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Synthesis and Polymerization of Crotonic acid – co-Proflavin and substituted with different acid anhydride

Faris H. Mohammed[1]*, Sana H.Awad, SanaA.Saheb

Department of chemistry- College Science / University of Babylon-Hilla-Iraq Bagdad University - Department of chemistry-college science for women-Bagdad-Iraq

Abstract : Series of N- substituted poly crotonic acid **(**A1-A5**)** were prepared in satisfactory yields by reaction of polycrotonic acid (proflavin, phthalic anhydride, citraconicanhydride, methylsuccinic anhydride with The structure of synthesized has been established on the basis of their spectral (FT-IR,1HNMR,). The synthesized compounds were screened for their antibacterial activity against two microorganisms *Staphylococcus aureus, Escherichia Coli* they were found to exhibit good to moderate antibacterial activity. Thermal stability of compound was measured by DSC they were found high thermal stability.
Keywords : crotonic acid, proflavin , antibacterial activities.

Introduction

Phthalimide and *N*-substituted phthalimides are an important class of compounds because they possess important biological activities including anti-inflammatory activity[1], analgesic activity[2] and hypolipidemic activity, and also it is used in organic synthesis and other industrial fields such as in drugs synthesis for the acetylenicphthalimides showed pharmaceutical activity to be anticholinergic agents and anti-Parkinsonian agent[4], survey of the literature has revealed that phthalimides derivative and analogues of their potential in a number of areas such as amino piptidase inhabitation[5]anticonvulsants activity[6] and promotion of tumor necrosis factor alpha (TAIF alpha) production[8] Many amides can be used for the preparation of synthetic polymers, which can be used as insulating coating in electrical equipment9 and plastic heat resistant glass fiber[9].A number of imides also can be used as plant growth regulators and some of them are usefully as herbicides[10,11] also some of them have been employed as inhibitors against mammalian, plant, bacterial and fungal copper-containing amine oxidases[12]. Whereas other substituted phthalimides demonstrated inhibitory effect on the tested microorganisms[13,14], moreover they also employed as prevulcanization inhibitor used in sulphur cured rubber polymer systems[15].Proflavine has been used clinically since 1917[16], but its use as a cytological tool isn't widespread despite its numerous advantages. Its ability to intercalate DNA has provided many applications including anti-cancer, anti-bacterial, and anti-viral drugs[17]. Common research applications include endoscopy and microendoscopy imaging, modalities that benefit from contrast agents that allow for rapid topical staining of intact epithelium, where proflavineis used as a topical contrast agent for histological analysis[18,19]. There has also recently been renewed interest in proflavine for point-of-care diagnostic applications in low-resource settings due to its physical and chemical stability in solution, lasting at least 12 months underrefrigeration[20]Proflavine can be used to rapidly stain fresh cells due to its small molecular size and amphipathic chemistry, enabling the molecule to easily pass through the lipid bilayer of the cell and nuclear membrane[21]strong nuclear contrast[22,23]. Aromatic diamine polymers have a lot of novel functions compared with polyaniline and polypyrrole, such as changeable electro activity, highperm selectivity to various

electroactive species, unique electrochromism, linear sensitivity of conductivity to moisture, regular variation in conductivity with temperature and external electric field, high sensibilities of the polymer-modified electrode to biosubstances at an extremely low concentration, good detecting ability of electroinactive anions, pronounced electrocatalytic properties, effective absorptivity to heavy metal ions, anticorrosion ability, strong adhesion to metal, and high capacitance. In addition, proflavine exhibits less prominent staining of cytoplasmic structures, which can be beneficial for cell classification, allowing for applications in cytological analysis.[25]

Experimental:-

2.1. Materials And Instruments:-

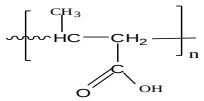
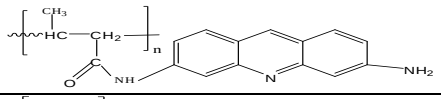
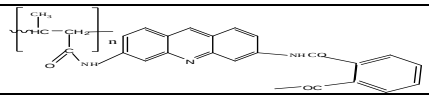
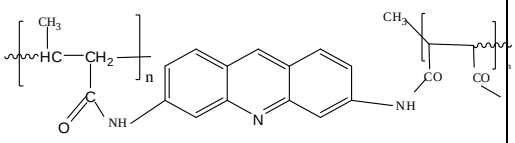
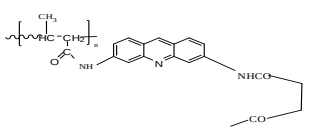
Crotonic acid was obtained from Aldrich. Dimethylformamide was purchased from Merck. 1H-NMR spectra were recorded on a Shimatzu spectrophotometer in Dimethylsulphoxide (DMSO). The FTIR spectra were recorded by (4000-400cm-1) on a Shimatzu spectrophotometer. Melting points were determined on call Enkamp MF B-600 Melting point apparatus.

