SYNTHESIS OF DENDRIMER MOLECULES BASED ON TRIAZINE

M. PHIL THESIS

SUBMITTED IN THE PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF PHILOSOPHY (M. PHIL) IN CHEMISTRY

Submitted By

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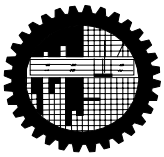
Session: **October, 2006**



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It is hereby declared that this thesis or any part of it has not been submitted elsewhere for the award of any degree or diploma.

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THESIS ACCEPTANCE LETTER

The thesis titled "**Synthesis of dendrimer molecules based on triazine**" Submitted by Fatima Tahura-E Jannat. Roll No: 100603117 F, Registration No: 100603117, Session: October, 2006 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Master of Philosophy (M. Phil) in Chemistry on 31 March, 2012.

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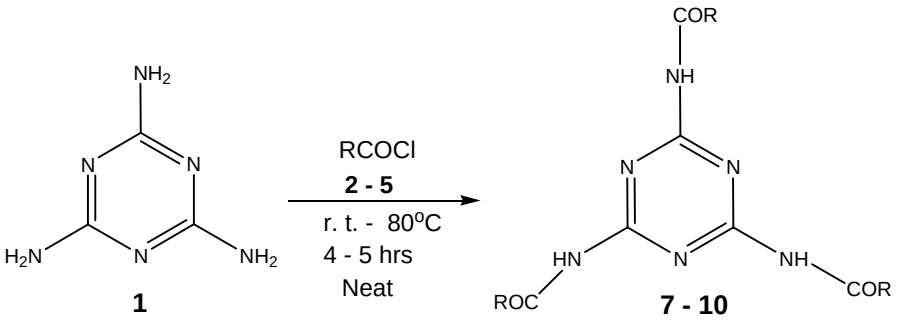
Author

Fatima Tahura –E Jannat

Abstract

Dendrimers are highly branched, globular, multivalent, monodisperse molecules with synthetic versatility and many possible applications ranging from catalysis to electronics and drug delivery. Due to versatile applications it was planned to develop a method to synthesis dendrimer molecules based on triazine.

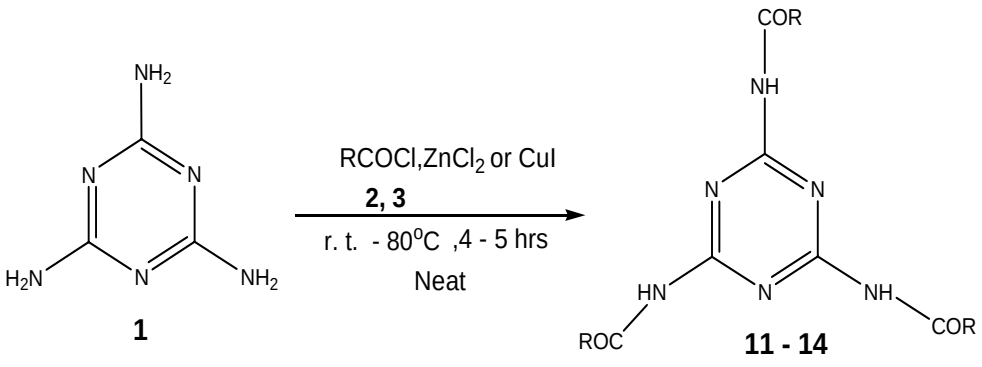
A convenient method for the synthesis of dendrimer molecule **(7-10)** was developed from the reaction of melamine with different acylchlorides **(2-5)** as shown in **scheme 1.**



Compound	R
2, 7	*p*-CH_3-C_6H_4
3, 8	CH_3
4, 9	C_6H_5
5, 10	*p*-Cl-C_6H_5

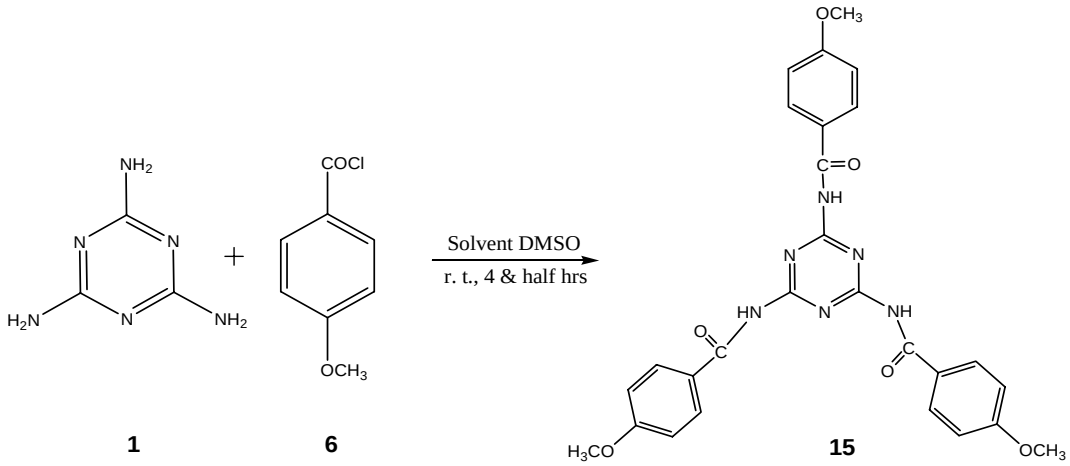
Scheme – 1

Another method for synthesis of metallodendrimer **(11-14)** was developed from the reaction of melamine with different acyl chloride **(2, 3)** as shown in **scheme 2.**



Compound	R
3, 11	CH_3
3, 12	CH_3
2, 13	*p*-CH_3-C_6H_4
2, 14	*p*-CH_3-C_6H_4

Scheme – 2



1 **6** **15**

Scheme - 3

All the synthesized compounds were characterized by NMR, IR, and UV to establish the structure. EDX was taken for metal investigation and SEM was also taken for analysis of surface morphology. Compound **11,12,13,14** were found having a homogeneous morphology with the particle size range from 1 µm to 7.69 µm. The particle sizes detected by SEM indicated that, all the molecules were supramolecules.

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Chapter – 3

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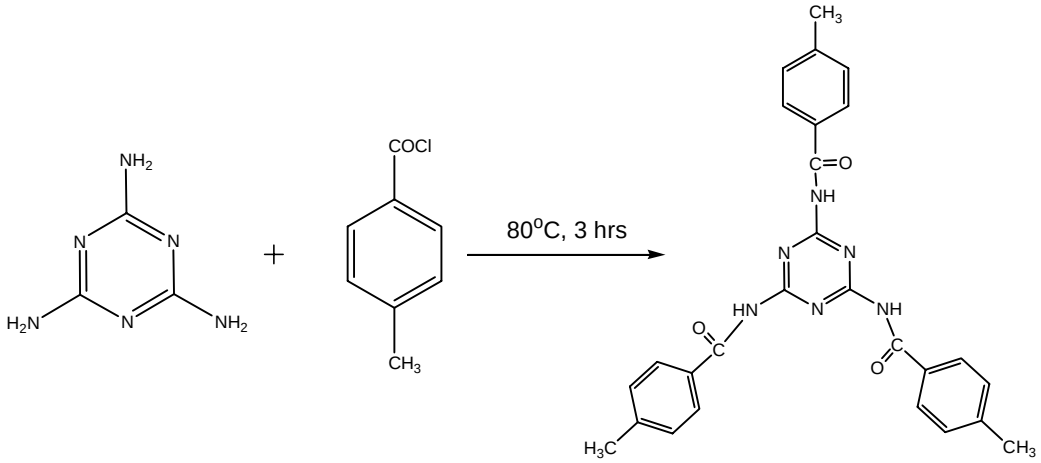
3.0 General experimental

Melting points were determined in open capillary tubes in melting point apparatus (Model BUCHI, B-540). NMR spectra were taken on BRUKER DPX–400 spectrophotometer using tetramethylsilane as an internal standard. UV spectra were recorded on a UV-1800, SHIMADZU spectrophotometer. IR spectra were recorded on a SHIMADZU FTIR spectrophotometer. SEM images were taken in a Scanning Electron Microscope (Model JSM-6490). Then the EDX spectrums were taken with EDS (Model JEOL 6490LA) by selecting several spots or zone of the sample.

3.1 Synthesis of 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine, 7:

In a 250 ml round bottle flask, provided with a reflux condenser, 1 g of melamine and 10 ml *p*- toluoylchloride were added and the reaction mixture was shaken steadily. The reaction mixture was stirred overnight at room temperature and then refluxed for an additional 3 hrs with constant stirring at 80^{o}C. The progress of the reaction was monitored. At the starting of the reaction, the mixture was turned into a clear solution and gradually it turned into white solid. After completion of the reaction, the flask was allowed to cool at first room temperature and then at 0^{o}C. After cooling the reaction mixture it was filtered under suction on a Buchner funnel and washed with sufficient distilled water. Finally the compound was washed with acetone for at least 3 times and was kept in desiccator.



1 **2** **7**

Scheme-1

MF: $C_{27}H_{24}N_6O_3$

MW: 480

Physical analysis: White powdered solid, mp. 210 – 294.8 ^oC, odorless and 81 % yield.

Analytical analysis:

^{1}H NMR (400 MHz, CD_3OD): δ_H 7.90 (d, 2H, Ar-H, J= 8.0 Hz), 7.27 (d, 2H, Ar-H, J= 8.0 Hz), 4.92 (s, 3H,-NH-), 2.39 (s, 9H,-CH_3).

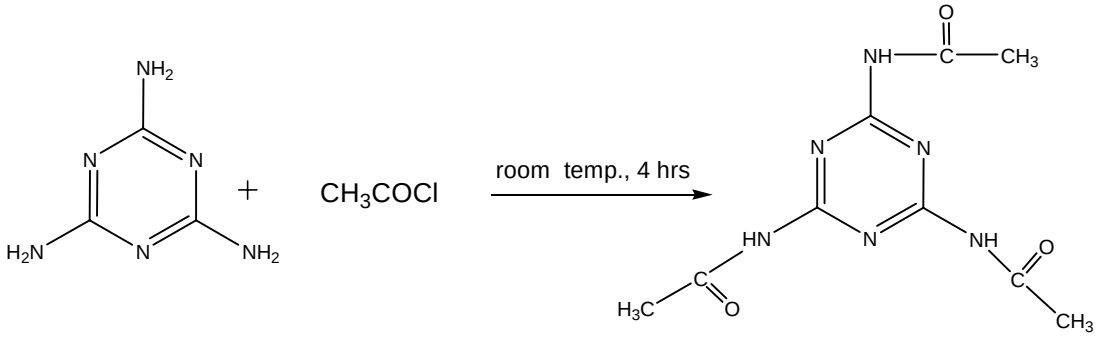
^{13}C NMR (100.40 MHz, CD_3OD): δ_C 169.99, 144.96, 129.09, 130.79, 130.07.

IR (KBr): ν_{max} 3350, 3049.2, 2976.0, 1678.0, 1612.4, 1284.5, 754.1 cm^{-1}

UV (EtOH): λ_{max} 253, 242 nm.

3.2 Synthesis of 2,4,6-Tris(acetamido)-1,3,5-triazine, 8 :

In a 250 ml round bottle flask, 1 g of melamine and 10 ml acetylchloride were added and the reaction mixture was shaken steadily. The reaction mixture was stirred for 4 hrs. at room temperature. The progress of the reaction was monitored. After 3 hrs the change of the reaction mixture was observed and it became concentrated. Finally the colour of the reaction turned to white. After completion the reaction, the reaction solution was allowed to cool at low temperature (25-0^{o}C). After cooling the reaction mixture it was filtered under suction on a Buchner funnel with sufficient distilled water. Finally the compound was washed with acetone for at least 3 times and dried in desiccator.



1 **3** **8**

Scheme – 2

MF: $C_9H_{12}N_6O_3$

MW: 252

Physical analysis: White powdered solid, mp: not melt up to 400 ^oC, odorless and 52 % yield.

Analytical analysis:

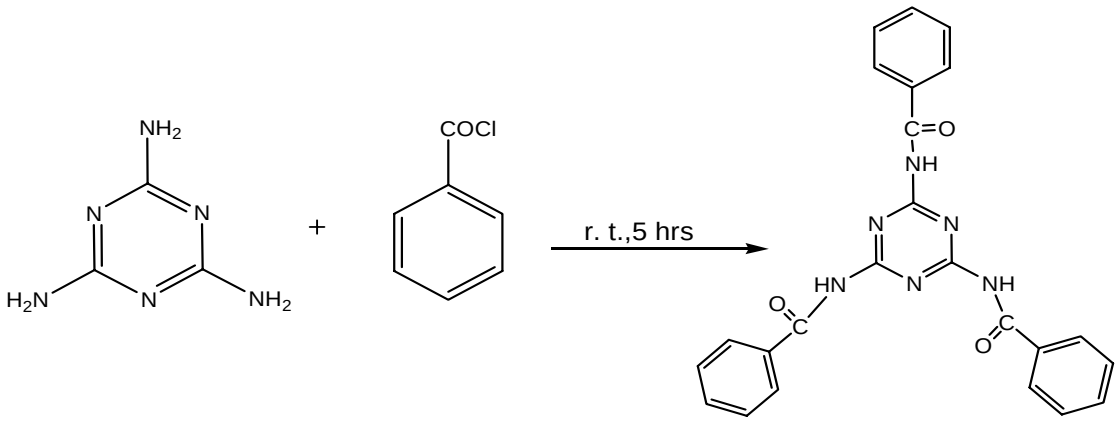
^{1}H NMR (400 MHz, D_2O): δ_H 5.31 (s, 3H, -NH-), 2.08 (s, 9H,-CH_3,).

^{13}C NMR (100.40 MHz, D_2O): δ_C 160.44, 151.82, 68.23.

IR (KBr): ν_{max} 3342.4, 2950.0, 1691.5, 1336.6, 773.4 cm^{-1}

3.3 Synthesis of 2,4,6-Tris(benzamido)-1,3,5-triazine, 9:

A mixture of 5 g of melamine and 10 ml benzoyl chloride were added In a 250 ml round bottle flask and the reaction mixture was shaken steadily. The mixture was stirred overnight at room temperature. After completion the reaction, the mixture was turned into white solid. The reaction mixture was allowed to cool at low temperature (25-0^{o}C). After cooling it was filtered under suction on a Buchner funnel and washed with sufficient distilled water. Then the compound was washed with sodium hydrogen carbonate solution to remove benzoic acid. Finally the product was washed by acetone and dried in desiccator.



1 **4** **9**

Scheme – 3

MF: $C_{24}H_{18}N_6O_3$

MW: 396

Physical analysis: White powdered solid, mp: partially melt in 315 ^oC, odorless and 70 % yield

Analytical analysis:

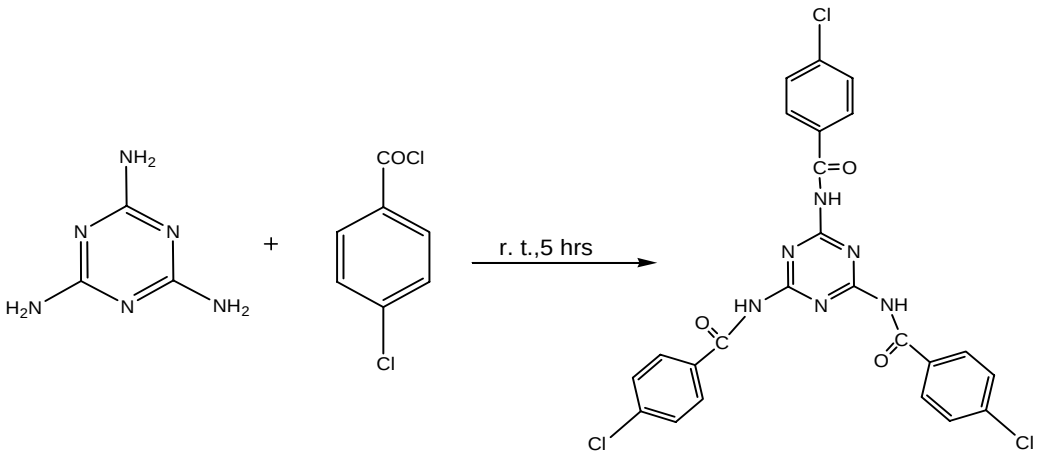
^{1}H NMR (400 MHz, D_2O): δ_H 7.89 (d, 6H, Ar-H, J=7.2 Hz), 7.51 (d, 6H, Ar-H, J=7.2 Hz), 7.37 (t, 3H, Ar-H, J=6.4 Hz), 5.32 (s, 3H, -NH-) ppm.

^{13}C NMR (100.40 MHz, D_2O): δ_C 169.99, 144.96, 130.79, 130.07, 129.09, 21.57.

IR (KBr): ν_{max} 3344.3, 3072.4, 1681.8, 1652.9, 1326.9, 707.8 cm^{-1}

3.4 Synthesis of 2,4,6-Tris(4-chlorobenzamido)-1,3,5-triazine, 10:

A mixture of 5 g of melamine and 10 ml of 4 - chlorobenzoyl chloride were added In a 250 ml round bottle flask and the reaction mixture was shaken steadily. The mixture was overnight stirred at room temperature. After completion the reaction, the mixture was turned into white solid. The reaction mixture was allowed to cool at low temperature (25-0^oC). After cooling it was filtered under suction on a Buchner funnel and washed with sufficient distilled water. Then the compound was washed with sodium hydrogen carbonate solution to remove p-chlorobenzoic acid. Finally the product was washed by acetone for at least 3 times and dried in desiccator.



1 **5** **10**

Scheme – 4

MF: $C_{24}H_{15}N_6O_3Cl_3$

MW: 541.5

Physical analysis: White powdered solid, mp: partially melt in 252.3^oC, odorless and 73 % yield

Analytical analysis:

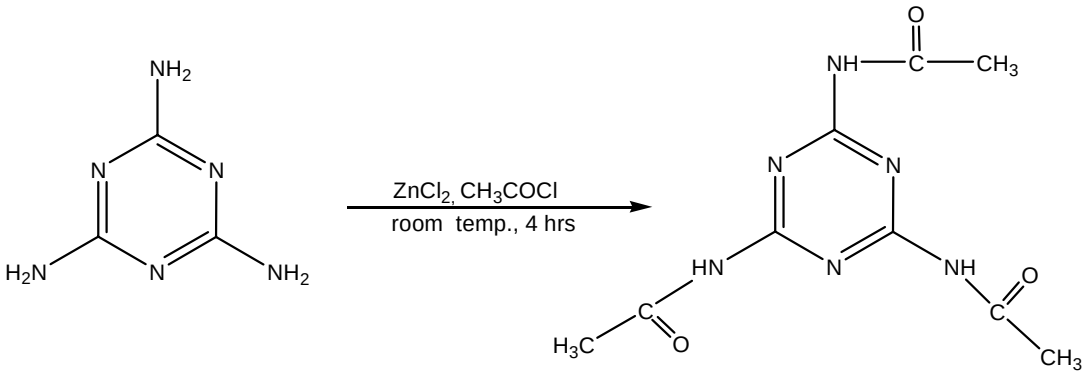
^{1}H NMR (400 MHz, CD_3OD): δ_H 7.9 - 8.0 (m, 6H, Ar-H, J= 8.8 Hz), 7.46 -7.49 (m, 6H, Ar-H, J= 8.08 Hz), 4.87 (s, 3H,-NH-).

IR (KBr): ν_{max} 3357.8, 3095.5, 2969.5, 1689.5, 1595.5, 1321.5, 848.6, 761.8 cm^{-1}

UV (EtOH): λ_{max} 255, 248.50 nm.

3.5 Synthesis of 2,4,6-Tris(acetamido)-1,3,5-triazine, 11:

A mixture of 1 g (0.0079 mol) of melamine and 3.24 g (0.02 mol) of zinc (ii) chloride were taken into a 250 ml round bottle flask and then 2.26 ml (0.03 mol) of acetyl chloride was added drop wise in it and the reaction mixture was shaken steadily. The reaction mixture was allowed to stirred overnight (18 -19 hrs) at room temperature. At the starting time the reaction mixture was white but at the end of the reaction it changed into yellow color. After completion of the reaction, the flask was allowed to cool at low temperature (25-0^oC). After 5 minutes the flask was set in an ice bath and some pieces of ice were poured in the flask very carefully. Then the solution was filtered under suction on a Buchner funnel and washed with sufficient distilled water. Finally the compound was washed by acetone for at least 3 times and was kept in desiccator.



11

Scheme – 5

MF: $C_9H_{12}N_6O_3$

MW: 252

Physical analysis: White crystal, mp: partially melt in 360^oC, odorless and 58 % yield

Analytical analysis:

IR (KBr): ν_{max} 3440, 2945.1, 1689.5, 1375.2 cm^{-1}

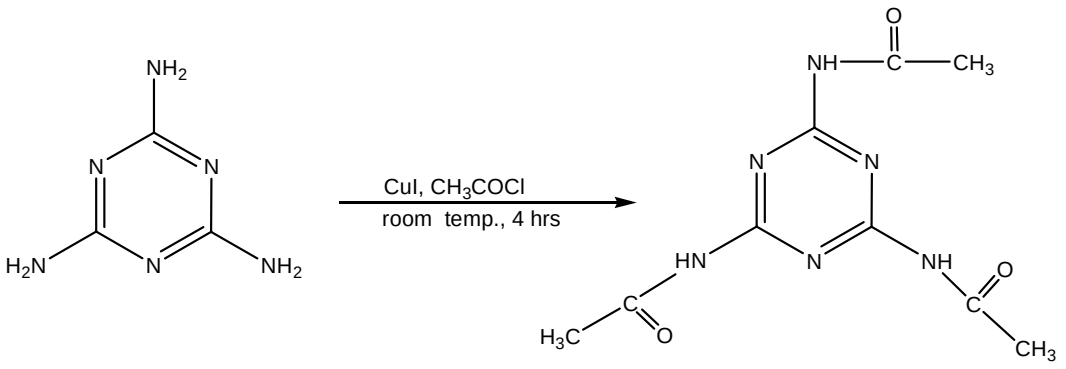
^{1}H NMR(400 MHz, DMSO): δ_H 7.66 (s, 3H, -NH-), 2.50 (s, 9H, -CO-CH_3) ppm.

^{13}C NMR (100.40 MHz, DMSO): δ_C 159.79, 77.83, 40.13 ppm.

UV (MeOH): λ_{max} 247.90 nm.

3.6 Synthesis of 2,4,6-Tris(acetamido)-1,3,5-triazine, 12:

A sample of 0.5 g (0.0039 mol) of melamine and 2.26 g (0.01 mol) of copper(ii) iodide were taken into a 250 ml round bottle flask and then 1.13 ml (0.01 mol) of acetyl chloride was added drop wise in it. The reaction mixture was allowed to stirred overnight (19 -20 hrs) at room temperature. The mixture turned into pink color gradually and at the end of reaction it turned into deep pink color. After completion of the reaction, the flask was allowed to cool at low temperature (25-0^oC). After 5 minutes the flask was set in an ice bath and some pieces of ice were poured in the flask very carefully. Then the solution was filtered under suction on a Buchner funnel and washed with sufficient distilled water. Finally the compound was washed by acetone and was kept in desiccator.



1 **12**

Scheme – 6

MF: $C_9H_{12}N_6O_3$

MW: 252

Physical analysis: Grey color powder, mp: 287.1-377.6^oC, odorless and 62 % yield

Analytical analysis:

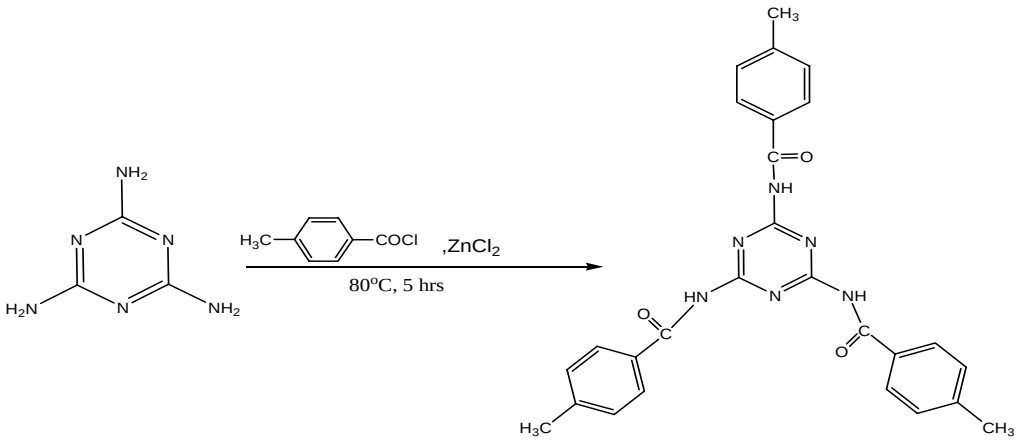
^{1}H NMR (400 MHz, DMSO): δ_H 6.79 (s, 3H,-NH-), 2.51 (s, 9H,-$COCH_3$) ppm.

^{13}C NMR (100.40 MHz, DMSO): δ_C 159.79, 77.83, 40.13 ppm.

IR (KBr) : ν_{max} 3328.9, 2941.2, 1662.5, 1463.9 cm^{-1}

3.7 Synthesis of 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine , 13:

In a 250 ml round bottle flask, provided with a reflux condenser 1 g (0.0079 mol) of melamine and 3.24 g (0.02 mol) of zinc (ii) chloride were taken and then 4.19 ml (0. 03 mol) of *p*- Toluoyl chloride was added drop wise in it. At that time the reaction mixture appeared as pink color. The reaction mixture was then refluxed for around 5 hrs with constant stirring at 80^oC. The progress of the reaction was monitored. When the temperature reached in 70 ^oC, all the reactants were dissolved and clear solution turned into purple color. Gradually it turned to black color. After 4 hrs yellowish product was observed in the solution. After completion of the reaction, the flask was allowed to cool at low temperature (25-0^oC). After 5 minutes the flask was set in an ice bath and some pieces of ice were poured in the flask very carefully. Then the solution was filtered under suction on a Buchner funnel and washed with sufficient distilled water. Finally the compound was washed in sodiumbycarbonate followed by distilled water to remove any remaining acid and was kept in desiccator.



1 **13**

Scheme – 7

MF: $C_{27}H_{24}N_6O_3$

MW: 480

Physical analysis: White powdered solid, mp: 187.3 ^oC, odorless and 67 % yield

Analytical analysis:

^{1}H NMR (400 MHz, CD_3OD): δ_H 7.90 (d, 6H, Ar-H, J=8.0 Hz), 7.27 (d, 6H, Ar-H, J=8.0 Hz), 4.89 (s, 3H, -NH-), 2.40 (s, 9H, Ar-CH_3) ppm.

^{13}C NMR (100.40 MHz, CD_3OD): δ_C 169.99, 144.97, 130.80, 130.09, 129.10,21.58 ppm.

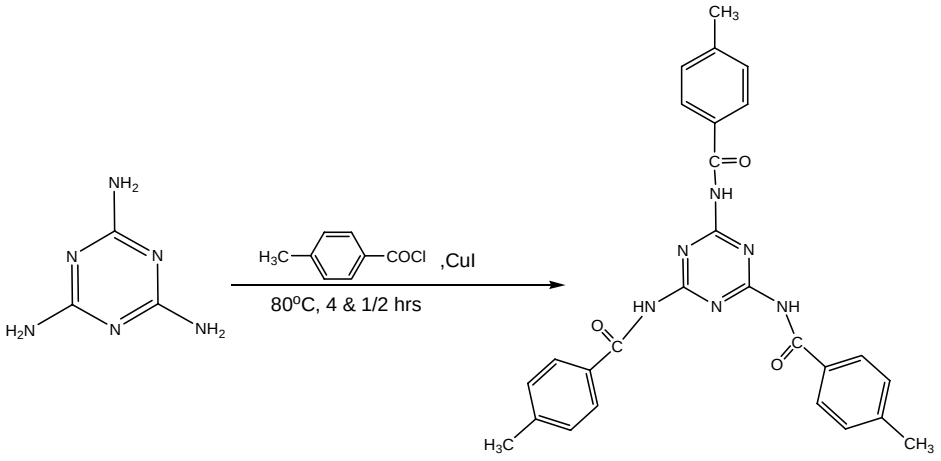
IR (KBr) : ν_{max} 3300, 3049.2, 2976, 1678.0, 1575.7, 1284.5, 754.1 cm^{-1}

UV (MeOH): λ_{max} 255.30, 239.80 nm.

3.8 Synthesis of 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine, 14:

In a 250 ml round bottle flask, provided with a reflux condenser 0.5 g (0.0039 mol) of melamine and 2.26 g (0.01 mol) of copper (ii) iodide were taken and then 2.09 ml (0. 01mol) of *p*- Toluoyl chloride was added drop wise in it and the reaction mixture was

shaken steadily. The reaction mixture was then refluxed for 4 and ½ hrs with constant stirring at 80 ^{o}C. The progress of the reaction was monitored. After completion of the reaction, the flask was allowed to cool at low temperature (25-0^{o}C). After 5 minutes the flask was set in an ice bath and some pieces of ice were poured in the flask very carefully. Then the solution was filtered under suction on a Buchner funnel .Finally the compound was washed in sodiumbycarbonate and water to remove any remaining acid and was kept in desiccator.



1 **14**

Scheme - 8

MF: $C_{27}H_{24}N_6O_3$

MW: 480

Physical analysis: Grey color powder, mp: partially melt in 340^{o}C, odorless and 78 % yield

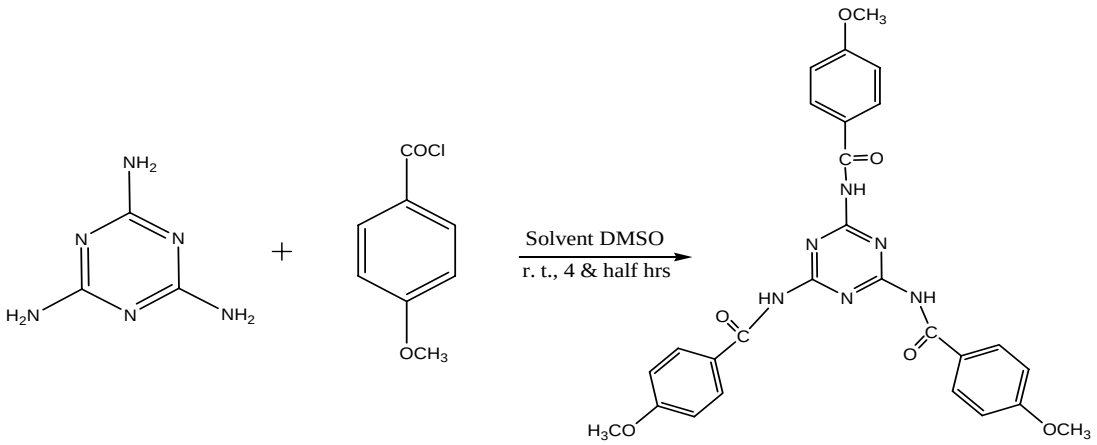
Analytical analysis:

^{1}H NMR (400 MHz, DMSO): δ_H 7.90 (d, 6H, Ar-H, J=8.0 Hz), 7.26 – 7.27 (d, 6H, Ar-H, J=8.0 Hz), 4.89 (s, 3H, -NH-),2.40 (s, 9H, Ar-CH_3)ppm.

IR (KBr) : ν_{max} 3313.5, 3155.3, 2945.1, 1652.9, 1539.1,1458.1, 781.1 cm^{-1}

3.9 Synthesis of 2,4,6-Tris(4-methoxybenzamido)-1,3,5-triazine , 15:

In a 250 ml round bottle flask 0.5 g (0.0039 mol) of melamine was dissolved in 10 ml Dimethylsulfoxide (DMSO) and then 2.16 g (0.01 mol) of Anisoyl chloride was added drop wise in it. The reaction mixture was allowed to stir for 3 and 1/2 hrs at room temperature and refluxed for an additional 1 hr with constant stirring at 80^{o}C. The progress of the reaction was monitored. Within the half an hour the reaction was gradually started and the reaction mixture started to become concentrated and at the same time the colorless mixture turned to white color. After completion of the reaction, the flask was allowed to cool at first room temperature and then at low temperature (25-0^{o}C) for 5 minutes. After that the flask was set in an ice bath and some pieces of ice were poured in the flask very carefully. After a while it was filtered under suction on a Buchner funnel and washed with sufficient distilled water, washed with Sodiumbicarbonate to remove completely any remaining acid. Finally the compound was washed with water and was kept in desiccator.



1 **8**

Scheme – 9

MF: $C_{27}H_{24}N_6O_6$

MW: 528

Physical analysis: White color powder, mp: partially melt in 315^{o}C, odorless and 56 % yield

Analytical analysis:

^{1}H NMR (400 MHz, D_2O): δ_H 7.73 (d, 6H, Ar-H, J=9.2 Hz), 6.87 (d, 6H, Ar-H, J=8.8 Hz), 4.68 (s, 3H, -NH-), 3.72 (s, 9H,-OCH_3) ppm.

IR (KBr): ν_{max} 3384.8, 3014.5, 2962.5, 1577.7, 1508.2, 1350.1, 813.9 cm^{-1}

Introduction:

1.1 General remarks: Dendrimers and dendritic molecules are the subject of significant academic and industrial interest.[1(a,b)]Dendrimers are repetitively branched molecules.[2(a,b)] The name comes from the Greek word "δένδρον" (pronounced dendron), which translates to "tree". Synonymous terms for dendrimer include arborols and cascade molecules. However, dendrimer is currently the internationally accepted term. A dendrimer is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. The word dendron is also encountered frequently. A dendron usually contains a single chemically addressable group called the focal point. The difference between dendrons and dendrimers is illustrated in figure one, but the terms are typically encountered interchangeably.[3]

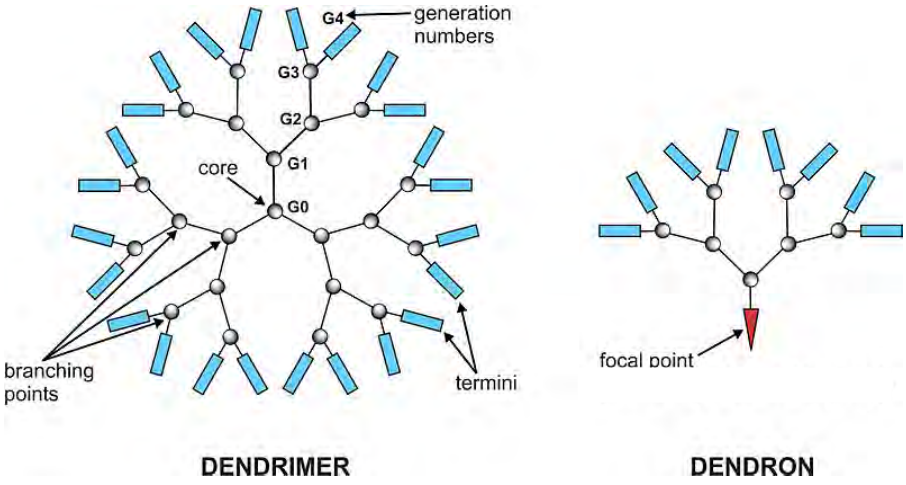


Figure 1: Dendrimer and Dendron

Dendrimers are an interesting unique class of polymers with controlled structures. A dendrimer is both a covalently assembled molecule and also a well-defined nanoparticle. The first dendrimers were made by divergent synthesis approaches by Fritz Vögtle in 1978,[5] R.G. Denkewalter at Allied Corporation in 1981,[6,7] Donald Tomalia at Dow Chemical in 1983[8] and in 1985,[9,10] and by George Newkome in 1985.[11] In 1990 a convergent synthetic approach was introduced by Jean Fréchet.[12] Dendrimer popularity then greatly increased, resulting in more than 5,000 scientific papers and patents by the year 2005.

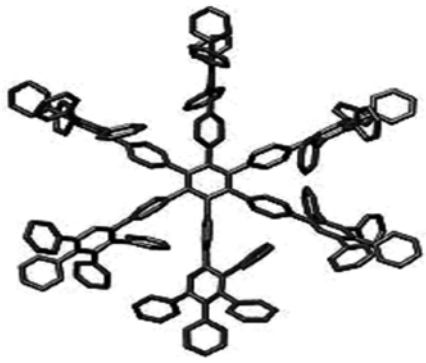


Figure 2: Crystal structure of a first-generation polyphenylene dendrimer reported by Müllen et al.[4]

1.2 Properties

The field of dendritic molecules can be roughly divided into low-molecular weight and high-molecular weight species. The first category includes dendrimers and dendrons, and the latter includes dendronized polymers, hyperbranched polymers, and the polymer brush. Dendrimers and dendrons are monodisperse and usually highly symmetric, spherical compounds. Dendritic molecules are characterized by structural perfection. The properties of dendrimers are dominated by the functional groups on the molecular surface, however, there are examples of dendrimers with internal functionality.[13, 14, 15]

Dendritic encapsulation of functional molecules allows for the isolation of the active site, a structure that mimics that of active sites in biomaterials.[16,17,18] Also, it is possible to make dendrimers water soluble, unlike most polymers, by functionalizing their outer shell with charged species or other hydrophilic groups. Other controllable properties of dendrimers include toxicity, crystallinity, tecto-dendrimer formation, and chirality.[3]

Dendrimers are also classified by generation, which refers to the number of repeated branching cycles that are performed during its synthesis. For example if a dendrimer is made by convergent synthesis, and the branching reactions are performed onto the core molecule three times, the resulting dendrimer is considered a third generation dendrimer. Each successive generation results in a dendrimer roughly twice the molecular weight of the previous generation. Higher generation dendrimers also have more exposed functional groups on the surface, which can later be used to customize the dendrimer for a given application.[19]

1.3 Synthesis

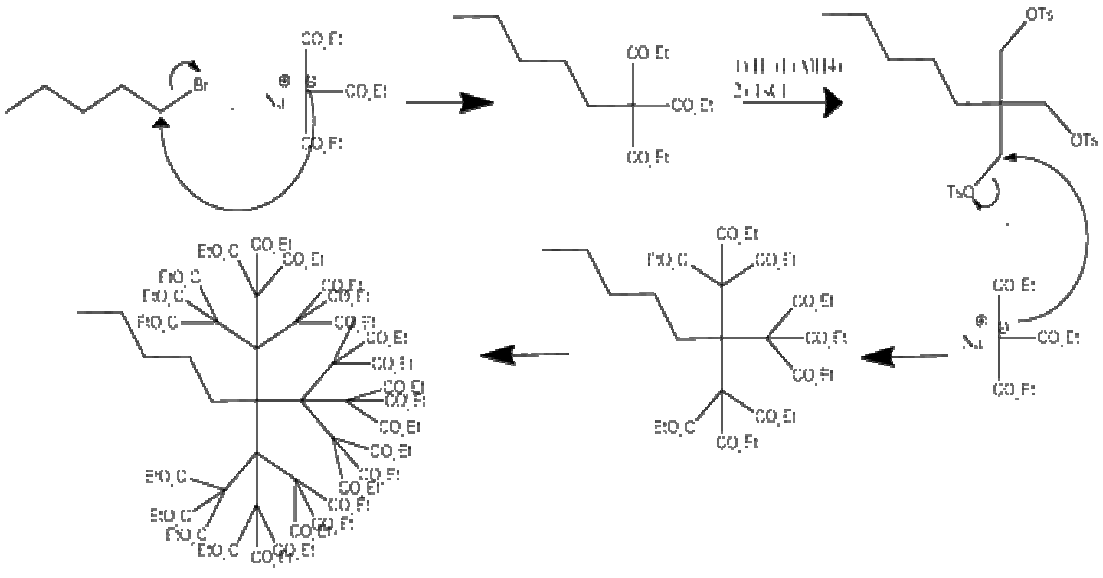


Figure 3: Synthesis to second generation arborol

In 1985 one of the very first dendrimers, the Newkome dendrimer, was synthesized. Figure 3 outlines the mechanism of the first two generations of arborol through a divergent route. The synthesis is started by nucleophilic substitution of 1-bromopentane by triethyl sodiomethanetricarboxylate in dimethylformamide and benzene. The ester groups were then reduced by lithium aluminium hydride to a triol in a deprotection step. Activation of the chain ends was achieved by converting the alcohol groups to tosylate groups with tosyl chloride and pyridine. The tosyl group then served as leaving groups in another reaction with the tricarboxylate, forming generation two. Further repetition of the two steps leads to higher generations of arborol.[11]

Poly(amidoamine), or PAMAM, is perhaps the most well known dendrimer. The core of PAMAM is a diamine (commonly ethylenediamine), which is reacted with methyl acrylate, and then another ethylenediamine to make the generation-0 (G-0) PAMAM. Successive reactions create higher generations, which tend to have different properties. Lower generations can be thought of as flexible molecules with no appreciable inner regions, while medium sized (G-3 or G-4) do have internal space that is essentially separated from the outer shell of the dendrimer. Very large (G-7 and greater) dendrimers can be thought of more like solid particles with very dense surfaces due to the structure of their outer shell. The functional group on the surface of PAMAM

dendrimers is ideal for click chemistry, which gives rise to many potential applications.[20]

Dendrimers can be considered to have three major portions: a core, an inner shell, and an outer shell. Ideally, a dendrimer can be synthesized to have different functionality in each of these portions to control properties such as solubility, thermal stability, and attachment of compounds for particular applications. Synthetic processes can also precisely control the size and number of branches on the dendrimer. There are two defined methods of dendrimer synthesis, divergent synthesis and convergent synthesis. However, because the actual reactions consist of many steps needed to protect the active site, it is difficult to synthesize dendrimers using either method. This makes dendrimers hard to make and very expensive to purchase. At this time, there are only a few companies that sell dendrimers; Polymer Factory Sweden AB[21] commercializes biocompatible bis-MPA dendrimers and Dendritech[22] is the only kilogram-scale producers of PAMAM dendrimers. Dendritic Nanotechnologies Inc.,[23] from Mount Pleasant, Michigan, USA produces PAMAM dendrimers and other proprietary dendrimers.

