

Reaction of Poly (Propylene Imine) Dendrimer with Carboxylated Amines

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In this research, new derivatives of poly (propylene imine) dendrimer were synthesized using propylamine and ethylenediamine. First, amines reacted with methyl acrylate *via* aza-Michael addition, then their products were treated with poly (propylene imine) dendrimer (PPI). The products were identified by FT-IR, ¹H NMR and ¹³C NMR methods. Morphology and size of particles were evaluated by scanning electron microscopy.

Keywords: Propylamine, Ethylenediamine, Aza-Michael addition reaction, Poly (propylene imine) dendrimer

INTRODUCTION

Dendrimers are a group of macromolecules that are made for purposeful and scheduled drug delivery. Dendrimers are spherical ramose units containing polymer branches with different sizes. They have a single particle size distribution and a monodisperse spherical symmetry [1]. These compounds can attach many materials to their own surface and can carry them due to their multiple agent groups at on the surface. This feature can be used to connect targeted macromolecules (*e.g.*, substrates of a variety of cell receptors [2-5]).

Other applications of dendrimer's drug delivery are controlled drug delivery to eyes [6,7], drug delivery through clonal [8], *etc.* Nano dendrimers are also used for angiography, vascular examination or examination of various tissues [9-13].

Some of the most widely used and oldest known dendrimers are polypropylene imine (PPI) dendrimers which were synthesized and introduced for the first time by Vogtle [14]. In addition, the water-soluble PPI dendrimer is colorless and transparent [15]. Some of the unique features of dendrimerous structures are their regular and ramose

structure, active multi-functional end-groups and empty spaces between branches. These empty spaces provide the possibility of acceptance of guest molecules and encapsulation of particles at different sizes [16]. That is why researchers use dendritic structures and especially dendrimers in medical sciences, pharmacology, biology, drug delivery systems, growth of stem cells, treatment of various tumors, improvement of genetic disorders, identification of cancer cells and anti-viral and antibacterial uses in recent years [17-21].

Many drugs have been found with a β -amino carbonyl or nitrile structure that have had widespread pharmacological and medical applications [18]. Aza-Michael addition is one of the widely used reactions for the synthesis of these compounds. A wide variety of Lewis acids [19,20] Brønsted acid [21,22], base [23,24] or other catalysts [25] have been explored for this reaction.

Furthermore, there are a few reports of using sulfonamides as Michael donor. However, most of these methods suffer from limitations including harsh reaction conditions with low yields, tedious work-up procedures, use of expensive, toxic or unavailable reagents and solvent and the necessity of column chromatography for purification.

This research work includes two parts: in the first part, each one of inesam is carboxylated with methyl acrylate

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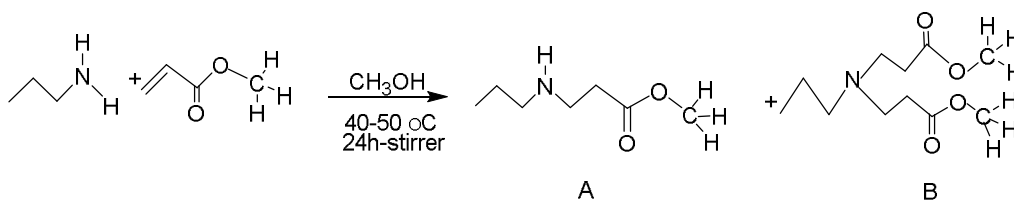


Fig. 1. Reaction of propylamine with methyl acrylate.

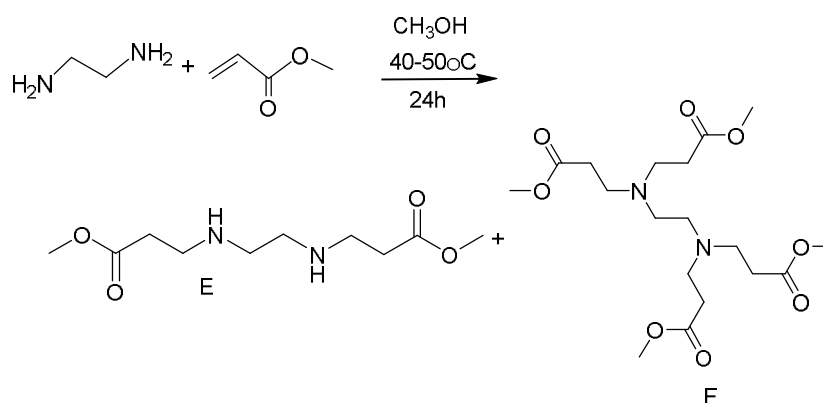


Fig. 2. Reaction ethylenediamine with methyl acrylate.

between intended amines through Aza-Michael addition reaction, and in the second part, the carboxylated amines are exposed to the reaction with poly (propylene imine) dendrimer (PPI) (G1) to turn them to the target molecules.

EXPERIMENTAL

Materials and Instrument

Propylamine, ethylenediamine, methanol, poly (propylene imine) dendrimer (PPI) and methyl acrylate were all purchased from Merck company. FT-IR device from Thermo-Nicolet company with model of Nexus670 made in USA was used to identify functional groups. ^1H and ^{13}C NMR were recorded on Bruker (400 MHz) NMR spectrometer. NMR was used to detect the type and number of protons and carbons. A scanning electron microscope was used to investigate the morphology and size of structures.

Methods

At the beginning, Aza-Michael reaction was done by interaction of type primary amines with methyl acrylate at

the range of 40-50 °C for 24 h with uniform mixing. In the next step, the created products from the first step were exposed to the effect of the reaction so that arms grew and a newer dendruff was synthesized. The reaction conditions and molar ratio of raw materials were selected in a way that only desired products were made and side products or higher generations of dendrimers were prevented.

The general method for the synthesis of β -alkylamino methyl acrylate derivatives using Aza-Michael addition reaction. At this step, a certain amount of amine was dissolved in methanol solvent. Then, the obtained solution was added dropwise to methyl acrylate while stirring. The reaction mixture was stirred at the temperature range of 40-50 °C for 24 h.

A. Reaction of propylamine with methyl acrylate: Propylamine (or PA is called) (4.1 ml, 50 mmol) was dissolved in 5 ml of methanol. Then, the above solution was drop wisely added to methyl acrylate (9.1 ml). The reaction mixture was stirred at room temperature for 24 h. After the end of the reaction, the solvent was separated using rotary. The bright yellow viscous liquid obtained was very odorous

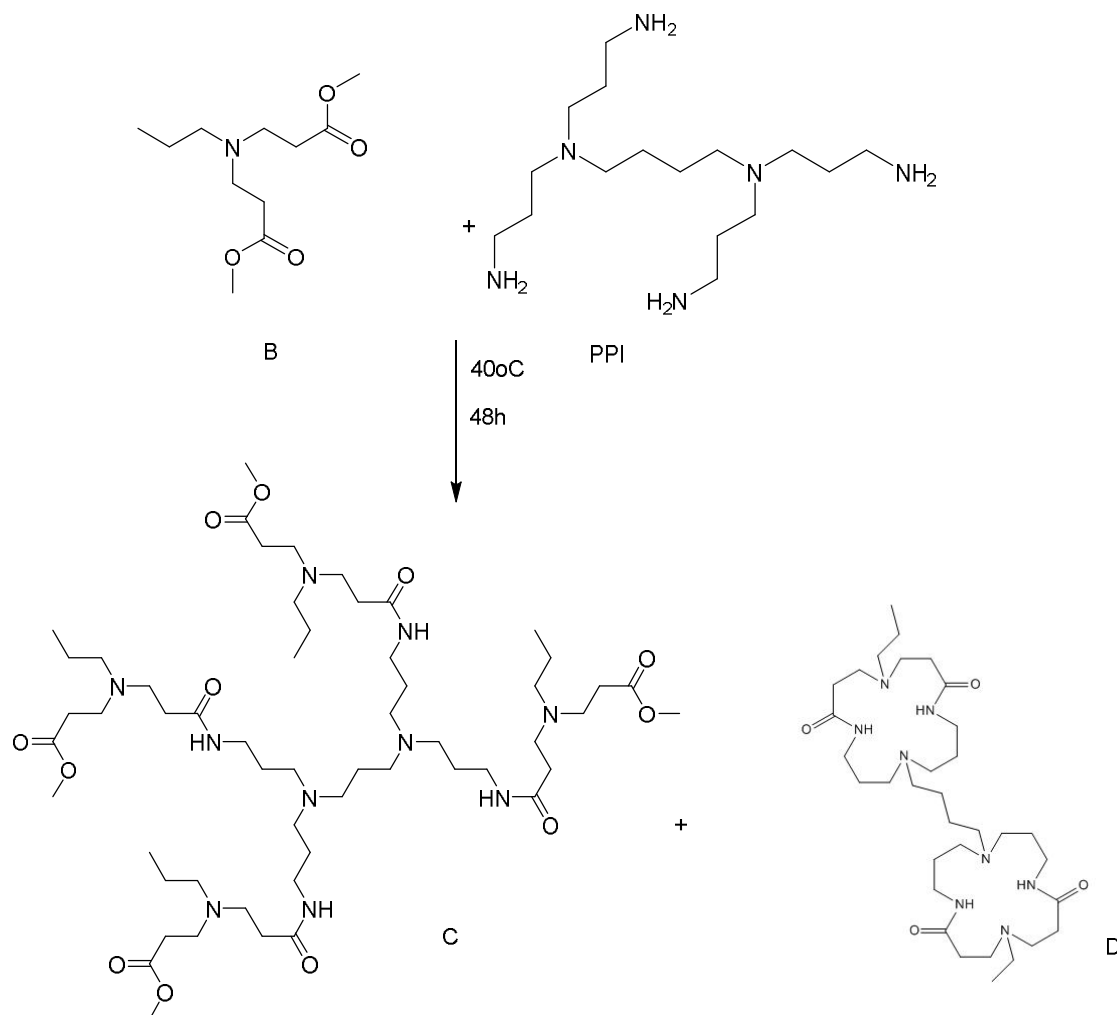


Fig. 3. Reaction of B product with PPI. B is produced from the reaction of propylamine with methyl acrylate.

(Fig. 1). The product created at this stage is called PA-derivative.

