New prodrug polymers functionalized based on Maleimide

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New prodrug polymers functionalized based on Maleimide

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Abstract. In this work, three new drug substituted monomers and new homogenous and heterogeneous polymers were synthesized which loaded with medical properties to extend the controlled drug. The first step includes preparing Maleimic acid (L_1) and (L_2) via reaction of maleic anhydride with 5-amino salicylic acid. Then compound (L_2) was converted to its corresponding acyl chloride derivative which reacted with amino drug (Pseudoephedrine, 4-aminoantipyrine, Paracetamol) afforded (L_3-L_5) monomers. Homogeneous polymers (L_6 and L_7) prepared through polymerization reaction of the free radicals of the monomers (L_1) and (L_2) under nitrogen using (MEKP) as initiator. Heterogeneous polymers (L_8 and L_9) prepared through polymerization reaction of the free radicals of the monomers (L_1), (L_2) separately with acrylic acid under nitrogen using (MEKP) as initiator. All these prepared monomer and polymers were characterized by FT-IR and ^{1}H-NMR, ^{13}C-NMR techniques. Controlled drug release and swelling % was studied in different pH values at 37 °C. Intrinsic viscosities were measured at 25°C with Ostwald viscometer and applied the characteristic of solubility for these polymers. The physical properties of all prepared monomer and polymers were studied.

1. Introduction

Maleic anhydride is a chemical compound which used in many applications of industrial chemistry [1]. Maleimides derivatives prepared from maleic anhydride by treatment with amines followed by dehydration [2]. N-substituted maleimides are prepared from the amino group is replaced with alkyl or aryl groups, respectively followed by ring closure to afford the target molecule [3,4]. Maleic anhydride easily polymerized in the presence of free radical catalysts as well as under gamma and UV radiations [5-7]. Prodrug polymers have been used in various bioactive applications [8]. They are converted into the main active drug in the organism by chemical or enzymatic reactions or by combining the two. [9-11]. Prodrugs designed to improve the absorption of drugs from the gastrointestinal tract and to improve selectively the drug interacts with cells or processes that are not its intended target [12]. Pharmaceutical modification used to improve absorption, secretion, metabolism, and reduction the toxicity of drugs [13,14]. Functional groups with the ability to design adjuvant drugs include the most common compound substances such as carboxylic acid, phosphate amine, hydroxyl, and carbonyl aggregates. A drug assistant is usually produced to compensate for these aggregates (oxides, esters, amides, carbonates, phosphates)[15]. In order to examine the possibility of obtaining better polymers

from N-substituted maleimide, we reported here the synthesis of N-[5-salicylic maleimide] monomer and its polymerization and co-polymerization with acrylic acid. The physical, chemical and thermal properties have been studied to characterize the prepared compounds.

2. Experimental and Methods

The densities of polymer samples were determined at 25 °C by the displacement method with a single stem pycnometer [16] using water as a non-solvent. The intrinsic viscosity [ ] measurements were carried out in acetone at 30°C using an Ostwald Viscometer suspended level viscometer. The IR spectra measurements were recorded using a device Fourier Trans Infrared Spector Promoter –Shimadzu within range (400 4000). ^{1}H NMR was taken at 300 MHz in DMSO-d6 on a VXR-300 spectrometer. TMS was used as reference. ^{13}C NMR spectra were recorded at 75.5 MHz in DMSO-d6 on Bruker-300A spectrometer. Starting chemical compounds were obtained from Fluka or Aldrich.

2.1 Preparation of Maleimic acid Compound (L_1) [17-18].

Mixture of maleic anhydride (1.0 gm, 0.002 mmol.) with 5-aminosalicylic acid (0.7gm, 0.005 mmol.) with constant stirring for 30 min. The reaction mixture was cooled externally and the greenish yellow solid 5-aminosalicylic maleimic acid was filtered and dried at 50 °C afforded compound [L_1] molecular formula $C_{11}H_9O_6N$ (**Scheme 1)**, color: Greenish Yellow, yield: 93%, m.p = 191 - 194°C. It was recrystallized from ethanol. FTIR (cm^{-1}): 3307 (OH Alcohol), 2500 and 3500 (OH, carboxylic acid), 1677 (C=O, six membered imide ring), 1526 (C=O, carboxylic acid), 1484 and 1447 (C=C, aromatic), 1377 (C-H bending), 1191 (C-N stretching), 846 (cis-CH=CH, phenyl ring). ^{1}H NMR (300 MHz, TMS, , ppm):4.14 (s, H, OH), 6.43, 6.98 (2H, HC=CH), 7.15 (s, H, Ar-H), 7.69 (s, H, Ar-H), 7.86 (s, H, Ar-H), 8.15 (s, H, N-H), 10.41(H, COOH), 10.57 (H, COOH). ^{13}C NMR (300 MHz, TMS, , ppm): 142.859 (2C, HC=CH), 112.897 (C, C-OH), 133.321 (6C, Ar-C), 117.233, 157.590 (C, N-C=O), 162.959(C, COOH), 166.668 (C, COOH). Anal. Calcd. for L_1: C, 52.689; H, 3.585; N, 5.577%; Found: C, 52.677; H, 3.601; N, 5.598%.

2.2 Preparation of Compound 5-SMI (L_2).

Maleimic acid (0.50 g, 0.1mol), (0.33 g, 0.2mol) sodium acetate and 5mL Ac_2O in 5mL DMF were mixed and heated for 2h at 45°C. The cooled mixture was poured into crushed ice to produced a yellow needles of 5-SMI which filtered, washed with 5% NaHCO solution and dried at 55°C for several hours. The product was further recrystallized from chloroform afforded target molecule (**Scheme 1)**. Compound [L_2]: molecular formula $C_{11}H_7O_5N$, color: Black (Viscous) , yield: 91%. FTIR (cm^{-1}): 3287 (OH, alcohol), 3106 (C-H), 2982 and 2918 (C-H) ,1709 (C=O, six member imide ring), 1663 (C=O, amide), 1553 and 1492 (C=C, aromatic), 1439 (C-H bending), 1288 (C-N stretching), 827 (phenyl ring). ^{1}H NMR (300 MHz, TMS, , ppm): 5.70 (s, H, OH), 7.51-8.71 (m, 3H, Ar-H), 6.8-7.30 (d, 2H, HC=CH), 10.56 (s, H, COOH). ^{13}C NMR (300 MHz, TMS, , ppm): 29.649 (C, CH_3), 31 (C, CH_3), 45.648(C, C-OH), 106.387-147.024 (6C, Ar-C), 151.176 (2C, N-C=O), 160.275 (2C, N-C=O), 166.711 (C, N-C=O). Anal. Calcd. for L_2: C, 56.652; H, 3.004; N, 6.008%; Found: C, 56.681; H, 3.012; N, 8.979%.

2.3 Preparation of monomer Drug (L_3 - L_5) [19].

5-Salicylic maleimide (1mmol, 0.20g) added to 3mmol of triethylamine (Et_3N) in 10 mL of DMSO, then 1mmol of $SOCl_2$ was added for (15min) at room temperature. After that, (1mmol) of drugs

(Pseudoephedrine, 4-aminoantipyrine, Paracetamol) was added to the mixture and left for (30min). The cooled reaction mixture was poured into crushed ice, left for (30min), filtered with further crystallized from dichloromethane (**Scheme 1**). Table (1) shows some of the physical properties of the compounds (L1-L5).

Compound [L_3]: molecular formula $C_{21}H_{20}O_5N_2$, colour: Brown, m.p.= 80 – 83 °C, yield : 58% ; FT-IR (cm^{-1}) : 3361 (OH, alcohol), 3093(OH, phenol), 3002 (C-H bending of sp^2), 2919 (C-H bending of sp^3),1711 (C=O, membered imide ring), 1677 (C=O, amide), 1611(cis CH=CH), 1491 (C=C, aromatic), 1198 (C-H bending), 1001(C-N stretching), 935(C-O, alcohol). ^{1}H NMR (300 MHz, TMS, , ppm): 1.2(d, 3H, CH_3), 2.4(s, 3H, CH_3), 3.3 (s, H, OH), 4.8(s, H, OH), 6.2, 6.4(2H, H, HC=CH), 7.049-7.758(m, 8H, Ar-H).^{13}C NMR (300 MHz, TMS, , ppm): 21.779(C, CH_3), 25.413(C, N-CH_3), 43 (C, C-OH), 59.286 (C, CH), 115.174-134.277 (12C, Ar- C), 141.123 (C, C=O), 160.236 (C, N-C=O). Anal. Calcd. for L_3: C, 66.315 ; H, 5.263 ; N, 7.368, %; Found: C, 66.320; H, 5.227; N, 7.359%.

Compound [L_4] : molecular formula $C_{22}H_{18}O_5N_4$, colour: Black (Viscous), yield : 76% ; FT- IR (cm^{-1}) : 3100 (OH, alcohol), 2983 (N-H Sec.), 2983(C-H bending of sp^2), 2823 and 2923 (C-H bending of sp^3),1708(C=O, membered imide ring), 1670 (C=O, amide), 1613(C=C, alkene), 1560 and 1490 (C=C, aromatic), 1290(C-N, aromatic amine), 1193(C-N, aliphatic amine), 1004 (C-O, alcohol). ^{1}H NMR (300 MHz, TMS, , ppm): 1.17 (C-CH_3), 3.5 (N-CH_3), 4.7 (2 H-C=C-H), 7.04-7.75 (7H, C-H aromatic), 6.27 (1H, aromatic), 6.65 (OH), 8.15 (NH). Anal. Calcd. L_4: C, 63.157; H, 4.306 ; N, 13.397, %; Found: C, 63.145; H, 4.311; N, 13.401%.

Compound [L_5]: molecular formula $C_{19}H_{14}O_6N_2$, colour: Black, m.p.=70-73°C yield : 66% ; FT-IR (cm^{-1}) : 3065 (OH, alcohol), 3011 (OH, alcohol), 2920 (C-H bending of sp^2), 2800 (C-H bending of sp^3), 1668 (C=O Ketone), 1572 (C=O in a two membered imide ring), 1486 (C=O, amide), 1433(cis CH=CH), 1330 (C=C, aromatic), 1280 (C-N, aromatic amine), 1199 (C-N, aliphatic amine), 997 (C-O, phenols). ^{1}H NMR (300 MHz, TMS, , ppm): 1.1 (s, 3H, CH_3), 1.8 (s, H, OH), 2.2 (s, H, OH), 6.346, 6.718 (d, 2H, HC=CH), 7.076-7.656 (m, 7H, Ar-H). ^{13}C NMR (300 MHz, TMS, , ppm): 8.672 (C, CH_3), 44.072 (C, C-OH), 114.923-127.383 (C, Ar-C), 139. 993 (2C, HC=CH), 153.045 (C, HC-C=O), 162.921 (C, C-OH), 167.445 (C, N-C=O). Anal. Calcd. L_5: C, 62.295 ; H, 3.825; N ,7.650, %; Found: C, 62.311; H, 3.813; N, 7.661%.

