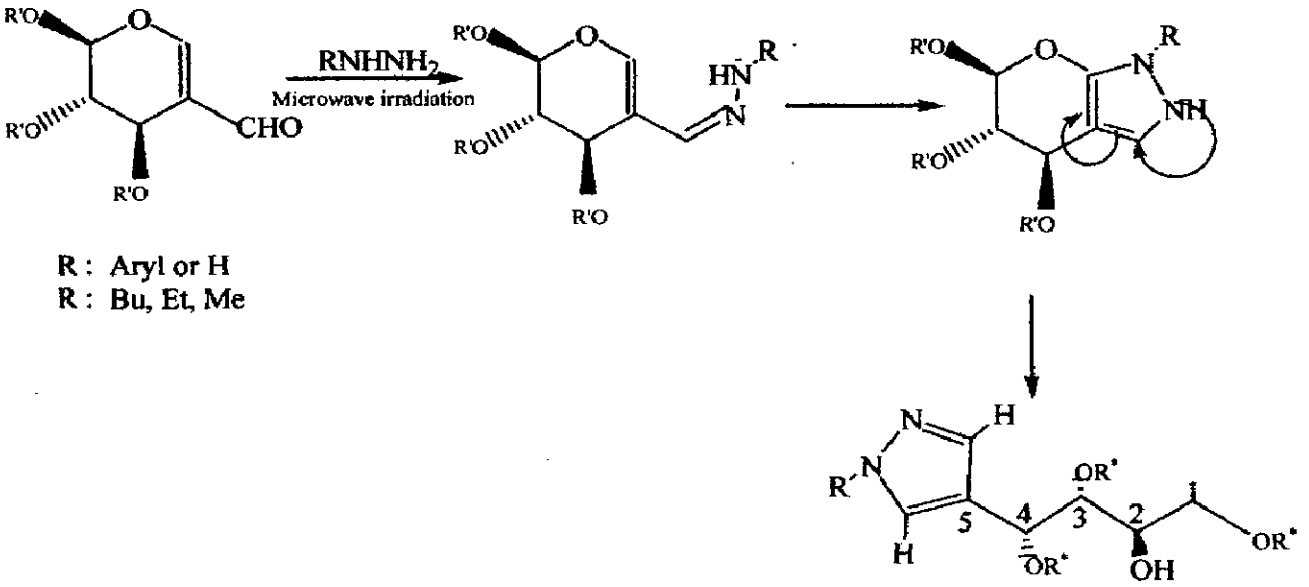
17

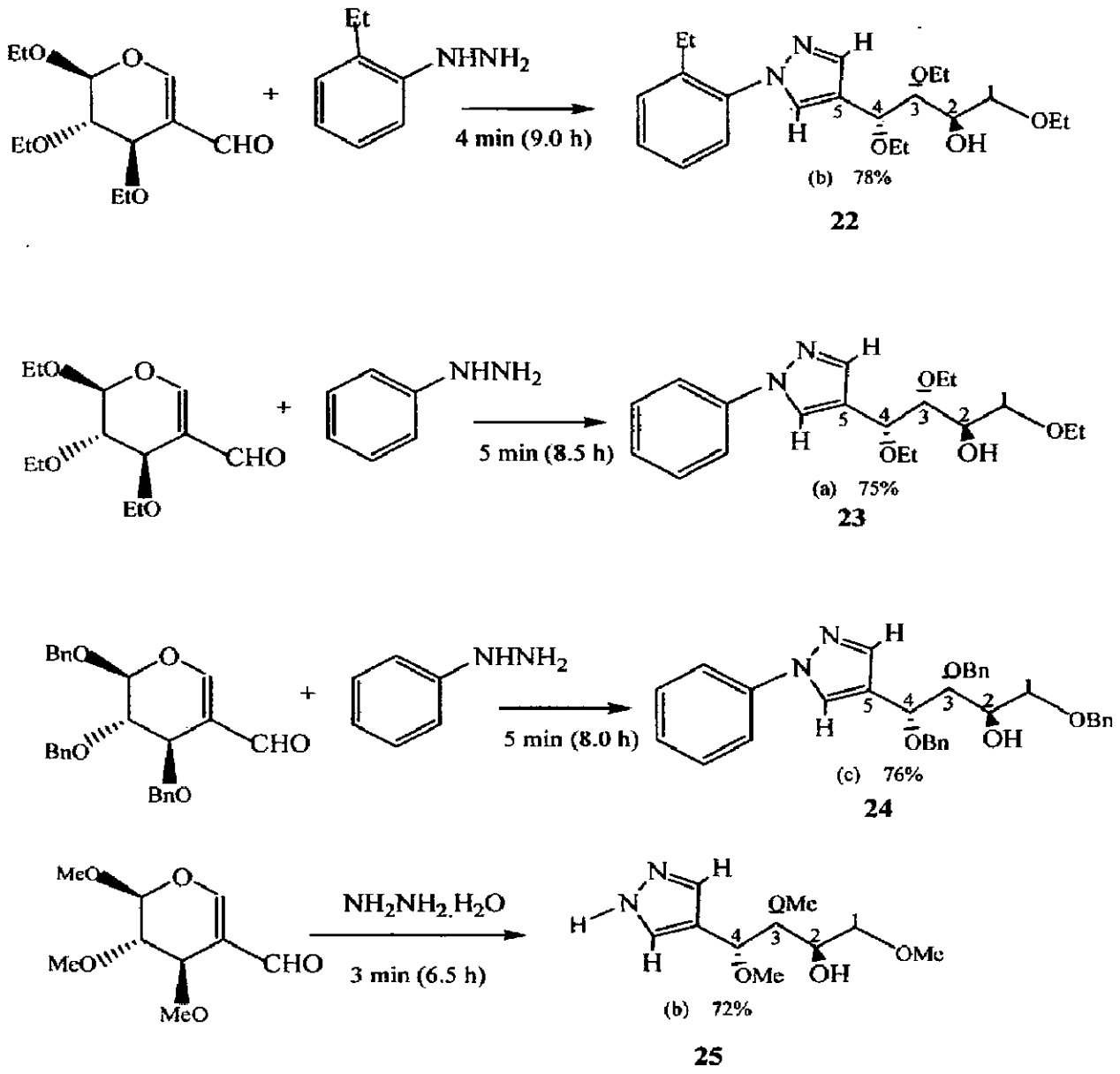
Brunner et. al. reported the synthesis of such pyrazoles by condensing optically active amines with a dimer derived from pyrazole carboxylic acid [15] as shown in Scheme-1.1.3.



Scheme-1.1.3

Yadav et. al. reported the efficient synthesis of optically active pyrazoles under solvent free conditions; 2-formyl glycols undergo rapid condensation with aryl hydrazines to give the corresponding optically pure 4-substituted pyrazoles in good yield with high selectivity as shown in Scheme-1.1.4. They also assigned the stereochemistry of the products by NMR experiments [20].





Scheme-1.1.4

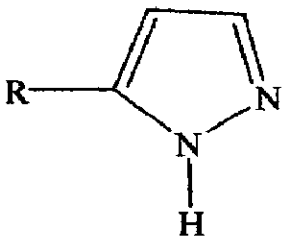
Reger et. al. reported that the addition of the tris(pyrazolyl)methane ligand $HC(3,5\text{-}Me_2pz)_3$ (pz = pyrazolyl ring) to a THF solution of $TlPF_6$ resulted in the immediate precipitation of $\{[HC(3,5\text{-}Me_2pz)_3]_2Tl\}PF_6$. The structure was determined crystallographically. The arrangement of the nitrogen donor atoms about the thallium was best described as a trigonally distorted octahedron. The thallium atom sits on a crystallographic center of inversion; thus the planes formed by the three nitrogen donor atoms of each ligand are parallel. The lone pair on thallium is clearly stereochemically inactive and does not appear to influence the structure. The pyrazolyl rings are planer, but are tilted with respect to the thallium atom so as to open up the N···N intra-ligand bond

distances. They also reported that the thallium (I) complex by taking ligand to metal ratio of 1:1, $\{[HC(3,5\text{-}Me_2pz)_3]Tl\}PF_6$, in acetone. The structure of the cation was a trigonal pyramid, with Tl-N bond distances that range from 2.64 to 2.70 Å [71].

Pettinari et. al. reported that the reaction of $RSnCl_3$ (R = Me, Ph or Bu^n) and SnX_4 acceptors (X = Cl, Br or I) with equimolar amounts of tris(pyrazol-1-yl)methane ligands L; (L = $HC(pz)_3$, $HC(4\text{-}Mepz)_3$, $HC(3,5\text{-}Me_2pz)_3$, $HC(3,4,5\text{-}Me_3pz)_3$, or $HC(3\text{-}Mepz)_2(5\text{-}Mepz)$ yielded ionic 1:1 $[\{LSnRCl_2\}^+][\{SnRCl_4\}^-]$ or $[\{LSnX_3\}^+][\{SnX_5\}^-]$ and 2:1 $[\{LSnRCl_2\}^+]_2[\{SnRCl_5\}^{2-}]$ or $[\{LSnX_3\}^+]_2[\{SnX_6\}^{2-}]$ complexes, depending strongly on the number and position of the methyl groups on the azoles ring of the neutral ligand. The crystal and molecular structure of $[\{HC(4\text{-}Me_2pz)_3Sn^nBuCl_2\}^+]_2$ $[\{Sn^nBuCl_5\}^{2-}]$, $[\{HC(3,5\text{-}Me_2pz)_3SnMeCl_2\}^+][\{MeSnCl_4\}^-]$, and $[\{HC(3,4,5\text{-}Me_3pz)_3$ $SnBr_3\}^+][\{SnBr_5\}^-]$ were determined by X-ray crystallography. The structures of the cations are very similar, the Sn atom being in a strongly distorted octahedral environment with the Sn-N bonds in the range 2.22-2.33 Å, whereas in the anions the Sn atoms are five-coordinated (trigonal-bipyramidal) [72].

Domenico et. al. suggested that the reaction between CuX_2 ($X = ClO_4^-$, NO_3^-, Cl^-, Br^- and CH_3COO^-), and excess of tris(pyrazol-1-yl)methane ligands L, {L = $CH(pz)_3$, $CH(4\text{-}Mepz)_3$, $CH(3,5\text{-}Me_2pz)_3$, $CH(3,4,5\text{-}Me_3pz)_3$ or $CH(3\text{-}Mepz)_2(5\text{-}Mepz)$} yields $[CuX_2(L)]$, $[\{CuX_2\}_3(L_2)_2]$ or $[Cu(L_2)]X_2$ - type complexes. They also found that ligand to metal ratio is dependent on the number and disposition of the methyl substituents on the azole-type ligand and mainly on the nature of the counter-ion (X) [73].

Klein et. al. prepared a new class of optically active pyrazoles **26** [R = 1,2,3,4,5-pentahydroxy-β-D-gluco-penty-β-L-lyxopyranosyl, 3-(β-D-glucopyranosyloxy)-1,2,4,5-tetrahydroxy-D-gluco-pentyl-(4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl, (4S,5S)-2,2-dimethyl-1,3-dioxolan-4,5-diyl-4-ClC_6H_4] from optically active carboxylic acids (RCO_2H) by amidation with $H_2NCHPhCO_2CHCH{:}CMe_2$ · ozonolysis of $RCONHCHPhCO_2CH_2CH{:}CMe_2$ and cyclization with N_2H_4 [74].

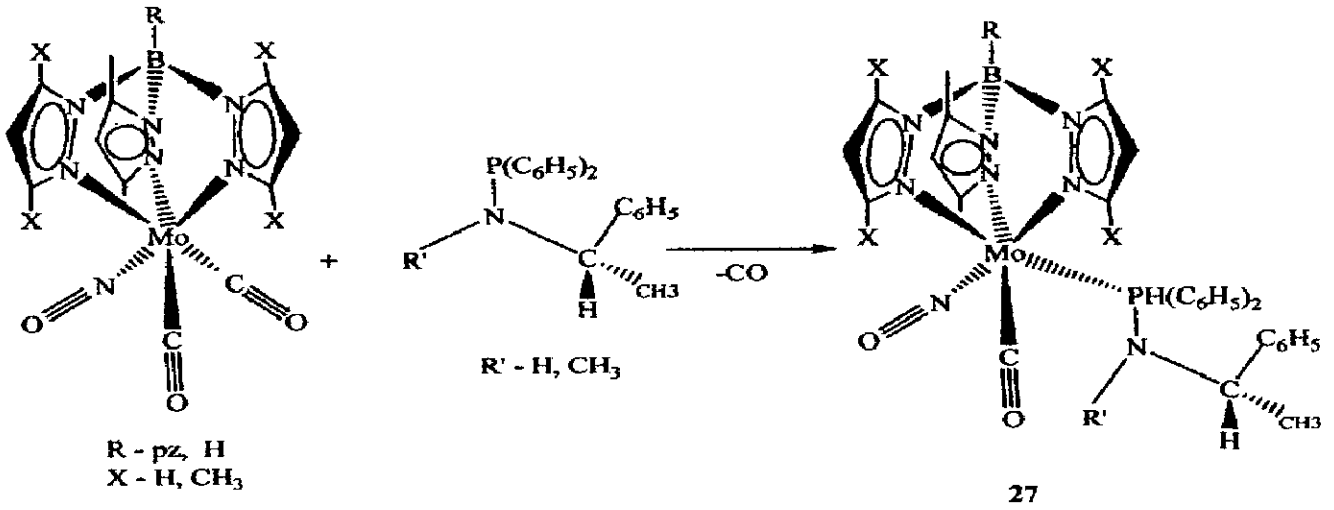


26

Frauendorfer et. al. treated pyrazolylborate metal complexes (M = Mo, W; L = CO) with isonitriles RNC (R = Et, CH_2Ph, CHMePh) and obtained isonitrile complexes of molybdenum and tungsten or enantiomer (L = CNEt, $CNCH_2Ph$) and diastereomer (L = CNCHMePh) with optically active M centers. Diastereomer showed different ^1H NMR signals but could not be separated by liquid chromatography or by crystallization [75]. They also suggested that the reaction of 3,5-dimethylpyrazole hydrochloride with lithium borohydride give 3,5-dimethylpyrazolylborate. This compound losses hydrogen at 114 °C to give 1,3,5,7-tetramethylpyrazabole. Treatment of 3,5-dimethylpyrazolylborate with sodiumhydride gives trihydro(3,5-dimethylpyrazolyl)borate ($[H_3B(3,5\text{-}Me_2pz)]^-$), whose reaction with pyrazole in dimethylacetamide gives the unsymmetrical (pyrazolyl)borate $[H_2B(pz)(3,5\text{-}Me_2pz)]^-$. The dichelate complexes of this ligand with Ni^{2+}, Zn^{2+} and Co^{2+} were prepared and studied. These complexes classified into two categories corresponding to the square-planer (Ni) and tetrahedral (Zn, Co) chelates. The ^1H NMR spectra of diamagnetic Ni and Zn complexes show in each case the presence of several distinct isomers. Symmetric bis(pyrazolyl)borates puckered metallocycle $M(pz)(3,5\text{-}Me_2pz)B$ presents no plane of symmetry [22].

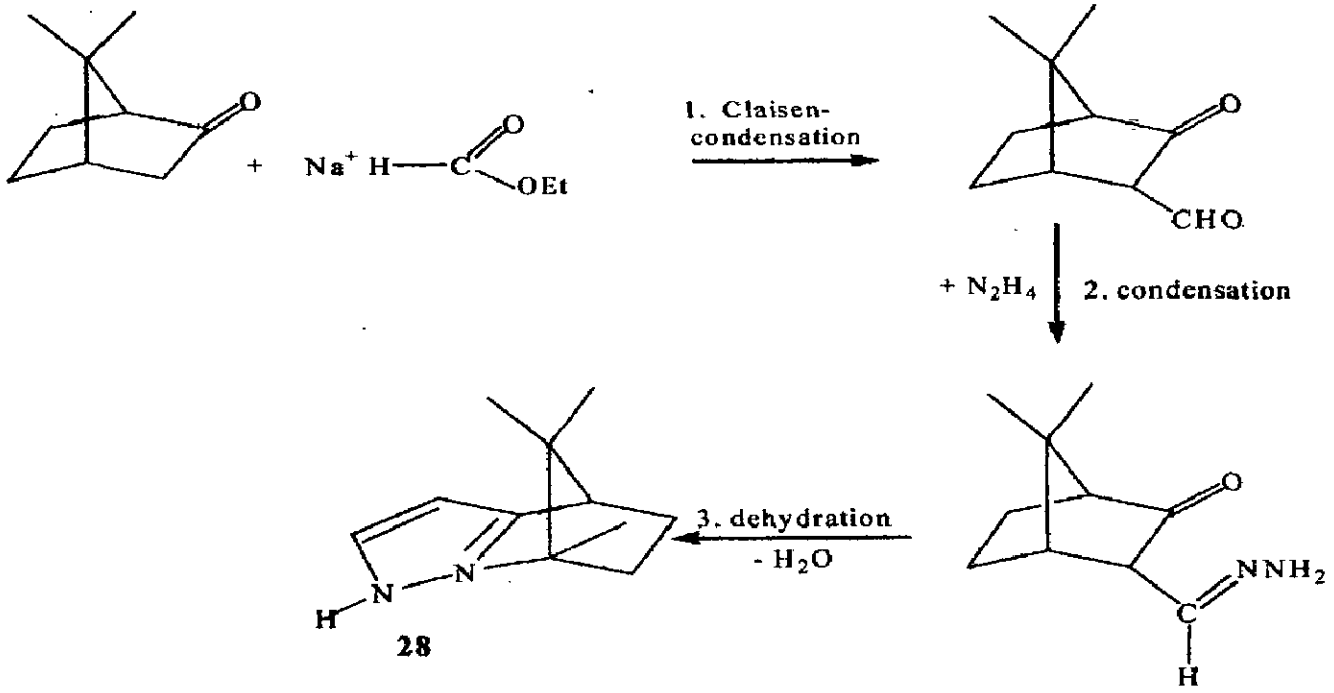
The synthesis of chiral pyrazolylmethylpyridines, pyrazolylmethyl-pyrazoles, their chiral derivatives and chiral methylenebisindazoles were reported by House et. al. These bidentate ligands formed stable 1:1 complexes with $PdCl_2$. A single-crystal X-ray structure determination of dichloro[(4S,7R)-7,8,8-trimethyl-2-(pyridin-2-ylmethyl)-4,5,6,7-tetrahydro-4,7-methano-2H-indazole]palladium (II) was also reported [76]. Poly(pyrazolyl)borate complexes $[R\text{-}B(3,5\text{-}X_2\text{-}pz)_3]Mo(CO)_2(NO)$ (R = pz, X = H; R = H, X = CH_3), react with the optically active aminophosphines {L = $(C_6H_5)_2PNRCH(CH_3)(C_6H_5)$ (R = H, CH_3)}, to give the monosubsitution products [R-

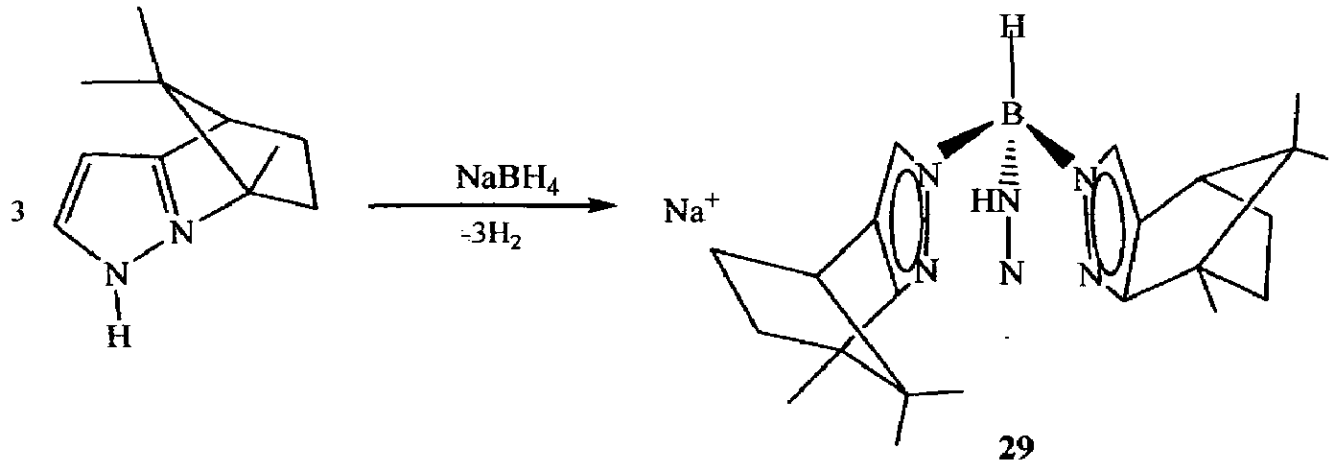
$B(3,5\text{-}X_2\text{-}pz)_3]Mo(CO)(NO)L$, in which the metal atom is a new chiral center (Scheme-1.1.5). The separations of distereoisomers were completed by preparative liquid chromatography and fractional crystallization. Their ^{1}H-NMR spectra are also discussed [10].



Scheme-1.1.5

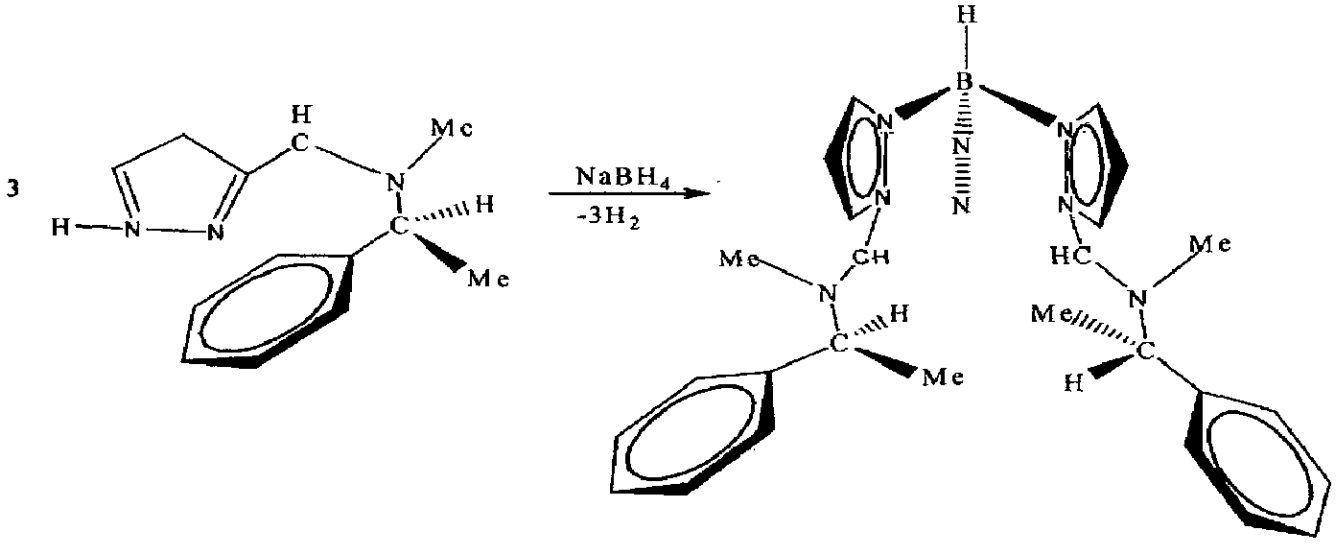
Singh et. al. reported the synthesis of optically active pyrazole hydrotris(4,5,6,7-tetrahydro-7,8,8-trimethyl-2H-4,7-methnoindazole) by refluxing hydroxy-methylenecamphor with hydrazinesulphate at 120 °C for 5hrs. The borate salt $[NaHB(Campz)_3]$ was prepared by heating the above compound with $NaBH_4$ at 200-220 °C as shown in Scheme-1.1.6 [77].





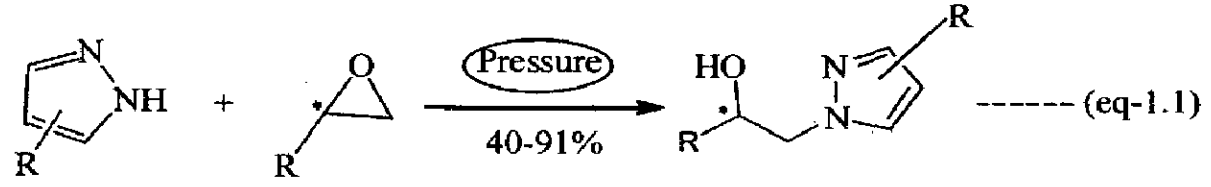
Scheme-1.1.6

For the preparation of $[NaHB(PI)_3]$, they also performed the reaction of (-)-3(5)-methyl-1-phenylethylaminomethylpyrazole with $NaBH_4$ as shown in Scheme-1.1.7 [78].



