CHAPTER – III

SYNTHESIS AND CHARACTERIZATION OF LIGANDS

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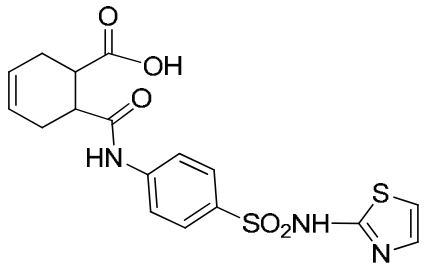
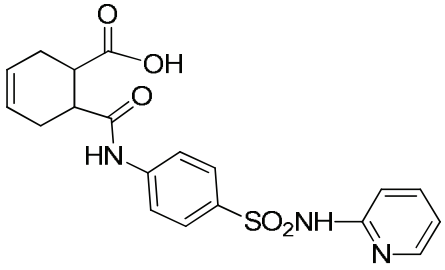
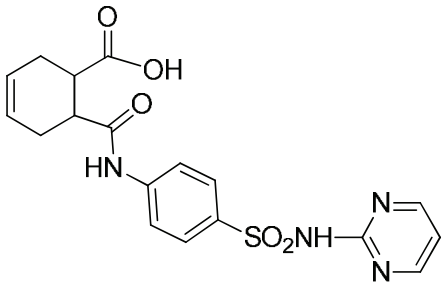
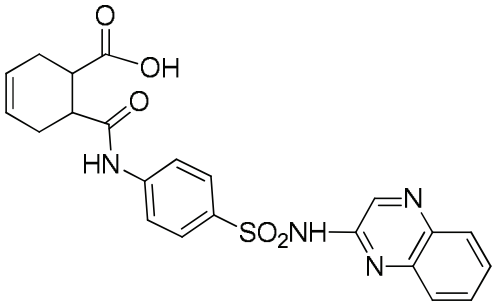
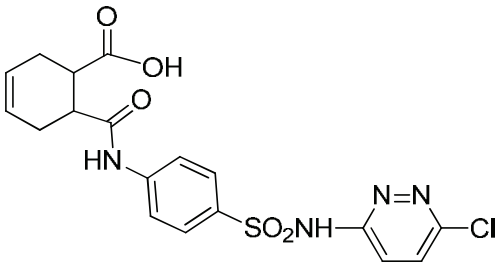
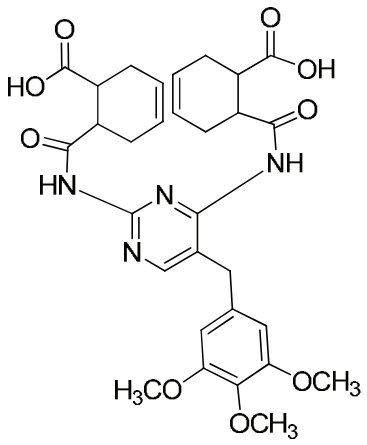
3.1 INTRODUCTION

Synthesized and characterized fine ligands based on sulfa drugs. These are designated as TPAS-1 to TPAS-5. One bis-ligand was also synthesized from trimethoprim and it was designated as TPTB.

Reaction of various sulfa drugs (as an amine source) were carried out with tetrahydrophthalic anhydride to obtain ligand. The details of these ligands are given in Table 3.1.

Table 3.1: List of ligands

Structure	Name	Molecular weight	Melting point (°C)	Yield (%)
	**TPAS-1**	407.46	181-182	86
	**TPAS-2**	401.44	188-189	87
	**TPAS-3**	402.42	198-199	82

	**TPAS-4**	452.48	195-196	85
	**TPAS-5**	436.87	178-179	86
	**TPTB**	594.61	166-167	87

3.2 EXPERIMENTAL

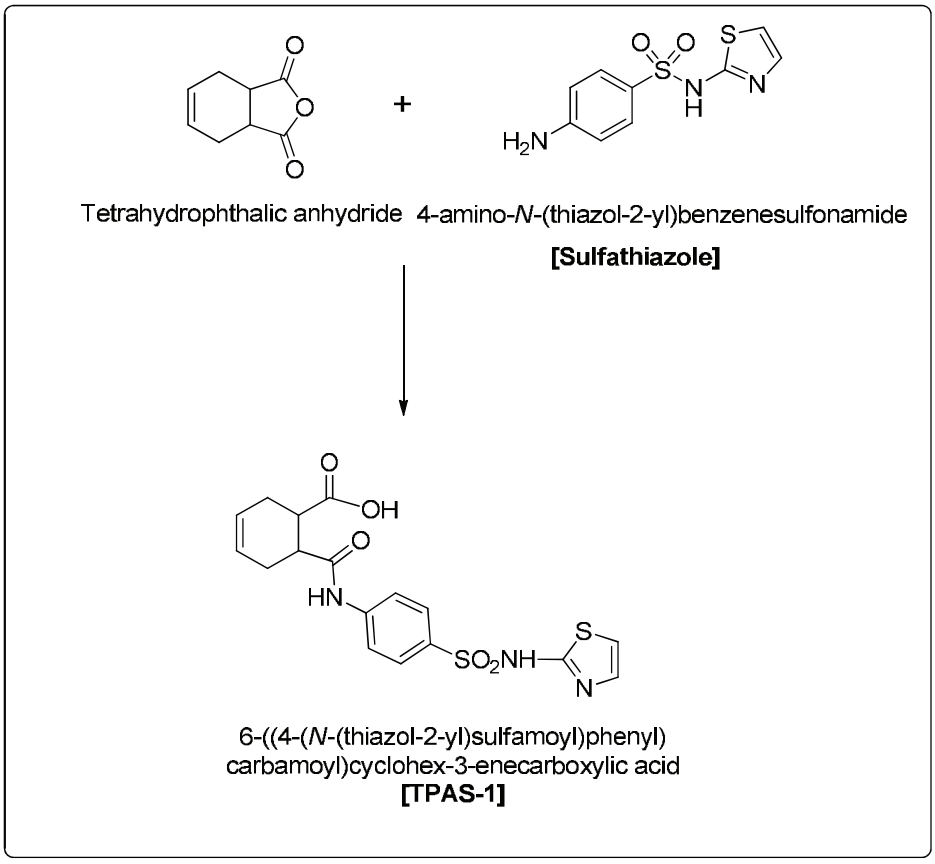
3.2.1 Synthesis of Tetrahydrophthalamic acid derivatives as ligands [TPAS-1 to TPAS-5].

Tetrahydrophthalamic acid derivatives of such drugs as ligands (TPAS-1 to TPAS-5) were prepared by using/reacting tetrahydrophthalic anhydride and various amine derivatives as Sulpha drugs. The method of preparation was based on earlier literature[1-4].

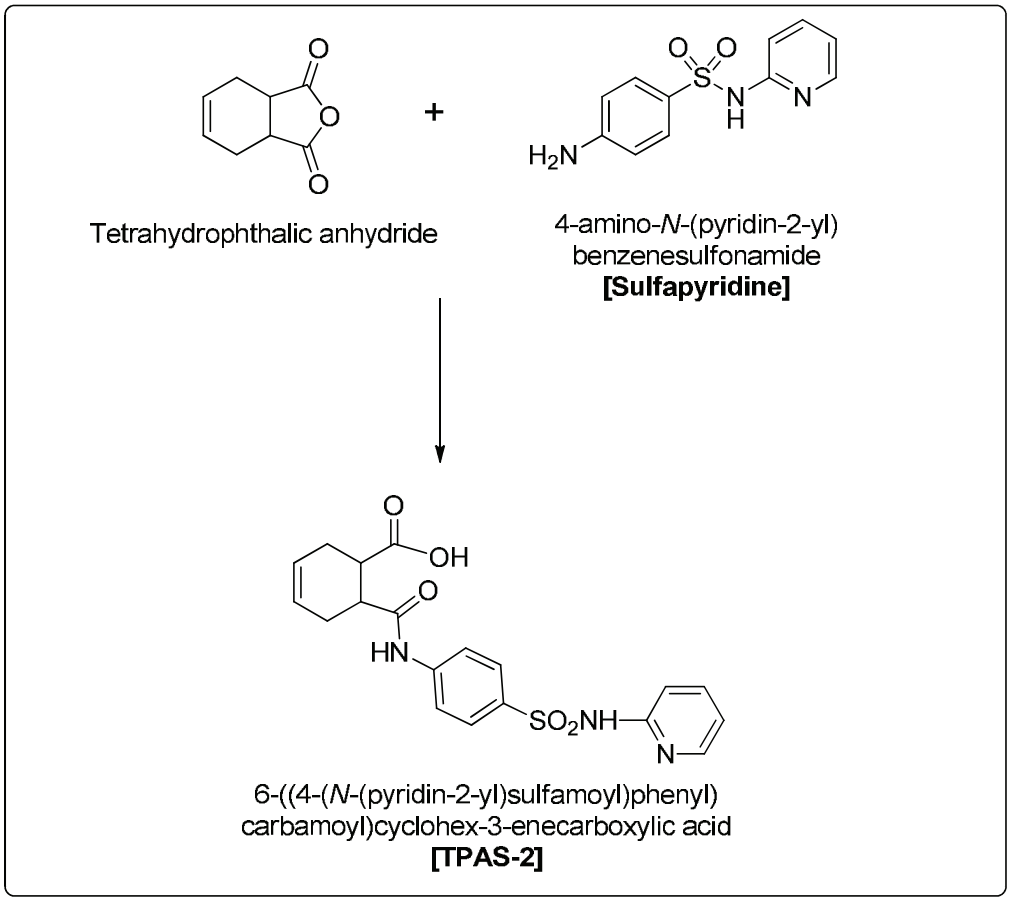
100 mmol of Tetrahydrophthalic anhydride and few dops of pyridine were mixed in 100 ml of 2-propanone solvent in a conical flask then 100 mmol of a sulfa drug dissolved in 100 ml 2- propanol was added portion wise and stirred. The assembly was stirred frequently by placing in an ice bath by maintaing temperature 0-5 ^{o}C. The rection mixture was placed in on the table with stirring at room temperature. The resultant solid product obtained was filtered off, washed with 2-propanone, Then petroleum ether and air – dried (Ligands TPAS-1 to TPAS-5).