Table (1): some of the physical properties of the compounds (L_1-L_5).

Compo. No.	Color	M . P ^{0}C	Yield%	TLC Solvent	R_f
L_1	Greenish Yellow -(Solid)	191 - 194	93 %	Acetone : Chloroform 1 : 1	0.5
L_2	Black-(Viscous)	———	91 %	Acetone : Chloroform 1 : 1	0.45
L_3	Brown -(Solid)	80 – 83	58 %	Acetone : Hexane 3 : 1	0.48
L_4	Black-(Viscous)	———	76%	Acetone : Hexane 3 : 1	0.65
L_5	Black-(Solid)	70 – 73	66%	Acetone : Hexane 3 : 1	0.51

2.4 Homopolymerization of synthesized drug substituted monomer (L_6 and L_7) [20].

In a 50 ml round bottom flask, (0.5 g), of prepared monomer (Pseudoephedrine, 4-aminoantipyrine) , 15 ml of toluene and (0.05 g, 0.00023mmol) or three drops of the initiator methyl ethyl ketone peroxide (MEKP) passed nitrogen gas for (10 min) after which the tube was sealed tightly and placed in a water bath at 90 ºC for 2 h when the polymerization is completed with the formation of precipitate. The precipitate was washed with ether and then dry in oven at 50 ºC (**Scheme 1)**.

Compound [L_6] Pseudoephedrine homopolymer : color: Brown (Viscous), FT-IR(cm^{-1}): 3150 (OH, alcohol), 3075 (OH, phenol), 2914(C-H bending of sp^2), 2874(C-H bending of sp^3), 1711(C=O, membered imide ring), 1675 (C=O, amide), 1618 (C=C, aromatic), 1436 (C-C bending), 1396 (C-N stretching), 1291(C-O, phenol),1188(OH, alcohol). ^{1}H NMR (300 MHz, TMS, , ppm):1.176(H, CH_3), 2.087 (H, CH_3), 5.071 (H, OH), 6.234 (H, OH), 7.046-7.751(H, Ar-H), 2.5 (DMSO).

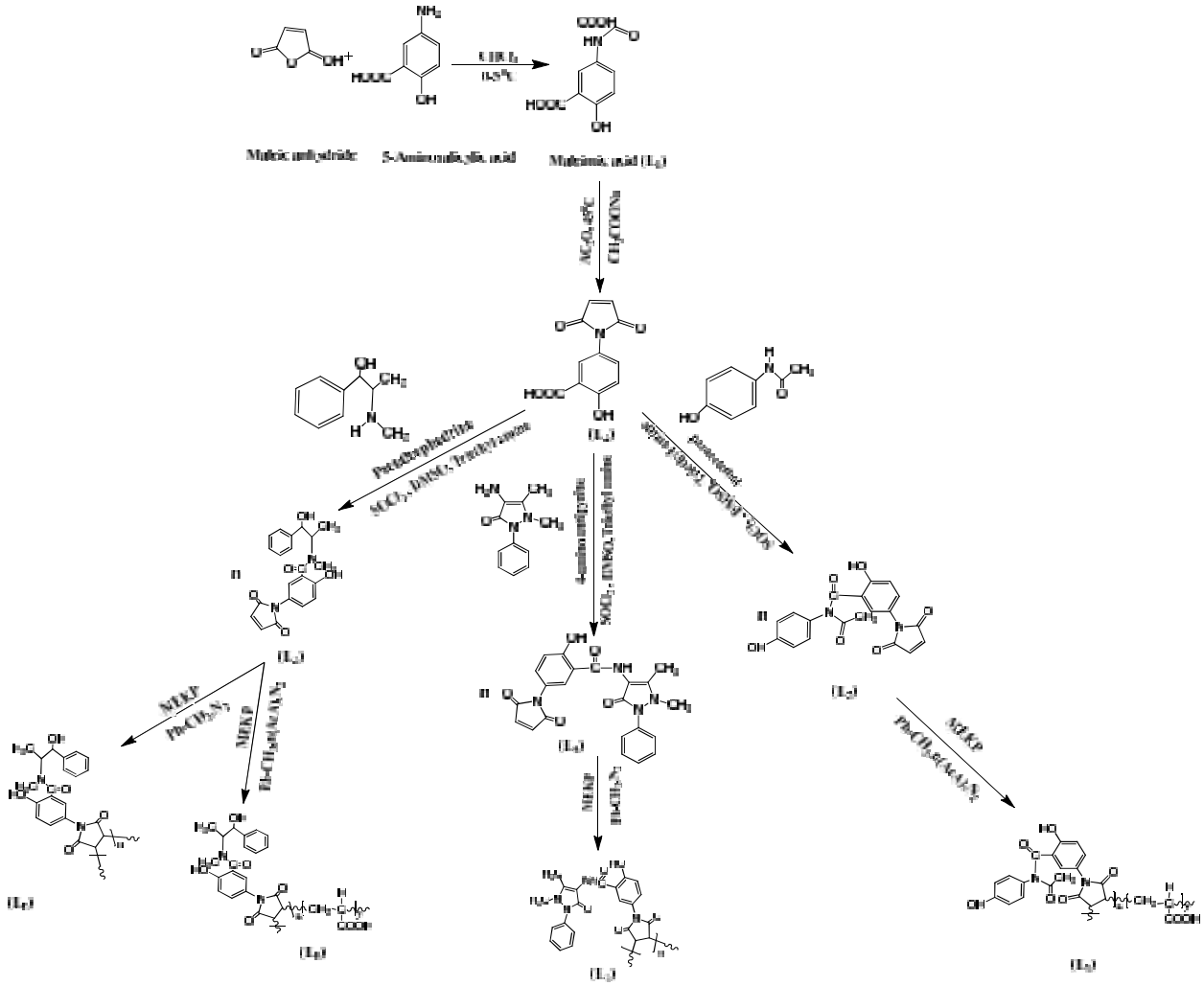
Compound [L_7] 4-aminoantipyrine homopolymer : color: Dark Brown (Viscous), FT-IR(cm^{-1}) : 3100(OH, phenol), 2920 (N-H, Sec.), 2874(C-H bending of sp^2), 2800(C-H bending of sp^3), 1707(C=O, membered imide ring), 1675(C=O, amide),1616 (C=C, aromatic),1490(C-H bending),1393(C-N, aromatic amine), 1289(C-N, aliphatic amine), 1183(C-O, alcohol). ^{1}HNMR (300 MHz, TMS, , ppm): 1.181(C-CH_3), 3.06(N-CH_3), 3.4(H_2O), 4.1(H-C-C-H), 5.3(OH), 6.661(Benzene ring), 7.06, 7.46, 7.76(phenol ring), 9.7(NH), 2.5 (DMSO).

2.5 Co polymerization of synthesized drug substituted monomer (L_8 and L_9).

In a 50 ml round bottom flask, (0.5 g), of prepared monomer (Pseudoephedrine, Paracetamol), acrylic acid with the same moles of the drug monomer , 15 ml of toluene and (0.05 g, 0.00023mmol) or three drops of the initiator methyl ethyl ketone peroxide (MEKP) passed nitrogen gas for (10 min) after which the tube was sealed tightly and placed in a water bath at 90 ºC for 2 h when the polymerization is completed with the formation of precipitate. The precipitate was washed with ether and then dry in oven at 50 ºC (**Scheme 1)**.

Compound [L_8]: Pseudoephedrine copolymer color: Dark Brown (Viscous), FTIR (cm^{-1}): 3461-2929 (OH, Carboxylic acid), 3461 (OH, alcohol), 3100 (OH, phenol), 2929 (2C-H bending of sp^3), 1714(C=O, Carboxylic acid), 1618(C=O, membered imide ring), 1565(C=O amide), 1490 (C=C, aromatic), 1393 (C-N, aromatic amine), 1286 (C-N aliphatic amine), 1173 (C-O, phenol), 1100(C-O, alcohol). ^{1}H NMR (300 MHz, TMS, , ppm): 1.180 (H, CH_3), 2.695 (H, CH_3), 3.410 (H, CH_2), 3.608 (H, HC-COOH), 3.825 (H, OH), 4.203 (H, OH), 6.965-8.087 (H, Ar-H), 9.215 (H, COOH), 2.5 (DMSO).

Compound [L_9]:color: Paracetamol copolymer Brown (Viscous), FTIR (cm^{-1}): 3500-2875 (OH, Carboxylic acid), 3277 (OH, alcohol), 3082 (OH, phenol), 2875 (2C-H bending of sp^3), 1718(C=O, Carboxylic acid), 1657 (C=O, membered imide ring), 1548 (C=O, amide), 1510 (C=C, aromatic), 1490 (C-H, bending), 1480 (C-N, aromatic amine), 1360 (C-N, aliphatic amine), 1194 (C-O, phenol). ^{1}H NMR (300 MHz, TMS, , ppm): 1.173 (H, CH_3), 1.974 (H, CH_2), 4.210 (H, HC-COOH), 5.932 (H, OH), 6.292 (H, OH), 6.792-7.693 (H, Ar-H), 10.454 (H, COOH), 2.5 (DMSO).



Scheme 1: Synthesis rout of compounds [L_1-L_9]

3. RESULTS AND DISCUSSION

A new drug delivery systems can provide the modifications and improve the therapeutic efficiency and safety of drugs. DDS may cause reducing the size, doses, side effects, biological inactivation and elimination. Also, they have advantages includes lower toxicity and specificity of action. The double bond variation which is electron deficient bond occurring in the maleimide ring due to exist of an electron withdrawing carbonyl group on both sides [5]. The maleimide double bond can be polymerized to give polymaleimides or it can be further polymerized, by addition of nucleophilic difunctional reagents [19]. Polymerization resulted by the proliferation of solvent molecules in the polymer network within the crystalline network in the process of bloating in polymers with high molecular weight and volume changes causing polymer collapse during the process of mechanical stress through the process of bloating is known as the degree of polymer tangle, because the more the degree of entanglement challenged resistance to swelling and thus carried out the process of swelling of these polymers (**Scheme 1**).