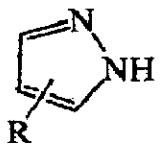
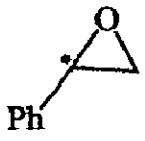
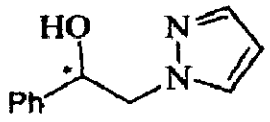
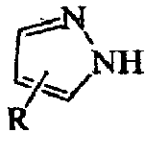
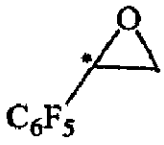
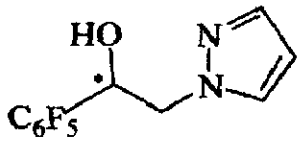
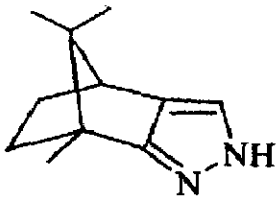
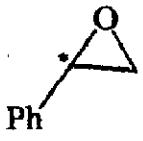
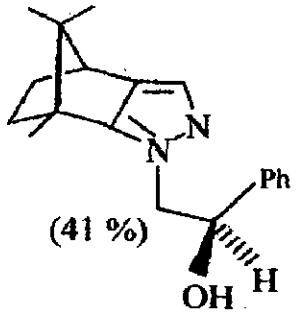
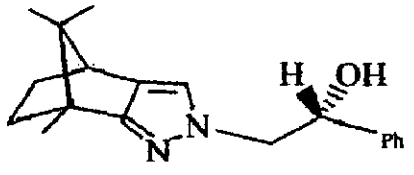
Scheme-1.1.7

Etienne et. al. reported the preparation of a variety of chiral pyrazole ligands by N-alkylation of pyrazoles with optically active epoxides under high-pressure conditions (eq-1.1 and Table-1.1) [79].



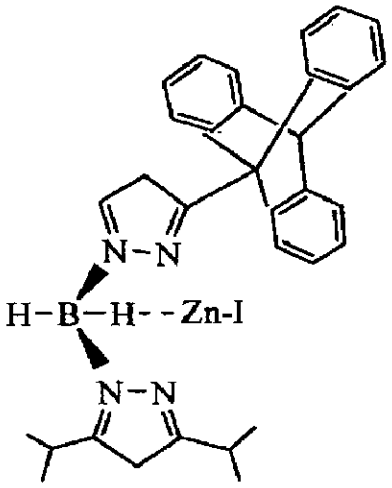
------ (eq-1.1)

Table 1.1

Run	Substrate	Epoxide	Product(s) (yield, %)
1.			 (50 %)
2.			 (76 %)
3.			 (41 %)
			 (50 %)

Ghosh et. al. reported the synthesis of asymmetric ligands, $[H_2B(pz)(pz^{tBu2})]^-$, $[H_2B(pz^*)(pz^{tBu2})]^-$and $[H_2B(pz^{trip})(pz^{tBu2})]^-$ were obtained by reaction of $LiBH_4$ with a 1:1 mixture of two different pyrazoles and their thallium complexes $[H_2B(pz)(pz^{tBu2})]Tl$, containing an agostic B-H-Tl bond. These complexes were characterized together the zinc derivatives $[H_2B(pz)(pz^{tBu2})ZnI(Hpz^{tBu,iPr})]$, $[H_2B(pz^*)(pz^{tBu2})]ZnI$, and

$[H_2B(pz^{trip})(pz^{tBu2})]ZnI$. In this zinc ion was in tetrahedral environment, due to the presence of an agostic B-H-Zn bond [80].

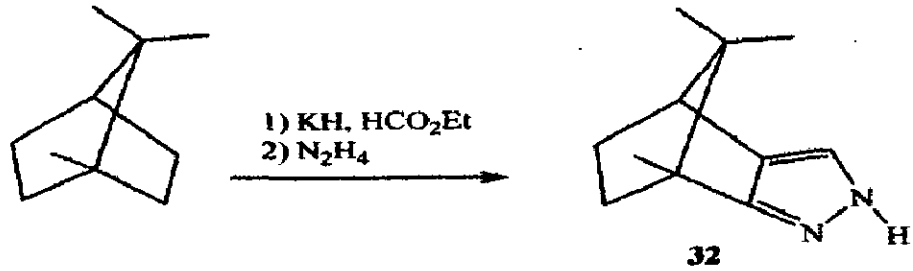


31

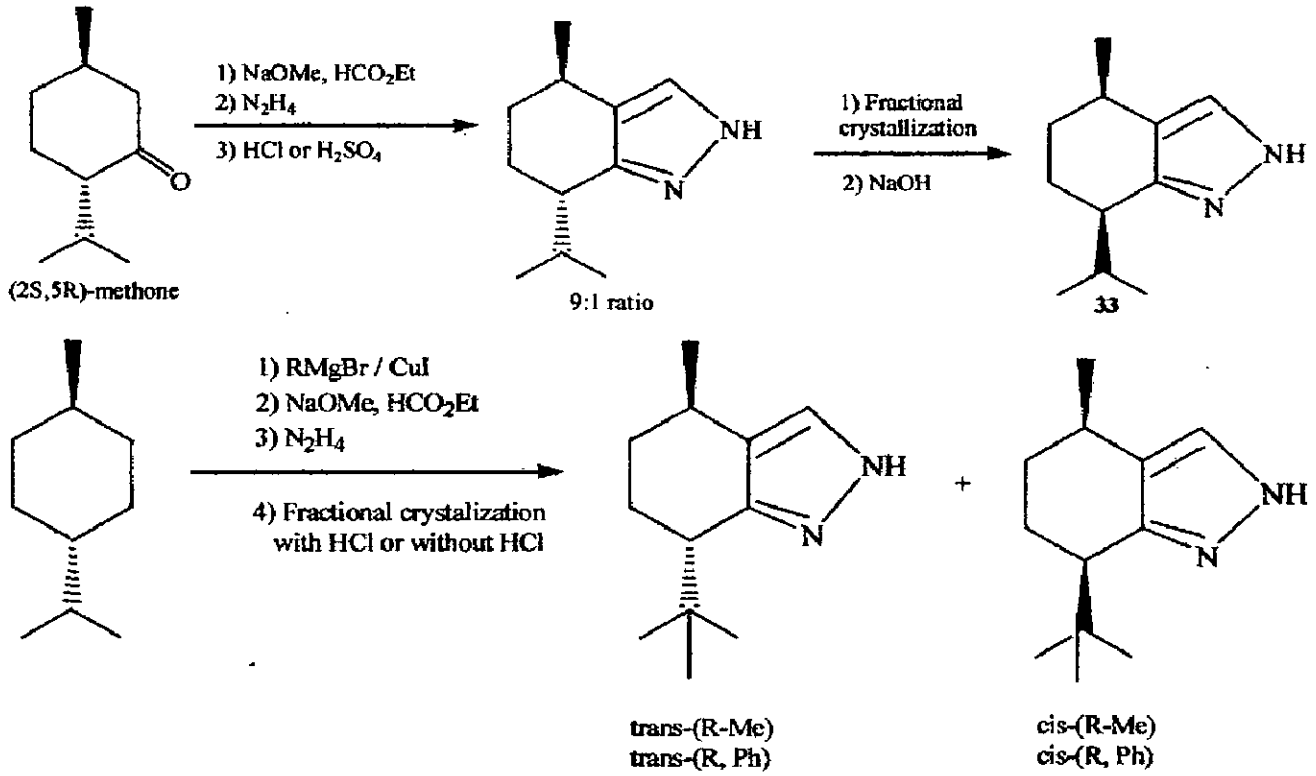
Reger et. al. obtained the new ligands $C_6H_4[CH_2OCH_2C(pz)_3]_2$ (pz = pyrazolyl ring), (ortho), (meta), and (para) that can potentially bond two or more metal centers in a single step from the reaction of the appropriate dibromoxylene, 2 equivalent of tris-2,2,2-(1-pyrazolyl)ethanol and excess NaH. Although the arrangement of the tris(pyrazolyl)methane units in the solid-state structures of ortho and meta are similar, the orientation of these groups with respect to the phenyl ring are different, with ortho showing a twisted structure and with meta showing a stepped structure. The reaction of $[Cd_2(THF)_5][BF_4]_4$ with the appropriate ligand yielded each of the three coordination polymers of the formula $\{C_6H_4[CH_2OCH_2C(pz)_3]_2Cd\}(BF_4)_2\}_n$, (ortho), (meta), and (para). In the solid-state structures of all three each tris(pyrazolyl)methane unit is tridentate, with each ligand bonded to two different cadmium (II) atoms, forming a coordination polymer containing 6-coordinate, pseudooctahedral cadmium (II) centers [81].

N,N'-Bis(2-pyridylmethyl)-3-hydroxyglutaramide {abbreviated as H_3(pmg), optically active N,N'-bis{2-pyridylmethyl and 2-(2-pyridyl)ethyl}-(S)-malamide {H_3(lpm) and H_3(lpe) respectively} and the optically inactive analogues {H_3(ppm) and H_3(pem)} gave dimeric copper (II) complexes $[Cu_2XL].nH_2O$ (L = lpm, lpe, pmm, pem, and pmg; X = an anionic, exo-bridging ligand such as chloride, hydroxide, acetate (OAc), pyrazolate (pz), and nitrite ions). These complexes were characterized by magnetic

susceptibilities, electronic, circular dichroism, and infrared spectra. The amides act as a trivalent anionic ligand coordinating through the pyridine- and deprotonated amido-nitrogen atoms and through the deprotonated, pendant alkoxo-oxygen atom bridging two copper ions. Many of the complexes were magnetically subnormal at room temperature, the magnetic interaction between the two copper ions depending upon both L and the exo-bridges, X. The antiferromagnetic interaction increased in the order of X, Cl < OAc < OH < NO_2 < pz. Temperature dependence of the magnetic susceptibilities of some of the lpm complexes ensured the order. A diamagnetic nickel (II) complex, Ni_2(pz)(lpm).$2H_2O$ and a heterometallic CuNi(pz)(lpm).$2H_2O$ were also obtained. The binuclear structure of Cu_2(pz)(ppm).$3H_2O$ was confirmed by X-ray analysis [82]. Popov et. al. reported that the reactions of chiral diketone with racemic hydrazines as well as reaction of chiral pyrazole with cyclohexene epoxide and trans-stilbene epoxide as the routes to prepare optically active pyrazolylethanols. Diastereomerically pure products have been isolated by crystallization or column chromatography in good yields [11]. An alternative synthesis of optically active pyrazoles involves the usual cyclocondensation between hydrazine and a 1,3-dicarbonyl compound, but with the latter having a stereogenic center α to one carbonyl unit. This center would then reside at the R_3 pyrazolyl ring position (proximate to a bound metal ion) in the final ligand. In this route, the problematic synthesis step is constructing the optically active 1,3-dicarbonyl without epimerizing the α–carbon. In the synthesis of pyrazole from (+)-camphor, loss of α–carbon stereochemistry was circumvented because the critical sterogenic center is quaternary (Scheme-1.1.8) [83, 84].

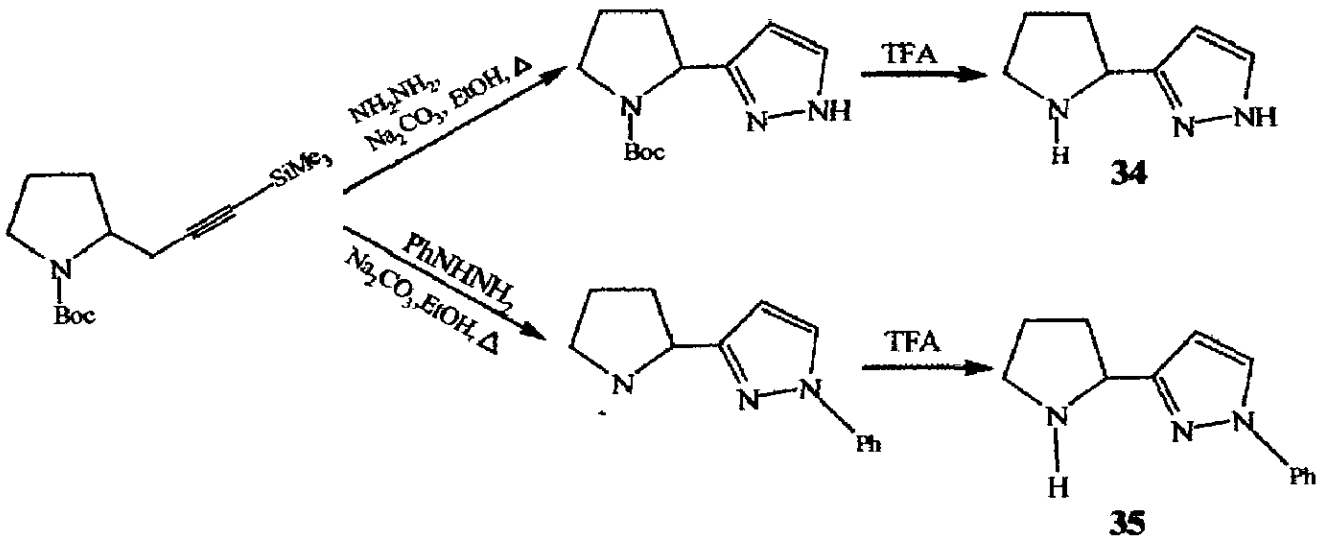


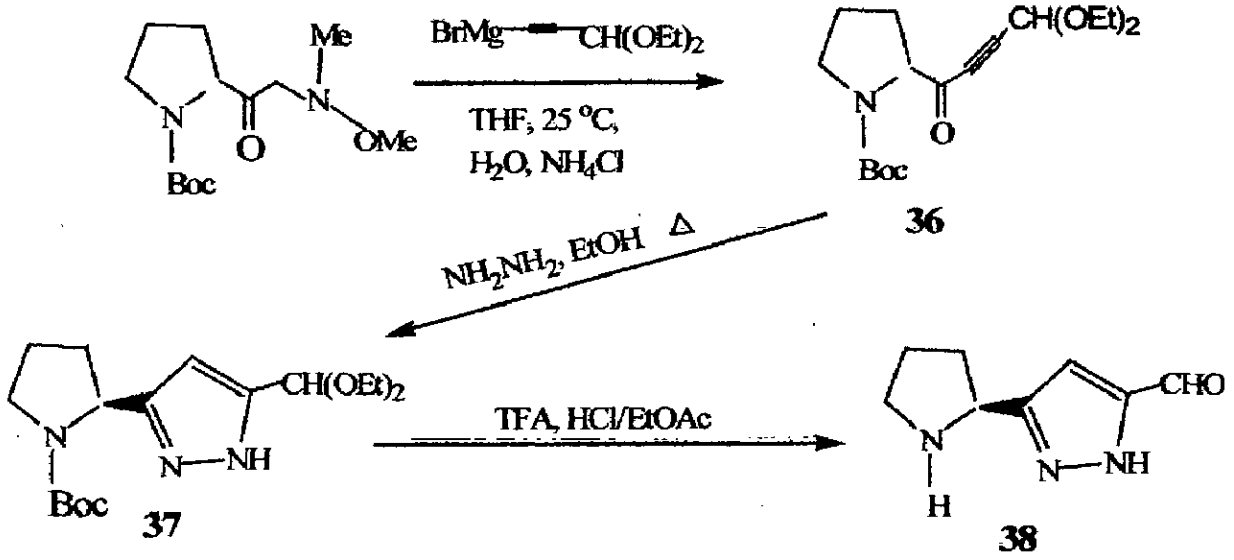
32



Scheme-1.1.8

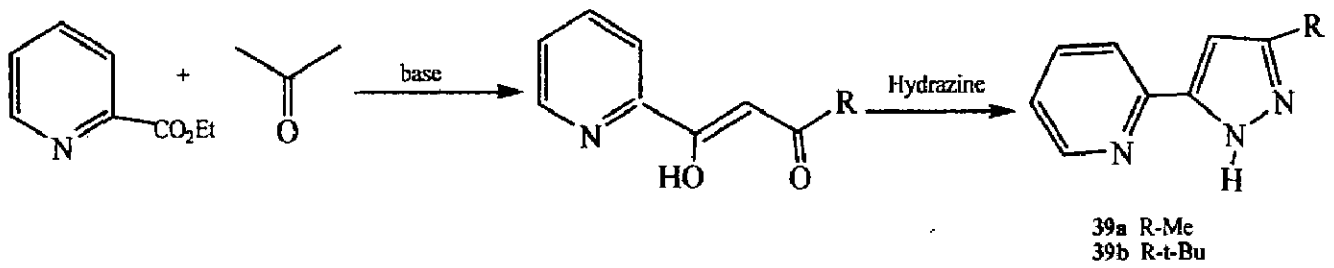
Falorni et. al. suggested that the optically active pyrazoles derived from L-proline (S)-N-tert butoxycarbonylproline is converted to prolinamide reacting with 2 equivalent of N,O-dimethylhydroxylamine after the treatment with ethylformate. Prolinamide then reacted with trimethylsilylethynyl magnesium bromide to give (S)-1-trimethylsilyl-3-(2′-N′-tert-butoxycarbonylpirrolidiny-l)propin-3-one. Starting from this ketone they reported the synthesis of different pyrazoles as in Scheme-1.1.9 [85].





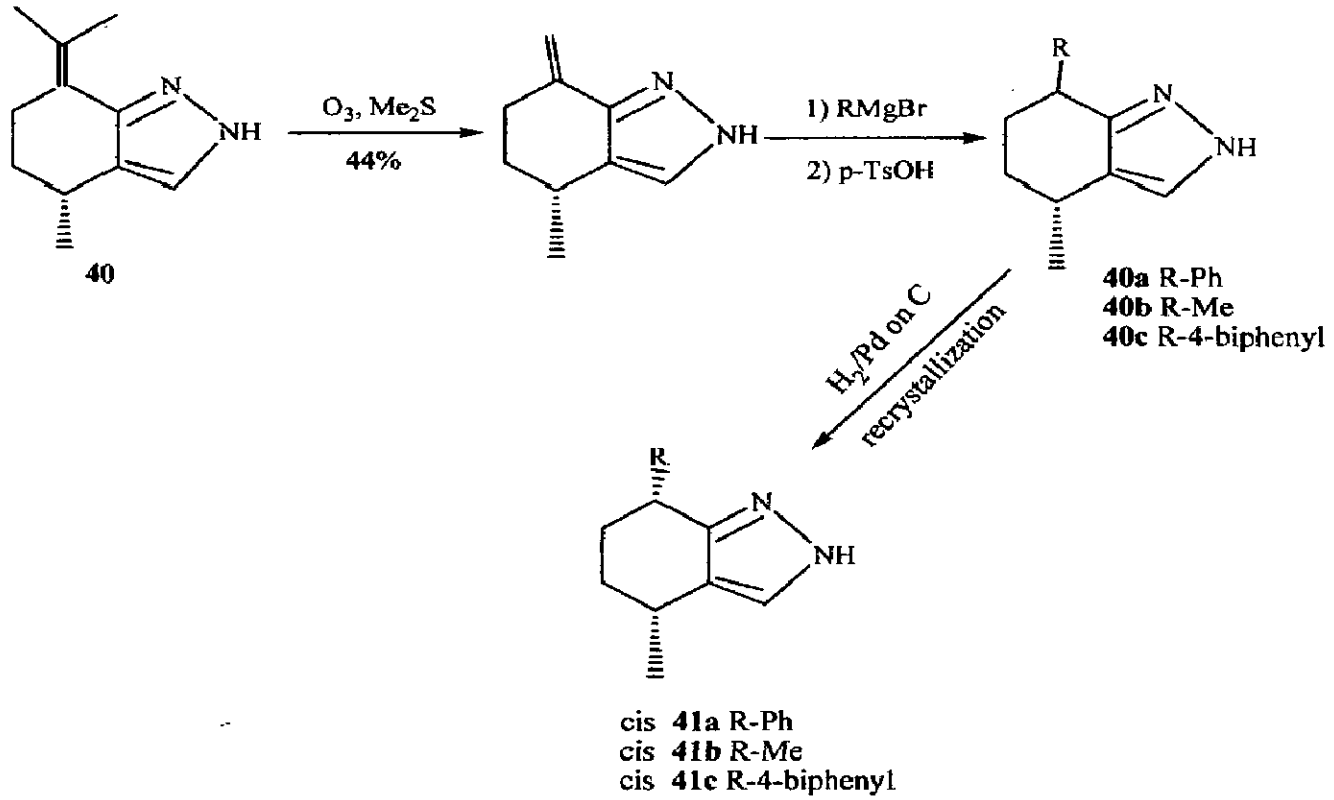
Scheme-1.1.9

Other optically active pyrazole: pyridinylpyrazole (MePPH) and (t-BuPPH) (Scheme-1.1.10) were obtained by claisen condensation of ethylpyridinecarboxylate with methylketone and subsequent formation of the pyrazole ring with hydrazine [86].



Scheme-1.1.10

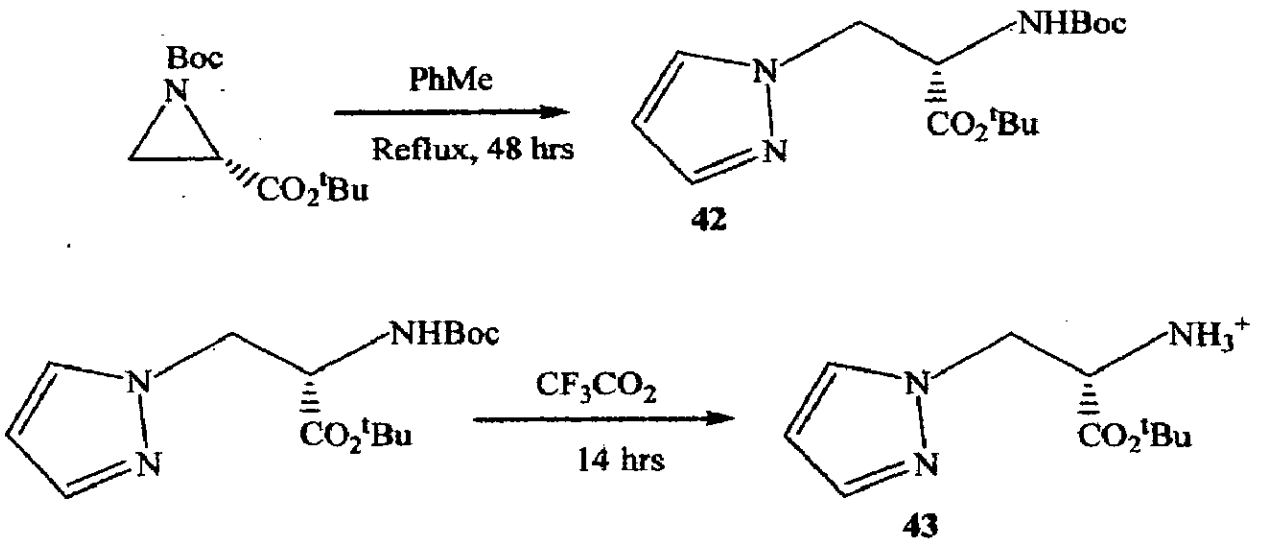
A new family of enantiomerically pure pyrazoles with a variety of substituted on a key stereogenic center was synthesized from (R)-(+)-pulegone by a straightforward, large scale route involving initial construction of the pyrazole ring via formylation/dehydration with hydrazine followed by ozonolysis to yield a readily functionalized ketone **40**. Alkylation of **40** with a variety of grignard reagents, dehydration, hydrogenation, and recrystalization afforded the set of new chiral pyrazoles (Scheme-1.1.11) [87].



Scheme-1.1.11

Farthing et. al. synthesized the naturally occurring amino acids (S)-pyrazolylalanine and (S)-quisqualic acid via the nucleophilic ring-openings of an

optically active aziridine by pyrazole and 1,2,4-oxadiazolidine-3,5-dione (Scheme-1.1.12) [88].