2.1. Methods of preparation:

2.1.1A-:Synthesis of N- substituted poly crotonic acid :-

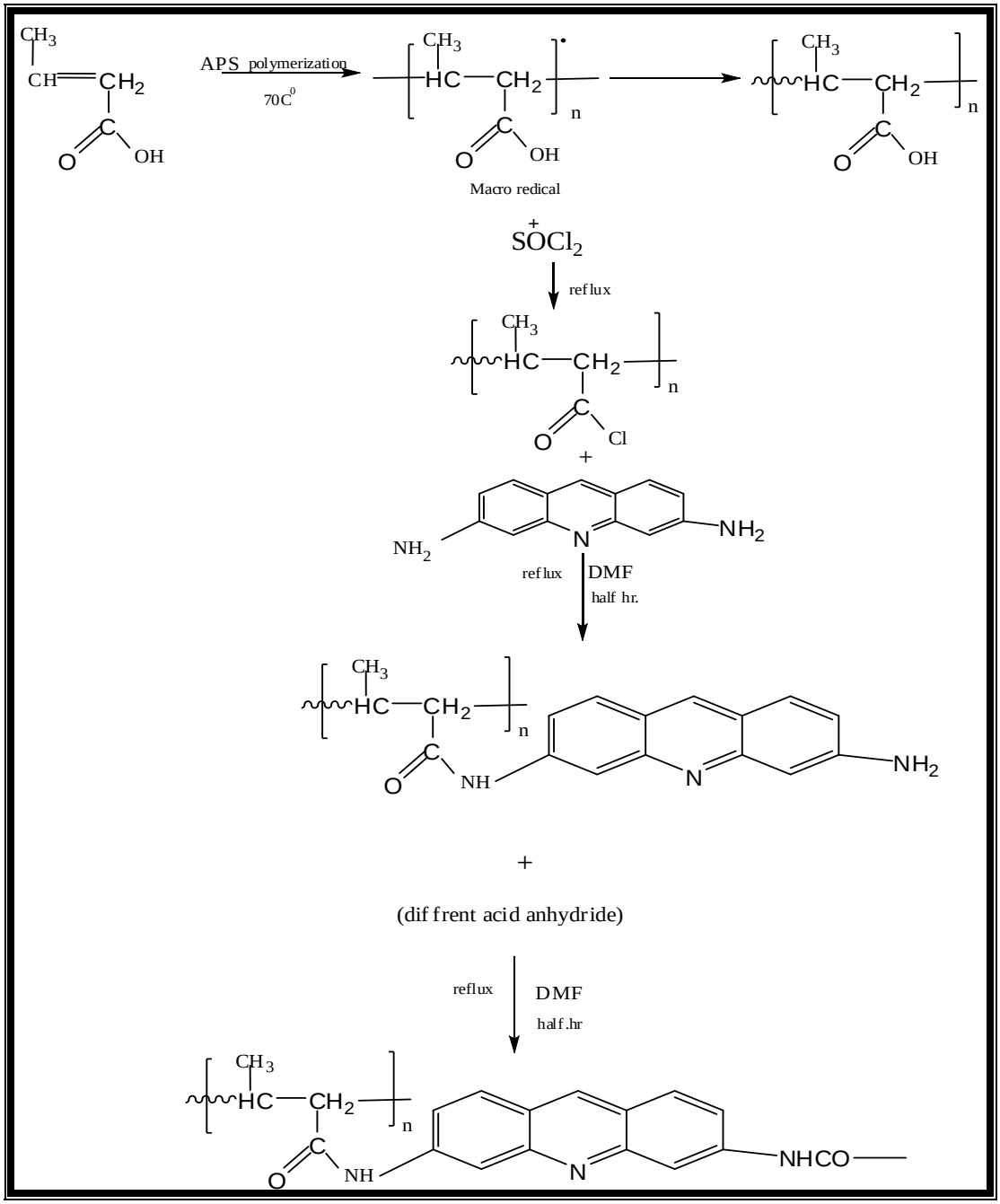
(1gm,0.013mol) of crotonic acid ,(0.1 gm) of APS dissolved in 1ml of distilled water introduced in polymerization bottle it was flashed with nitrogenfor few minutes inside a glove box and firmly stopped the mixture was heated at $70C^0$,using water bath for 15minutes .the yellow product (A1)was cooled and washed with ether. (1gm,0.00471mole) proflavine dissolved in 10ml of ethanol was added to(A1) the mixture was refluxed about 1hr .the orange viscous polymer (A2)was separated and reprecipitate with ether . (0.9gm) of (A2)dissolved in 10ml of DMF and(1.48gm, 0.01 mole) of Phthalic anhydride was added to (A2) the mixture were refluxed in (50 ml) acetic acid for 4hour.The brown precipitate (A3) was filtered and the solvent was evaporated ,The solid separated was filtered and re- precipitate from ethanol, same producer used to prepared other anhydride(citraconicanhydride, methylsuccinicanhydride) . The physical properties shown in Table(1)