The reaction scheme are:

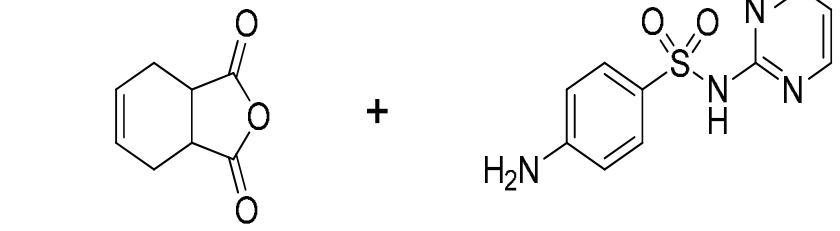
Ligand TPAS-1:



Ligand TPAS-2:

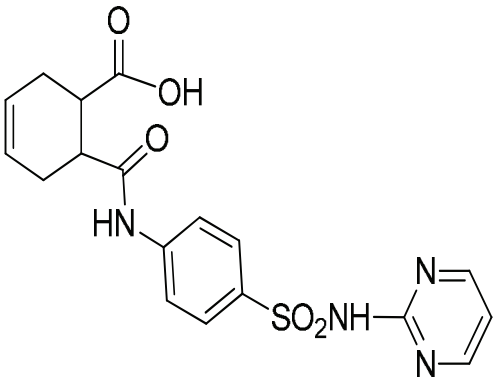


Ligand TPAS-3:



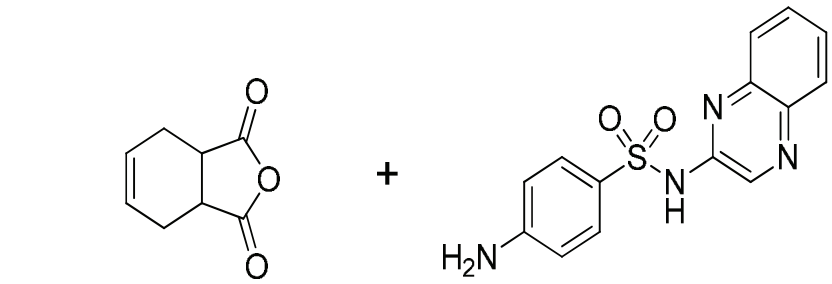
Tetrahydrophthalic anhydride

4-amino-*N*-(pyrimidin-2-yl) benzenesulfonamide
[Sulfadiazine]



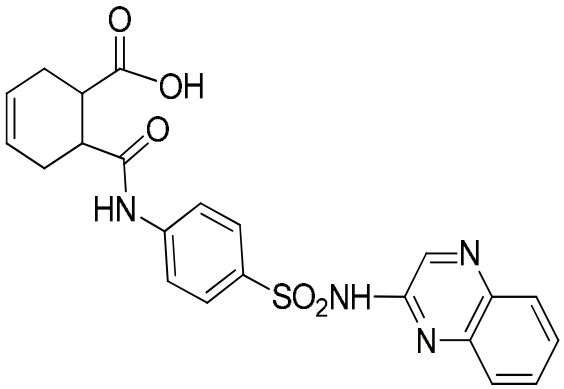
6-((4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl) carbamoyl)cyclohex-3-enecarboxylic acid
[TPAS-3]

Ligand TPAS-4:



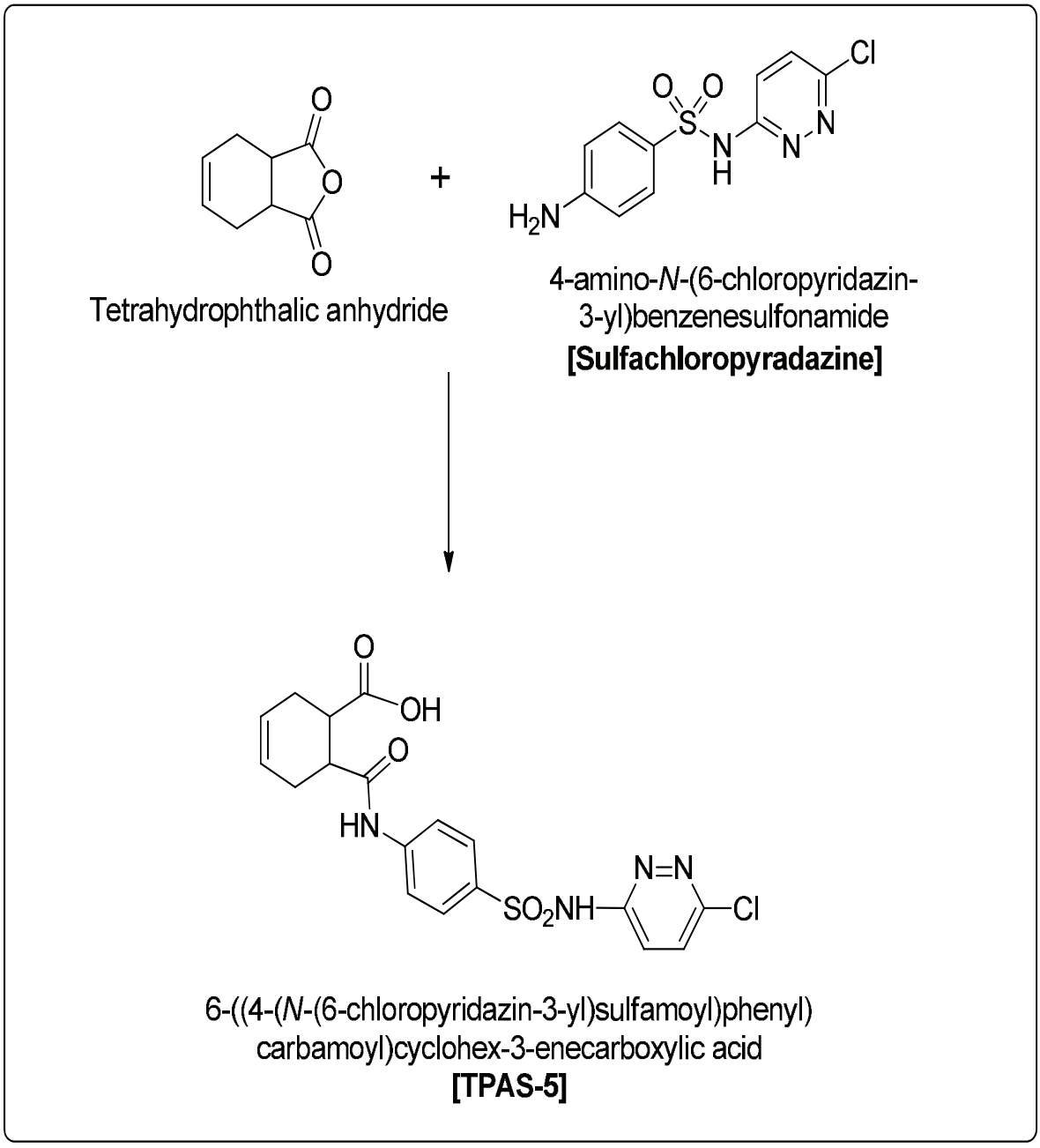
Tetrahydrophthalic anhydride

4-amino-*N*-(quinoxalin-2-yl) benzenesulfonamide
[Sulfaquinoxaline]



6-((4-(*N*-(quinoxalin-2-yl)sulfamoyl)phenyl) carbamoyl)cyclohex-3-enecarboxylic acid
[TPAS-4]

Ligand TPAS-5:

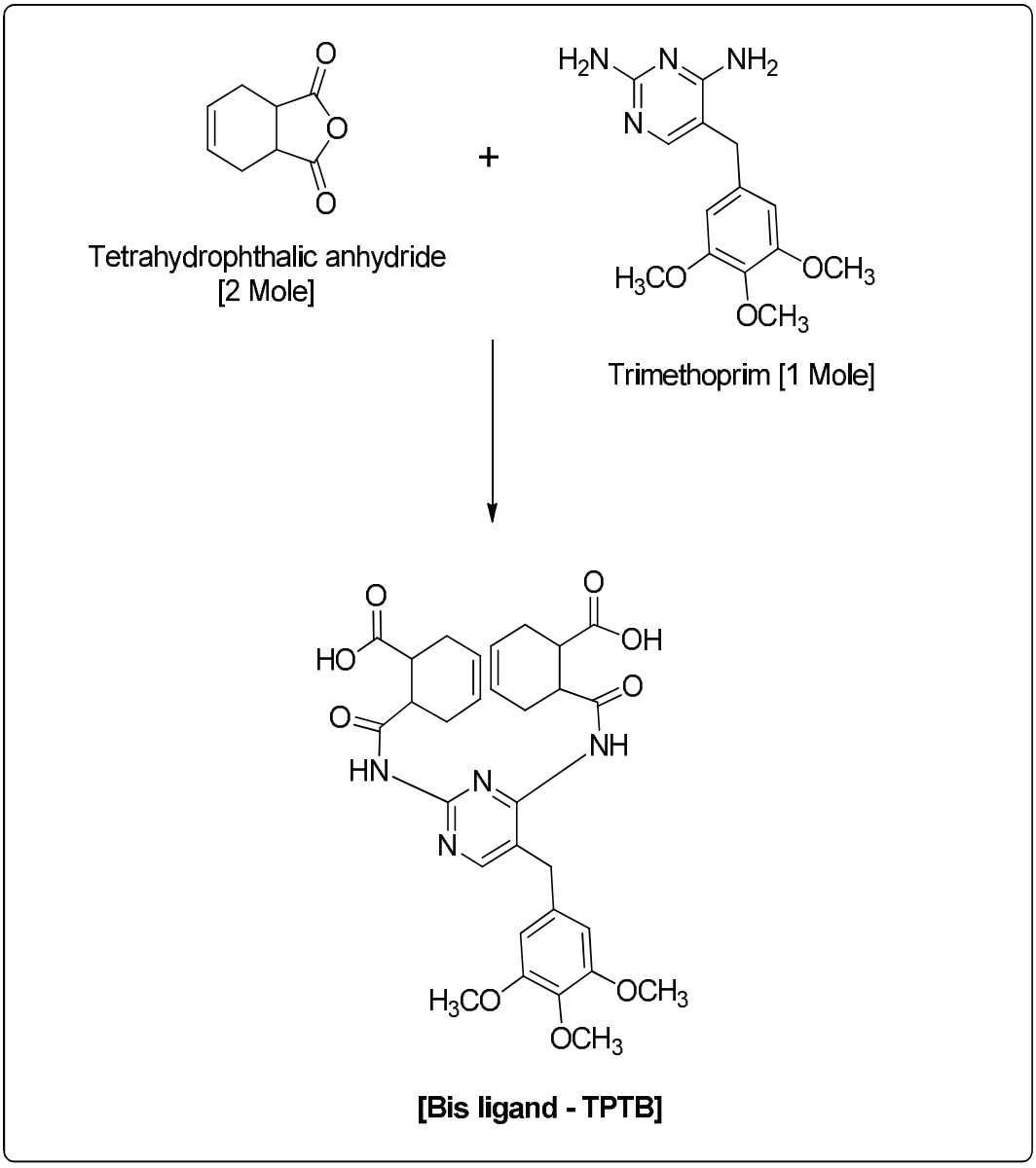


3.2.2 Synthesis of tetrahydrophthalamic trimethoprim bis-ligand (TPTB).

Tetrahydrophthalamic trimethoprim bis-ligand (TPTB) was prepared by condensing 2 mole of tetrahydrophthalic anhydride with trimethoprim. The reported method & were used[1-4].