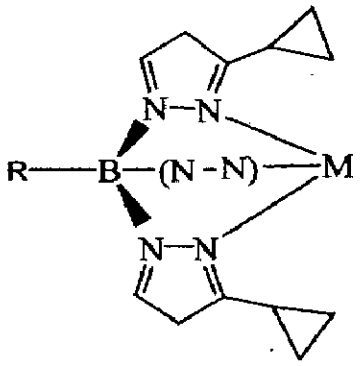
Scheme-1.1.12

The (+)-(S)-isoxazoles (I, n = 0, 1, 2, substituted in the 3, 4, and 5 positions) and the (+)-(S)-pyrazoles (II, n = 0, 1, 2, substituted in the 3 and 4 positions) were prepared by Botteghi et. al. (S)-$EtCHMeCH_2CH_2MgCl$ was treated with $(EtO)_3CH$ and the product treated with sulfanilic acid to give (+)-(S)-$EtCHMeCH_2CH{:}CHOEt$ which was treated with $HC(OEt)_3$ to give (+)-(S)-$[EtCHMeCH_2CH[CH(OEt)_2]_2$ (III). III and $NH_2OH.HCl$ gave I (n = 1, substituted in the 4 position). III and $NH_2NH_2.HCl$ gave II (n = 1, substituted in the 4-position [89].

Takao et. al. have been reported the synthesis of optically active pyrazole (with protecting group and H, alkyl, Ph or alkyl substituted] by treating drop-wise with NH_2NHCH_2Ph in AcOEt under argon atmosphere at 40 °C and stirred 4hrs at 45 °C to give 65% (1′S,2′R)-I (R_1 - Me, R_2 - CH_2Ph), which was hydrogenolyzed over Pd/C in presence of HCl, followed by reflux in HCl, to give 86.4% (4R,5S,6R)-4-amino-5-carboxy-6-methyltetrahydropyran-2-onehydrochloride [90].

Trofimenko et. al. reported that the hydrotris(3-tertbutylpyrazole-1-yl)borate [$HB(3\text{-}^tBupz)_3 = Tp^{tBu}$] coordinative behavior reflects the sever screening of metal in the $Tp^{tBu}M$ fragment, so that with first row transition metal (Mn to Zn) only four coordinate tetrahedral complex of type $Tp^{tBu}MX$ were obtained (X = Cl, NCS, NCO, N_3) which

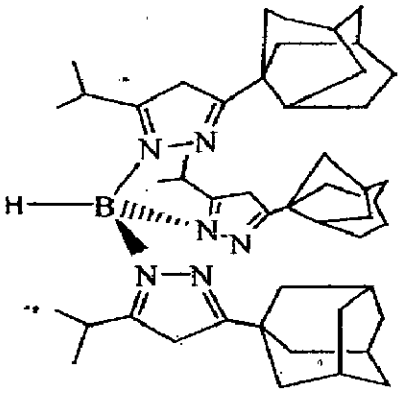
resisted solvation. No $(Tp^{tBu})_2M$ species could obtained, in contrast to Tp and Tp^* [91]. Rheingold et. al. reported that the structure of TptBuCoNCS was established by X-ray crystallography. The new scorpionate ligands hydrotris(3-cyclopropylpyrazol-1-yl)borate (Tp^{cpr}) and tetrakis(3-cyclopropylpyrazol-1-yl)borate (Pz^*Tp^{cpr}) have been synthesized. They readily form octahedral homoleptic and hetroleptic complexes with first row transition metal compounds, but their $[M(Tp^{cpr})(X)]$, **44** complexes are unstable with respect to octahedral ones. The metal complexes $[M(Tp^{cpr})(CO)_2(\eta^3\text{-}CH_2CMeCH_2)]$ were also reported [92].



1.[Tl(Tp^{cpr}) R = H, M = Tl
2. [Tl(Pz^*Tp^{cpr})], R = 3-(cpr)Pz, M = Tl

44

The most hindered hydrotris(pyrazolyl)borate with adamantly substitution at three position of their pyrazole rings. $[HB(3\text{-}Ad\text{-}5\text{-}Pr^{ipz})_3]^-$, (hydrotris(3-adamantyl-5-isopropyl-1-pyrazolyl)borate anion) **45** reported with Cu (II) complexes $[Cu(Cl)\{HB(3\text{-}Ad\text{-}5\text{-}Pr^{iPz})_3\}]$ [93].



$HB(3\text{-}Ad\text{-}5\text{-}Pr^{i}pz)_3]^-$

45

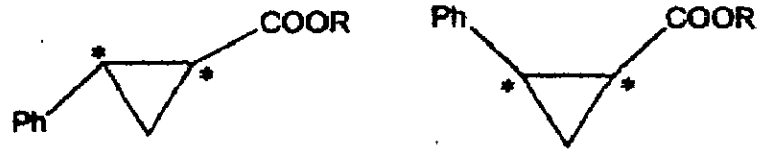
Rheingold et. al. reported two novel ligands, hydrotris(3-mesitylpyrazol-1-yl)borate $[HB(3\text{-}Mspz)_3]^-$ (= Tp^{Ms}) and its isomer hydrobis(3-mesitylpyrazol-1-yl) (5-mesitylpyrazol-1-yl)borate (= Tp^{Ms*}), were synthesized; the later is the first example of an asymmetric tris(pyrazolyl)borate ligand. Such ligands permit reactions at the metal without the interfering oxidative addition of phenyl group. This orthogonality was to be achieved by means of 2,6-substituents, which preclude or inhibit rotation of the phenyl group around the C-C bond to the pyrazole ring. These ligands were used to form the complexes $Tp^{Ms}ZnX$, $Tp^{Ms*}X$ (M = Zn, Cd; X = Cl, I, NCS), $Tp^{Ms}Pd(\eta^3\text{-methallyl})$, $Tp^{Ms*}Pd(\eta^3\text{-methallyl})$, $Tp^{Ms}Rh(COD)$, $Tp^{MS*}Rh(COD)$, $Tp^{Ms}Rh(CO)_2$, $Tp^{Ms*}Rh(CO)_2$, $Tp^{Ms}Mo(CO)_2(\eta^3\text{-methallyl})$, $Tp^{Ms*}Mo(CO)_2(\eta^3\text{-methallyl})$. Above 220 °C some of the Tp^{Ms*} complexes rearranges in to their Tp^{Ms} analogs [16]. Calabrese et. al. reported the new ligand hydrotris[3-(2′-thienyl)pyrazol-1-yl)borate (= L^*) was prepared and shown to have the second-lowest steric hindrance among the known poly(pyrazolyl)borates. It forms octahedral L^*_2M complexes with first row transition metal ions but fails to yield stable L^*MX species, except with Zn (II). It also reacts with $HB(3\text{-}Pr^i\text{-}4\text{-}Br\text{-}pz)_3CoCl$ to form octahedral $HB(3\text{-}Pr^i\text{-}4\text{-}Br\text{-}pz)_3CoL^*$ having C_{3v}-symmetry. In the hierarchy of increasing steric hindrances around the metal in 3-substituted tris(pyrazolyl)borates, the currently known series is $H < CH_3 < C_6H_5 < Pr^i < Bu^t$. In terms of forming octahedral L_2M complexes, ligands with R = H and CH_3 do so readily, those with R = C_6H_5 do so reluctantly, and those with R = Pr^i do not form L_2M complexes. The ligands with R = Pr^i form octahedral complexes only with rearrangement of each L to $HB(3\text{-}Pr^ipz)_2(5\text{-}Pr^ipz)$; they will also form mixed octahedral LML complexes provided L is a relatively unhindered tris(pyrazolyl)borate ligand. Finally, ligand with R = Bu^t do not form octahedral complexes at all with first row transition metals [94].

Eichhorn et. al. isolated the sterically congested complexes $M(tppb)_2$ (M = Fe, Mn; tppb = hydrotris(3-phenylpyrazol-1-yl)borate) in good yield from reaction mixture containing 1 equivalent of $M(CF_3SO_3)_2$ and 2 equivalent of Ktppb [95].

ASYMMETRIC CYCLOPROPANATION

[2.0] ASYMMETRIC CYCLOPROPANATION:

The cyclopropyl group is one of the most important structures with biological activity and surprisingly found in plants and microorganisms as natural compounds [96, 97]. Therefore, studies on the synthesis of the cyclopropyl group and its function attract lots of attention in synthetic organic chemistry [98]. The cyclopropanation catalyzed by transition metals, which is defined as a [2+1] cycloaddition between a carbene type species and an alkene is an important synthetic method to obtained cyclopropane rings [99, 100]. Since the three-member ring exists widely in a variety of systems of chemical and biological interest, cyclopropanation can be used to stimulate various experimental studies with the purpose of understanding the mechanistic aspects and of developing new synthetic methods [101-108]. Many transition metals such as Rh, Ru, Pd, Pt, Zn, Ni, Co, Fe, Mn, and Ti were found to be able to catalyze cyclopropanation reaction [109-111]. Nozaki et. al. reported the first cupper catalyzed asymmetric cyclopropanation of styrene with ethyldiazoacetate in 1966 [64, 112]. They mixed ethyldiazoacetate with styrene in presence of chiral copper complexes as a catalyst to give the products, trans- and cis 2-phenylcyclopropanecarboxylate (Fig-2.1) both in an optically active form. It is demonstrated that the carbene derived from ethyldiazoacetate is not free but combined with the chiral cupper complexes to from a carbene copper complexes, which is responsible for the asymmetric induction. Further more the reaction provided a new method for the preparation of optically active cyclopropane derivatives of practical use, although the enantiomeric excess (ee) attained at that time was less than 10%.



(+)-trans (+)-cis

Fig-2.1

Copper catalysts have been very attractive for the cyclopropanation because they are more advantageous in regards with their catalytic activity compared with other metal catalysts. In the metal catalyzed asymmetric cyclopropanation, the metal-carbene

complexes play an important role because metal-carbenes have better stabilization and enantioselectivity, compaired with free carbene [113]. Cyclopropane derivatives have a great importance as insecticides, the biological activity of which is strongly depends on the stereochemistry [114, 115].

Photodegradable and low mammalian-toxic insecticides, namely pyrethroids are made by stereocontrolled reactions of substituted cyclopropanes [116]. Pyrethroids are the group of man-made pesticides similar to the natural pesticide pyrethrum, which is produced from the extract of dried and powdered flower heads of *Chrysanthemum cinerariaefolium* [117]. The active principles of these (Fig-2.2) are esters of chrysanthemumic acid ($R_1 = CH_3$) or pyrethric acid ($R_1 = CH_3O_2C$), with one of three cyclopentanone alcohols (cinerolone, $R_2 = CH_3$; jasomolone, $R_2 = CH_2CH_3$; or pyrethrolone, $R_2 = CHCH_2$), giving six possible structures. These natural pyrethrins have the disadvantage that they are rapidly decomposed by light.

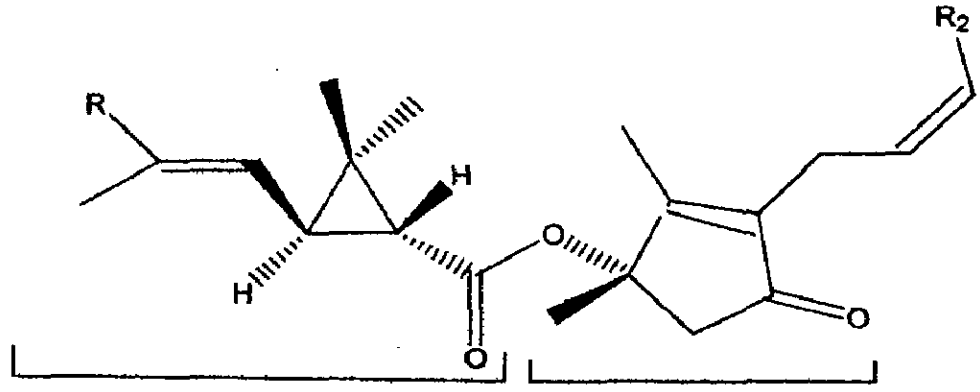
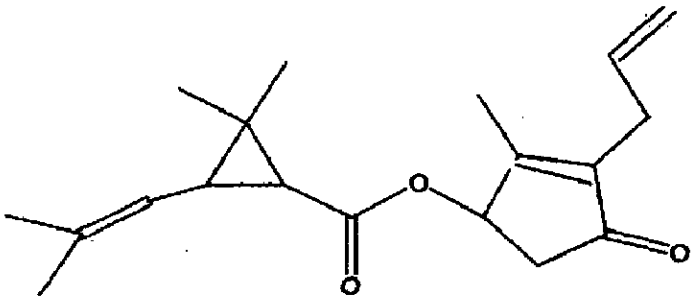


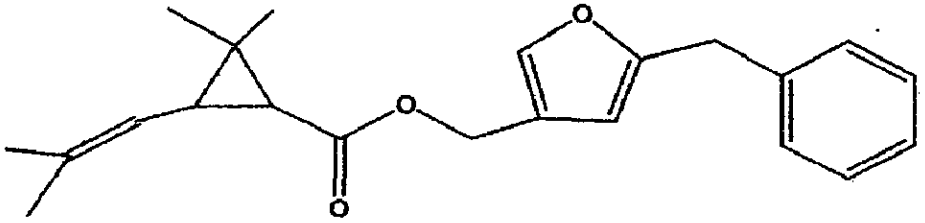
Fig-2.2 Structure and absolute configuration of the six esters known collectively as pyrethrins

Once the basic structure of the pyrethrins had been discovered, synthetic analogues of pyrethroids, were developed. Initially esters were produced using the same cyclopropane carboxylic acids, with variations in the alcohol portion of the compounds. The first commercial synthetic pyrethroid, allethrin (Fig-2.3), was produced in 1949, followed in the 1960s by dimethrin, tetramethrin, resmethrin (Fig-2.3) prothrin, and proparthrin. 3-Phenoxybenzyl esters were also found to be active as pesticides (phenothrin, permethrin)

(Fig-2.4). Synthetic pyrethroids with this basic cyclopropane carboxylic ester structure are known as type-I pyrethroids (Fig-2.5).

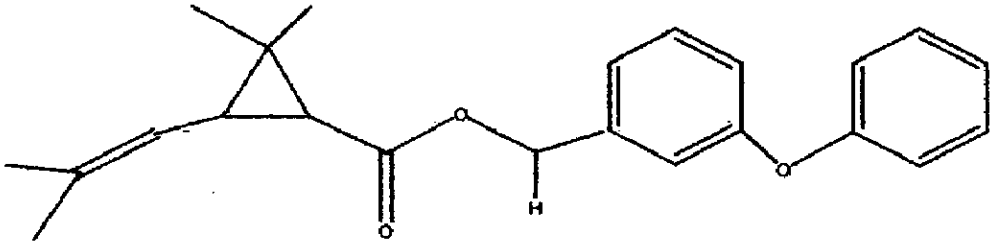


allethrin

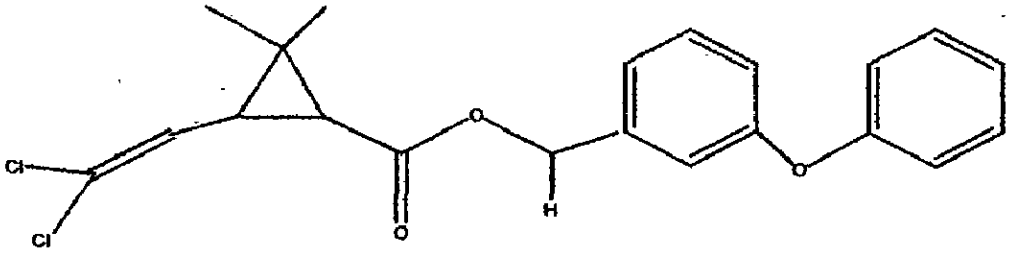


resmethrin

Fig-2.3 Structure of allethrin and resmethrin



phenothrin



permethrin

Fig-2.4 Structure of phenothrin and permethrin

Numerous synthetic methods, including asymmetric Simmons-Smith reaction, metal-catalyzed reaction of diazo compounds with olefins, and asymmetric cyclopropanation, have been used for preparing optically active cyclopropanes, some of which are new industrial processes [118, 119]. Synthetic pyrethroids are more stable in light and have higher insecticidal activity than products made from chrysanthemum flowers. Because of this efficiency, only small amounts of pyrethroids need be applied to control pests (about 100 grams/hectare). Pyrethroids are esters of chrysanthemic acid ($C_{21}H_{28}O_3$ or $C_{22}H_{28}O_5$) or its dihalogenovinyl analogue that are used as insecticides. The high insecticidal activity depends on the overall shape of the molecule [120]. Because of this strong dependence of the activity of pyrethroids on shape, the effect of structure variation are analyzed in relation to the segmented of pyrethrin-I as shown in (Fig-2.5).

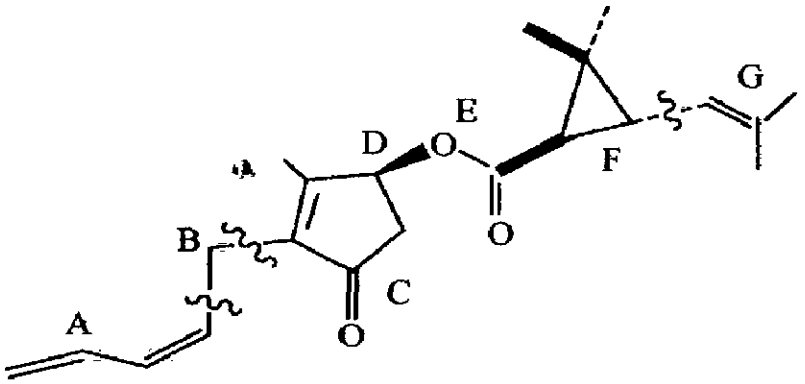


Fig-2.5

Segment-A: A center of unsaturation at this site in the molecule is essential for high activity. Synthetic analogues with vinyl or ethyl group extended the range, but substituents on vinyl or ethyl do not improve activity. The most important unsaturated unit identified is phenyl, present in all recently discovered pyrethroids as a phenoxy or benzene group (oxygen or CH_2 in segment-B), substitution on phenyl [121] and its replacement by a heteroaromatic ring usually diminish activity.

Segment-B: This unit is methylene, in the natural esters and in many active synthetic compounds. Its function is steric rather than chemical generally it produces a favorable change in the properties of great practical importance when segment-A is phenyl [122].

When segment-A and -B are combined as a cyclopentenyl (cyclethrin) or a penta-1,3-dienyl (isopyrethrin-I) [123] side chain, activity is also less.

Segment-C: Recognition of this structural unit has been very important in the discovery of the new synthetic pyrethroids. The methyl group on C-3 of the cyclopentenone ring (a consequence of the biosynthetic route, which may involve acetate) [124] affects activity little, for one methyl compound was more potent than the parent (benzyl substituted in segment-A and -B). Apart from this variation no pyrethroids in segment-D is incorporated in the same ring as segment-C show significant activity. However with segment-D outside the ring, there is much effective variation with planer or near planer aromatic heteroaromatic rings or acyclic units. An increase in activity when an unsaturated substitutent was placed at position-4 [125] confirmed the structural analog; latter some 3-substituted benzene was shown to be even more active. Heteroaromatic replacements, especially furan, close in size and shape to cyclopentenone also has greatest at 3,5-substituted. Literatures also revealed the acyclic compounds are in generally less active insecticides than the cyclic compounds.

Segment-D: All active pyrethroids reported are esters in which the carbon atom joined to the ester oxygen is SP^3-hybridized; it is either incorporated in a cyclopentenone ring (Fig-2.6) or connects; for example, benzene ring attached to ester oxygen if SP^2-hybridised is much less active.

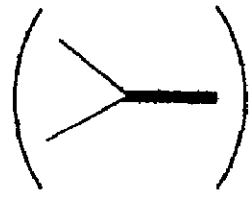


Fig-2.6

Segment-E: Even small alteration in this unit at the center of the molecule would be expected to produce large stereo chemical differences with consequent effects on potency variation in segment-E (oxygen is replaced by nitrogen, carbon, or sulpher) do indeed diminish or remove activity.

Segment-F: Both methyl groups are present in the most active compounds but that cis to segment-E has been shown [126] in some cases to be the more important. All known cyclopropyl esters with no substituents are inactive. The function of the methyl groups in the active molecule is probably related their steric characteristic because dichloro and spiro substituted cyclopropane shows significant insecticidal activity, but ester with larger groups is less active. Inversion of stereochemistry at C-1 (Fig-2.7) eliminates or greatly diminishes insecticidal activity in all dimethyl cyclopropane esters expect when there is no substituted at C-3.

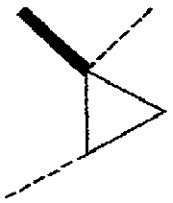


Fig-2.7

Segment-G: Many compounds with diverse substituents in this segment are active. The activity of both cis (R_1, R_2 = methyl) and trans (Fig-2.8) indicates the broad steric latitude within unsaturated groups on C-3 confirm activity. Replacing the methyl group in either isomer with halogens gives a considerable increase in insectidal activity [127] and with appropriates alcohols, and having valuable property of photostability.

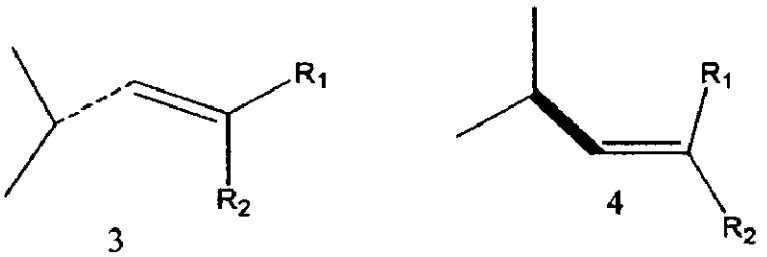
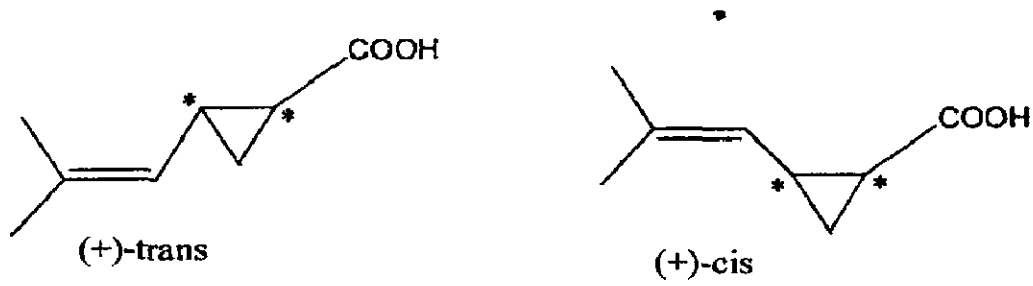


Fig-2.8

The biological activity of pyrethroids is strongly depending on the configuration of the asymmetric carbon atom in cyclopropane ring. Cyclopropane ring is an important component of chrysanthemic acid, 2,2-dimethyl-3-(2-methylpropenyl)-cyclopropane carboxylic acid. Among four optical isomers of chrysanthemic acid, the most effective

isomer (allethrin) (Fig-2.9) is shown to be (+)-trans isomer, followed by (+)-cis isomer. (-)-Trans and (-)-cis isomers are almost ineffective [128].



(+)-trans (+)-cis

Fig-2.9

Asymmetric synthesis of chrysanthemic acid, an important intermediate of pyrethroids, has advantage in producing such compounds and a small quantity of catalyst can provide a large amount of enantiomer product.

EXPERIMENTAL DETAILS

[3.0] EXPERIMENTAL DETAILS:

3.1 Materials/Chemicals:

Chemicals used during the synthesis are summarized in Table-3.1.1.