Table (1) Physical properties of compounds

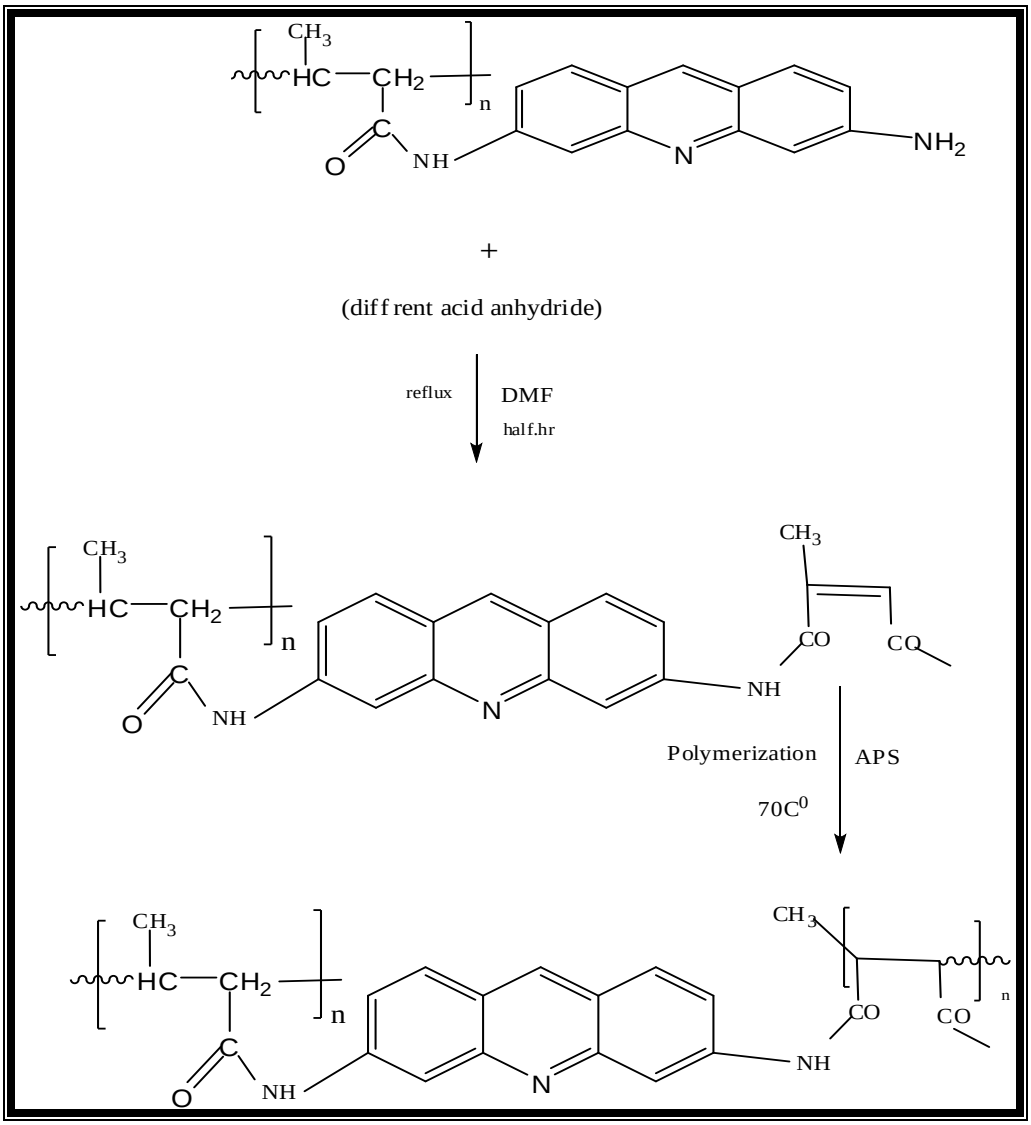
Comp. No	compound	Color	m.p	Yield%
A_1		Yellow	227	85
A_2		Orange	234	77
A_3		brown	271	74
A_4		yellowish	277	63
A_5		red	248	65

Result and Discussion:

The product (A_1-A_5) was formed by the polymerization of crotonic acid using of ammonium persulphate as initiator. Polycrotonic acid reaction with one group of amine of proflavine explained in scheme (1), the second group of proflavin was used to ring opening of different acid anhydride.



Scheme(1) Mechanism of reaction



Scheme (2)substitution and polymerization ofcitraconic anhydride

Figure(1) indicates the FTIR spectrum ofA1. The –OH stretching of PCA (attached at the chain end) appeared at 3371cm–. The aliphatic symmetric and antisymmetric stretching could be seen at 2970 and 2860 cm –1 respectively. The amid carbonyl stretching from PCA-co-Proflavin(A2) segments were noted at 1647 cm^{-1} [26]. The infrared of products(A2) exhibited characteristic peak at (1703)cm-1 due to ν (C=N) absorption band (3078cm-1) due to NH[27].Other Compound show different absorption showing in the table (2).