B. Reaction of ethylenediamine with methyl acrylate: Ethylenediamine (or EDA is called) (1.67 ml, 25 mmol) was dissolved in 5 ml of methanol. Then, the above solution was drop wisely added to methyl acrylate (9.1 ml). The reaction mixture was stirred at room temperature for 24 h. After the end of the reaction, the solvent was separated using rotary. The yellow viscous liquid obtained was very odorous (Fig. 2). The product created at this stage is called EDA-derivative.

The reaction of intermediate products with PPI. At this step, derivatives of β -alkylamino methyl acrylate that

aza-micheal addition reaction in the previous step reacted with PPI at the presence of minimum amount of methanol as solvent, under the temperature of 40 °C with stirring for 48 hours. Then, the rotary solvent was separated and the purity of the product was tested by TLC.

A) Reaction of PA-derivative with PPI: PPI (0.3 ml) was dissolved in methanol (1 ml). Then PA-derivative (0.5 ml) was added to the mixture dropwise. The reaction mixture was stirred at 40 °C for 48 h. Solvent was extracted after reaction using rotary. The product is a very viscous yellow liquid similar to honey. The product is highly sticky and completely sticks to the walls of container. Interestingly, at the first step, the product had a very sharp smell, but

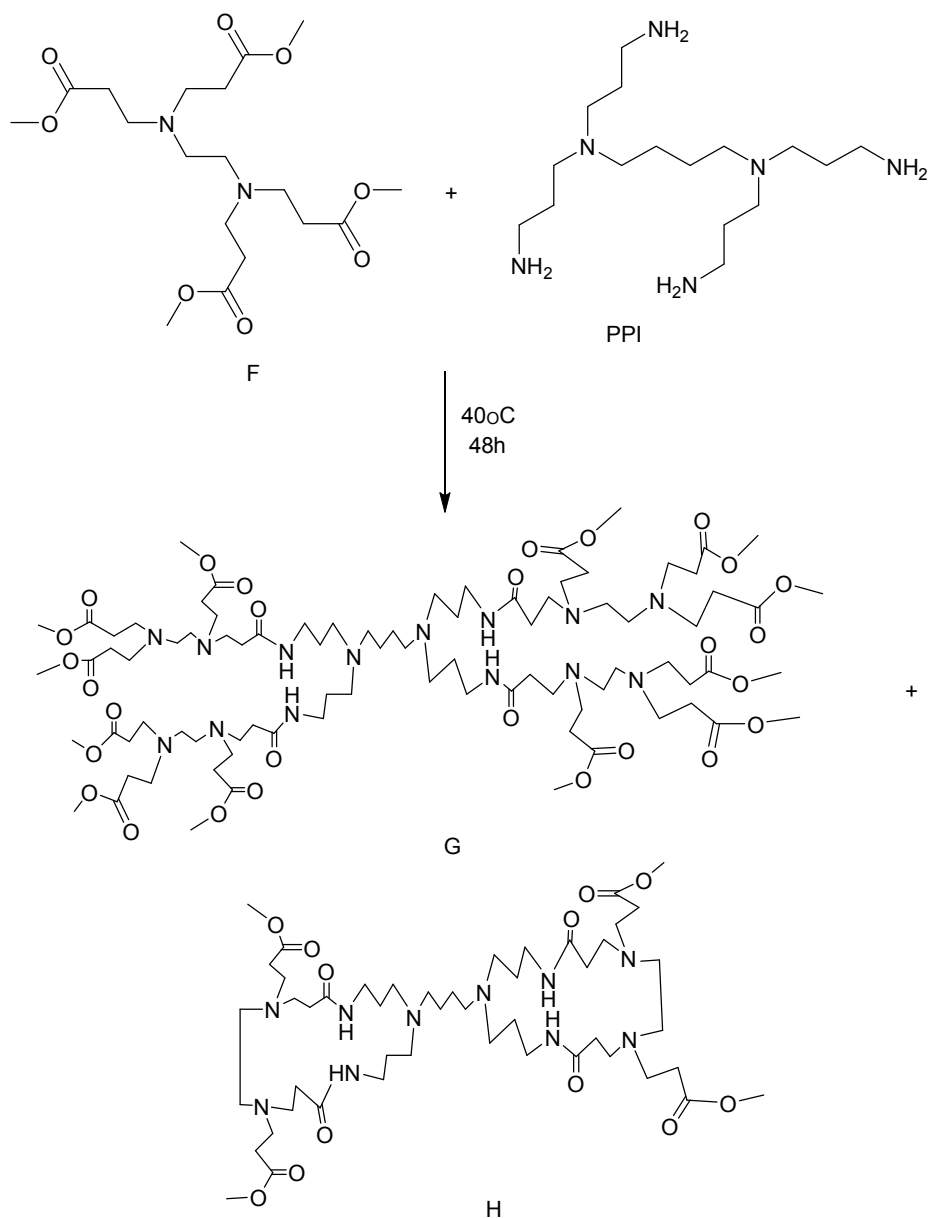


Fig. 4. Reaction of F product with PPI. F is produced from the reaction of ethylenediamine with methyl acrylate.

products of the second step we not the same. The PPA derivative formed dissolves greatly in water (Fig. 3).

B) Reaction of EDA- derivative with PPI: PPI (0.3 ml) was dissolved in methanol (1 ml). Then EDA-derivative (0.5 ml) was added to the mixture dropwise. The reaction mixture was stirred at 40 °C for 48 h. Solvent was extracted after reaction using rotary. The product is a yellow solid paste similar to honey (Fig. 4).

RESULT AND DISCUSSION

Evaluation of Reaction of Propylamine with Methyl Acrylate

Based on spectral evidence and molar ratio considered for initial materials, it is expected that both N-hydrogen atoms of propylamine are involved in reaction with methyl acrylate, hence, the B product is the main product of this

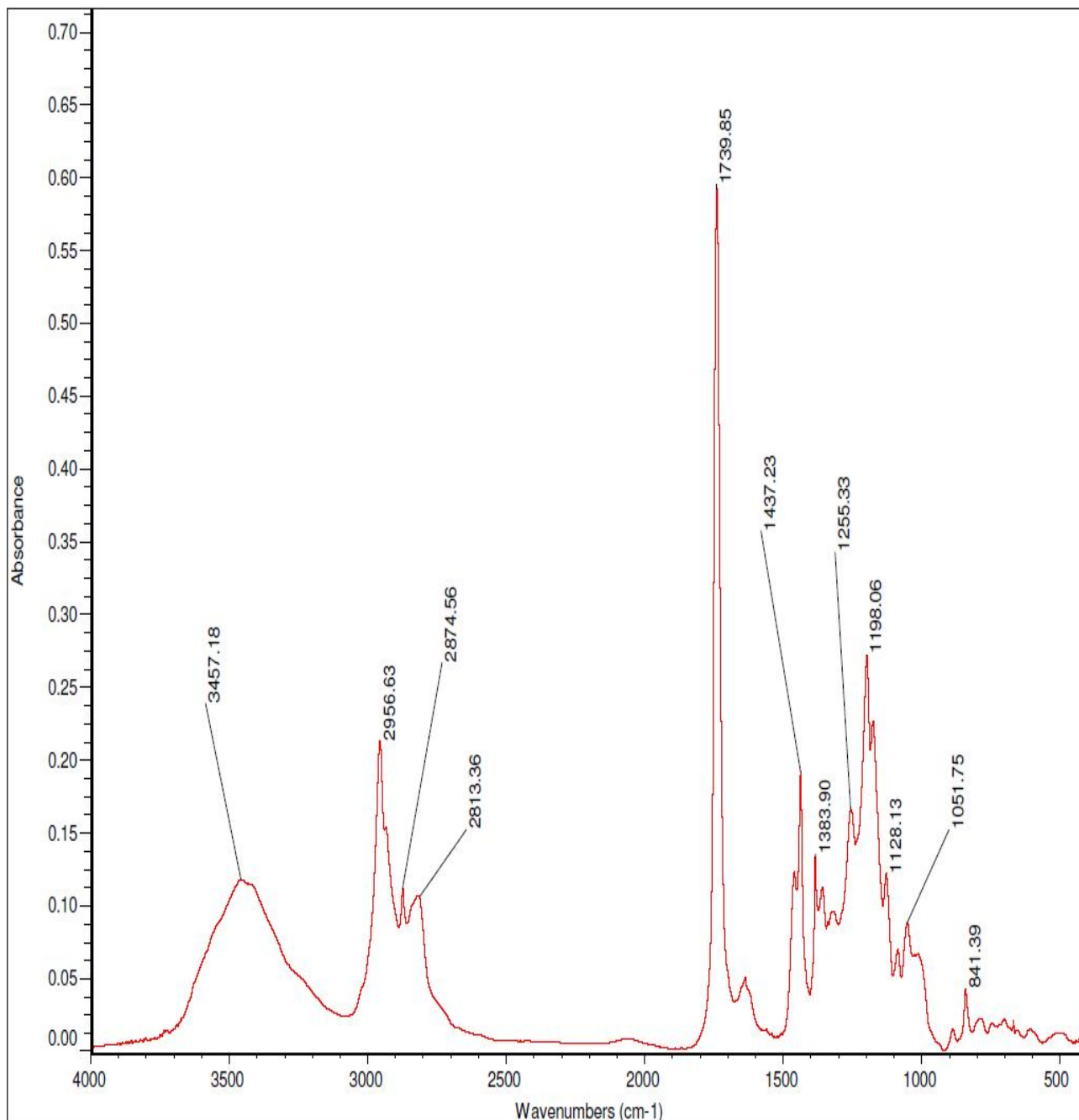


Fig. 5. IR spectrum of B.

reaction. The obtained product was a yellow viscous liquid with a boiling point of 192 °C.