TABLE-3.1.1: Details of the Reagents and Chemicals

S.No	Chemicals/reagents	Grade	Make
(i)	3-Methylpyrazole	AR	Acros
(ii)	(S)-(+)-Cyclohexylethylamine	AR	Lancaster
(iii)	Lithium aluminum hydride	AR	Acros
(iv)	Potassium permagnate	GR	Lobo Chemie.
(v)	Sodium borohydride	LR	Merck
(vi)	Thionyl chloride	LR	s. d. fine Ltd.
(vii)	Aniline	LR	Rankem
(viii)	Benzaldehyde	LR	Rankem
(ix)	Magnesium sulfate	LR	s. d. fine Ltd.
(x)	Sodium chloride	LR	Merck
(xi)	Sodium carbonate	LR	Merck
(xii)	Potassium hydroxide	LR	Merck
(xiii)	Chloroform	LR	Rankem
(xiv)	Hydrochloric acid	LR	Rankem
(xv)	Ethanol	AR	Yangyuan Cmem. Ltd.
(xvi)	n-Pentane	AR	Sisco Lab. Ltd.
(xv)	Diethylether	LR	Rankem
(xvi)	Tetrahydofuran	LR	Rankem

3.2 Materials:

All the solvents used were regent quality. Removal of all solvents was carried out under reduced pressure and all commercial grade reagents were used without additional purification. Elemental analyses were carried microanalytically at Elemenlar Vario EL III. Melting point was obtained using Perfit melting point apparatus. IR spectra were obtained as KBr pellets with Thermo Nikolet Nexus FT-IR spectrometer, using 16 scans and are reported in cm^{-1}. GC-MS data were obtained on a quadrupole Perkin Elemer Clarus 500 MS coupled to a Perkin Elemer Clarus 500 GC fitted with an Elite-1 column and mass detector was operated at 70 eV. Electronic spectras were recorded in methanol on a Shimadzu 1601 UV-Visible spectrophotometer. ^1H NMR spectra were recorded on Brucker Avance 500 MHz spectrometer (^1H, 500.13 MHz), chemical shift for ^1H NMR spectra are related to internal Me_4Si all residual protium in the deutrated solvent (DMSO, δ-2.5).

3.3 Synthesis of starting material:

3.3.1 Synthesis of 4H,9H-Dipyrazolopyrazin-4,9-dione(diketopiprazine) (3a):

With continuous stirring 3-methylpyrazol (10 g, 0.12 mol) and distilled water (140 mL) was refluxed in a two-necked round bottom flask on an oil bath at 90 °C. The potassium permagnate (36 g, 0.22 mol) was added portion wise an account of high exothermic reaction in cold condition to the above reaction mixture. The reaction mixture was again refluxed at 90 °C for 6 hrs with continuous stirring. It was cooled to an ambient temperature and filtered. The volume was reduced to 5 mL and solution was acidified to pH = 2 by drop wise addition of concentrated HCl. The obtained white solid was filtered, washed with distilled water and dried in vacuum. To this white solid (4.5 g), thionyl chloride (18 g) was added drop wise and stirred at room temperature for ½ hrs. The reaction mixture was then refluxed at 80 °C for 12 hrs. The mixture was distilled under reduced pressure to remove thionyl chloride. Obtained solid was dissolved in diethylether and refluxed for 1 hrs (to remove remaning thionyl chloride) filtered, washed with diethylether and white solid was dried in vacuum. Yield 42% (4.0 g, 21.0 mmol). IR (KBr), cm^{-1}): 1709 ν (C=O), 1432 ν (C=N), 1637 ν (C=C). Anal. calcd for $C_8H_4N_4O_2$: C, 51.0; H, 2.1; N, 29.7 Found: C, 51.1; H, 2.1; N, 28.9.

3.3.2 Synthesis of (+)-Cyclohexylethyl-3(5)-pyrazolecarboxylicamide (3b):

To the hot solution of (+)-cyclohexylethylamine (5.0 g, 39 mmol), diketopiprazine (2.82 g, 15 mmol) was added slowly with vigorous stirring. The reaction mixture was allowed to reflux for 2 hrs at 100 °C. To the resulting colloidal reaction mixture $CHCl_3$ was added and filtered. The filtrate was extracted with 2 N HCl, dried with Na_2CO_3 for over night and then organic layer was evaporated under reduced pressure. Obtained yellow solid was recrystalized with distilled water. Yield 28%, (2.4 g, 10.8 mmol). IR (KBr, cm^{-1}): 2934 ν (C-H), 3469 ν (N-H), 1640 ν (C=O), 1552 ν (C=N), 1453 ν (C=C). Anal. calcd for $C_{12}H_{19}N_3O$: C, 65.1; H, 8.6; N, 19.0 Found: C, 65.3, H, 8.3; N, 18.7.

3.3.3 Synthesis of (+)-3(5){(Cyclohexylethylamino)methyl}pyrazole (3c):

A solution of lithium aluminium hydride (0.67 g, 17.85 mmol) in (40 mL) absolute THF was added slowly to the solution of (+)-cyclohexylethyl-3(5)-pyrazolecarboxylicamide (2.4 g, 10.2 mmol) in (20 mL) in absolute THF with constant stirring in 250 mL round bottom flask and refluxed for 12 hrs. Then distilled water added to hydrolyzed the reaction mixture by which LiOH and $Al(OH)_3$ was precipitated and filtered out. The white precipitated was extracted with boiling THF, filtrates were combined, dried with Na_2CO_3 for over night and then solvent was evaporated under vacuum to get yellow solid. Yield 70%, (1.70 g, 8.21 mmol). IR (KBr, cm^{-1}): 2928 ν (C-H), 3395 ν (N-H), 1618 ν (C=C), 1548 ν (C=N). ^1H NMR (DMSO/TMS), δ (ppm): 7.7 (s, H, pzC(5)-H), 6.6 (s, H, pzC(4)-H), 3.83-3.75 (q, 3H, methine), 1.16 (d, H, CH_3), 1.5 (s, 2H, CH_2), 11.7 (s, H pzN(1)-H). Anal. calcd for $C_{12}H_{21}N_3$: C, 69.5; H, 10.1; N, 20.2 Found: C, 69.3; H, 11.2; N, 20.0.

3.3.4 Synthesis of Sodiumtetrakis((+)-3(5)-cyclohexylethylaminomethylpyrazolyl)borate (3d):

To a round bottom flask (+)-(cyclohexylethylamino)methylpyrazole (1.67 g, 8 mmol) and sodium borohydride (0.076 g, 2.01 mmol) were heated gradually at 210-240 °C with monitoring oh hydrogen evaluation. Heating was continued at that temperature till four equivalent of hydrogen gas (180 mL) was evolved. The mixture was then allowed to cool at room temperature. The solid mass was refluxed with petroleum ether (100 mL) for 2 hrs. Obtained white solid was filtered, washed with hot petroleum ether

and dried under vacuum. Yield 8.79% (0.35 g, 0.42 mmol). IR (KBr, cm^{-1}): 2934, 2912, 2851 ν (C-H), 3459 ν (N-H), 1615, 1550, 1526, 1460 ν {(C=N), (C=C)}. ^1H NMR (DMSO/TMS), δ (ppm): 7.36 (s, 3H, pzC(5)-H), 3.40 (q, 3H, methine), 1.7 (s, 2H, CH_2). Anal. calcd for $C_{48}H_{80}BN_{12}Na$: C; 67.1, H; 9.3; N; 19.5 Found: C; 66.9, H; 9.5, N; 19.2.

3.3.5 Synthesis of N-benzylidene benzenamine (3e):

For the synthesis of N-benzylidene benzenamine a mixture of benzaldehyde (2.65 g, 25 mmol) and aniline (2.32 g, 25 mmol) was taken in a round bottom flask in methanol (25 mL). Then pyridine (3 mL) was added drop wise with constant stirring and refluxed for 2 hrs on a water bath. The residue was cooled by adding water (10 mL) on ice bath and was stirred until the yellow solid precipitated out. This was filtered, washed with water, dried under vacuum and recrystalized with petroleum ether. Yield 82% (3.70 g, 20 mmol). m.p. 55-60 °C. IR (KBr, cm^{-1}): 2882 ν (C-H), 1280 ν (C-N), 1626 ν (C=N), 3061 ν (ar. C-H str), 1491 ν (ar. C=C str), 908 ν (ar. C-H def). UV {(MeOH), nm}: 207, 261, 314. GC-MS (MeOH, m/z): 181 M^+ (80%), 77 (100%), 180 (95%). ^1H NMR (DMSO/TMS), δ (ppm): 8.62 (s, H, benzylideniminC-H), 7.2 (m, 6H, C_6H_5), 7.7(m, 6H, C_6H_5). Anal. calcd for $C_{13}H_{11}N$: C, 86.1; H, 6.0; N, 7.7 Found: C, 85.9; H, 6.3; N, 7.6.

3.3.6 Synthesis of (-)-(N-(Phenylmethylene)benzenamine (3f):

At room temperature a solution of lithium aluminium hydride (0.759 g, 20 mmol) in distilled THF (10 mL) was slowly added to a solution of N-benzylidene benzenamine (3.7 g, 20 mmol) in distilled THF (10 mL). After 3 hrs THF was removed in vacuum and hydrolyzed with 2 N methanolic HCl (30 mL) at 10-15 °C for 3 hrs After removal of methanol under reduced pressure, the residue was dissolved in distilled water (10 mL), basified to pH >13 with 10% KOH solution saturated with sodium chloride and extracted with $CHCl_3$ (3x5 mL). The combined extracts were dried over anhydrous magnesium sulfate and evaporated in vacuum to give yellow solid, which was recrystalized with *n*-pentane. Yield 55% (2.0 g, 11 mmol). m.p. 55-65 °C. IR (KBr, cm^{-1}): 2930 ν (C-H), 1278 ν (C-N), 3414 ν (N-H), 3056 ν (ar. C-H str), 1509 ν (ar. C=C), 852 ν (ar. C-H def). UV (MeOH), nm): 246, 296. GC-MS (MeOH, m/z): 183 M^+ (32%), 91 (100%), 77 (22%). ^1H NMR (DMSO/TMS), δ (ppm): 7.04 (m, 6H, C_6H_5), 4.0 (s, ar. C-NH), 2.78 (s, H, methyl). 2.35 (s, 1H, methyl). Anal. calcd for $C_{13}H_{13}N$: C, 85.2; H, 7.1; N, 7.6 Found: C, 85.0; H, 7.1; N, 7.5.

3.3.7 Synthesis of (-)-(N-(Phenylmethylene)benzene-3(5)-pyrazolecarboxylicamide (3g):

To the hot solution of (-)-N-(phenylmethylene)benzenamine (1.94 g, 10.50 mmol), diketopiprazine (1.15 g, 4.83 mmol) was added slowly under vigorous stirring and reaction mixture was refluxed for 2 hrs at 100 °C. To the resulting colloidal reaction mixture $CHCl_3$ was added and filtered. The filtrate was extracted with 2 N HCl. and dried with Na_2CO_3 for over night then organic layer was evaporated under reduced pressure, yellow solid obtained was recrystalized with methanol. Yield 69% (2.0 g, 7.3 mmol). m.p. 106-110 °C. IR (KBr, cm^{-1}): 2986 ν (C-H), 1309 ν (C-N), 3415 ν (N-H), 1699 ν (C=O), 1506 ν (C=N), 3056 ν (ar. C-H), 1506 ν (ar. C=C str), 755 ν (ar. C-H def). Anal. calcd for $C_{17}H_{15}N_3O$: C, 73.6; H, 5.4; N, 15.1 Found: C, 73.8; H, 5.6; N, 14.9.

3.3.8 Synthesis of (-)-3(5)-N-{(Phenylmethylene)benzenamino)}pyrazole (3h):

A solution of lithium aluminium hydride (0.435 g, 11.47 mmol) in (25 mL) absolute THF was added to (-)-(N-(Phenylmethylene)benzene-3(5)-pyrazolecarboxylicamide (2.004 g, 7.26 mmol) in absolute THF (15 mL) and refluxed with constant stirring for 12 hrs. To this reaction mixture distilled water was added to hydrolyzed reaction mixturev so that LiOH and $Al(OH)_3$ was precipitated and filtered. White precipitated was extracted with boiling THF. Filtrates were combined and dried with Na_2CO_3 for over night, solvent was evaporated under low pressure and yellow solid dried under vacuum. Yield is 80% (1.51 g, 5.70 mmol). m. p. 120 °C IR (KBr, cm^{-1}): 2916 ν (C-H), 1181 ν (C-N), 3424 ν (N-H), 1504 ν (C=N), 3029 ν (ar. C-H), 1812 ν (ar. C=C str), 868 ν (ar. C-H def). ^1H NMR (DMSO/TMS), δ (ppm): 6.7 (d, H, pz C(4)-H), 7.7 (m, 6H, C_6H_5), 13.7 (s, H, pz N(1)-H). Anal. calcd for $C_{17}H_{17}N_3$: C, 77.5; H, 6.4; N, 15.9 Found: C, 76.2; H, 6.3; N, 15.3.

3.3.9 Synthesis of Sodiumtetrakis (-)-3(5)-N-{(Phenylmethylene)benzenamino) }pyrazolyl)borate (3i):

To a round bottom flask (-)-3(5)-N-{(Phenylmethylene)benzenamino)}pyrazole (1.506 g, 5.7 mmol) and sodium borohydride (0.054 g, 1.42 mmol) were heated gradually at 210-230 °C with monitoring oh hydrogen evaluation. Heating was continued

at that temperature till four equivalent of hydrogen gas (120 mL) was evolved. The mixture was then allowed to cool at room temperature. The solid mass was refluxed with petroleum ether (100 mL) for 2 hrs. Obtained white solid was filtered, washed with hot petroleum ether and dried under vacuum. Yield 3.40% (0.21 g, 0.19 mmol). IR (KBr, cm^{-1}): 2963, 2851 ν (C-H), 1261, 1177 ν (C-N), 1506, 1468 ν (C=N), 3060, 3029 ν (ar. C-H), 1812 ν (ar. C=C str.), 800, 867 ν (ar. C-H, def). ^1H NMR (DMSO/TMS), δ (ppm): 6.7 (d, H, pz C(4)-H), 7.7 (m, 6H, C_6H_5). Anal. calcd for $C_{68}H_{64}BN_{12}Na$: C; 75.4, H; 5.9; N; 15.5 Found: C; 74.9, H; 5.2; N; 15.3.

3.4 Cyclopropanation Procedure:

To styrene (4.0 mmol) and the catalyst (0.04 mmol of metal salt and 0.04 mmol of ligand (3d)/(3i), ethyldiazoacetate (5.0 mmol) was added drop wise with a syringe pump over a period of 3 hrs in a N_2 atmosphere. The reaction was carried out at 50 °C temperature with stirring. After the evolution of N_2 has ceased, the product ethyl cis/trans-2-phenylcyclopropanecarboxylate was obtained by distillation of the reaction mixture under vacuum at 60 °C. The chemical yield was determined by gas chromatography. The amounts of ethyl cis/trans-2-phenylcyclopropanecarboxylate, present in the reaction mixture, are measured using the internal standard biphenyl and calibrating according to equation (i),

$$G_i = \frac{KF_i . G_{st} . Fi}{F_{st}} \quad \text{.....(i)}$$

G_i = amount of ethyl cis/trans-2-phenylcyclopropanecarboxylate (mg)

KFi = correlation factor of ethyl cis/trans-2-phenylcyclopropanecarboxylate, determined by measuring standarad solution of known concentration

G_{st} = weighed amount of standard (mg)

F_i = integrated area of ethyl cis/trans-2-phenylcyclopropanecarboxylate

F_{st} = integrated area of standard

3.5 Determination of the enantiomeric excess (ee):

The enantiomeric excess of ethyl cis/trans-2-phenylcyclopropanecarboxylate was measured after transesterification with (-)-2-octanol. Cis/trans-2-phenylcyclopropane

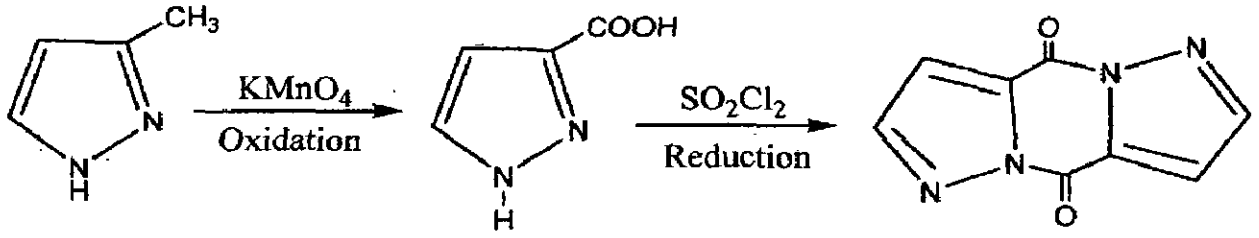
carboxylate (30 mg) was suspended in 2.0 mL of 1.2 N KOH solution (H_2O/EtOH 1:1) and refluxed for 30 min. in 2.5 mL of distilled water and 1.0 mL of 10% HCl were added. The solution was extracted with $CHCl_3$ (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4. After removal of the solvent the residue was treated with CH_2N_2. To complete the esterfication, the reaction mixture was refluxed for ½ hrs. After cooling to room temperature the solution was used for a GC analysis with an achiral 50 m glass capillary (HP Ultra, OV 1701). The derivative enantiomers of the cis and trans isomers gave baseline separation. The retation times: cis (1R, 2S), 54.5 min.; cis (1S, 2R), 56.1 min; trans (1S, 2S), 65.9 min; trans (1R, 2R), 67.1 min. Column temperature 110 °C; p(H_2) 2.1 bar; injector temperature 130 °C.

Equation (ii) is used to calculate the enantiomeric excess of the cis- and trans compounds (A_R, A_S = integrated area).

$$ee = \frac{|A_R - A_S|}{A_R + A_S} \cdot 100\ \% \quad \text{.....(ii)}$$

RESULTS AND DISCUSSION

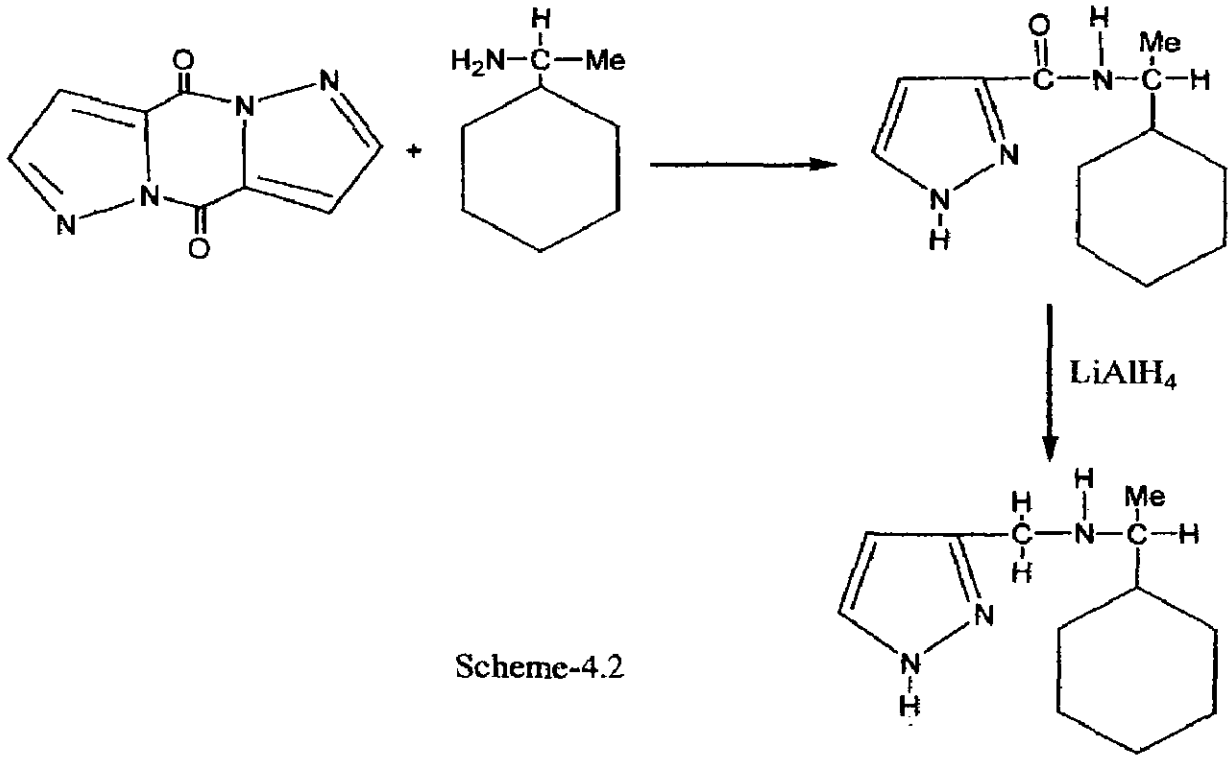
Diketopiprazine was synthesized from 3-methylpyrazole by oxidation with $KMnO_4$ and the reduction with thionyl chloride (Scheme-4.1).



Scheme-4.1

Its IR spectrum shows ν (C=O) band at 1709 cm^{-1}, ν (C=N) band at 1432 cm^{-1} and ν (C=C) band at 1637 cm^{-1}. The calculated data of CHN for $C_8H_4N_4O_2$ is C, 51.0; H, 2.1; N, 29.7 and found: C, 51.1; H, 2.1; N, 28.9.

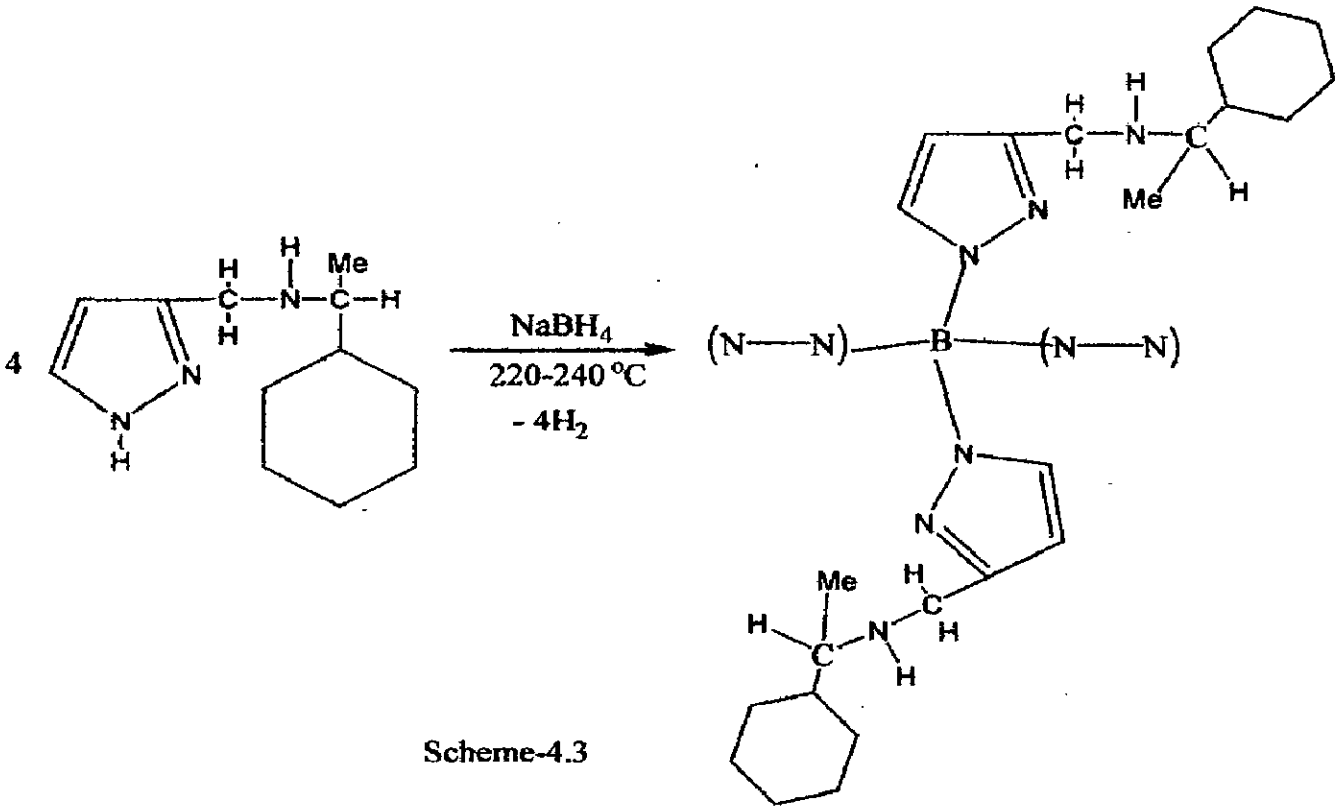
From diketopiprazine, (+)-3(5){(cyclohexylethylamino)methyl}pyrazole was prepared by the reaction of (+)-cyclohexylethylamine with diketopiprazine (Scheme-4.2) which on reduction with $LiAlH_4$ gives the pyrazole in good yield (70%).



Scheme-4.2

Its IR spectrum shows ν (N-H) band at 3395 cm^{-1}, ν (C-H) band at 2928 cm^{-1}, ν (C=C) band at 1618 cm^{-1}, and ν (C=N) band at 1548 cm^{-1}. The calculated data for $C_{12}H_{21}N_3$: C, 69.5; H, 10.1; N, 20.2 Found: C, 69.3; H, 11.2; N, 20.0.