Tetrahydrophthalic anhydride (0.2 mole) and 0.1 mL of pyridine in 100 mL acetone were taken in round bottom flask, and stirred. Then a solution of Trimethoprim (0.1 mole) in 100 mL acetone was added in parts within 30-60 min. The whole assembly was placed in ice-cooled bath and maintaing the temperature between 0-5°C during the addition of sulfa drug. The reaction mixture was kept aside with stirring for two hours at room temperature. After completion of the reaction, the precipitates were filtered off, washed with acetone and air-dried to give dry product (Ligand TPTB).

Ligand TPTB:



[Bis ligand - TPTB]

3.3 CHARACTERIZATION OF LIGANDS

3.3.1 General analysis:

The general analysis of ligands TPAS-1 to TPAS-5 and Bis-ligand (TPTB) observed.

- Melting points (°C) of all the compounds were measured by DSC method. All the melting points checked are uncorrected.
- The yields of all compounds were also measured. All solvents used were distilled and dried. The purity of the compounds was checked by TLC. Column chromatography was also performed using silica gel having 60-120 mesh, if required.

All the ligands were analyzed for their elemental contents. The C, H, N and S elements of all the samples were measured by Elemental analyzer Thermofinigan flash1101 EA. The results are reported in Tables 3.2 and 3.3. The values are in consistence with the proposed structures.

Table 3.2: Characterization of Ligands TPAS-1 to TPAS-5 and bis ligand TPTB

Ligand	Molecular Formula	Mol. Wt.	Yield (%)
TPAS-1	$C_{17}H_{17}N_3O_5S_2$	407.46	87%
TPAS-2	$C_{19}H_{19}N_3O_5S$	401.44	85%
TPAS-3	$C_{18}H_{18}N_4O_5S$	402.42	86%
TPAS-4	$C_{22}H_{20}N_4O_5S$	452.48	85%
TPAS-5	$C_{18}H_{17}N_4O_5SCl$	436.87	86%
TPTB (Bis Ligand)	$C_{30}H_{34}N_4O_9$	594.61	84%

Table 3.3: Elemental analysis of ligands

Ligand No.	Elemental analysis							
	C (%)		H (%)		N (%)		S(%)	
	Cal.	Found	Cal.	Found	Cal.	Found	Cal.	Found
TPAS-1	50.06	50.00	4.17	4.20	10.30	10.30	15.70	15.70
TPAS-2	56.79	56.80	4.73	4.70	10.46	10.50	7.97	8.00
TPAS-3	53.67	53.70	4.47	4.50	13.91	14.00	7.95	8.00
TPAS-4	68.07	68.00	4.42	4.40	12.37	12.40	7.07	7.10
TPAS-5	49.44	49.50	3.89	3.90	12.82	12.80	7.32	7.30
TPTB (Bis Ligand)	60.54	60.50	5.72	5.70	9.42	9.40	-	-

The anticipated IR spectral frequencies of all the ligands are given in Table 3.3. The infrared spectra of selected ligands are presented in Figures 3.1 to 3.3. The infrared spectra of all the ligands indicate that-

I. All the IR spectra are identical in almost all aspects. The important bands are observed at their respective positions.

II. The bands at 3450, 1680 and 1580 cm^{-1} are due to –CONH- (secondary amide) group.

III. A strong band at 1700 cm^{-1} is due to carbonyl group of –COOH group.

IV. The bands at 3030, 1600 and 820 cm^{-1} are mainly from 1, 4-disubstituted aromatic ring.

V. The bands at 1160, 1350, 1610 and 3320 cm^{-1} are due to $–SO_2NH-$ (sulphonamide) group.

Table 3.4: IR spectral features for ligands TPAS-1 toTPAS-5 and TPTB (Bisligand)

Groups	**IR frequencies (cm^{-1})**
Amide group -NHCO-	3450, 1680, 1580
Aromatic.	820, 1600, 3030
-C=O of –COOH.	~ 1700
$-SO_2NH-$	1160, 1350, 1610, 3320