1.3.1 Divergent Methods

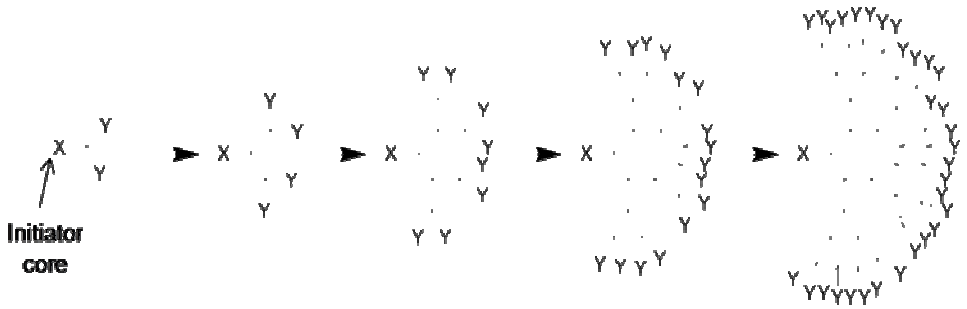


Figure 4: Schematic of divergent synthesis of dendrimers

The dendrimer is assembled from a multifunctional core, which is extended outward by a series of reactions, commonly a Michael reaction. Each step of the reaction must be driven to full completion to prevent mistakes in the dendrimer, which can cause trailing generations (some branches are shorter than the others). Such impurities can impact the functionality and symmetry of the dendrimer, but are extremely difficult to purify out because the relative size difference between perfect and imperfect dendrimers is very small.[19]

1.3.2 Convergent Methods

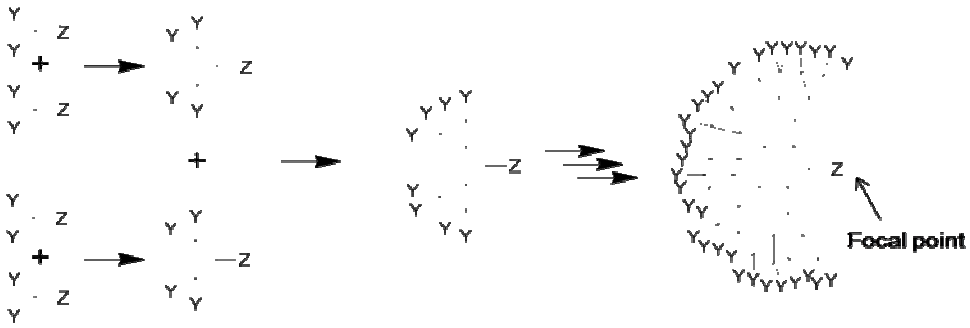


Figure 5: Schematic of convergent synthesis of dendrimers

Dendrimers are built from small molecules that end up at the surface of the sphere, and reactions proceed inward building inward and are eventually attached to a core. This method makes it much easier to remove impurities and shorter branches along the way, so that the final dendrimer is more monodisperse. However dendrimers made this way are not as large as those made by divergent methods because crowding due to steric effects along the core is limiting.[19]

Dendrimers have been prepared via click chemistry, employing Diels-Alder reactions,[24] thiol-ene reactions [25] and azide-alkyne reactions.[26,27,28] An example is the synthesis of certain polyphenylene dendrimers can be seen in figure 6.[29]

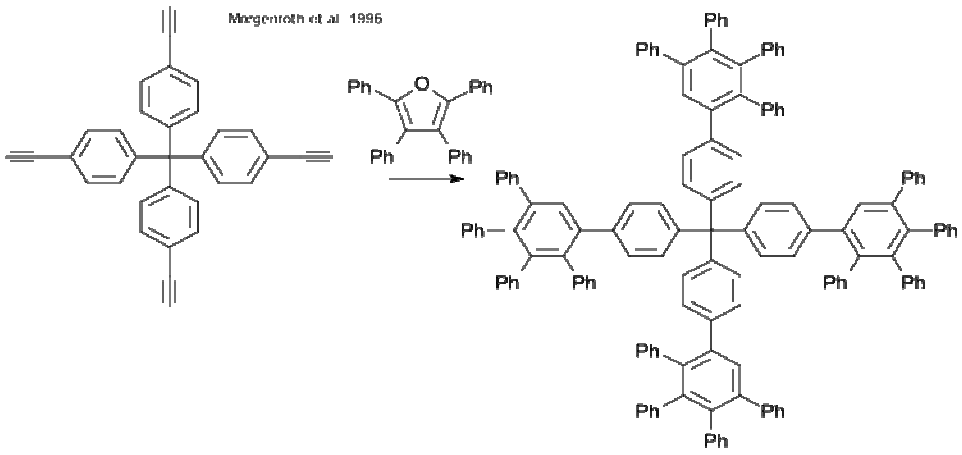


Figure 6: Dendrimer DA reaction Mullen 1996

1.4 Applications

Applications of dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radioligands, imaging agents, or pharmaceutically active compounds. Dendrimers have very strong potential for these applications because their structure can lead to multivalent systems. In other words, one dendrimer molecule has hundreds of possible sites to couple to an active species. Researchers aimed to utilize the hydrophobic environments of the dendritic media to conduct photochemical reactions that generate the products that are synthetically challenged. Carboxylic acid and phenol terminated water soluble dendrimers were synthesized to establish their utility in drug delivery as well as conducting chemical reactions in their interiors.[30] This might allow researchers to attach both targeting molecules and drug molecules to the same dendrimer, which could reduce negative side effects of medications on healthy cells.[20]

1.4.1 Dendrimers as solubilizing agent

This novel class of dendrimer architecture has been a prime candidate for hosts guest chemistry since their introduction in the mid-1980s,.[31] Dendrimers with hydrophobic core and hydrophilic periphery have shown to exhibit micelle-like behavior and have container properties in solution.[32] The use of dendrimers as unimolecular micelles was proposed by Newkome in 1985.[33] This analogy highlighted the utility of dendrimers as solubilizing agents.[34] The majority of drugs available in pharmaceutical industry are hydrophobic in nature and this property in particular creates major formulation problems. This drawback of drugs can be ameliorated by dendrimeric scaffolding, which can be used to encapsulate as well as to solubilize the drugs because of the capability of such scaffolds to participate in extensive hydrogen bonding with water.[35,36,37,38,39,40] Dendrimer labs throughout the planet are persistently trying to manipulate dendrimer's solubilizing trait, in their way to explore dendrimer as drug delivery[41,42] and target specific carrier.[43,44,45]

1.4.2 Drug Delivery

There are three methods for using dendrimers in drug delivery: first, the drug is covalently attached to the periphery of the dendrimer to form dendrimer prodrugs,

second the drug is coordinated to the outer functional groups via ionic interactions, or third the dendrimer acts as a unimolecular micelle by encapsulating a pharmaceutical through the formation of a dendrimer-drug supramolecular assembly.[46,47] Approaches for delivering unaltered natural products using polymeric carriers is of widespread interest, dendrimers have been explored for the encapsulation of hydrophobic compounds and for the delivery of anticancer drugs. The physical characteristics of dendrimers, including their monodispersity, water solubility, encapsulation ability, and large number of functionalizable peripheral groups, make these macromolecules appropriate candidates for evaluation as drug delivery vehicles. The use of dendrimers as drug carriers by encapsulating hydrophobic drugs is a potential method for delivering highly active pharmaceutical compounds that may not be in clinical use due to their limited water solubility and resulting suboptimal pharmacokinetics.

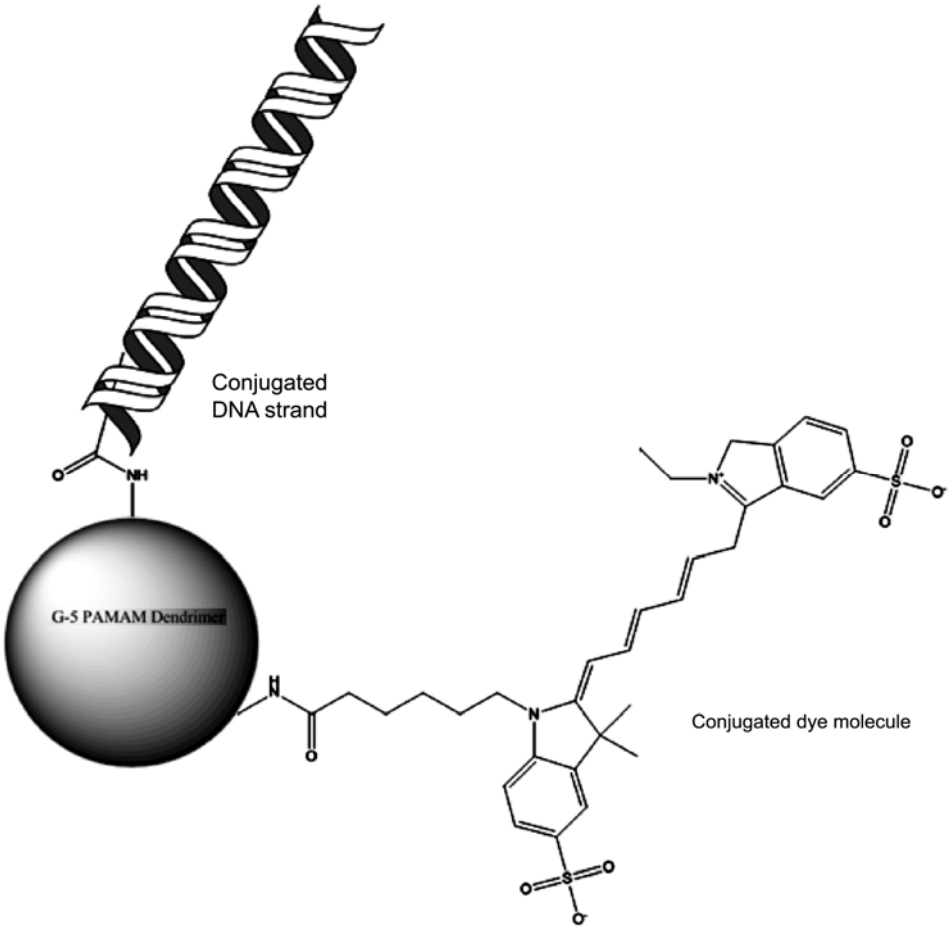


Figure 7: Schematic of a G-5 PAMAM dendrimer conjugated to both a dye molecule and a strand of DNA.

Dendrimers have been widely explored for controlled delivery of antiretroviral bioactives.[48] The inherent antiretroviral activity of dendrimers enhances their efficacy as carriers for antiretroviral drugs.[49,50] The dendrimer enhances both the uptake and retention of compounds within cancer cells, a finding that was not anticipated at the onset of studies. The encapsulation increases with dendrimer generation and this method may be useful to entrap drugs with a relatively high therapeutic dose. Studies based on this dendritic polymer also open up new avenues of research into the further development of drug-dendrimer complexes specific for a cancer and/or targeted organ system. These encouraging results provide further impetus to design, synthesize, and evaluate dendritic polymers for use in basic drug delivery studies and eventually in the clinic.[46,51]

The term “magic bullet” was first introduced by Paul Ehrlich. Ehrlich’s work with immunology led to his receiving the Nobel Prize in Physiology or Medicine in 1908. Among his contributions was the belief that compounds with specific structures could be found which would recognize and bind a specific disease-causing target in an organism to provide therapeutic action to this target without causing harm to the organism itself – a magic bullet.[52]Among many other accomplishments, Ehrlich’s work contributed to the establishment of chemotherapeutic techniques.[53] Pharmacologically active polymers have been recognized as important targets for decades, especially in the field of cancer therapeutics due to the non-specificity of many drugs. These “magic bullets” could enter tumor cells and deliver a payload of drug without harming the individual. In 1975, Ringsdorf defined the ideal structure and properties of polymeric drug agents.[54] He described a carrier with a biostable or biodegradable backbone comprised of three parts. First, the polymer carrier should have a group that renders the macromolecule soluble and nontoxic. The second group is for the attachment of the drug, which would be performed under mild conditions and would incorporate a spacer to separate the drug from the polymer. These conditions would need to be met in order to ensure there would be no adverse effects on the drug’s biological activity once attached to the polymeric carrier. The linkage between the polymer and the drug would need to be stable under normal body conditions but able to release the drug rapidly by hydrolysis or enzymatic processes once the site of action is reached. The third group would transport the entire carrier to the target cells by use of a homing device or through nonspecific enhancement of cellular-uptake.

Polymers, and therefore polymer drug conjugates, enter cell membranes by endocytosis rather than by diffusion. The macromolecules are engulfed by the plasma membrane and form endosomes which can fuse with enzyme-containing lysosomes. Provided the linker connecting the drug and carrier meets the aforementioned conditions,the linker may be cleaved to release the drug either enzymatically or by hydrolysis induced by the decrease in pH from 7.4 in the cytoplasm to pH 5 found in the lysosome.Macromolecules show specificity to tumor cells due to a phenomenon known as the enhanced permeability and retention effect (EPR).[55] Maeda and co-workers coined the term EPR effect in 1986.[56] They attributed the EPR effect to two main factors: leaky tumor vessels allowing entry of macromolecules, an activity which is not usually allowed in normal tissues, and an ineffective tumor lymphatic drainage system which prevents clearance of the macromolecules and promotes their accumulation. (Figure 8) The typical value for the molecular weight of macromolecules which can exploit the EPR effect is greater than 40 kDa, [57] but studies have shown polymers with molecular weights between 20 and 800 kDa are able to access tumors. Studies of nonuniform accumulation of polymers in tumor tissue demonstrate that the threshold of vascular permeability actually varies with polymer architecture, tumor size and type, and even vessel to vessel in the local microenvironment of the tumor.[58]

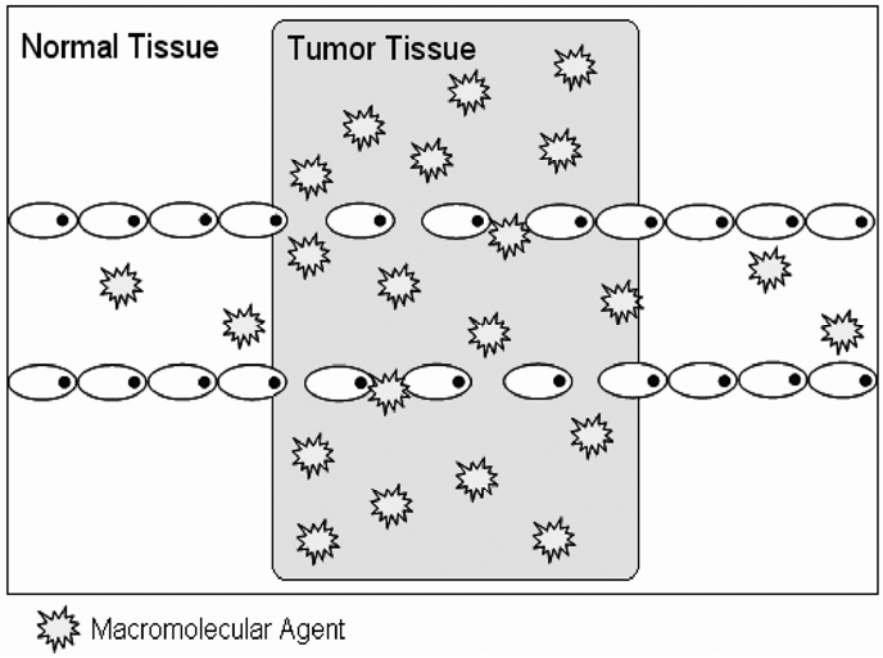


Figure 8. The EPR effect.

Dendrimers are highly branched, symmetric, synthetic polymers emanating from a central core. These multivalent molecules are globular in shape, monodisperse, and allow control of molecular weight, surface groups, and interior groups.[59-62] Due to these properties, dendrimers are attractive targets for drug delivery agents.[55,63-71] Figure 9 shows the possible uses of the multivalency of dendrimers.Synthetic manipulations to the functional groups in the core of the dendrimers would facilitate noncovalent encapsulation of drugs in the interior. Also, covalent attachment of solubilizing groups, targeting moieties, and drugs to the periphery of dendrimers is possible with modifications of the surface groups.

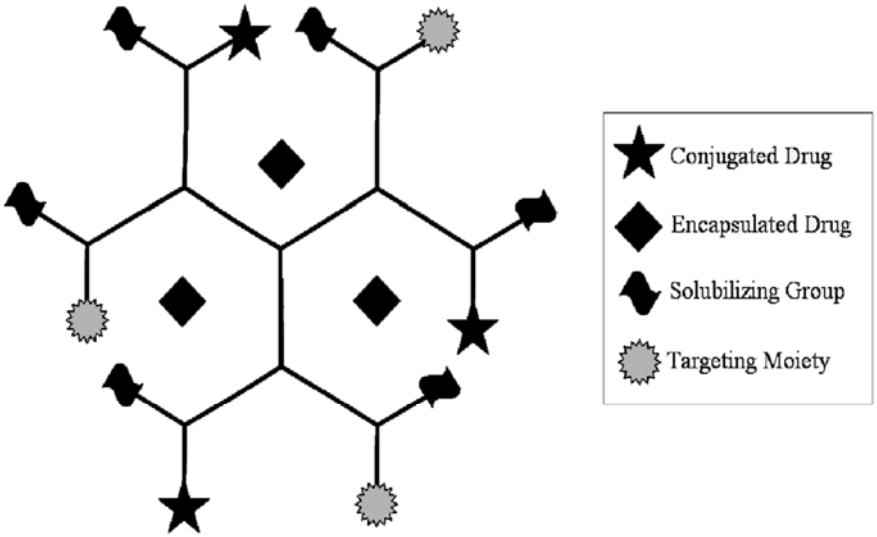


Figure 9. Possible functionalization of a dendritic drug delivery agent.

Noncovalent encapsulation of drugs with dendrimers can be accomplished using hydrogen bonding, hydrophobic, or electrostatic interactions between the guests and host.[72] One method of encapsulation is the construction of dendritic 'unimolecular micelles'.[73-76] Conventional polymeric micelles are amphiphilic block copolymers which form thermodynamic aggregates in proper solvents above the critical micelle concentration (c.m.c.). This property is also the limiting factor in micellar drug delivery applications. Under physiological conditions, the concentration may drop below the c.m.c. causing dissociation of the micelle into free polymer chains. With unimolecular micelles, the hydrophobic and hydrophilic segments are covalently bound together imparting stability to the micellar structure. Hydrophobic drugs can be solubilized in

the hydrophobic core of the dendrimer while the hydrophilic portion, usually polyethylene glycol (PEG) chains, on the periphery solubilizes the entire carrier.[68]

Interactions between dendrimers and guests to afford encapsulation have been exploited by many groups.[77-88] Twyman, *et al*. synthesized water-soluble, hydroxyl terminated poly(amido amine) (PAMAM) dendrimers capable of solubilizing several small, acidic, hydrophobic model compounds including benzoic acid and salicylic acid.The complexes were stable at pH 7, but under acidic conditions, precipitation of the model hydrophobic compounds occurred. It was thought that protonation of the internal tertiary amines of the dendrimer interrupted the noncovalent interactions with the acidic guests causing this dissociation.[89]

1.4.3 Gene Delivery

The ability to deliver pieces of DNA to the required parts of a cell includes many challenges. Current research is being performed to find ways to use dendrimers to traffic genes into cells without damaging or deactivating the DNA. To maintain the activity of DNA during dehydration, the dendrimer/DNA complexes were encapsulated in a water soluble polymer, and then deposited on or sandwiched in functional polymer films with a fast degradation rate to mediate gene transfection. Based on this method, PAMAM dendrimer/DNA complexes were used to encapsulate functional biodegradable polymer films for substratemediated gene delivery. Research has shown that the fast degrading functional polymer has great potential for localized transfection.[90, 91, 92]

1.4.4 Sensors

For use in sensor technologies scientists have also studied dendrimers. Studied systems include proton or pH sensors using poly(propylene imine),[93] cadmium-sulfide/polypropylenimine tetrahexacontaamine dendrimer composites to detect fluorescence signal quenching,[94] and poly(propylenamine) first and second generation dendrimers for metal cation photodetection[95] amongst others. Research in this field is vast and ongoing due to the potential for multiple detection and binding sites in dendritic structures.

1.5 Dendronized polymers :

Dendronized polymers are linear polymers to every repeat unit of which dendrons are attached. Dendrons are regularly branched, tree-like fragments and for larger ones the polymer backbone is wrapped to give sausage-like, cylindrical molecular objects.

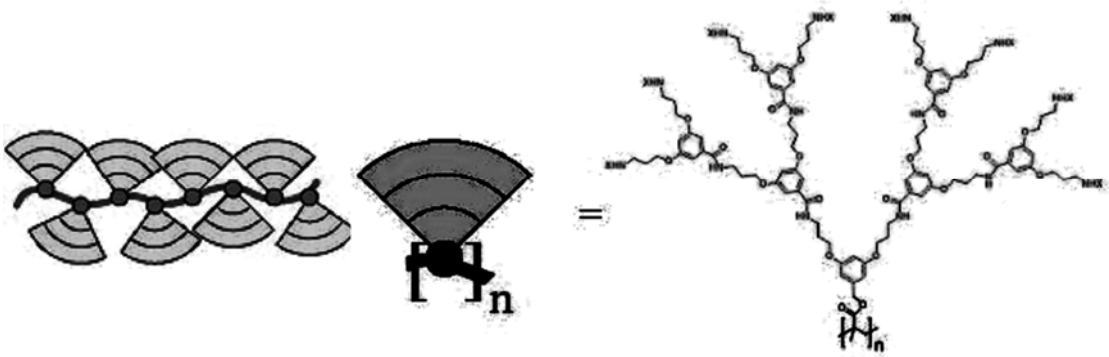


Figure 10. Cartoon representation (left) and a concrete example of a third generation dendronized polymer (right).

Figure 10 shows a cartoon representation with the backbone in red and the dendrons like cake slices in green. It also provides a concrete chemical structure showing a polymethylmethacrylate (PMMA) backbone, the methyl group of which is replaced by a dendron of the third generation (three consecutive branching points).

The peripheral amine groups are modified by a substituent X which often is a protection group. Upon deprotection and modification substantial property changes can be achieved. The subscript n denotes the number of repeat units.

1.6 Metallodendrimer

A Metallodendrimer is a type of dendrimer with incorporated metal atoms. The development of this type of material is actively pursued in academia.[96,97,98]

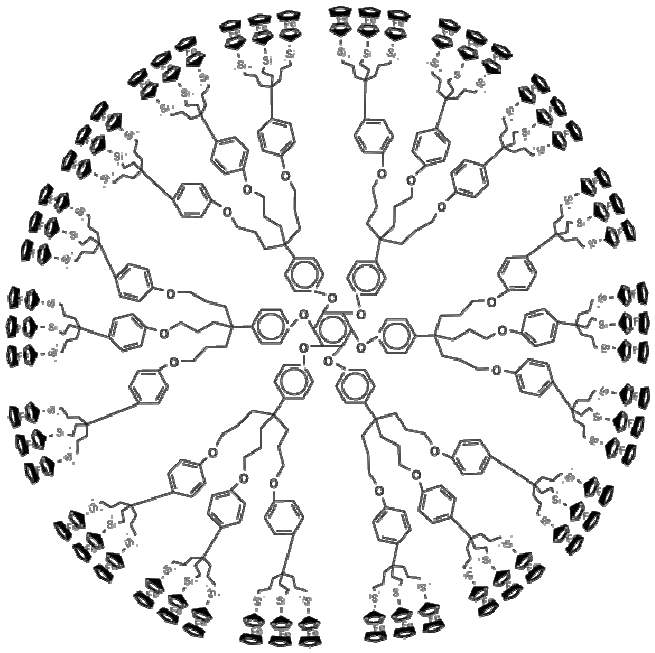


Figure 11: Ferrocene containing dendrimer

1.6.1 Structure

The metal can be situated in the repeat unit, the core or at the extremities as end-group. Elements often encountered are palladium and platinum. These metals can form octahedral six-coordinate M(IV) linking units from organic dihalides and the corresponding 4-coordinate M(II) monomers. Ferrocene-containing dendrimers and dendrimers with cobaltocene and arylchromiumtricarbonyl units have been reported in end-functional dendrimers. Metallodendrimers can form as metal complexes with dendritic counter ions for example by hydrolysis of ester terminated PAMAM dendrimers with sodium hydroxide.

1.6.2 Applications

Metallodendrimers are investigated as equivalents to nanoparticles. Applications can be expected in the fields of catalysis, as chemical sensors in molecular recognition - for example of bromine and chloride anions [99] - or as materials capable of binding metals. Metallodendrimers can also mimic certain biomolecules for example haemoprotein in dendrimer with a porphyrin core. Further uses are reported as electrocatalyst.[100,101]

Examples of metallodendrimer heterogeneous catalysis are a nickel-containing dendrimer active in the Kharasch addition,[102] palladium-containing dendrimers active in ethylene polymerization [103] and in the Heck reaction.[104]

1.7 Triazine:

Triazine are six membered aromatic heterocycles comprised of three carbon and three nitrogen atoms. A triazine is one of three organic chemicals, isomeric with each other, whose molecular formula is $C_3H_3N_3$ and whose empirical formula is CHN.

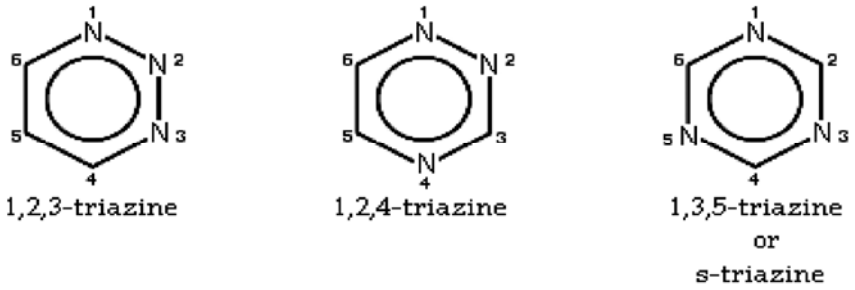


Figure 12: The three isomers of triazine, with ring numbering.

1.7.1 Structure:

The triazine structure is a heterocyclic ring, analogous to the six-membered benzene ring but with three carbons replaced by nitrogens. The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and are referred to as 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine. Other aromatic nitrogen heterocycles are pyridines with 1 ring nitrogen atom, diazines with 2 nitrogen atoms in the ring and tetrazines with 4 ring nitrogen atoms. Triazines are weaker bases than pyridine.

1.7.2 Uses:

The best known 1,3,5-triazine derivative is melamine with three amino substituents used in the manufacture of resins. Another triazine extensively used in resins is benzoguanamine. Triazine compounds are often used as the basis for various herbicides such as cyanuric chloride (2,4,6-trichloro-1,3,5-triazine). Chlorine-substituted triazines are also used as reactive dyes. These compounds react through a chlorine group with

hydroxyl groups present in cellulose fibres in nucleophilic substitution, the other triazine positions contain chromophores. Mixtures of Triazines and water are also used to remove H_2S from natural gas.

A series of 1,2,4-triazine derivatives known as BTPs have been considered in the liquid-liquid extraction community as possible extractants for use in the advanced nuclear reprocessing of used fuel.[105,106,107,108,109] BTPs are molecules containing a pyridine ring bonded to two 1,2,4-triazin-3-yl groups.

1.7.3 Synthesis

1,2,3-Triazines can be synthesized by thermal rearrangement of 2-azidocyclopropenes. 1,2,4-Triazines are prepared from condensation of 1,2-dicarbonyl compounds with amidrazones. A classical triazine synthesis is also the Bamberger triazine synthesis. Symmetrical 1,3,5-triazines are prepared by trimerization of cyanogen chloride or cyanimide. Benzoguanamine (with one phenyl and 2 amino substituents) is synthesised from benzonitrile and dicyandiamide in dimethoxyethane with potassium hydroxide.[110]. In the Pinner triazine synthesis (named after Adolf Pinner)[111] the reactants are an alkyl or aryl amidine and phosgene [112,113]

1.7.4 Reactions

Although triazines are aromatic compounds, the resonance energy is much lower than in benzene and electrophilic aromatic substitution is difficult but nucleophilic aromatic substitution more frequent. 2,4,6-Trichloro-1,3,5-triazine is easily hydrolyzed to cyanuric acid by heating with water at elevated temperatures. 2,4,6-Tris(phenoxy)-1,3,5-triazine reacts with aliphatic amines in aminolysis, and this reaction can be used to give dendrimers.[114] Pyrolysis of melamine under expulsion of ammonia gives the tri-s-triazine melem.[115] Cyanuric chloride assists in the amidation of carboxylic acids.[116]

The 1,2,4-triazines can react with electron-rich dienophiles in an inverse electron demand Diels-Alder reaction. This forms a bicyclic intermediate which normally then extrudes a molecule of nitrogen gas to form an aromatic ring again. In this way the 1,2,4-triazines can be reacted with alkynes to form pyridine rings. An alternative to using an alkyne is to use norbornadiene which can be thought of as a masked alkyne.

1.7.5 1,3,5-Triazine:

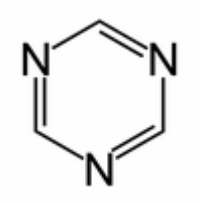


Figure 13: 1,3,5-Triazine

1,3,5-triazine, also called s-triazine, is an organic chemical compound with the formula $(HCN)_3$. It is a six-membered heterocyclic aromatic ring, one of several isomeric triazines. S-triazine and its derivatives are useful in a variety of applications.

1.7.6 Use in organic chemistry

As a reagent in organic synthesis, s-triazine is used as the equivalent of hydrogen cyanide (HCN). Being a solid (vs a gas for HCN), triazine is sometimes easier to handle in the laboratory. One application is in the Gattermann reaction, used to attach the formyl group to aromatic substrates.[117]

It is a common reagent, and readily forms derivatives, which are used as pharmaceutical products, as well as herbicides, such as atrazine.[118]

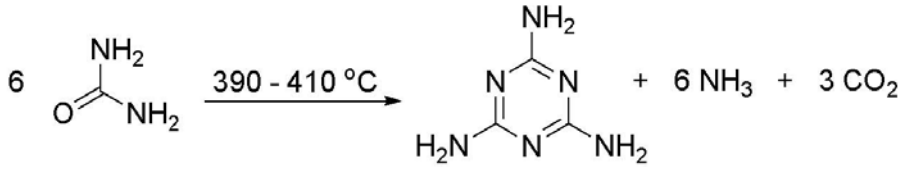
1.7.7 Substituted triazines

The most common derivative of 1,3,5-triazine is 2,4,6-triamino-1,3,5-triazine, commonly known as melamine or cyanuramide. Trichloro-1,3,5-triazine (Cyanuric chloride) is the starting point for the manufacture of many herbicides such as Simazine, as well as of many fiber reactive dyes. Another important derivative is 2,4,6-trihydroxy-1,3,5-triazine better known as cyanuric acid**.**

1.7.8 Melamine:

Melamine was prepared in 1834 by Liebig by fusing potassium thiocyanate with ammonium chloride. The product was mostly melamine thiocyanate, but treating it with base provides the free melamine.[119,120,121] It took over a century before commercial applications were fully realized. Melamine is now produced in large quantities, mostly for the formation of resins. In 1994, over 610,000 tons were produced worldwide.

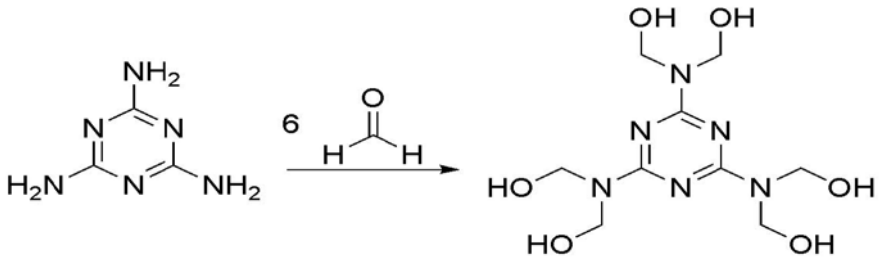
Currently industrial synthesis of melamine is from urea at 390–410 °C either non-catalytically under high pressure processes or catalytically using low-pressure processes. The net reaction is the same using any of these processes as shown in Scheme 2.[121] Naturally occurring melamine has been discovered in several meteorites which have reached earth.[120]



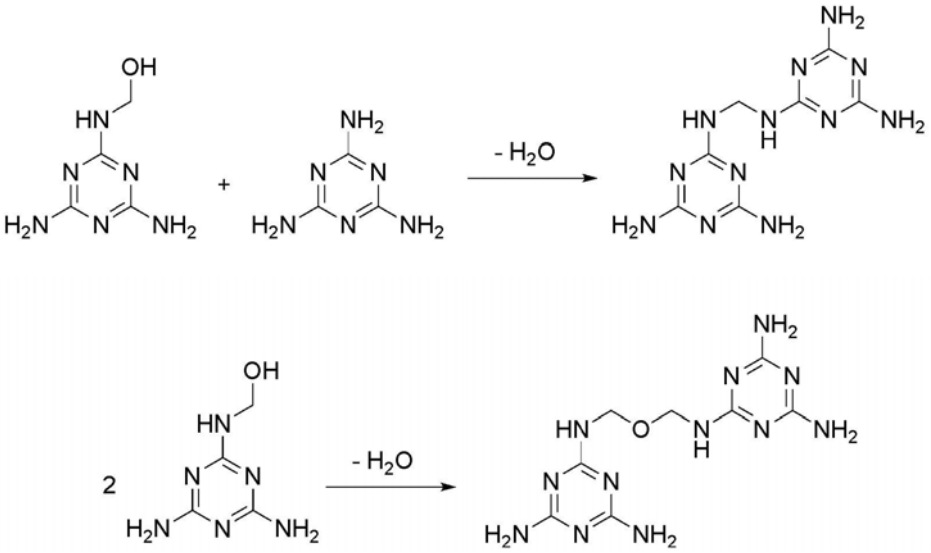
Scheme 1. Industrial synthesis of melamine

Melamine is most often reacted with formaldehyde for the production of resins.This practice began in 1935 in Germany.[122] The polymers formed from melamineformaldehyde resins have excellent chemical and physical properties. The resins have numerous applications including laminates, glues and adhesives, molding compounds, coatings, and paper and textiles.[122] The reaction of melamine with formaldehyde is shown below in Scheme 2. Anywhere from one to six of the hydrogen atoms on the amine groups of melamine may be replaced by methylol groups. Methylolmelamines are unstable due to the possibility of further condensation or resinification, as shown in Scheme 3 with a monomethylolmelamine, but similar reactions occur with the other di or tri-methylolmelamines.[121]

The oldest application of melamine resins is adhesives for wood such as plywood or particle board.[122] Creating a foamed resin produces hard, yet flexible, lightweight materials which are used for sound insulation, fire protection, and cleaning products.[123,124] Other applications include impregnating resins to treat papers for decorative purposes, paper auxiliaries to enhance wet tensile strength, leather tanning agents, strengtheners for building materials, concrete additives, ion-exchange resins, and wood preservatives.[122]



Scheme 2. Initial reaction of formaldehyde and melamine



Scheme 3: Condensation and resinification of methylolmelamine

1.8 Molecular Recognition:

Triazines especially melamines can recognize other molecules by the donation and acceptance of hydrogen bonds, metal chelation, and π–π interactions (Chart 1). This opportunity has enabled various supramolecular structures to be prepared on the basis of hydrogen-bonding interactions to form ribbons and other types of interesting oligomers and polymers. The synthesis and characterization of these types of triazine-based supramolecular structures have been reviewed elsewhere.[125–128]

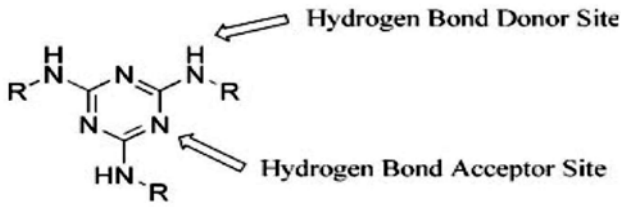
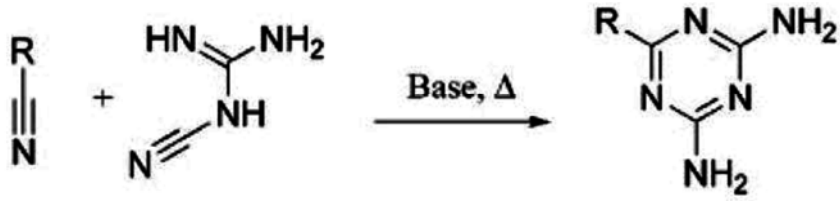


Chart 1: Sites of triazine/melamine derivatives that can participate in hydrogen bonding.

1.8.1 Synthesis

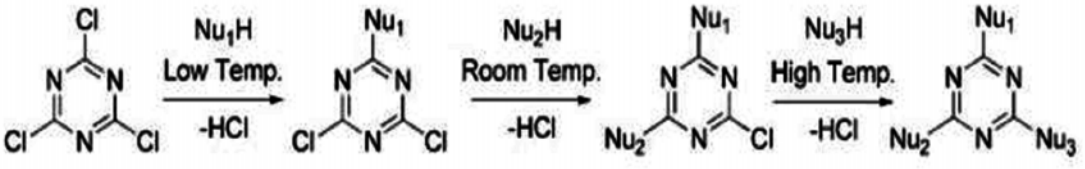
The synthesis of triazine derivatives is well established and has been reviewed elsewhere in detail.[129,130] Triazines can be synthesized by a variety of routes; however, for the sake of brevity, we will focus on the two most common methods that have been employed for the preparation of triazine-based dendrimers. Initial efforts in this field focused on cycloaddition reactions to form the triazine ring (Scheme: 4). This reaction is carried out at higher temperatures by the treatment of the nitrile of interest with a nitrile-substituted guanidine derivative in the presence of a base, typically sodium or potassium hydroxide.



Scheme:4 Cycloaddition reaction to form a diaminotriazine derivative.

Later efforts describe the nucleophilic aromatic substitution of cyanuric chloride ($C_3N_3Cl_3$) in a chemoselective fashion using temperature and the judicious choice of the nucleophile to produce a single product with high chemical complexity (Scheme: 5). Thus, when architectures that feature different types of peripheral groups are desired, triazine-based dendrimers offer a powerful and versatile synthetic strategy to well-defined products. The nucleophilic aromatic substitution of alkoxy-substituted triazine derivatives by amine nucleophiles is also a route that has been exploited;

however, higher temperatures in excess of 100 °C are required to achieve the conversion to the desired product.



Scheme: 5 Chemoselective reactivity of cyanuric chloride.

Triazines can also be prepared by cyclotrimerization of organic cyanates, but to date, the use of this route for the synthesis of dendrimers has not been pursued. Rather, this chemistry is employed to prepare hyper-branched polymers.[131]

The goal of this review is to trace the origins of triazine dendrimers, a field that we perceive is expanding (Figure 14). The advances in the syntheses of these materials receive the majority of the attention. Numerous examples of multiple triazine units tethered to a single core are included because these can be construed as first-generation dendrimers and can be readily elaborated to larger structures because of the functionality at the periphery.