Table (2) FT-IR compound [A1-A5]

No. of com.	C=O cm-1	C=N cm-1	N-H	C=C Arom	C-H cm-1 Aram.	C-H cm-1 Aliph.	O-H cm-1	C-C cm-1
1A	1656					2970 2860	3371	1460
2A	1647	1703-1614	3078	1481	3082	2959-2800		1450
A3	1650	1778	3183	1460	3190	2966-2800		1456
4A	1600	1778	3190	1456	3190	2966-2800		1433
5A	1643	1730	3188	1465	3111	2970-2879		1435

NMR spectral study

The ^{1}H.NMR spectrum of compounds (1) shows Characteristic Signals at (d,1.226) to (d,1H tic-CH) respectively. Also signal at (δ 3.024) (s,3H,CH_3) and at (δ 3.644-4.018) (s,1H,-O-H) The ^{1}H.NMR spectrum of compounds (2) shows Characteristic Signals at (δ 6.56-7.501) due to (m,5H aromatic-CH) respectively. Also signal at (δ 2.5) (d,2H,CH_2) (s,5.29,1H,C=-O-NH) signal at (δ 1.5) (d,2H,CH_3) (d,4.59,2H,NH2)[28].

The ^{1}H.NMR spectrum of compounds (3) shows Characteristic Signals at (δ 7.01-8) due to (m,5H aromatic-CH) respectively. Also signal at (δ 2.5) (d,2H,CH_2) (s,7.0,1H,C=-O-NH) (δ 2.1) (d,2H,CH_3) (s,5.29,1H,C=-O-NH) The ^{1}H.NMR spectrum of compounds (4) shows Characteristic Signals at (δ 7.226-8.501) due to (m,5H aromatic-CH) respectively. Also signal at (δ 3.5) (q,2H,CH_2) and at (δ 3.644-4.018) (s,1H,C=ONH

Also signal at (δ 3.8) (q,2H,CH_2) and at (δ 2.844-4.018) (s,1H,C=ONH) The ^{1}H.NMR spectrum of compounds (5) shows Characteristic Signals at (δ 7.66-8.501) due to v3.644-4.018) (s,3H,C=ONH) Also signal at (δ 3.024) (s,3H,CH_3) . Also signal at (δ 3.5) (q,2H,CH_2) and at (δ 3.1(s1H,C=ONH)

DSC study

This high thermal resistance indicated the high molecular weight of the prepared polymers with high interaction through the polymer chain and the drug in compound (A4) .

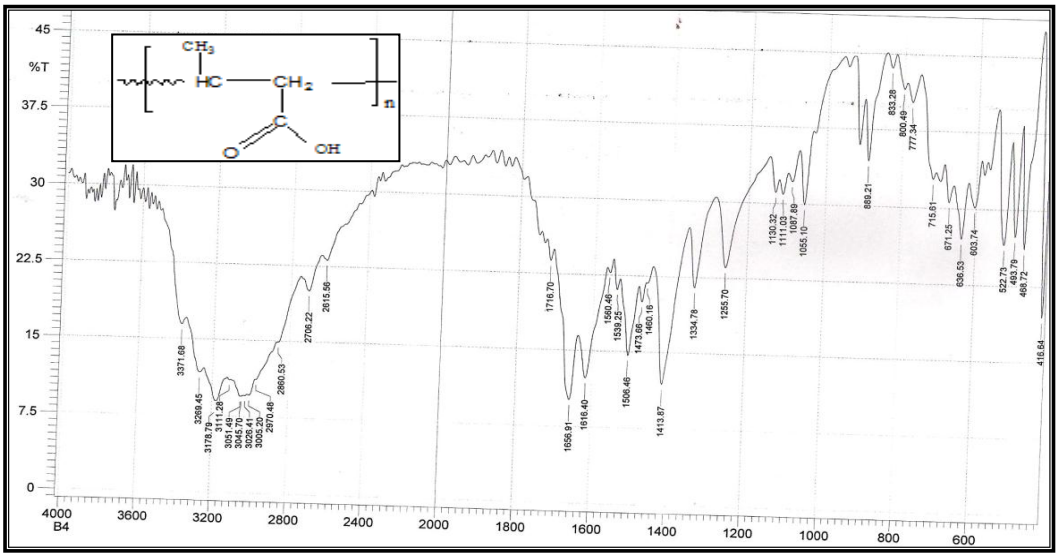
Biological study:-

Antimicrobial activity

The antimicrobial activity of both categories of compounds was determined by the disc diffusion method. The *in vitro* antimicrobial activity was carried out in gram positive bacteria, gram negative bacteria The gram positive bacteria used were *Staphylococcus aureus*and gram negative bacteria used were *Escherichia coli. The* compounds were tested at a concentration of 100μg/ml in Dimethylsulfoxide. The zone of inhibition was compared after 24 h of incubation at 37° against Ciprofloxacin (100μg/ml) as standards for comparison of antibacterial activity (table 3) In general, all synthesized compounds exhibited good inhibitory activity against tested pathogenic microorganism (***S. aureus, , E. coli,)*** against [29]

Table(3) :Antibacterial activity of prepared compounds

Comp. No.	***Inhibition zone diameter(mm)***	
	Staphylococcus aureus	***Escherichia coli***
A1	16	7
A2	15	6
A3	16	8
A4	16	10
A5	14	6
DMSO	-	-