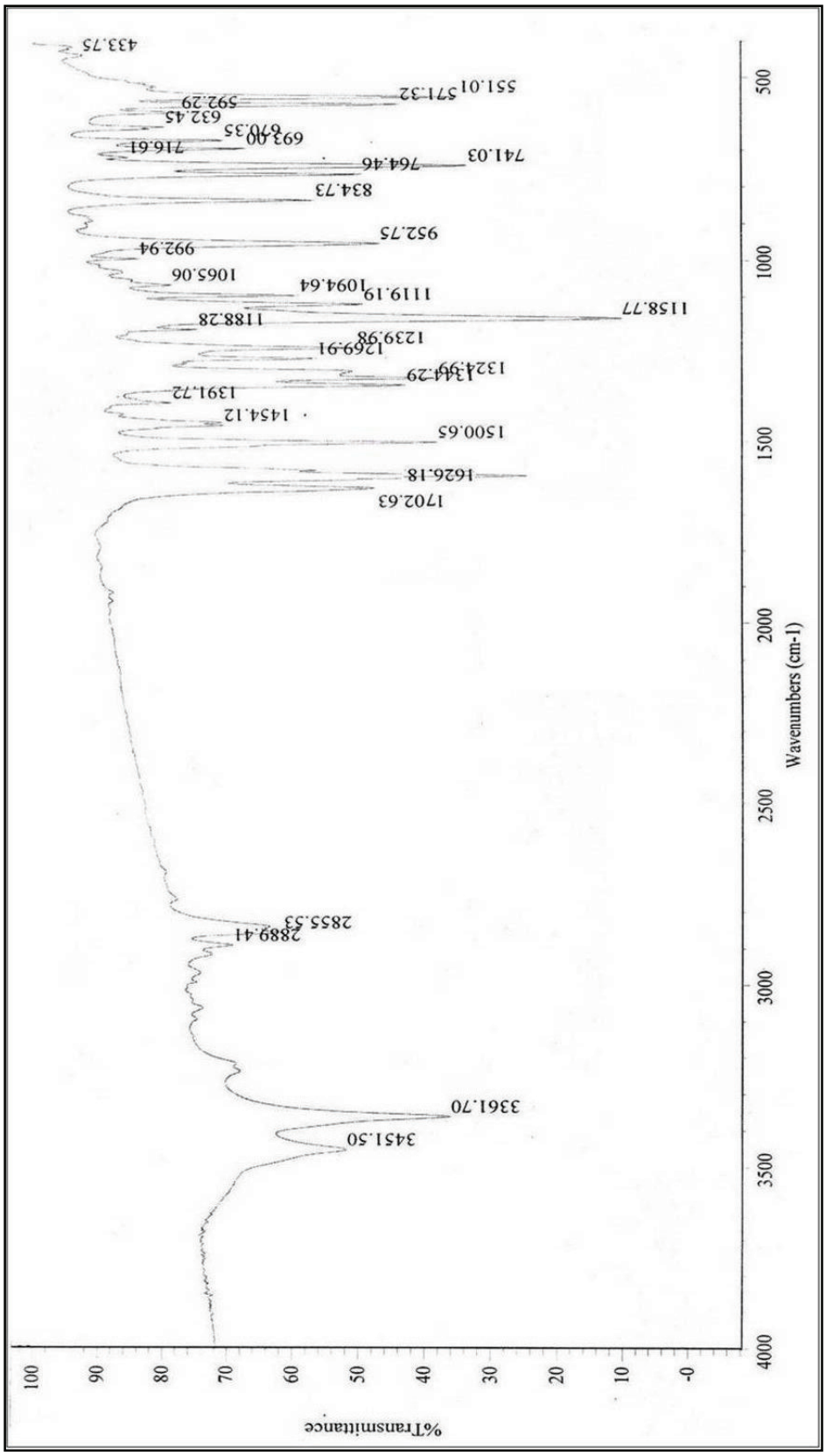


Fig. 3.1: IR spectrum of ligand TPAS-1

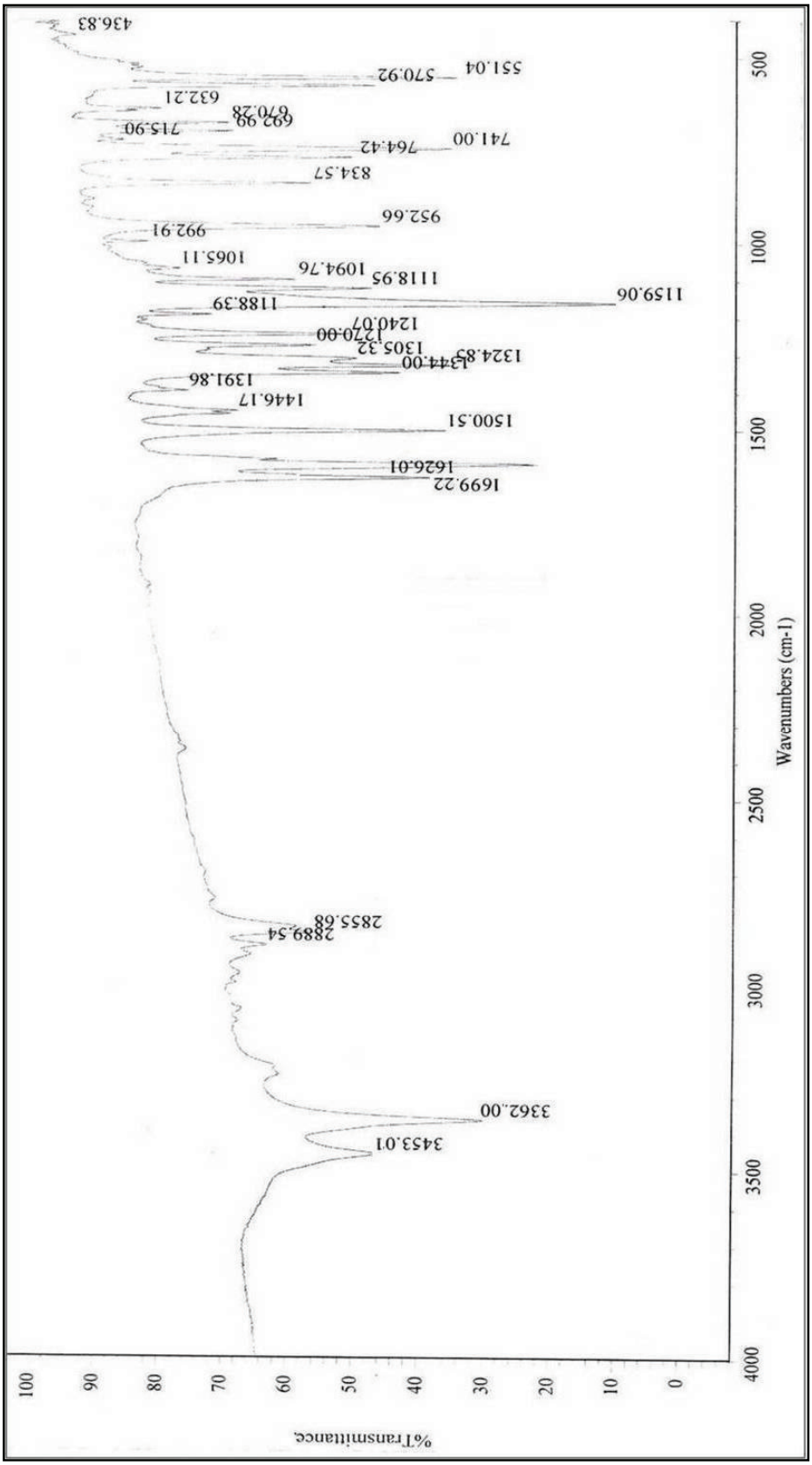


Fig. 3.2: IR spectrum of ligand TPAS-3

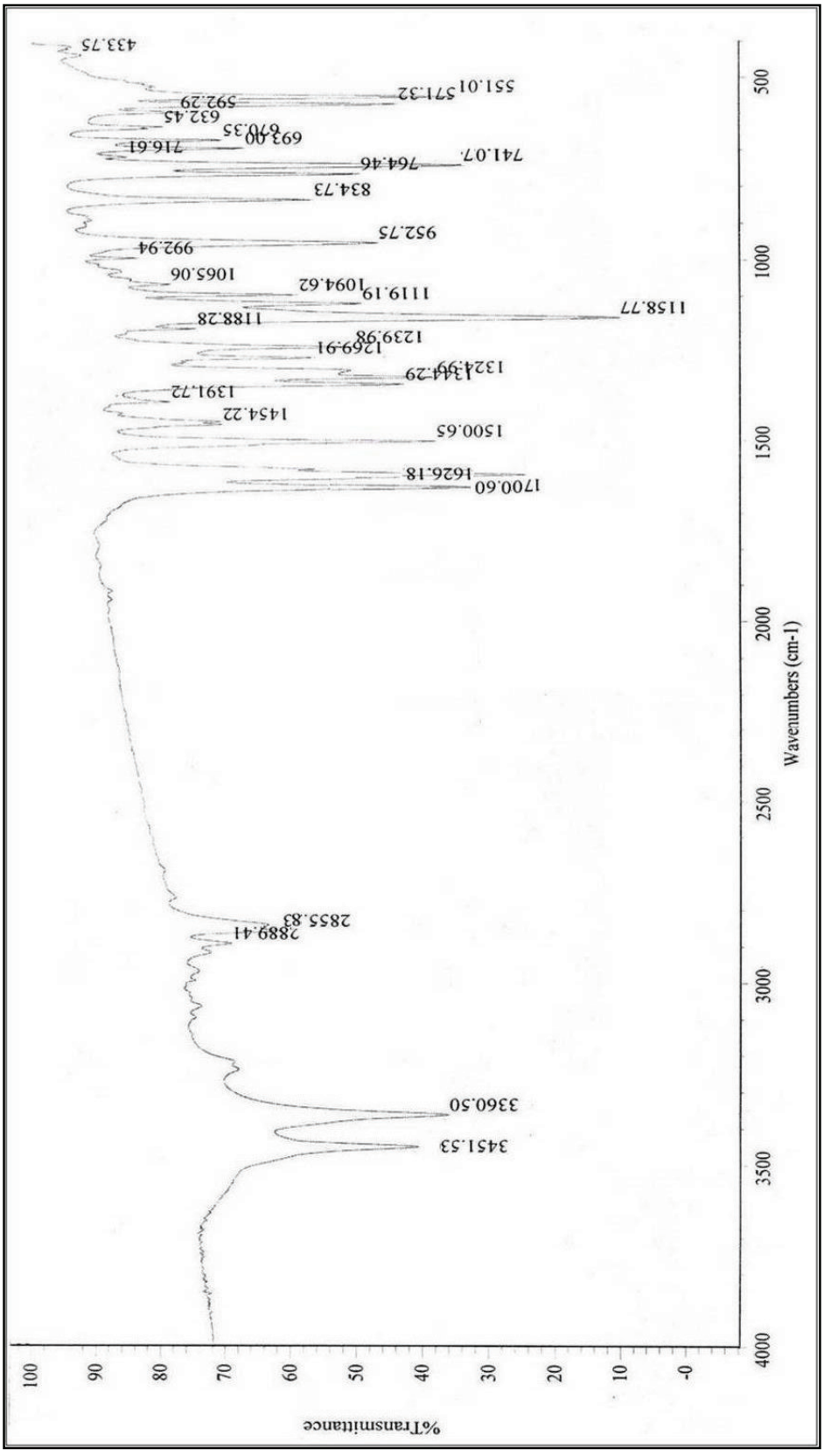


Fig. 3.3: IR spectrum of ligand TPAS-5

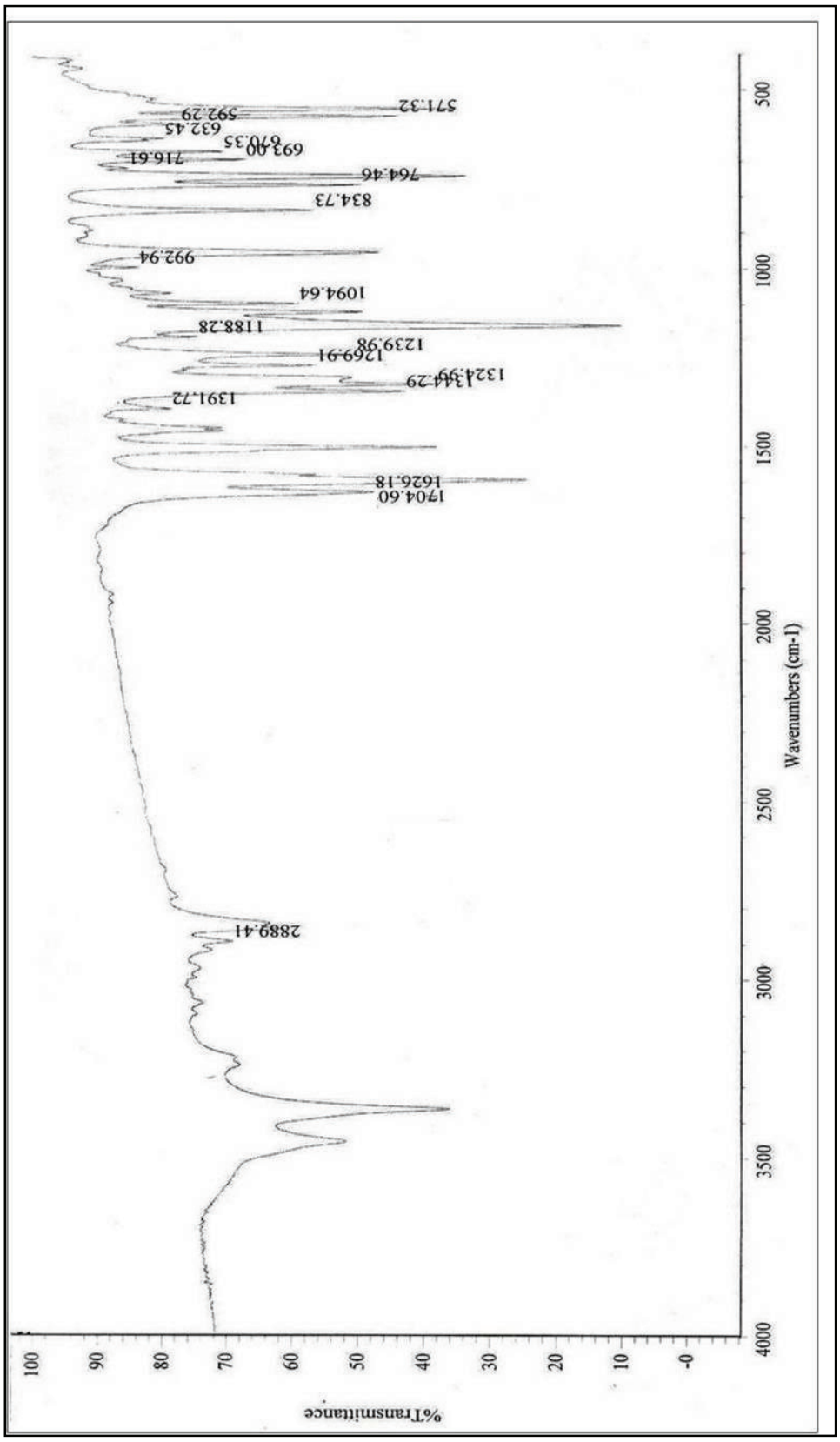


Fig. 3.4: IR spectrum of bis-ligand TPTB

3.3.3 Proton nuclear magnetic resonance spectroscopy

It was observed that that all NMR spectra are almost identical in nature. The NMR spectra of TPAS-1 to TPAS-5 and Bis-ligand TPTB are given in Figs: 3.5 to 3.7. All the spectra comprise the multiplet at 6.3 to 8.1 δ ppm due to from aromatic protons including NH of CONH group. The singlet at around 12 δ ppm might be responsible for H of COOH group.