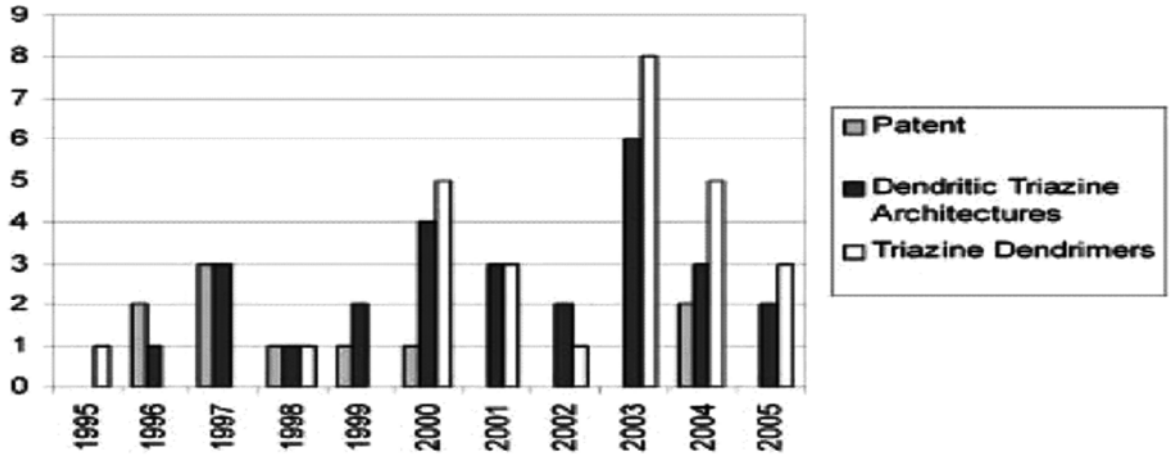


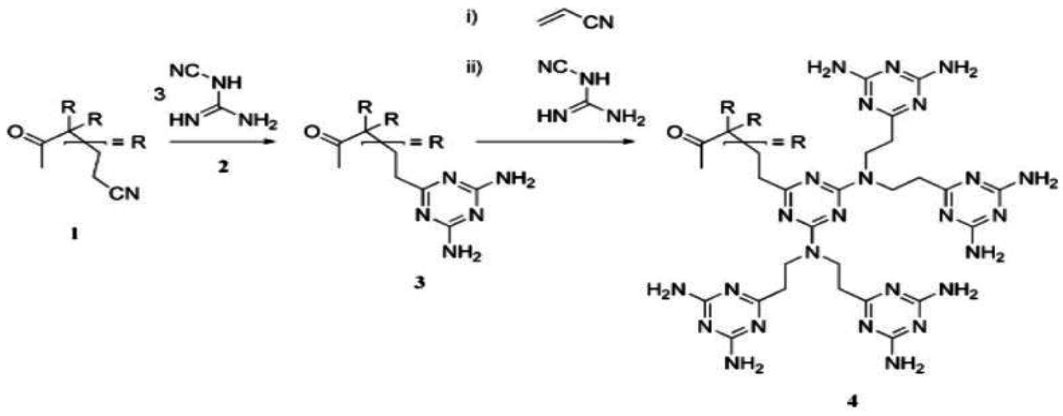
Figure 14: Graph showing that reports of triazine-based dendritic structures have increased during the previous decade (2005 data are as of April 29, 2005).

1.9 Synthetic Routes to Triazine Dendrimers

Much of the early work in the area focused on the optimization of routes for the synthesis of these species using either cycloaddition reactions or triazine substitution reactions.

1.9.1 Cycloaddition Method:

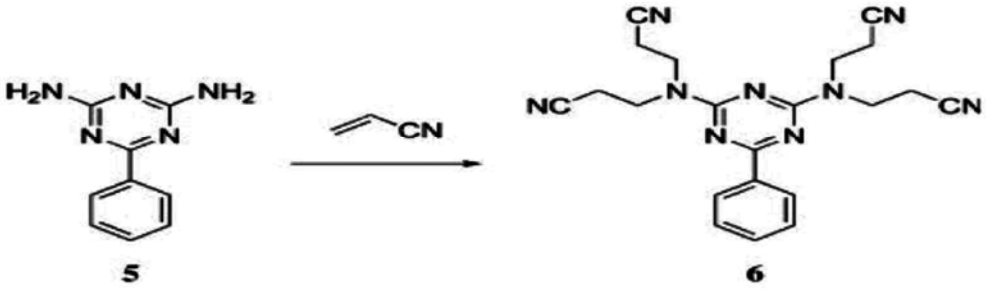
To the best of our knowledge, the first example of the synthesis of a triazine-based dendrimer using a divergent approach was detailed in two patents that were submitted in 1994,[132] one of which was reviewed in a separate account in 1995 (Scheme: 6).[133] In both cases, an iterative synthesis was developed in which the triazine units were prepared by the cycloaddition of terminal nitrile-functional groups, **1**, with nitrile-substituted guanidine, **2**, to afford an amino-terminated dendrimer, **3**. Iteration produces higher generations such as **4**. The synthesis outlined in the patent by Meijer et al.[97] is of particular interest because it details a procedure that can be used to prepare commercially relevant quantities of dendrimer product. More recent reports have demonstrated the utility of the cycloaddition method to afford triazine-based dendritic and hyperbranched materials,[134] some of which have found application in the construction of porous, hydrogen-bonded networks. In addition, cyclotrimerization routes have been used to produce materials relevant for integrated optics.[135]



Scheme 6: Initial efforts to prepare triazine-based dendrimers employed cycloaddition methods.

In all the cycloaddition procedures, the chemistry of the iterative process is the same: cyanoethylation of a pendant amine forms a dendron with twice the number of nitrile groups. Subsequent elaboration of the dendron by cycloaddition between the peripheral nitriles and nitrile-substituted guanidine derivatives increases the dendrimer generation. Maciejewski[136] wrote one of the earliest theoretical articles on the subject of dendrimers that could be prepared with this method in 1982. Moreover, cyanoethylation was the method used by Vögtle[137] in what is commonly described as the first dendrimer synthesis, although his dendrimer did not contain triazine derivatives.

A method resulting in compound **6**, with features strikingly similar to that of Vögtle's, was described in a patent by Niederhauser[138] in 1951, 27 years before Vögtle's work (Scheme:7). Niederhauser knew of the ability to reduce nitrile groups to amines: he described such a method in a patent filed in 1945.[139] Either through the reduction of the nitriles to amines or further cycloaddition reactions with the nitriles, Niederhauser might have laid claim to the first dendrimer. Here was a near miss to the beginning of dendrimer chemistry. Although a more exhaustive (and wholly impractical) search of the literature may provide more near misses, our interest in triazines necessitates its inclusion. The elaboration of Niederhauser's tetracyanoethyl benzoguanamine to afford a structurally imperfect generation-four dendrimer, however, took over 40 years to accomplish.



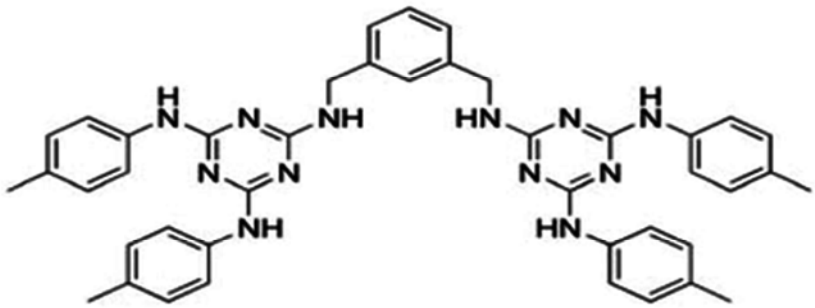
Scheme 7 : Niederhauser's route to tetracyanoethyl benzo guanamine.

In 1993, two groups described the successful synthesis of Vögtle's route to give dendrimers through iterative reactions.[140,141] These methods eventually led to the commercial production of this class of dendrimers known as poly(propylene imine)

dendrimers. In general, the cycloaddition/cyanoethylation method is attractive because it requires no functional group interconversions or the use of protecting groups as long as there are no other functional groups present that can interfere with this iterative process.

1.9.2 Nucleophilic Aromatic Substitution

The vast majority of triazine-based dendrimers are synthesized by nucleophilic aromatic substitution on cyanuric chloride. One of the earliest examples of the use of nucleophilic aromatic substitution to afford a dendritic product that incorporated triazine groups was reported in 1996 and described the treatment of *m*-bis(methylamino)benzene with 2 equiv of cyanuric chloride. A subsequent treatment with excess amine afforded the desired product, **7**. These dendritic structures were tested as chelating ligands for Gd in magnetic resonance imaging (MRI) applications (Chart 2).[142]

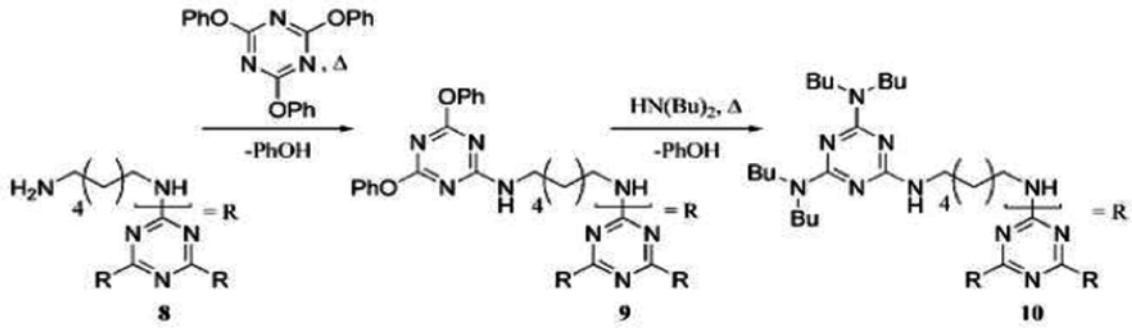


7

Chart 2 : Dendritic molecule designed for use as a chelating agent for Gd in MRI applications.

The first report concerned specifically with the construction of dendrimers by the substitution of cyanuric chloride with diamine linkers is a German patent filed in 1995 that describes a series of linear and dendritic polymer architectures synthesized with divergent and convergent methods.[143] Trisphenoxytriazine was used instead of trichlorotriazine to reduce hydrolysis. These derivatives still display a gradient of

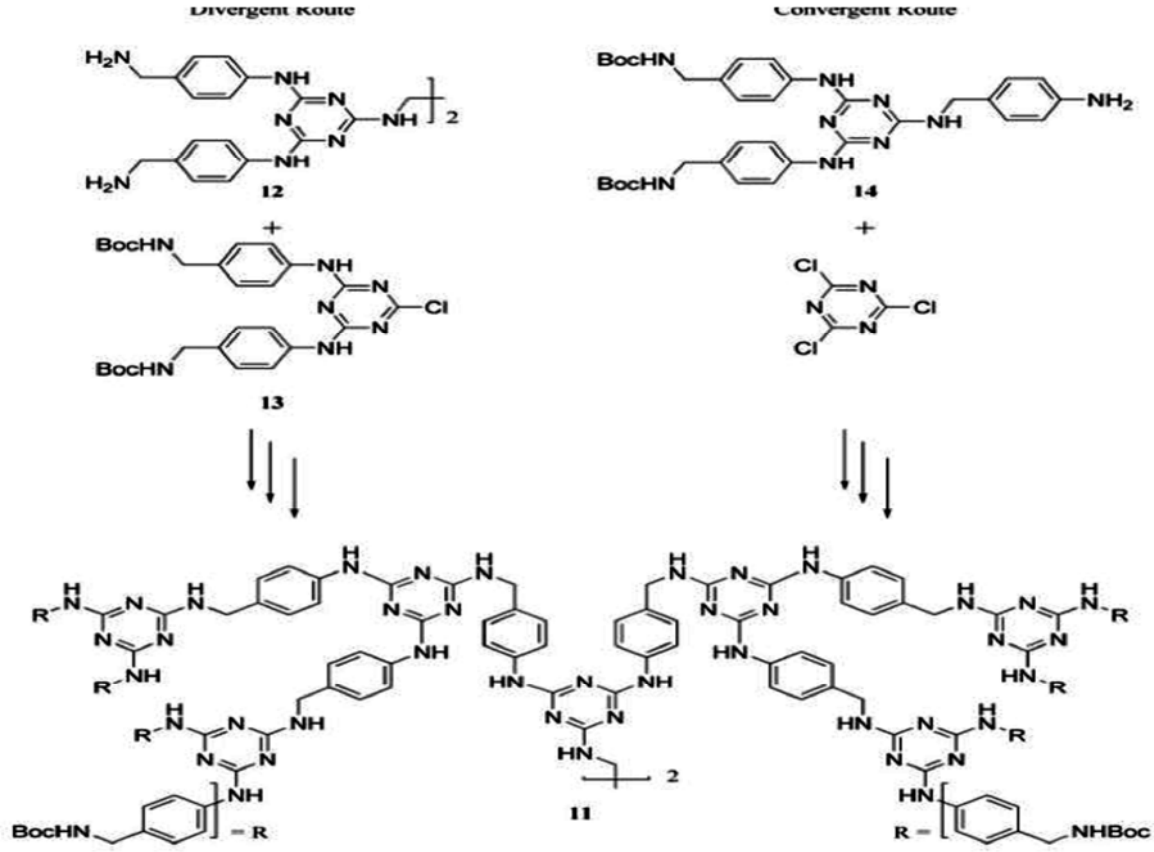
reactivity that has been investigated with activation energies measured in *N*-methylpyrrolidine with octylamine of 25, 53, and 82 kJ/mol. A separate account released in 2000 described the synthesis of a first-generation dendrimer by the treatment of a symmetrical melamine derivative, **8**, with tris(phenoxy)triazine (Scheme:8).[144] Once complete substitution had been achieved to give **9**, the phenoxy groups were exchanged by a treatment with excess secondary amine to afford the product, **10**. The products of this synthesis, derived from dibutylamine (**10**), dihexylamine and dioctylamine, were viscous oils. Additional complexity was incorporated with a similar divergent approach that commenced with an excess of $HN(CH_2CH_2NH_2)_2$ and trisphenoxytriazine.



Scheme 8: Convergent synthesis of a triazine-based dendrimer with nucleophilic aromatic substitution, with dibutylamine as an example of a precursor amine.

In 2000, we described methods for the construction of melamine-based dendrimers with diamine linkers and cyanuric chloride.[145,146] A third-generation dendrimer, **11**, was constructed with divergent (Scheme:9) and convergent routes. The divergent route connected a tetraamine core, **12**, with a BOC-protected monochlorotriazine synthon, **13** (BOC = *t*-butoxycarbonyl). The convergent route used a BOC-protected peripheral group, **14**, and an iterative reaction with cyanuric chloride and *p*-amino-benzylamine. Impurities that were implied by a tailing in the size exclusion chromatography (SEC) data were removed with chromatography purification techniques to obtain materials that had a single ion peak in the matrix-assisted laser desorption/ionization mass spectrometry spectrum. To us, this report represents a significant advance in triazine-based dendrimer synthesis because it was the first example reported in the mainstream

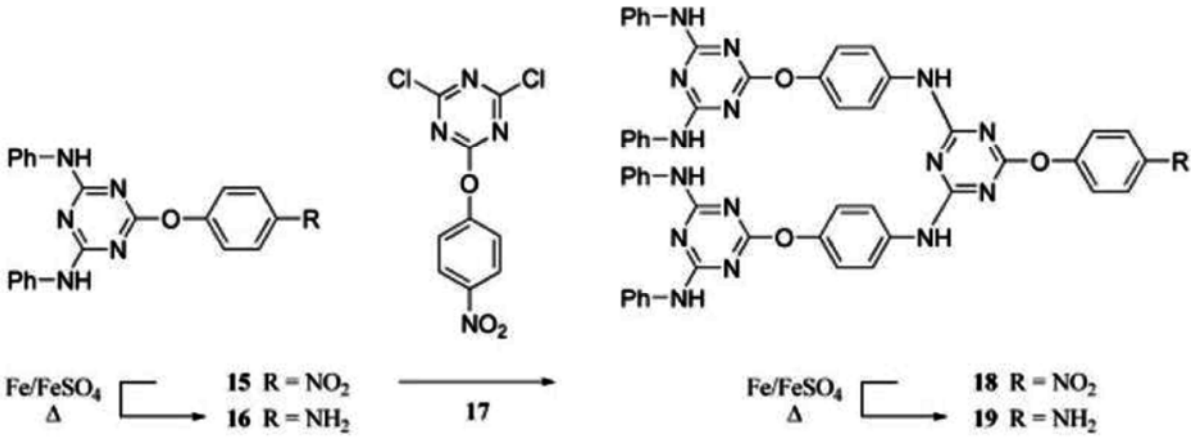
literature of nucleophilic aromatic substitution under moderate synthetic conditions to yield a triazine dendrimer. These efforts complement the original work described in the dissertation work of Jens Neumann-Rodekirch of the University of Bremen.[147]



Scheme 9: Convergent and divergent syntheses of a melamine-based dendrimer.

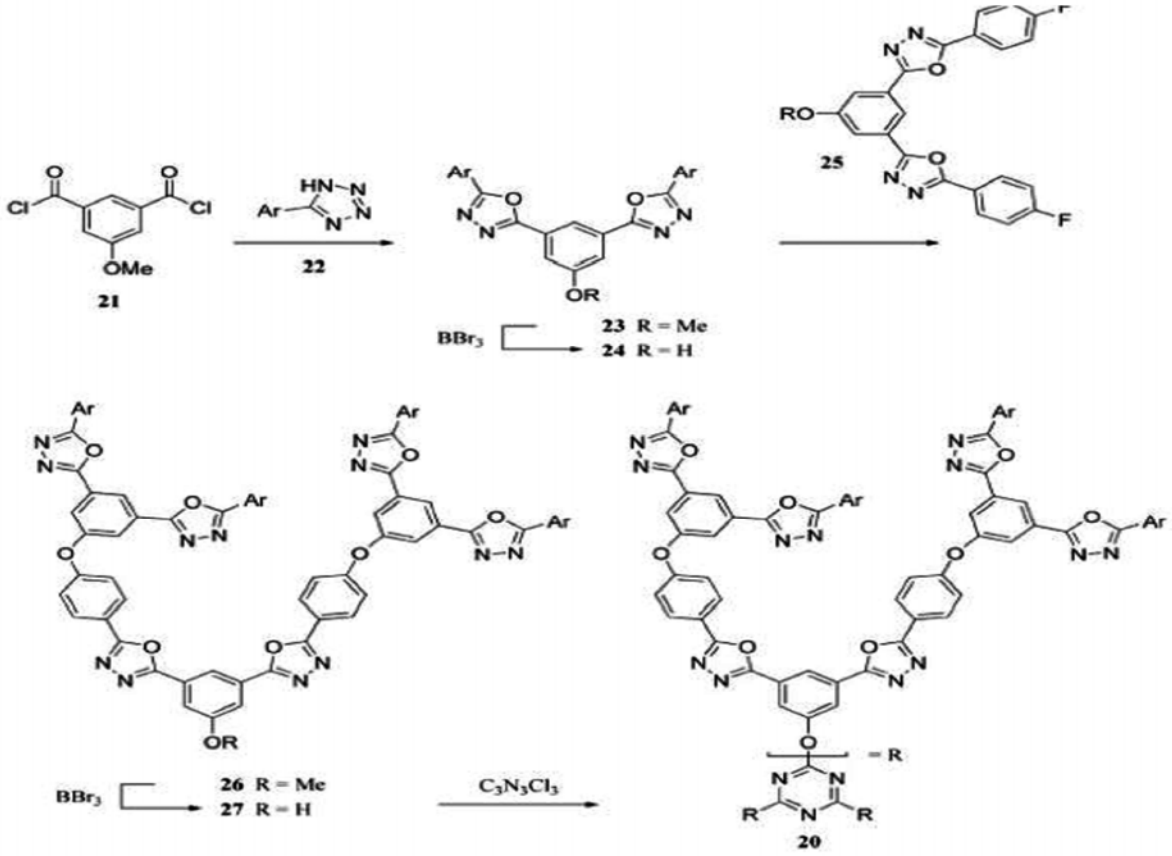
Takagi and coworkers[148,149] published two articles on the syntheses of structurally related triazine dendrimers. Their first report described the convergent synthesis of a second-generation dendrimer and several third-generation dendrons. The synthesis involved the treatment of a disubstituted triazine derivative with *p*-nitroaniline (**15**), followed by the reduction of the nitro group to unmask an amine group (**16**). The product of this reaction was then treated with a dichlorotriazine derivative, **17**, to increase the generation of the dendron (**18** and **19**, Scheme 10).[148] The second article described convergent and divergent methods for the preparation of second-generation triazine-based dendrimers with a different linkage group to accomplish each approach. The divergent route described in the second article employed the same iterative process

as the convergent route outlined in their first article. However, the second-generation dendron prepared by the convergent route was prepared with aryloxy substitution of cyanuric chloride. Subsequent generations of dendrons were achieved through the double substitution of the dichlorotriazine building block by an aryl amine.[149]

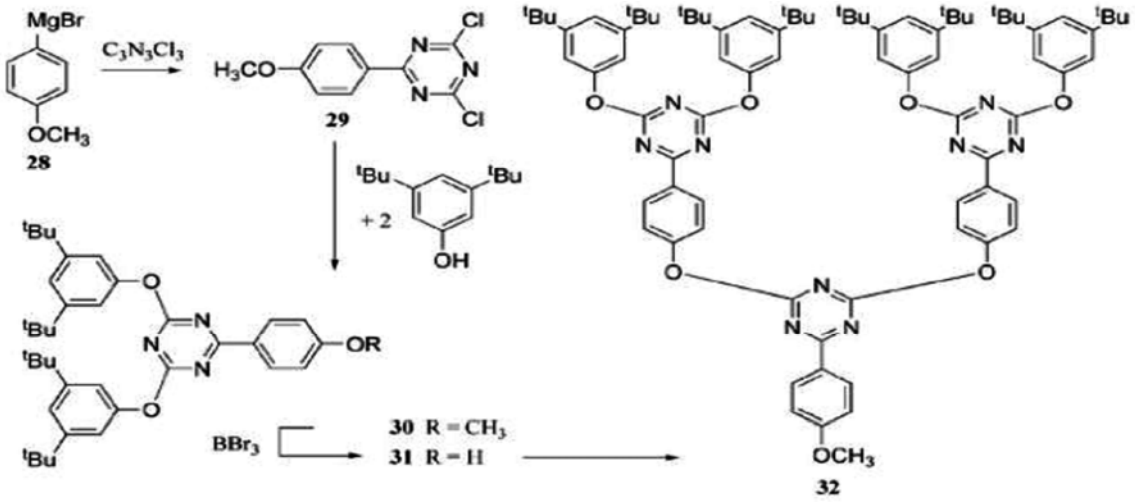


Scheme 10 : Iterative synthesis of a dendron with functional group interconversions.

Verheyde and Dehaen[150] synthesized dendrimers made up of 1,3,4-oxadiazole repeating units with a single triazine at the core (**20**, through **21**–**27**, Scheme 11). In a separate account, Dehaen et al.[151] produced dendrimers with triazines as the branching units. The first anisole was added to the triazine ring with a Grignard reagent, **28**, to give the dichlorotriazine product, **29**. Surface groups were attached to the triazine ring through aryloxy nucleophilic displacement of the chlorides to prepare **30**. The methoxy functionality of anisole was unmasked to reveal a phenol (**31**) that was subsequently treated with a half-equivalent of cyanuric chloride to afford the next generation of dendron (**32** Scheme 12,). A more recent report describes the use of click chemistry to prepare a similar dendritic structure, also from a triazine core.[152]



Scheme 11: Triazine as the core of a dendrimer.



Scheme 12: Different nucleophiles are used to synthesize a dendron.

In 2001, the synthesis of the first tailored triazine-based dendrimer, **33**, was described. A convergent approach permitted access to pure melamine dendrons (Chart 3) or

dendrimers in which one or two of the peripheral sites (out of a possible 16) were different from the remaining peripheral groups.[153] Interestingly, the addition of only one oligo(ethyleneoxy)ethylamine group to the exterior dramatically influenced the ability of the dendrimers to be characterized by SEC. This clearly illustrates that even subtle changes imparted by tailored dendrimers can result in properties dramatically different from those of their monofunctionalized counterparts.

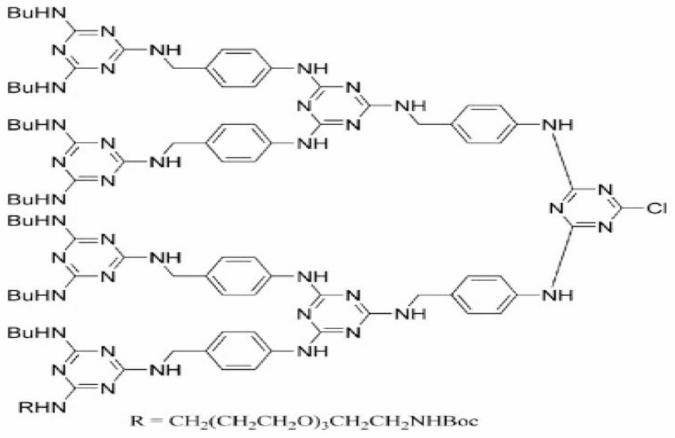


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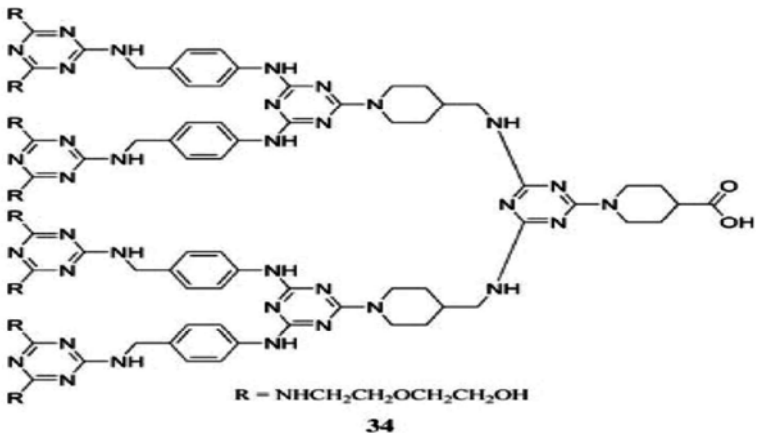
Chart 3 : Tailored dendron.

Another improvement in dendrimer synthesis was achieved when a third-generation dendron, **34**, was prepared in the absence of protecting groups or functional group manipulations (Chart 4).[154,155]



34

Chart 4 : Dendron that was synthesized without protecting group manipulations or functional group interconversions.

The strategy expanded the use of chemoselective diamines from *p*-amino-benzyl amine to additional diamines. Diamines comprising amines with reactivity differences greater than 20 were found to be useful for chemoselective reactions.

The same strategy that was applied for the synthesis of a tailored dendrimer was also successfully employed to prepare a dendrimer or dendron with five (**35**) or six (**36**) orthogonal reactive sites, respectively (Chart 5).[156] The inference to the potential utility of this dendrimer for drug delivery and related biological applications was based on the demonstration that the functional groups could be manipulated after the synthesis of the dendrimer with little formation of byproducts. The power of triazine chemistry is best exemplified in these targets.

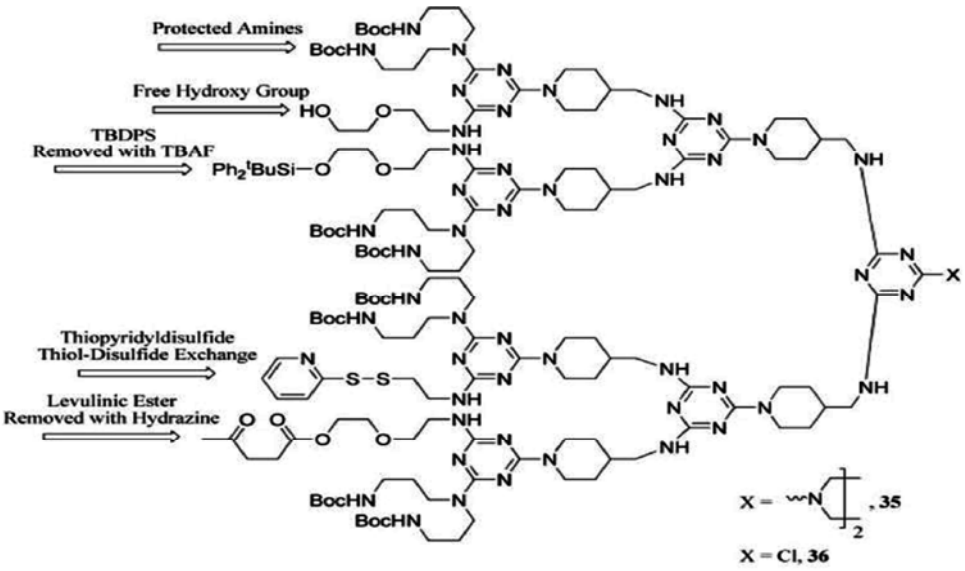
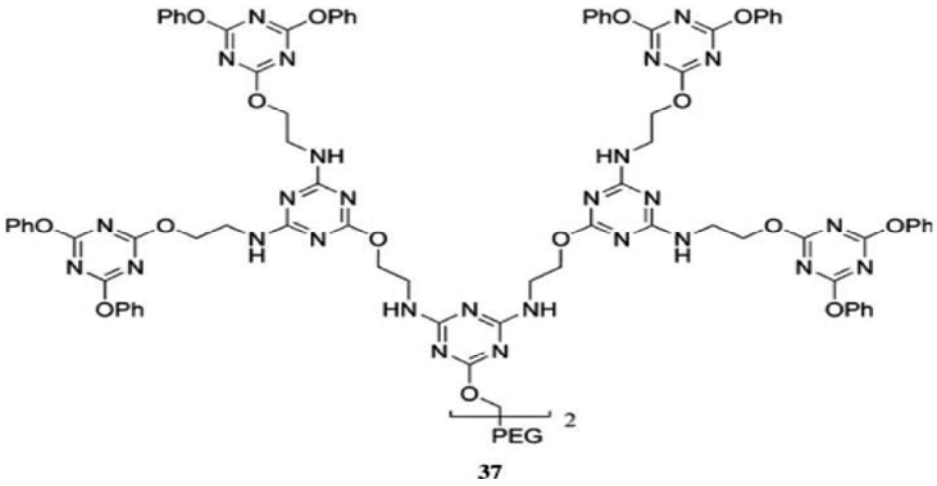


Chart 5 : Pure dendron and dendrimer with a high degree of functional group diversity for postsynthetic manipulation (TBAF = tetrabutylammonium fluoride; TBDPS = *tert*-butyl diphenylsilane).

The most recent example of the use of nucleophilic aromatic substitution to prepare a triazine-based dendrimer was demonstrated by the treatment of a poly(ethylene glycol) (PEG) diamine derivative with cyanuric chloride.[157] An iterative treatment with ethanol amine and cyanuric chloride resulted in the formation of a third-generation dendrimer, **37**, tethered by a PEG oligomer (Chart 6). The result was an amphiphilic material, and the critical micelle concentrations of the first-and second-generation versions of the block copolymer were 5.5×10^{-5} M and 7.6×10^{-4} M, respectively.

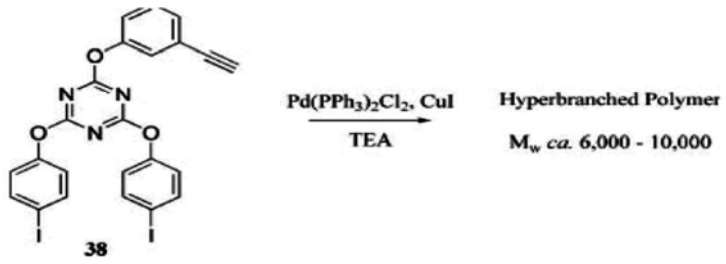


37

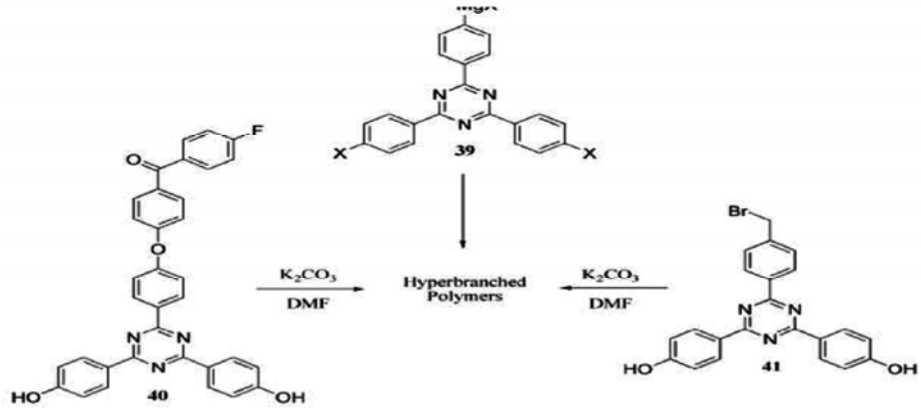
Chart 6 : Triazine-based dendritic block copolymer.

1.9.3 Hyperbranched Molecules:

A third synthetic route to triazine-containing dendritic materials involves the preparation of hyperbranched molecules. Polycyanurate ester resins dating to the 1960s could be regarded as progenitors of these materials.[131] Early efforts by Neumann-Rodekirch[147] using the homopolycondensation of diphenyoxytriazines substituted with amines, including *p*-aminobenzylamine, *N*-methyl-*p*-aminobenzylamine, and masked amines such as acetylaniline, mono-BOC protected hydrazine, and hexane diamine, were conducted in *N*-methylpyrrolidine at 200–240 °C with the intent of producing stationary phases for chromatography. More recent examples of hyperbranched triazines include work by Kim et al.,[158] who prepared hyperbranched triazine polymers by performing a Heck coupling of an AB_2 triazine monomer, **38**, to produce materials with a weight-average molecular weight (M_w) of 6000–10,000 g mol^{-1}, as estimated by SEC (Scheme 13). This novel route to hyperbranched triazine products is of interest because of the ability to prepare relatively high-molecular-weight material with a single-pot procedure. A related protocol has been reported in which hyperbranched triazine polymers are prepared from an AB_2 triazine monomer (**39**, Scheme 14) that incorporates a Grignard reagent.[159,160]



Scheme 13: Heck coupling of a triazine AB_2 monomer results in hyperbranched materials (TEA = triethylamine).

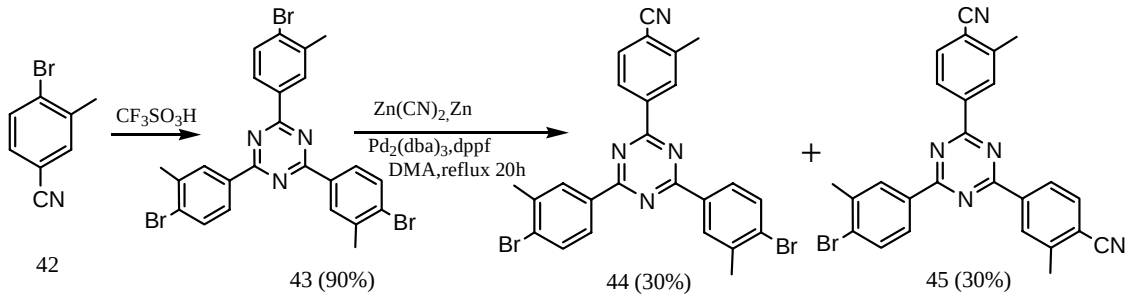


Scheme 14: Additional routes to hyperbranched materials .

This separate series of articles were published by Kim and coworkers,[161–164] who described a similar strategy to obtain hyperbranched polymers from AB_2 triazine monomers **40** and **41**. In these cases, the polymer was obtained by heating the monomer in the presence of potassium carbonate to 140 °C (Scheme 14). The polymers had M_w values of 11,000–15,000 g mol^{-1}, as estimated by gel permeation chromatography, and displayed excellent thermal stability, as evidenced by thermogravimetric analysis (TGA). More recently, the free hydroxyl end groups of one of the hyperbranched polymers were functionalized with Mitsunobu or dicyclohexylcarbodiimide reactions to install oligoethyleneoxy or stearyl groups, respectively.[163] The incorporation of these groups significantly lowered the glass-transition temperature of these materials with respect to the precursor polymer.

1.9.4 Cyclotrimerization Method :

The synthesis of the title dendritic molecule was first attempted by cyclotrimerization of the corresponding nitrile as shown in scheme 15. The tris(bromoaryl)triazine **43** was prepared in high yield by cyclotrimerization of 4-bromo-3-methylbenzonitrile **(42)** with neat trifluoromethanesulphonic acid.



Scheme 15

In the next step, cyanation of **43** was achieved by the use of palladium Pd_2 (dba)3, dppf and Zn as the catalyst and $Zn(CN)_2$ as the cyanide source, in accordance with a known protocol for the cyanation of aryl chlorides. Although the ratio of Br/CN was kept at 2.5: 1, cyanation was not selective, leading to unreacted **43** (32%) and a mixture of mono and dicyanated derivatives **44** and **45,** in yields of 30 % and 16 % respectively.[165(a)]

Introduction:

1.1 General remarks: Dendrimers and dendritic molecules are the subject of significant academic and industrial interest.[1(a,b)]Dendrimers are repetitively branched molecules.[2(a,b)] The name comes from the Greek word "δένδρον" (pronounced dendron), which translates to "tree". Synonymous terms for dendrimer include arborols and cascade molecules. However, dendrimer is currently the internationally accepted term. A dendrimer is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. The word dendron is also encountered frequently. A dendron usually contains a single chemically addressable group called the focal point. The difference between dendrons and dendrimers is illustrated in figure one, but the terms are typically encountered interchangeably.[3]

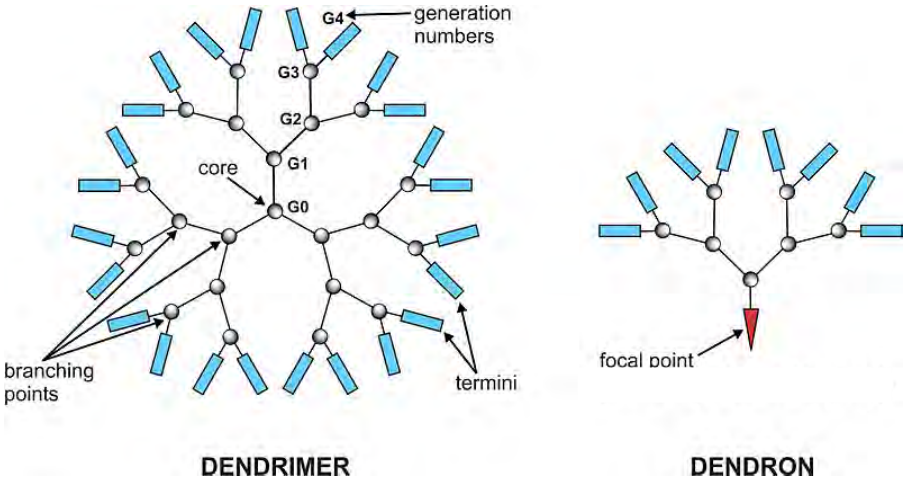


Figure 1: Dendrimer and Dendron

Dendrimers are an interesting unique class of polymers with controlled structures. A dendrimer is both a covalently assembled molecule and also a well-defined nanoparticle. The first dendrimers were made by divergent synthesis approaches by Fritz Vögtle in 1978,[5] R.G. Denkewalter at Allied Corporation in 1981,[6,7] Donald Tomalia at Dow Chemical in 1983[8] and in 1985,[9,10] and by George Newkome in 1985.[11] In 1990 a convergent synthetic approach was introduced by Jean Fréchet.[12] Dendrimer popularity then greatly increased, resulting in more than 5,000 scientific papers and patents by the year 2005.