Maleimic acid (L_1) was synthesized by cyclodehydration reaction. FTI.R spectrum shows that the OH of carboxylic acid appeared from (2500-3500). ^{1}H-NMR (, ppm) spectrum show appearance single-signal at 8.15 for (s, H, N-H), and single signal at 4.14 for (s, H, OH), single signal at 10.57 for (s, H, COOH), and 10.41 for (s, H, COOH). ^{13}C-NMR (, ppm) spectrum exhibit signal at 117.233, for (6C, Ar-C). 5-Aminomaleimide (5-SMI) (L_2) was synthesized by condensation of maleic anhydride with 5-amionsalicylic acid. FTI.R spectrum shows disappear the NH group. ^{1}H-NMR (, ppm) spectrum shows signal at 6.80-7.30 for (d, 2H, H-C=C-H), 7.50-8.71 (m, 3H, Ar-H).^{13}C-NMR (, ppm) spectrum exhibit signal at 42.488, for (C, C-OH). Monomers (L_3) were synthesized from the reaction of compound L_2 with triethylamine and then ignited the carboxylic group with $SOCl_2$ and was substituted by drugs such as (Pseudoephedrine,4-aminoantipyrine, Paracetamol). FTI.R spectrum of compound (L_3) shows that at 3461 (OH), at signal 3002 and 2919 (C-H bending of sp^3), 1677 (C=O amide). ^{1}H-NMR (, ppm): 2.4 (s, 3H, CH_3), 4.8 (s, H, OH). ^{13}C-NMR (, ppm): 21.779 (C, CH_3), 25.413(C, N-CH_3), 1160.23 (C, N-C=O).

FT I.R spectrum of compound (L_4) appear a new peak at 2983 (N-H sec.amine), 2923 and 2823 (C-H bending of sp^3), 1670 (C=O amide) .^{1}H-NMR (, ppm): 1.17(C-CH_3), 3.5(N-CH_3), 4.7(2 H-C=C-H), 7.04-7.75(7H C-H, aromatic), 6.27(1H, aromatic), 6.65 (OH), 8.15(NH). FT I.R spectrum of compound (L_5) appear a new peak at 3065 (OH, alcohol), 2920 (C-H bending of sp^3), 1486 (C=O, amide). ^{1}H-NMR (, ppm): 1.1 (s, 3H, CH_3), 1.8 (s, H, OH), 2.2 (s, H, OH). ^{13}C-NMR (, ppm): 8.672 (C, CH_3), 167.445 (C, N-C=O).

The homogeneous polymers (L_6-L_7) were synthesized from monomers (L_3-L_5) by free radicals reaction using methyl ethyl ketone peroxide (MEKP) initiator at 90°C. FTI.R spectrum of compound (L_6) shows disappearance of the double bond (C=C). ^{1}H-NMR (, ppm): 2.087 (H, CH_3), 6.234 (H, OH). FTI.R spectrum of compound (L_7) shows disappearance of the double bond (C=C). ^{1}H-NMR (, ppm): 1.181(C-CH_3), 3.06 (N-CH_3), 4.1(H-C-C-H), 5.3(OH), 9.7(NH). Also, the heterogeneous polymers (L_8-L_9) were synthesized from monomers (L_3-L_5) with the acrylic acid (AcA) equal quantities, by free radicals using methyl ethyl ketone peroxide (MEKP) initiator at 90°C. FT I.R spectrum of compound (L_8) shows disappearance of the double bond (C=C) and the OH of carboxylic acid appeared at (2929-3461). ^{1}H-NMR (, ppm): 2.695 (H, CH_3), 3.608 (H, HC-COOH), 4.203 (H, OH), 6.965-8.087 (H, Ar-H), 9.215 (H, COOH). FT I.R spectrum of compound (L_9) shows disappearance of the double bond (C=C) and the OH of carboxylic acid appears at (2875-3500). ^{1}H-NMR (, ppm): 1.173 (H, CH_3), 1.974 (H, CH_2), 4.210 (H, HC-COOH), 5.932 (H, OH), 6.792-7.693 (H, Ar-H), 10.454 (H, COOH).

3.1 Physical properties of polymers

1. Solubility

Synthesized monomers, homopolymers, and copolymers are soluble in acetone, DMSO, whereas some of them are partial in ethanol, diethyl ether, toluene, chloroform, and H_2O. The polymer showed solubility in polar solvents indicates the presence of polar group (Table 2).

Table (2): the solubility of the drug monomers and drug polymers.

Compound No.	H_2O	Acetone	Ethanol	Ether	Toluene	Chloroform	DMSO	n-Hexane
Monomers								
L_1	Partial	+	+	+	Partial	+	+	+
L_2	Partial	+	+	Partial	Partial	Partial	+	+

L_3	Partial	+	–	Partial	–	Partial	+	Partial
L_4	Partial	+	Partial	Partial	Partial	+	+	Partial
L_5	Partial	+	–	Partial	–	Partial	+	+
Homo polymer								
L_6	+	+	–	–	–	Partial	+	+
L_7	+	+	Partial	–	Partial	Partial	+	–
Co polymer								
L_8	+	+	Partial	–	Partial	Partial	+	–
L_9	+	+	Partial	–	–	Partial	+	Partial

2. Density and Viscosity

The density of homopolymers and copolymers were determined at 25 ºC using densito 30px meter. Density values of homopolymers and copolymers are given in Table (3). Viscosity determinations of 5-salicylic maleimide in acetone were carried out at the same concentration of homopolymer and copolymer in acetone at 25 ºC using an Ostwald viscometer with a capillary diameter of 0.49 mm. The density, intrinsic viscosity and average molecular weight (M_w) of the present polymer samples are listed in Table (3).

Table (3): The property of viscosity and the density of pharmaceutical polymers.

polymers	**color**	**time$_{unk}$S**	**d$_{unk}$**	**ŋ$_{unk}$ poise**
L_6	Brown	59	0.782	0.69
L_7	Dark Brown	55	0.785	0.64
L_8	Dark Brown	56	0.783	0.65
L_9	Brown light	50	0.786	0.58

3. Swelling and release

The rapid release and functions of (L_6, L_7, L_8, L_9) polymers was studied in acidic, basic and neutral medium, where hydrolysis was gradually. As a pharmaceutical unit of the hydrolysis of the polymer loaded with the drug, where pH = 2.2, pH = 7 and pH = 8. Tables (4,5) and figures (1-12) shows that the pharmacological release is progressively concluded that the end of the process of medical liberation after five hours, and appears that the medical release in the basic pH environment faster than the acid and this is due to the attack seeking the nucleus of the ion($^-$ OH). The carbon atom of the carbonyl group is more strong than the ($^+$ H) proton or the water molecule.

Table (4): Swelling ratio % and release of drug for homo-polymer at pH=2.2, pH=7.0 and pH=8.0 and 37 °C

Time	pH=2.2		pH=7.0		pH=8.0		pH=2.2		pH=7.0		pH=8.0	
Hour	**L_6**		**L_6**		**L_6**		**L_7**		**L_7**		**L_7**	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	**1.0954**	**0.175**	**0.7936**	**0.274**	**1.3861**	**0.802**	**0.8899**	**0.129**	**0.5964**	**0.267**	**1.0302**	**0.727**
2	**1.1592**	**0.198**	**0.875**	**0.289**	**1.4852**	**0.825**	**1.0395**	**0.159**	**0.734**	**0.274**	**1.1583**	**0.759**
3	**1.2373**	**0.222**	**1.1832**	**0.3**	**1.6013**	**0.853**	**1.1471**	**0.172**	**0.9909**	**0.283**	**1.2451**	**0.785**
4	**1.4695**	**0.243**	**1.9607**	**0.318**	**2.3531**	**0.881**	**1.3081**	**0.191**	**1.1977**	**0.298**	**1.7121**	**0.801**
5	**1.7288**	**0.265**	**1.9678**	**0.323**	**2.7528**	**0.918**	**1.5581**	**0.231**	**1.2992**	**0.301**	**2.3522**	**0.860**

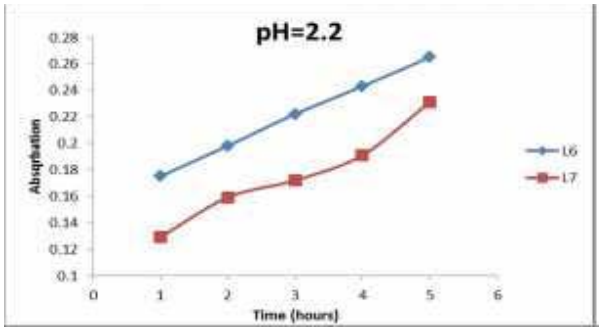


Figure (1):pharmacologic release diagram of homogeneous polymers (L_6, L_7) at PH= 2.2

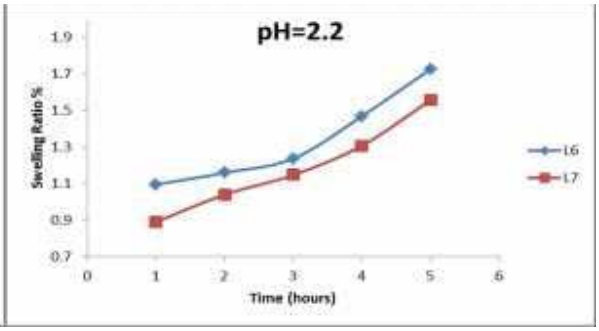


Figure (2): Swelling diagram of homogeneous polymers (L_6, L_7) at PH= 2.2

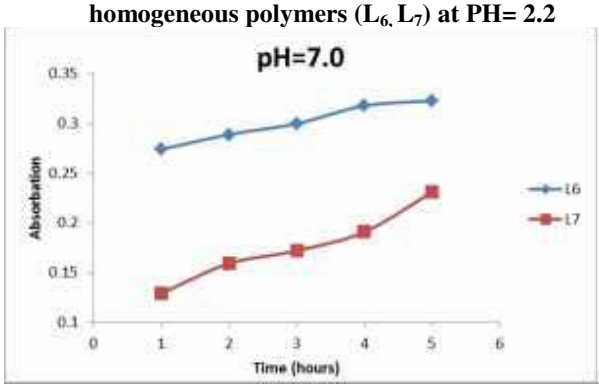


Figure (3):pharmacologic release diagram of homogeneous polymers (L_6, L_7) at PH= 7

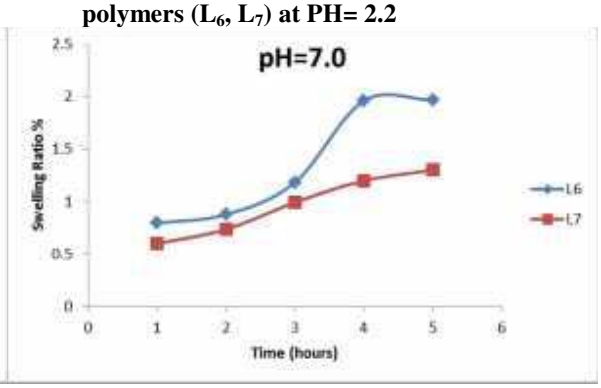


Figure (4): Swelling diagram of homogeneous polymers (L_6, L_7) at PH= 7

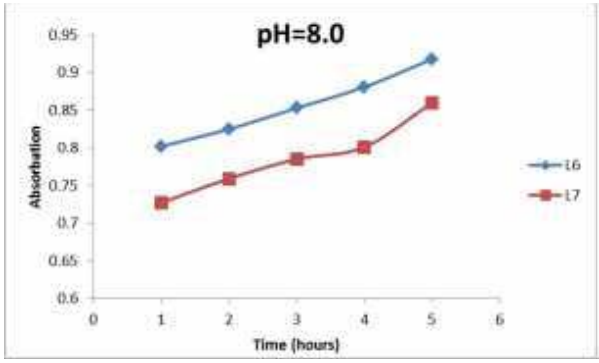


Figure (5):pharmacologic release diagram of homogeneous polymers (L_6, L_7) at PH= 8