^{1}H-NMR spectrum of this compound shows a singlet at δ (ppm) = 7.7 (s, H, pz C(5)-4), 6.6 (s, H, pzC(4)-H) and 11.7 (s, H, pz(N)(1)-H) which shows that it has one proton attached to N of pyrazole ring and two proton attached to carbon of pyrazole ring at position 4 and 5. Borate salt of this pyrazole was prepared by heating a mixture of $NaBH_4$ with 4 equivalent of (+)-3(5){(cyclohexylethylamino)methyl}pyrazole at 220-240 °C untill four equivalent hydrogen has been evolved (Scheme-4.3). Its calculated data of CHN for $C_{48}H_{80}BN_{12}Na$: C; 67.1, H; 9.3, N; 19.5 Found: C; 66.9, H; 9.5, N; 19.2

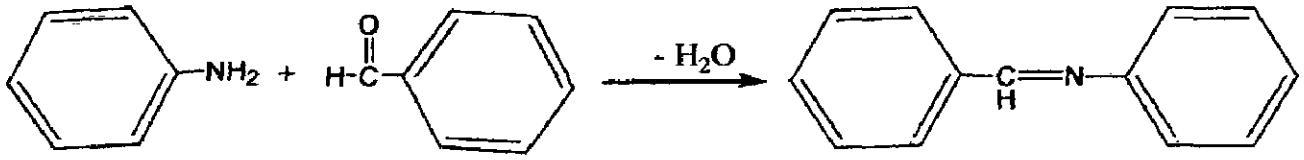


Scheme-4.3

IR spectrum of sodiumtetrakis((+)-3(5)-cyclohexylethylaminomethylpyrazolyl)borate shows ν (C-H) band at 2934, and 2851 cm^{-1}, ν (N-H) band at 3450 cm^{-1}, ν {(C=N), (C=C)}bands at 1526 and 1615 cm^{-1} respectively. ^{1}H NMR of its shows δ (ppm) at 7.36 (s, 3H, pzC(5)-H), 3.40 (q, 3H, methine), 1.7 (s, 2H, CH_2). Thus from NMR spectrum it is confirmed that the proton which appear in (+)-3(5){(cyclohexylethylamino)methyl} pyrazole at δ = 11.7 ppm is not appear in sodiumtetrakis((+)-3(5)-cyclohexylethyl aminomethylpyrazolyl)borate and also in IR no B-H band appear which confirms all

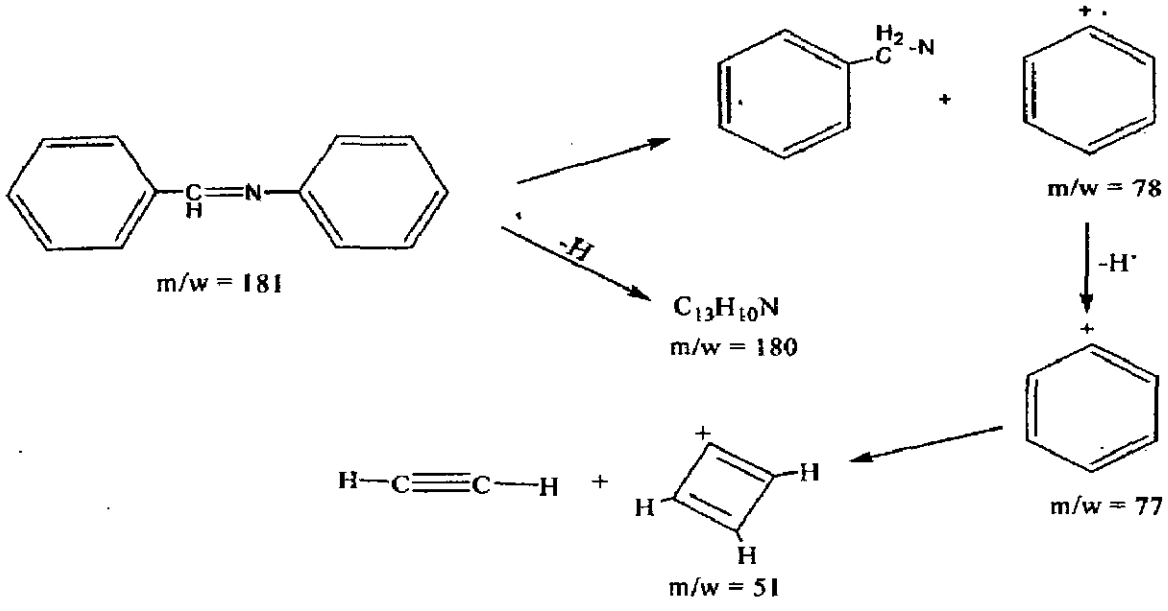
hydrogen from $NaBH_4$ was transfered by four molecule of (+)-3(5) {(cyclohexylethylamino)methyl}pyrazole.

Another amine was prepared by condensation of benzaldehyde and aniline (Scheme-4.4),



Scheme-4.4

during the condensation process N-benzylidene benzenamine was formed. N-benzylidene benzenamine have 55% yields and its melting point was 55-65 °C. In IR spectrum it shows ν (C-H) band at 2930 cm^{-1}, ν (N-H) band at 3414 cm^{-1} also show aromatic ν (C-H) and ν (C=C) str. at 3056 cm^{-1} and 1509 cm^{-1} respectively. UV of this compound was recorded in MeOH, shows three pick at 207.50 nm, 261.50 nm, and 314.50 nm. Its GC-MS in MeOH shows molecular mass (M^+) at 181 of $C_{13}H_{11}N$ other fragments appear at m/w = 180 ($C_{13}H_{10}N$), 78 (C_6H_6), 77 (C_6H_5), and 51 (C_4H_3). The possible fragmentation pattern of this compound is shown in Scheme-4.5. Its ^1H NMR spectra shows a singlet at δ (ppm) = 8.62 due to benzylidenimin C-H and at 7.2 (ppm) a multiplet which is due to benzene ring. Its calculated data for $C_{13}H_{11}N$: C, 86.1; H, 6.0; N, 7.7 Found: C, 85.9; H, 6.3; N, 7.6.

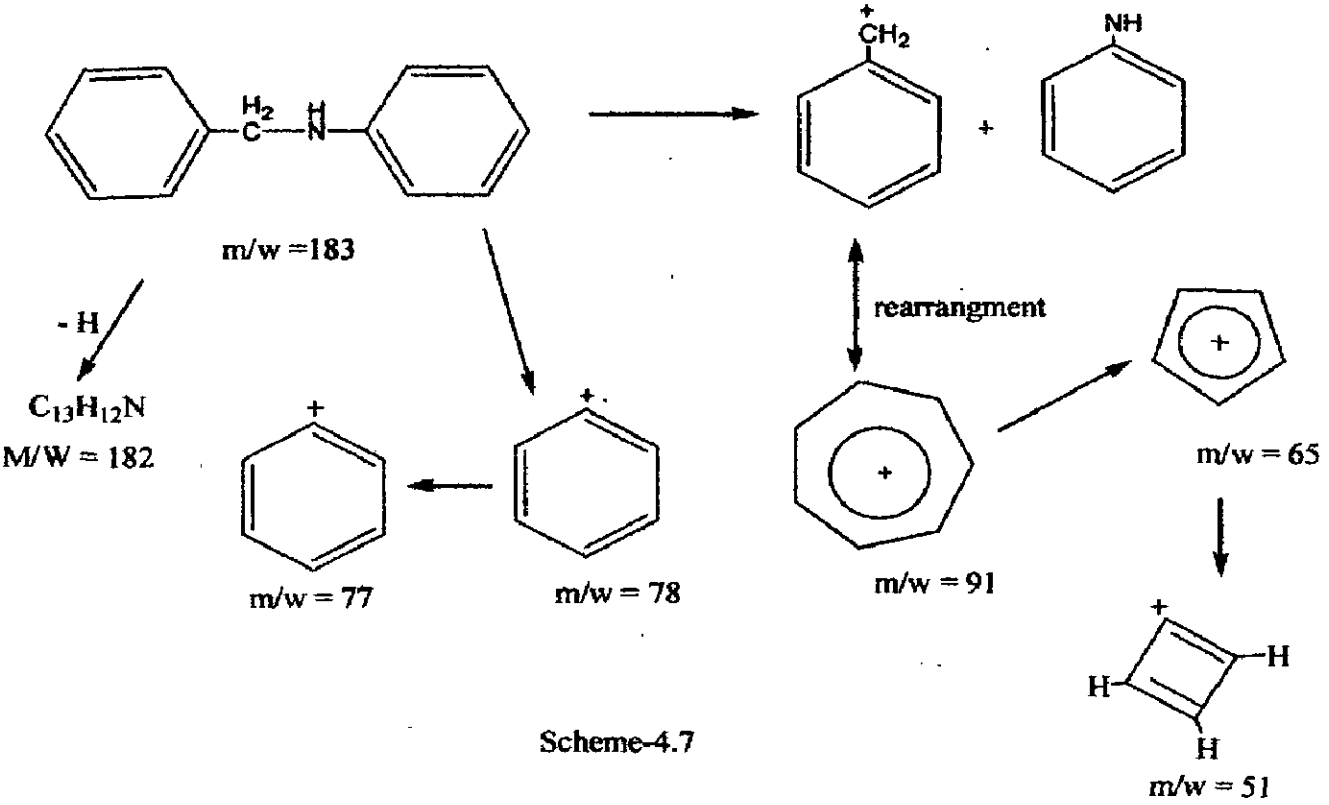


Scheme-4.5

From this oxime (-)-(N-(Phenylmethylene)benzenamine was prepared by reduction with $LiAlH_4$ (Scheme-4.6) in good yield 60%, and melting points ranges between 55-65 °C .

Scheme-4.6

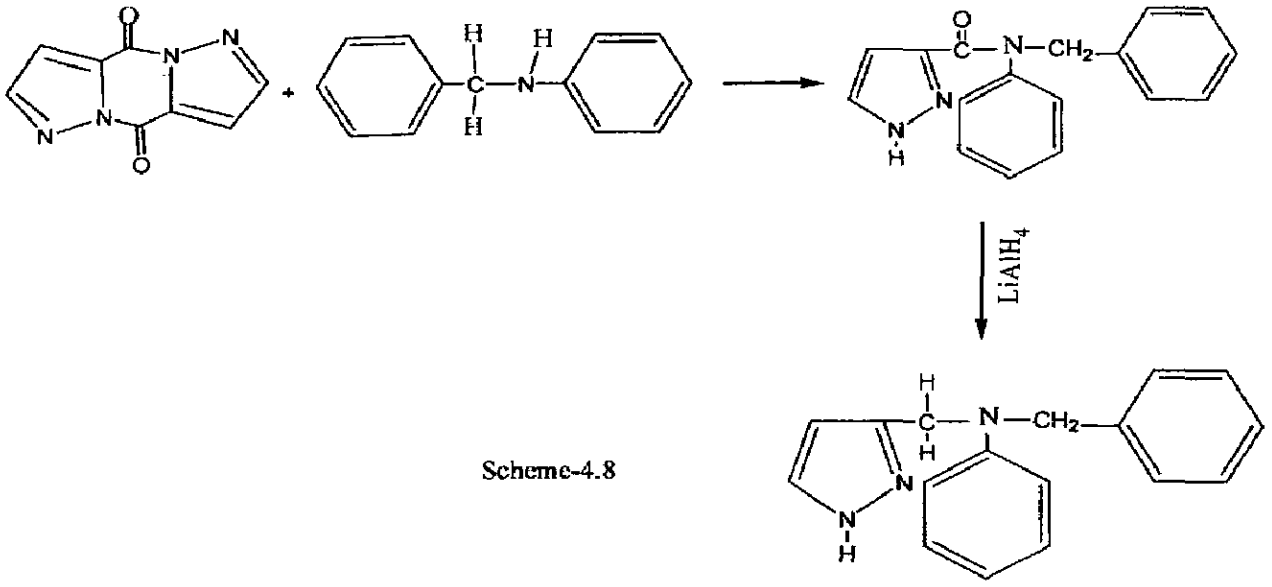
Its IR spectra show ν (C-H) band at 2930 cm^{-1}, ν (N-H) at 3414 $cm^{-1}$and aromatic ν (C-H) and ν (C=C) str. at 3056 cm^{-1} and 1509 cm^{-1} respectively. UV of this compound shows a shift to 246.50 nm and 296.50 nm due to double bond shift. GC-MS showed the molecular ion peak at m/w = 183 ($C_{13}H_{13}N$) M^+, 182 ($C_{13}H_{12}N$), 77 (C_6H_5), 91 (C_7H_7), 65 (C_5H_5), 51 (C_4H_3), fragmentation pattern is shown in Scheme-4.7.



Scheme-4.7

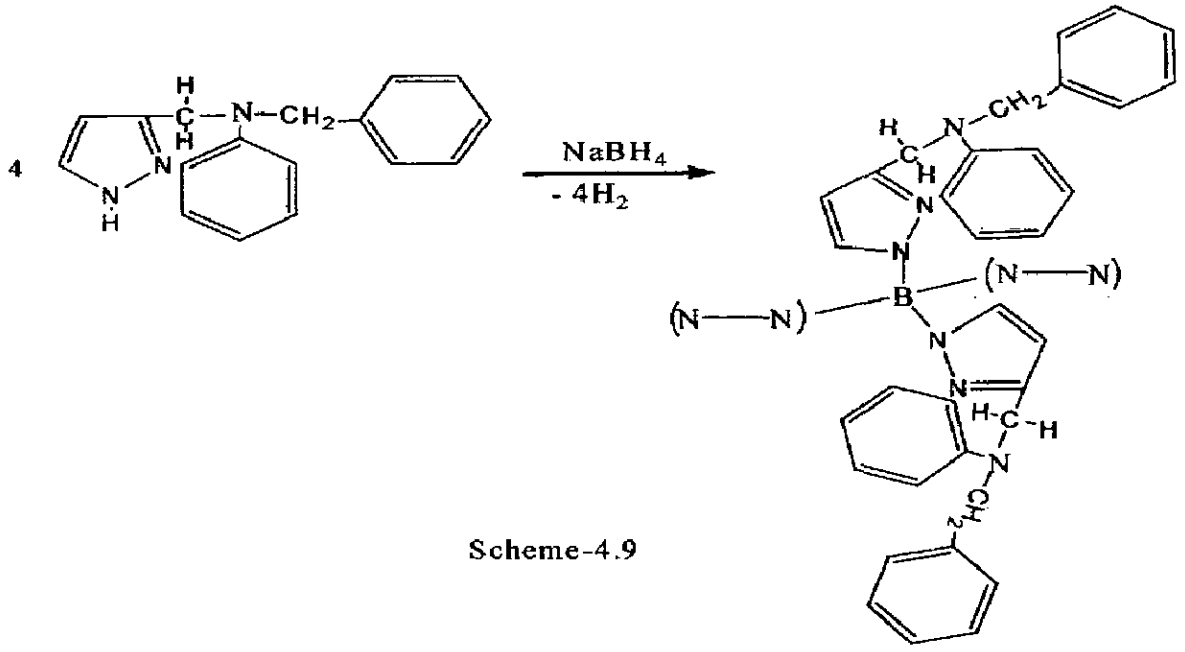
Its ^1H NMR show a multiplet at δ = 7.04 ppm due to six proton of benzene, at δ= 4.0 a singlet due to ar. (C-NH) proton. This amine when treated with diketopiprazine gives (-)-(N-(Phenylmethylene)benzene-3(5)-pyrazolecarboxylicamide which on reduction with

$LiAlH_4$ give (-)-3(5)-N-{(Phenylmethylene)benzenamino)}pyrazole in good yield 80%. As shown in Scheme-4.8.



Scheme-4.8

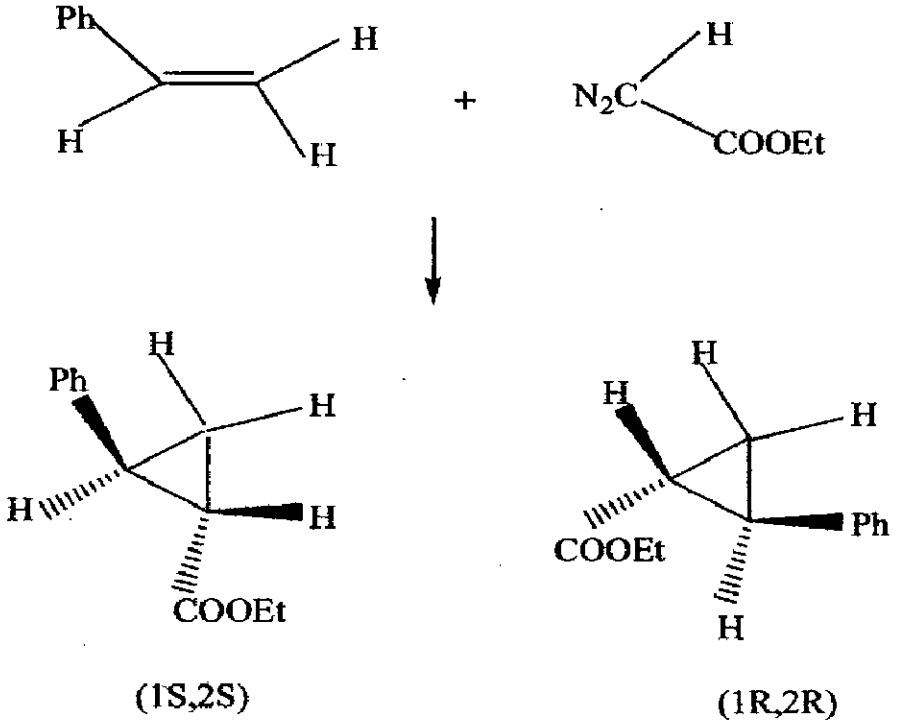
Its IR spectra shows (C-H) band at 2916 cm^{-1}, (C=N) band at 1504 cm^{-1} (N-H) band at 3424 cm^{-1}, aromatic (C=C) and (C-H) str. at 3029 cm^{-1} and 1812 cm^{-1} repectively. ^1H NMR shows δ at 6.7 (ppm) (d, H, pzC(4)-H) and 7.7 (m, 6H, C_6H_5) also at δ (ppm) = 13.7 (s, H, pzN(1)-H) this δ = 13.7 (ppm) is due to pyrazolic proton which is attached to nitrogen of pyrazole. From this pyrazole tetrakis salt prepared in the same way by heating it with $NaBH_4$ (Scheme-4.9) and a very low yield was obtained because of steric hindrances around the boron atom.



Scheme-4.9

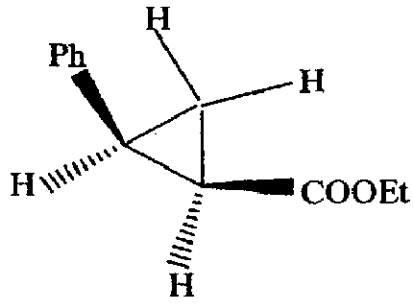
This compound was characterized by IR and ^{1}H NMR. Its IR gives ν (C-H) band at 2963 cm^{-1} and 2851 cm^{-1}, ν (C-N) at 1261 cm^{-1}, ν (C=N) at 1506 cm^{-1}, aromatic ν (C-H) and ν (C=C) str at 3060 cm^{-1} and 1812 cm^{-1} respectively. No B-H band appear at 2400-2500 cm^{-1} appear which showed all hydrogen from $NaBH_4$ was removed. Its ^{1}H NMR spectra showed δ at 7.7 (m, 6H, C_6H_5) and δ (ppm) at 6.6 doublet due to pyrazolic carbon proton at 3 and 4 position no frequency at 13.7 ppm is appear which confirms that pyrazolic proton was removed.

In continuation of our efforts to develop optically active ligands for enantioselective catalysis, we have examined the use of optically active (pyrazolyl)borates (3d) and (3i) in cyclopropanation of styrene and ehtyldiazoacetate by using different salts of copper *in situ* (Scheme-4.10). The cyclopropanation of styrene and ethyldiazoacetate was performed by the reported method with slight modification as discussed in experimental section. The chemical yields; the cis/trans ratio and the enantiomeric excesses were determined as described previously.

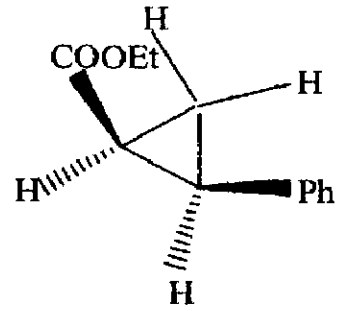


(1S,2S) (1R,2R)

Trans



(1R,2S)



(1S,2R)

Cis

Scheme-4.10

As shown in Table-4.1 and Table-4.2, the product is a mixture of cis/trans isomers, with cis isomer the main component. The chemical yields are in range 12-40%. The enantiomeric excess is 30-65% for the cis isomer of compound and 32-46% for the trans isomer of compound. The maximum enantiomeric excess of 56% and 65 % for the cis isomer was obtained with both ligands using $Cu(OAc)_2$ salt whereas the maximum enantiomeric excess of 46% for the trans isomer was obtained with ligand (3d) and $Cu(F_3SO_3)$ salt as shown in Table 4.1.

Table-4.1: Enantioselective cyclopropanation with ligand (3d) and different salts of copper.

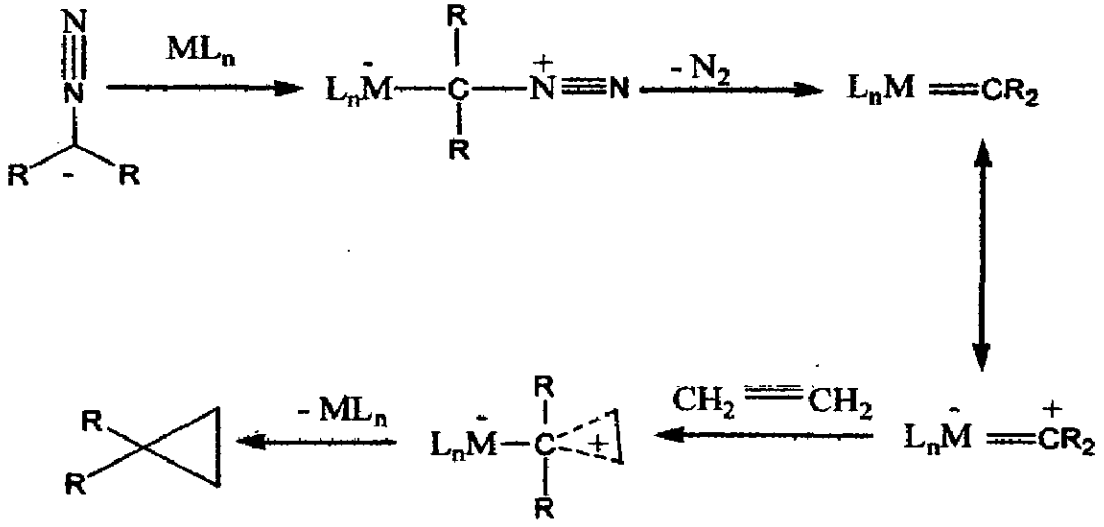
Run	In situ catalysts	Yield (%)	Cis/trans	% ee(cis)	% ee(trans)
1	$Cu(OAc)_2$/IB	40	73/23	56 (1R, 2S)	40 (1R, 2R)
2	CuI/IB	38	58/42	45 (1R, 2S)	35 (1R, 2R)
3	$Cu(F_3SO_3)$/IB	26	71/29	50 (1R, 2S)	46 (1R, 2R)

Table-4.2: Enantioselective cyclopropanation with ligand (3i) and different salts of copper.

Run	In situ catalysts	Yield (%)	Cis/trans	% ee(cis)	% ee(trans)
1	$Cu(OAc)_2$/IIB	15	70/30	65 (1R, 2S)	38 (1R, 2R)
2	CuI/IIB	12	60/40	38 (1R, 2S)	46 (1R, 2R)
3	$Cu(F_3SO_3)$/IIB	18	52/48	48 (1R, 2S)	32 (1R, 2R)

Although the observed ee for the cis product in present work is 56 & 65% less than the literature value, is promising indication of useful applications of compounds (3d) and (3i) respectively.

The exact mechanism of cyclopropanation in present case is not known. Based on the mechanism reported for asymmetric cyclopropanation in literatures, it may be proposed that the metal (pyrazolyl)borate complex reacts with diazoacetate compound and form the metal stabilized carbine with the extrusion of nitrogen (Scheme-4.11).