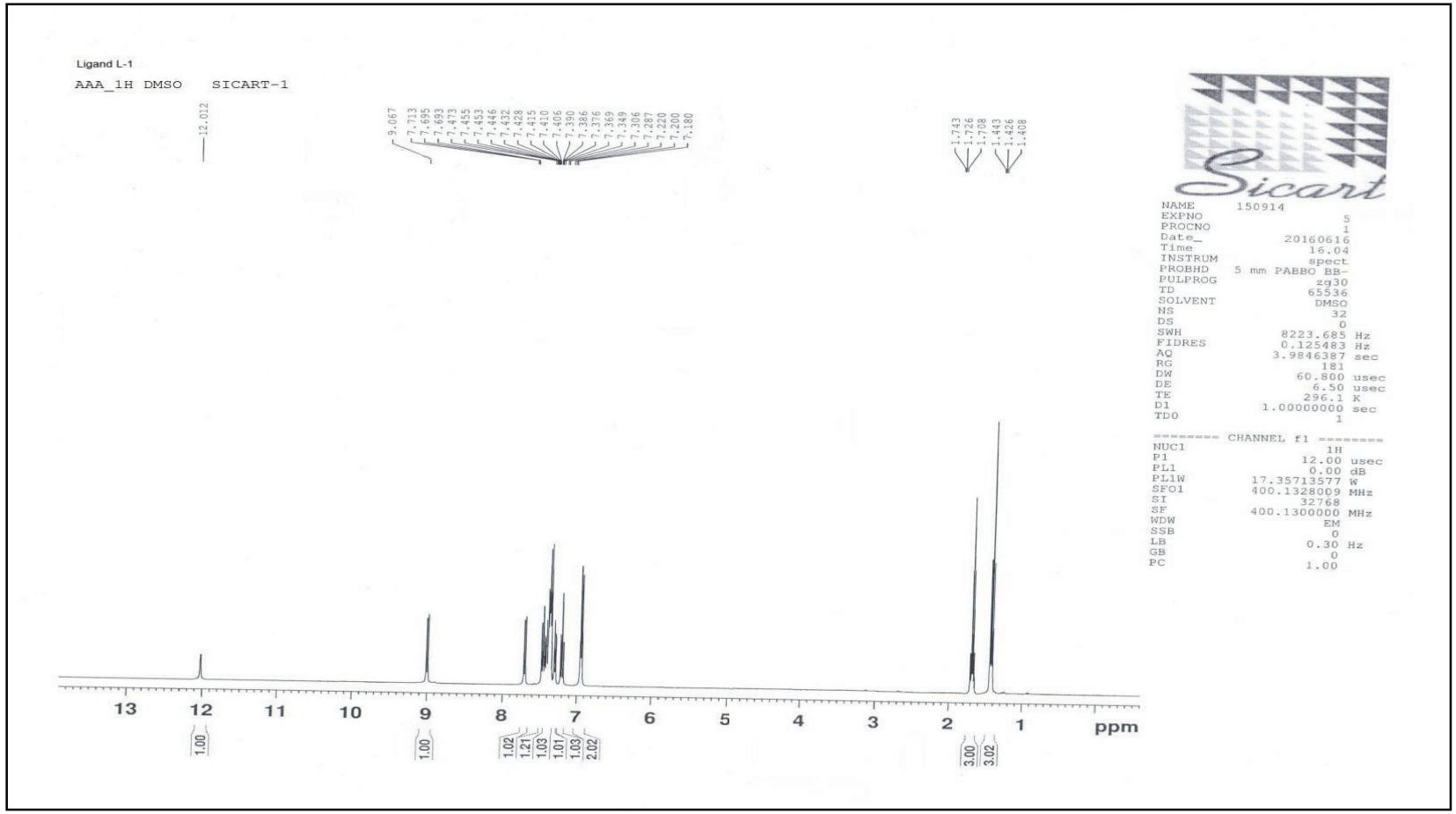


Fig 3.5: NMR spectrum of ligand TPAS-1

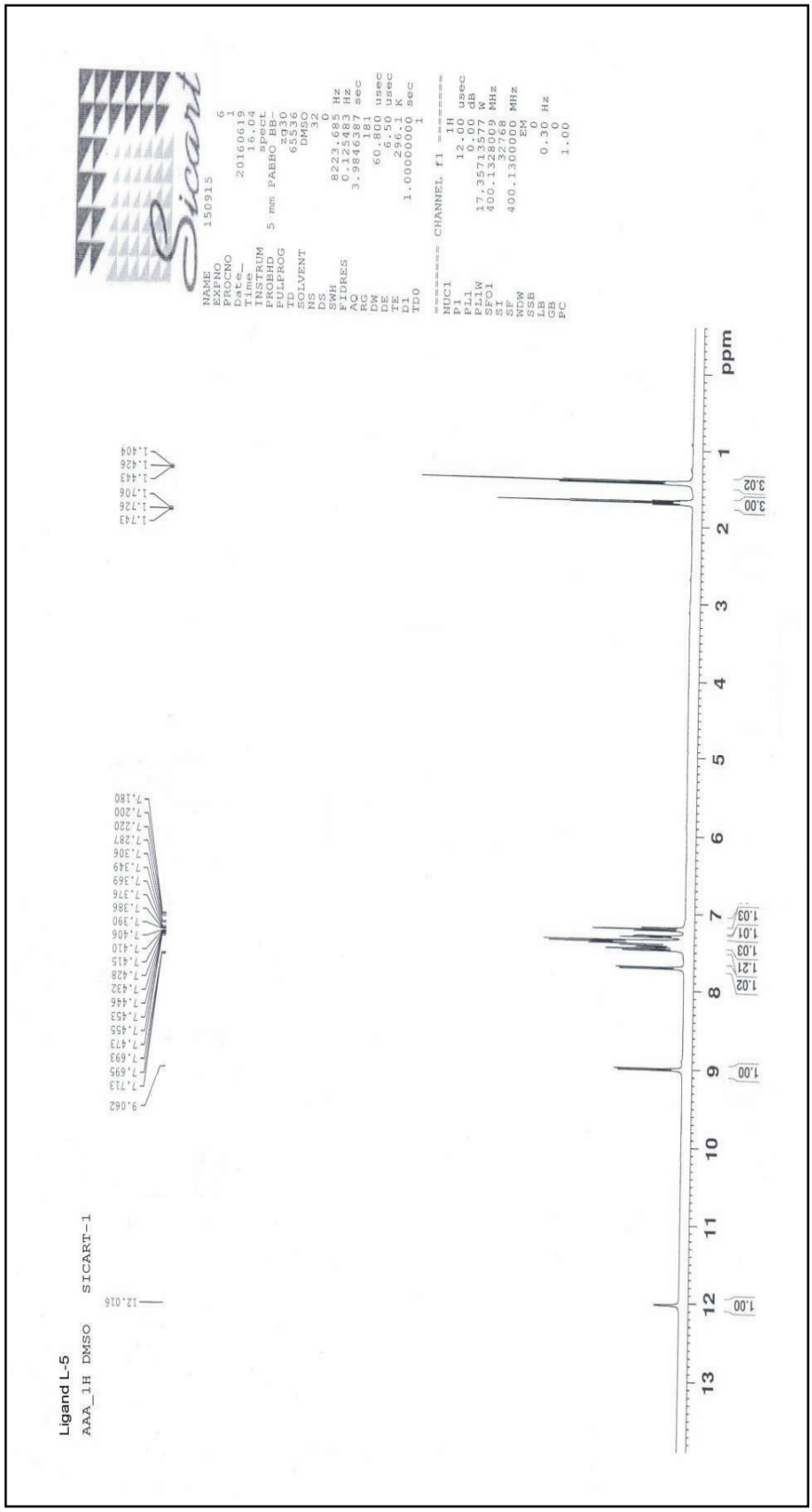


Fig. 3.6: NMR spectrum of ligand TPAS-3

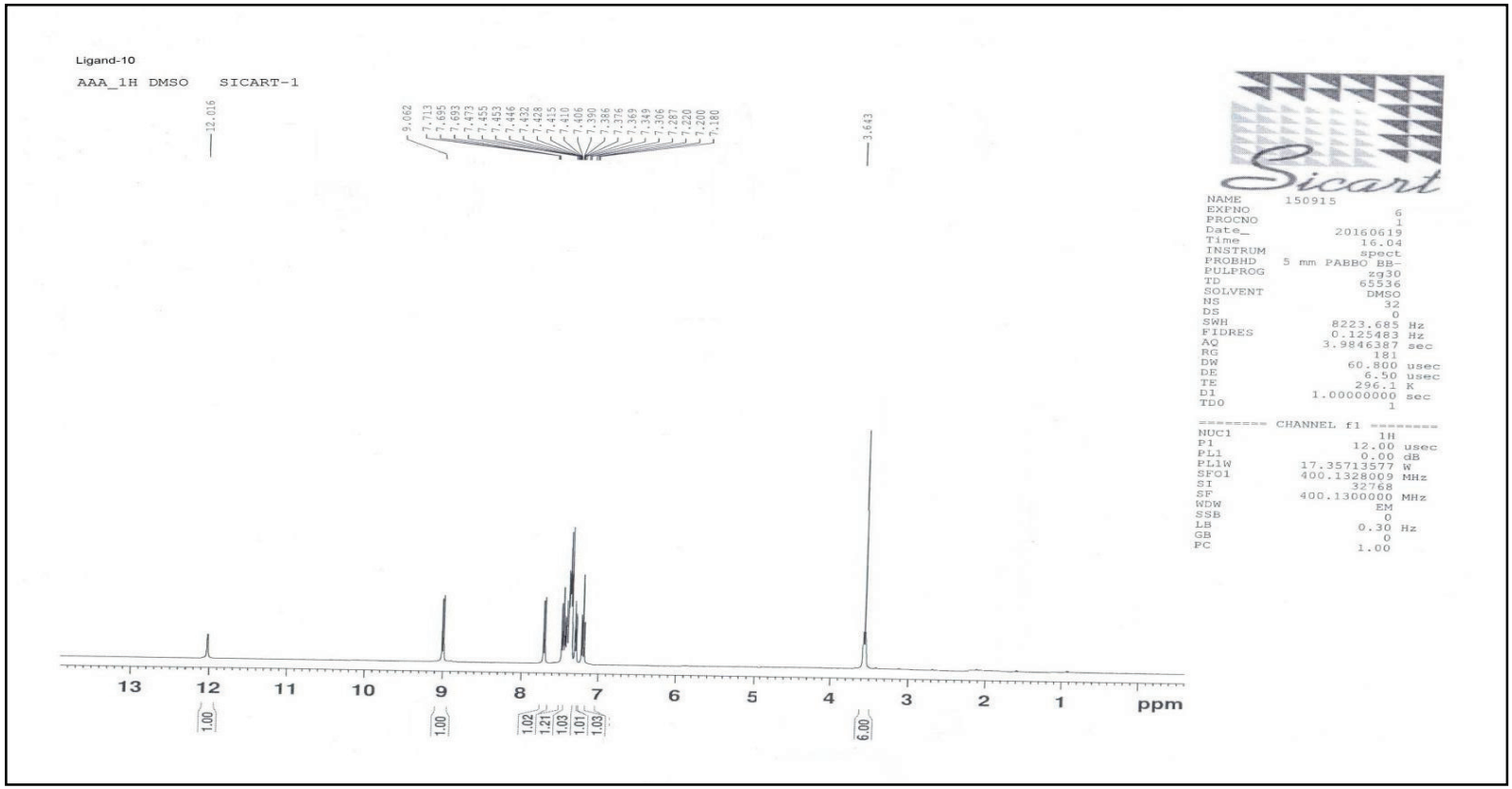


Fig. 3.7: NMR spectrum of ligand TPAS-5

3.3.4 Estimation of Number of carboxylic acid (-COOH) groups in ligands TPAS-1 to TPAS-5 and Bis ligand (TPTB).

The structure of ligand was tested by estimation of number of carboxylic groups (-COOH) per mole of ligands. The nonaqueous conductometric titration was used for -COOH group estimation by method reported in the literature[5]. The titrant used for this non-aqueous titration was tetra-n-butyl ammonium hydroxide (TBAH) in pyridine.

Non-aqueous conductometric titration

The ligand sample was dried at 70°C and finely powdered. This dried sample was used for non-aqueous conductometric titration. Exactly weighed amount of ligand sample was dissolved in 40 mL of anhydrous pyridine.