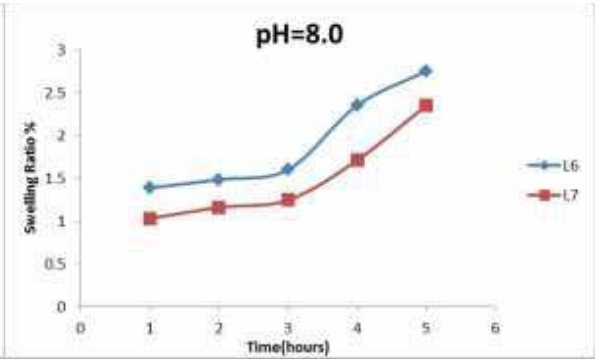


Figure (6): Swelling diagram of homogeneous polymers (L_6, L_7) at PH= 8

Table(5): Swelling ratio % and release of drug for Co-polymer at pH=2.2, pH=7.0 and pH=8.0and 37 °C

Time	pH=2.2		pH=7.0		pH=8.0		pH=2.2		pH=7.0		pH=8.0	
Hour	**L_8**		**L_8**		**L_8**		**L_9**		**L_9**		**L_9**	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	**1.3983**	**0.221**	**0.7936**	**0.266**	**1.3757**	**0.551**	**0.8992**	**0.199**	**0.5964**	**0.235**	**0.6106**	**0.322**
2	**1.6952**	**0.241**	**0.991**	**0.299**	**1.5706**	**0.592**	**1.2215**	**0.211**	**0.7936**	**0.263**	**0.7648**	**0.398**
3	**1.8913**	**0.262**	**1.1212**	**0.332**	**1.6981**	**0.692**	**1.5432**	**0.243**	**0.9908**	**0.301**	**1.0648**	**0.453**
4	**2.2000**	**0.289**	**1.3806**	**0.444**	**1.9507**	**0.801**	**1.7327**	**0.253**	**1.1876**	**0.332**	**1.2621**	**0.503**
5	**2.3320**	**0.318**	**1.9212**	**0.515**	**2.3973**	**0.922**	**1.8559**	**0.255**	**1.7681**	**0.383**	**1.5558**	**0.551**

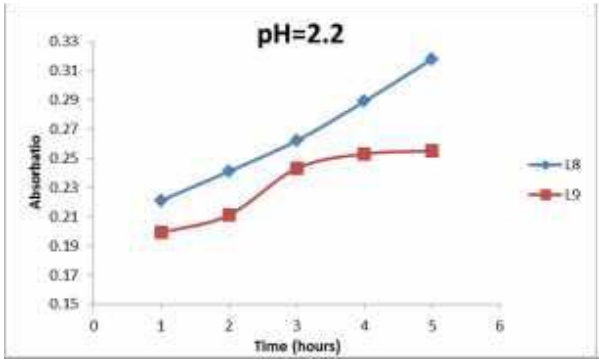


Figure (7):pharmacologic release diagram of heterogeneous polymers (L_8 , L_9) at pH= 2.2

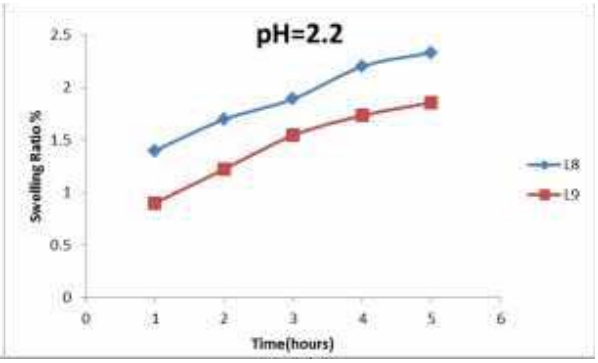


Figure (8): Swelling diagram of heterogeneous polymers (L_8 , L_9) at PH= 2.2

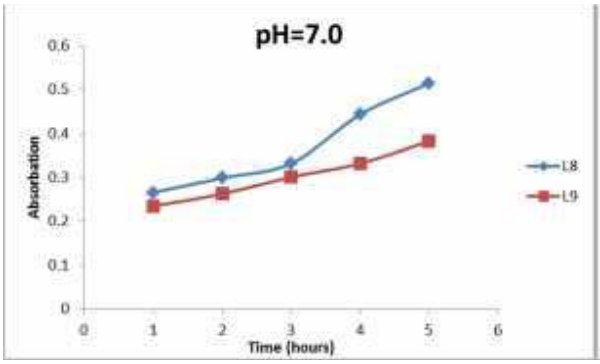


Figure (9):pharmacologic release diagram of heterogeneous polymers (L_8 , L_9) at pH= 7

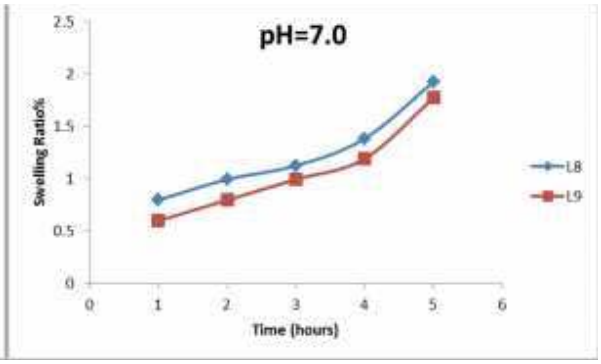


Figure (10): Swelling diagram of heterogeneous polymers (L_8 , L_9) at PH= 7

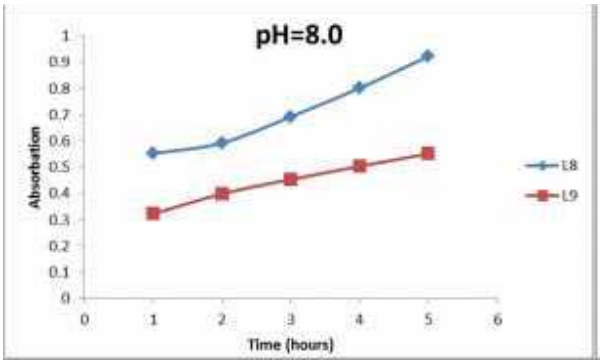


Figure (11):pharmacologic release diagram of heterogeneous polymers (L_8 , L_9) at pH= 8

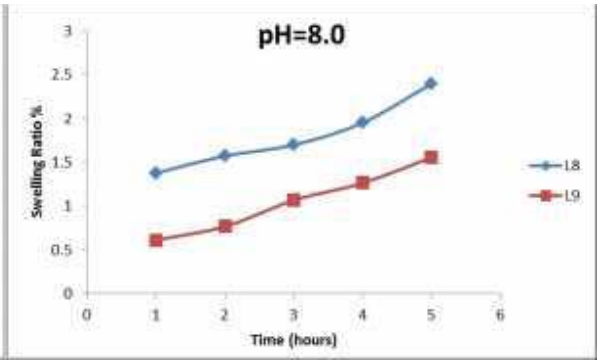
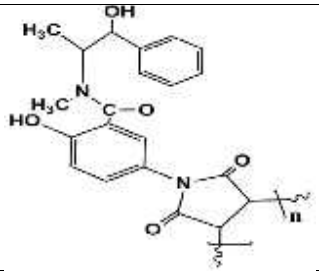
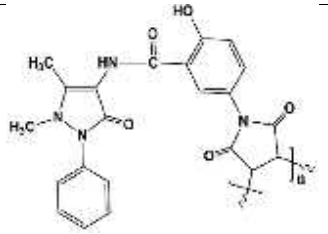
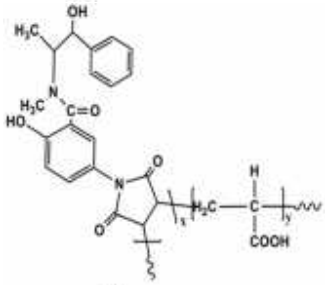
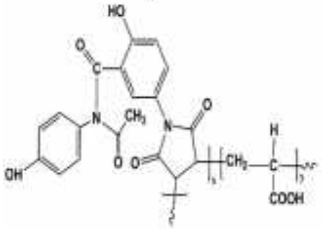


Figure (12): Swelling diagram of heterogeneous polymers (L_8 , L_9) at PH= 8

Table (6) shows some of the physical properties of the recorded polymers (L_6-L_9)

Comp No.	Compound Structure	Colour	Viscosity η ln =dl /g	Density
L_6		Brown	0.69	0.782

L_7		**Dark Brown**	**0.64**	**0.785**
L_8		**Dark Brown**	**0.65**	**0.783**
L_9		**Brown**	**0.58**	**0.786**

4- **Conclusion**

In this work, new prodrug system compounds as substituted monomers and their new homogenous and heterogeneous polymers were synthesized which loaded with medical properties to extend the controlled drug. Compounds (L5 and L6) prepared through homogeneous polymerization reaction of free radicals of monomers (L1 and L2) under nitrogen using MEKP as initiator. Polymers (L7 and L8) prepared through heterogeneous polymerization reaction of free radicals of the monomers (L3 and L4) separately with acrylic acid under nitrogen using methyl ethyl ketone peroxide as initiator. All these prepared monomers and polymers were characterized by FTIR, CHN and ^{1}H NMR, ^{13}C NMR techniques. Controlled drug release and swelling % was studied in different pH values at 37 ℃. The swelling percentage value is varied in different polymers and this difference can be attributed due to the release of drug. It is also observed that process of releasing the drug in basic medium (pH 8) is greater than in acid medium (pH 2.2).