Figure(1) FT-IR spectrum of A1

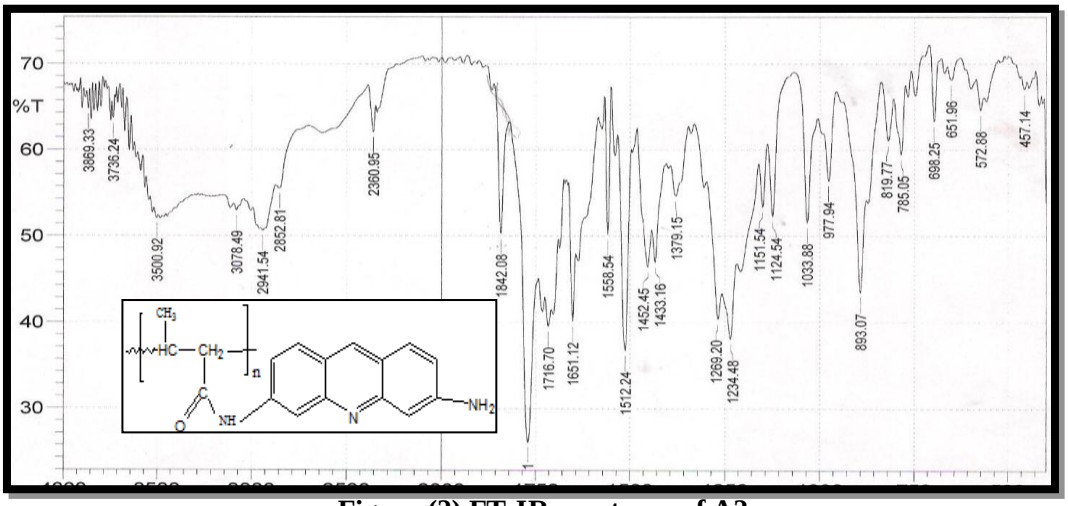
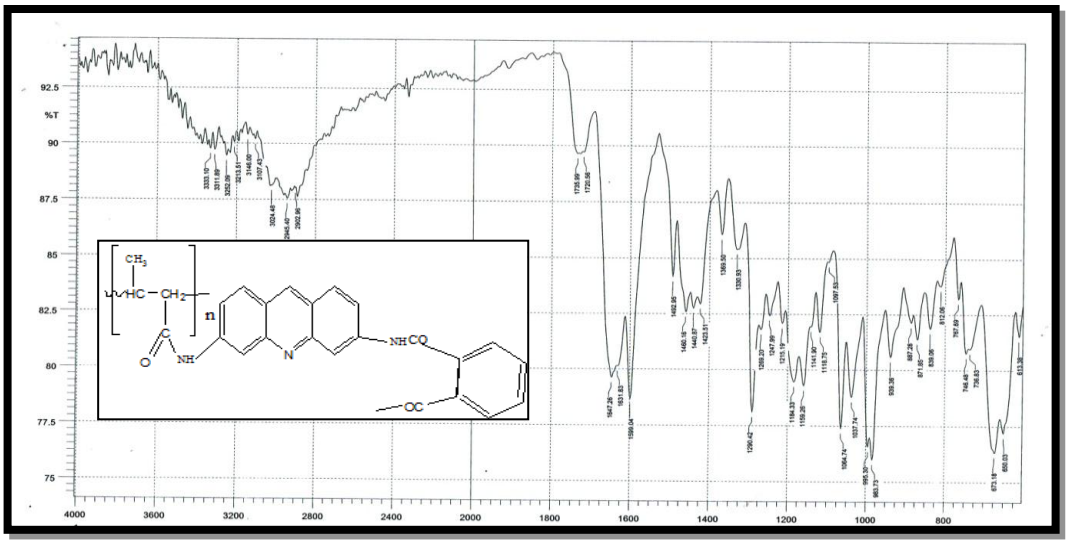
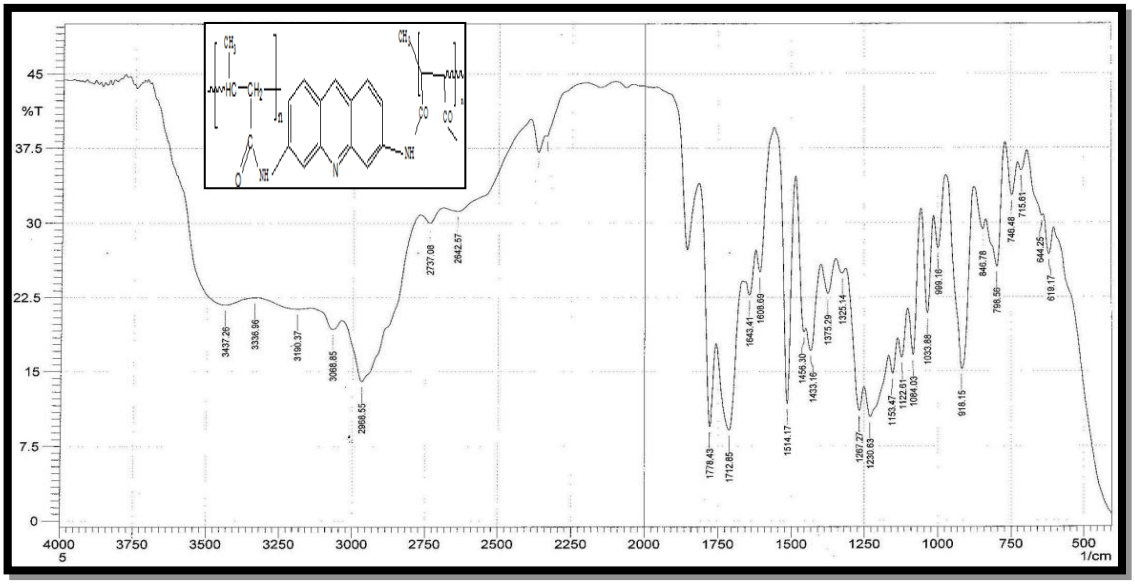
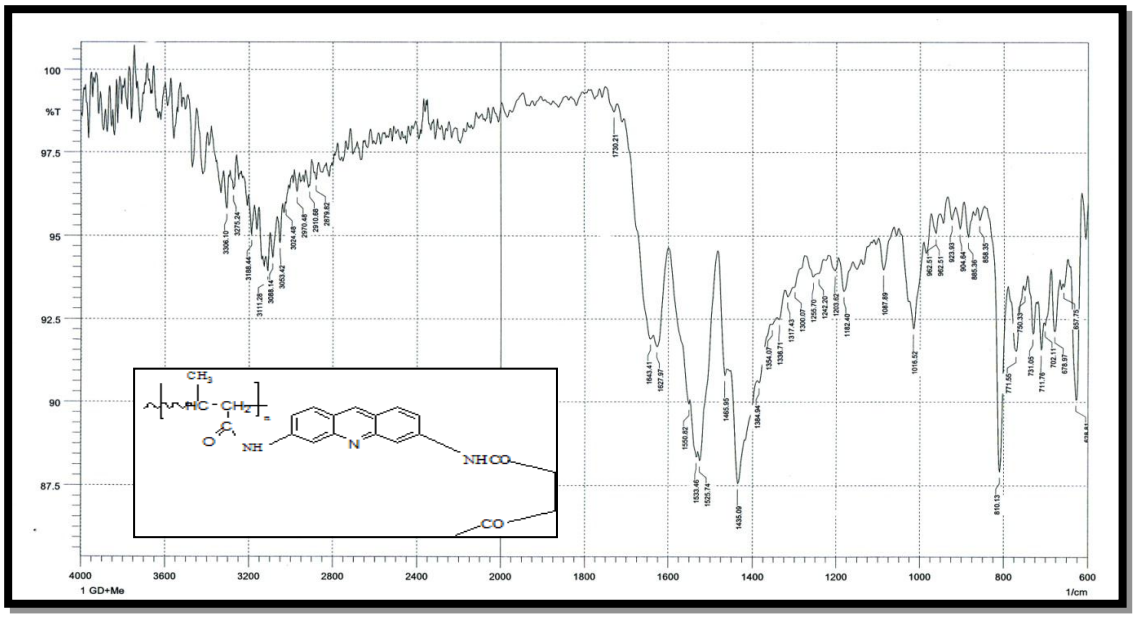