As it can be observed in IR spectrum, absorption peaks

in the areas of 2813-2966 cm⁻¹ are related to stretching vibrations of C-H aliphatic. The carbonyl stretching frequency of ester appeared at 1739.95 cm⁻¹. The lack of

H1-PA-1-(SalahVarzi)-

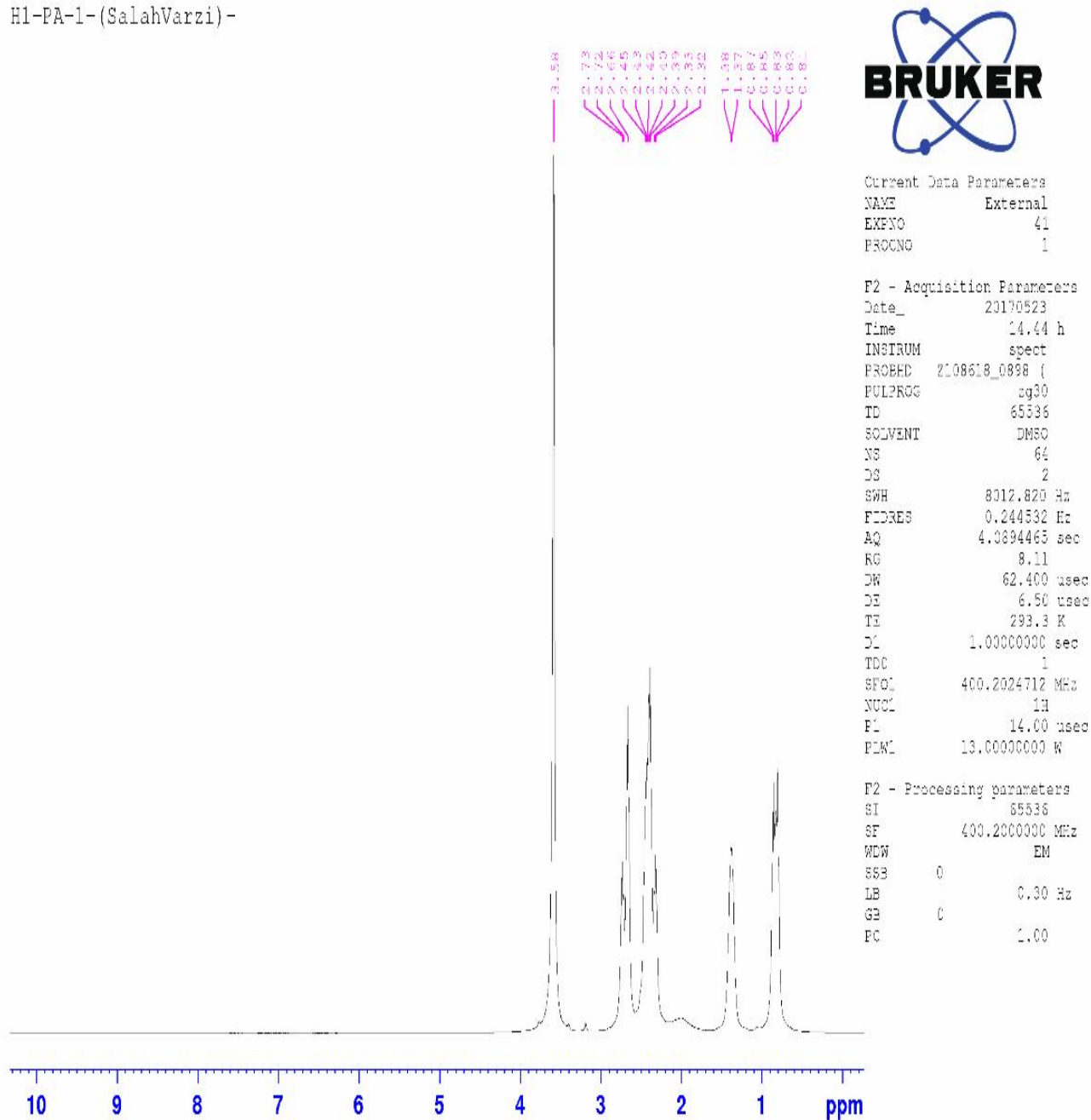


Fig. 6. ^1H NMR spectrum of B.

peak for NH shows that both hydrogens of amine of PA have been replaced indicating the formation of B product. The IR spectrum of B product has been shown in Fig. 5. The proton spectrum is taken in dimethyl sulfoxide (DMSO)

solvent and a few of its index signals were evaluated as the representative signals. No peak appeared for NH proton confirming the formation of B product. ^1H NMR spectrum of B product is shown in Fig. 6.

C13-PA-1-(SalahVarzi)-

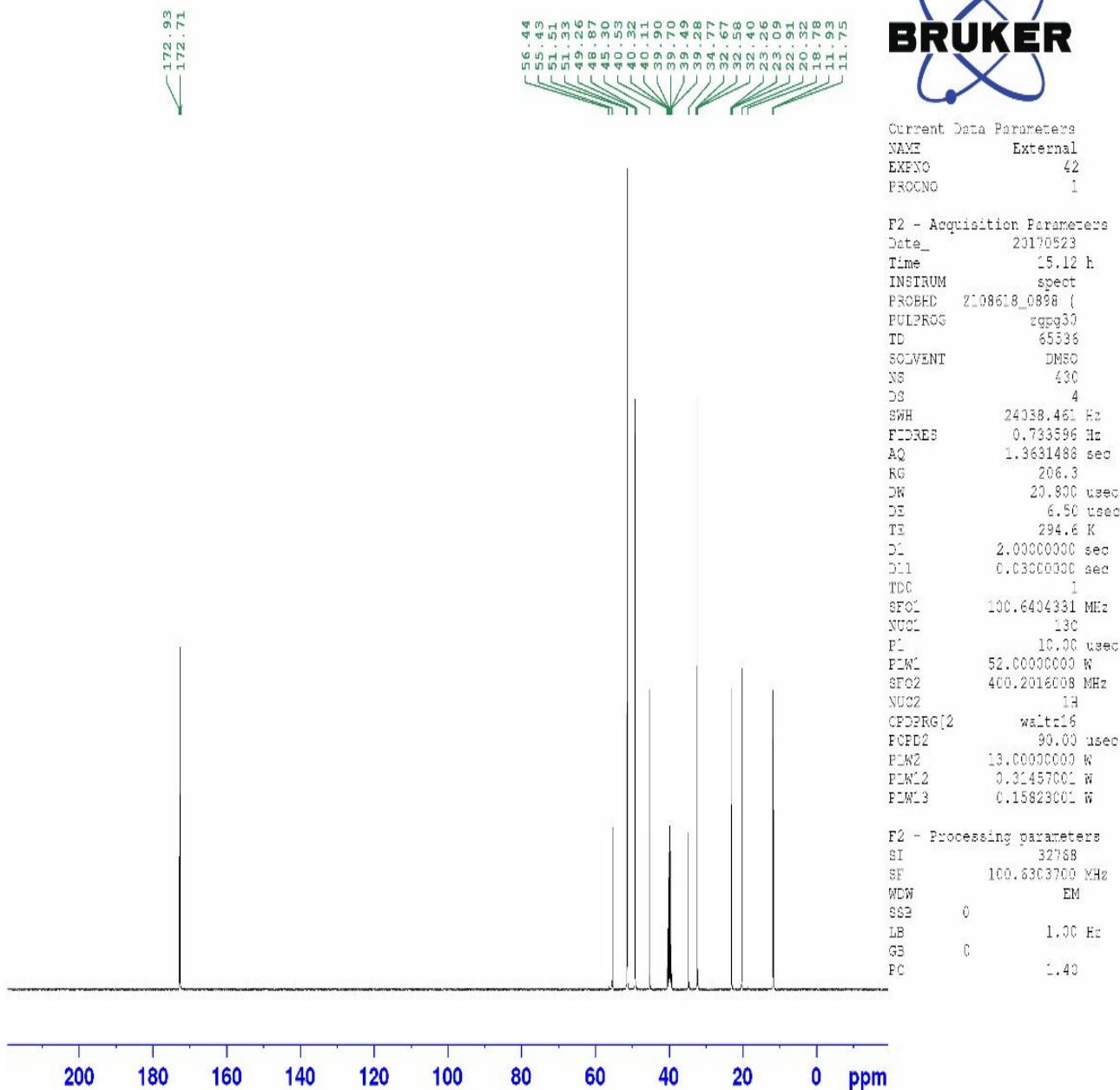


Fig. 7. ¹³C NMR spectrum of B.

The carbon spectrum was taken in dimethyl sulfoxide (DMSO) solvent. In this spectrum, in addition to the seven-point solvent peak appeared at 39.28 to 40.53 ppm, 10 other peaks related to the 10 atoms of carbon were observed. Peak related to carbonyl appeared at 172 ppm. The ¹³C NMR

spectrum of product B is shown in Fig. 7.

Evaluation of Reaction of B Product with PPI

Reaction of B with PPI is shown in Fig. 2 and it was determined based on spectral evaluations that C product has