Scheme-4.11

The metal stabilized carbene then reacts with styrene and generates the catalytically active species in the reaction. As shown here copper appears one of the most efficient catalyst *in situ* catalysis. So the electrophillic metal ion is capable of forming multiple coordination, which makes the cyclopropanation process extremely facile.

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REFERENCES

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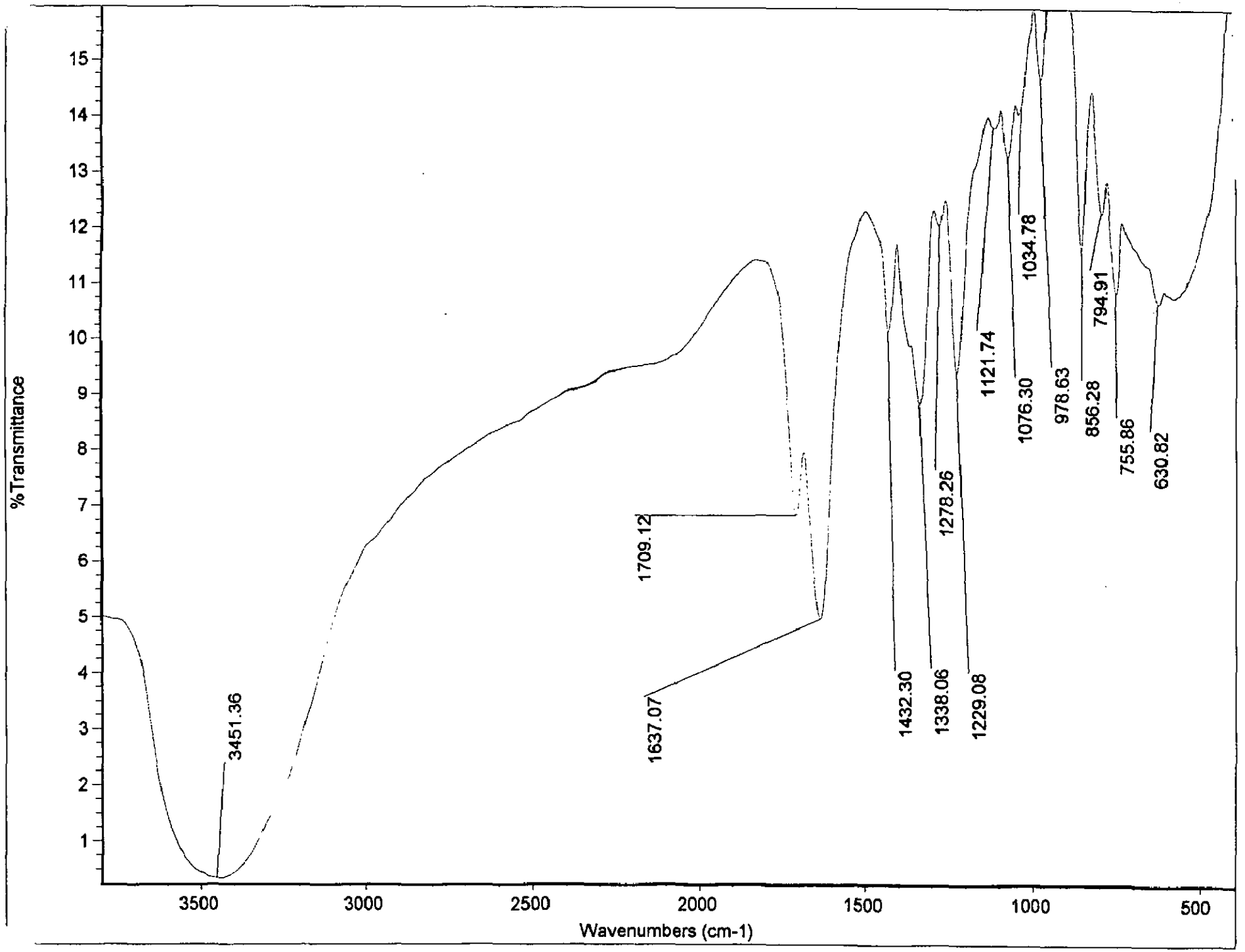
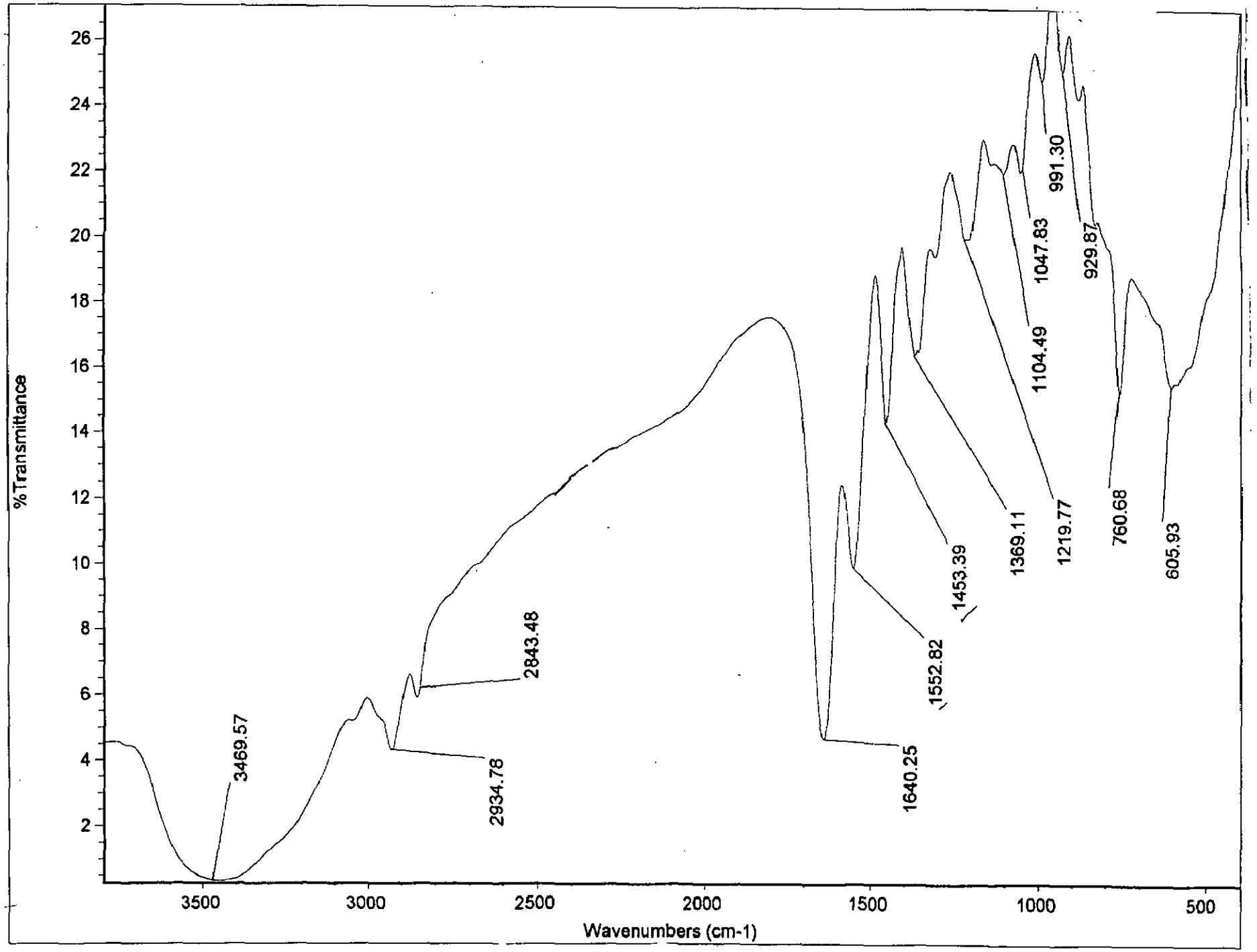
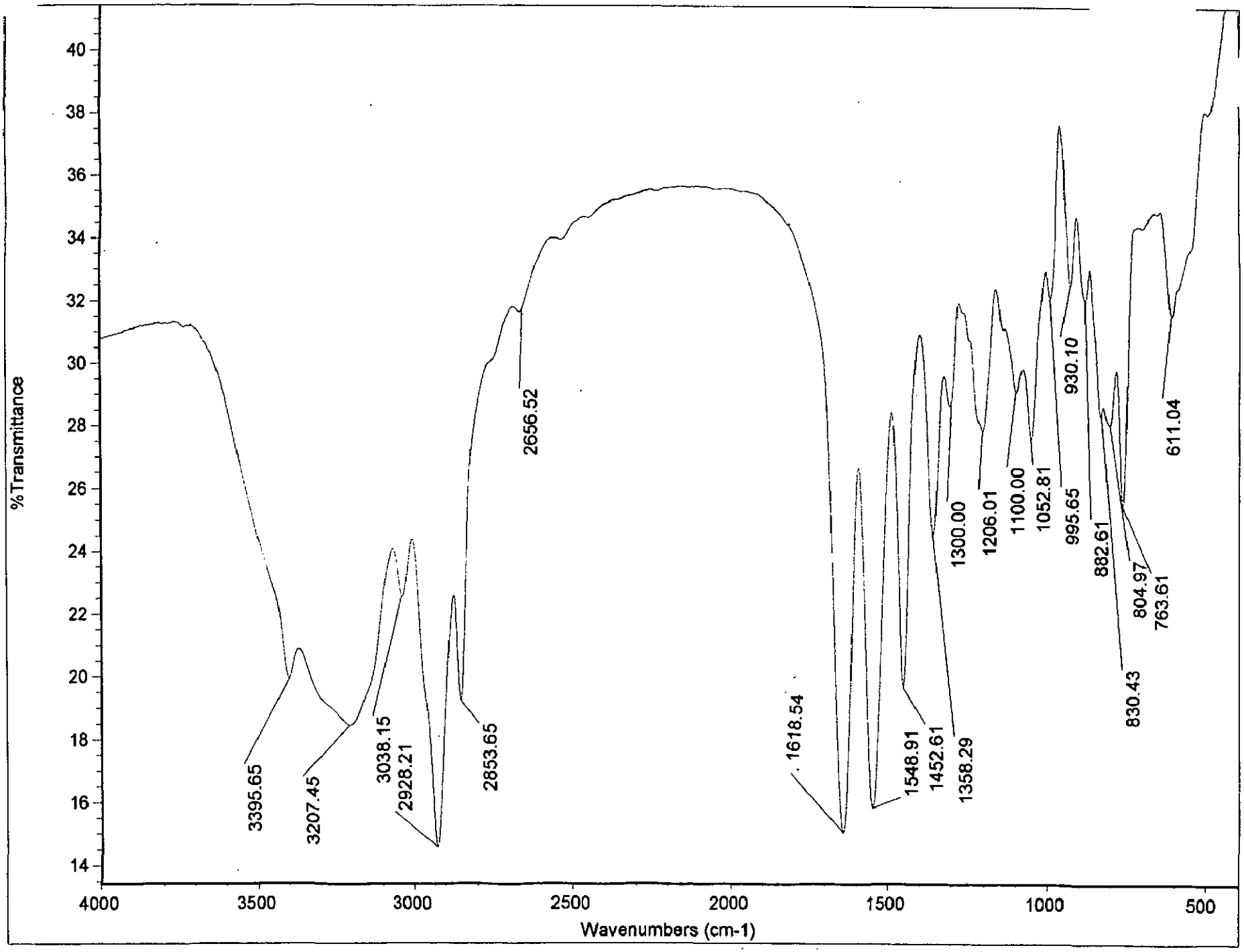
APPENDIX



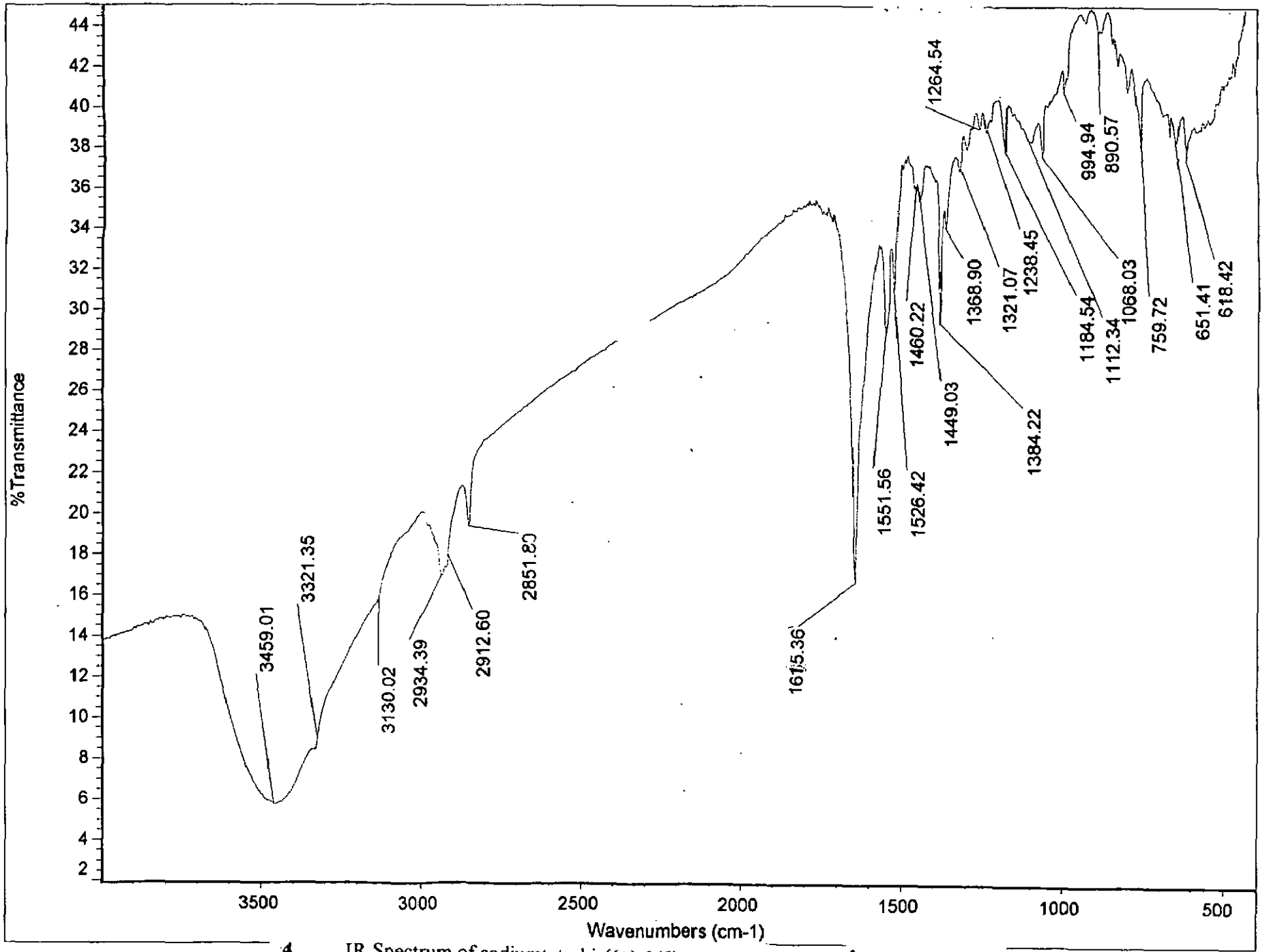
1. IR Spectrum of diketopiprazine



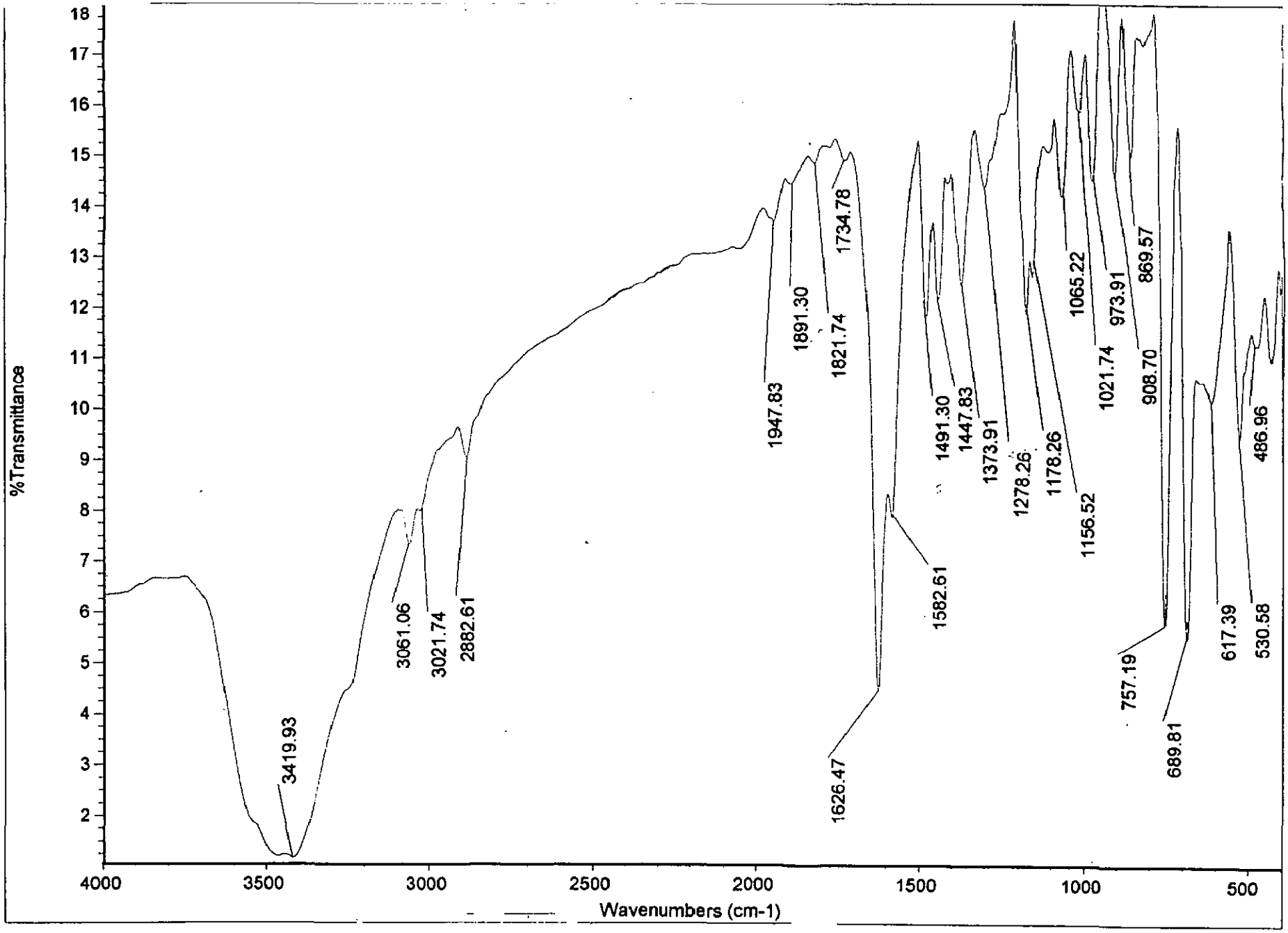
2. IR Spectrum of (+)-Cyclohexylethyl-3(5)-pyrazolecarboxylicamide



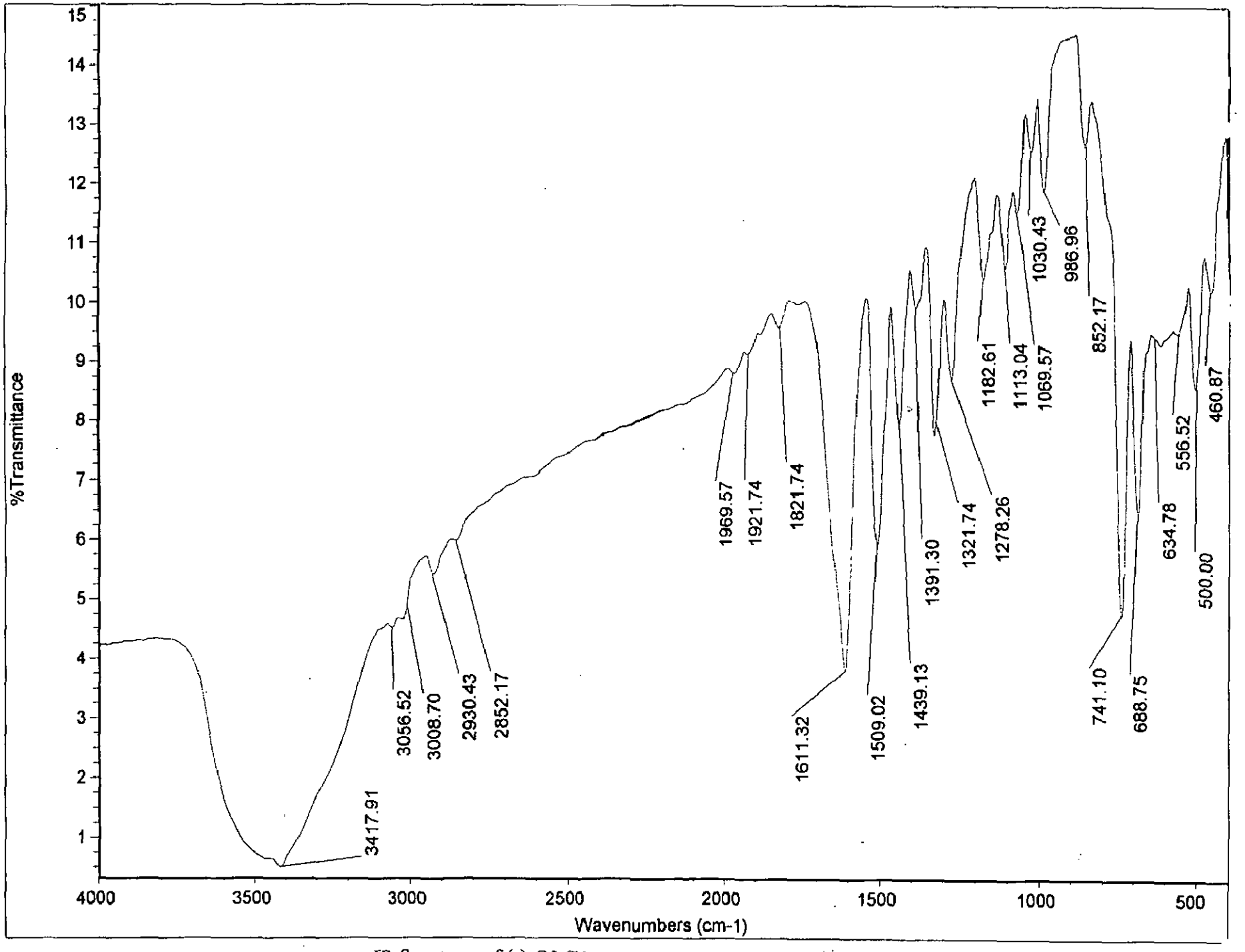
3. IR Spectrum of (+)-3(5){(Cyclohexylethylamino)methyl}pyrazole