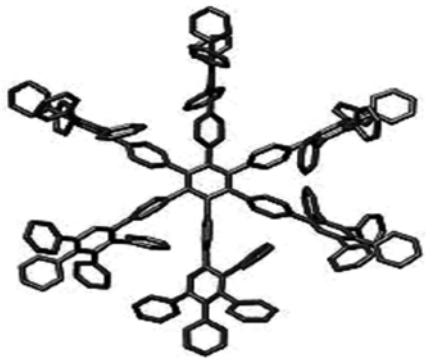


Figure 2: Crystal structure of a first-generation polyphenylene dendrimer reported by Müllen et al.[4]

1.2 Properties

The field of dendritic molecules can be roughly divided into low-molecular weight and high-molecular weight species. The first category includes dendrimers and dendrons, and the latter includes dendronized polymers, hyperbranched polymers, and the polymer brush. Dendrimers and dendrons are monodisperse and usually highly symmetric, spherical compounds. Dendritic molecules are characterized by structural perfection. The properties of dendrimers are dominated by the functional groups on the molecular surface, however, there are examples of dendrimers with internal functionality.[13, 14, 15]

Dendritic encapsulation of functional molecules allows for the isolation of the active site, a structure that mimics that of active sites in biomaterials.[16,17,18] Also, it is possible to make dendrimers water soluble, unlike most polymers, by functionalizing their outer shell with charged species or other hydrophilic groups. Other controllable properties of dendrimers include toxicity, crystallinity, tecto-dendrimer formation, and chirality.[3]

Dendrimers are also classified by generation, which refers to the number of repeated branching cycles that are performed during its synthesis. For example if a dendrimer is made by convergent synthesis, and the branching reactions are performed onto the core molecule three times, the resulting dendrimer is considered a third generation dendrimer. Each successive generation results in a dendrimer roughly twice the molecular weight of the previous generation. Higher generation dendrimers also have more exposed functional groups on the surface, which can later be used to customize the dendrimer for a given application.[19]

1.3 Synthesis

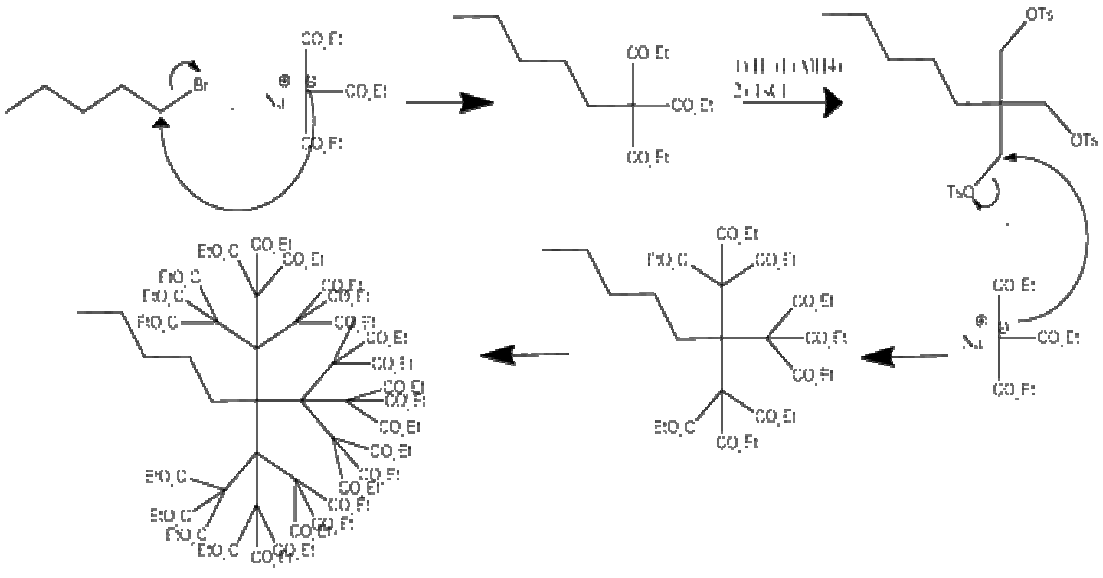


Figure 3: Synthesis to second generation arborol

In 1985 one of the very first dendrimers, the Newkome dendrimer, was synthesized. Figure 3 outlines the mechanism of the first two generations of arborol through a divergent route. The synthesis is started by nucleophilic substitution of 1-bromopentane by triethyl sodiomethanetricarboxylate in dimethylformamide and benzene. The ester groups were then reduced by lithium aluminium hydride to a triol in a deprotection step. Activation of the chain ends was achieved by converting the alcohol groups to tosylate groups with tosyl chloride and pyridine. The tosyl group then served as leaving groups in another reaction with the tricarboxylate, forming generation two. Further repetition of the two steps leads to higher generations of arborol.[11]

Poly(amidoamine), or PAMAM, is perhaps the most well known dendrimer. The core of PAMAM is a diamine (commonly ethylenediamine), which is reacted with methyl acrylate, and then another ethylenediamine to make the generation-0 (G-0) PAMAM. Successive reactions create higher generations, which tend to have different properties. Lower generations can be thought of as flexible molecules with no appreciable inner regions, while medium sized (G-3 or G-4) do have internal space that is essentially separated from the outer shell of the dendrimer. Very large (G-7 and greater) dendrimers can be thought of more like solid particles with very dense surfaces due to the structure of their outer shell. The functional group on the surface of PAMAM

dendrimers is ideal for click chemistry, which gives rise to many potential applications.[20]

Dendrimers can be considered to have three major portions: a core, an inner shell, and an outer shell. Ideally, a dendrimer can be synthesized to have different functionality in each of these portions to control properties such as solubility, thermal stability, and attachment of compounds for particular applications. Synthetic processes can also precisely control the size and number of branches on the dendrimer. There are two defined methods of dendrimer synthesis, divergent synthesis and convergent synthesis. However, because the actual reactions consist of many steps needed to protect the active site, it is difficult to synthesize dendrimers using either method. This makes dendrimers hard to make and very expensive to purchase. At this time, there are only a few companies that sell dendrimers; Polymer Factory Sweden AB[21] commercializes biocompatible bis-MPA dendrimers and Dendritech[22] is the only kilogram-scale producers of PAMAM dendrimers. Dendritic Nanotechnologies Inc.,[23] from Mount Pleasant, Michigan, USA produces PAMAM dendrimers and other proprietary dendrimers.

1.3.1 Divergent Methods

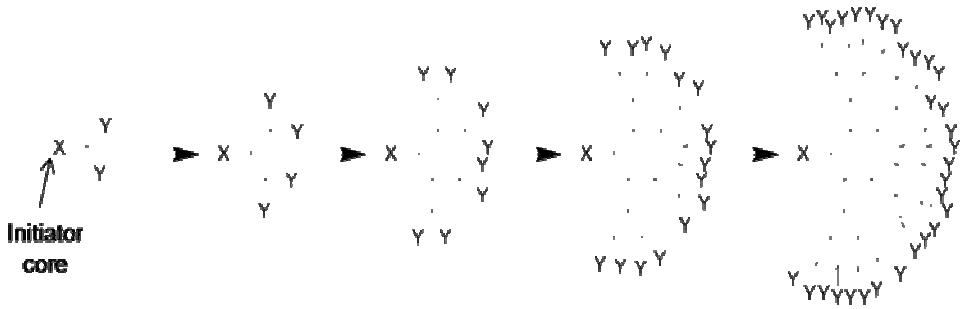


Figure 4: Schematic of divergent synthesis of dendrimers

The dendrimer is assembled from a multifunctional core, which is extended outward by a series of reactions, commonly a Michael reaction. Each step of the reaction must be driven to full completion to prevent mistakes in the dendrimer, which can cause trailing generations (some branches are shorter than the others). Such impurities can impact the functionality and symmetry of the dendrimer, but are extremely difficult to purify out because the relative size difference between perfect and imperfect dendrimers is very small.[19]

1.3.2 Convergent Methods

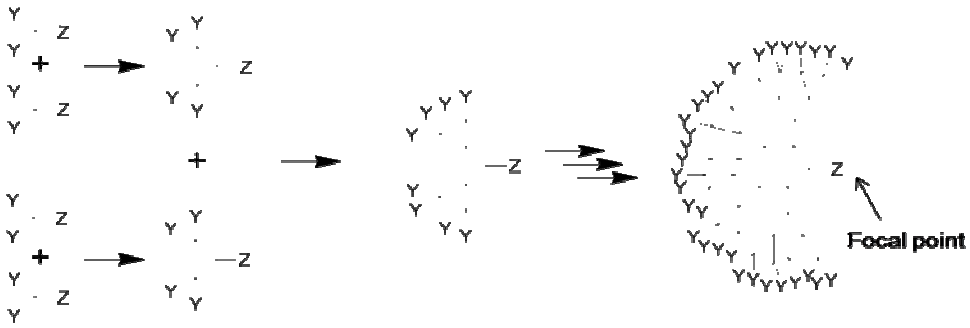


Figure 5: Schematic of convergent synthesis of dendrimers

Dendrimers are built from small molecules that end up at the surface of the sphere, and reactions proceed inward building inward and are eventually attached to a core. This method makes it much easier to remove impurities and shorter branches along the way, so that the final dendrimer is more monodisperse. However dendrimers made this way are not as large as those made by divergent methods because crowding due to steric effects along the core is limiting.[19]

Dendrimers have been prepared via click chemistry, employing Diels-Alder reactions,[24] thiol-ene reactions [25] and azide-alkyne reactions.[26,27,28] An example is the synthesis of certain polyphenylene dendrimers can be seen in figure 6.[29]

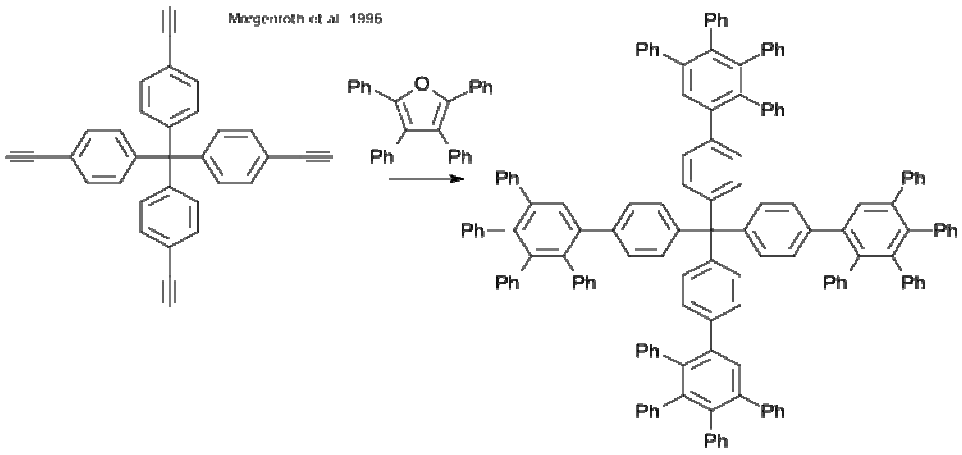


Figure 6: Dendrimer DA reaction Mullen 1996

1.4 Applications

Applications of dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radioligands, imaging agents, or pharmaceutically active compounds. Dendrimers have very strong potential for these applications because their structure can lead to multivalent systems. In other words, one dendrimer molecule has hundreds of possible sites to couple to an active species. Researchers aimed to utilize the hydrophobic environments of the dendritic media to conduct photochemical reactions that generate the products that are synthetically challenged. Carboxylic acid and phenol terminated water soluble dendrimers were synthesized to establish their utility in drug delivery as well as conducting chemical reactions in their interiors.[30] This might allow researchers to attach both targeting molecules and drug molecules to the same dendrimer, which could reduce negative side effects of medications on healthy cells.[20]

1.4.1 Dendrimers as solubilizing agent

This novel class of dendrimer architecture has been a prime candidate for hosts guest chemistry since their introduction in the mid-1980s,.[31] Dendrimers with hydrophobic core and hydrophilic periphery have shown to exhibit micelle-like behavior and have container properties in solution.[32] The use of dendrimers as unimolecular micelles was proposed by Newkome in 1985.[33] This analogy highlighted the utility of dendrimers as solubilizing agents.[34] The majority of drugs available in pharmaceutical industry are hydrophobic in nature and this property in particular creates major formulation problems. This drawback of drugs can be ameliorated by dendrimeric scaffolding, which can be used to encapsulate as well as to solubilize the drugs because of the capability of such scaffolds to participate in extensive hydrogen bonding with water.[35,36,37,38,39,40] Dendrimer labs throughout the planet are persistently trying to manipulate dendrimer's solubilizing trait, in their way to explore dendrimer as drug delivery[41,42] and target specific carrier.[43,44,45]

1.4.2 Drug Delivery

There are three methods for using dendrimers in drug delivery: first, the drug is covalently attached to the periphery of the dendrimer to form dendrimer prodrugs,

second the drug is coordinated to the outer functional groups via ionic interactions, or third the dendrimer acts as a unimolecular micelle by encapsulating a pharmaceutical through the formation of a dendrimer-drug supramolecular assembly.[46,47] Approaches for delivering unaltered natural products using polymeric carriers is of widespread interest, dendrimers have been explored for the encapsulation of hydrophobic compounds and for the delivery of anticancer drugs. The physical characteristics of dendrimers, including their monodispersity, water solubility, encapsulation ability, and large number of functionalizable peripheral groups, make these macromolecules appropriate candidates for evaluation as drug delivery vehicles. The use of dendrimers as drug carriers by encapsulating hydrophobic drugs is a potential method for delivering highly active pharmaceutical compounds that may not be in clinical use due to their limited water solubility and resulting suboptimal pharmacokinetics.

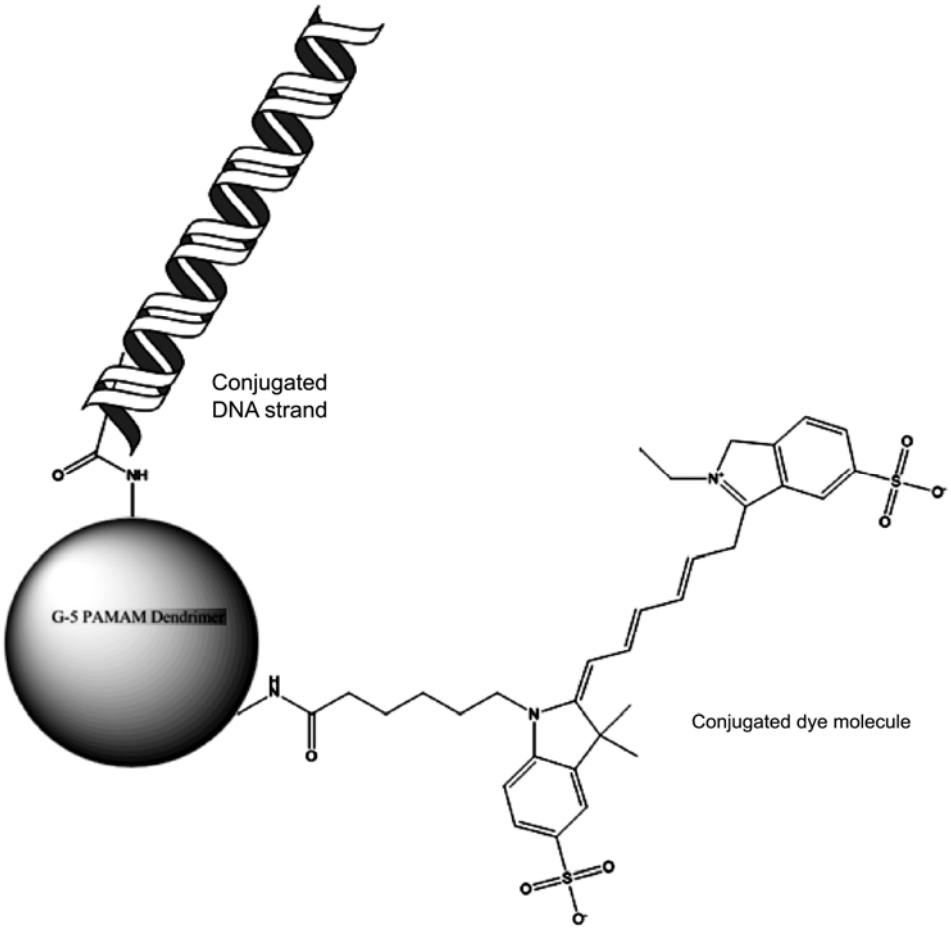


Figure 7: Schematic of a G-5 PAMAM dendrimer conjugated to both a dye molecule and a strand of DNA.

Dendrimers have been widely explored for controlled delivery of antiretroviral bioactives.[48] The inherent antiretroviral activity of dendrimers enhances their efficacy as carriers for antiretroviral drugs.[49,50] The dendrimer enhances both the uptake and retention of compounds within cancer cells, a finding that was not anticipated at the onset of studies. The encapsulation increases with dendrimer generation and this method may be useful to entrap drugs with a relatively high therapeutic dose. Studies based on this dendritic polymer also open up new avenues of research into the further development of drug-dendrimer complexes specific for a cancer and/or targeted organ system. These encouraging results provide further impetus to design, synthesize, and evaluate dendritic polymers for use in basic drug delivery studies and eventually in the clinic.[46,51]

The term “magic bullet” was first introduced by Paul Ehrlich. Ehrlich’s work with immunology led to his receiving the Nobel Prize in Physiology or Medicine in 1908. Among his contributions was the belief that compounds with specific structures could be found which would recognize and bind a specific disease-causing target in an organism to provide therapeutic action to this target without causing harm to the organism itself – a magic bullet.[52]Among many other accomplishments, Ehrlich’s work contributed to the establishment of chemotherapeutic techniques.[53] Pharmacologically active polymers have been recognized as important targets for decades, especially in the field of cancer therapeutics due to the non-specificity of many drugs. These “magic bullets” could enter tumor cells and deliver a payload of drug without harming the individual. In 1975, Ringsdorf defined the ideal structure and properties of polymeric drug agents.[54] He described a carrier with a biostable or biodegradable backbone comprised of three parts. First, the polymer carrier should have a group that renders the macromolecule soluble and nontoxic. The second group is for the attachment of the drug, which would be performed under mild conditions and would incorporate a spacer to separate the drug from the polymer. These conditions would need to be met in order to ensure there would be no adverse effects on the drug’s biological activity once attached to the polymeric carrier. The linkage between the polymer and the drug would need to be stable under normal body conditions but able to release the drug rapidly by hydrolysis or enzymatic processes once the site of action is reached. The third group would transport the entire carrier to the target cells by use of a homing device or through nonspecific enhancement of cellular-uptake.

Polymers, and therefore polymer drug conjugates, enter cell membranes by endocytosis rather than by diffusion. The macromolecules are engulfed by the plasma membrane and form endosomes which can fuse with enzyme-containing lysosomes. Provided the linker connecting the drug and carrier meets the aforementioned conditions,the linker may be cleaved to release the drug either enzymatically or by hydrolysis induced by the decrease in pH from 7.4 in the cytoplasm to pH 5 found in the lysosome.Macromolecules show specificity to tumor cells due to a phenomenon known as the enhanced permeability and retention effect (EPR).[55] Maeda and co-workers coined the term EPR effect in 1986.[56] They attributed the EPR effect to two main factors: leaky tumor vessels allowing entry of macromolecules, an activity which is not usually allowed in normal tissues, and an ineffective tumor lymphatic drainage system which prevents clearance of the macromolecules and promotes their accumulation. (Figure 8) The typical value for the molecular weight of macromolecules which can exploit the EPR effect is greater than 40 kDa, [57] but studies have shown polymers with molecular weights between 20 and 800 kDa are able to access tumors. Studies of nonuniform accumulation of polymers in tumor tissue demonstrate that the threshold of vascular permeability actually varies with polymer architecture, tumor size and type, and even vessel to vessel in the local microenvironment of the tumor.[58]

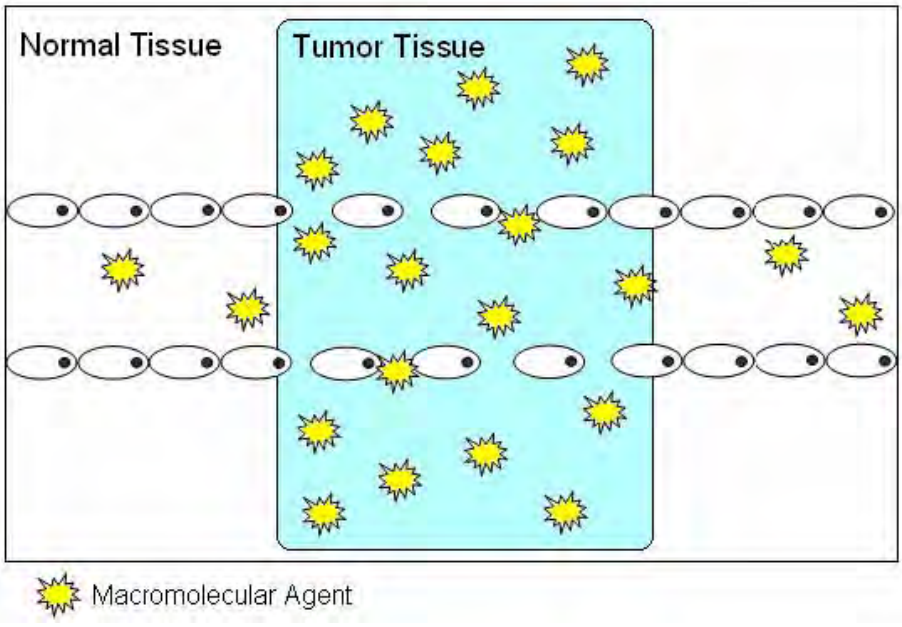


Figure 8. The EPR effect.

Dendrimers are highly branched, symmetric, synthetic polymers emanating from a central core. These multivalent molecules are globular in shape, monodisperse, and allow control of molecular weight, surface groups, and interior groups.[59-62] Due to these properties, dendrimers are attractive targets for drug delivery agents.[55,63-71] Figure 9 shows the possible uses of the multivalency of dendrimers.Synthetic manipulations to the functional groups in the core of the dendrimers would facilitate noncovalent encapsulation of drugs in the interior. Also, covalent attachment of solubilizing groups, targeting moieties, and drugs to the periphery of dendrimers is possible with modifications of the surface groups.

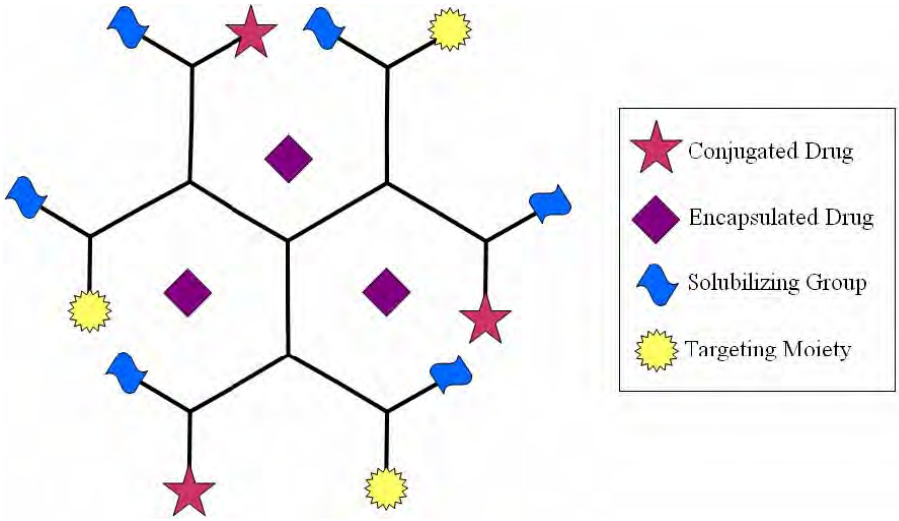


Figure 9. Possible functionalization of a dendritic drug delivery agent.

Noncovalent encapsulation of drugs with dendrimers can be accomplished using hydrogen bonding, hydrophobic, or electrostatic interactions between the guests and host.[72] One method of encapsulation is the construction of dendritic 'unimolecular micelles'.[73-76] Conventional polymeric micelles are amphiphilic block copolymers which form thermodynamic aggregates in proper solvents above the critical micelle concentration (c.m.c.). This property is also the limiting factor in micellar drug delivery applications. Under physiological conditions, the concentration may drop below the c.m.c. causing dissociation of the micelle into free polymer chains. With unimolecular micelles, the hydrophobic and hydrophilic segments are covalently bound together imparting stability to the micellar structure. Hydrophobic drugs can be solubilized in

the hydrophobic core of the dendrimer while the hydrophilic portion, usually polyethylene glycol (PEG) chains, on the periphery solubilizes the entire carrier.[68]

Interactions between dendrimers and guests to afford encapsulation have been exploited by many groups.[77-88] Twyman, *et al*. synthesized water-soluble, hydroxyl terminated poly(amido amine) (PAMAM) dendrimers capable of solubilizing several small, acidic, hydrophobic model compounds including benzoic acid and salicylic acid.The complexes were stable at pH 7, but under acidic conditions, precipitation of the model hydrophobic compounds occurred. It was thought that protonation of the internal tertiary amines of the dendrimer interrupted the noncovalent interactions with the acidic guests causing this dissociation.[89]

1.4.3 Gene Delivery

The ability to deliver pieces of DNA to the required parts of a cell includes many challenges. Current research is being performed to find ways to use dendrimers to traffic genes into cells without damaging or deactivating the DNA. To maintain the activity of DNA during dehydration, the dendrimer/DNA complexes were encapsulated in a water soluble polymer, and then deposited on or sandwiched in functional polymer films with a fast degradation rate to mediate gene transfection. Based on this method, PAMAM dendrimer/DNA complexes were used to encapsulate functional biodegradable polymer films for substratemediated gene delivery. Research has shown that the fast degrading functional polymer has great potential for localized transfection.[90, 91, 92]

1.4.4 Sensors

For use in sensor technologies scientists have also studied dendrimers. Studied systems include proton or pH sensors using poly(propylene imine),[93] cadmium-sulfide/polypropylenimine tetrahexacontaamine dendrimer composites to detect fluorescence signal quenching,[94] and poly(propylenamine) first and second generation dendrimers for metal cation photodetection[95] amongst others. Research in this field is vast and ongoing due to the potential for multiple detection and binding sites in dendritic structures.

1.5 Dendronized polymers :

Dendronized polymers are linear polymers to every repeat unit of which dendrons are attached. Dendrons are regularly branched, tree-like fragments and for larger ones the polymer backbone is wrapped to give sausage-like, cylindrical molecular objects.

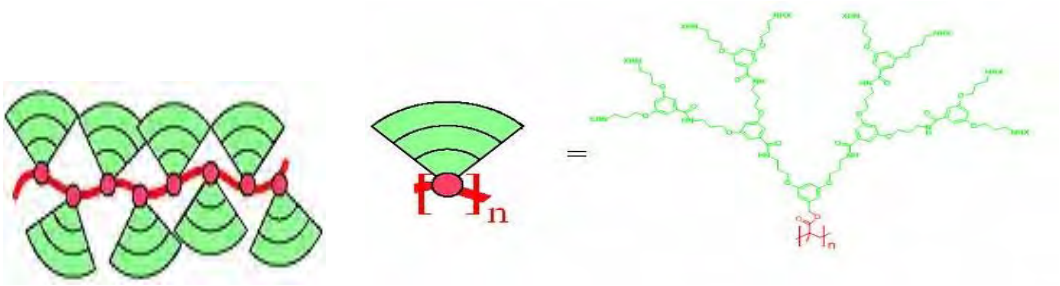


Figure 10. Cartoon representation (left) and a concrete example of a third generation dendronized polymer (right).

Figure 10 shows a cartoon representation with the backbone in red and the dendrons like cake slices in green. It also provides a concrete chemical structure showing a polymethylmethacrylate (PMMA) backbone, the methyl group of which is replaced by a dendron of the third generation (three consecutive branching points).

The peripheral amine groups are modified by a substituent X which often is a protection group. Upon deprotection and modification substantial property changes can be achieved. The subscript n denotes the number of repeat units.

1.6 Metallodendrimer

A Metallodendrimer is a type of dendrimer with incorporated metal atoms. The development of this type of material is actively pursued in academia.[96,97,98]

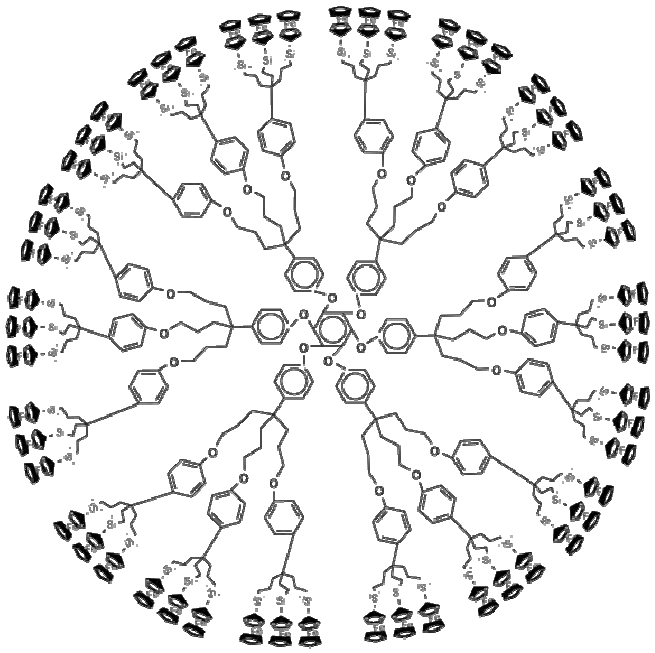


Figure 11: Ferrocene containing dendrimer

1.6.1 Structure

The metal can be situated in the repeat unit, the core or at the extremities as end-group. Elements often encountered are palladium and platinum. These metals can form octahedral six-coordinate M(IV) linking units from organic dihalides and the corresponding 4-coordinate M(II) monomers. Ferrocene-containing dendrimers and dendrimers with cobaltocene and arylchromiumtricarbonyl units have been reported in end-functional dendrimers. Metallodendrimers can form as metal complexes with dendritic counter ions for example by hydrolysis of ester terminated PAMAM dendrimers with sodium hydroxide.

1.6.2 Applications

Metallodendrimers are investigated as equivalents to nanoparticles. Applications can be expected in the fields of catalysis, as chemical sensors in molecular recognition - for example of bromine and chloride anions [99] - or as materials capable of binding metals. Metallodendrimers can also mimic certain biomolecules for example haemoprotein in dendrimer with a porphyrin core. Further uses are reported as electrocatalyst.[100,101]

Examples of metallodendrimer heterogeneous catalysis are a nickel-containing dendrimer active in the Kharasch addition,[102] palladium-containing dendrimers active in ethylene polymerization [103] and in the Heck reaction.[104]

1.7 Triazine:

Triazine are six membered aromatic heterocycles comprised of three carbon and three nitrogen atoms. A triazine is one of three organic chemicals, isomeric with each other, whose molecular formula is $C_3H_3N_3$ and whose empirical formula is CHN.

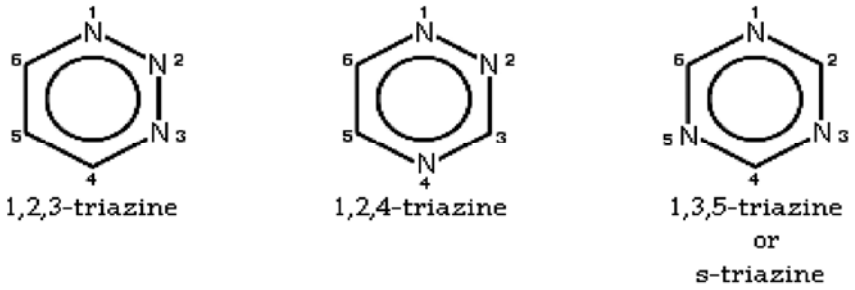


Figure 12: The three isomers of triazine, with ring numbering.

1.7.1 Structure:

The triazine structure is a heterocyclic ring, analogous to the six-membered benzene ring but with three carbons replaced by nitrogens. The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and are referred to as 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine. Other aromatic nitrogen heterocycles are pyridines with 1 ring nitrogen atom, diazines with 2 nitrogen atoms in the ring and tetrazines with 4 ring nitrogen atoms. Triazines are weaker bases than pyridine.

1.7.2 Uses:

The best known 1,3,5-triazine derivative is melamine with three amino substituents used in the manufacture of resins. Another triazine extensively used in resins is benzoguanamine. Triazine compounds are often used as the basis for various herbicides such as cyanuric chloride (2,4,6-trichloro-1,3,5-triazine). Chlorine-substituted triazines are also used as reactive dyes. These compounds react through a chlorine group with

hydroxyl groups present in cellulose fibres in nucleophilic substitution, the other triazine positions contain chromophores. Mixtures of Triazines and water are also used to remove H_2S from natural gas.

A series of 1,2,4-triazine derivatives known as BTPs have been considered in the liquid-liquid extraction community as possible extractants for use in the advanced nuclear reprocessing of used fuel.[105,106,107,108,109] BTPs are molecules containing a pyridine ring bonded to two 1,2,4-triazin-3-yl groups.

1.7.3 Synthesis

1,2,3-Triazines can be synthesized by thermal rearrangement of 2-azidocyclopropenes. 1,2,4-Triazines are prepared from condensation of 1,2-dicarbonyl compounds with amidrazones. A classical triazine synthesis is also the Bamberger triazine synthesis. Symmetrical 1,3,5-triazines are prepared by trimerization of cyanogen chloride or cyanimide. Benzoguanamine (with one phenyl and 2 amino substituents) is synthesised from benzonitrile and dicyandiamide in dimethoxyethane with potassium hydroxide.[110]. In the Pinner triazine synthesis (named after Adolf Pinner)[111] the reactants are an alkyl or aryl amidine and phosgene [112,113]

1.7.4 Reactions

Although triazines are aromatic compounds, the resonance energy is much lower than in benzene and electrophilic aromatic substitution is difficult but nucleophilic aromatic substitution more frequent. 2,4,6-Trichloro-1,3,5-triazine is easily hydrolyzed to cyanuric acid by heating with water at elevated temperatures. 2,4,6-Tris(phenoxy)-1,3,5-triazine reacts with aliphatic amines in aminolysis, and this reaction can be used to give dendrimers.[114] Pyrolysis of melamine under expulsion of ammonia gives the tri-s-triazine melem.[115] Cyanuric chloride assists in the amidation of carboxylic acids.[116]

The 1,2,4-triazines can react with electron-rich dienophiles in an inverse electron demand Diels-Alder reaction. This forms a bicyclic intermediate which normally then extrudes a molecule of nitrogen gas to form an aromatic ring again. In this way the 1,2,4-triazines can be reacted with alkynes to form pyridine rings. An alternative to using an alkyne is to use norbornadiene which can be thought of as a masked alkyne.

1.7.5 1,3,5-Triazine:

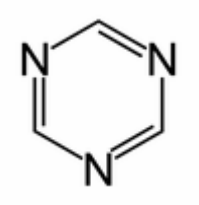


Figure 13: 1,3,5-Triazine

1,3,5-triazine, also called s-triazine, is an organic chemical compound with the formula $(HCN)_3$. It is a six-membered heterocyclic aromatic ring, one of several isomeric triazines. S-triazine and its derivatives are useful in a variety of applications.

1.7.6 Use in organic chemistry

As a reagent in organic synthesis, s-triazine is used as the equivalent of hydrogen cyanide (HCN). Being a solid (vs a gas for HCN), triazine is sometimes easier to handle in the laboratory. One application is in the Gattermann reaction, used to attach the formyl group to aromatic substrates.[117]

It is a common reagent, and readily forms derivatives, which are used as pharmaceutical products, as well as herbicides, such as atrazine.[118]

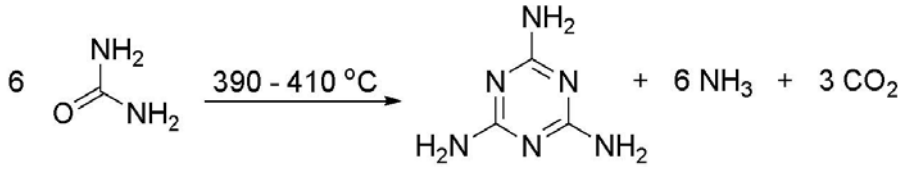
1.7.7 Substituted triazines

The most common derivative of 1,3,5-triazine is 2,4,6-triamino-1,3,5-triazine, commonly known as melamine or cyanuramide. Trichloro-1,3,5-triazine (Cyanuric chloride) is the starting point for the manufacture of many herbicides such as Simazine, as well as of many fiber reactive dyes. Another important derivative is 2,4,6-trihydroxy-1,3,5-triazine better known as cyanuric acid**.**

1.7.8 Melamine:

Melamine was prepared in 1834 by Liebig by fusing potassium thiocyanate with ammonium chloride. The product was mostly melamine thiocyanate, but treating it with base provides the free melamine.[119,120,121] It took over a century before commercial applications were fully realized. Melamine is now produced in large quantities, mostly for the formation of resins. In 1994, over 610,000 tons were produced worldwide.

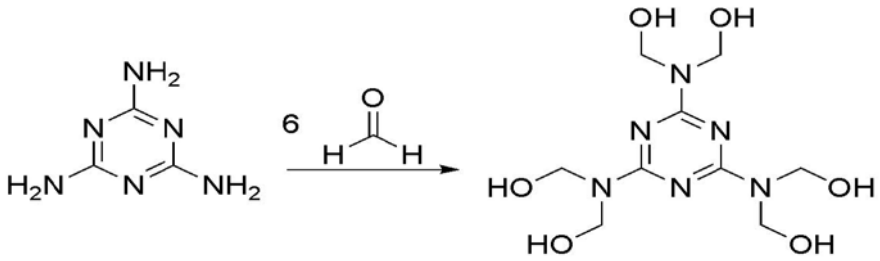
Currently industrial synthesis of melamine is from urea at 390–410 °C either non-catalytically under high pressure processes or catalytically using low-pressure processes. The net reaction is the same using any of these processes as shown in Scheme 2.[121] Naturally occurring melamine has been discovered in several meteorites which have reached earth.[120]



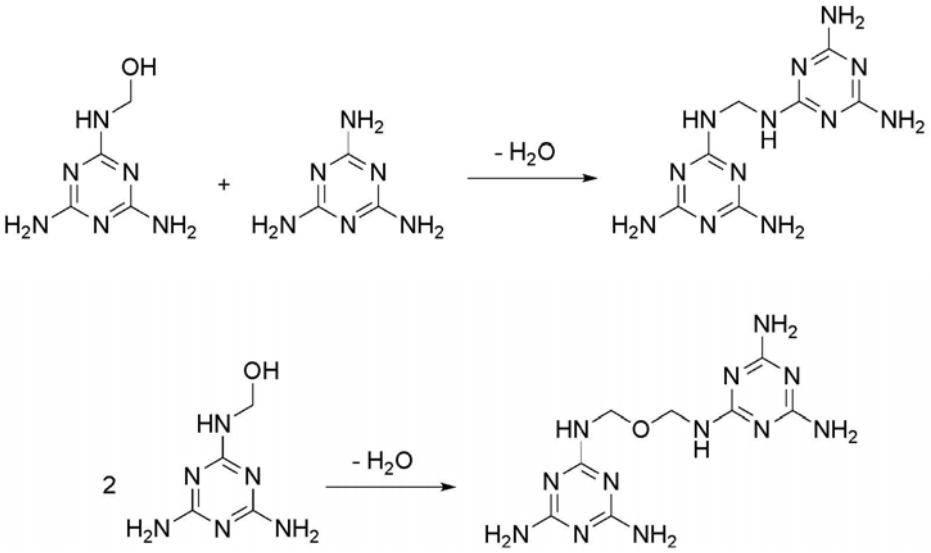
Scheme 1. Industrial synthesis of melamine

Melamine is most often reacted with formaldehyde for the production of resins.This practice began in 1935 in Germany.[122] The polymers formed from melamineformaldehyde resins have excellent chemical and physical properties. The resins have numerous applications including laminates, glues and adhesives, molding compounds, coatings, and paper and textiles.[122] The reaction of melamine with formaldehyde is shown below in Scheme 2. Anywhere from one to six of the hydrogen atoms on the amine groups of melamine may be replaced by methylol groups. Methylolmelamines are unstable due to the possibility of further condensation or resinification, as shown in Scheme 3 with a monomethylolmelamine, but similar reactions occur with the other di or tri-methylolmelamines.[121]

The oldest application of melamine resins is adhesives for wood such as plywood or particle board.[122] Creating a foamed resin produces hard, yet flexible, lightweight materials which are used for sound insulation, fire protection, and cleaning products.[123,124] Other applications include impregnating resins to treat papers for decorative purposes, paper auxiliaries to enhance wet tensile strength, leather tanning agents, strengtheners for building materials, concrete additives, ion-exchange resins, and wood preservatives.[122]



Scheme 2. Initial reaction of formaldehyde and melamine



Scheme 3: Condensation and resinification of methylolmelamine

1.8 Molecular Recognition:

Triazines especially melamines can recognize other molecules by the donation and acceptance of hydrogen bonds, metal chelation, and π–π interactions (Chart 1). This opportunity has enabled various supramolecular structures to be prepared on the basis of hydrogen-bonding interactions to form ribbons and other types of interesting oligomers and polymers. The synthesis and characterization of these types of triazine-based supramolecular structures have been reviewed elsewhere.[125–128]

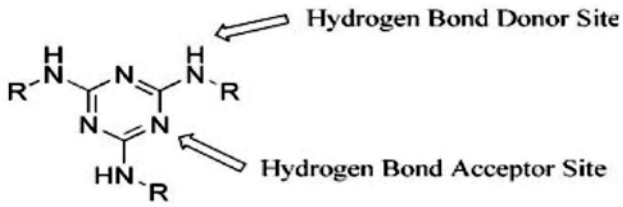
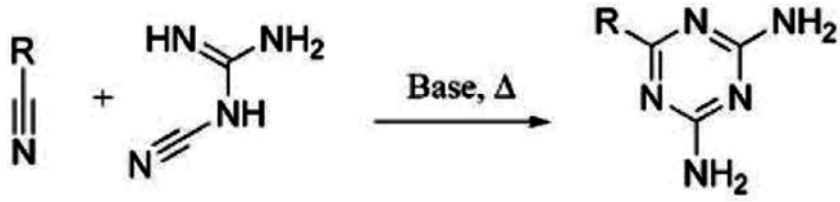


Chart 1: Sites of triazine/melamine derivatives that can participate in hydrogen bonding.

1.8.1 Synthesis

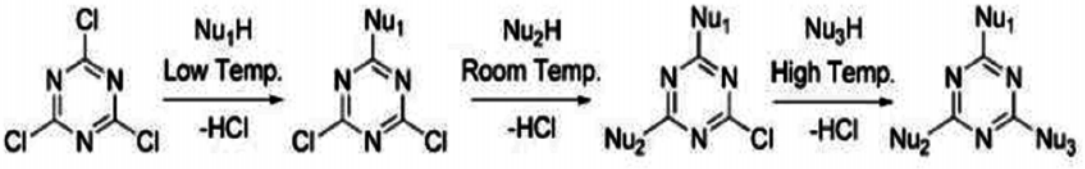
The synthesis of triazine derivatives is well established and has been reviewed elsewhere in detail.[129,130] Triazines can be synthesized by a variety of routes; however, for the sake of brevity, we will focus on the two most common methods that have been employed for the preparation of triazine-based dendrimers. Initial efforts in this field focused on cycloaddition reactions to form the triazine ring (Scheme: 4). This reaction is carried out at higher temperatures by the treatment of the nitrile of interest with a nitrile-substituted guanidine derivative in the presence of a base, typically sodium or potassium hydroxide.



Scheme:4 Cycloaddition reaction to form a diaminotriazine derivative.

Later efforts describe the nucleophilic aromatic substitution of cyanuric chloride ($C_3N_3Cl_3$) in a chemoselective fashion using temperature and the judicious choice of the nucleophile to produce a single product with high chemical complexity (Scheme: 5). Thus, when architectures that feature different types of peripheral groups are desired, triazine-based dendrimers offer a powerful and versatile synthetic strategy to well-defined products. The nucleophilic aromatic substitution of alkoxy-substituted triazine derivatives by amine nucleophiles is also a route that has been exploited;

however, higher temperatures in excess of 100 °C are required to achieve the conversion to the desired product.