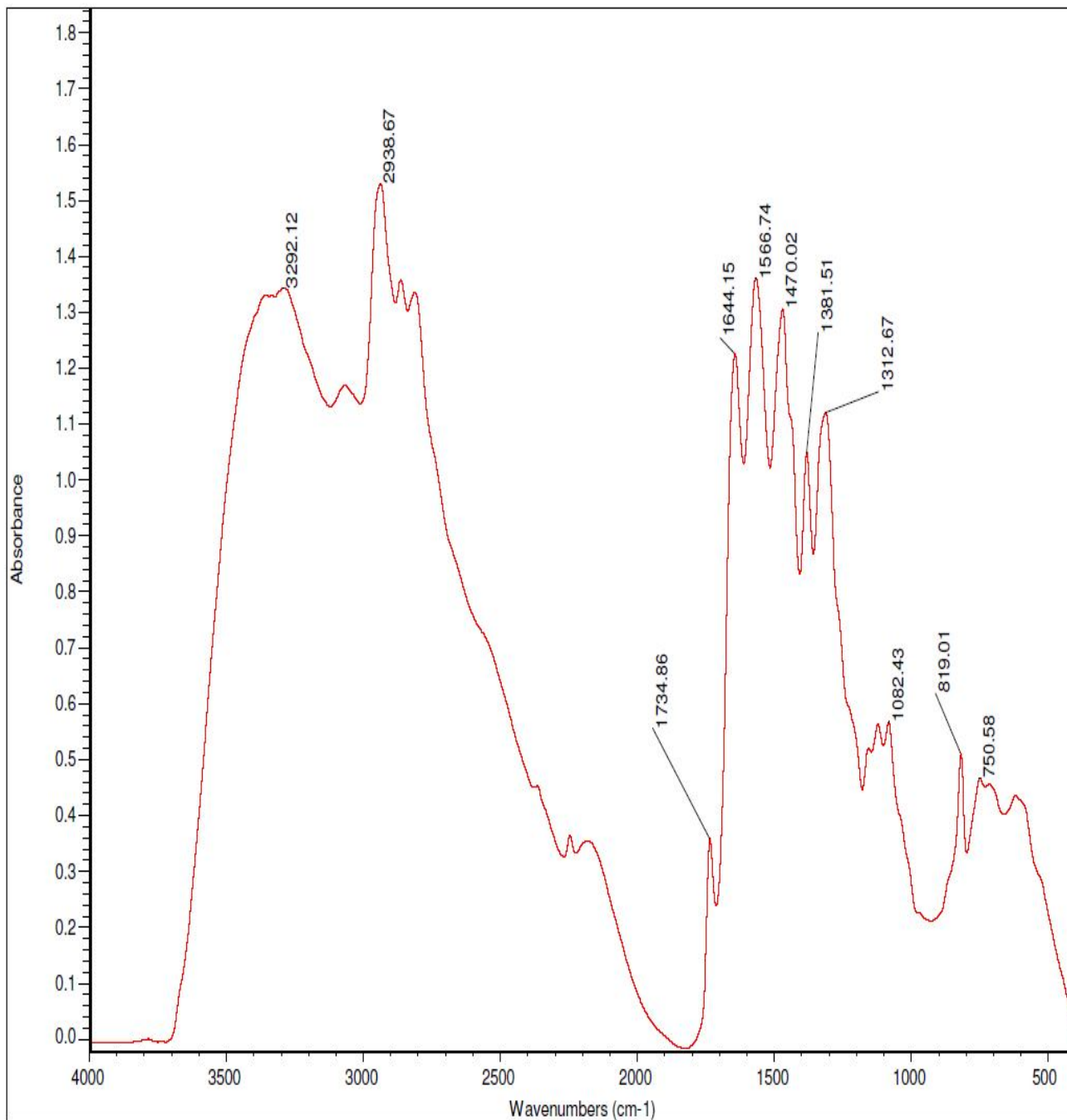
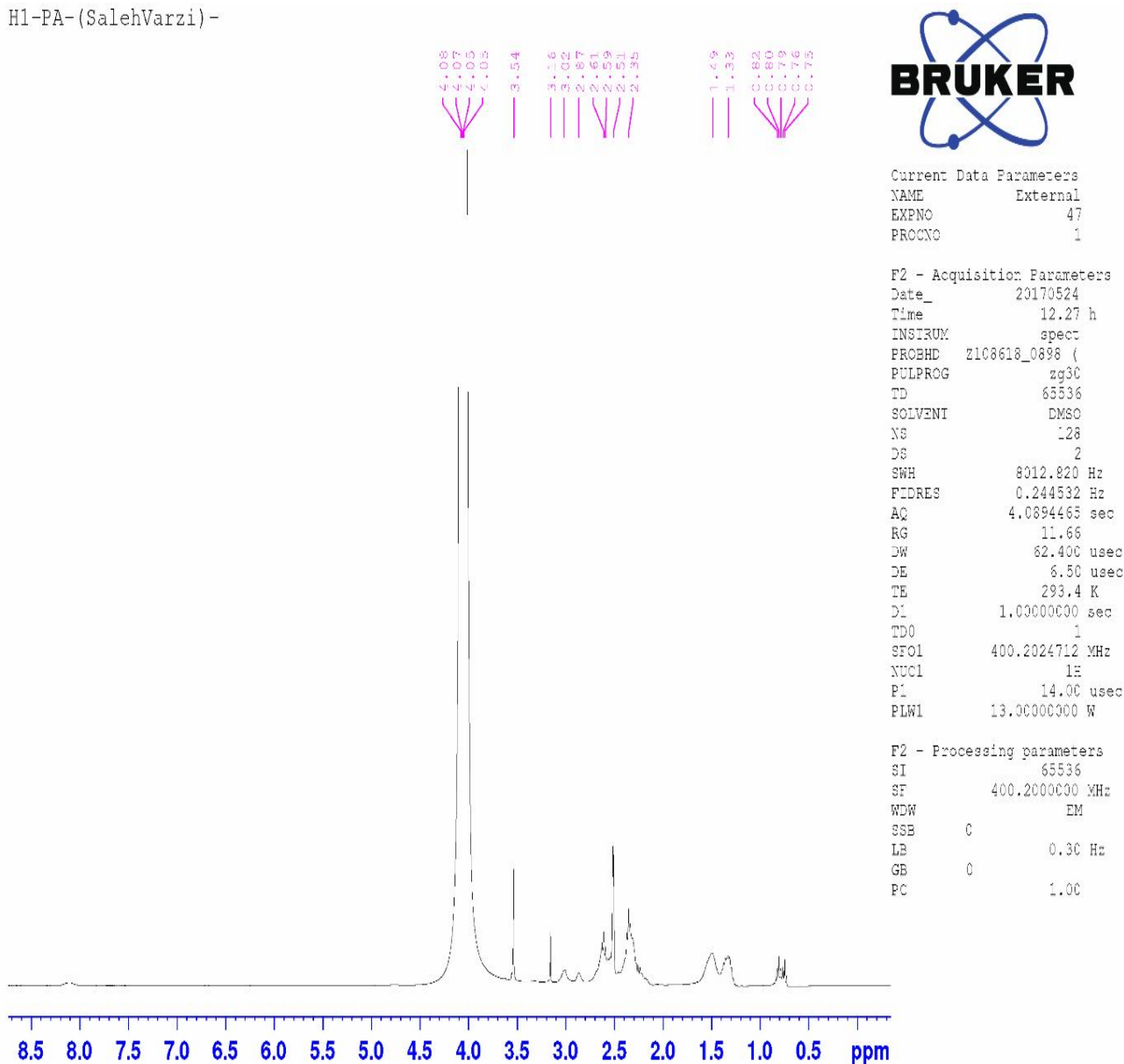


Fig. 8. IR spectrum of C.

been created. As it can be observed in IR spectrum, absorption peaks in the areas of 2813-2956 cm⁻¹ are related to stretching vibrations of C-H aliphatic. The stretch

vibrations related to carbonyl of ester appeared at 1739 cm⁻¹ and tensile vibrations related to carbonyl-epoxy appeared at 1640. The tensile vibration of the two H-N groups appeared

H1-PA-(SalehVarzi)-

Fig. 9. ^1H NMR spectrum of C.

at 3457 cm^{-1} . IR spectrum of product C is shown in Fig. 8.

The proton spectrum was taken in dimethyl sulfoxide (DMSO) solvent, and a few of its index signals were evaluated as the representative signals. For proton NH, a peak appeared at 3.5 ppm, also peak related to protons of two methoxy groups appeared at 4 ppm indicating the

formation of C product. The ^1H NMR spectrum of product C is shown in Fig. 9. The carbon spectrum was taken in dimethyl sulfoxide (DMSO) solvent. In this spectrum, in addition to the seven-point solvent peaks appeared at 39.28 to 40.53 ppm, 10 other peaks related to 15 atoms of carbon were observed. The peak related to carbon of carbonyl

C13-PA-(SalehVarzi)-

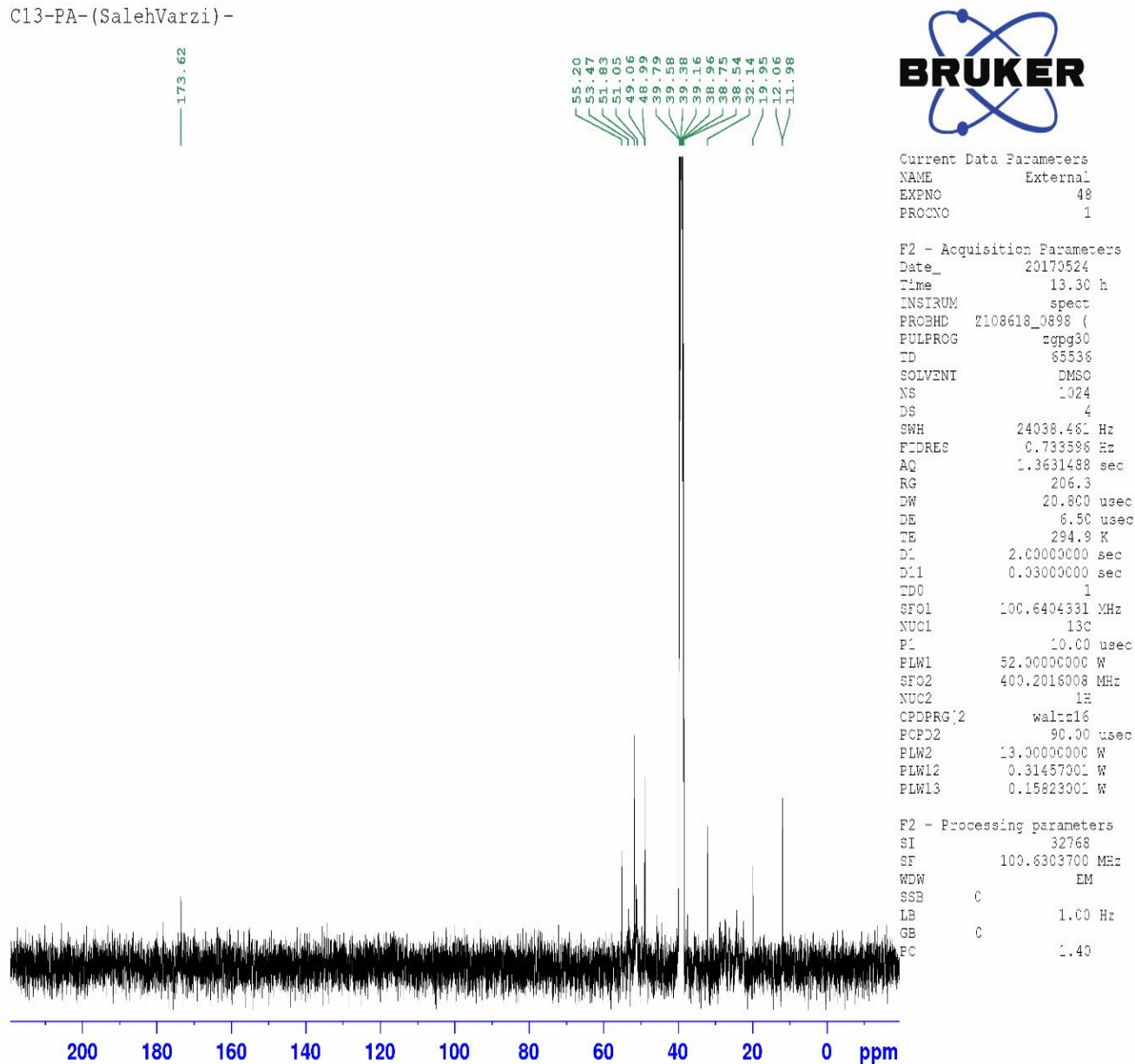


Fig. 10. ^{13}C NMR spectrum of C.

appeared at 173 ppm. The ^{13}C NMR spectrum of product C is shown in Fig. 10.