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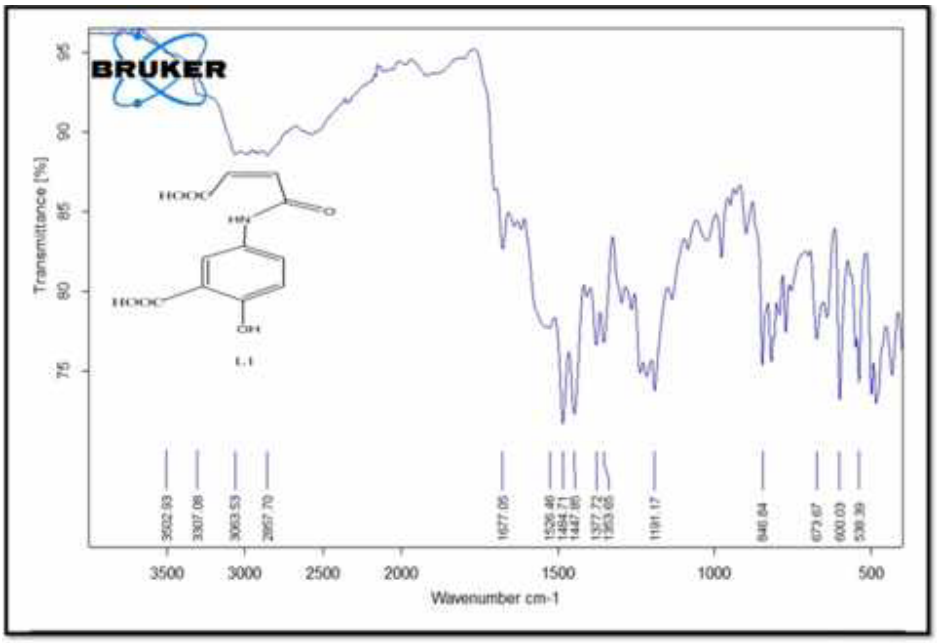

Figure 13: F.T-IR spectrum of compound [L_1]

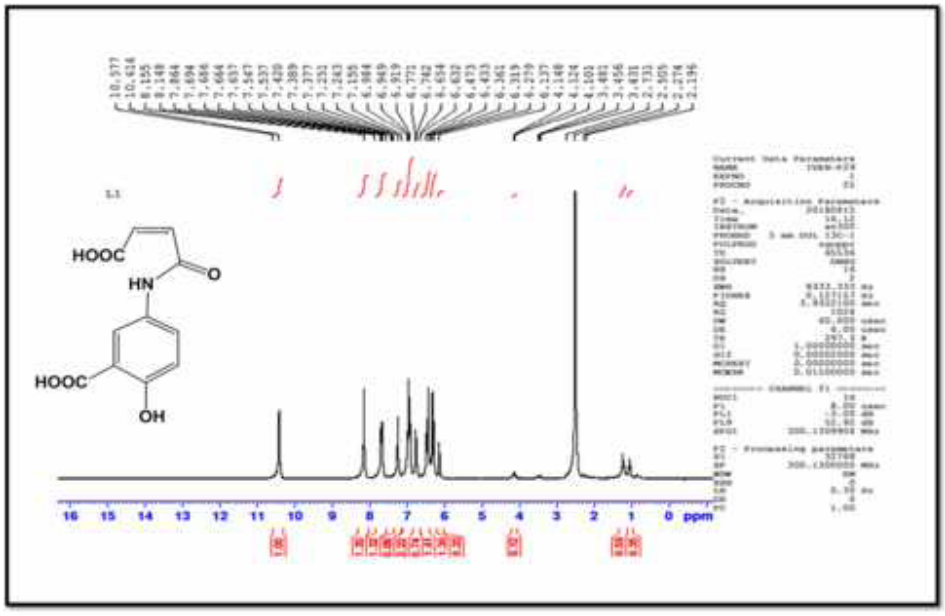

Figure 14: ^{1}H-NMR spectrum of compound [L_1]

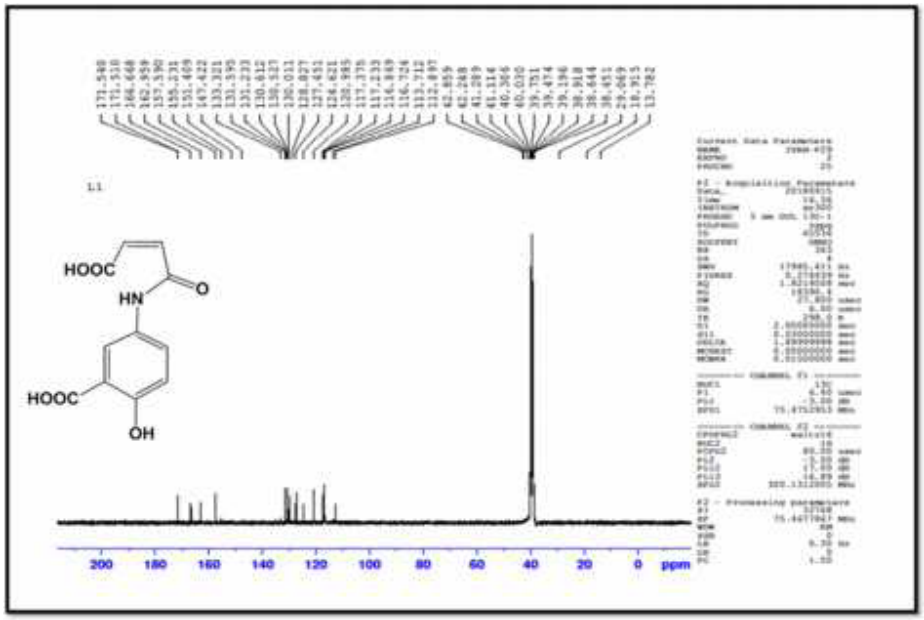

Figure 15: ^{13}C-NMR spectrum of compound [L_1]

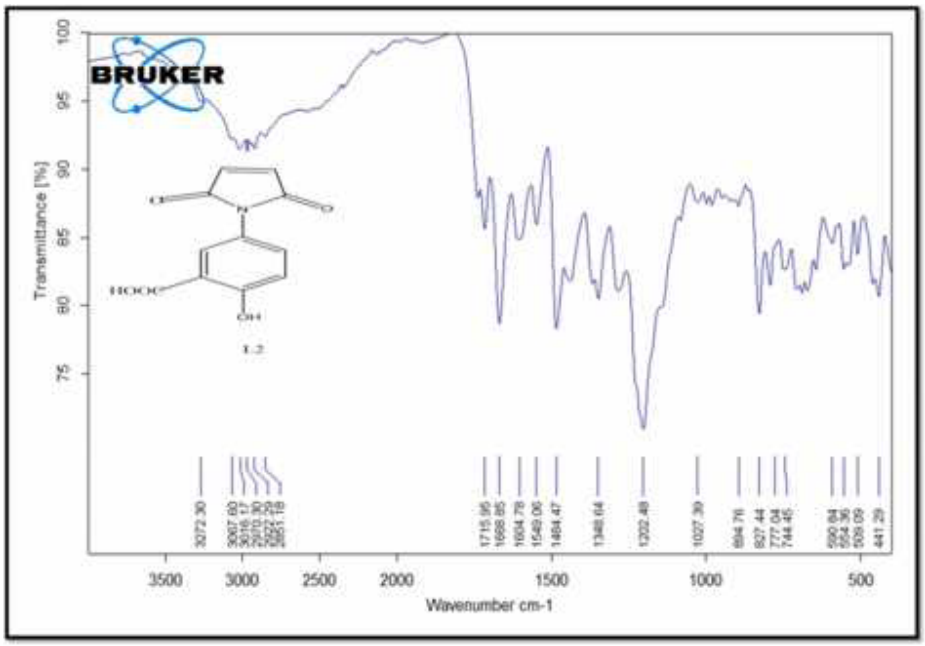

Figure 16: F.T-IR spectrum of compound [L_2]

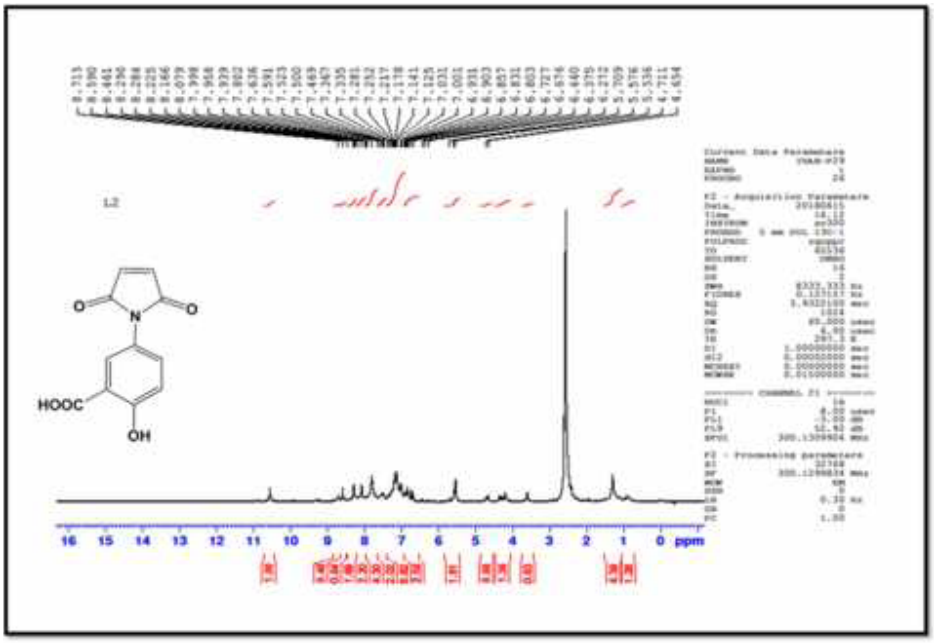

Figure 17: ^{1}H-NMR spectrum of compound [L_2]

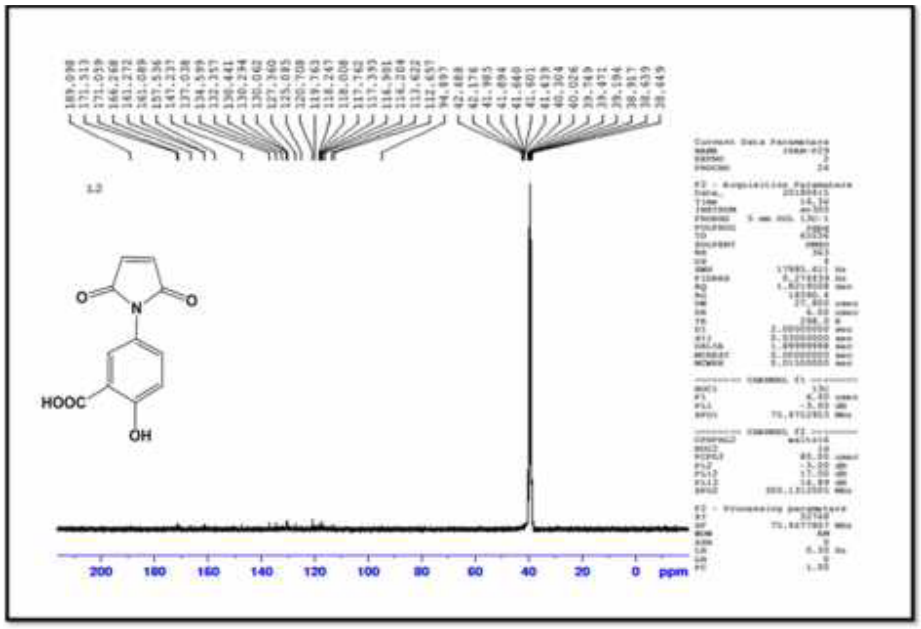

Figure 18: ^{13}C-NMR spectrum of compound [L_2]