Scheme: 5 Chemoselective reactivity of cyanuric chloride.

Triazines can also be prepared by cyclotrimerization of organic cyanates, but to date, the use of this route for the synthesis of dendrimers has not been pursued. Rather, this chemistry is employed to prepare hyper-branched polymers.[131]

The goal of this review is to trace the origins of triazine dendrimers, a field that we perceive is expanding (Figure 14). The advances in the syntheses of these materials receive the majority of the attention. Numerous examples of multiple triazine units tethered to a single core are included because these can be construed as first-generation dendrimers and can be readily elaborated to larger structures because of the functionality at the periphery.

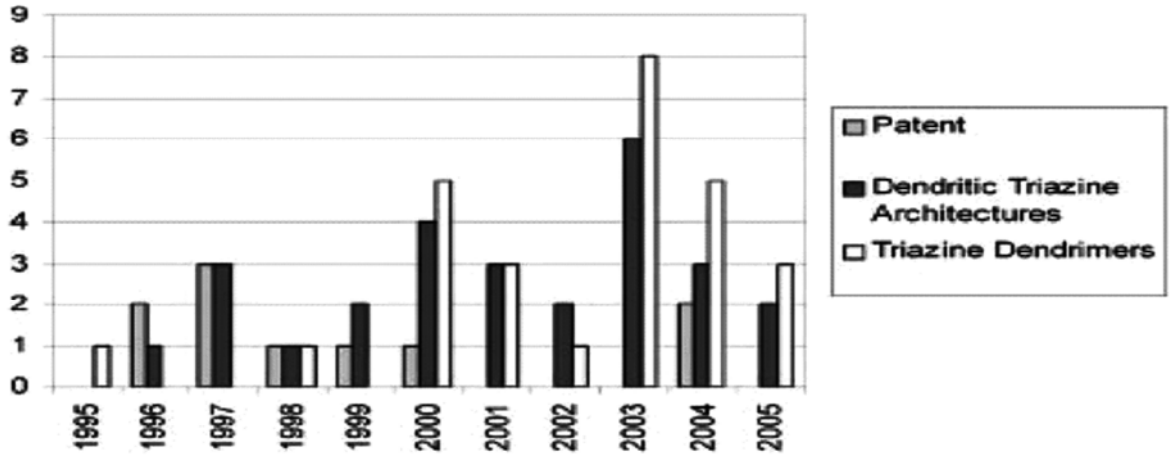


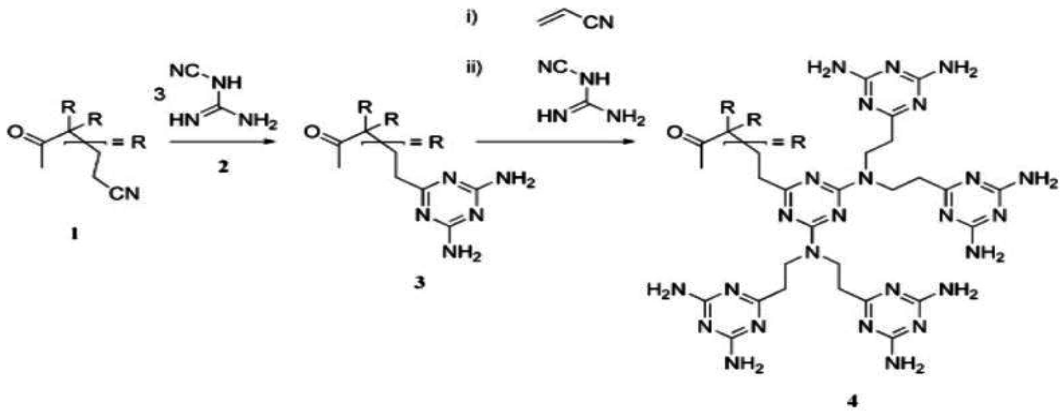
Figure 14: Graph showing that reports of triazine-based dendritic structures have increased during the previous decade (2005 data are as of April 29, 2005).

1.9 Synthetic Routes to Triazine Dendrimers

Much of the early work in the area focused on the optimization of routes for the synthesis of these species using either cycloaddition reactions or triazine substitution reactions.

1.9.1 Cycloaddition Method:

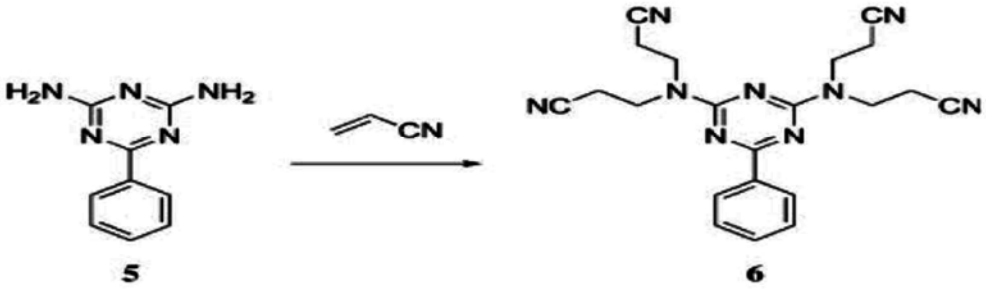
To the best of our knowledge, the first example of the synthesis of a triazine-based dendrimer using a divergent approach was detailed in two patents that were submitted in 1994,[132] one of which was reviewed in a separate account in 1995 (Scheme: 6).[133] In both cases, an iterative synthesis was developed in which the triazine units were prepared by the cycloaddition of terminal nitrile-functional groups, **1**, with nitrile-substituted guanidine, **2**, to afford an amino-terminated dendrimer, **3**. Iteration produces higher generations such as **4**. The synthesis outlined in the patent by Meijer et al.[97] is of particular interest because it details a procedure that can be used to prepare commercially relevant quantities of dendrimer product. More recent reports have demonstrated the utility of the cycloaddition method to afford triazine-based dendritic and hyperbranched materials,[134] some of which have found application in the construction of porous, hydrogen-bonded networks. In addition, cyclotrimerization routes have been used to produce materials relevant for integrated optics.[135]



Scheme 6: Initial efforts to prepare triazine-based dendrimers employed cycloaddition methods.

In all the cycloaddition procedures, the chemistry of the iterative process is the same: cyanoethylation of a pendant amine forms a dendron with twice the number of nitrile groups. Subsequent elaboration of the dendron by cycloaddition between the peripheral nitriles and nitrile-substituted guanidine derivatives increases the dendrimer generation. Maciejewski[136] wrote one of the earliest theoretical articles on the subject of dendrimers that could be prepared with this method in 1982. Moreover, cyanoethylation was the method used by Vögtle[137] in what is commonly described as the first dendrimer synthesis, although his dendrimer did not contain triazine derivatives.

A method resulting in compound **6**, with features strikingly similar to that of Vögtle's, was described in a patent by Niederhauser[138] in 1951, 27 years before Vögtle's work (Scheme:7). Niederhauser knew of the ability to reduce nitrile groups to amines: he described such a method in a patent filed in 1945.[139] Either through the reduction of the nitriles to amines or further cycloaddition reactions with the nitriles, Niederhauser might have laid claim to the first dendrimer. Here was a near miss to the beginning of dendrimer chemistry. Although a more exhaustive (and wholly impractical) search of the literature may provide more near misses, our interest in triazines necessitates its inclusion. The elaboration of Niederhauser's tetracyanoethyl benzoguanamine to afford a structurally imperfect generation-four dendrimer, however, took over 40 years to accomplish.



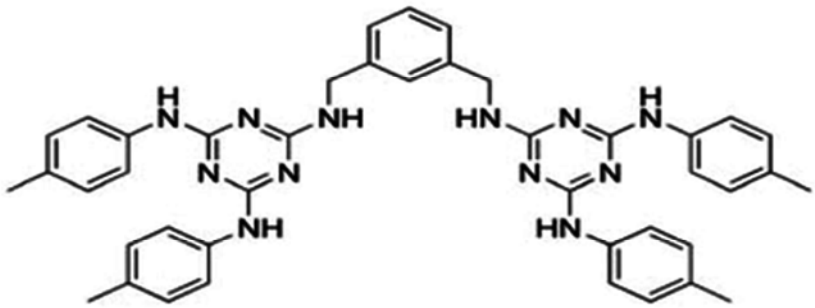
Scheme 7 : Niederhauser's route to tetracyanoethyl benzo guanamine.

In 1993, two groups described the successful synthesis of Vögtle's route to give dendrimers through iterative reactions.[140,141] These methods eventually led to the commercial production of this class of dendrimers known as poly(propylene imine)

dendrimers. In general, the cycloaddition/cyanoethylation method is attractive because it requires no functional group interconversions or the use of protecting groups as long as there are no other functional groups present that can interfere with this iterative process.

1.9.2 Nucleophilic Aromatic Substitution

The vast majority of triazine-based dendrimers are synthesized by nucleophilic aromatic substitution on cyanuric chloride. One of the earliest examples of the use of nucleophilic aromatic substitution to afford a dendritic product that incorporated triazine groups was reported in 1996 and described the treatment of *m*-bis(methylamino)benzene with 2 equiv of cyanuric chloride. A subsequent treatment with excess amine afforded the desired product, **7**. These dendritic structures were tested as chelating ligands for Gd in magnetic resonance imaging (MRI) applications (Chart 2).[142]

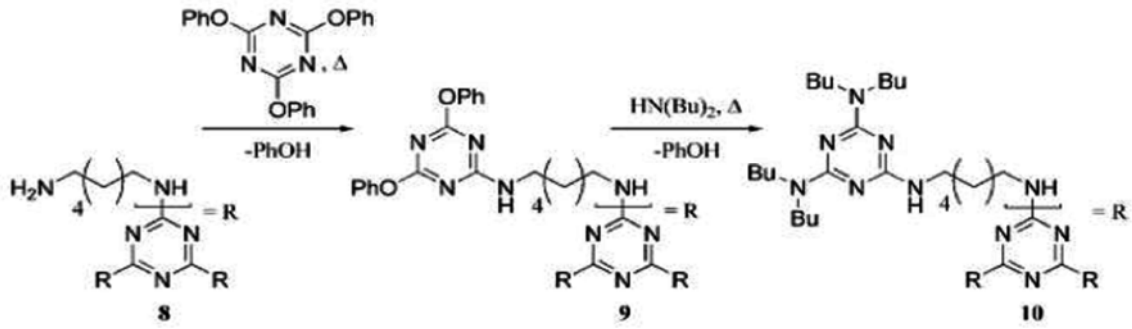


7

Chart 2 : Dendritic molecule designed for use as a chelating agent for Gd in MRI applications.

The first report concerned specifically with the construction of dendrimers by the substitution of cyanuric chloride with diamine linkers is a German patent filed in 1995 that describes a series of linear and dendritic polymer architectures synthesized with divergent and convergent methods.[143] Trisphenoxytriazine was used instead of trichlorotriazine to reduce hydrolysis. These derivatives still display a gradient of

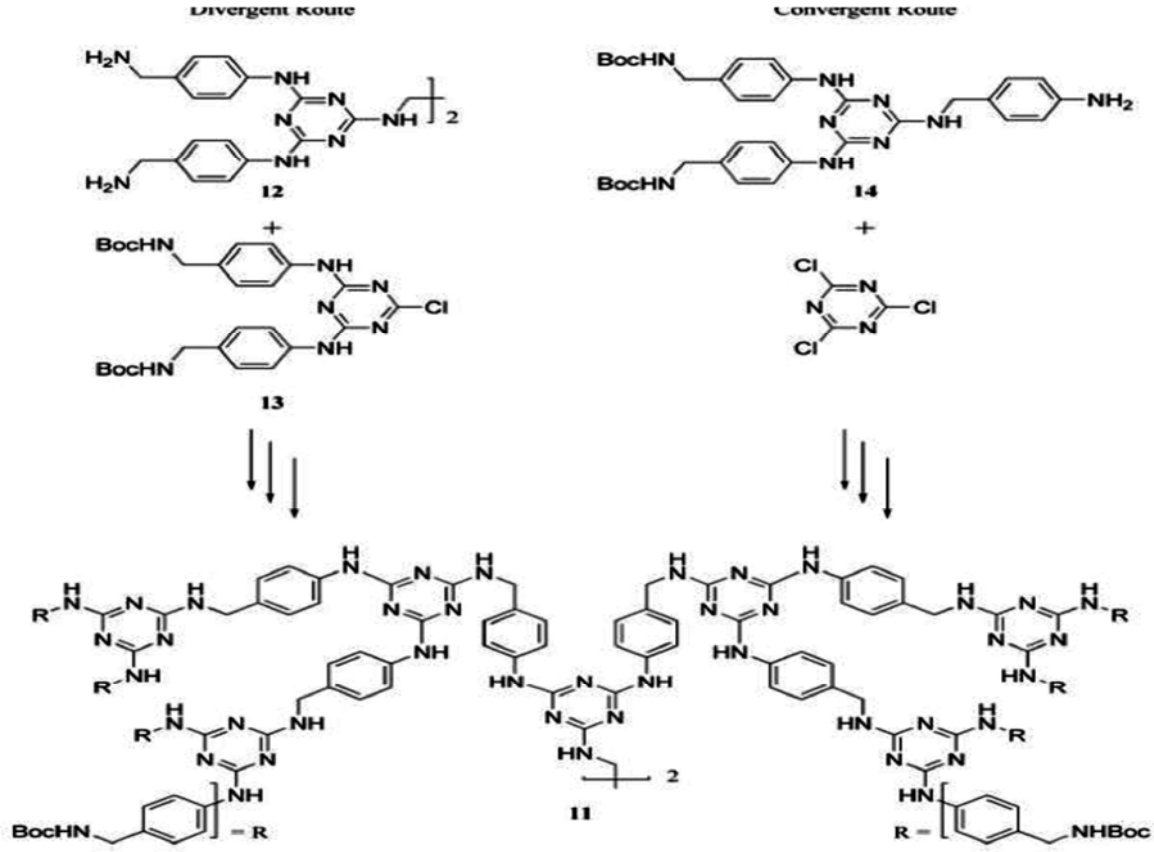
reactivity that has been investigated with activation energies measured in *N*-methylpyrrolidine with octylamine of 25, 53, and 82 kJ/mol. A separate account released in 2000 described the synthesis of a first-generation dendrimer by the treatment of a symmetrical melamine derivative, **8**, with tris(phenoxy)triazine (Scheme:8).[144] Once complete substitution had been achieved to give **9**, the phenoxy groups were exchanged by a treatment with excess secondary amine to afford the product, **10**. The products of this synthesis, derived from dibutylamine (**10**), dihexylamine and dioctylamine, were viscous oils. Additional complexity was incorporated with a similar divergent approach that commenced with an excess of $HN(CH_2CH_2NH_2)_2$ and trisphenoxytriazine.



Scheme 8: Convergent synthesis of a triazine-based dendrimer with nucleophilic aromatic substitution, with dibutylamine as an example of a precursor amine.

In 2000, we described methods for the construction of melamine-based dendrimers with diamine linkers and cyanuric chloride.[145,146] A third-generation dendrimer, **11**, was constructed with divergent (Scheme:9) and convergent routes. The divergent route connected a tetraamine core, **12**, with a BOC-protected monochlorotriazine synthon, **13** (BOC = *t*-butoxycarbonyl). The convergent route used a BOC-protected peripheral group, **14**, and an iterative reaction with cyanuric chloride and *p*-amino-benzylamine. Impurities that were implied by a tailing in the size exclusion chromatography (SEC) data were removed with chromatography purification techniques to obtain materials that had a single ion peak in the matrix-assisted laser desorption/ionization mass spectrometry spectrum. To us, this report represents a significant advance in triazine-based dendrimer synthesis because it was the first example reported in the mainstream

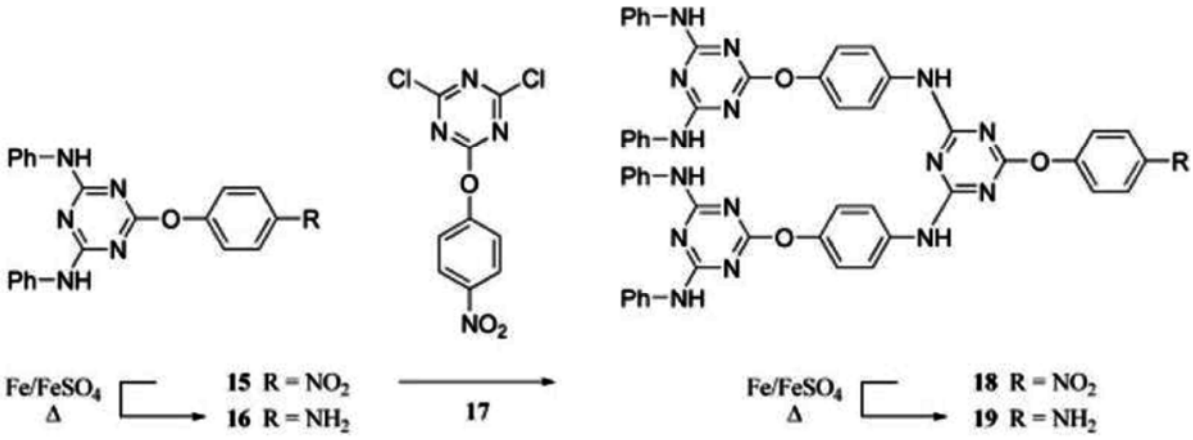
literature of nucleophilic aromatic substitution under moderate synthetic conditions to yield a triazine dendrimer. These efforts complement the original work described in the dissertation work of Jens Neumann-Rodekirch of the University of Bremen.[147]



Scheme 9: Convergent and divergent syntheses of a melamine-based dendrimer.

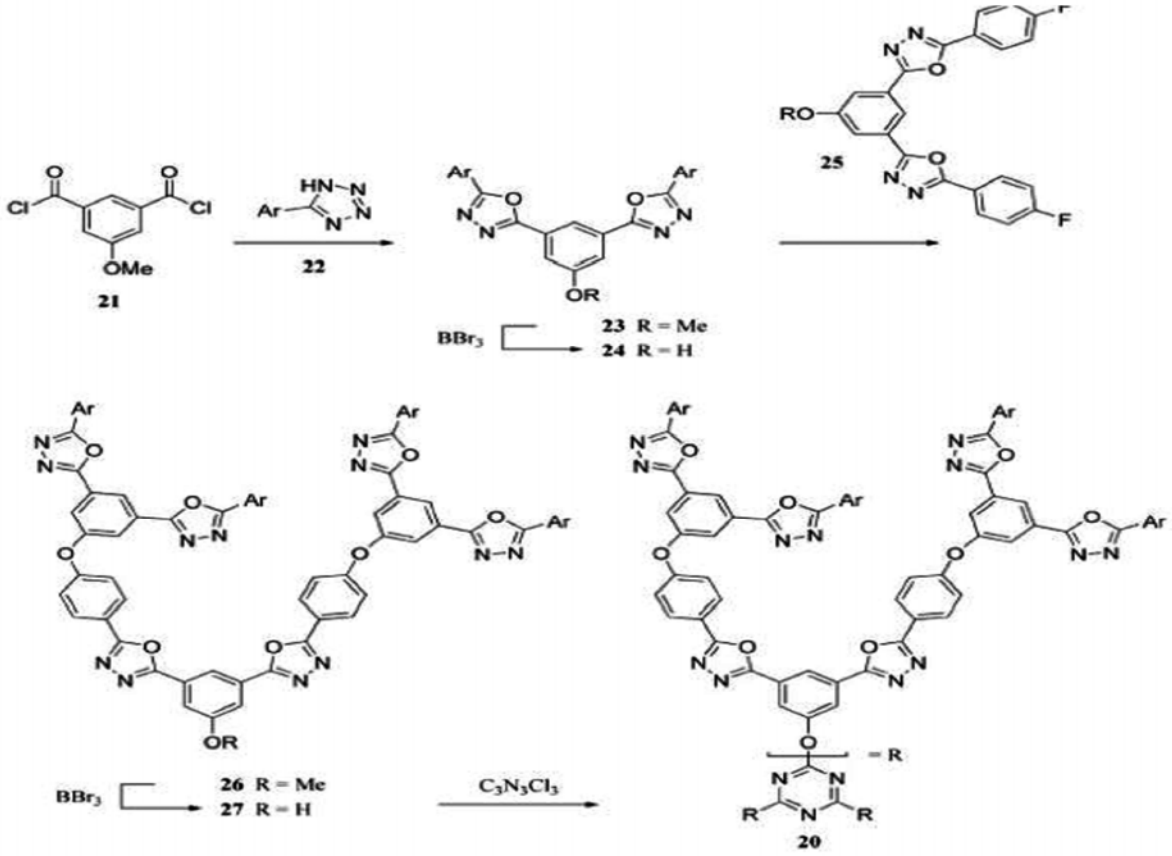
Takagi and coworkers[148,149] published two articles on the syntheses of structurally related triazine dendrimers. Their first report described the convergent synthesis of a second-generation dendrimer and several third-generation dendrons. The synthesis involved the treatment of a disubstituted triazine derivative with *p*-nitroaniline (**15**), followed by the reduction of the nitro group to unmask an amine group (**16**). The product of this reaction was then treated with a dichlorotriazine derivative, **17**, to increase the generation of the dendron (**18** and **19**, Scheme 10).[148] The second article described convergent and divergent methods for the preparation of second-generation triazine-based dendrimers with a different linkage group to accomplish each approach. The divergent route described in the second article employed the same iterative process

as the convergent route outlined in their first article. However, the second-generation dendron prepared by the convergent route was prepared with aryloxy substitution of cyanuric chloride. Subsequent generations of dendrons were achieved through the double substitution of the dichlorotriazine building block by an aryl amine.[149]

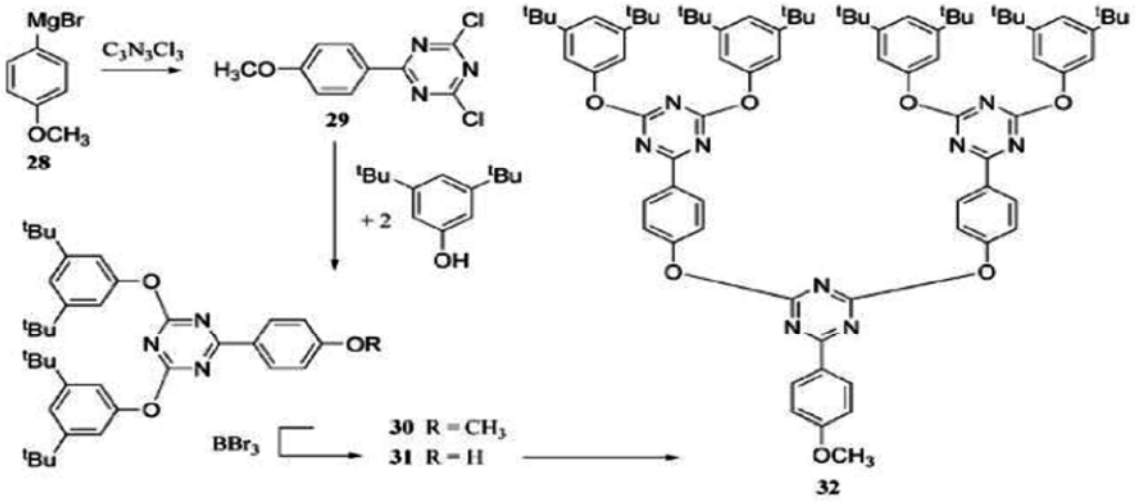


Scheme 10 : Iterative synthesis of a dendron with functional group interconversions.

Verheyde and Dehaen[150] synthesized dendrimers made up of 1,3,4-oxadiazole repeating units with a single triazine at the core (**20**, through **21**–**27**, Scheme 11). In a separate account, Dehaen et al.[151] produced dendrimers with triazines as the branching units. The first anisole was added to the triazine ring with a Grignard reagent, **28**, to give the dichlorotriazine product, **29**. Surface groups were attached to the triazine ring through aryloxy nucleophilic displacement of the chlorides to prepare **30**. The methoxy functionality of anisole was unmasked to reveal a phenol (**31**) that was subsequently treated with a half-equivalent of cyanuric chloride to afford the next generation of dendron (**32** Scheme 12,). A more recent report describes the use of click chemistry to prepare a similar dendritic structure, also from a triazine core.[152]



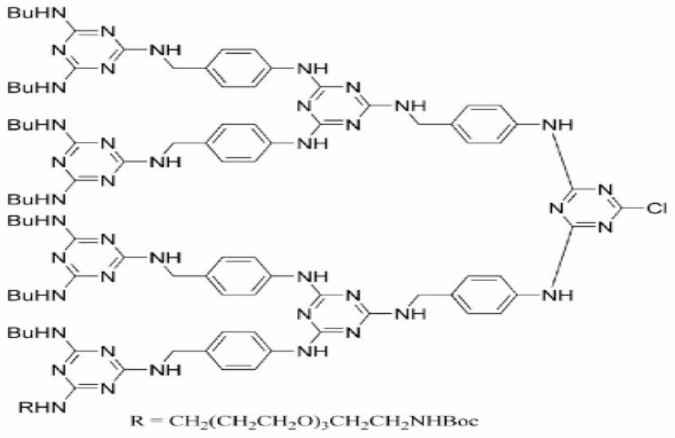
Scheme 11: Triazine as the core of a dendrimer.



Scheme 12: Different nucleophiles are used to synthesize a dendron.

In 2001, the synthesis of the first tailored triazine-based dendrimer, **33**, was described. A convergent approach permitted access to pure melamine dendrons (Chart 3) or

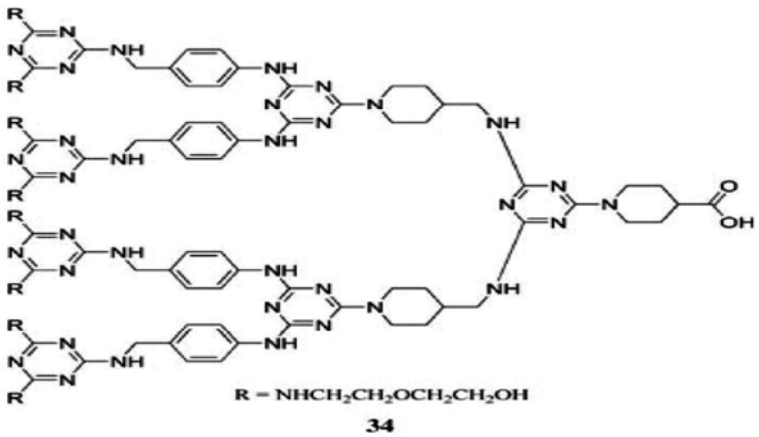
dendrimers in which one or two of the peripheral sites (out of a possible 16) were different from the remaining peripheral groups.[153] Interestingly, the addition of only one oligo(ethyleneoxy)ethylamine group to the exterior dramatically influenced the ability of the dendrimers to be characterized by SEC. This clearly illustrates that even subtle changes imparted by tailored dendrimers can result in properties dramatically different from those of their monofunctionalized counterparts.



33

Chart 3 : Tailored dendron.

Another improvement in dendrimer synthesis was achieved when a third-generation dendron, **34**, was prepared in the absence of protecting groups or functional group manipulations (Chart 4).[154,155]



34

Chart 4 : Dendron that was synthesized without protecting group manipulations or functional group interconversions.

The strategy expanded the use of chemoselective diamines from *p*-amino-benzyl amine to additional diamines. Diamines comprising amines with reactivity differences greater than 20 were found to be useful for chemoselective reactions.

The same strategy that was applied for the synthesis of a tailored dendrimer was also successfully employed to prepare a dendrimer or dendron with five (**35**) or six (**36**) orthogonal reactive sites, respectively (Chart 5).[156] The inference to the potential utility of this dendrimer for drug delivery and related biological applications was based on the demonstration that the functional groups could be manipulated after the synthesis of the dendrimer with little formation of byproducts. The power of triazine chemistry is best exemplified in these targets.

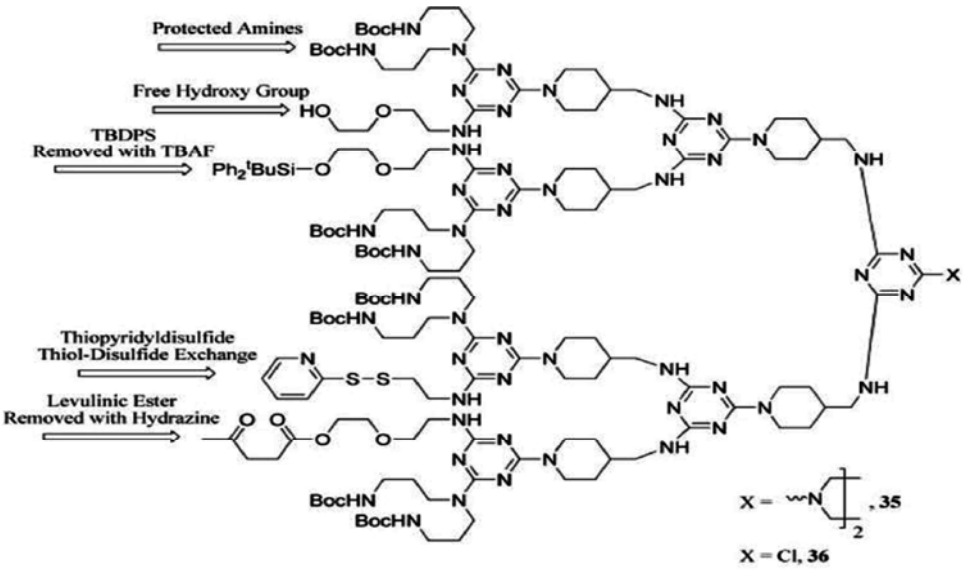
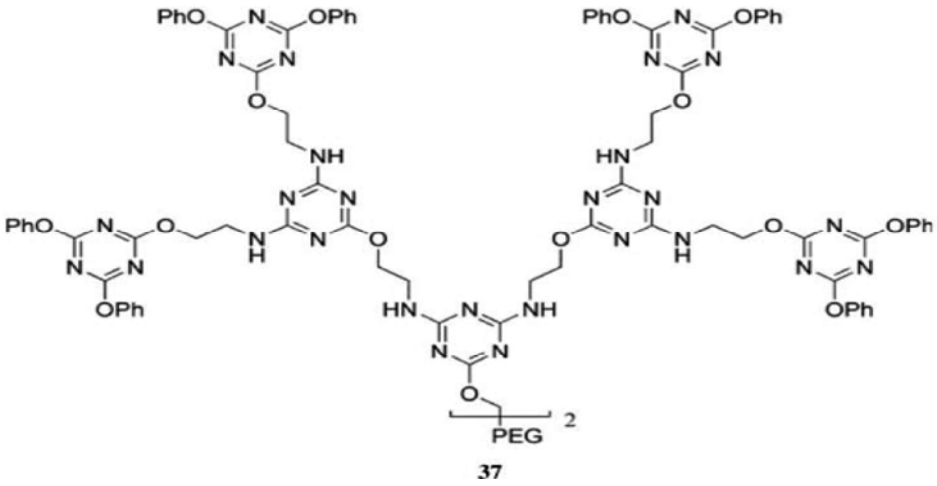


Chart 5 : Pure dendron and dendrimer with a high degree of functional group diversity for postsynthetic manipulation (TBAF = tetrabutylammonium fluoride; TBDPS = *tert*-butyl diphenylsilane).

The most recent example of the use of nucleophilic aromatic substitution to prepare a triazine-based dendrimer was demonstrated by the treatment of a poly(ethylene glycol) (PEG) diamine derivative with cyanuric chloride.[157] An iterative treatment with ethanol amine and cyanuric chloride resulted in the formation of a third-generation dendrimer, **37**, tethered by a PEG oligomer (Chart 6). The result was an amphiphilic material, and the critical micelle concentrations of the first-and second-generation versions of the block copolymer were 5.5×10^{-5} M and 7.6×10^{-4} M, respectively.

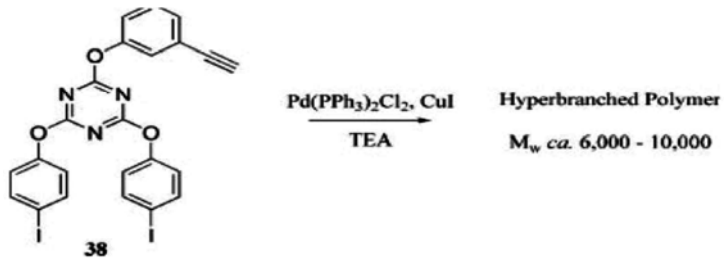


37

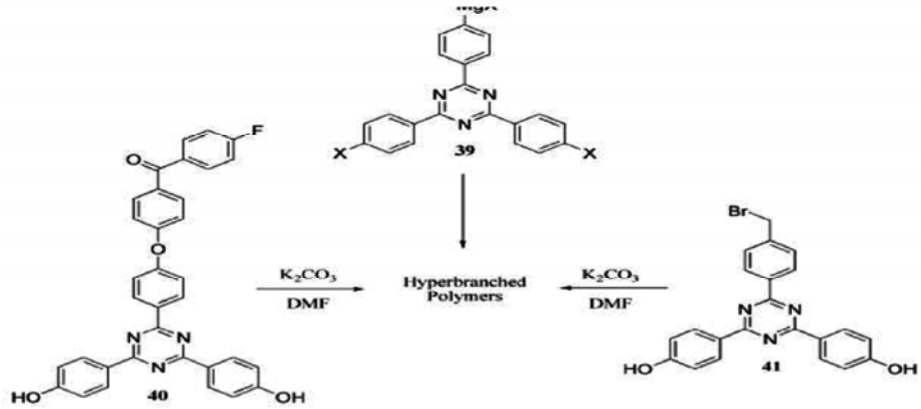
Chart 6 : Triazine-based dendritic block copolymer.

1.9.3 Hyperbranched Molecules:

A third synthetic route to triazine-containing dendritic materials involves the preparation of hyperbranched molecules. Polycyanurate ester resins dating to the 1960s could be regarded as progenitors of these materials.[131] Early efforts by Neumann-Rodekirch[147] using the homopolycondensation of diphenyoxytriazines substituted with amines, including *p*-aminobenzylamine, *N*-methyl-*p*-aminobenzylamine, and masked amines such as acetylaniline, mono-BOC protected hydrazine, and hexane diamine, were conducted in *N*-methylpyrrolidine at 200–240 °C with the intent of producing stationary phases for chromatography. More recent examples of hyperbranched triazines include work by Kim et al.,[158] who prepared hyperbranched triazine polymers by performing a Heck coupling of an AB_2 triazine monomer, **38**, to produce materials with a weight-average molecular weight (M_w) of 6000–10,000 g mol^{-1}, as estimated by SEC (Scheme 13). This novel route to hyperbranched triazine products is of interest because of the ability to prepare relatively high-molecular-weight material with a single-pot procedure. A related protocol has been reported in which hyperbranched triazine polymers are prepared from an AB_2 triazine monomer (**39**, Scheme 14) that incorporates a Grignard reagent.[159,160]



Scheme 13: Heck coupling of a triazine AB_2 monomer results in hyperbranched materials (TEA = triethylamine).

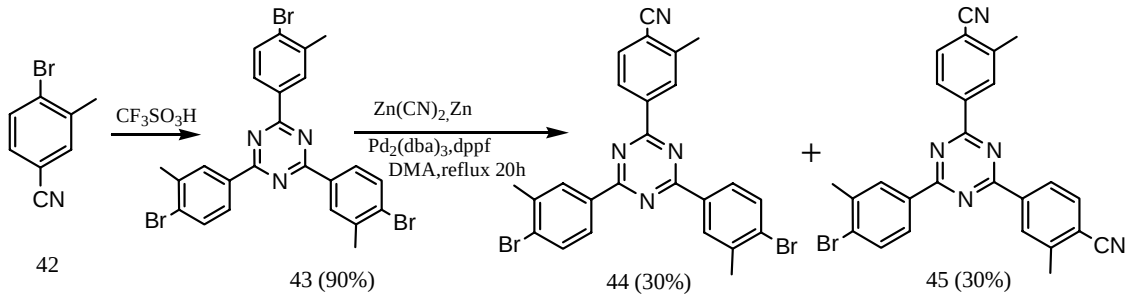


Scheme 14: Additional routes to hyperbranched materials .

This separate series of articles were published by Kim and coworkers,[161–164] who described a similar strategy to obtain hyperbranched polymers from AB_2 triazine monomers **40** and **41**. In these cases, the polymer was obtained by heating the monomer in the presence of potassium carbonate to 140 °C (Scheme 14). The polymers had M_w values of 11,000–15,000 g mol^{-1}, as estimated by gel permeation chromatography, and displayed excellent thermal stability, as evidenced by thermogravimetric analysis (TGA). More recently, the free hydroxyl end groups of one of the hyperbranched polymers were functionalized with Mitsunobu or dicyclohexylcarbodiimide reactions to install oligoethyleneoxy or stearyl groups, respectively.[163] The incorporation of these groups significantly lowered the glass-transition temperature of these materials with respect to the precursor polymer.

1.9.4 Cyclotrimerization Method :

The synthesis of the title dendritic molecule was first attempted by cyclotrimerization of the corresponding nitrile as shown in scheme 15. The tris(bromoaryl)triazine **43** was prepared in high yield by cyclotrimerization of 4-bromo-3-methylbenzonitrile **(42)** with neat trifluoromethanesulphonic acid.



Scheme 15

In the next step, cyanation of **43** was achieved by the use of palladium Pd_2 (dba)3, dppf and Zn as the catalyst and $Zn(CN)_2$ as the cyanide source, in accordance with a known protocol for the cyanation of aryl chlorides. Although the ratio of Br/CN was kept at 2.5: 1, cyanation was not selective, leading to unreacted **43** (32%) and a mixture of mono and dicyanated derivatives **44** and **45,** in yields of 30 % and 16 % respectively.[165(a)]

2. Present work: Synthesis of Dendrimer molecules based on triazine.

2.1 Rationale:

Dendrimers are highly branched, globular, multivalent, monodisperse molecules with synthetic versatility and many possible applications ranging from catalysis to electronics and drug delivery.[165(b),166-168]

Dendritic structures based on melamine usually present periphery groups that are able to participate in hydrogen bonding. In an elegant example, Fréchet and coworkers[169,170]demonstrated the self-assembly of higher ordered dendrimer structures by attaching two complementary hydrogen-bonding moieties to the focal point of different dendrons.

One of the applications of the smaller generation triazine-decorated dendrimers pioneered by Wuest and coworkers has been their use as tectons in solid-state networks of controlled porosity. In one case, the triazine ring was substituted by three different functional groups, which gave rise to a solid-state network comprising interconnected helical channels when crystallized from a solution of acetone, dimethyl sulfoxide, and water. The development of this technology has already demonstrated potential in practical applications, particularly for use in inkjet printing as phase-changing inks.[171,172]

Dendrimers based on melamine also aggregate in solution because of the extensive hydrogen-bonding sites that are available. Remarkably, the addition of copper (II) to a solution of a dendrimer comprising triazines linked by *p*-aminobenzyl groups induces a line-sharpening effect in SEC (size exclusion chromatography) traces.[173]

Dendritic resins with the triazine unit tethered to an alcohol-functionalized Wang resin have been prepared for the explicit purpose of capitalizing on the ability of melamine dendrimers to scavenge protons.[174] The dendritic dichlorotriazine precursors were also examined to determine their ability to scavenge nucleophiles from solution. Both materials performed with similar efficiency in comparison with commercially available scavenging resins.

The patent literature has many accounts that detail the use of dendritic materials to modify silica surfaces for various purposes. One of the earliest accounts of the incorporation of triazines into a dendrimer was published in 1997 when triazine-based dendrimers were used to modify a silica surface for use in chromatographic applications.[175] More recently, Su et al.[176] reported a fourth-generation melamine

dendrimer that was synthesized on a treated silica surface by an iterative process in which 1,6-diaminohexane and cyanuric chloride were alternated to generate a dendrimer with amine groups at the periphery. The modified silica gel was used in a microcolumn to effect the preconcentration and separation of platinum from heterogeneous samples, demonstrating potential utility in analytical applications.

There are several accounts of discrete inorganic complexes that contain dendritic structures that are composed of triazine functional groups. More recently, the research groups of Gamez and Reedikj[177,178] designed and prepared a series of ligands based on the triazine scaffold by nucleophilic aromatic substitution, several of which are dendritic in nature. When these ligands were treated with copper(II) in water, the catalyst systems that were generated *in situ* successfully performed the oxidation of 3,5-di-*t*-butylcatechol.[178] The copper complex generated from ligand resulted in the most active and most stable catalyst system, and the authors attributed this observation to additional stabilization of the active catalyst through the use of a dendritic ligand.

In 1998, an early report described the use of triazine-based dendrimers as potential light-harvesting antennae.[179] The electroluminescence was investigated to determine its potential as a light-emitting diode by the preparation of luminescent films from the dendritic material.