Evaluation of Reaction Ethylenediamine with Methyl Acrylate

Based on spectral evidence and the molar ratio

considered for initial materials, it is expected that all four hydrogen atoms of ethylenediamine are involved in reaction with methyl acrylate. Hence, F product will be the main product of this reaction. The obtained product was a viscous yellow liquid with a boiling point of 170 °C.

As it can be observed in IR spectrum, absorption peaks

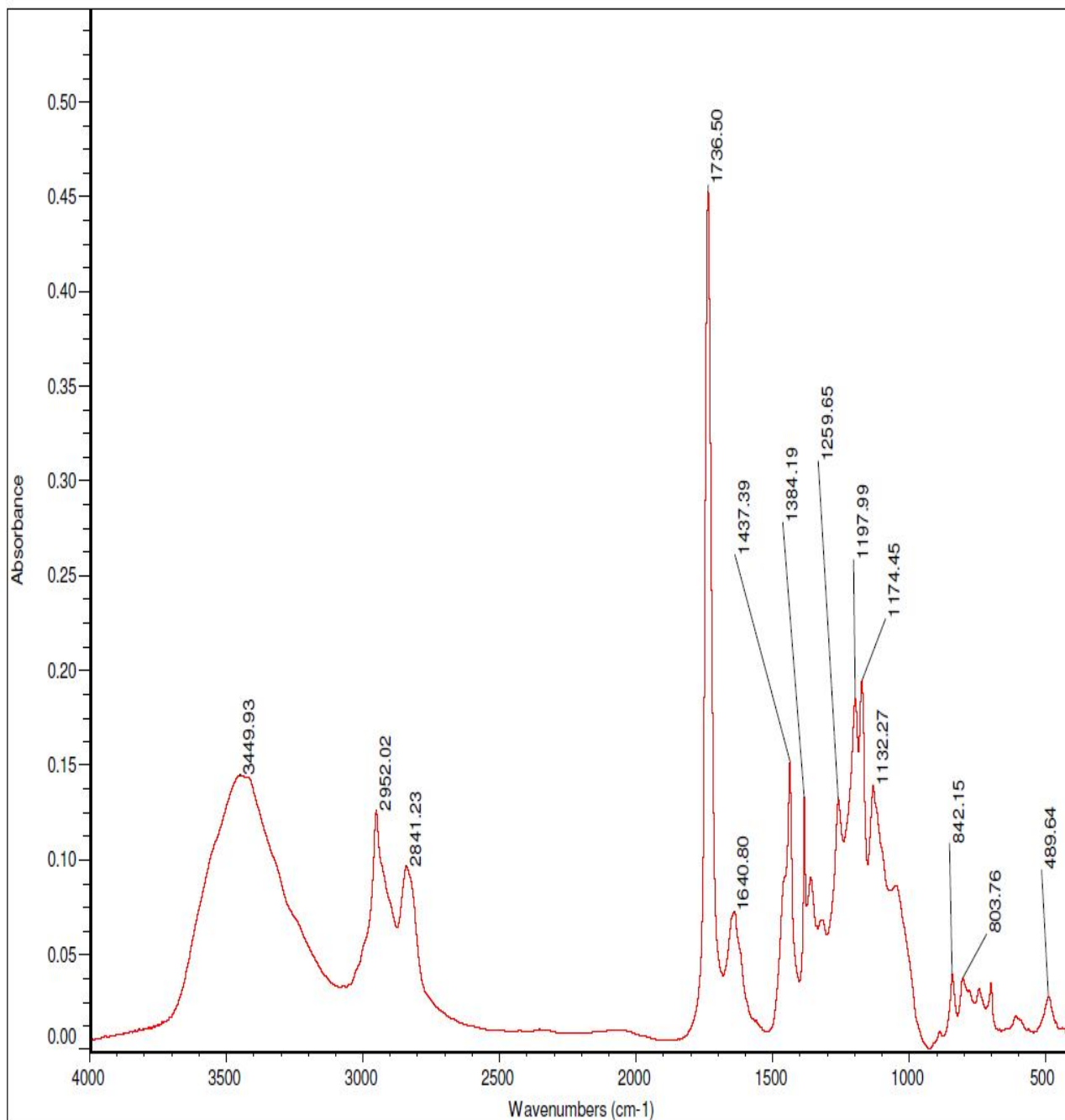


Fig. 11. IR spectrum of F.

in the areas of 2841-2952 cm⁻¹ are related to stretching vibrations of C-H aliphatic. The stretch vibrations related to carbonyl of ester appeared at 1736 cm⁻¹. The IR spectrum of

product F is shown in Fig. 11.

The proton spectrum was taken in dimethyl sulfoxide (DMSO) solvent, and a few of its index signals were

H1-EDA-1-(SalahVarzi)-

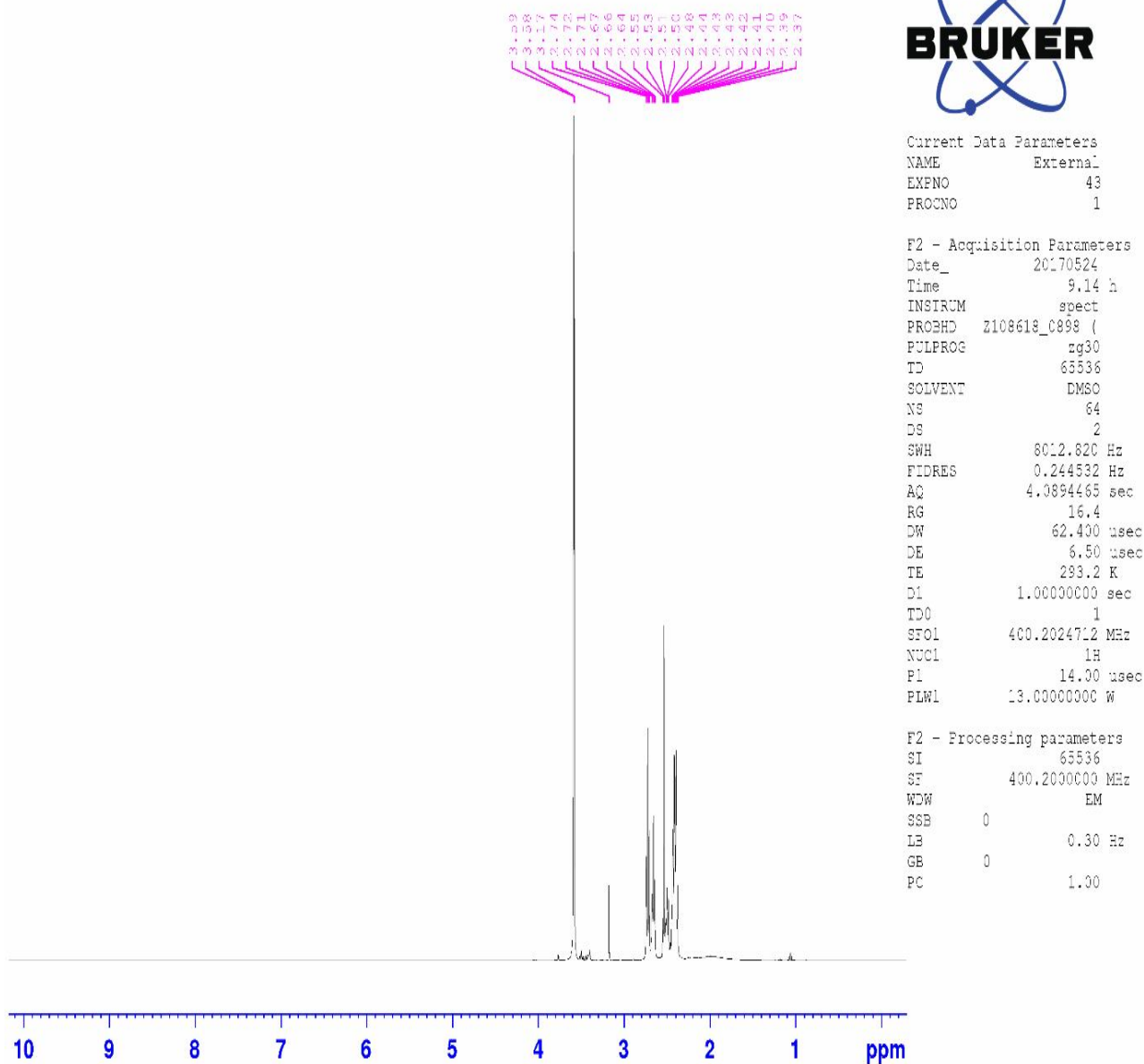


Fig. 12. ^1H NMR spectrum of F.

evaluated as the representative. The protons related to four methoxy groups are observed at 3.58 ppm. Other CH_2s also appeared before that. There has been no peak for NH proton indicating the formation of F product. The ^1H NMR spectrum of product F is shown in Fig. 12.

The carbon spectrum was taken in dimethylsulfoxide

(DMSO) solvent. In this spectrum, in addition to the seven-point solvent peak appeared from 39.28 to 40.53 ppm, 5 other peaks related to 5 atoms of carbon were also observed. Peak related to carbon of carbonyl group appeared at 172.9 ppm. The ^{13}C NMR spectrum of product F is shown in Fig. 13.