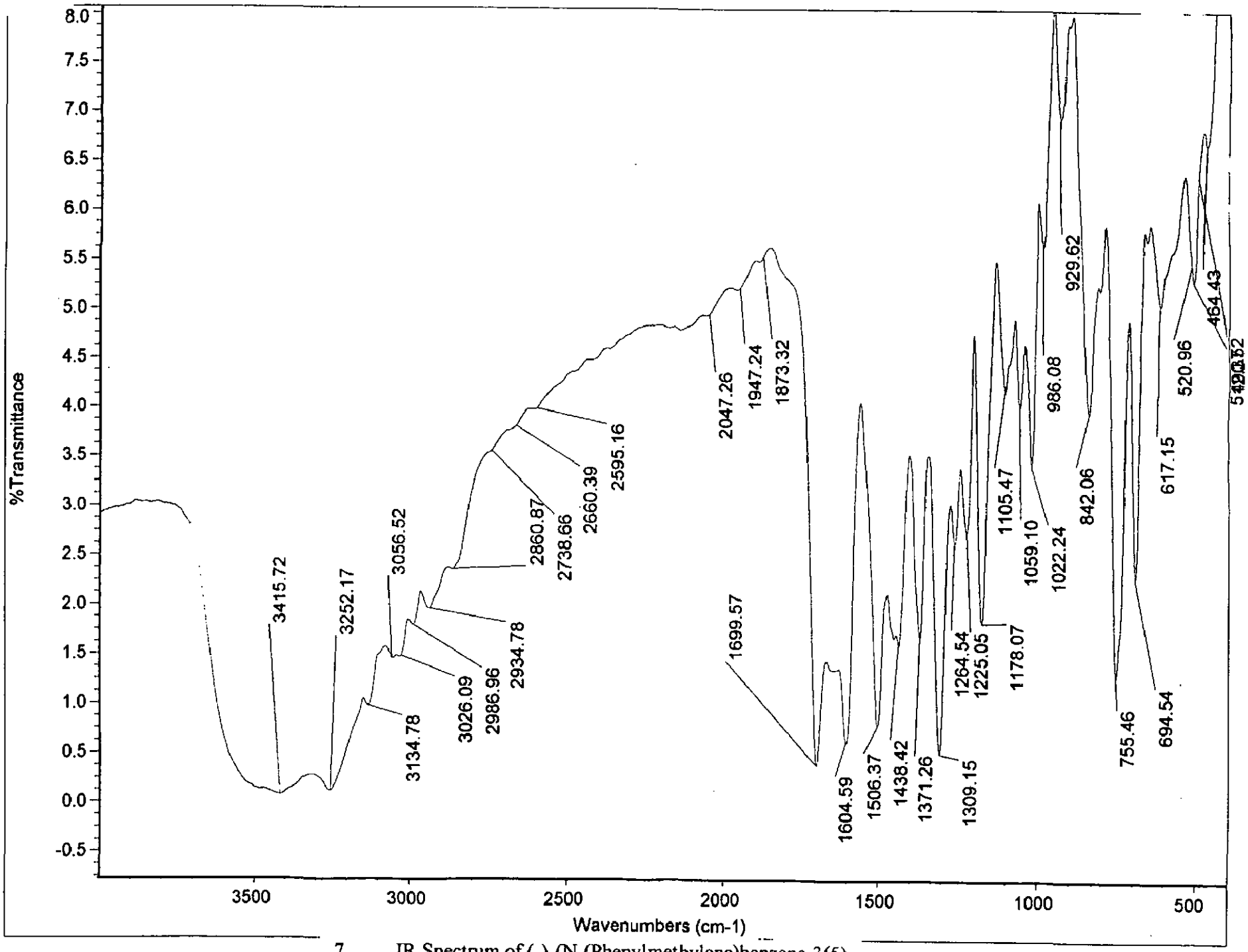
4. IR Spectrum of sodiumtetrakis((+)-3(5)-cyclohexylethylaminomethylpyrazol yl)borate



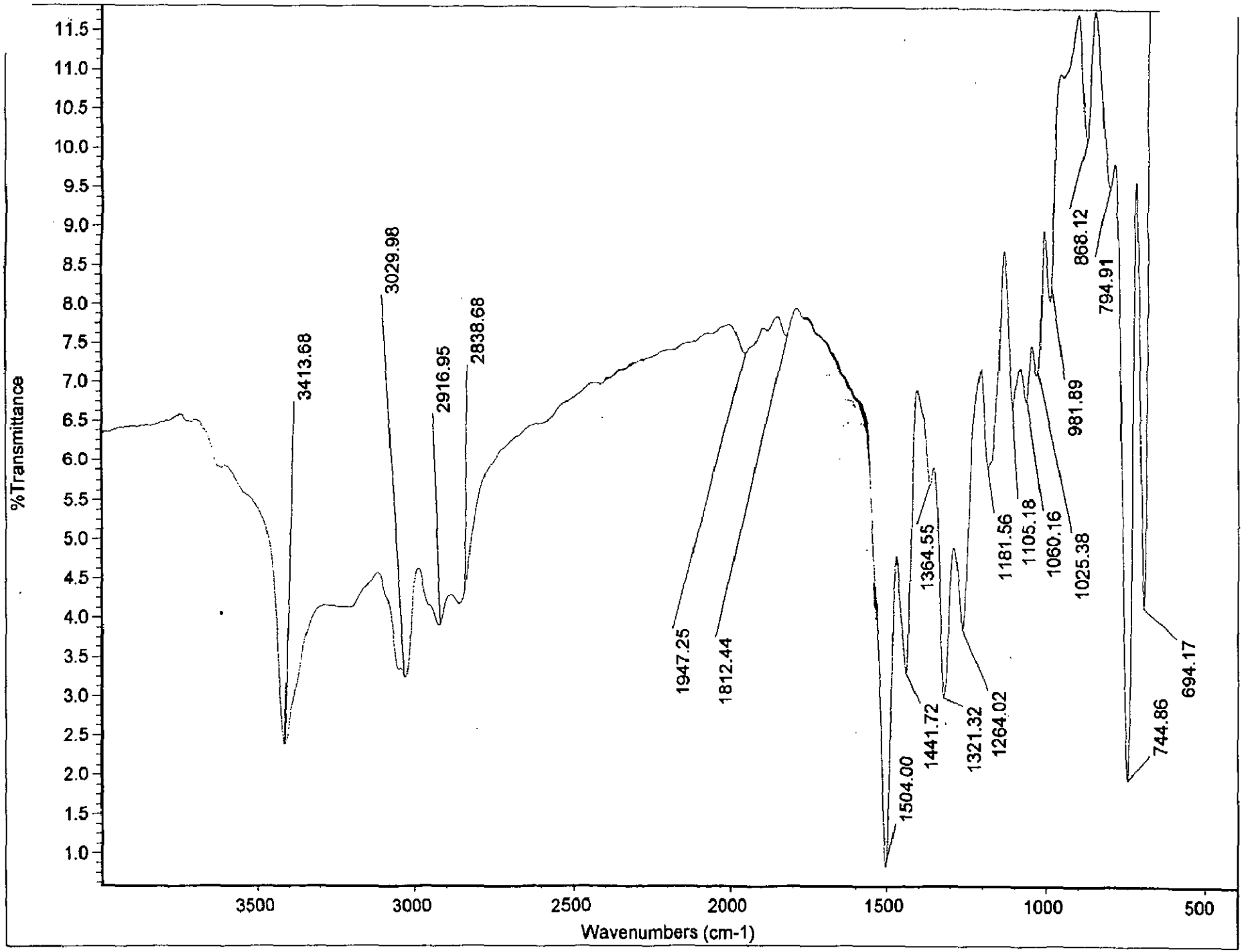
5. IR Spectrum of (N)-benzylidene benzenamine



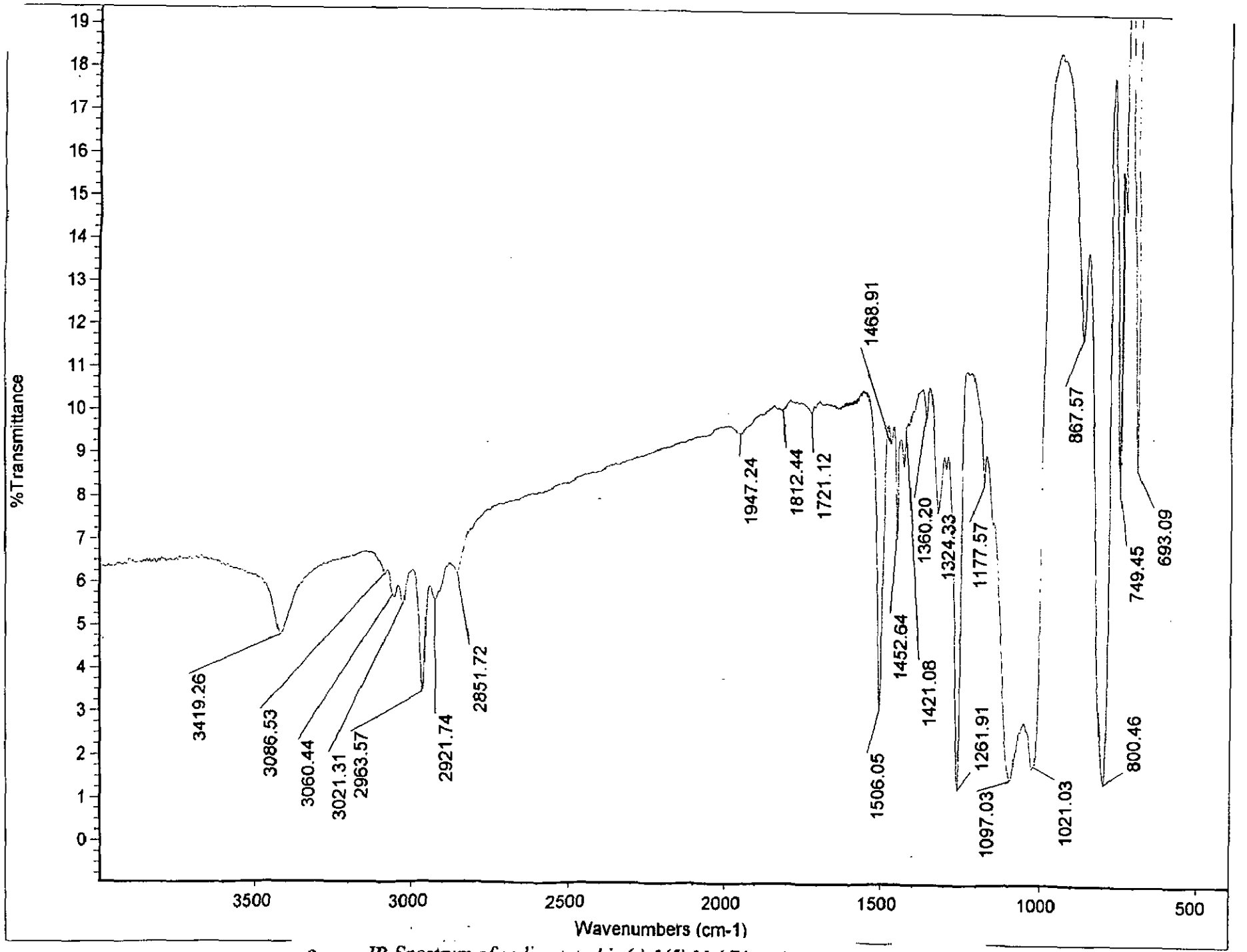
IR Spectrum of (-)-(N-(Phenylmethylene)benzenamine



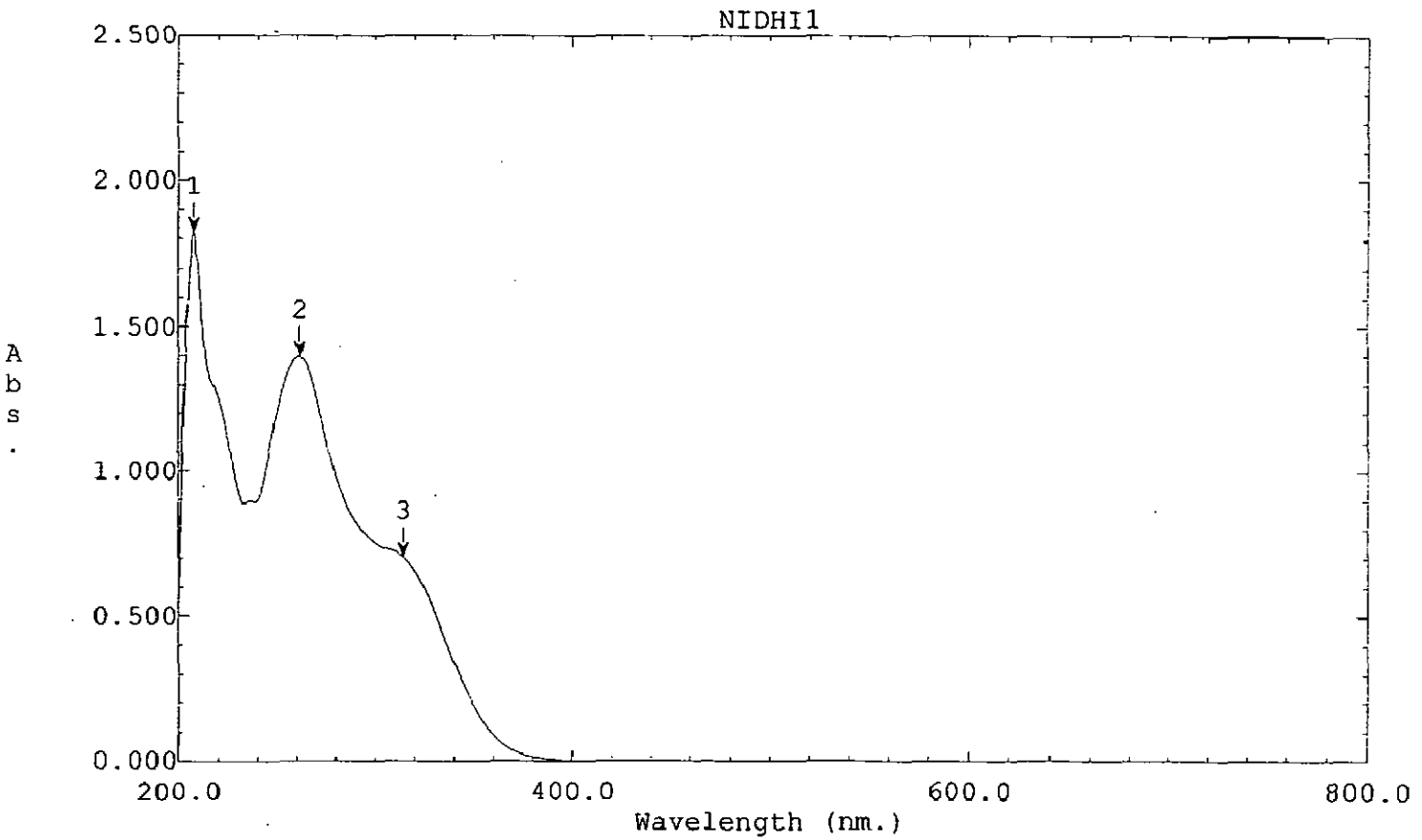
7. IR Spectrum of (-)-(N-(Phenylmethylene)benzene-3(5)-pyrazolecarboxylicamide



8. IR Spectrum of (-)-3(5)-N-{(Phenylmethylene)benzenamino)}pyrazole



9. IR Spectrum of sodiumtetrakis (-)-3(5)-N-{(Phenylmethylene)benzenamino) }pyrazolyl)borate



Point Pick

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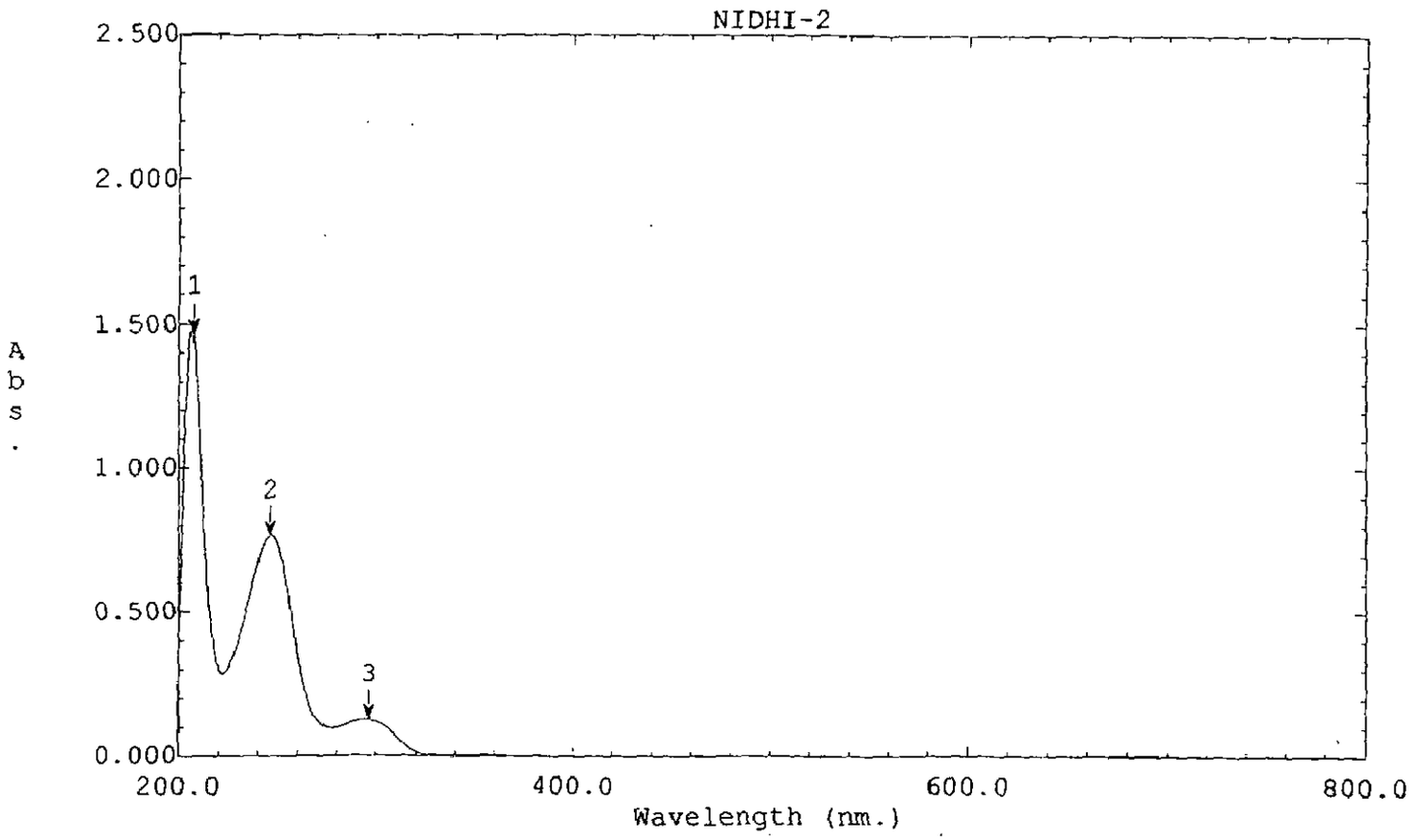
10. UV Spectrum of N-benzylidene benzenamine



Point Pick

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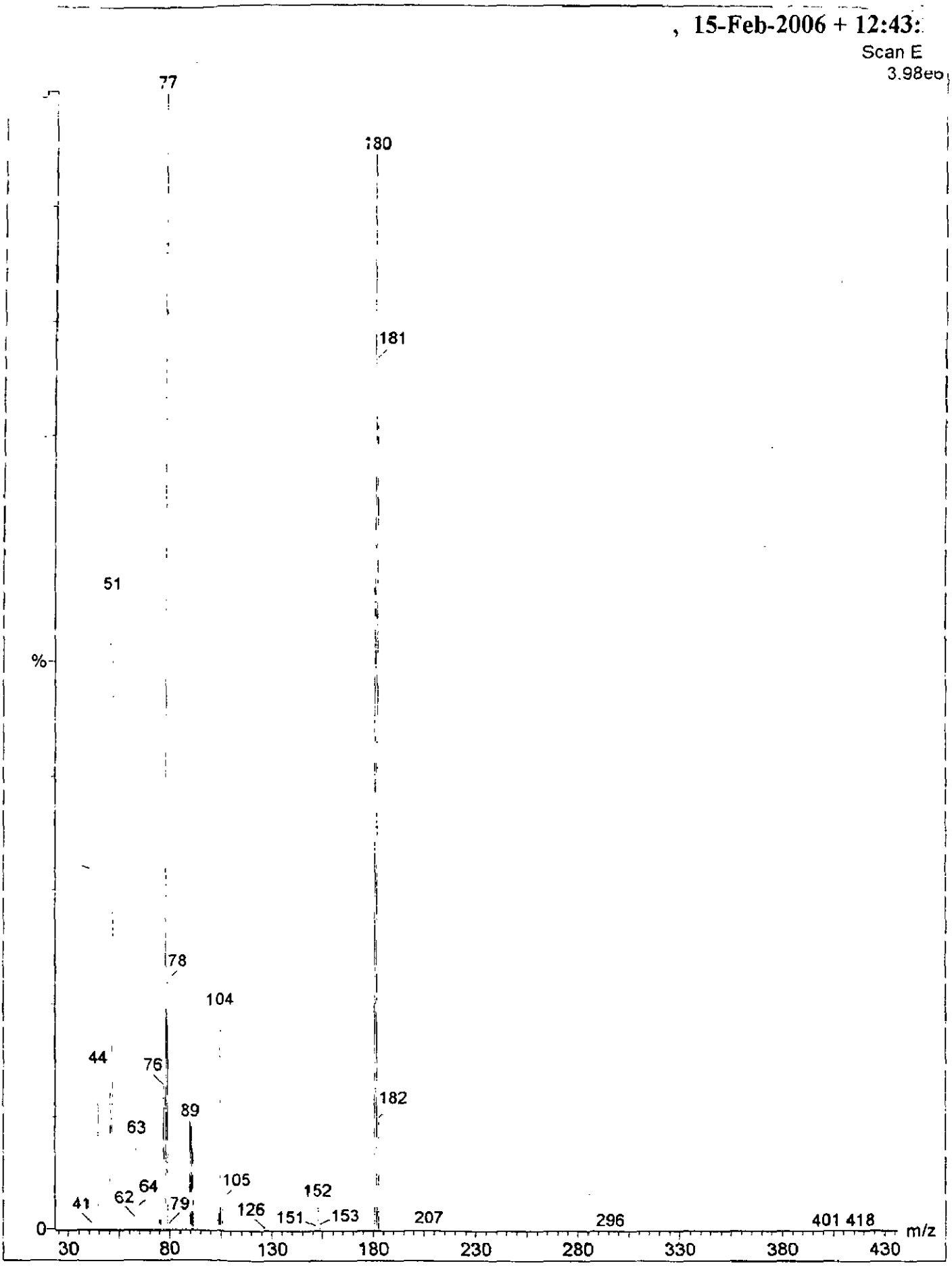
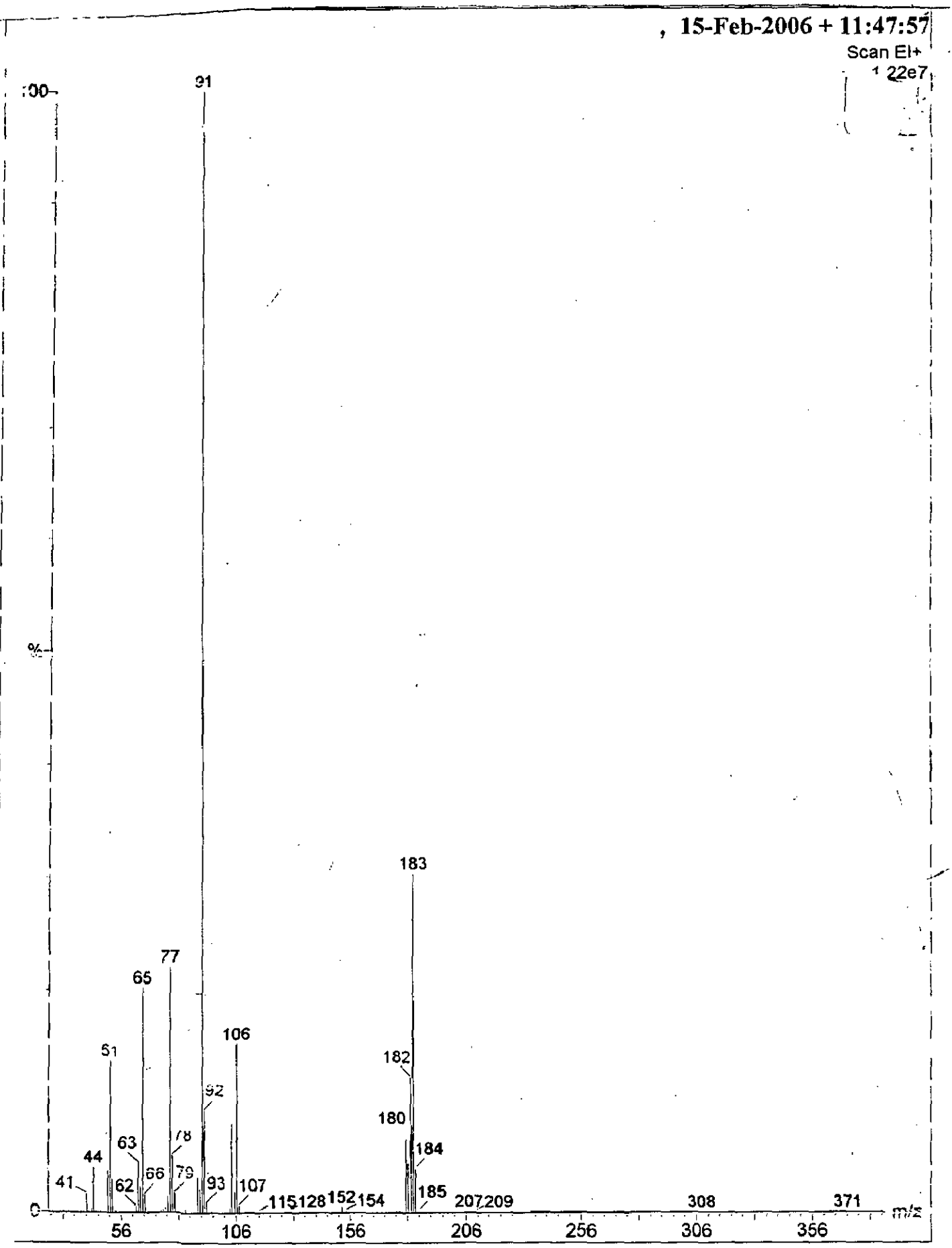
3	296.50	0.1267