The solution was allowed to stand overnight for complete solubility. This ligand solution was transferred into conductance cell and it was then stirred magnetically. The base tetran-butyl ammonium hydroxide (TBAH) (0.1 N), in pyridine was added to the conductance cell at regular intervals of 0.01 mL of titrant beyond the stage of equivalence. The conductance measurement after addition of each volume of titrant base was carried out by allowing 2-3 mins lapse. During the titration, the temperature of solution was maintained constant about 25°C when the point of equivalence was exceeded, there was a continuous increase in conductance on addition of every additional aliquot of tetra-n-butyl ammonium hydroxide (TBAH) indicating the stage of complete neutralization of all the –COOH groups in the given amount of ligand sample. The volume of base added is converted into millimoles of tetra-n-butyl ammonium hydroxide required for 100 g of ligand. A plot of conductance against millimoles of tetra-n-butyl ammonium hydroxide per 100 g of ligand sample was plotted in (Fig. 3.8 and 3.9). Inspection of such plot revealed one break. From the plot, the millimoles per 100 g of ligand sample corresponding to the break were noted. From this value, the number of -COOH groups were estimated from this value

- Thus millimoles of TBAH required for complete neutralization of –COOH groups present in the sample was found by following formula using break of the titration curve. Finally one no. of COOH group calculated by:

No. of -COOH Groups per mole of Ligand = Millimoles of TBAH per 100 gm of sample × Molecular weight of ligand × 10^{-5}

$$A = B \times M \times 10^{-5}$$

e.g. For TPAS-2 $A = 247 \text{ X } 401.44 \text{ X } 10^{-5}$

$= 0.99$

Thus value of -COOH group for all the ligands are preferred in Table 3.4.

Results and Discussion:

The Titration Plot of each ligands contain one break so the value of -COOH groups is in the range of 0.99 to 1.02. The values confirming the structures.

Table 3.5: Non-aqueous Conductometric titration of Ligands TPAS-1 to TPAS-5 and Bis ligand (TPTB)

Estimation of –COOH groups.

Solvent: - Anhydrous pyridine.

Reagent: - 0.1 N tetra-n-butyl ammonium hydroxide (TBAH) in pyridine.

Ligands	**Molecular Weight**	**Millimoles of TBAH at break per 100 gm of sample.**	**Estimated No. of –COOH group.**
TPAS-1	407.46	245	1.00
TPAS-2	401.44	247	0.99
TPAS-3	402.42	244	0.98
TPAS-4	452.48	225	1.02
TPAS-5	436.87	229	1.00
TPTB	594.61	168	2.00

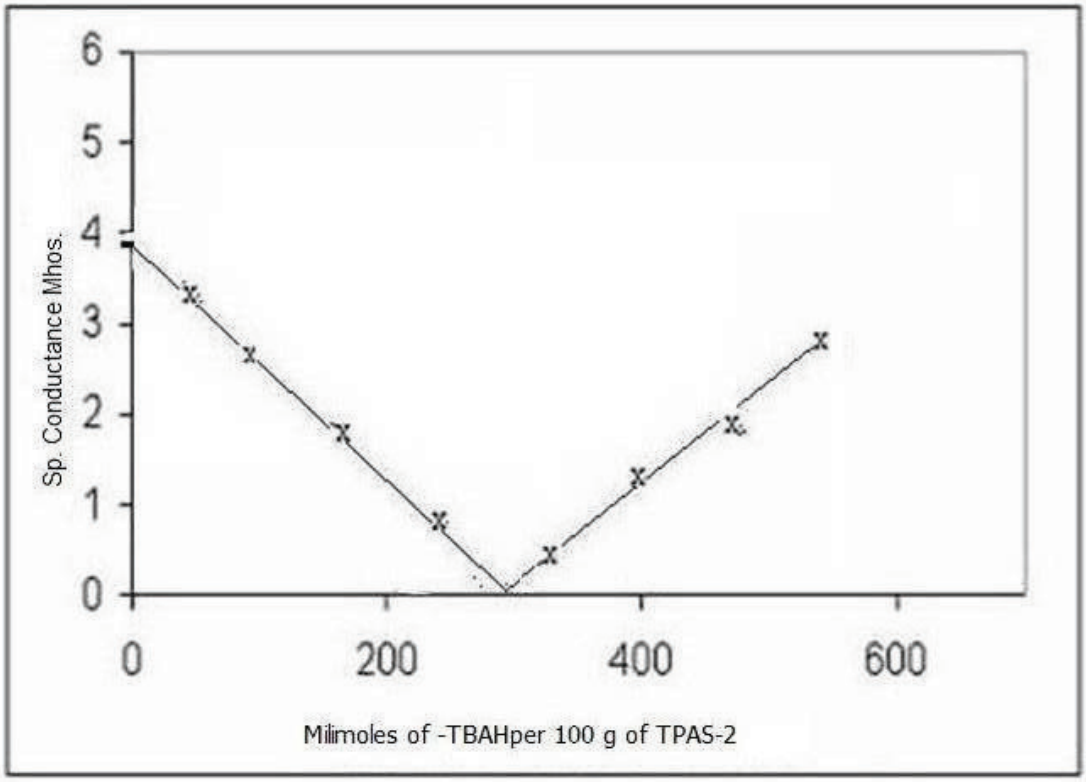


Fig. 3.8: Non-aqueous conductometric titration curve of ligand TPAS-2

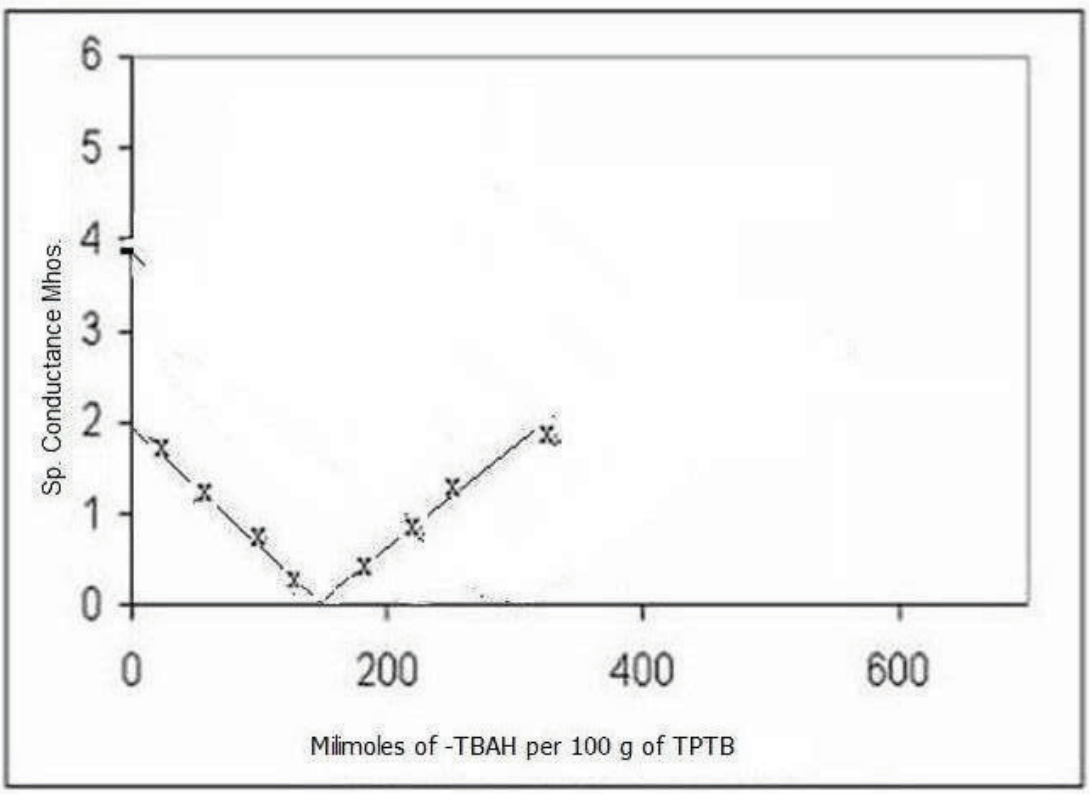


Fig. 3.9: Non-aqueous conductometric titration curve of ligand TPTB

3.3.5 Thermogravimetric study

The TG analysis of all the produced ligand sample was done by "Perkin Elmer Pyris 1 TGA" in an air. The test samples of 5.0 mg was placed in suspended platinum boat. The boat was covered by glass tube and placed in instrument furnace. The heating at the rate of 10^{o}k/min was started with air flow. The automatic plot of wt. of ion vs temperature up to 700^{o}C was obtained. The data were noted and selected TG thermograms are presented in Fig 3.10 to 3.12.

Inspection of the TG plot of all the samples reveals that (i) Each sample degrade in two steps (ii) The initial wt. of ions observed below 200^{o}C - 230 ^{o}C for all samples in the range at 15 to 22%. This value id due to decarboxylation of ligand. The ion of -Co2 is consisted with the value of sample weight. The next step of degrading beyond 230^{o}C was rapid which is depending upon the nature of the ligand.

The calculated value of Co_2 of each ligand and 1st step degradation are shown in Table 3.6.

Table 3.6: Degradation data of ligands

Ligand	Wt. loss in 1st stage of degradation. (%)	Calculated value of decarboxylation (%)
TPAS-1	12.10	12.04
TPAS-2	12.50	12.62
TPAS-3	12.00	11.84
TPAS-4	12.40	12.44
TPAS-5	12.00	12.05
TPTB	11.70	11.68