C13-EDA-1-(SalahVarzi)-

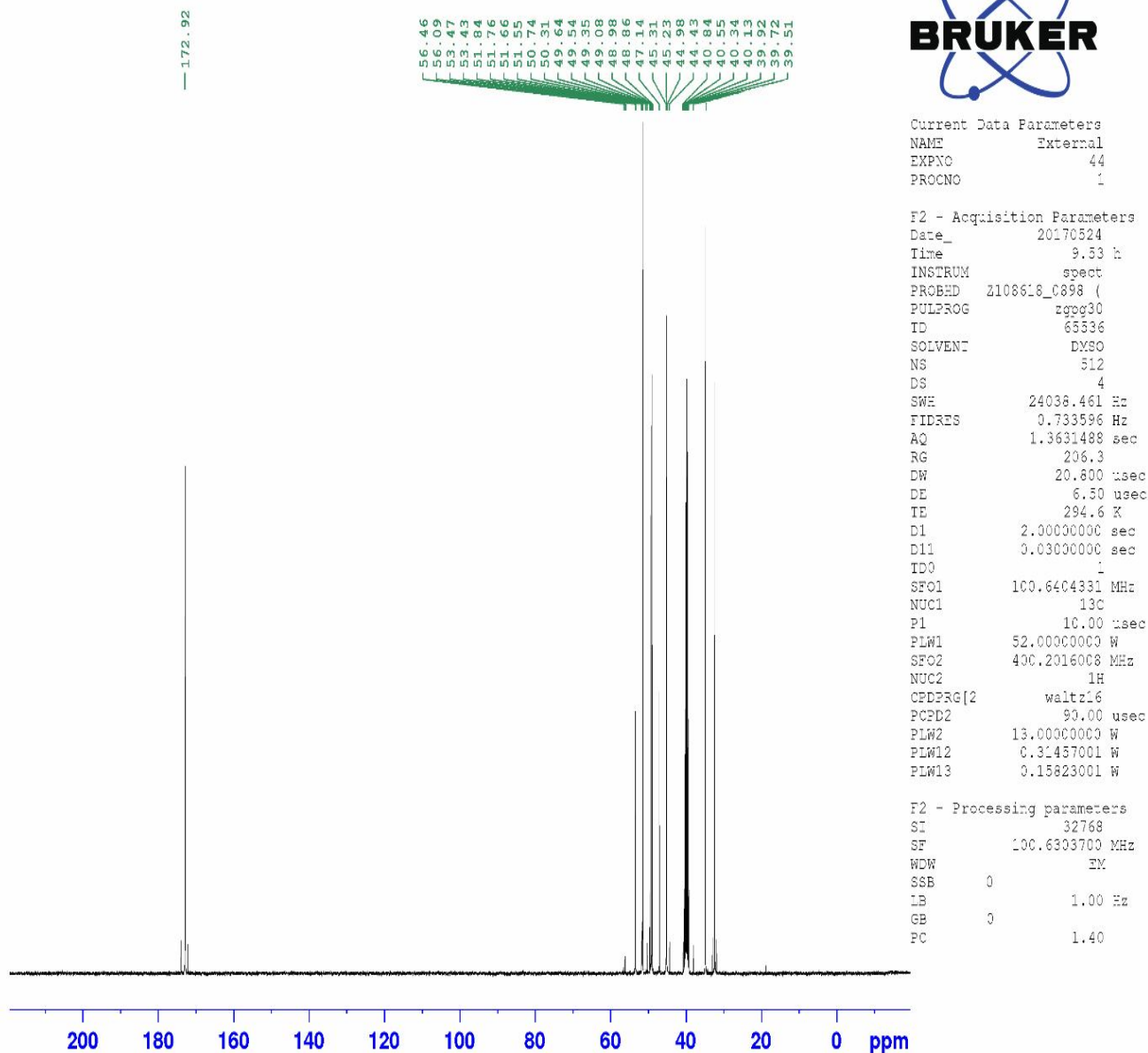


Fig. 13. ^{13}C NMR spectrum of F.

Evaluation of Reaction of F Composition with PPI

Reaction of F compound with PPI is shown in Fig. 4 and it was determined based on the spectral analysis that H product is created. The tensile vibration has appeared at 1736 cm^{-1} for carbonyl of ester and at 1640 cm^{-1} for carbonyl of amid. The tensile vibration of the two H-N

groups appeared at 3449 cm^{-1} . The IR spectrum of product H is shown in Fig. 14.

The peak for protons of 4 groups of NH appeared at 3.58 ppm. Also, peak related to protons of two methoxy groups appeared at 3.39 ppm and peak related to protons of other CH_2 groups appeared before this range indicating the

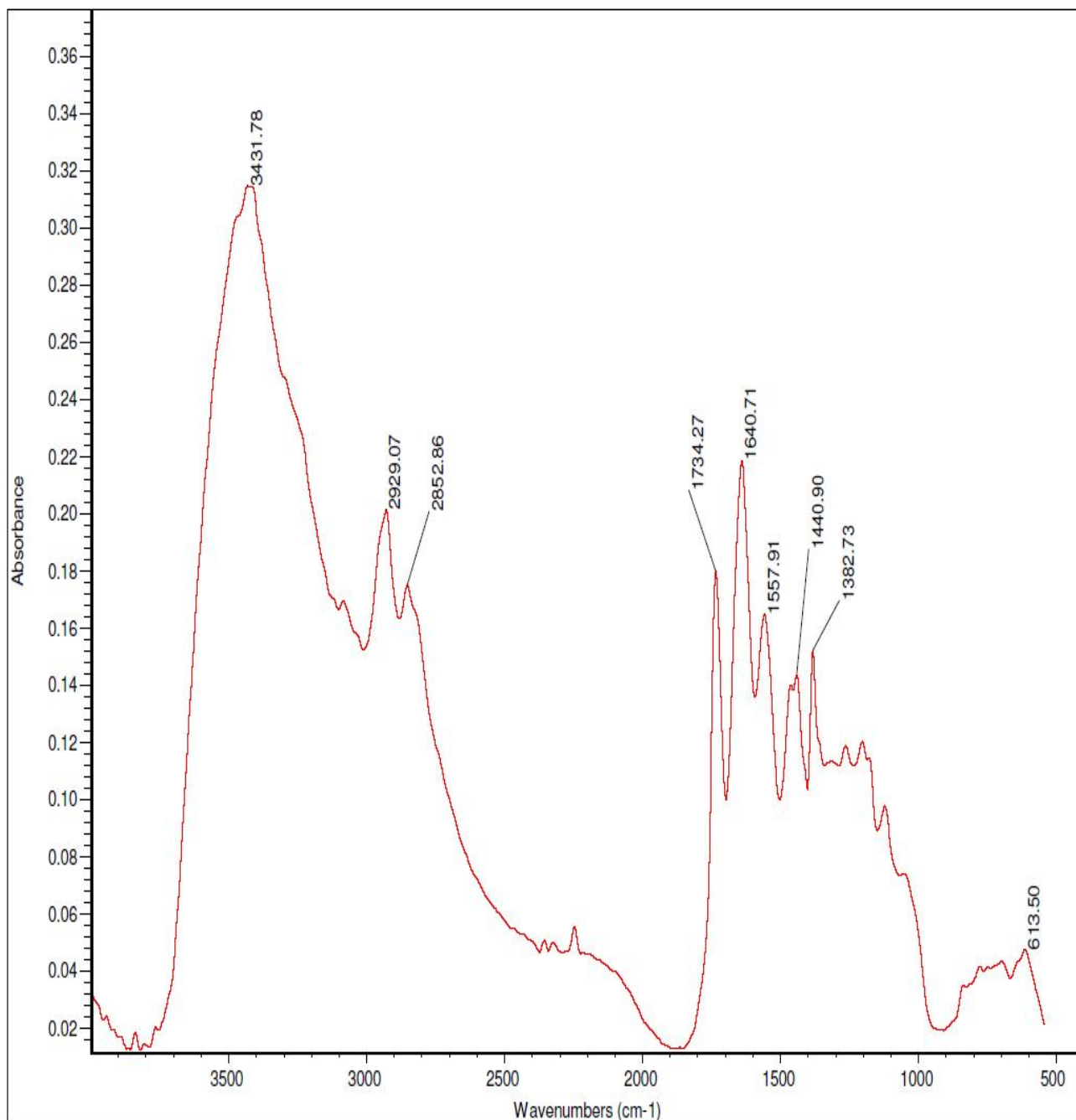


Fig. 14. IR spectrum of H.

formation of H product. The ¹H NMR spectrum of product H is shown in Fig. 15.

The carbon spectrum was taken in dimethyl sulfoxide

(DMSO) solvent. In this spectrum, in addition to the seven-point solvent peak appeared from 39.30 to 40.55 ppm, 12 other peaks related to 12 atoms of carbon could be

H1-EDA-(SalehVarzi)-

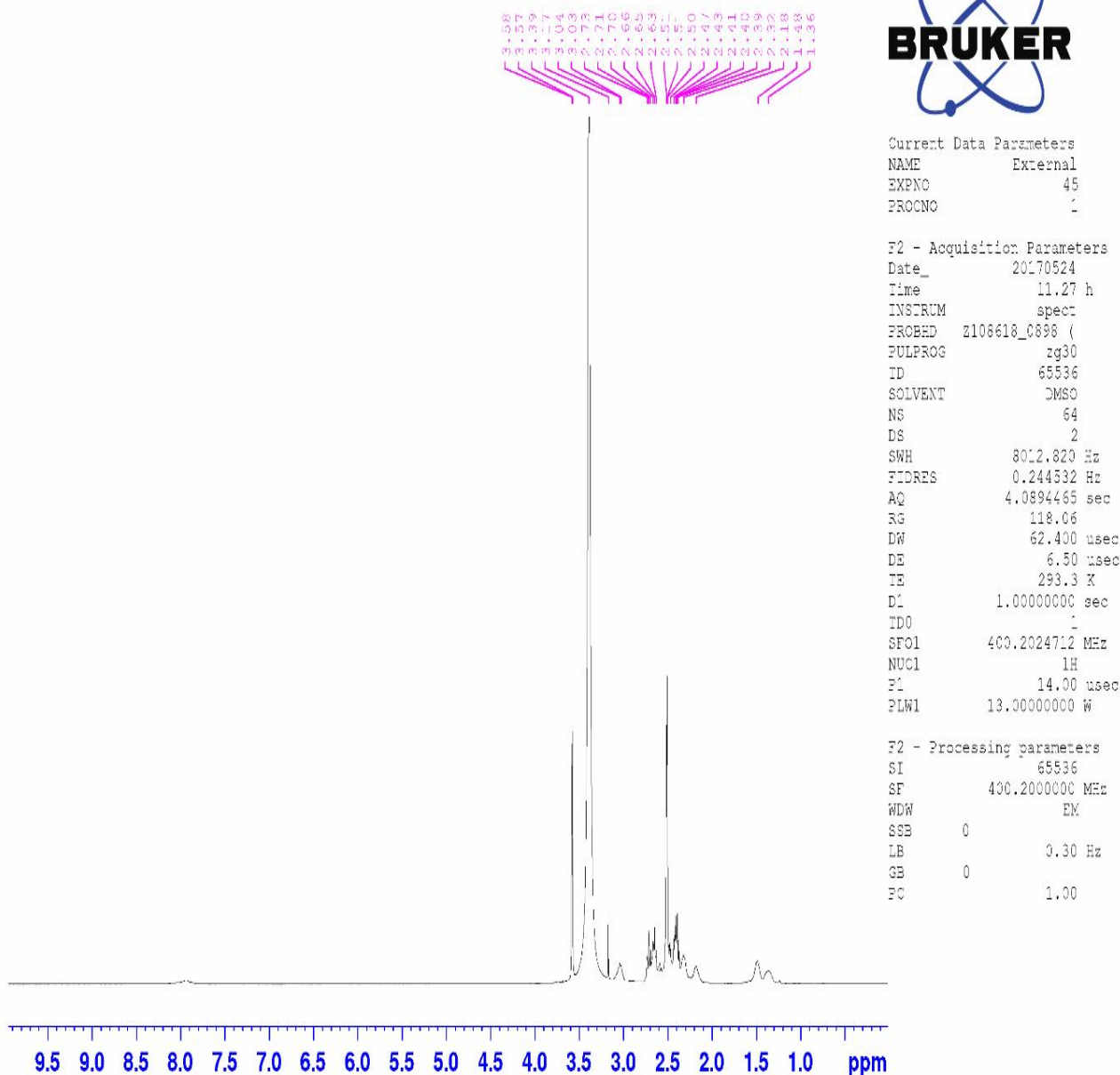


Fig. 15. ^1H NMR spectrum of H.

observed. The peak related to carbon of carbonyl appeared at 173.01 ppm. The ^{13}C NMR spectrum of product H is shown in Fig. 16.