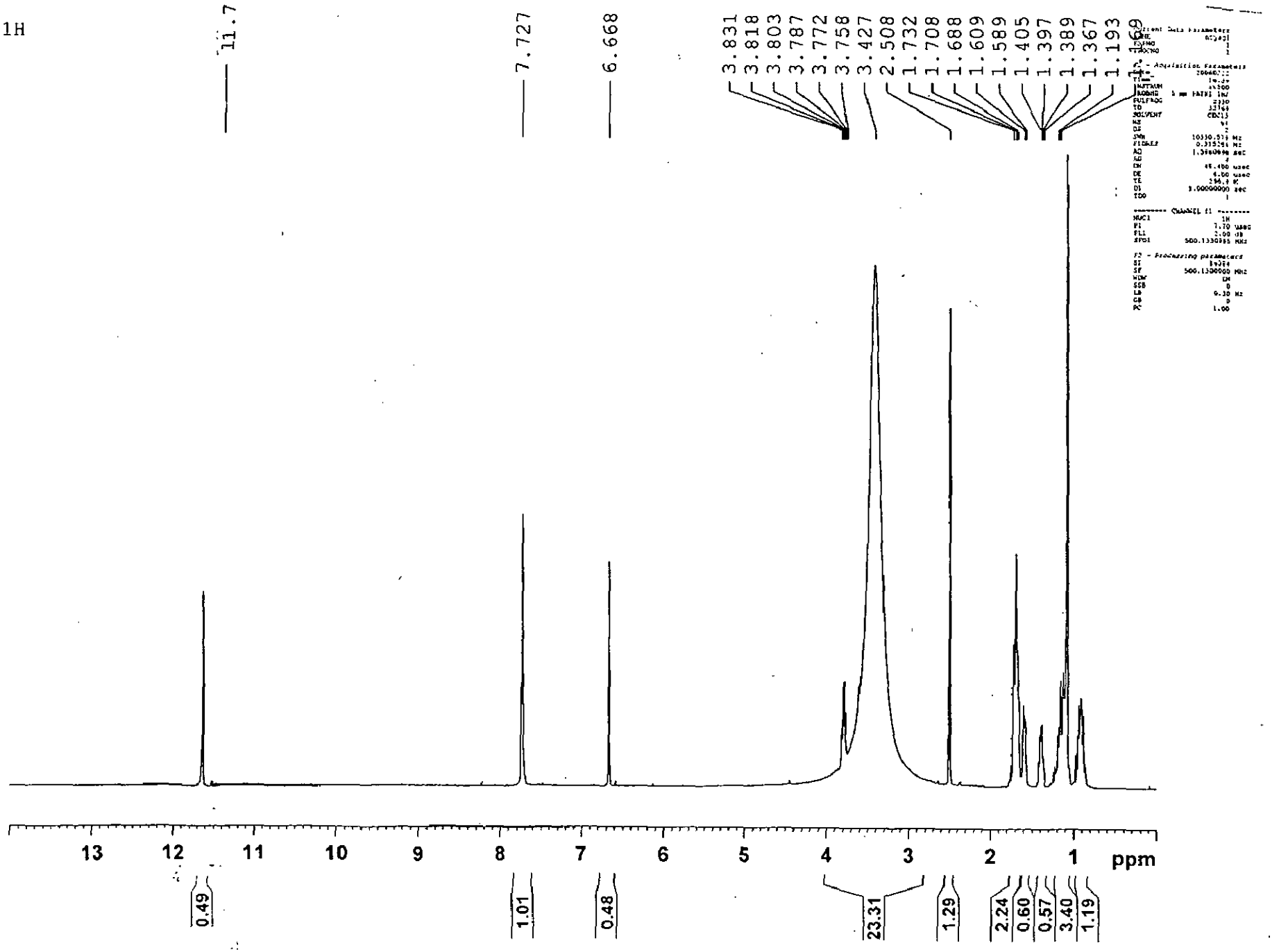
11. UV Spectrum of (-)-(N-(Phenylmethylene)benzenamine



12. Mass Spectrum of N-benzylidene benzenamine



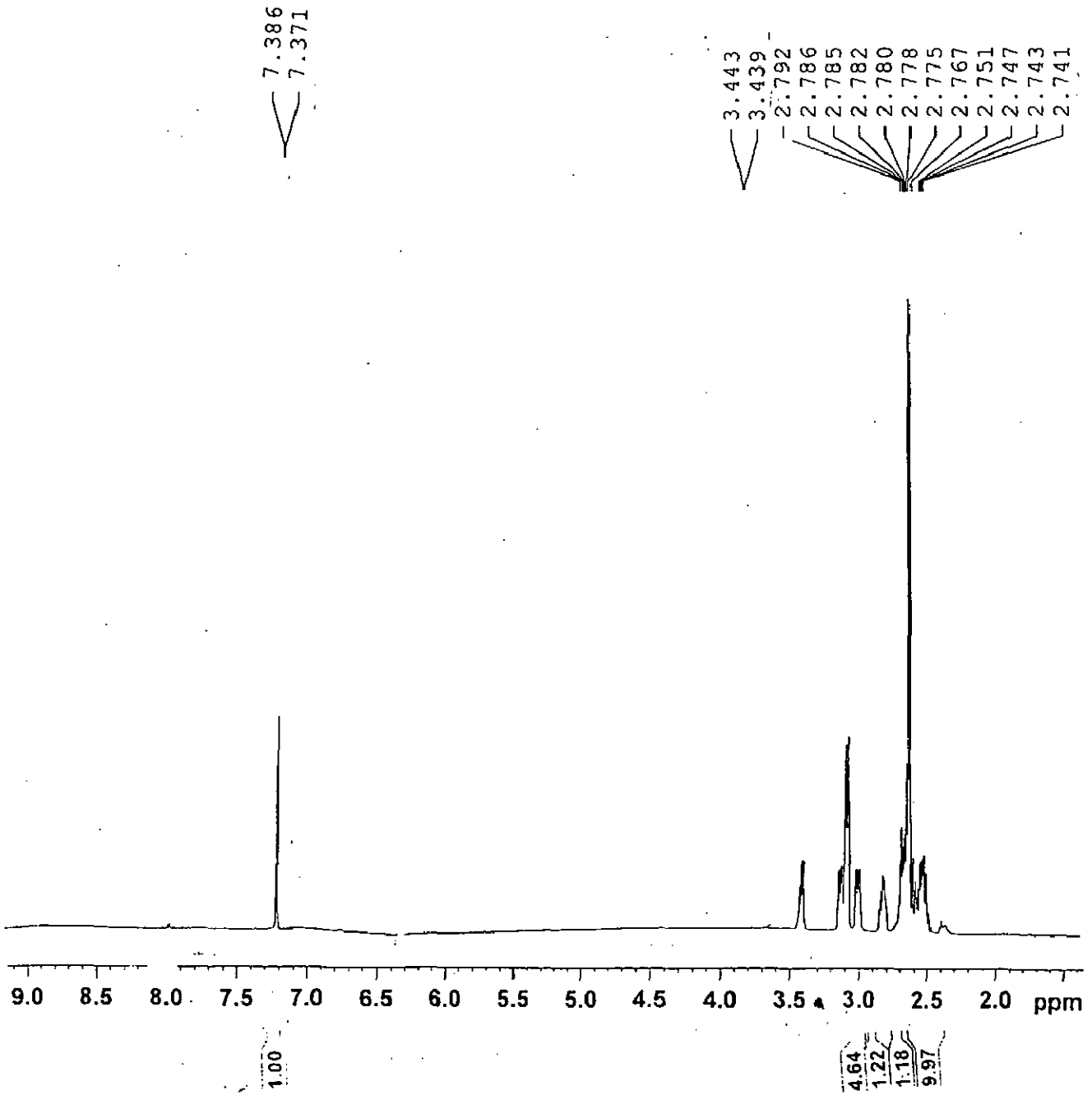
13. Mass Spectrum of (-)-(N-(Phenylmethylene)benzenamine



14. NMR Spectrum of (+)-3(5){(Cyclohexylethylamino)methyl}pyrazole

15. NMR Spectrum of sodiumtetrakis((+)-3(5)-cyclohexylethylaminomethyl pyrazolyl)borate

1H



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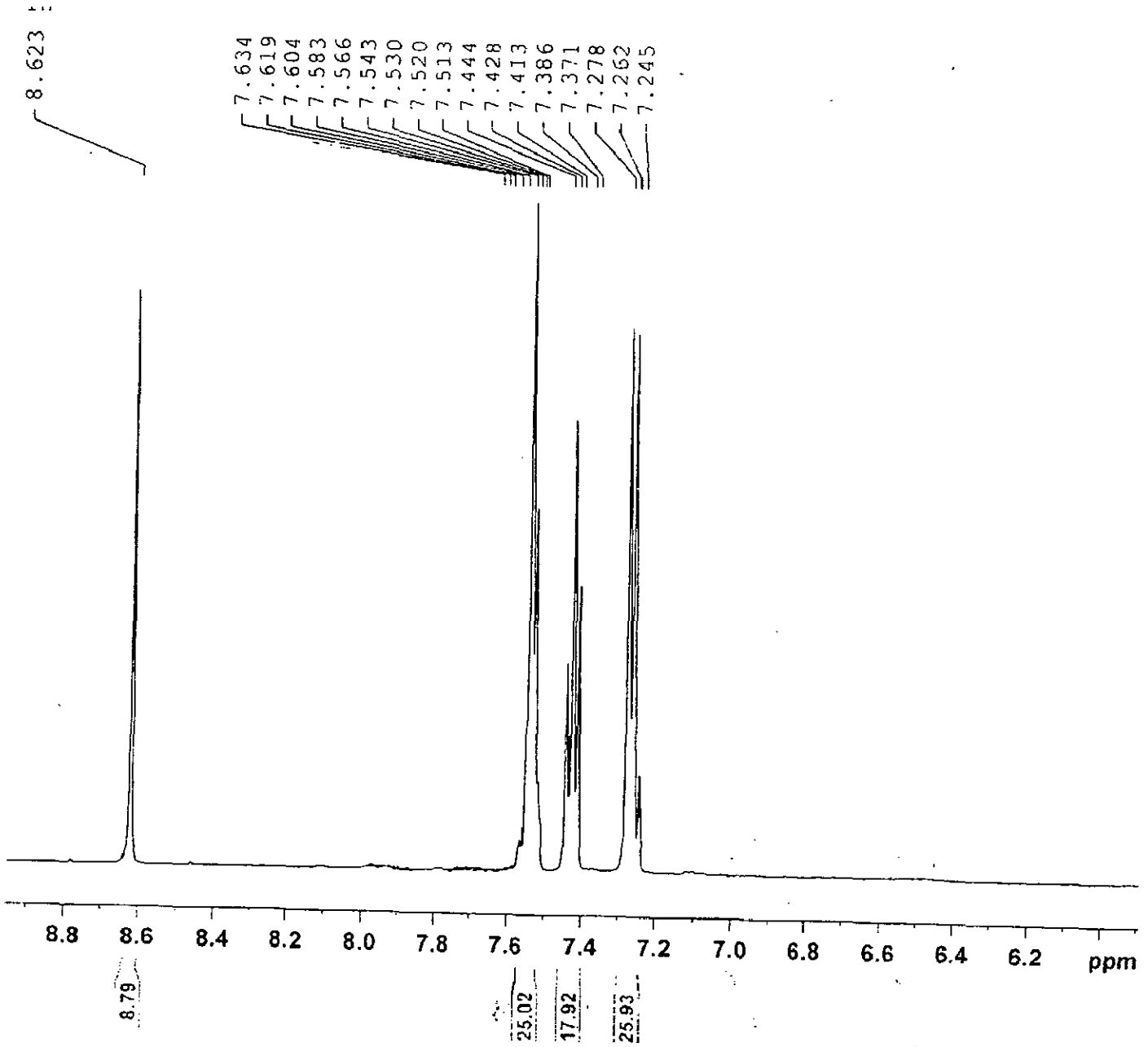


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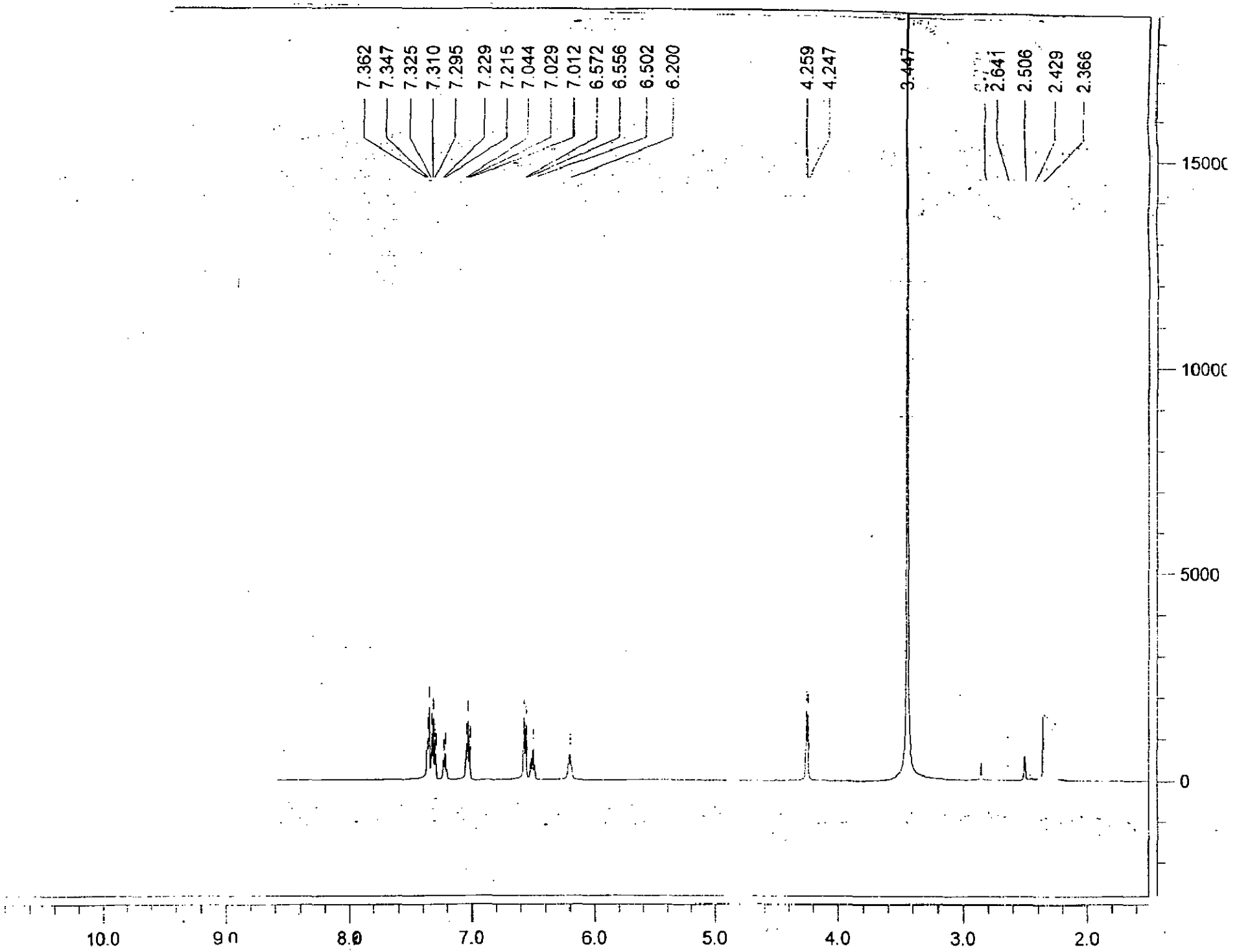
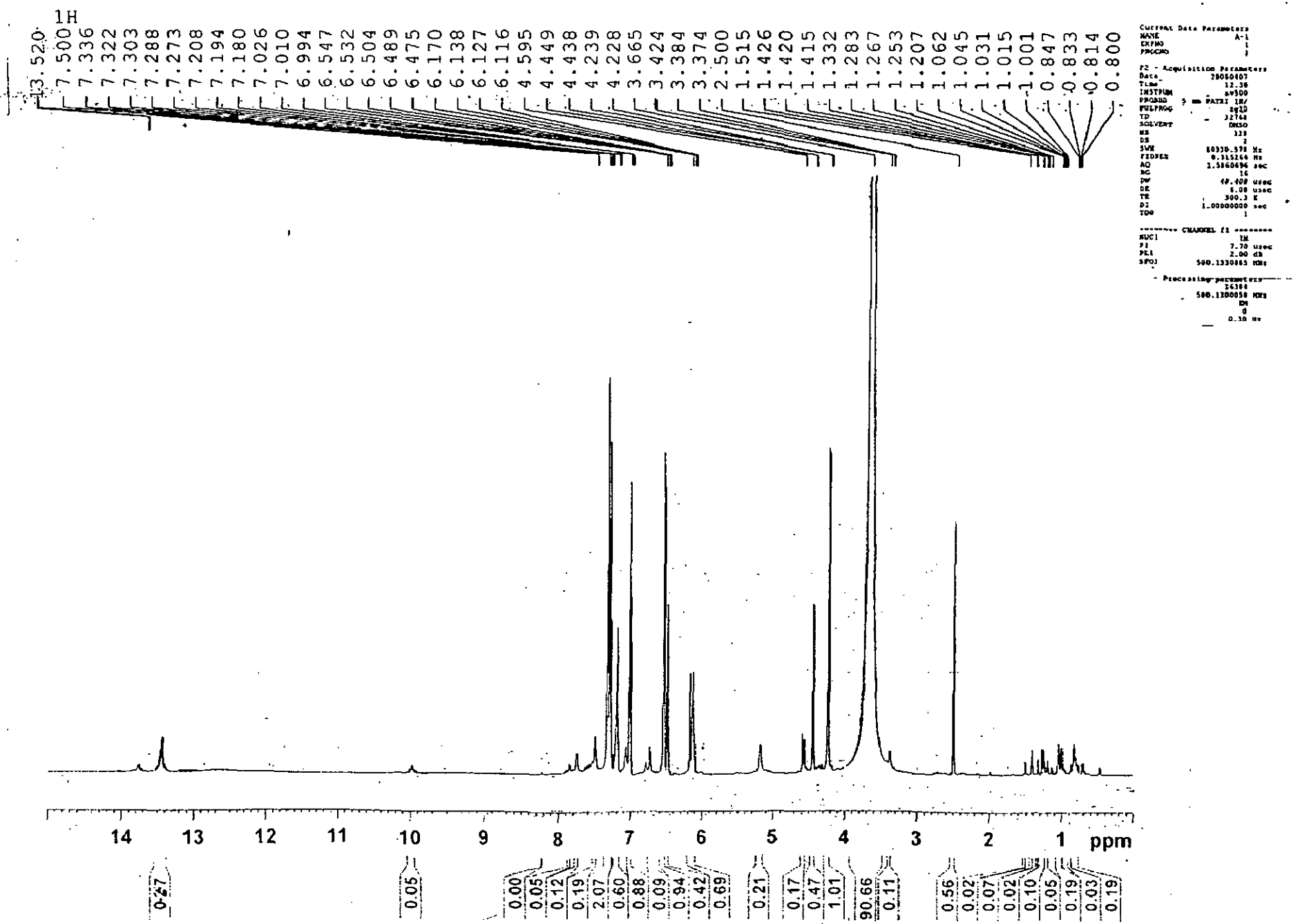
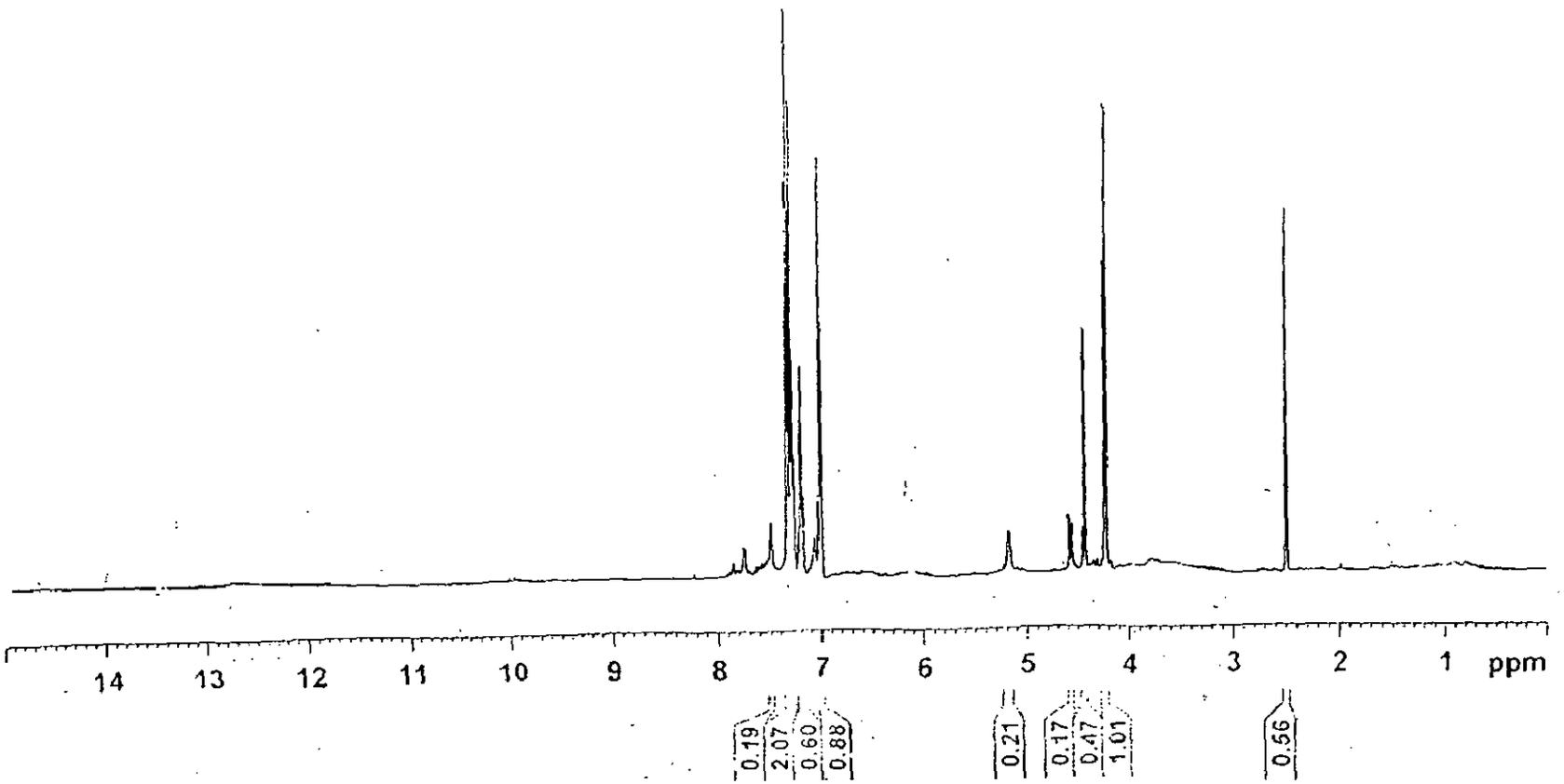
16. NMR Spectrum of N-benzylidene benzenamine



17. NMR Spectrum of (-)-(N-(Phenylmethylene)benzenamine



18. NMR Spectrum of (-)-3(5)-N-{(Phenylmethylene)benzenamino)}pyrazole



19. NMR Spectrum of sodiumtetrakis (-)-3(5)-N-{(Phenylmethylene)benzen-amino)}pyrazolyl)borate