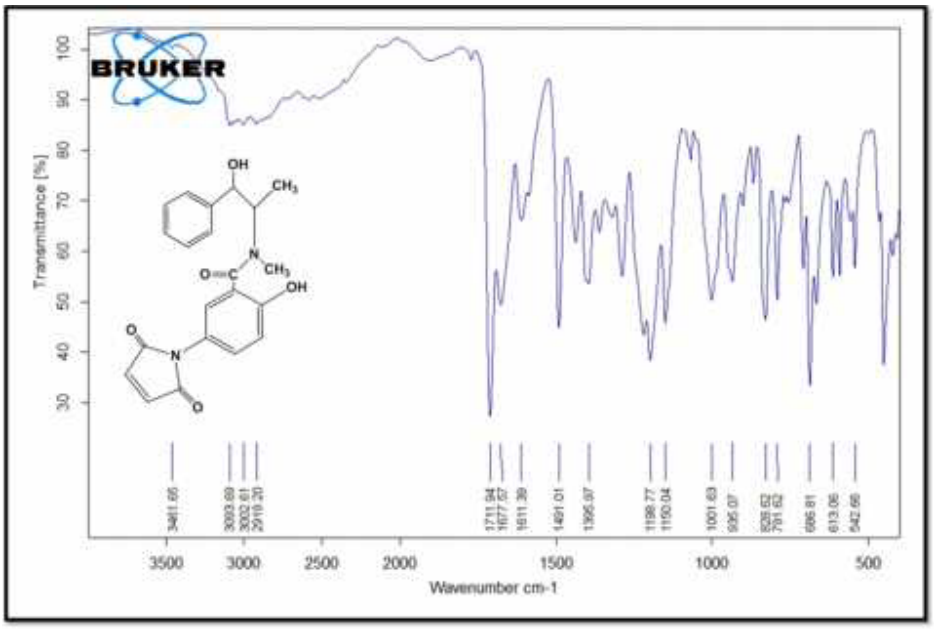

Figure 19: F.T-IR spectrum of compound [L_3]

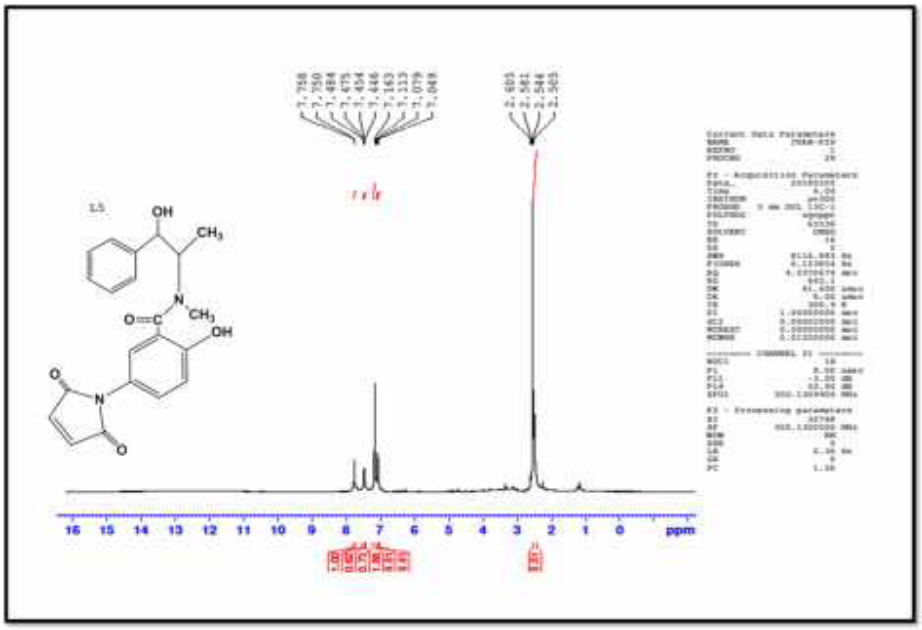

Figure 20: ^{1}H-NMR spectrum of compound [L_3]

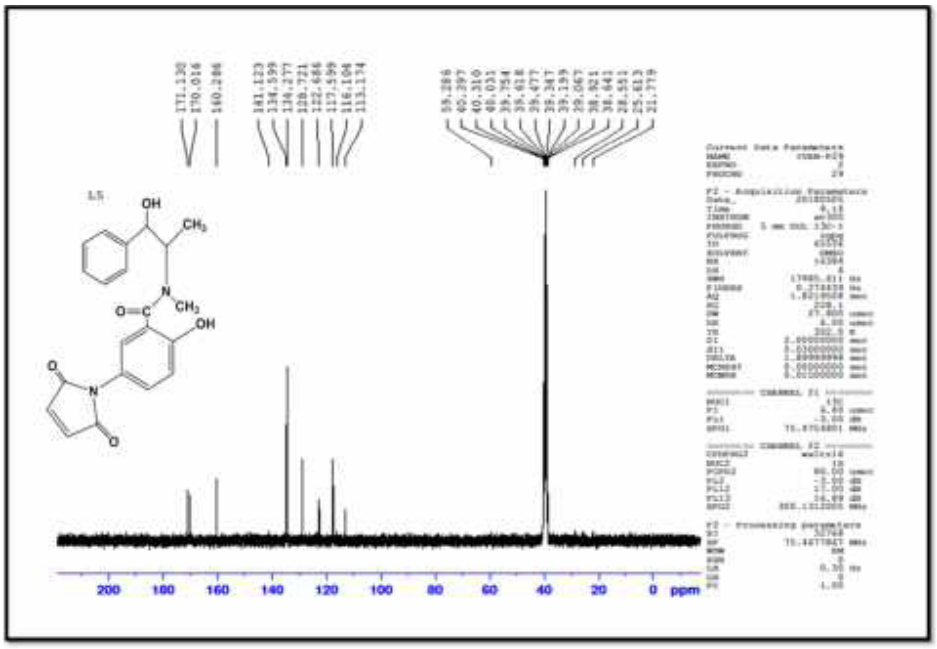

Figure 21: ^{13}C-NMR spectrum of compound [L_3]

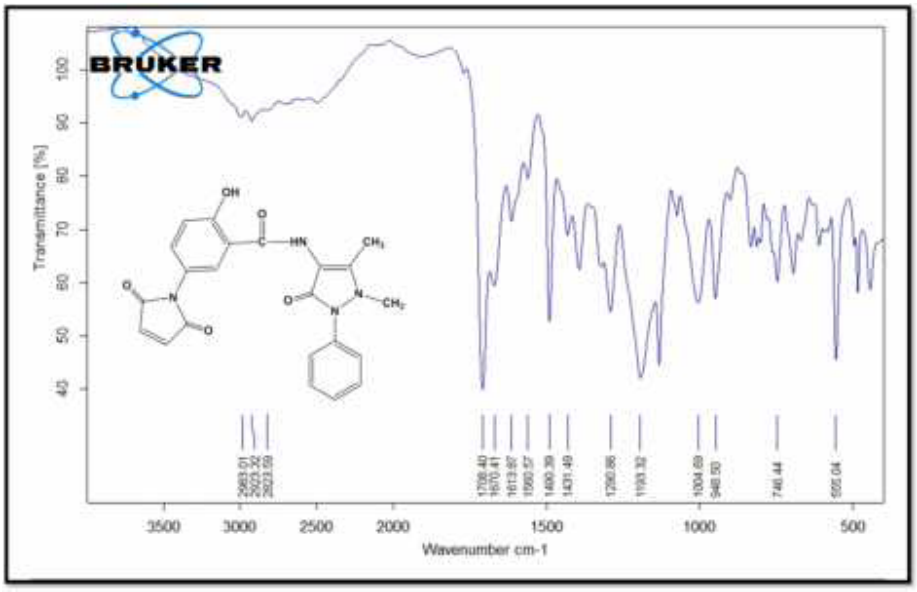

Figure 22: F.T-IR spectrum of compound [L_4]

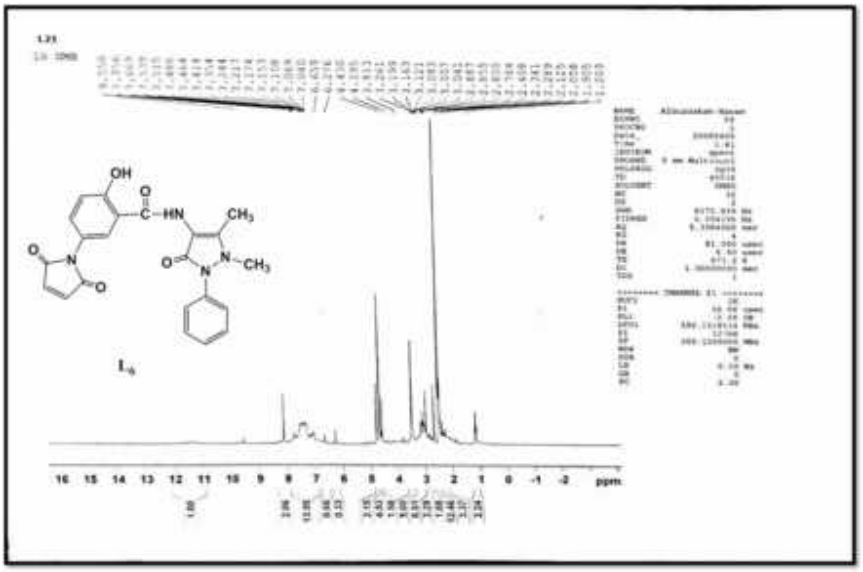

Figure 23: ^{1}H-NMR spectrum of com pound [L_4]