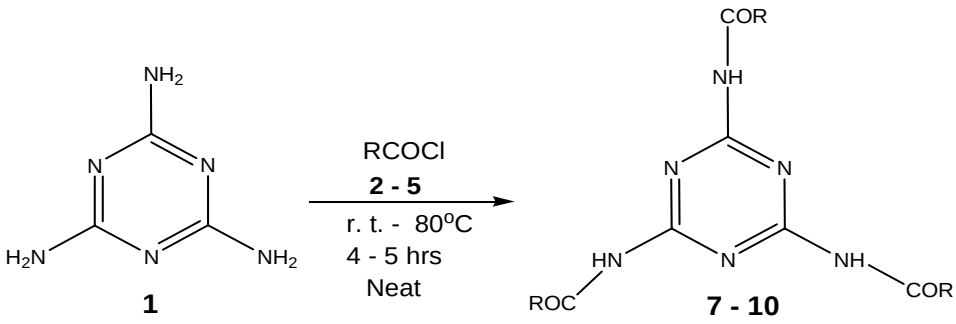
Specific cases have been reported in which a dendritic structure containing multiple triazine groups has displayed efficacy as antiviral agents.[180] In 1992, Wyeth-Ayerst initiated a program to identify novel inhibitors of the human respiratory syncytial virus (RSV).[181]

Promising triazine-based antibiotics have been developed by their examination as part of a dendrimer bound to a polystyrene resin.[182]

A significant advance in the application of triazine-based dendrimer chemistry has been the preparation of dendrimers that present disulfide linkages at the periphery. Several precursor dendrimers and dendrons, which were prepared with the nucleophilic aromatic substitution strategy, were decorated with pyridyl disulfide groups at the periphery or at the terminal of a dendron. These disulfide groups readily underwent exchange with biotin, captopril, a small peptide sequence, or even a DNA oligonucleotide, although the characterization and purification of the latter were challenging, and no general protocols emerged.[183,184,185]

Additional recent results are promising because the data suggest that the hepatoxicity of the anticancer drugs methotrexate and 6-mercaptopurine were reduced upon noncovalent encapsulation of these pharmacophores by a melamine-based dendrimer.[186] The accumulation of these data and other animal studies[187] suggests that dendrimers based on melamine have potential for a variety of biomedical applications.

So it was planned to develop a facile method to synthesis dendrimer molecule from triazine and different acylchloride using catalytic and non-catalytic reaction by divergent method as shown in scheme – 1.



Scheme – 1

2.2 Mechanism: Nucleophilic Acyl Substitution (addition / elimination) reaction.

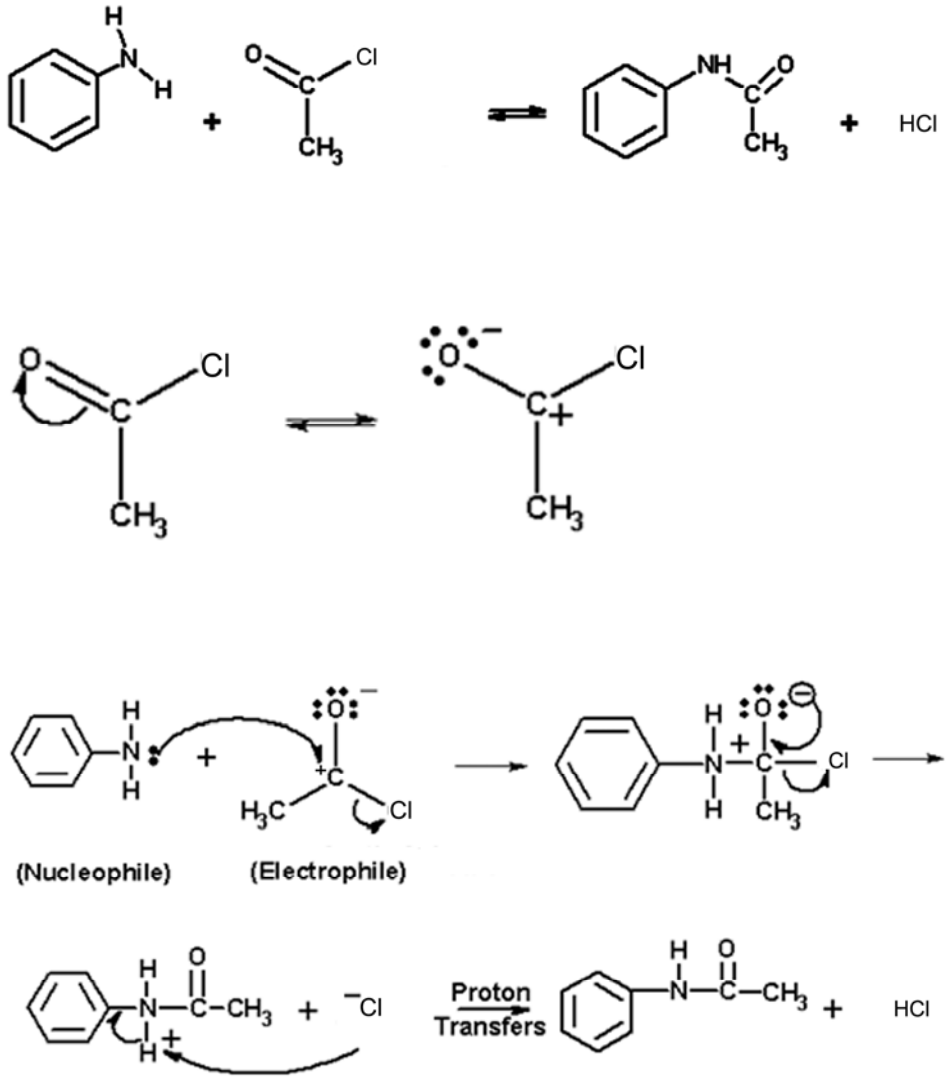
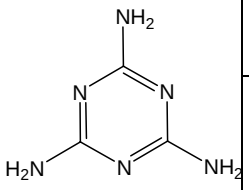
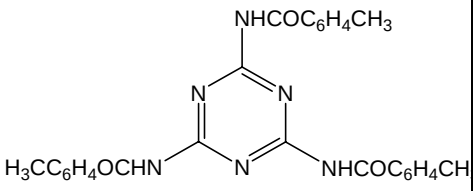
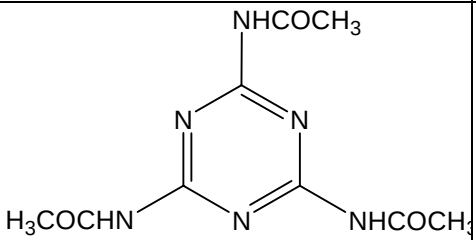
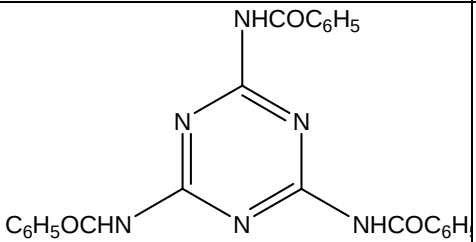
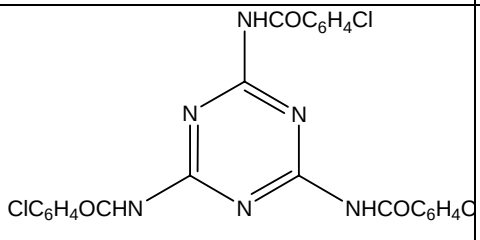
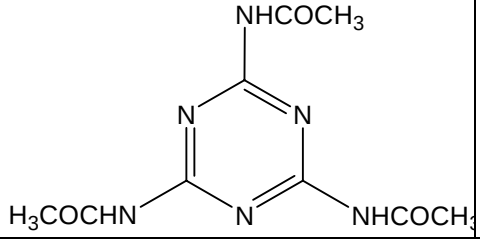
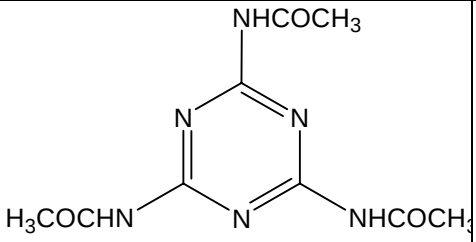
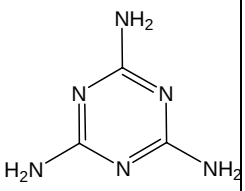
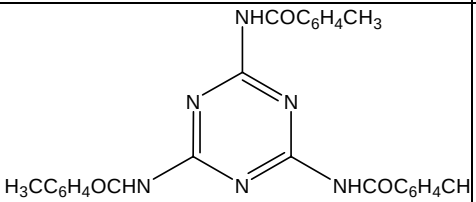
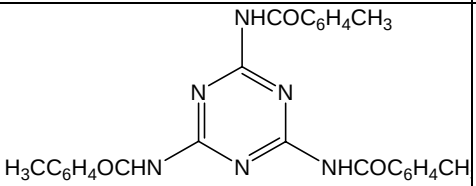
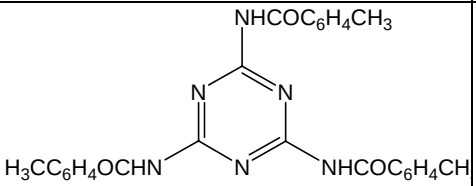


Table 1: Synthesis of different dendrimers **7-15:**

Entry	Substrate	Reagent and condition	Product	**Yie**ld %
1	 **1**	*p*-$CH_3C_6H_4COCl$, 80 ^{0}C, 3 hrs	 **7**	81
2		CH_3COCl, r. t., 4 hrs	 **8**	52
3		C_6H_5COCl, r. t., 5 hrs	 **9**	70
4		*p*-ClC_6H_4COCl, r. t., 5 hrs	 **10**	73
5		$ZnCl_2$,CH_3COCl, r. t., 4 hrs		58

			11	
6		CuI, CH_3COCl, r. t., 4 hrs	 **12**	62
7	 **1**	*p*-$CH_3C_6H_4COCl$ $ZnCl_2$, 80 ^{0}C, 5 hrs	 **13**	67
8		*p*-$CH_3C_6H_4COCl$ CuI,, 80 ^{0}C, 4 & 1/2 hrs	 **14**	78
9		*p*-$CH_3OC_6H_4COCl$, Solvent DMSO r. t., 4 & 1/2 hrs	 **15**	56

Yield % was calculated on the basis of melamine (2,4,6-triamino-1,3,5-triazine).

2.3 Characterization

2.3.1 Characterization of 2,4,6-Tris(4-methylbenzamido)1,3,5-triazine, 7:

Compound **7** was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of p-toluoyl chloride by refluxing at 80 ^{0}C for 3 hours.

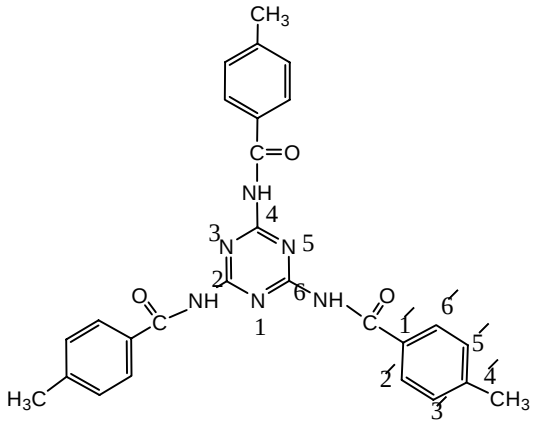
A white solid was obtained with 81% yield, mp 210-294.8^0 C, soluble in methanol. The structure of the compound was established by ^{I}H NMR, ^{13}C NMR, IR and UV spectral data.

IN ^{I}H NMR spectrum of the compound **7,** the chemical shift at δ 2.39 (s, 9H,-CH_3) was found as a singlet for nine hydrogen in three -CH_3 groups and a singlet at δ 4.92 (s, 3H,-NH-) represent three N-H protons. Chemical shift at δ 7.27 (d, 6H, Ar-H, J=8.0 Hz) showed a doublet for similar protons of C-3′, C-5′ carbon of three benzene ring and δ 7.90 (d, 6H, Ar-H, J=8.0 Hz) showed another doublet for similar protons of C-2′, C-6′ carbon of three benzene ring.

In the ^{13}C NMR spectral data the chemical shift δ 21.57 indicated the presence of three identical carbons in three methyl groups (Ar- CH_3).The chemical shift at δ 130.07 and 130.79 represent similar carbon of C-3′, C-5′and similar carbon of C-2′, C-6′ in aromatic ring (Ar- C) respectively. The peak at δ 129.09 and 144.96 was found for the two tertiary carbons (C-4′, C-1′) of benzene ring. The chemical shift at δ 169.99 was obtained for carbonyl carbon (C=O).

In IR spectrum of compound the absorption band was found at 3350 cm^{-1}, due to the N-H stretching absorption, whereas a broad band at 1678 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. Strong absorption band at 1284.5 cm^{-1} display strong C-N stretching absorption. ν_{max} 3049.2, 2976 and 1612.4 cm^{-1} stretching bands indicated the presence of aromatic C-H, aliphatic C-H and aromatic C=C respectively. Strong absorption band at 754.1 cm^{-1} represents p-disubstitution of benzene ring.

The UV spectrum of the compound showed λ_{max} at 242 nm due to $\boldsymbol{\pi} \rightarrow \boldsymbol{\pi}^*$ transition of C = C – C =O and 253 nm due to $\boldsymbol{\pi} \rightarrow \boldsymbol{\pi}^*$ transition of C = C of benzene ring.



7

2.3.2 Characterization of 2,4,6-Tris(acetamido)-1,3,5-triazine, 8 :

Compound **8** was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of acetyl chloride by stirring at room temperature for 4 hours.

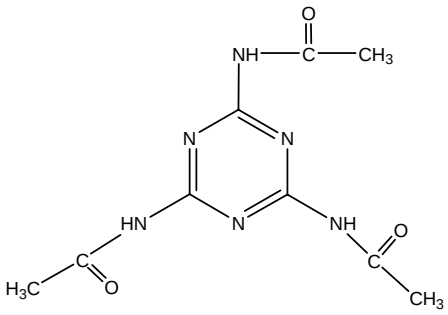
A white solid was obtained with 52 % yield, mp: not melt up to 410^0 C, sparingly soluble in water. The structure of the compound was established by various spectral data.

IN ^{I}H NMR spectrum of the compound **8**, the chemical shift at δ 2.08 (s, 9H,-CH_3,) was found as a singlet due to nine protons in three -CH_3 groups. The Chemical shift at δ 5.318 (s, 3H,-NH-) showed a singlet due to three similar N-H proton in the compound.

In ^{13}C NMR spectral data, the chemical shift δ 68.23 indicated three carbons in three similar methyl (-CH_3) groups, chemical shift at δ 151.82 revealed the presence of C-2, C-4 and C-6 similar carbon in hetero aromatic ring. The peak at δ 160.44 was found due to three carbonyl carbon (C=O).

In IR spectrum of compound the absorption band was found at 3342.4 cm^{-1}, due to the N-H stretching absorption, whereas a broad band at 1691.5 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. Strong absorption band at 1336.6 cm^{-1} displays

strong C-N stretching absorption. ν_{max} 2950 cm^{-1} stretching bands indicated the presence of aliphatic C-H in methyl (-CH_3) group.



8

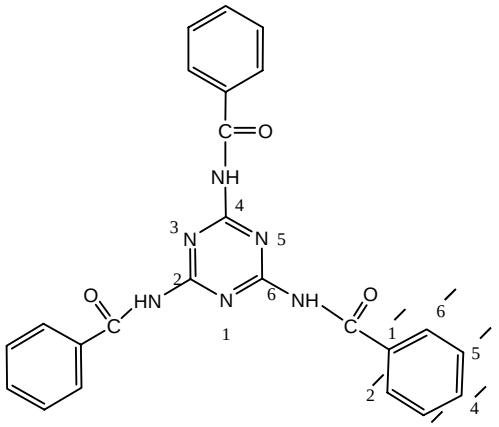
2.3.3 Characterization of 2,4,6-Tris(benzamido)-1,3,5-triazine, 9:

Compound **9** was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of benzoyl chloride by stirring at room temperature for 5 hours.

A white solid was obtained with 70 % yield, mp 315^0 C (Partially melt), sparingly soluble in water. The structure of the compound was established by various spectral data.

The ^{I}H NMR spectrum of the compound **9**, showed the peak at δ 5.32 (s, 3H,-NH-) as a singlet due to similar N-H protons. The chemical shift at δ 7.89 (d, 6H, Ar-H, J=7.2 Hz) was observed as doublet due to C-2′, C-6′ aromatic protons and δ 7.51 (d, 6H, Ar-H, J=7.2 Hz) was observed as doublet due to C-3′, C-5′ aromatic protons. The peak at 7.37 (t, 3H, Ar-H, J=6.4 Hz) showed as a triplet due to tertiary protons (C-4′) of three phenyl ring.

In IR spectrum of compound **9**, the absorption band was found at 3344.3 cm^{-1}, due to the N-H stretching absorption and a broad band at 1681.8 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. Strong absorption band at 1326.9 cm^{-1} display C-N stretching absorption. ν_{max} 3072.4 and 1652.9 cm^{-1} stretching bands indicated the presence of aromatic C-H and aromatic C=C respectively. Absorption band at 707.8 cm^{-1} represents mono - substitution of benzene ring.



9

2.3.4 Characterization of 2,4,6-Tris(4-chlorobenzamido)-1,3,5-triazine,10:

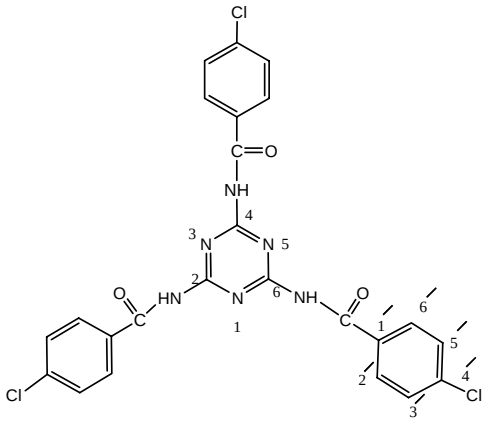
Compound **10** was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of 4-chlorobenzoyl chloride by stirring at room temperature for 5 hours.

A white solid was obtained with 73 % yield, mp 252.3^0 C (Partially melt), soluble in methanol. The structure of the compound was established by various spectral data.

IN ^{I}H NMR spectrum of the compound **10**, the chemical shift at δ 4.87 (s, 3H,-NH-) was found as a singlet for three similar N-H protons. Chemical shift showed a multiplet at δ 7.46 -7.49 (m, 6H, Ar-H, J=8.8 Hz) due to similar protons of C-3′, C-5′ carbon of three benzene rings and another multiplet at δ 7.9 – 8.0 (m, 6H, Ar-H, J=8.8 Hz) due to similar protons of C-2′, C-6 ′ carbon of three benzene rings.

In IR spectrum of compound **10,** the absorption band was found at 3357.8 cm^{-1}, due to the N-H stretching absorption, whereas a broad band at 1689.5 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. Absorption band at 1321.1 cm^{-1} display C-N stretching absorption. ν_{max} 3095.5, 2960 and 1595.5 cm^{-1} stretching bands indicated the presence of aromatic C-H, aliphatic C-H and aromatic C=C respectively. Strong absorption band in 761.8 cm^{-1} display C-Cl stretching absorption. Absorption band at 848.6 cm^{-1} represents p-substitution of benzene ring.

The UV spectrum of the compound showed λ_{max} at 248.50 nm due to $\pi \rightarrow \pi^*$ transition of C = C – C =O and 255 nm due to $\pi \rightarrow \pi^*$ transition of C = C of phenyl ring.



10

2.3.5 Characterization of 2,4,6-Tris(acetamido)-1,3,5-triazine, 11:

Compound **11** was synthesized from 2,4,6-triamino-1,3,5-triazine with the reaction of acetyl chloride and zinc chloride by stirring at room temperature for 4 hours.

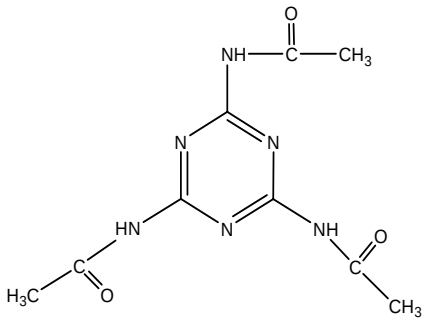
A white crystal was obtained with 58 % yield, mp: partially melt in 360^0 C, sparingly soluble in DMSO. The structure of the compound was established by various spectral data.

IN ^{I}H NMR spectrum of the compound **11**, the chemical shift at δ 2.50 ppm (m, 9H,-$COCH_3$) was found as a singlet due to nine similar protons in three -OCH_3 groups. The Chemical shift at δ 7.66 (s, 3H, -NH-) showed a singlet due to three N-H proton in the compound.

In ^{13}C NMR spectral data, the chemical shift δ 40.13 indicated three carbons in three similar methyl (-CH_3) groups, chemical shift at δ 77.83 revealed the presence of similar carbon of C-2, C-4 and C-6 position hetero aromatic ring. The peak at δ 159.79 was found due to three carbonyl carbon (C=O).

In IR spectrum of compound **11**, the absorption band was found at 3440.8 cm^{-1}, due to the N-H stretching absorption and a broad band at 1689.5 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. Strong absorption band at 1375.2 cm^{-1} display C-N stretching absorption. ν_{max} 2945.1 cm^{-1} stretching band indicated the presence of aliphatic C-H in methyl ($-CH_3$) group.

The UV spectrum of the compound showed λ_{max} at 247.90 nm



11

2.3.6 Characterization of 2,4,6-Tris(acetamido)-1,3,5-triazine, 12:

Compound **12** was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of acetyl chloride and copper(ii) iodide by stirring at room temperature for 4 hours.

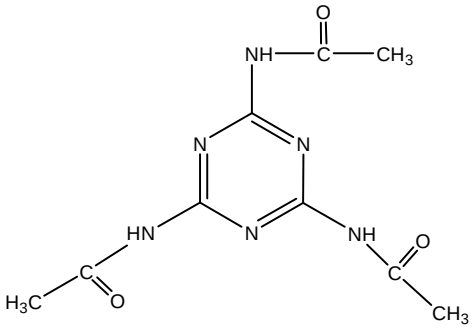
A grey colour solid was obtained with 62 % yield, mp 287.1-377.6^0 C, sparingly soluble in DMSO. The structure of the compound was established by various spectral data.

The ^{I}H NMR spectrum of the compound **12**, showed the peak at δ 2.51 ppm (s, 9H,-$COCH_3$,) as a singlet due to nine similar protons in three -OCH_3 groups. The Chemical shift at δ 6.79 (s, 3H,-NH-) showed a singlet due to three similar N-H proton in the compound.

In ^{13}C NMR spectral data, the chemical shift δ 40.13 indicated three carbons in three similar methyl ($-CH_3$) groups, chemical shift at δ 77.83 revealed the presence of similar

carbon of C-2, C-4 and C-6 position hetero aromatic ring. The peak at δ 159.79 was found due to three carbonyl carbon (C=O).

In IR spectrum of compound **12**, the absorption band was found at 3328.9 cm^{-1} due to N-H stretching absorption and a broad band at 1662.5 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. An absorption band at 1463.9 cm^{-1} displays C-N stretching absorption. ν_{max} 2941.2 cm^{-1} stretching band indicated the presence of aliphatic C-H in methyl ($-CH_3$) group.



12

2.3.7 Characterization of 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine, 13:

Compound **13** was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of p-toluoyl chloride and zinc chloride by refluxing at 80^0 C for 5 hours.

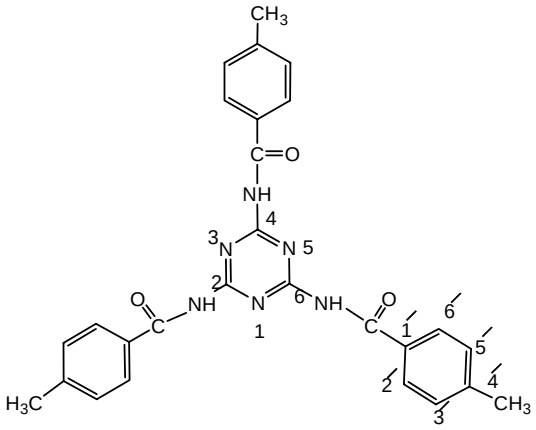
A white solid was obtained with 67 % yield, mp 187.3^0 C, sparingly soluble in methanol. The structure of the compound was established by ^{I}H NMR, ^{13}C NMR, IR and UV spectral data.

IN ^{I}H NMR spectrum of the compound **13**, the chemical shift at δ 2.40 (s, 9H, Ar-CH_3) was found as a singlet for nine hydrogen in three -CH_3 groups and a singlet at δ 4.89 (s, 3H,-NH-) represent three similar N-H protons. Chemical shift at δ 7.26 -7.28 (d, 6H, Ar-H, J=8.0 Hz) showed a doublet for similar protons of C-3′, C-5′ carbon of three benzene ring and δ 7.88- 7.90 (d, 2H, Ar-H, J=8.0 Hz) showed another doublet for similar protons of C-2′, C-6′ carbon of three benzene ring.

In the ^{13}C NMR spectral data the chemical shift δ 21.58 indicated the presence of three identical carbons in three methyl groups (Ar- CH_3).The chemical shift at δ 130.09 and 130.09 represent similar carbons of C-3′, C-5′and similar carbons of C-2′, C-6 ′ in three phenyl rings respectively. The peak at δ 129.10 and 144.97 was found for the two tertiary carbons (C-4′, C-1′) of benzene ring. The chemical shift at δ 169.99 was obtained for carbonyl carbon (C=O).

In IR spectrum of compound **13**, the absorption band was found at 3300 cm^{-1}, due to the N-H stretching absorption, whereas a broad band at 1678 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. Strong absorption band at 1284.5 cm^{-1} display strong C-N stretching absorption. ν_{max} 3049.2, 2976 and 1575.7 cm^{-1} stretching bands indicated the presence of aromatic C-H, aliphatic C-H and aromatic C=C respectively. Strong absorption band at 754.1 cm^{-1} represents p-disubstitution of benzene ring.

The UV spectrum of the compound showed λ_{max} at 239.80 nm due to $\boldsymbol{\pi} \rightarrow \boldsymbol{\pi}^*$ transition of C = C – C =O and 255.30 nm due to $\boldsymbol{\pi} \rightarrow \boldsymbol{\pi}^*$ transition of C = C in phenyl ring.



13

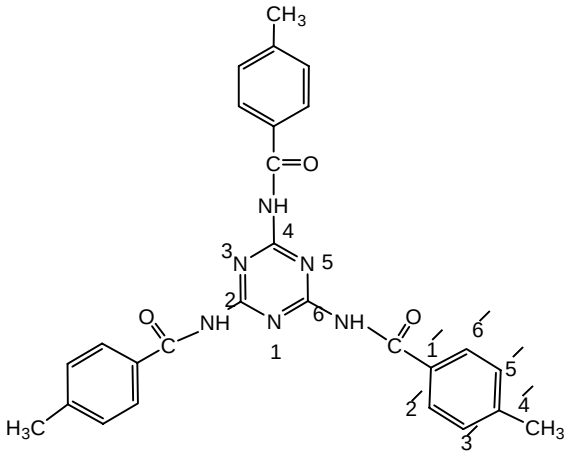
2.3.8 Characterization of 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine, 14:

Compound **14** was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of p-toluoyl chloride and copper(ii) iodide by refluxing at 80^0 C for 4 & ½ hours.

A white solid was obtained with 78 % yield, mp 340^0 C (Partially melt), sparingly soluble in methanol. The structure of the compound was established by various spectral data.

IN ^{I}H NMR spectrum of the compound the chemical shift at δ 2.40 (s, 9H, Ar-CH_3) was found as a singlet for nine hydrogen in three -CH_3 groups and a singlet at δ 4.89 (s, 3H,-NH-) represent three similar N-H protons. Chemical shift at δ 7.26 -7.28 (d, 6H, Ar-H, J=8.0 Hz) showed a doublet for similar protons of C-3′, C-5′ carbon of three benzene ring and δ 7.88- 7.90 (d, 2H, Ar-H, J=8.0 Hz) showed another doublet for similar protons of C-2′, C-6′ carbon of three benzene ring.

In IR spectrum of compound **14**, the absorption band was found at 3313.5 cm^{-1}, due to the N-H stretching absorption. A band at 1652.9 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. An absorption band at 1458.1 cm^{-1} displays C-N stretching absorption. ν_{max} 3155.3, 2945.1 and 1539.1 cm^{-1} stretching bands indicated the presence of aromatic C-H, aliphatic C-H and aromatic C=C respectively. Strong absorption band at 781.1 cm^{-1} represents p-disubstitution of benzene ring.



14

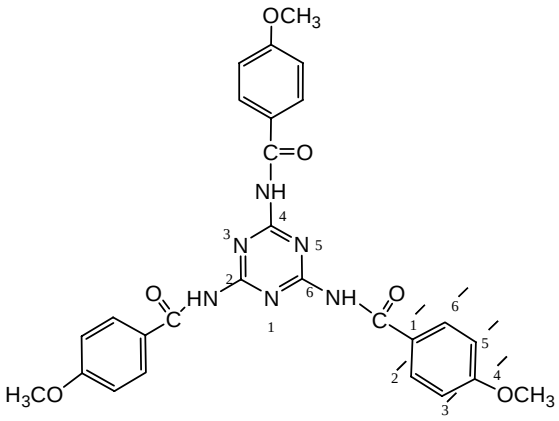
2.3.9 Characterization of 2,4,6-Tris(4-methoxybenzamido)-1,3,5-triazine,15:

Compound **15** was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of anisoyl chloride in presence of solvent DMSO by stirring at room temperature for 4 & 1/2 hours.

A white solid was obtained with 56 % yield, mp 315^0 C (Partially melt), sparingly soluble in water. The structure of the compound was established by various spectral data.

The ^{I}H NMR spectrum of the compound **15,** showed the peak at δ 3.72 ppm (s, 9H, -OCH_3,) as a singlet due to nine similar protons in three -OCH_3 groups. The Chemical shift at δ 4.68 (s, 3H,-NH-) showed a singlet due to three similar N-H proton. Chemical shift at δ 7.73 (d, 6H, Ar-H, J=9.2 Hz) was observed as doublet due to similar protons of C-2′, C-6 ′ carbon of three benzene rings and another doublet at δ 6.87 (d, 6H, Ar-H, J=8.8 Hz) due to similar protons of C-3′, C-5′carbon of three benzene rings.

In IR spectrum of compound **15,** the absorption band was found at 3384.8 cm^{-1} due to N-H stretching absorption and a band at 1577.7 cm^{-1} represents the keto group (C=O) adjacent to N-H bond. Absorption band at 1350.1 cm^{-1} display C-N stretching absorption. ν_{max} 3014.5, 2962.5 and 1508.2 cm^{-1} stretching bands indicated the presence of aromatic C-H, aliphatic C-H and aromatic C=C respectively. Strong absorption band at 813.9 cm^{-1} represents p-disubstitution of benzene ring.



15

2.4 Energy Dispersive X-ray (EDX) Spectrum:

Metal detection or investigation of metallodendrimer has been performed by employing Energy Dispersion X-ray or EDX method. The EDX spectrum was taken by selecting a zone or area of specific particle of the sample. The patterns of the EDX spectra of different compound are presented in Fig. 2.4.1 – 2.4.4.

2.4.1 EDX spectrum of compound 2,4,6-Tris(acetamido)-1,3,5-triazine, 11:

The accelerating voltage was 25 keV and counting rate was 1964 cps. The figure 2.4.1 shows the typical EDX spectrum of zinc containing metallodendrimer **11**.

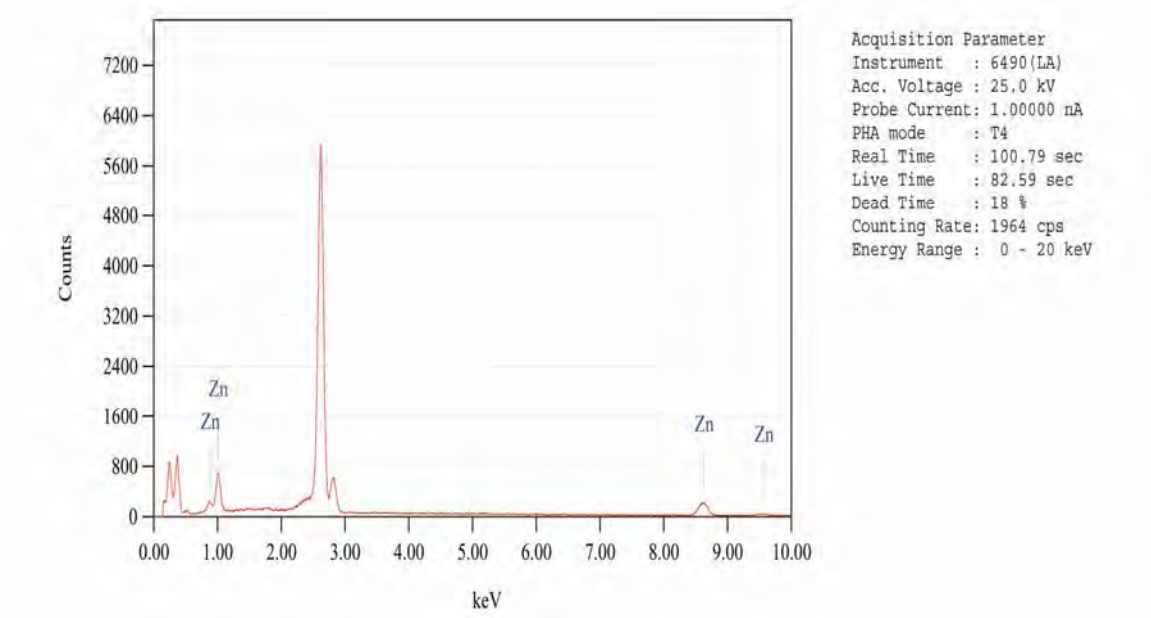


Fig: 2.4.1: EDX spectrum of compound 2,4,6-Tris(acetamido)-1,3,5-triazine, 11.

From the EDX spectrum of compound **11**, the presence of zinc is well observed.
The EDX spectrum shows K peaks of zinc at 8.60, 9.70 KeV and L peaks at 0.90, 1.00 KeV. There are some other peaks as they were constituent of the sample.
So it can be said that the reaction is successful for the preparation of metallodendrimer as supramolecule.

2.4.2 EDX spectrum of compound 2,4,6-Tris(acetamido)-1,3,5-triazine, 12:

The accelerating voltage was 25 keV and counting rate was 4211 cps. The figure 2.4.2 shows the typical EDX spectrum of copper containing metallodendrimer **12**.

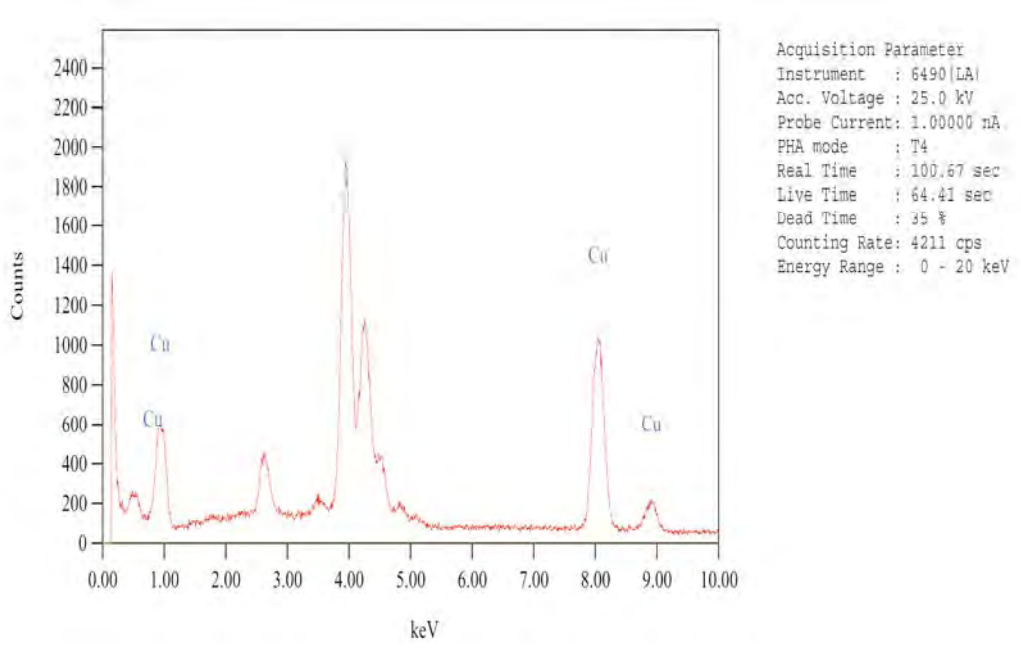


Fig: 2.4.2: EDX spectrum of compound 2,4,6-Tris(acetamido)-1,3,5-triazine, 12.

From the EDX spectrum of compound **12**, the presence of copper is well observed.
The EDX spectrum shows K peaks of copper at 8.00, 8.90 KeV and L peaks at 0.80, 0.90 KeV. There are some other peaks as they were constituent of the sample.
So it can be said that the reaction is successful for the preparation of metallodendrimer as supramolecule.

2.4.3 EDX spectrum of compound 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine, 13:

The accelerating voltage was 25 keV and counting rate was 1126 cps. The figure 2.4.3 shows the typical EDX spectrum of zinc containing metallodendrimer **13**.

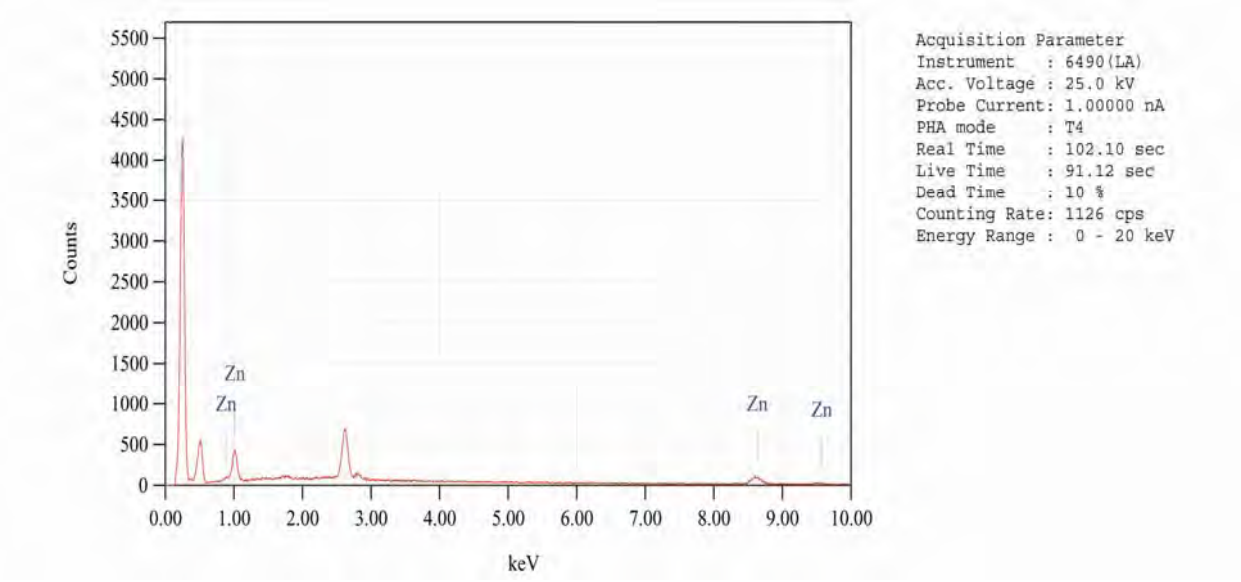


Fig: 2.4.3: EDX spectrum of compound 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine, 13.

From the EDX spectrum of compound **13**, the presence of zinc is well observed.
The EDX spectrum shows K peaks of zinc at 8.60, 9.70 KeV and L peaks at 0 .90, 1.00 KeV. There are some other peaks as they were constituent of the sample.
So it can be said that the reaction is successful for the preparation of metallodendrimer as supramolecule.

2.4.4 EDX spectrum of compound 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine, 14:

The accelerating voltage was 25 keV and counting rate was 6742 cps. The figure 2.4.4 shows the typical EDX spectrum of copper containing metallodendrimer **14**.

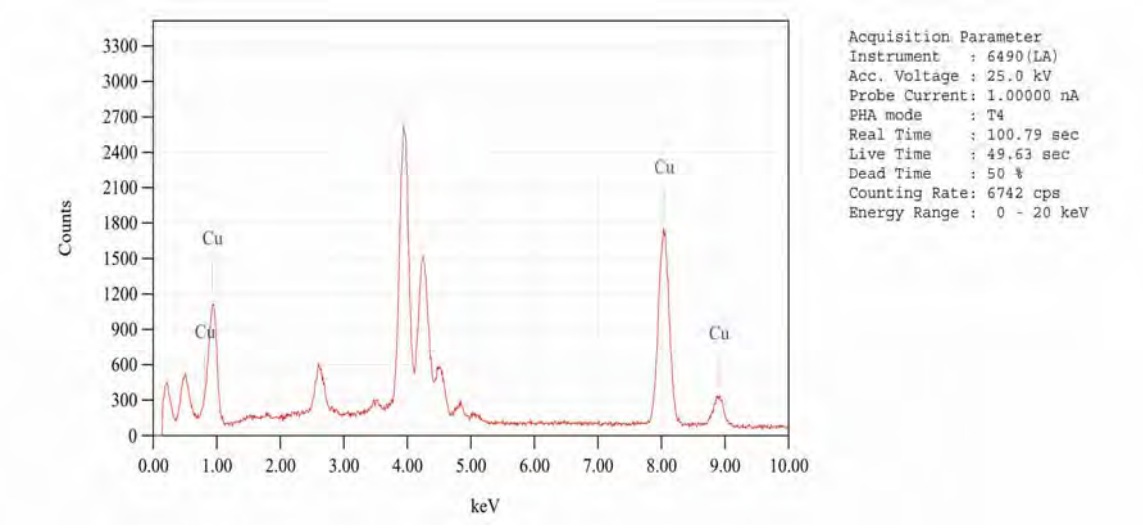


Fig: 2.4.4: EDX spectrum of compound 2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine, 14.