Scanning Electron Microscopy Imaging

SEM images clearly show the formation of arms and

their growth. A number of SEM images are shown in Fig. 17. Figure 17 shows that the diameter of the arms is an average of 31.27 nm. The second image represents particles with diameters of 28.5 to 38.99 nm indicating that particles are synthesized in the nanoscale. The fourth image shows branching morphology (formation of Dendrimer).

C13-EDA-(SalehVarzi)-

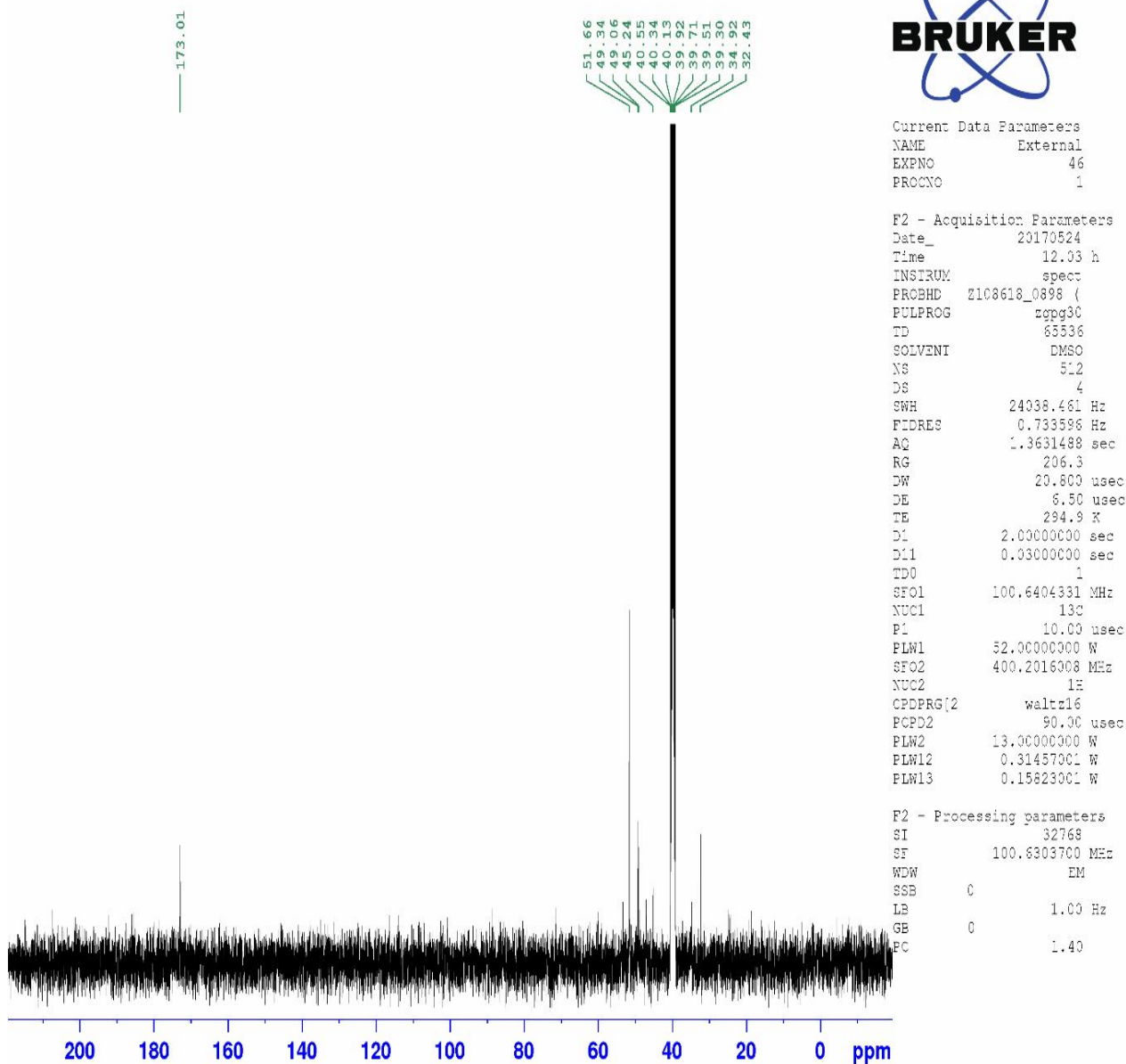


Fig. 16. ^{13}C NMR spectrum of H.

Quantitative and qualitative study of the sample were performed using EDS separation spectrometer confirming the formation of H product (Fig. 18).

CONCLUSIONS

The use of poly(propylene imine) dendrimer to design

an efficient core for the synthesis of a variety of dendrimers has been demonstrated by means of divergent method. The length of chains of dendrimers depends on the monomer/initiator ratio; hence the structure and morphology of dendrimers can be changed by using different monomer/initiator ratios. The structures of all compounds were characterized by IR, ^1H and ^{13}C NMR spectroscopies as

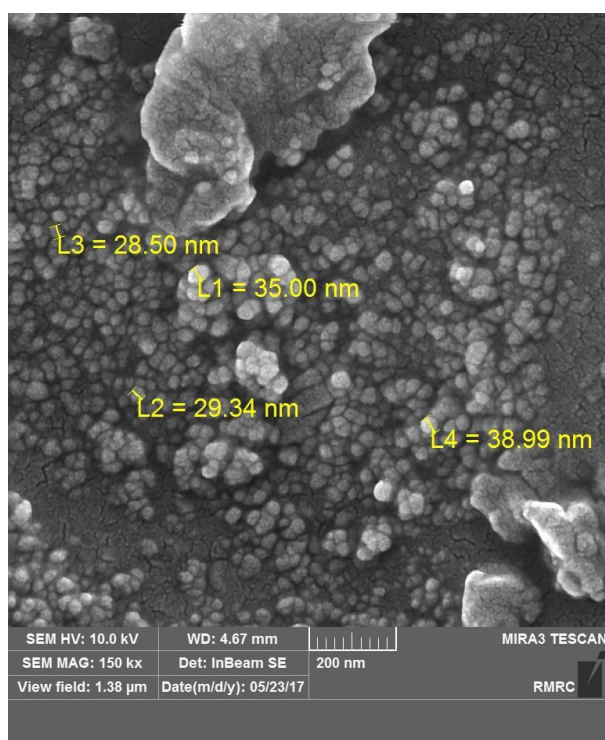
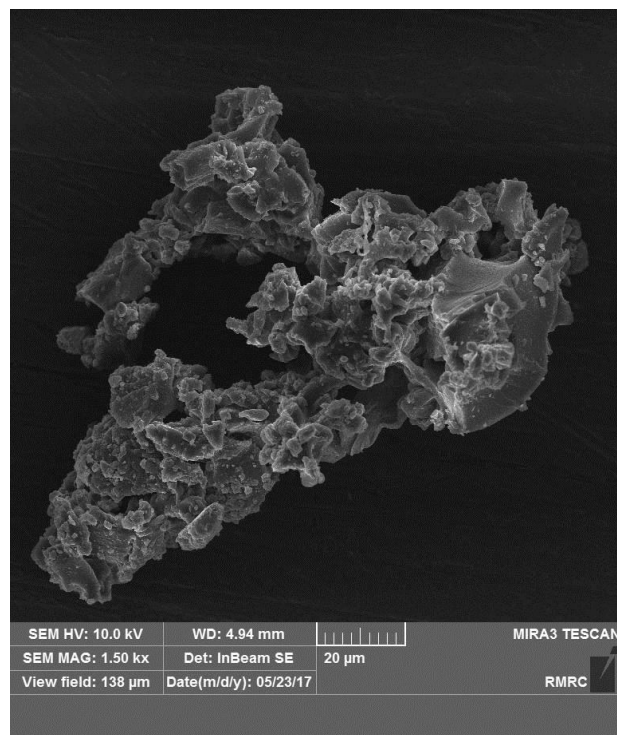


Fig. 17. SEM images of H. The SEM images clearly show the formation of arms and their growth.