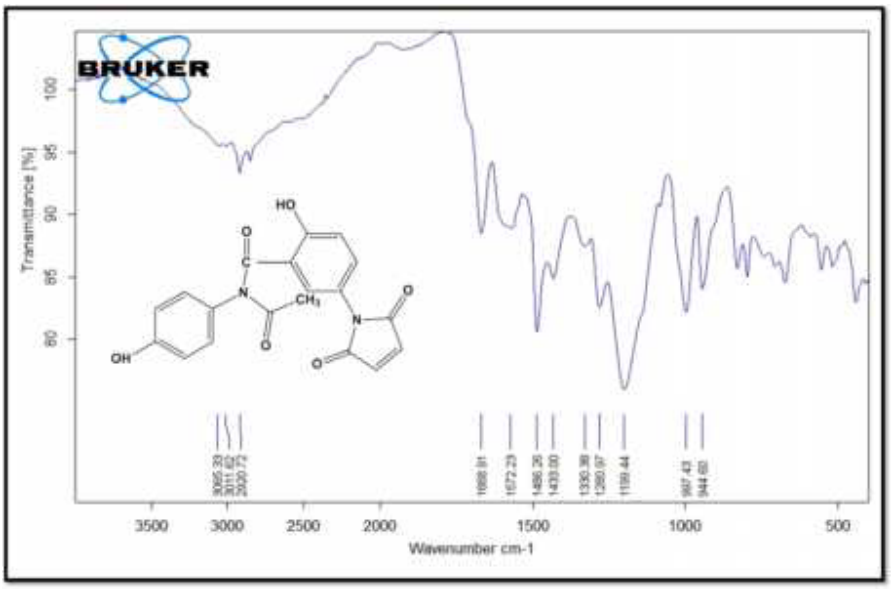

Figure 24: F.T-IR spectrum of compound [L_5]

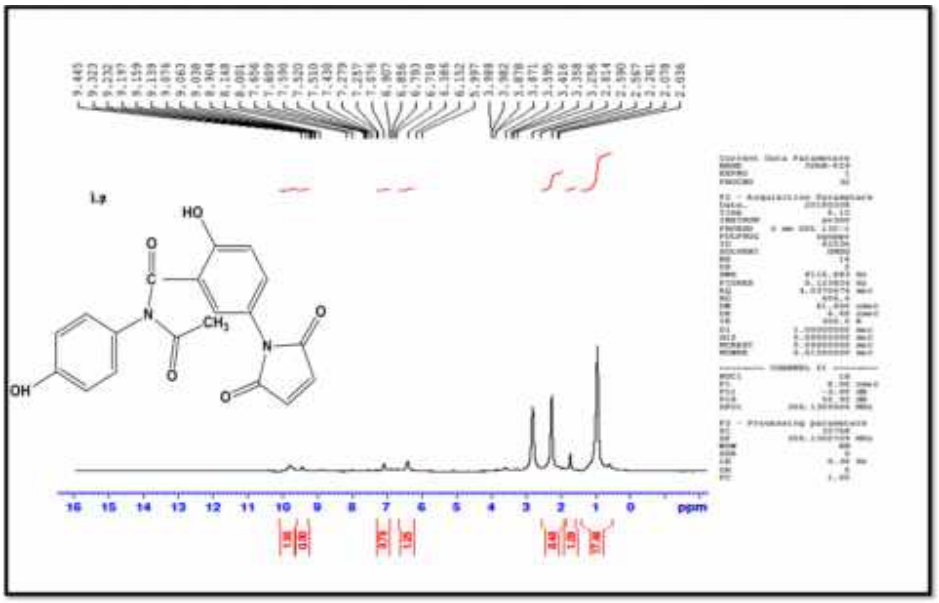

Figure 25: ^{1}H-NMR spectrum of compound [L_5]

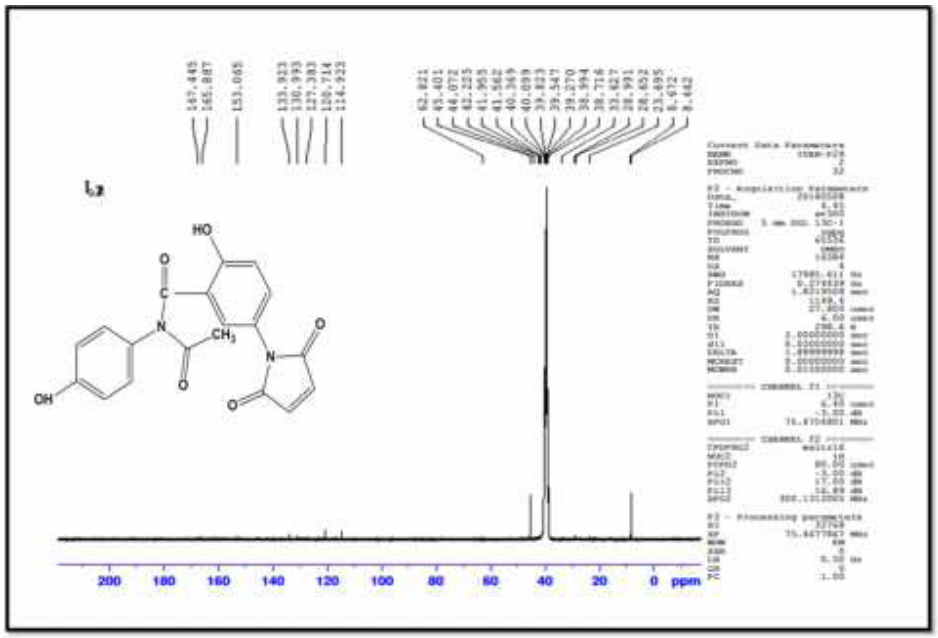

Figure 26: ^{13}C-NMR spectrum of compound [L_5]

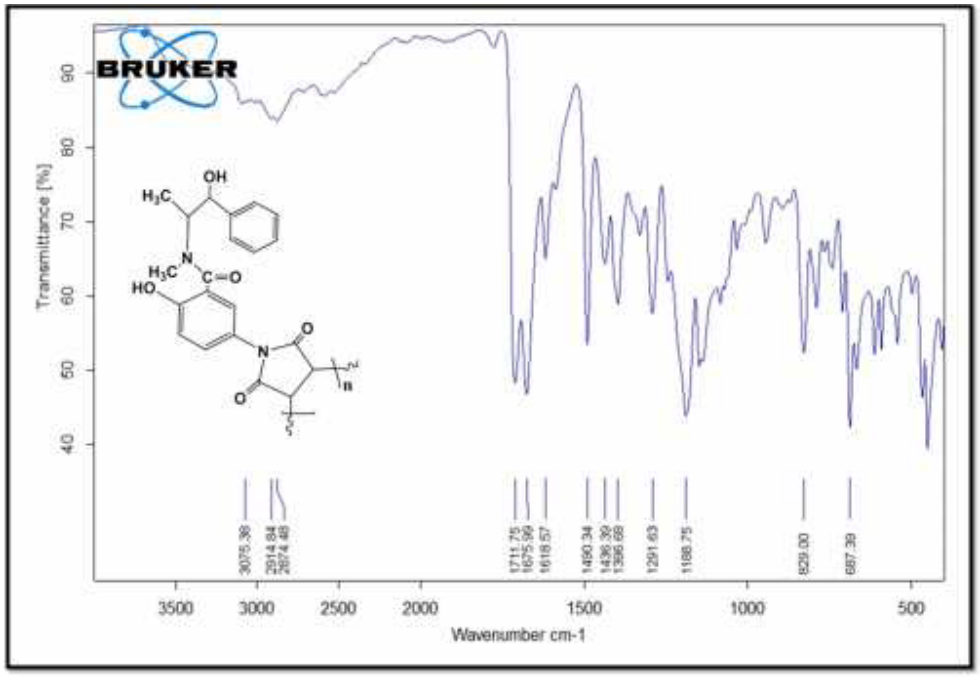

Figure 27: F.T-IR spectrum of compound [L_6]

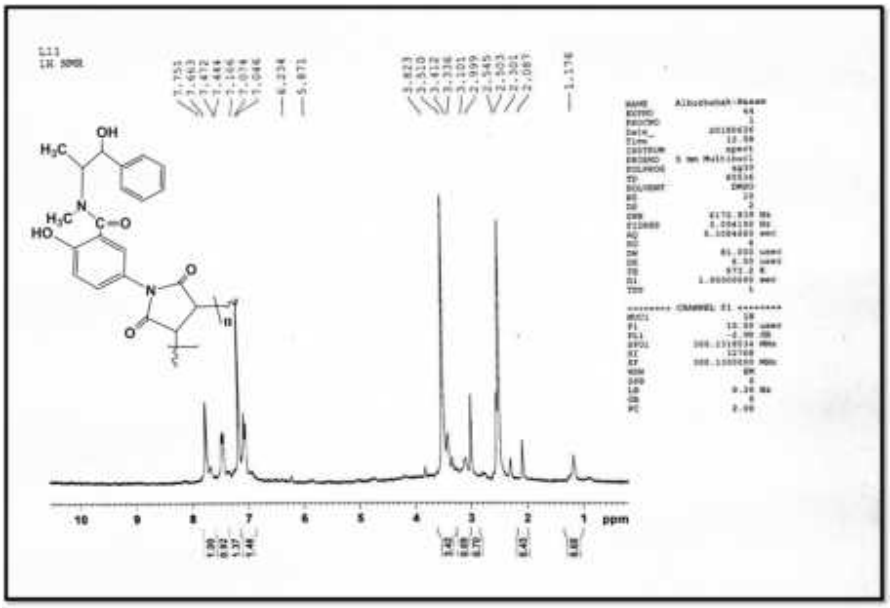

Figure 28: ^{1}H-NMR spectrum of compound [L_6]

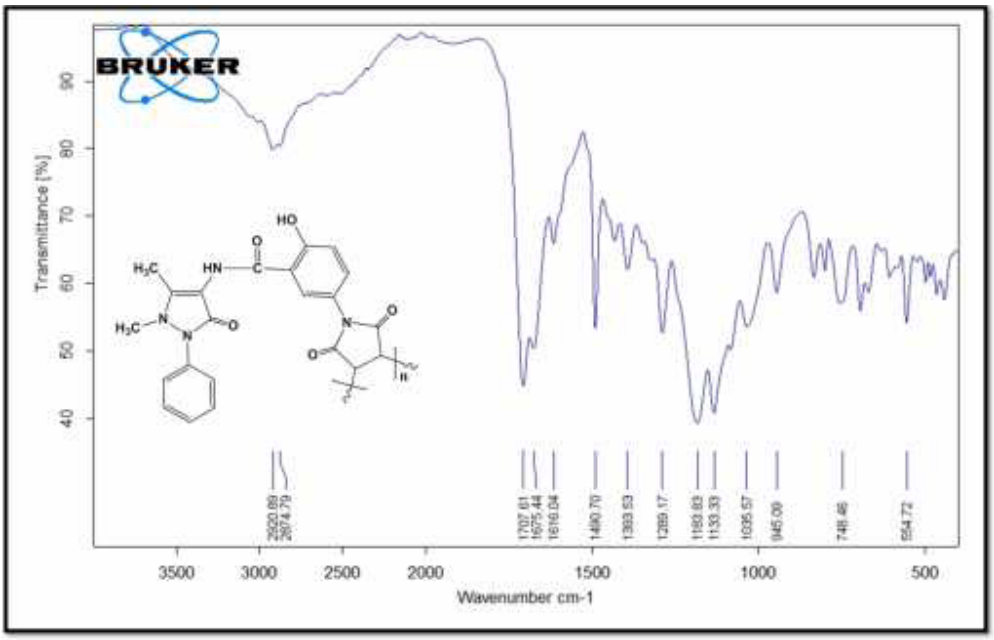

Figure 29: F.T-IR spectrum of compound [L_7]