From the EDX spectrum of compound **14**, the presence of copper is well observed. The EDX spectrum shows K peaks of copper at 8.00, 8.90 KeV and L peaks at 0.80, 0.90 KeV. There are some other peaks as they were constituent of the sample.
So it can be said that the reaction is successful for the preparation of metallodendrimer as supramolecule.

2.5 Scanning Electron Microscopic (SEM) analysis:

SEM is known to the best choice because of its potential in precise analysis of a solid surface. To get more clear insight about the surface morphology Scanning Electron Microscopic (SEM) analysis was employed. Chemical composition and morphological structure of a material depends on the synthesis conditions such as temperature, concentration of reactants and products etc. The SEM images of the compounds were taken in a Scanning Electron Microscope at an accelerating voltage of 20 KV with magnifications ranging from 400-5000.

Figure 2.5.1 (a) shows the SEM image (magnification: X 3000) of compound **7** synthesized as described in (Section: 3). This image represented “cloud like” structure. Here particles were not well distributed but some particles were seems to be granular and non globular. No metal particle was involved with this compound.

Figure 2.5.1 (b) shows the high magnification (X 4500) same image for the product **13,** synthesized as described in (Section: 3). From this image, some particle appear to be granular and aggregative. It can also be seen that particles get fused together and less uniformed at this stage. Most of the particles have the size range from 0.74 µm to 1.59 µm. Zn-metal was involved with this structure.

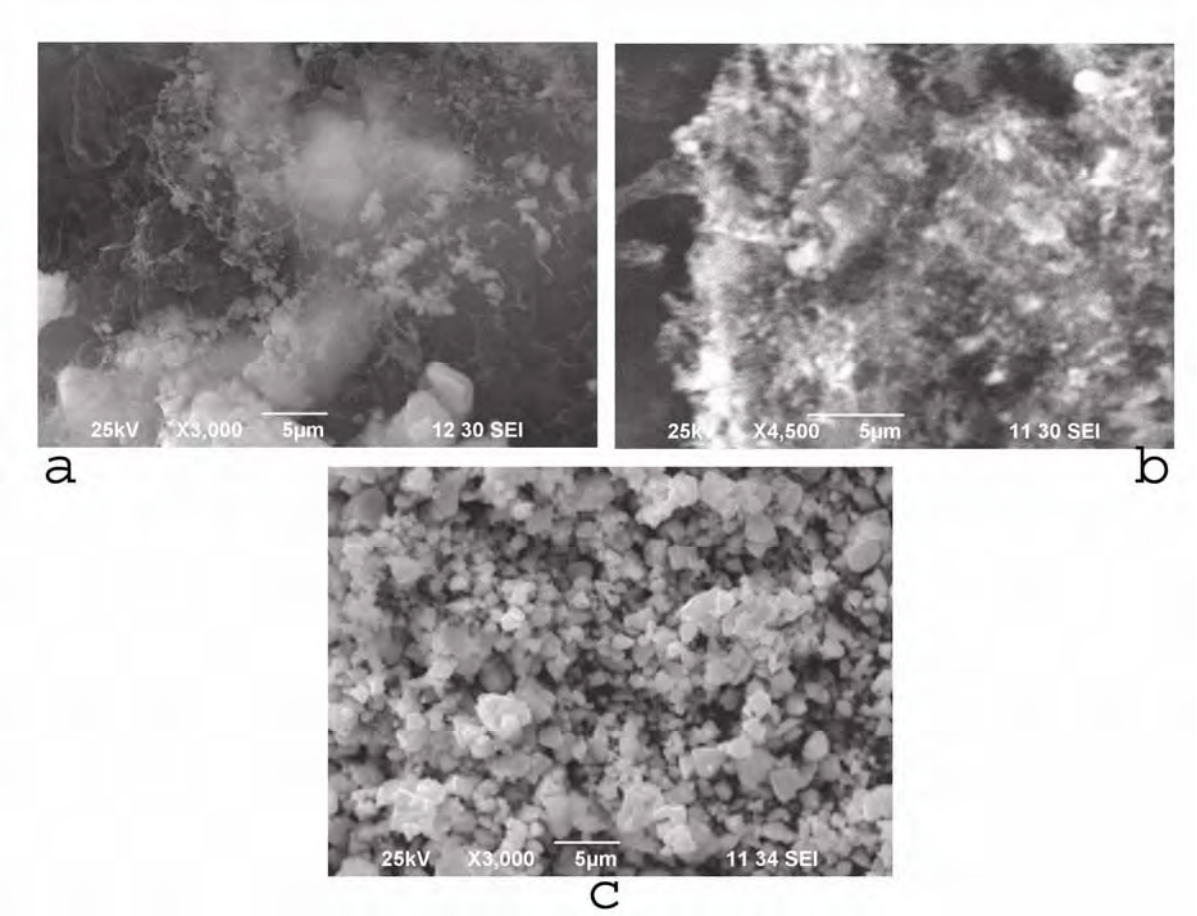


Fig.2.5.1: SEM micrographs of

a. Comopund **7** [2,4,6-Tris(4-methylbenzamido)1,3,5-triazine]
b. Comopund **13** [2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine]
c. Comopund **14** [2,4,6-Tris(4-methylbenzamido)-1,3,5-triazine]

Figure 2.5.1 (c) shows the SEM image (magnification: X 3000) of product **14**, synthesized as described in (Section: 3). From this image, stone like morphology was observed. In this case, surface of the particles are spherical and the particles exhibit very uniform and well distributed. This image shows clearly that the surface is indeed composed of macro particle unit with a size range from 2 µm to 3 µm. Cu-metal was associated with this particle.

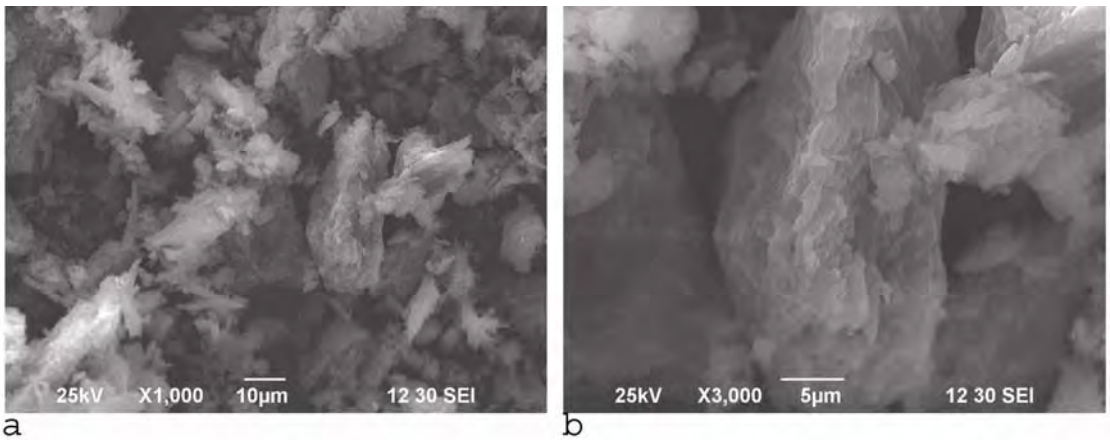


Fig.2.5.2: (a,b) SEM micrographs of Comopund **8** [2,4,6-Tris(acetamido)-1,3,5-triazine].

Figure 2.5.2 (a) shows the low magnification (X 1000) SEM image for the product **8.** There was no definite shape of the particle.

Figure 2.5.2 (b) shows the high magnification (X 3000) SEM image in which a layer-by- layer lump morphology was observed and compacted with sharp periphery. No metal was associated with this structure.

Figure 2.5.2 (c) shows the low magnification (X 400) SEM image for the product, **11** obtained after a reaction time of 4 hours. The synthesized processed as described in (section: 3). From this image it can be seen that the particles have fiber like shape.

Closed viewing of the high magnification (X 1400) SEM image in figure 2.5.2 (d) shows clearly the unavailability of the porous part. The fiber like structures is constructed by single fiber particle with a diameter ranging from about 5.94 µm to 9.45 µm. In this structure Zn-metal was involved.

2.5.2 (e) shows the SEM image (magnification: X 150) for the product, **11** after recrystalisation.

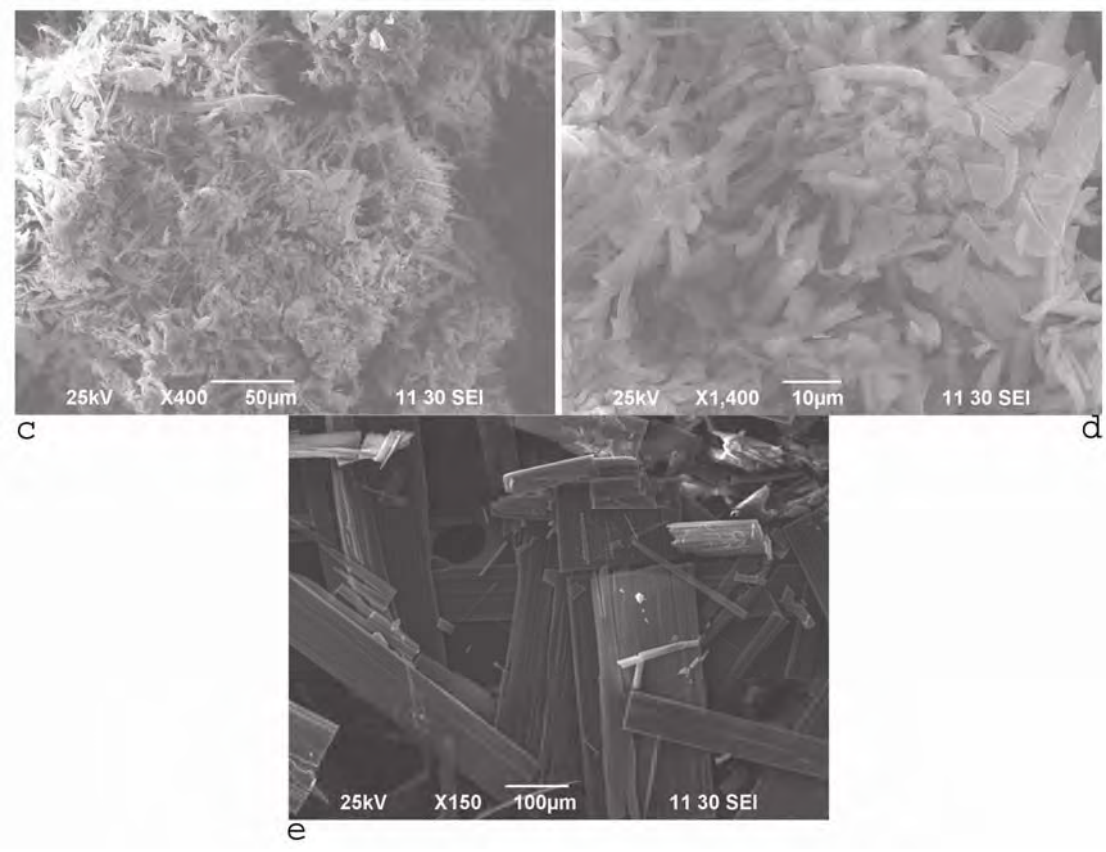
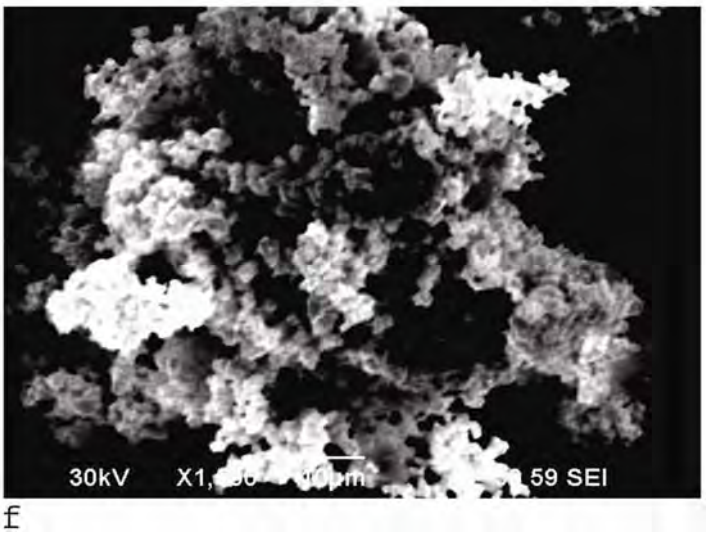


Fig.2.5.2: (c,d,e) SEM micrographs of Comopund **11** [2,4,6-Tris(acetamido)-1,3,5-triazine].



f

Fig.2.5.2: (f) SEM micrographs of Comopund **12**[2,4,6-Tris(acetamido)-1,3,5-Triazine]

Figure 2.5.2(f) shows the low magnification (X 1000) SEM image for the product **12**, obtained after a reaction time of 4 hours which synthesized as described in (Section: 3). From this image it can be seen that the particles appeared to be spherical and packed each other. The agglomerated structure was constructed by granular particle with a size of about 1 µm. Cu- metal was involved with this structure.

Name of compound	Average Particles Size(µm)
11	7.69
12	1.00
13	1.16
14	2.5

Table 2.5 : Average particle size of different compound.

From this study, it is clear that there is notable difference between the surface morphology of dendrimer and metallodendrimer. Perhaps the surface of metallodendrimer gets a homogeneous morphology due to dispersion of metal ion (Zn^{2+}, Cu^{2+}). Moreover, particles size investigation by SEM indicated that all synthesized molecule were supramolecules. So, from morphological analysis it can be concluded that, metal ion (Zn^{2+}, Cu^{2+}) from $ZnCl_2$ or CuI initially reduced onto the surface of non-metallodendrimers, resulting granular and spherical particles.