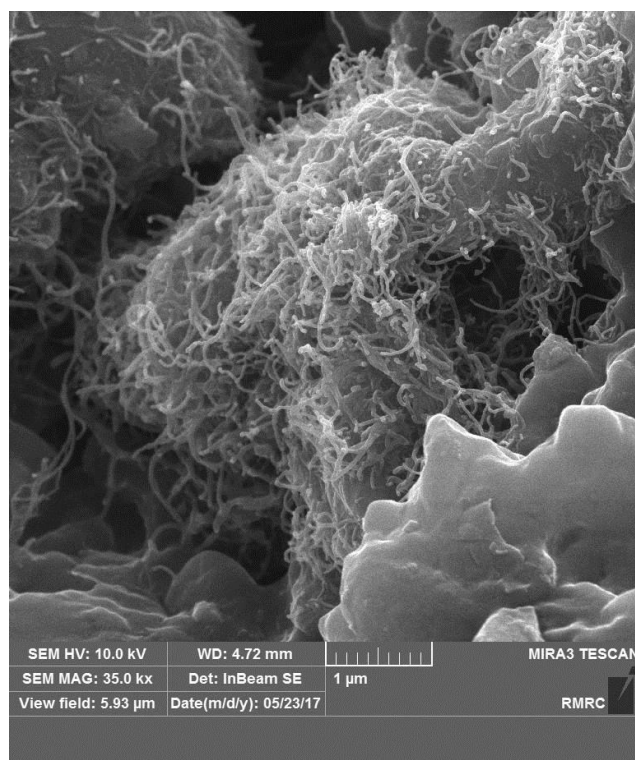
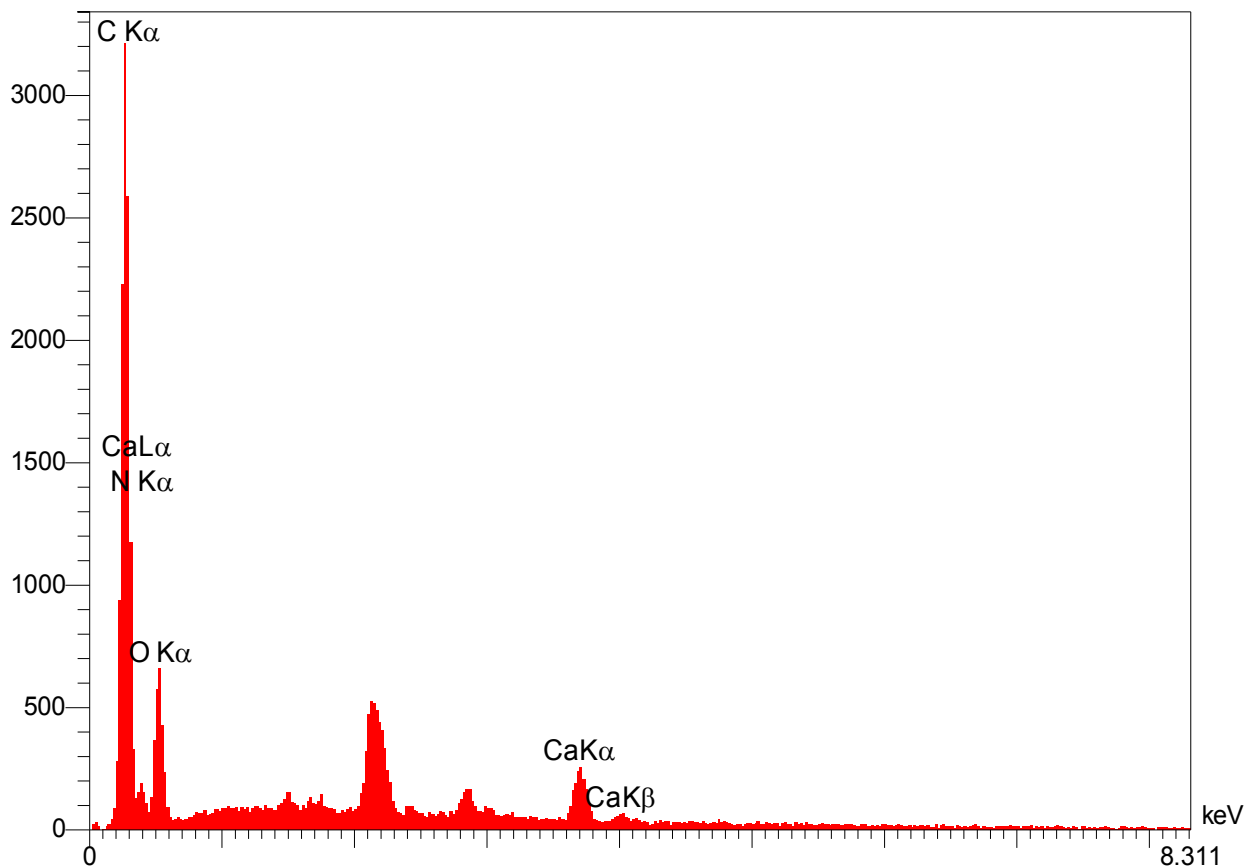


Fig. 17. Continued.



Elt	Line	Int	Error	K	Kr	W%	A%	ZAF	Formula	Ox%	Pk/Bg	Class	LConf	HConf	Cat#
C	Ka	345.2	17.6026	0.7598	0.4393	53.80	61.05	0.8165		0.00	139.90	A	52.75	54.86	0.00
N	Ka	19.3	17.6026	0.0633	0.0366	18.91	18.40	0.1934		0.00	14.96	A	17.34	20.48	0.00
O	Ka	77.2	17.6026	0.1018	0.0588	22.03	18.77	0.2670		0.00	50.93	A	21.12	22.95	0.00
Ca	Ka	43.7	1.0128	0.0752	0.0435	5.25	1.79	0.8277		0.00	7.88	A	4.96	5.54	0.00
				1.0000	0.5782	100.00	100.00			0.00					0.00

Fig. 18. EDS separation spectrometer of H.

well as SEM techniques that have fit and nano size morphology. This method offers several advantages including short reaction time, simple work-up and good yields that could be have proper prospects of applications in organic syntheses and pharmacy processes. Afterwards, the

prepared dendrimers are evaluated with in vitro methods, which show good antibacterial and antioxidant activity. Since the dendrimers are biocompatible materials and able to trap the small guest molecules hence they are promising materials as nano carrier for application in the biological

Table 1. Spectral (IR, ¹N MR and ¹³C NMR) Results of the Synthesized Compounds

Compound	Spectral results
H	1736 cm ⁻¹ (Ester, >C=O str), 1640 cm ⁻¹ (amide, >C=O str), 3449 cm ⁻¹ (N-H str two H-N groups), 3.58 ppm (4H, N-H), 3.39 ppm (6H, OCH ₃), 173.01 ppm (C=O).
F	2841-2952 cm ⁻¹ (Aliphatic C-H), 1736 cm ⁻¹ (Ester, >C=O str), 3.58 ppm (12H, OCH ₃), 3.58 ppm (Other CH ₂ groups), 172.9 ppm (C=O).
B	2813-2966 cm ⁻¹ (Aliphatic C-H), 1739.95 cm ⁻¹ (Ester, >C=O str), 172 ppm (C=O). The absence of peak for N-H in IR and H NMR indicating the formation of product B.
C	2813-2956 cm ⁻¹ (Aliphatic C-H), 1739 cm ⁻¹ (Ester, >C=O str), 1640 cm ⁻¹ (amide, >C=O str), 3457 cm ⁻¹ (N-H str two H-N groups), 3.5 ppm (4H, N-H), 4 ppm (6H, OCH ₃), 173 ppm (C=O).

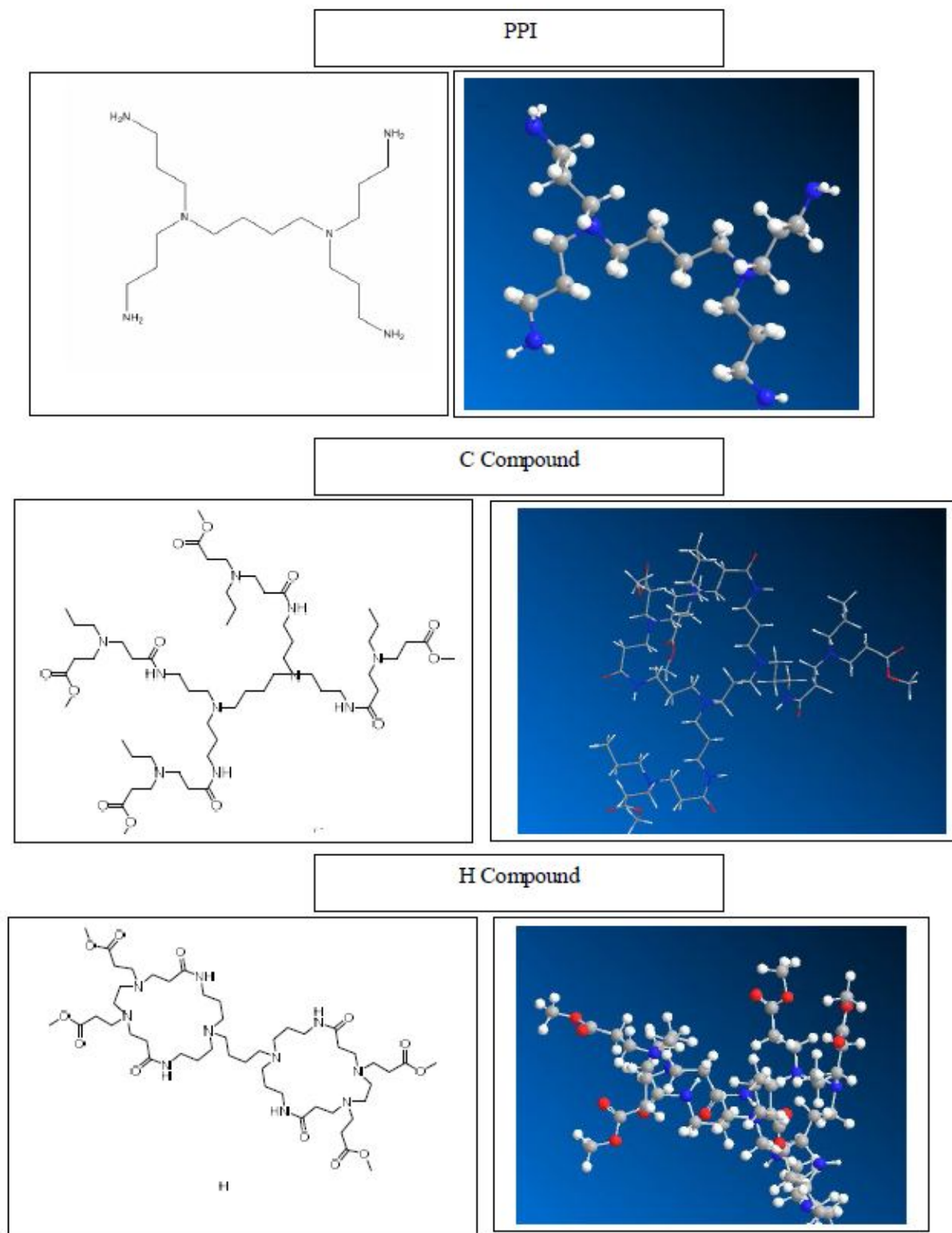
and medicinal systems.

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Scheme 1. Display model of ball-stick for PPI, C and H compounds

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