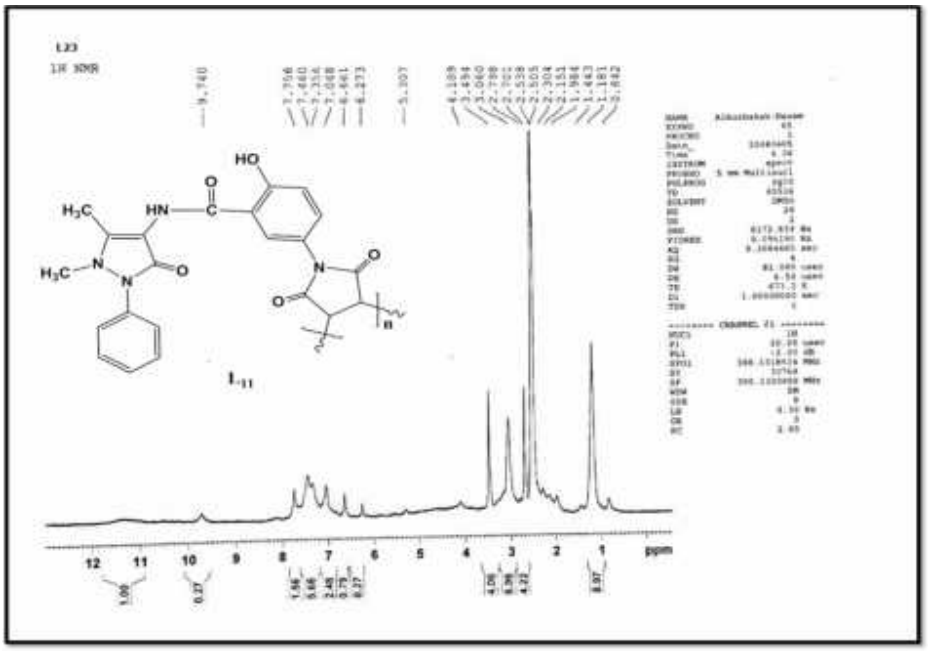

Figure 30: ^{1}H-NMR spectrum of compound [L_7]

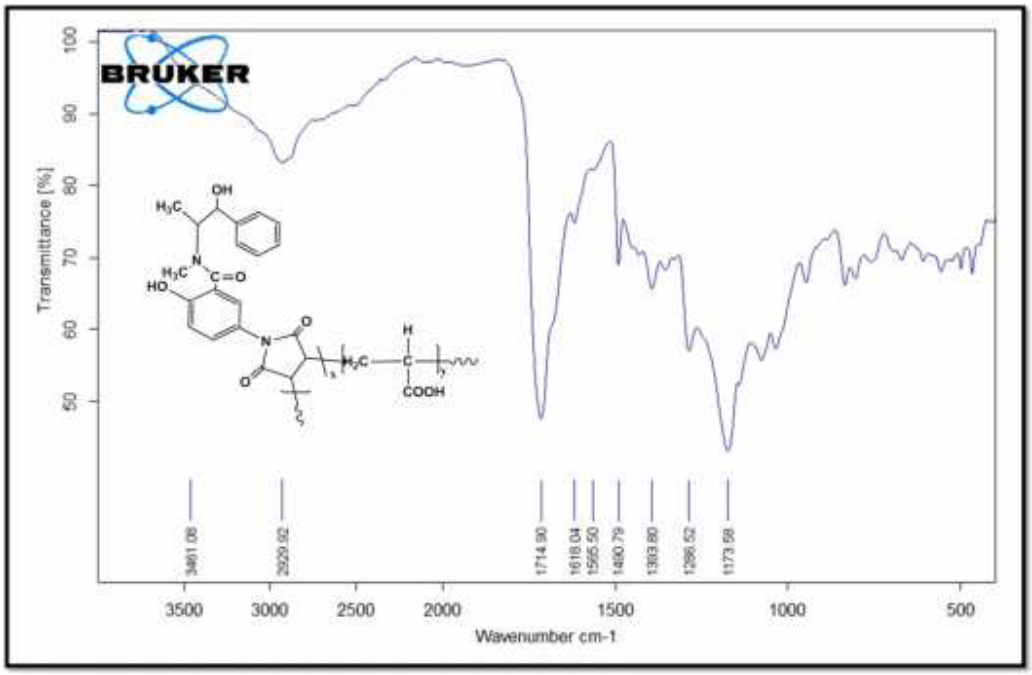

Figure 31: F.T-IR spectrum of compound [L_8]

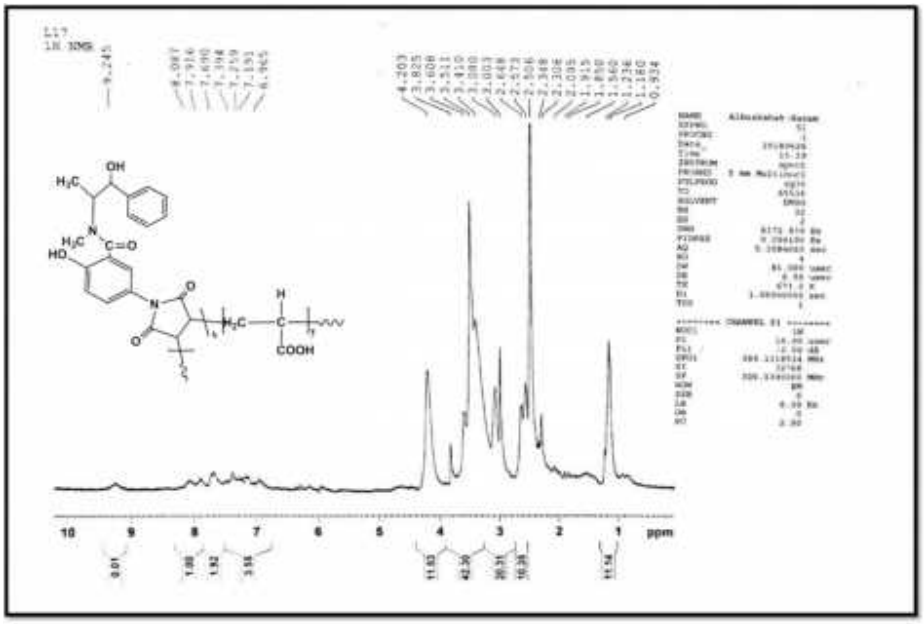

Figure 32: ^{1}H-NMR spectrum of compound [L_8]

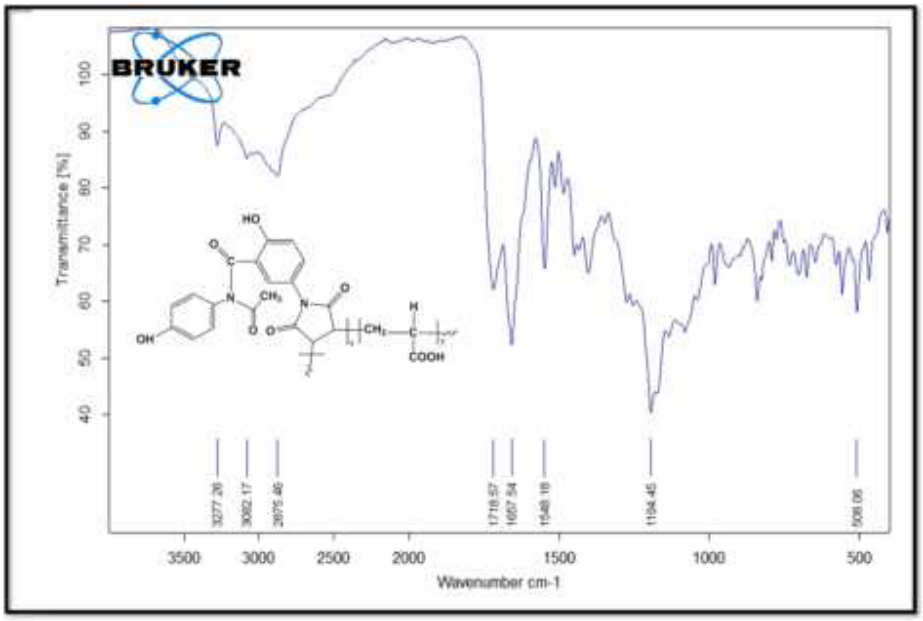

Figure 33: F.T-IR spectrum of compound [L_9]

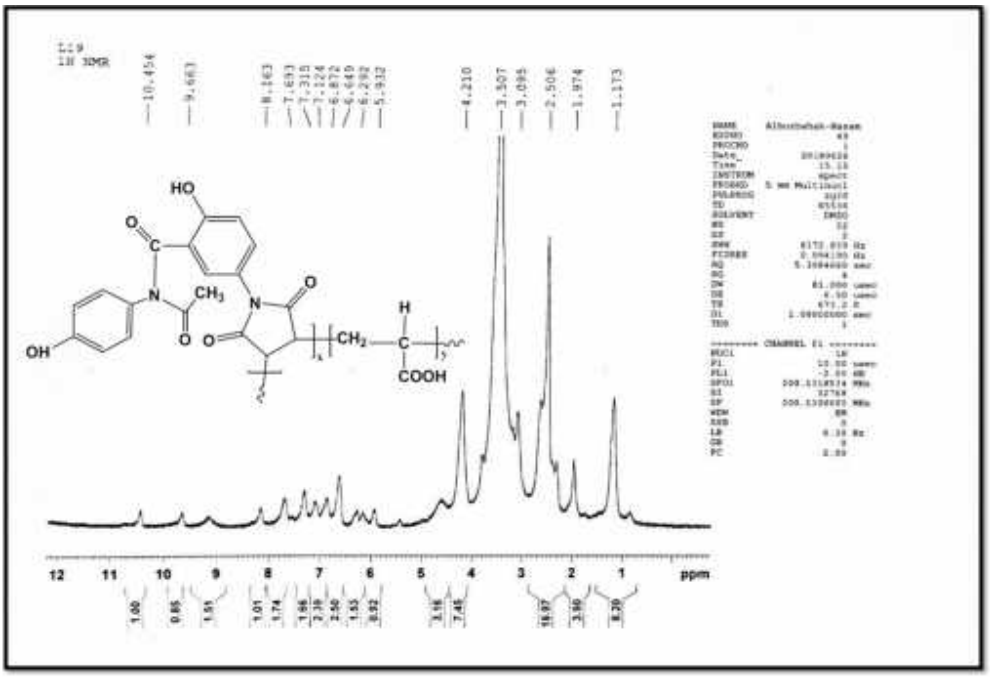

Figure 34: ^{1}H-NMR spectrum of compound [L_9]