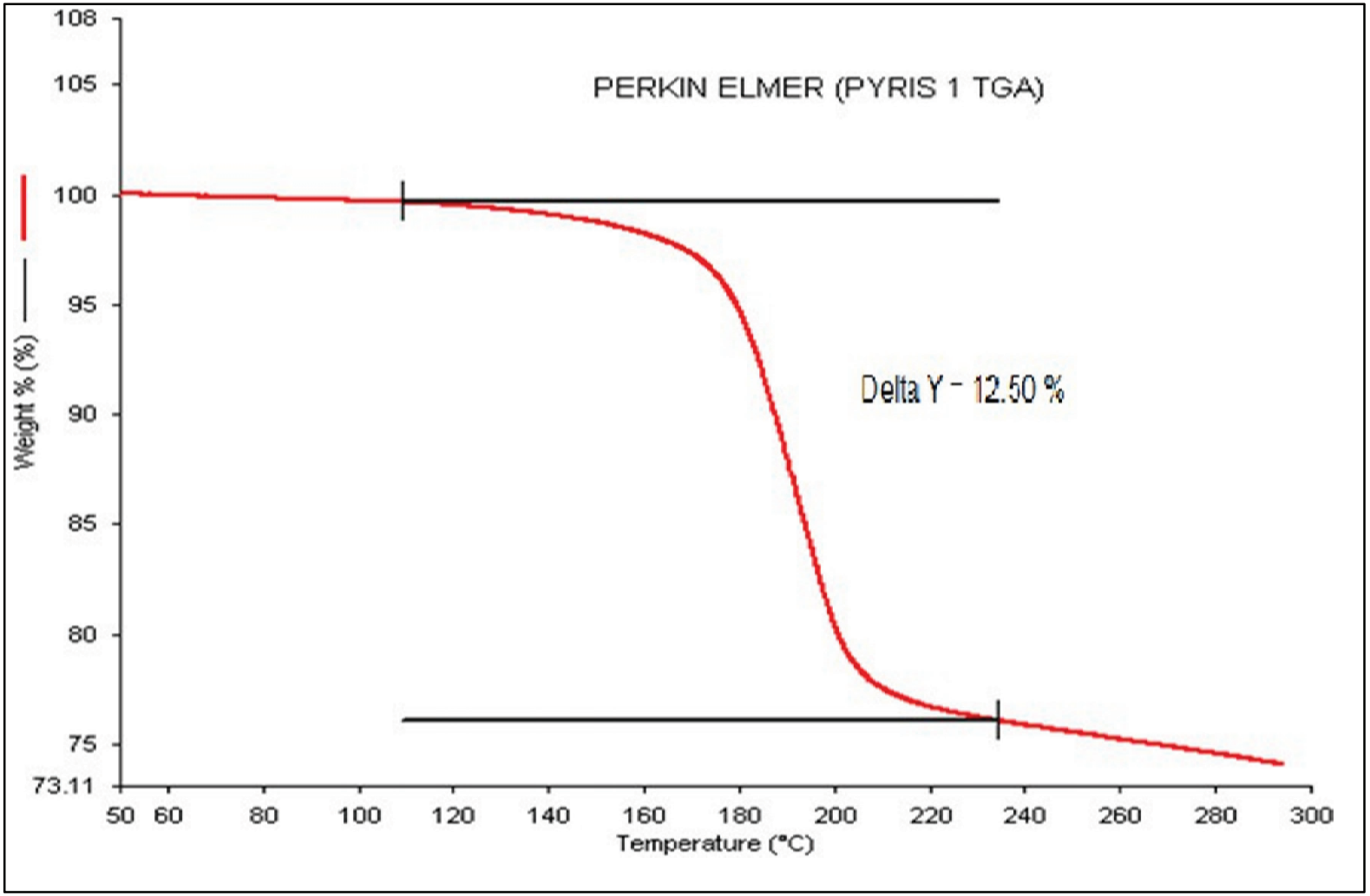


Fig 3.10: TGA thermogram of ligand TPAS-2

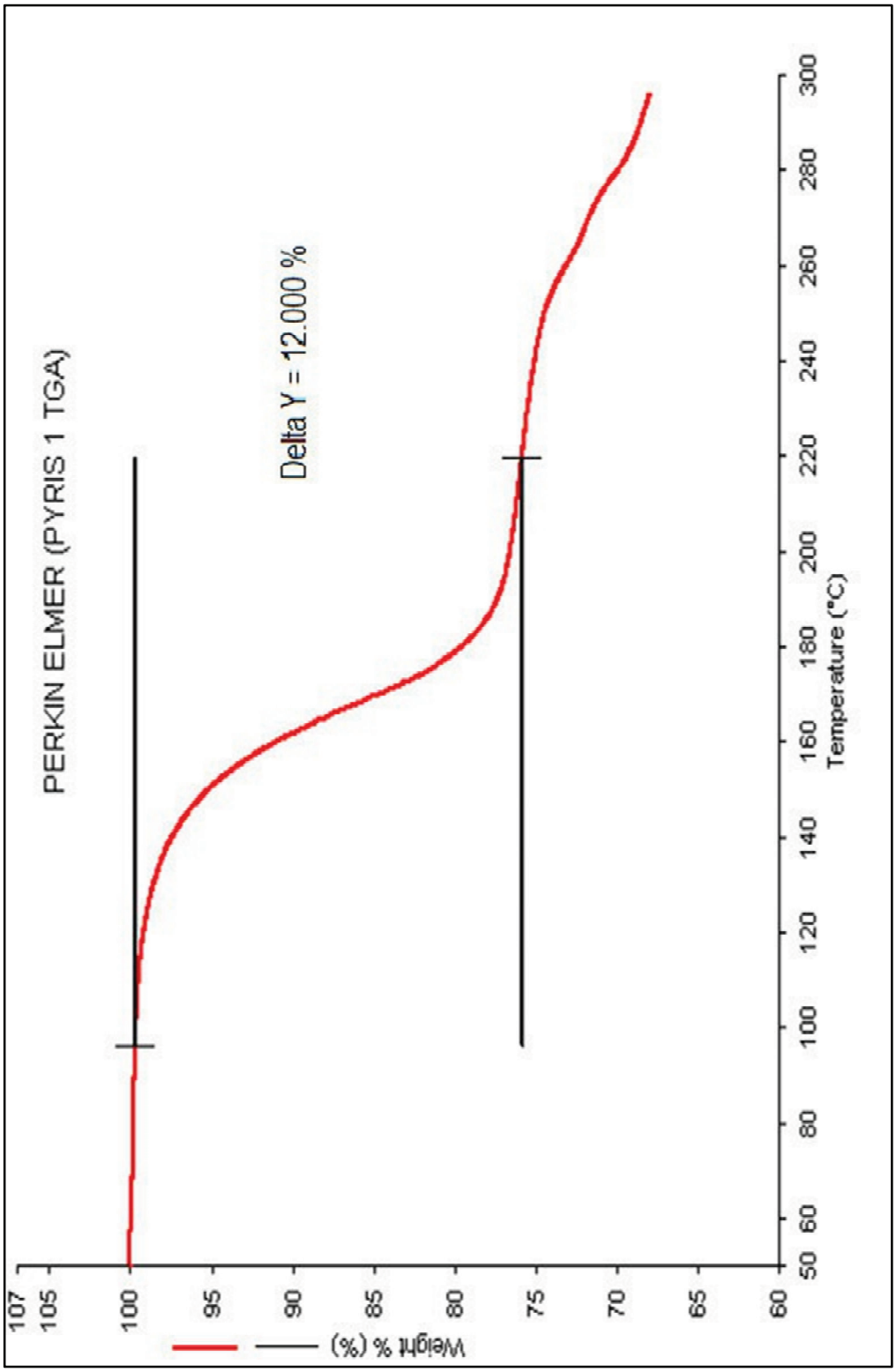


Fig. 3.11: TGA thermogram of ligand TPAS-3

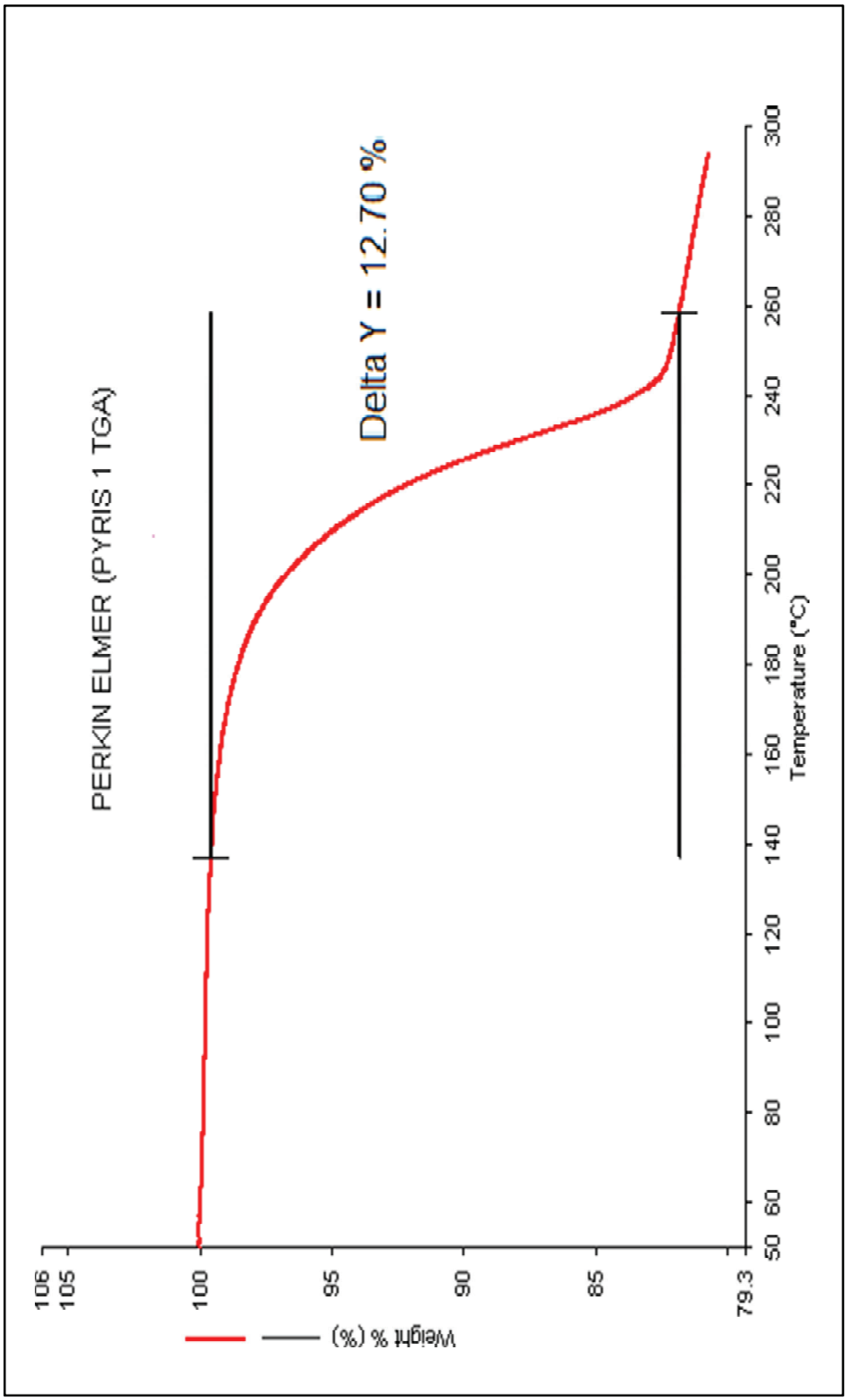


Fig. 3.12: TGA thermogram of Ligand TPTB

3.3.6 Differential scanning calorimeter [DSC]

Differential Scanning Calorimetry is generally applied for determine glass transition temperature and curing temperature, and melting point and exothermic or endothermic reaction of polymer or polymer systems. The ligands TPAS-1 to TPAS-5 and TPTB are big molecules. Their melting points could not be measured properly by capillary method. Hence, their melting points were determined by DSC. The melting point of each ligand was measured on PerkinElmer (Diamond DSC). The value of melting point was observed from DSC thermogram. Typical thermograms are shown in Figs -3.13 to Figure-3.15.