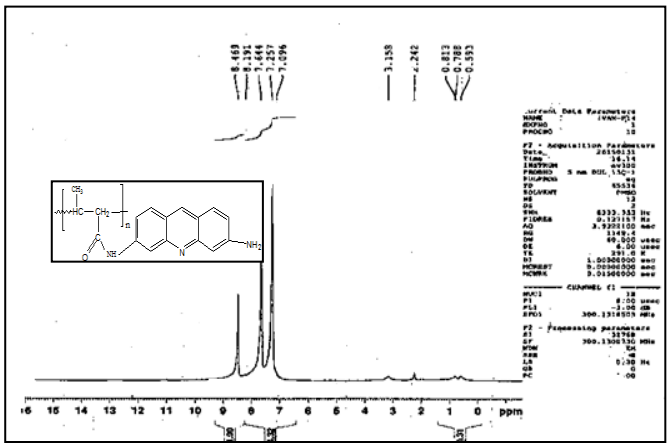
Figure (2) FT-IR spectrum of A2



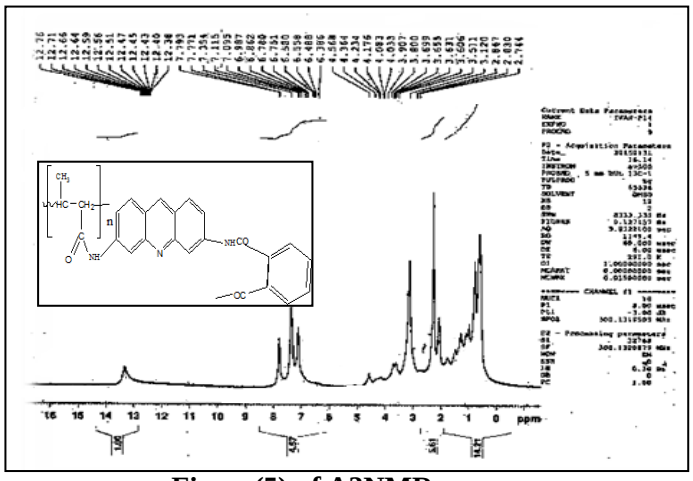
FT-IR spectrum of A3Figure (3)



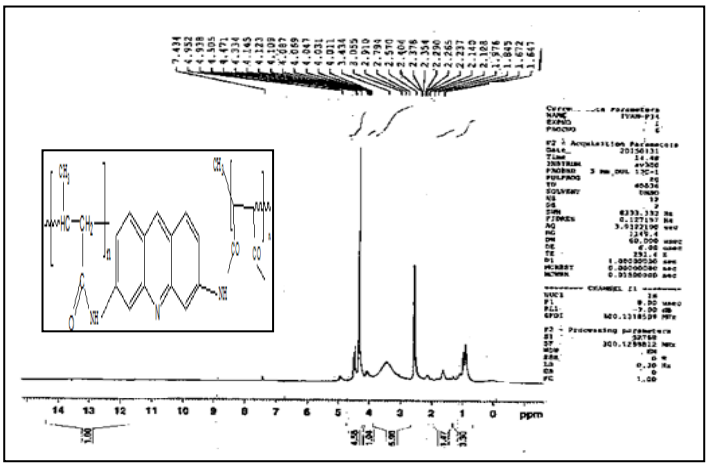




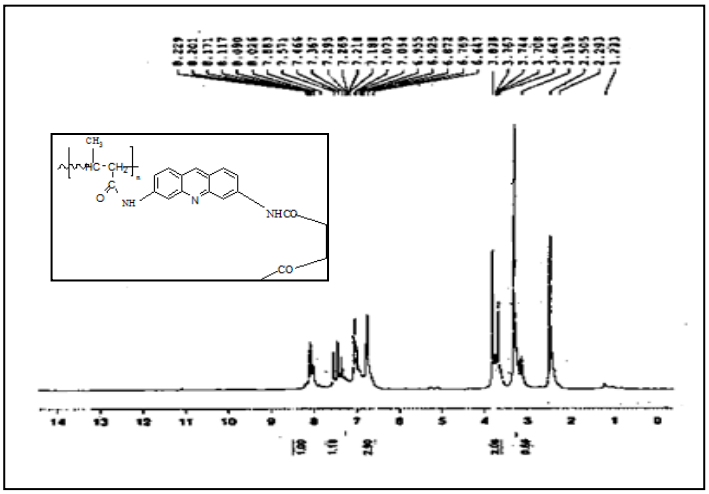
Figure(5) of A2NMR



Figure(5) of A3NMR



Figure(5) of A4NMR



Figure(5) of A5NMR

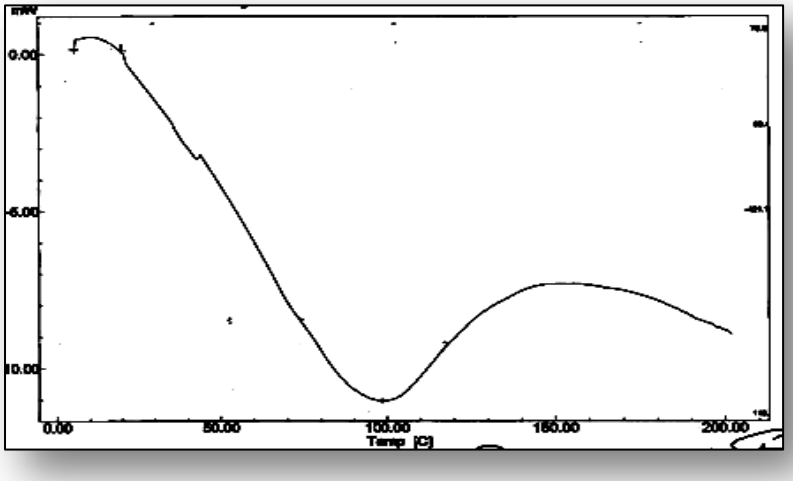


Figure (6) Thermal analysis (DSC) of compound (A1))

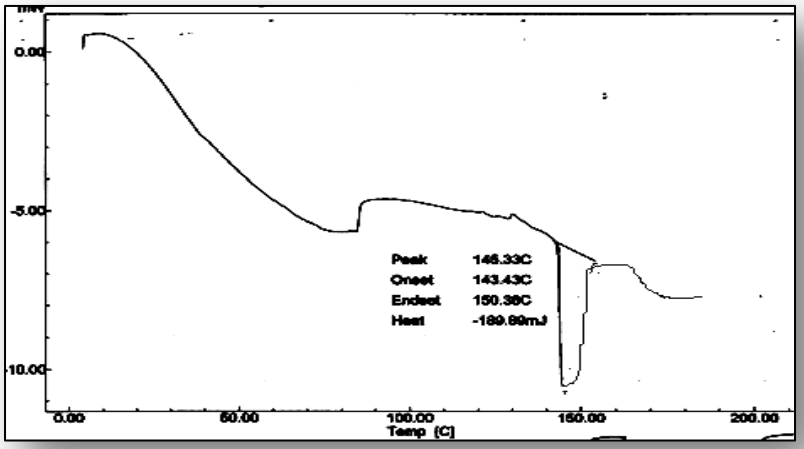


Figure (7) Thermal analysis (DSC) of compound (A2))