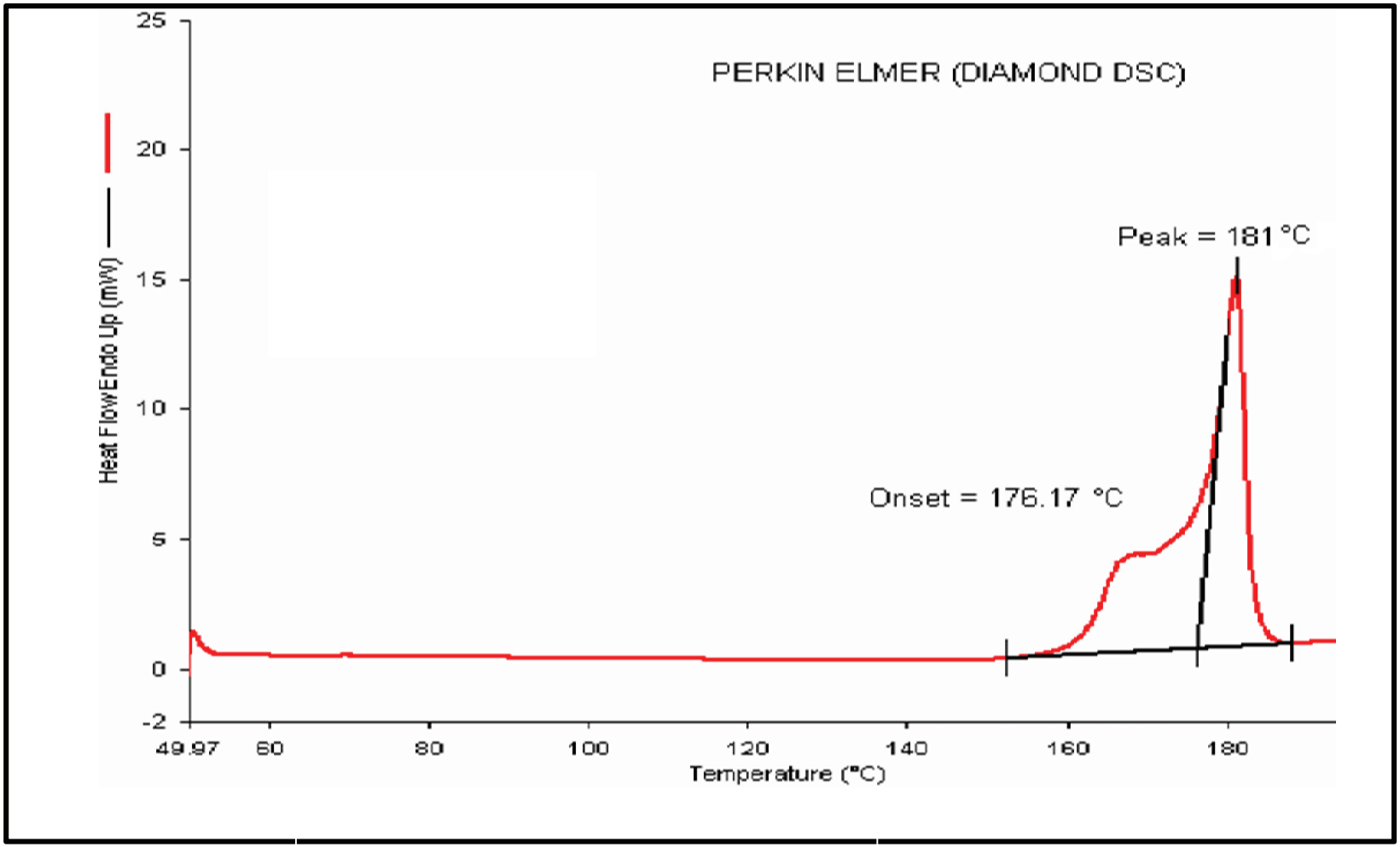


Fig. 3.13: DSC thermogram of ligand (TPAS-

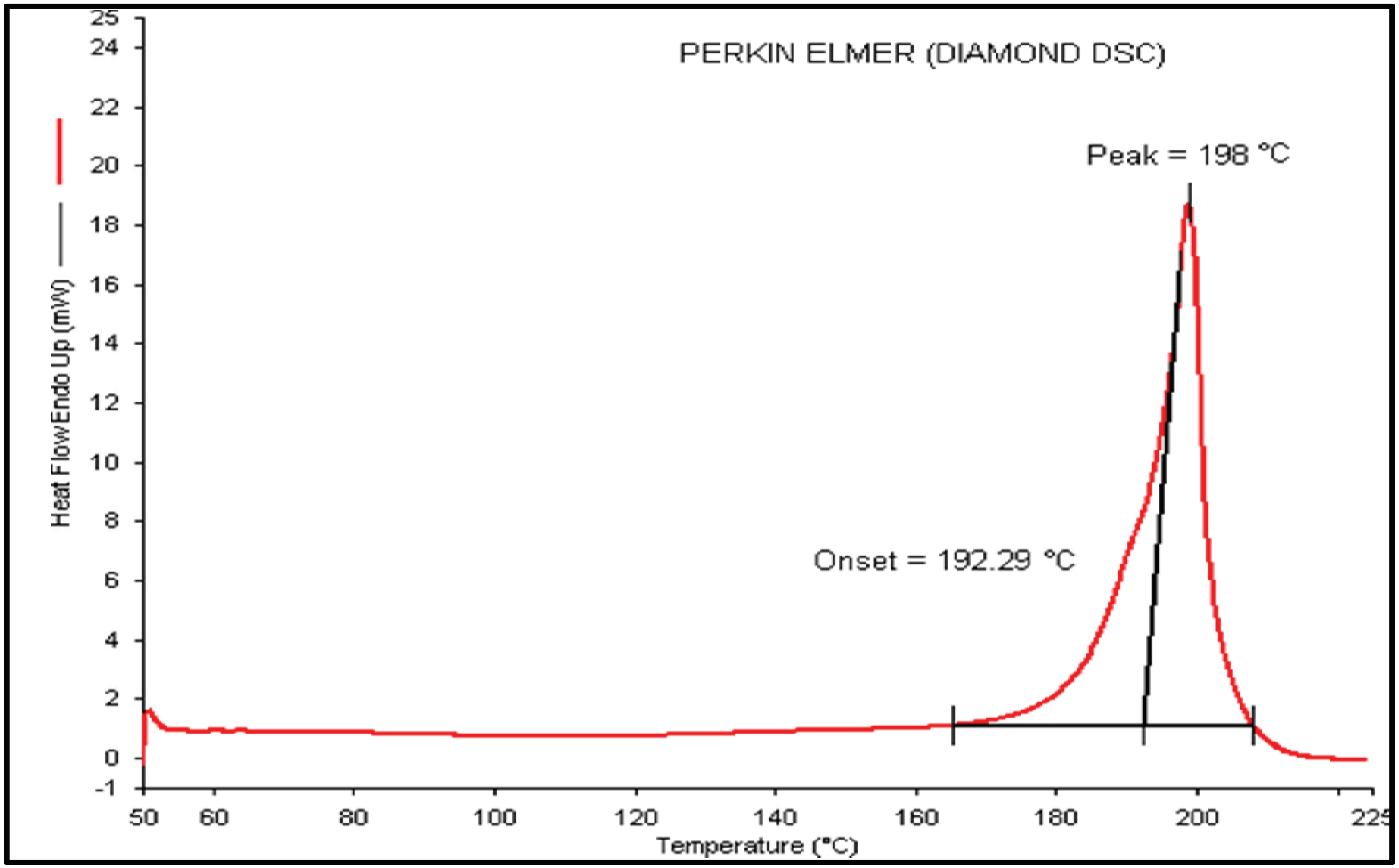


Fig. 3.14: DSC thermogram of ligand (TPAS-

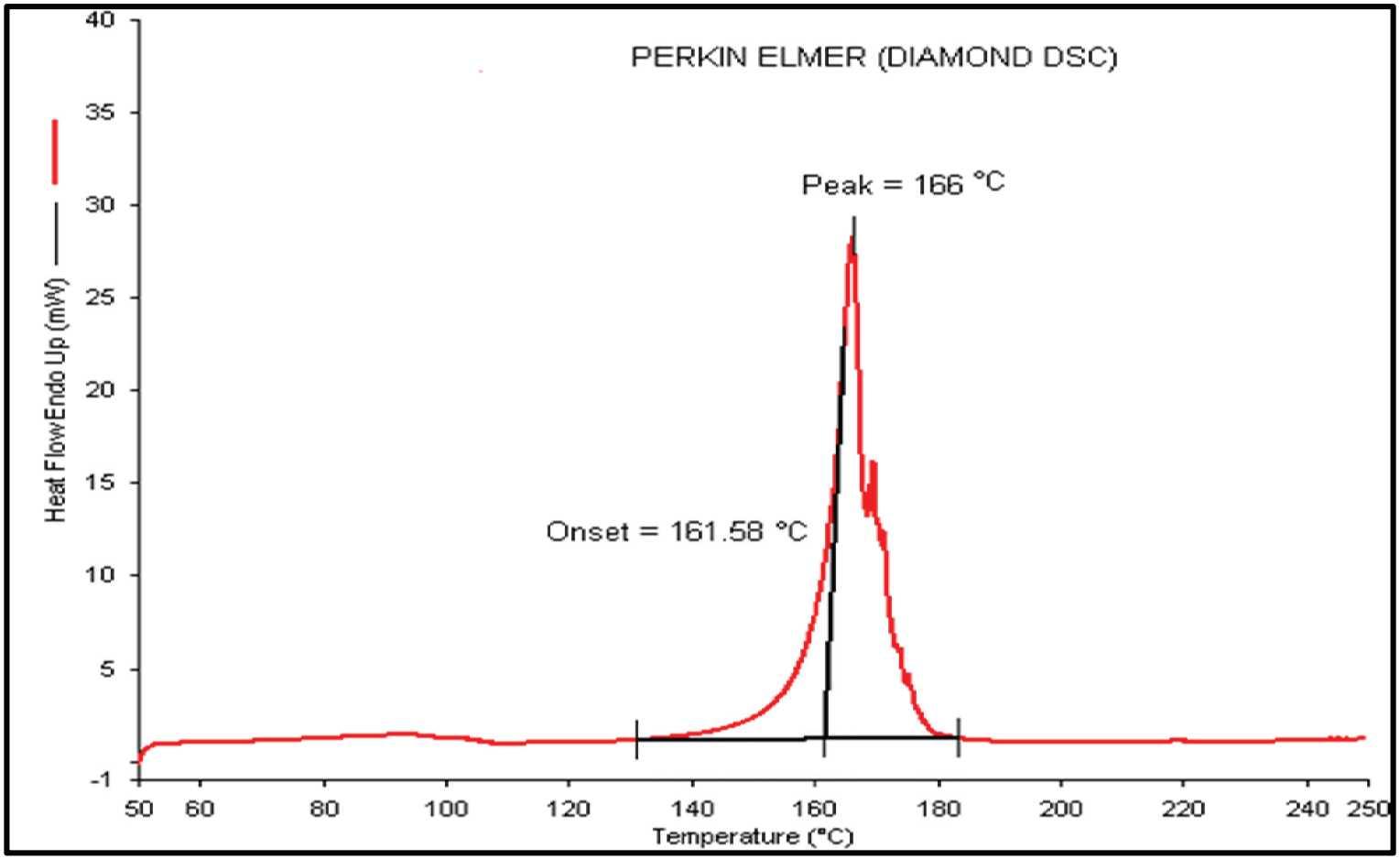


Fig. 3.15: DSC thermogram of ligand (TPTB)

REFERENCE

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