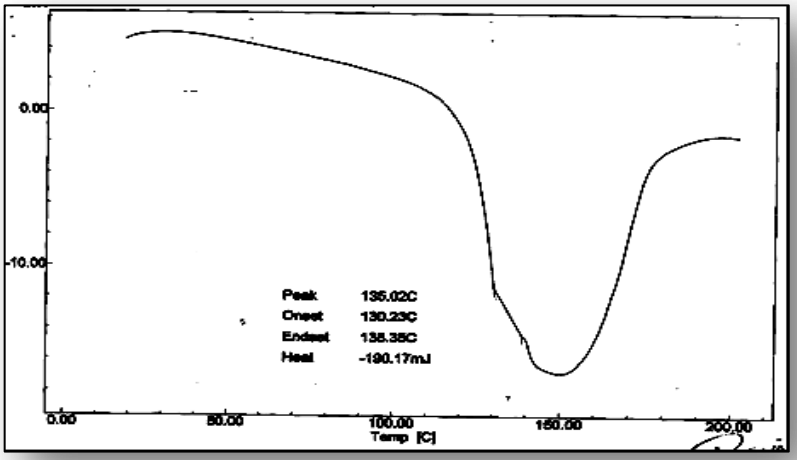


Figure (8) Thermal analysis (DSC) of compound (A3))

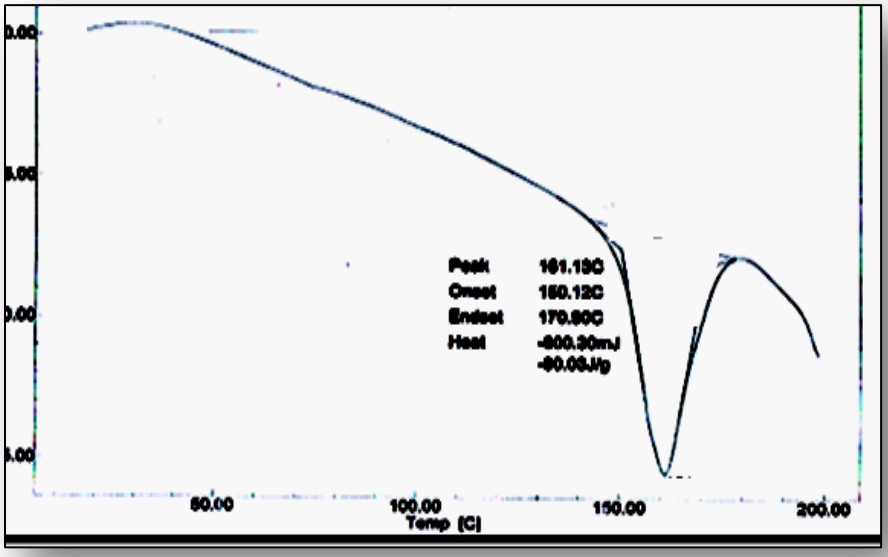


Figure (9) Thermal analysis (DSC) of compound (A4))

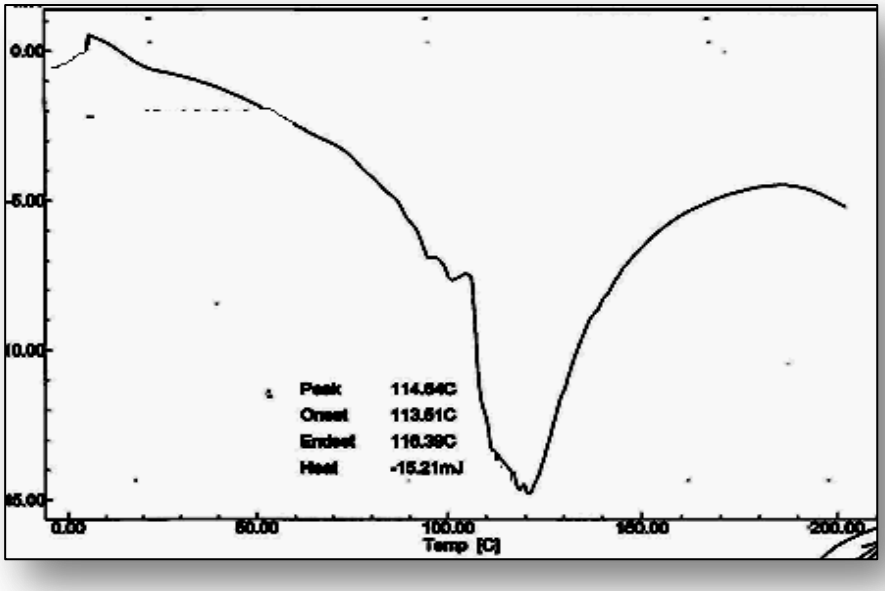


Figure 10-Thermal analysis (DSC) of compound (A5))

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