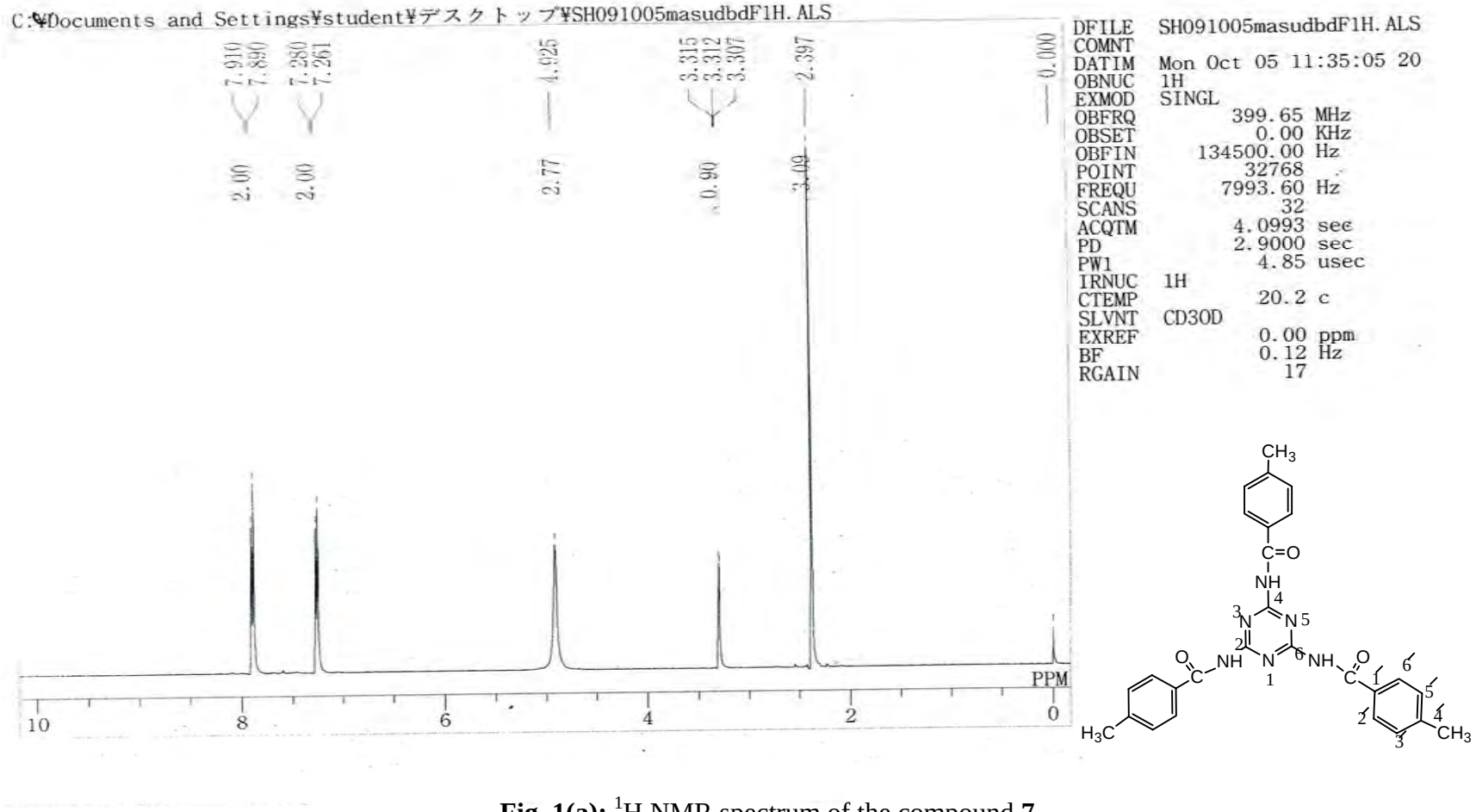


Fig. 1(a): ^{1}H NMR spectrum of the compound **7**

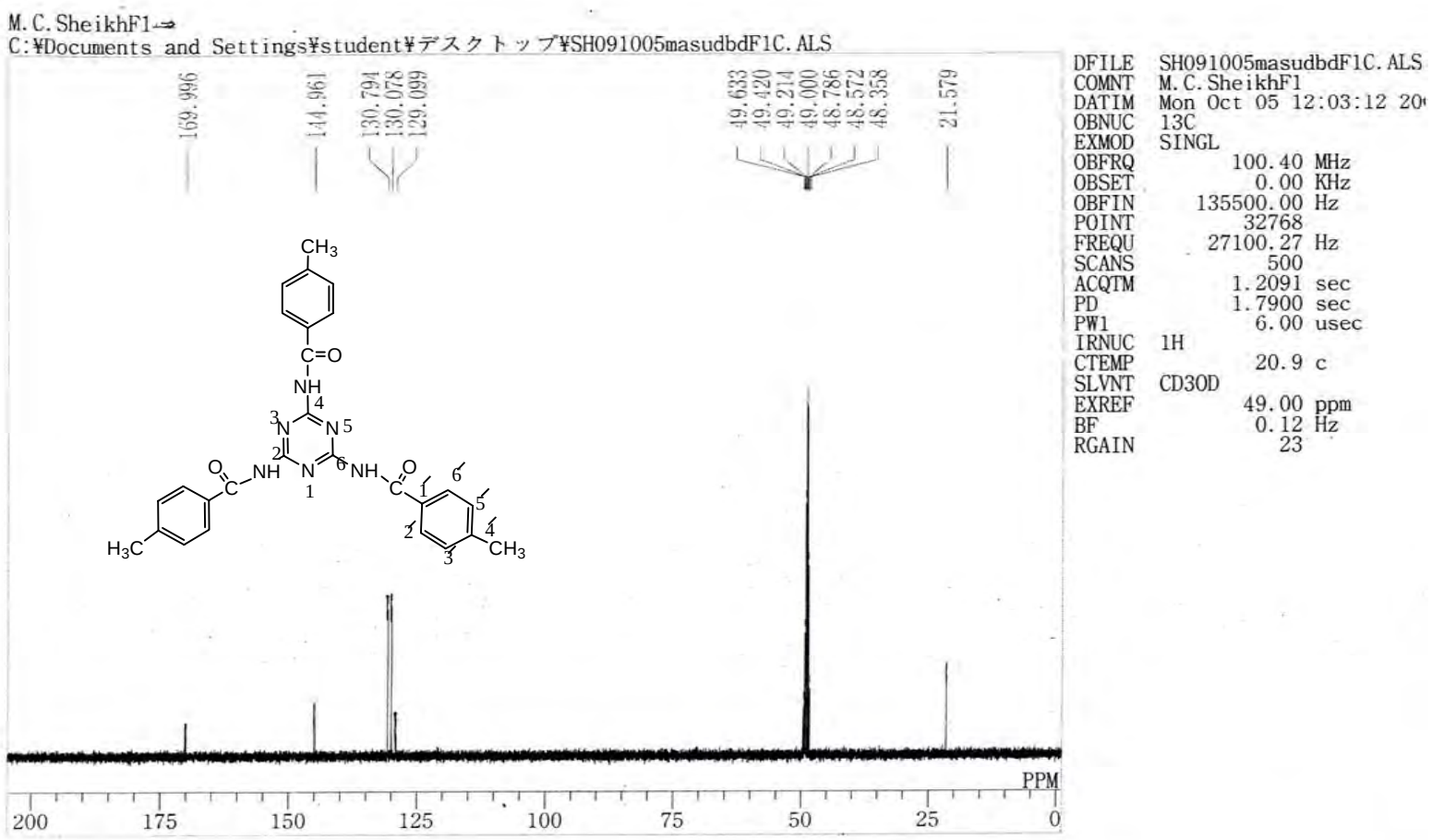


Fig. 1(b): ^{13}C NMR spectrum of the compound **7**

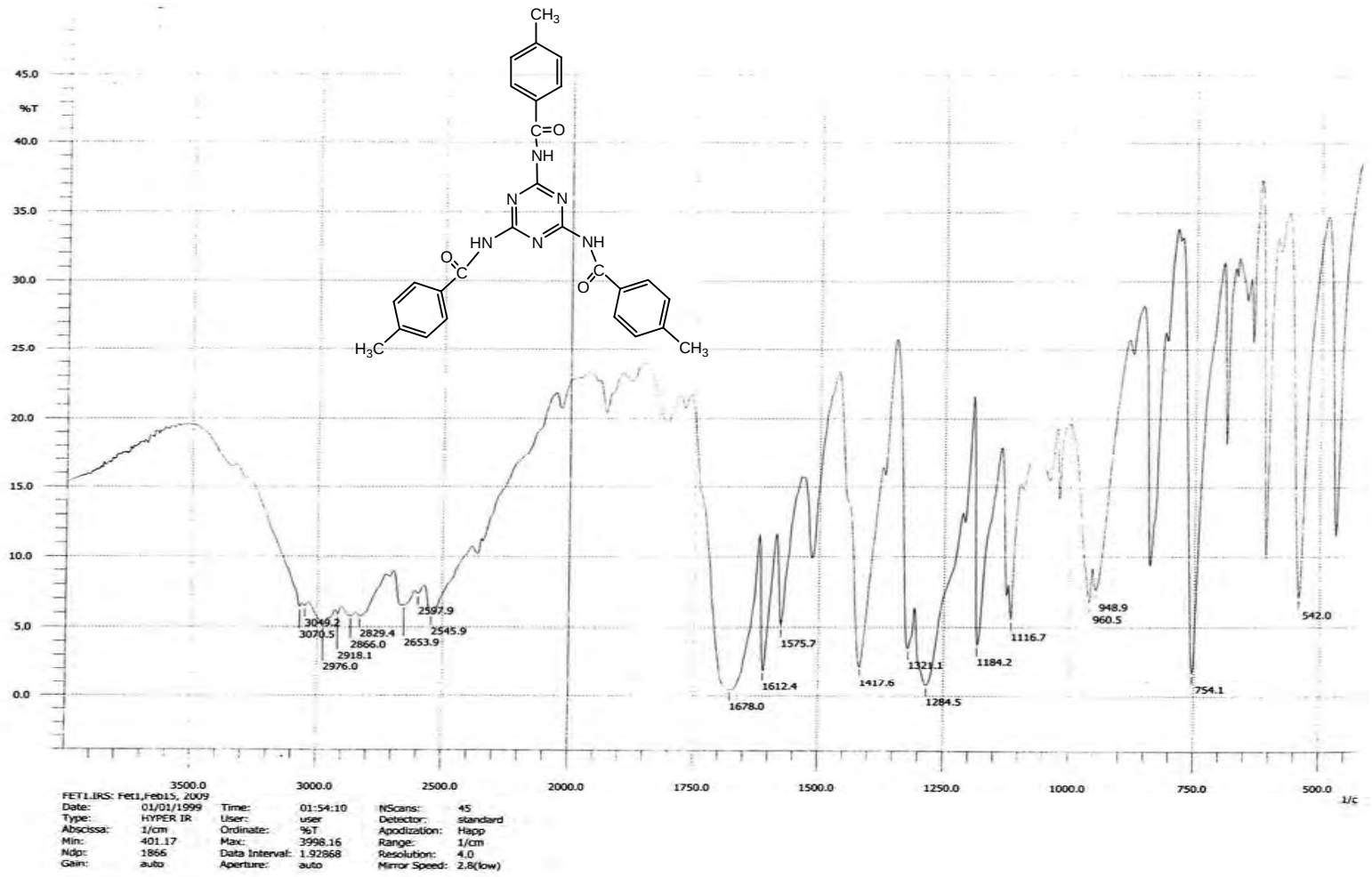


Fig. 1(c): IR spectrum of the compound **7**

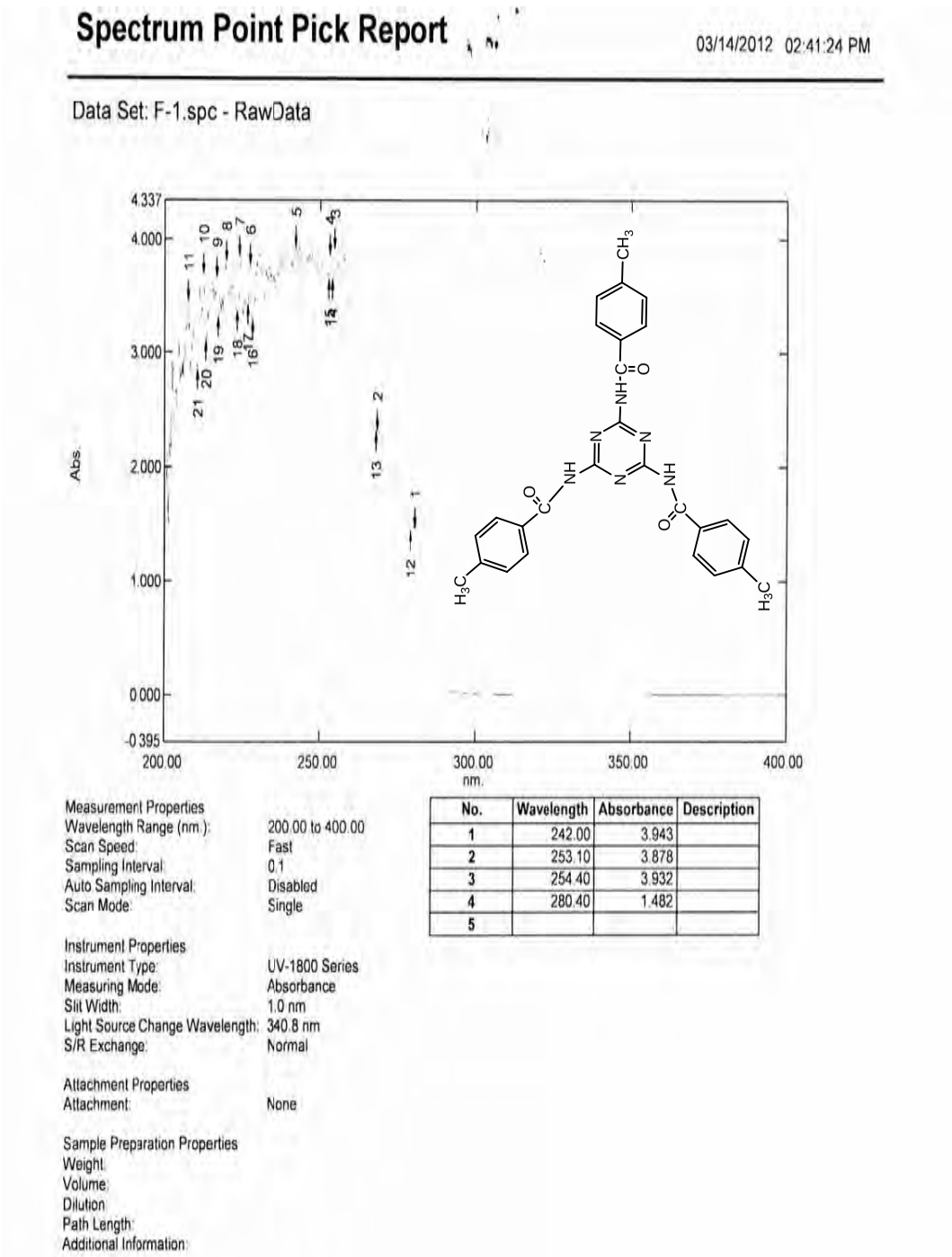


Fig. 1(d) : UV spectrum of the compound

7

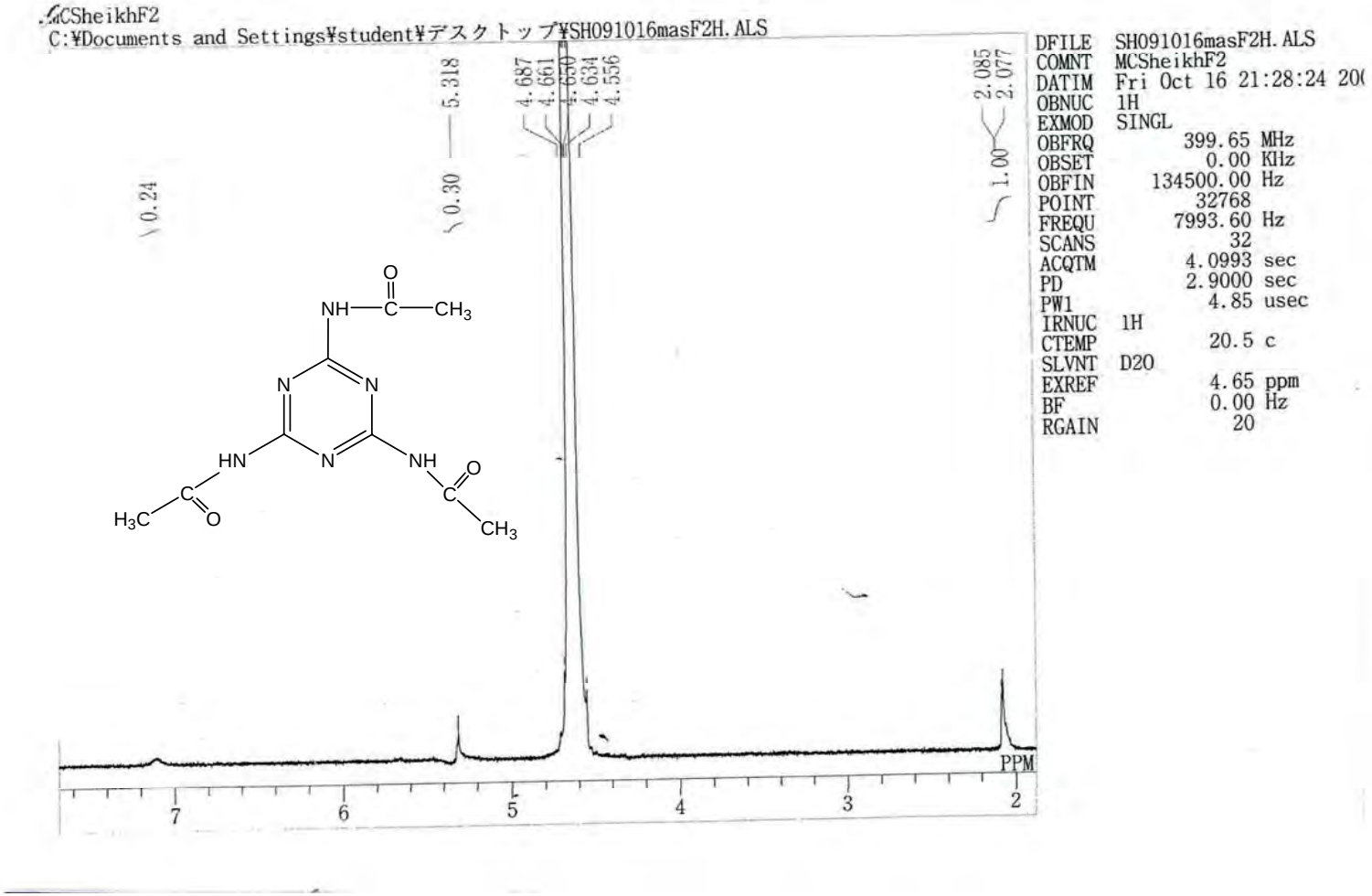


Fig. 2(a): ^{1}H NMR spectrum of the compound **8**

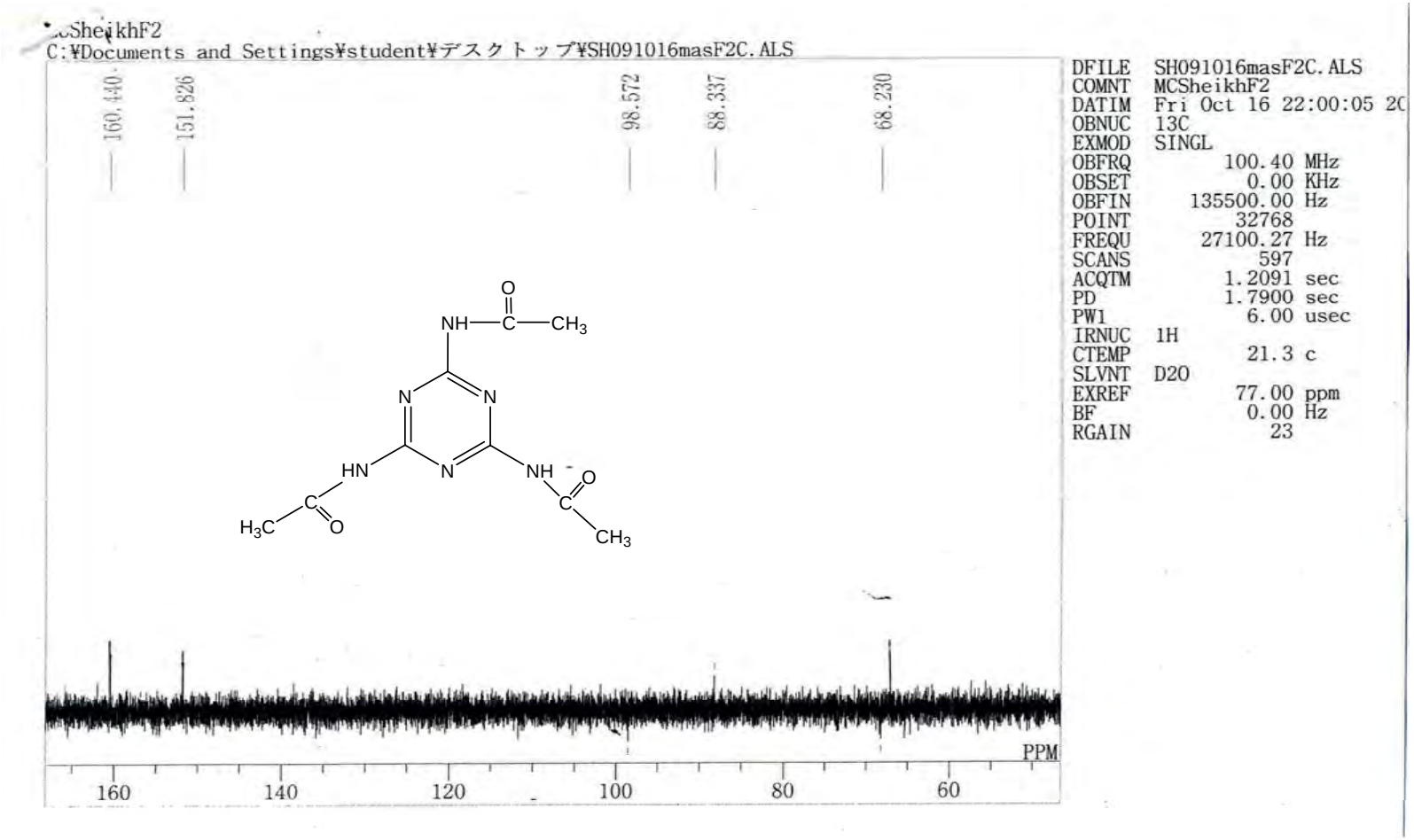


Fig. 2(b): ^{13}C NMR spectrum of the compound **8**

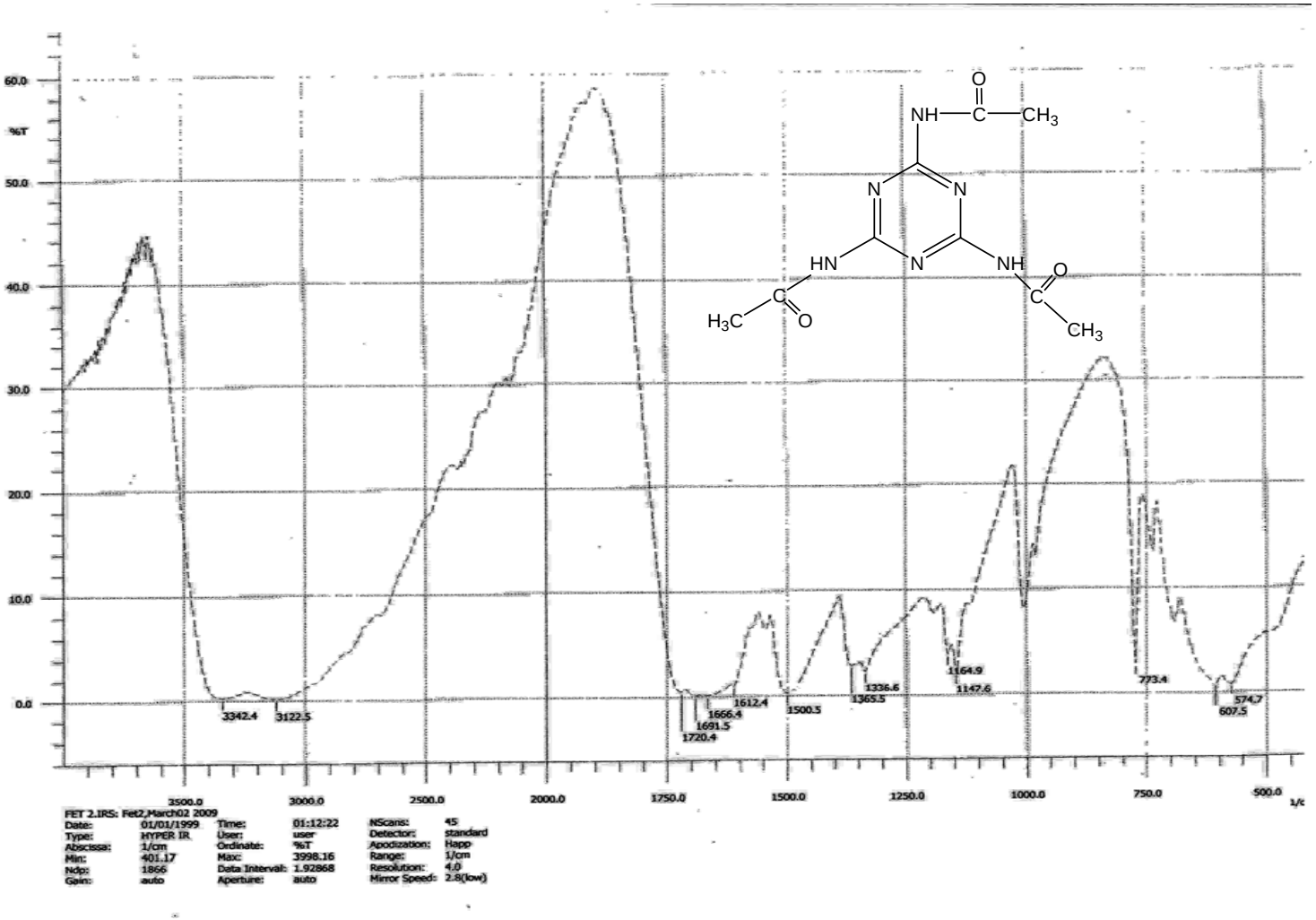


Fig. 2(c): IR spectrum of the compound **8**

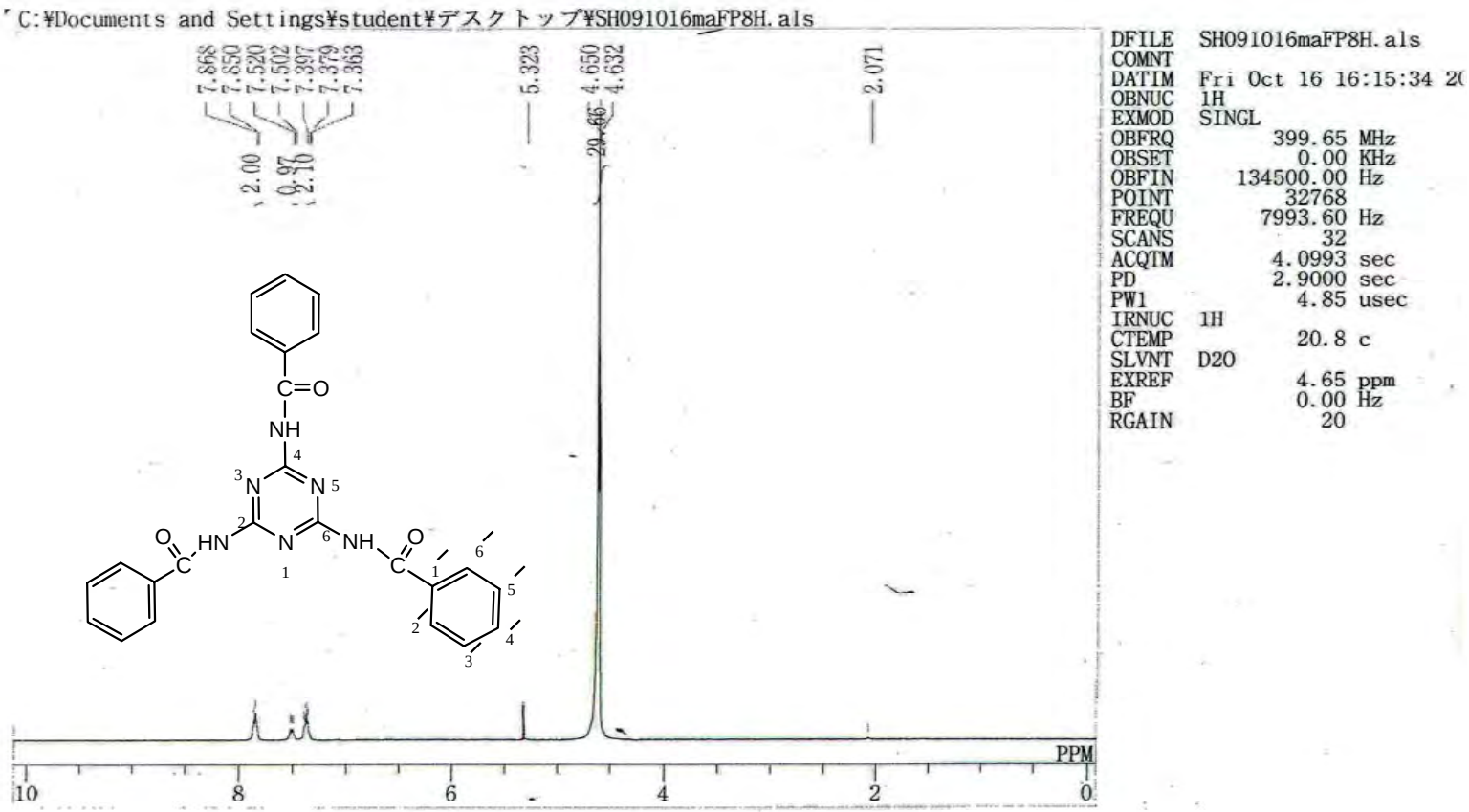


Fig. 3(a): ^{1}H NMR spectrum of the compound **9**

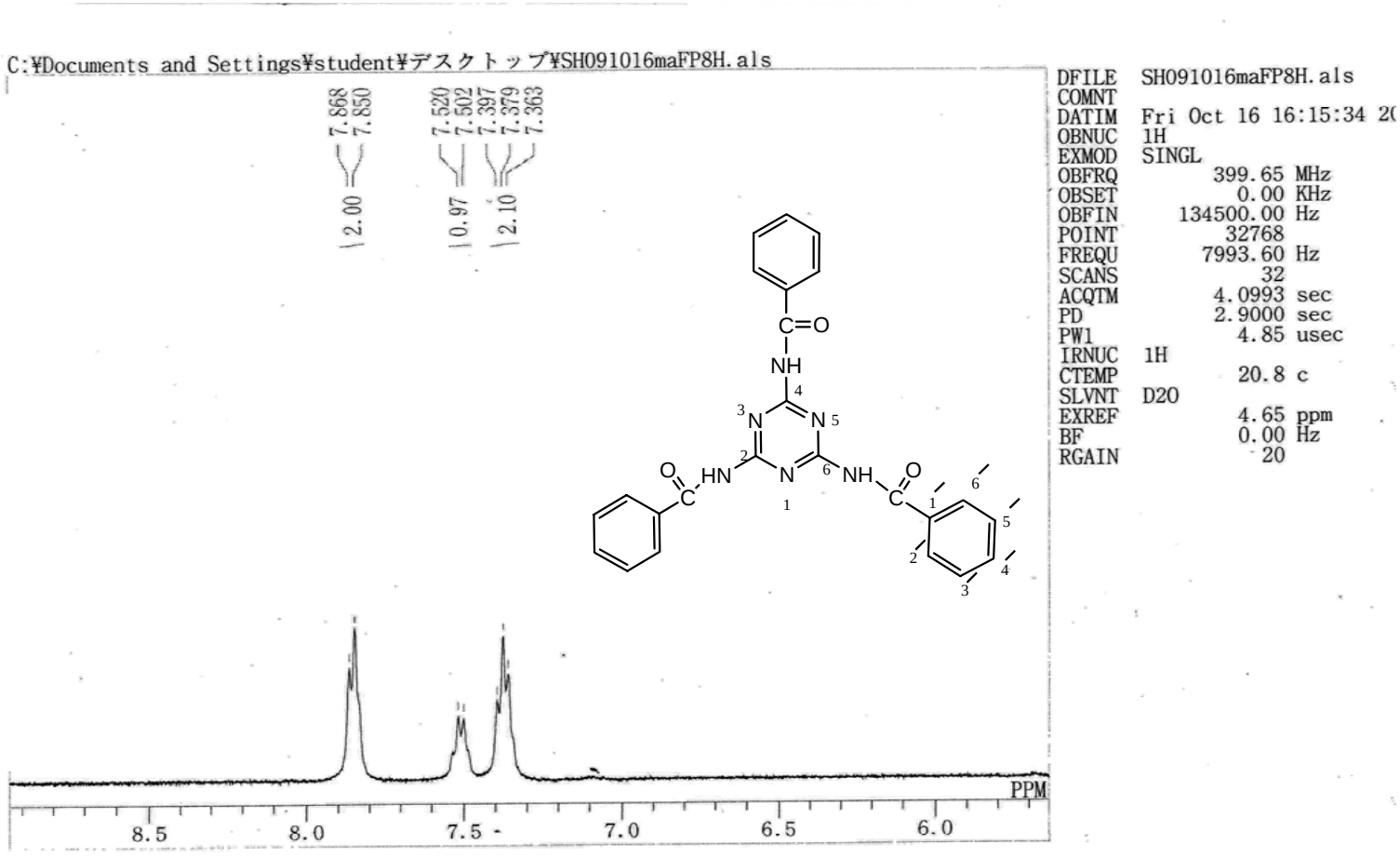


Fig. 3(b): ^{1}H NMR spectrum of the compound **9** (expanded)

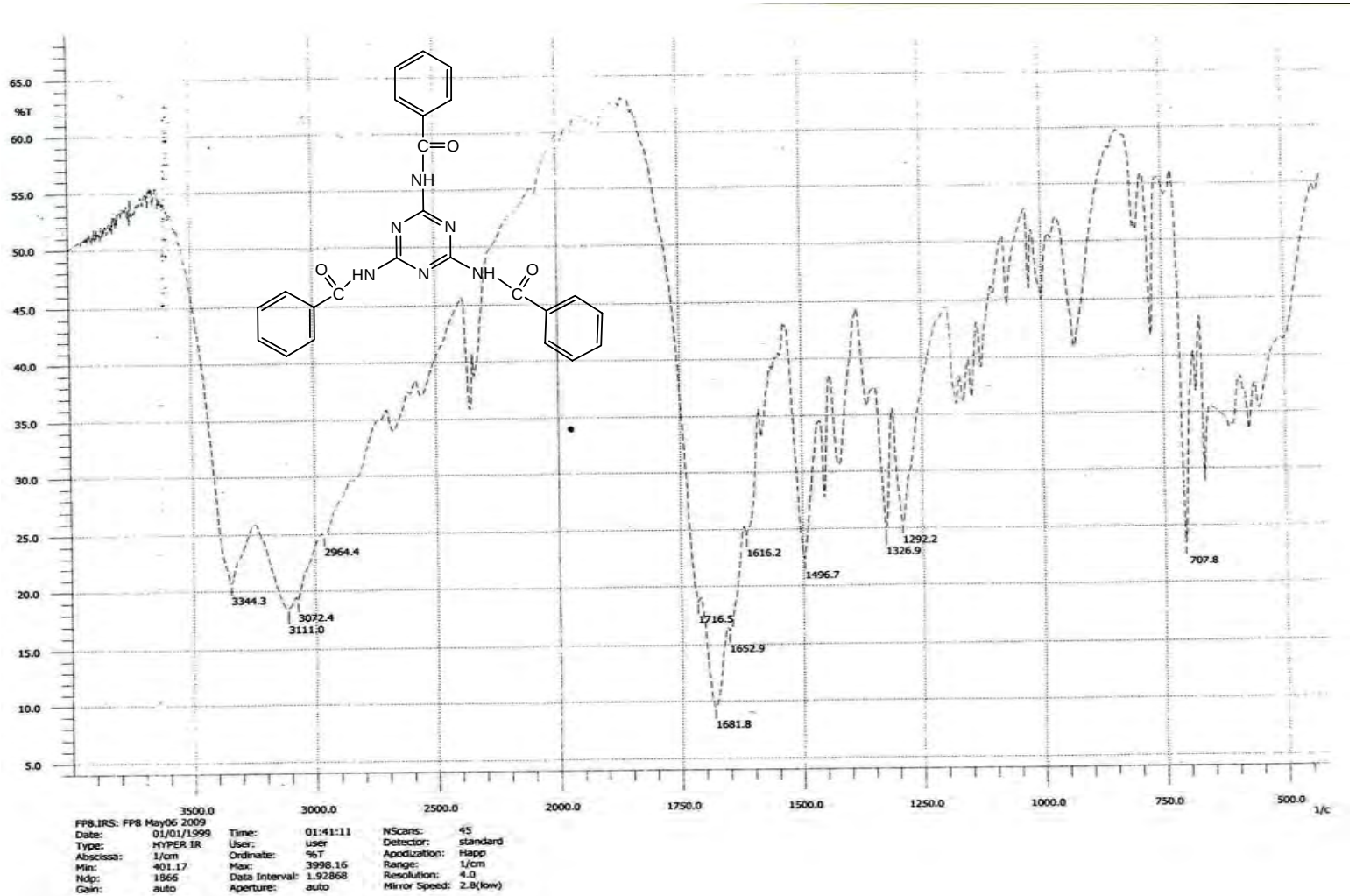


Fig. 3(c): IR spectrum of the compound **9**

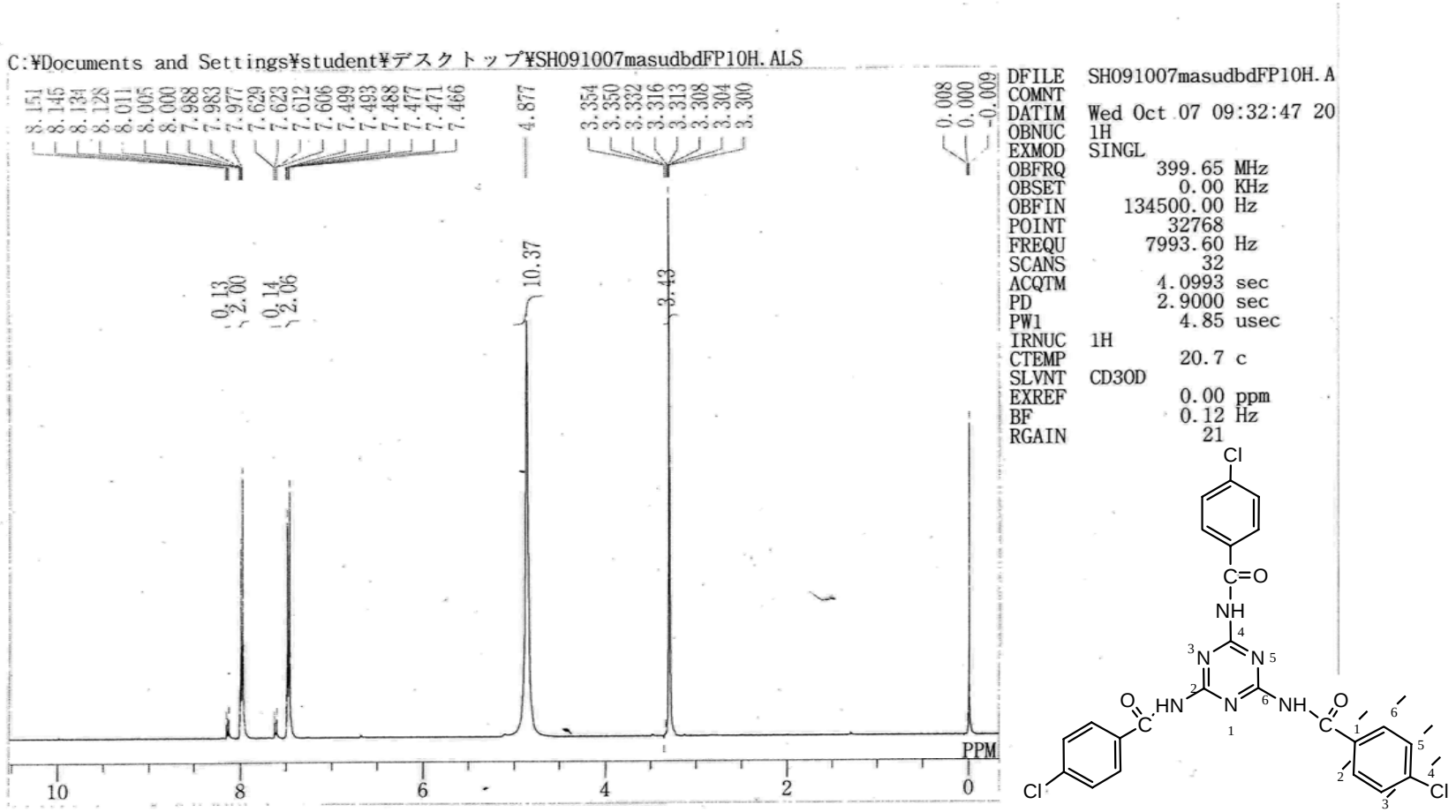


Fig. 4(a): ^{1}H NMR spectrum of the compound **10**

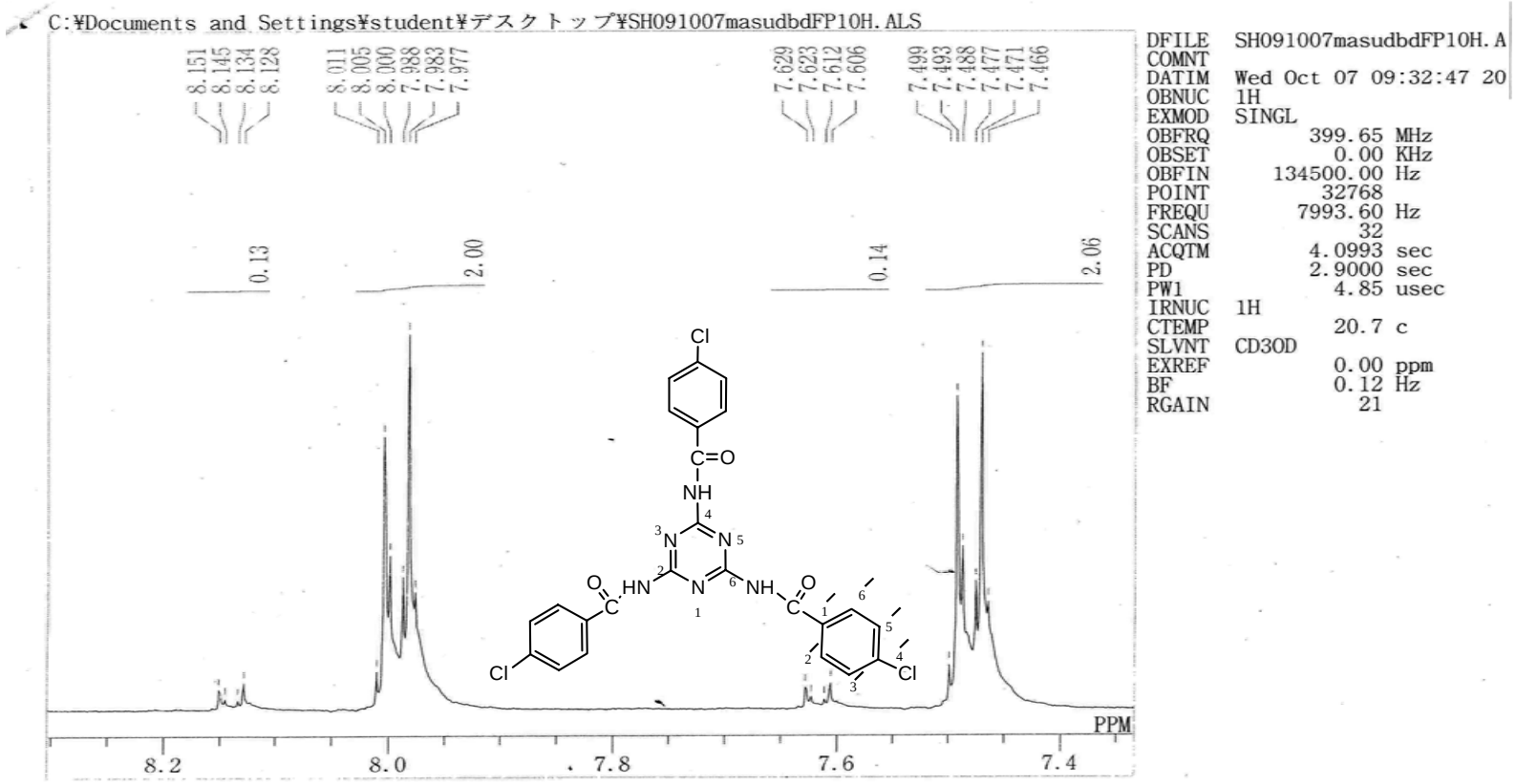


Fig. 4(b): ^{1}H NMR spectrum of the compound **10** (expanded)

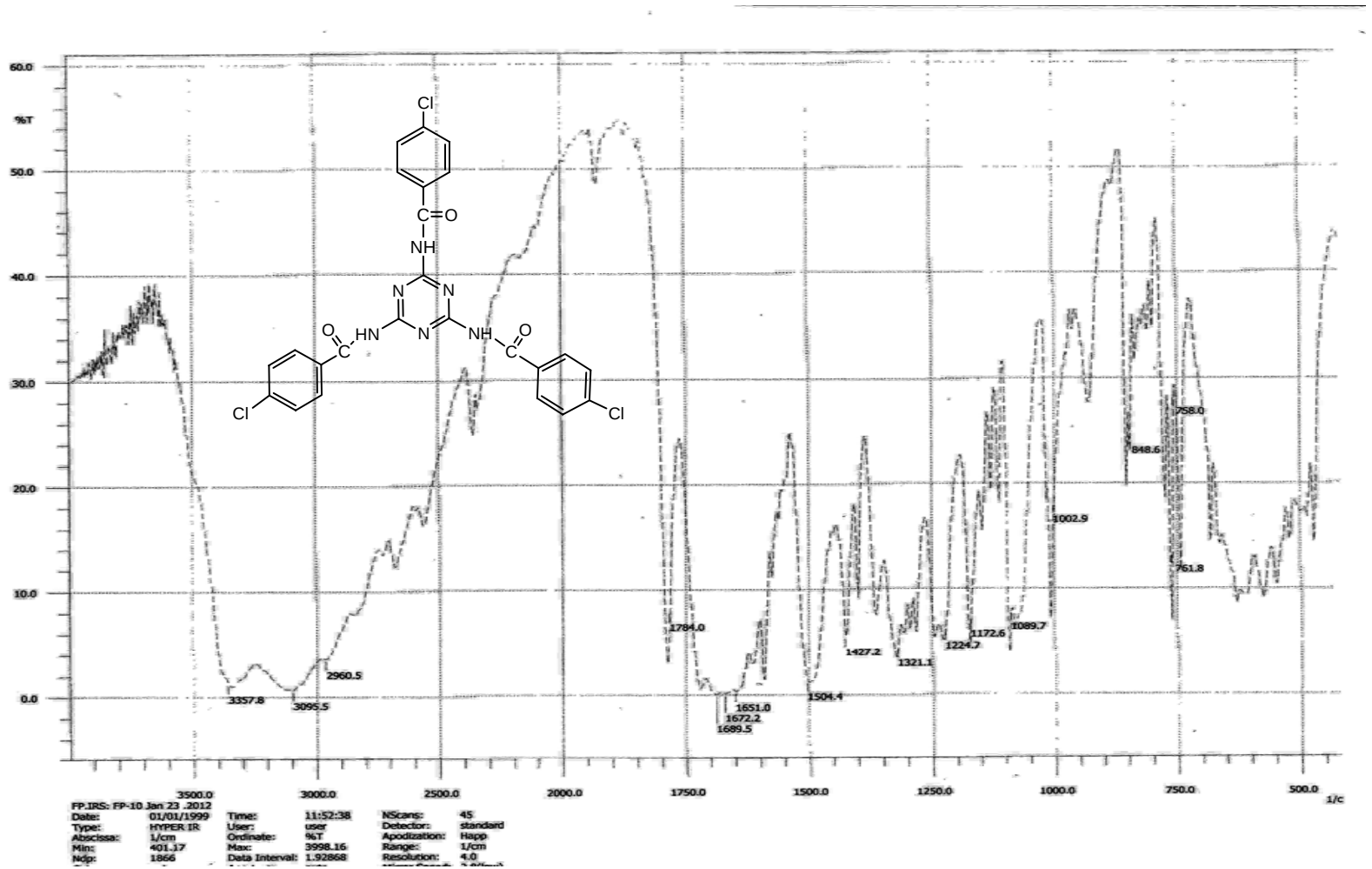
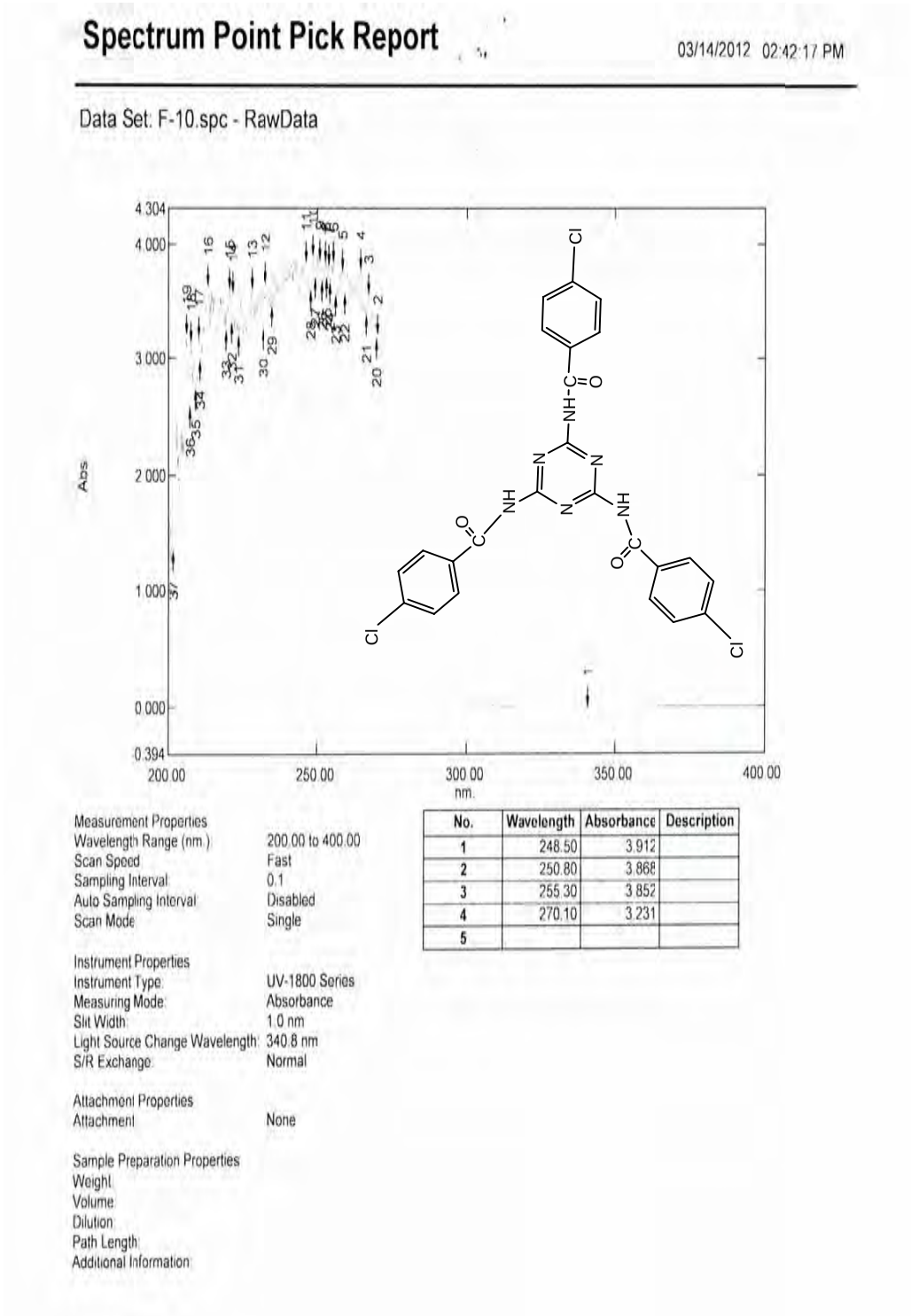


Fig. 4(c): IR spectrum of the compound **10**



- **Fig. 4(d) :** UV spectrum of the compound **10**

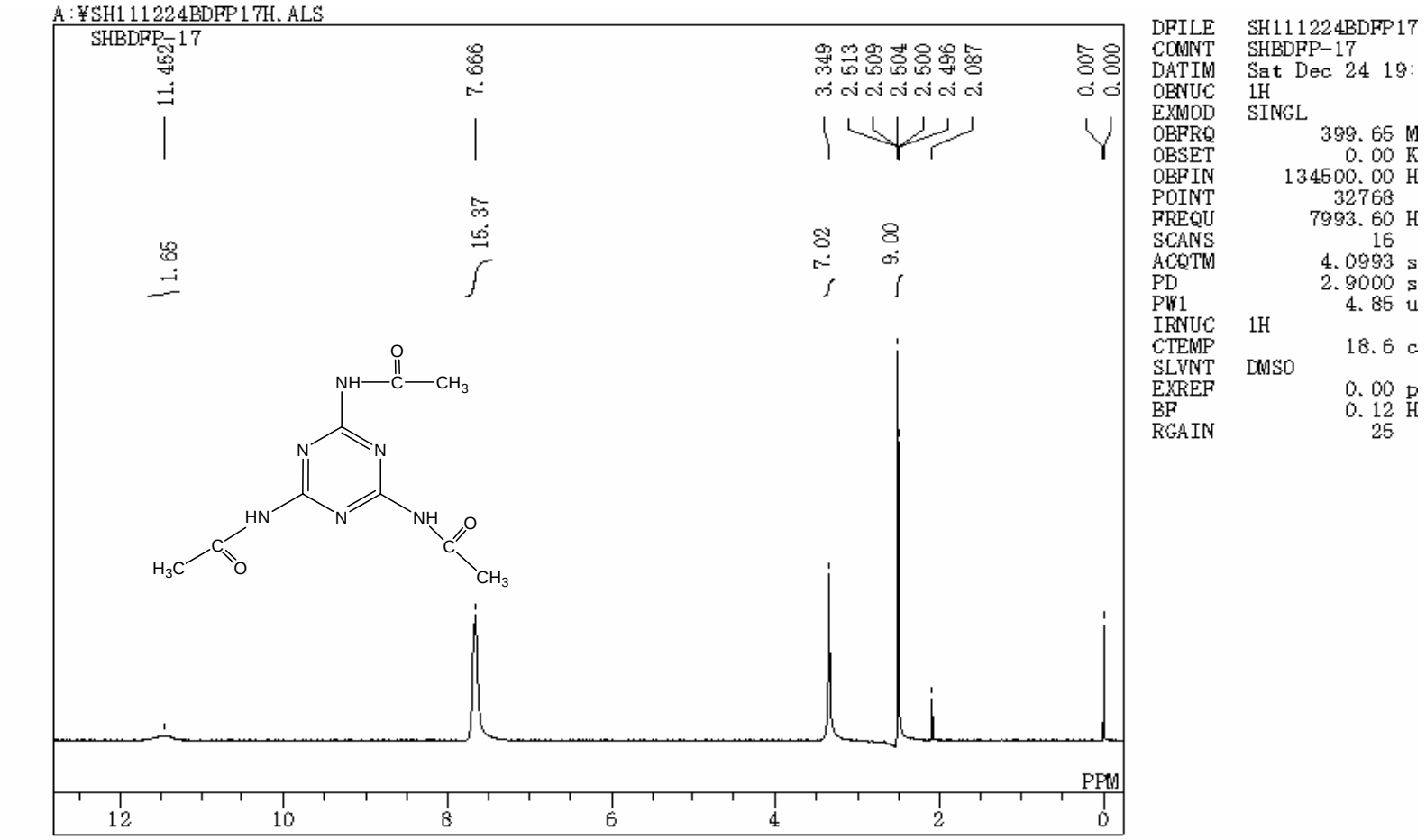


Fig. 5(a): ^{1}H NMR spectrum of the compound **11**

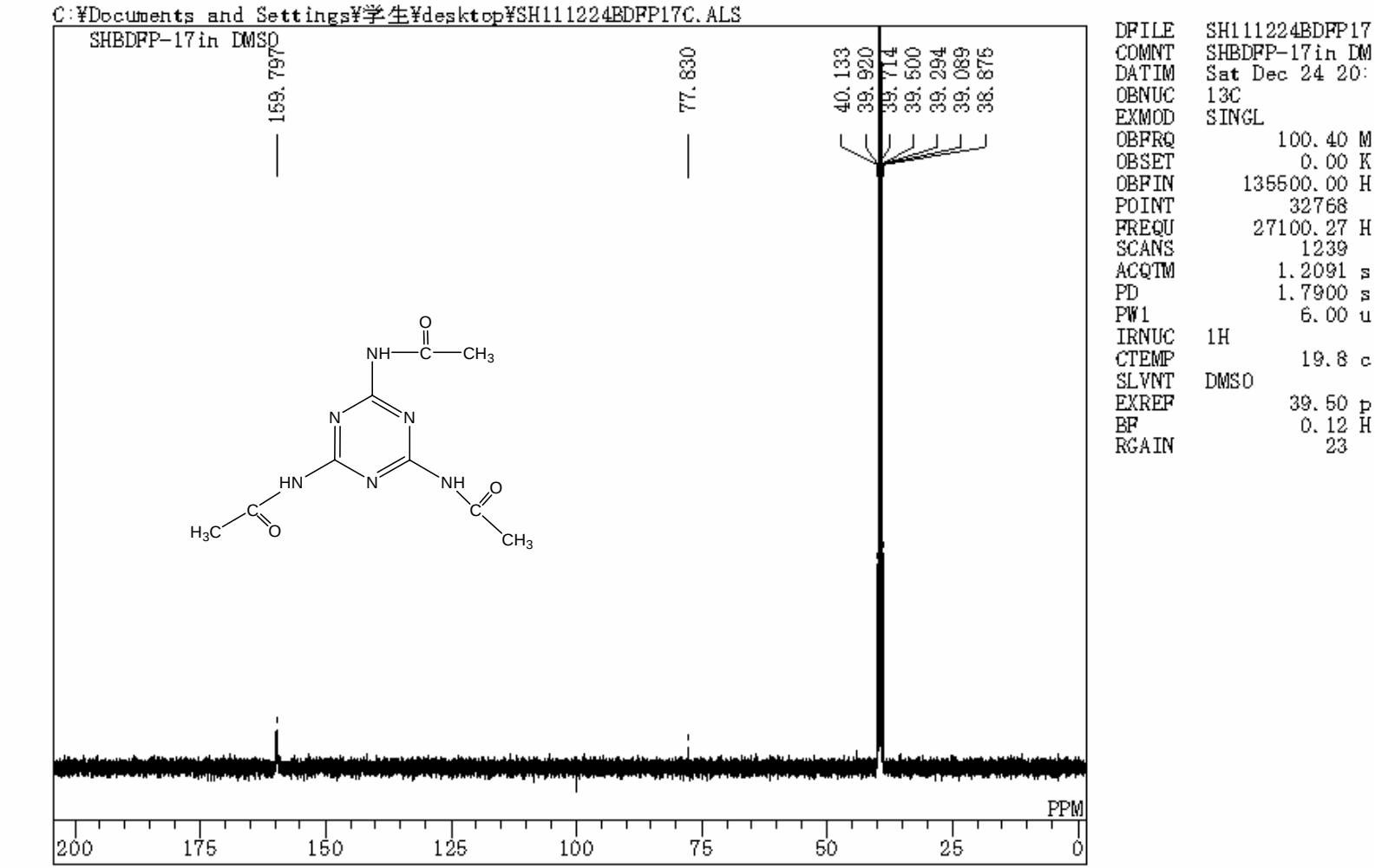


Fig. 5(b): ^{13}C NMR spectrum of the compound **11**

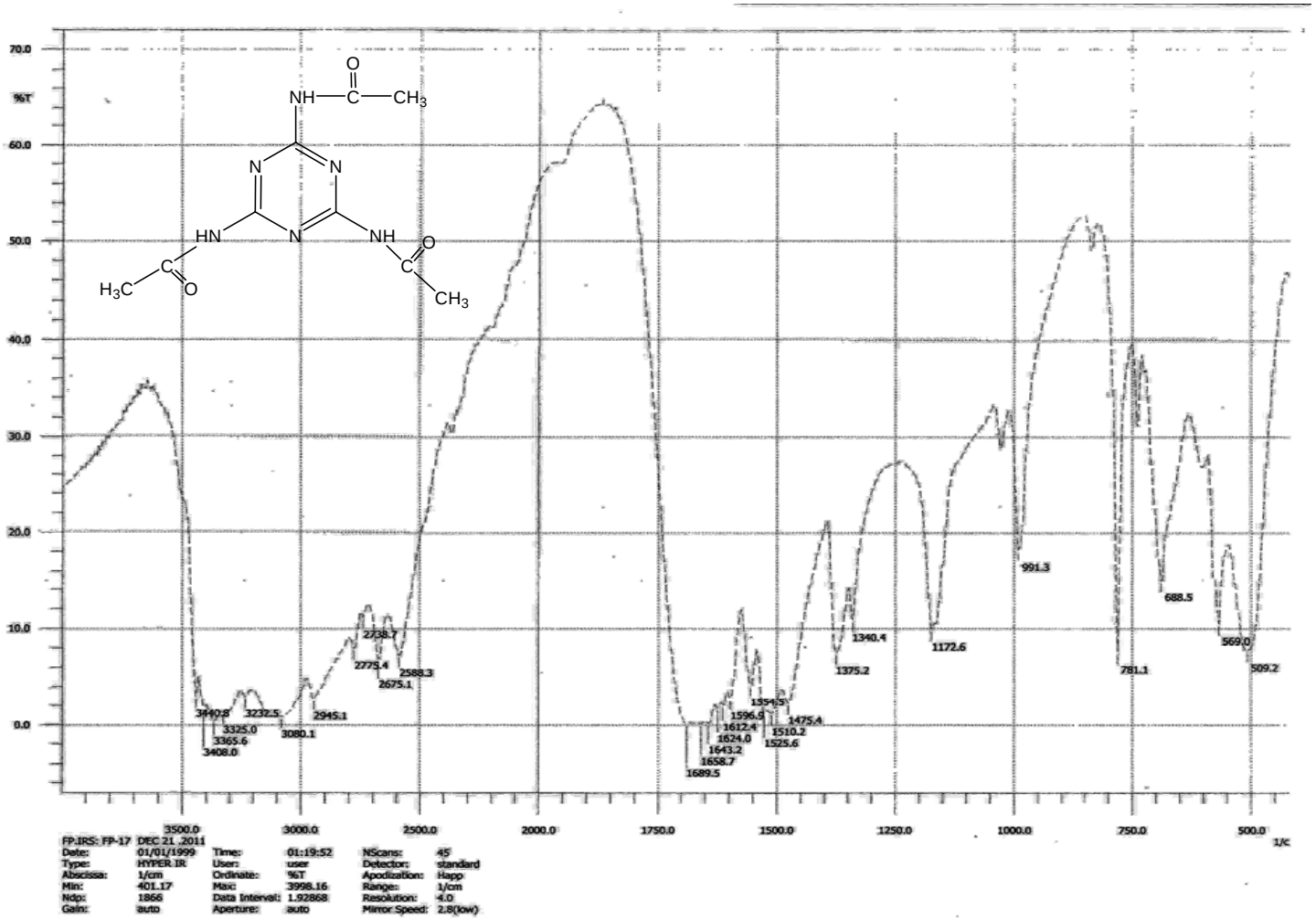


Fig. 5(c): IR spectrum of the compound **11**

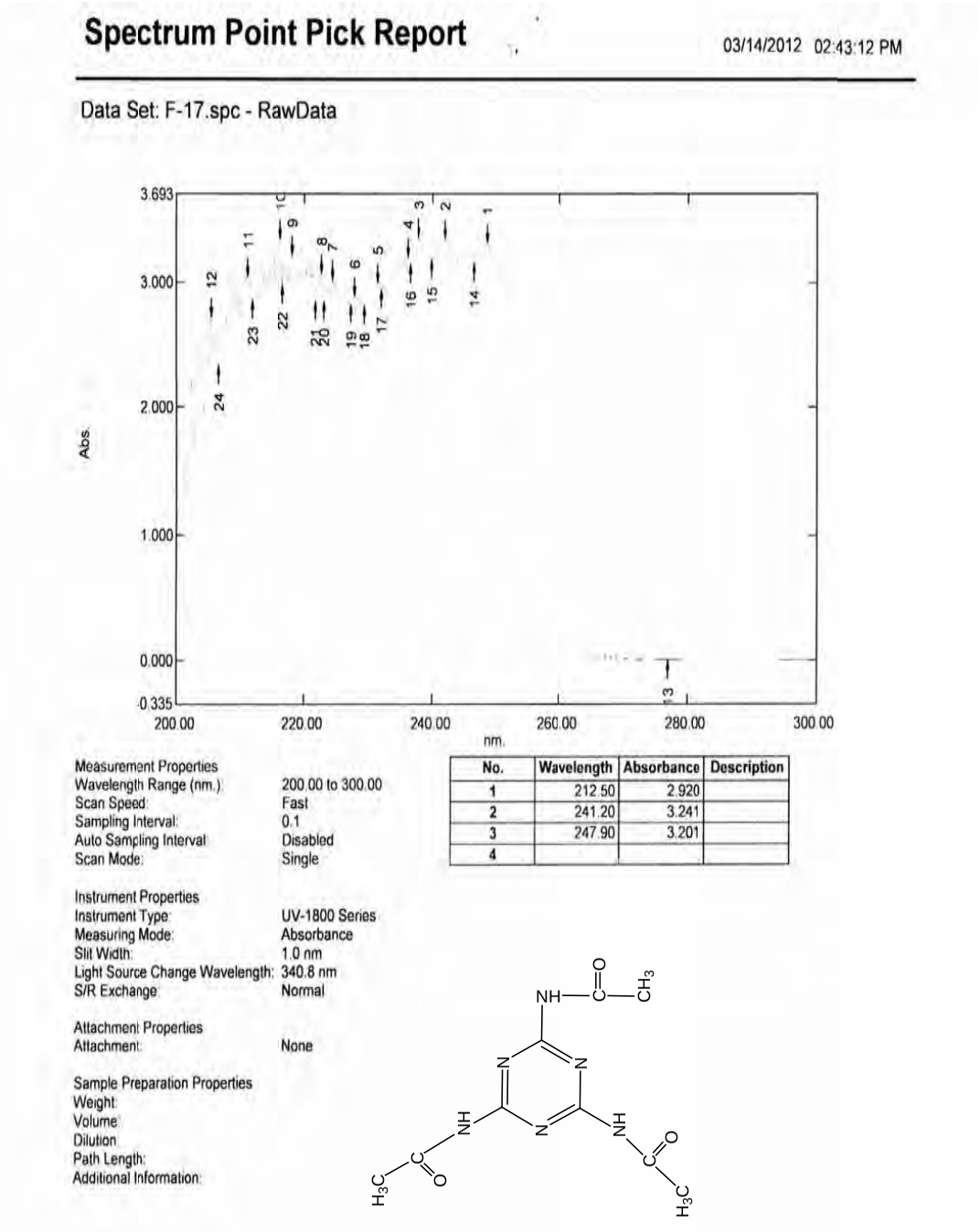


Fig. 5(d) : UV spectrum of the compound **11**

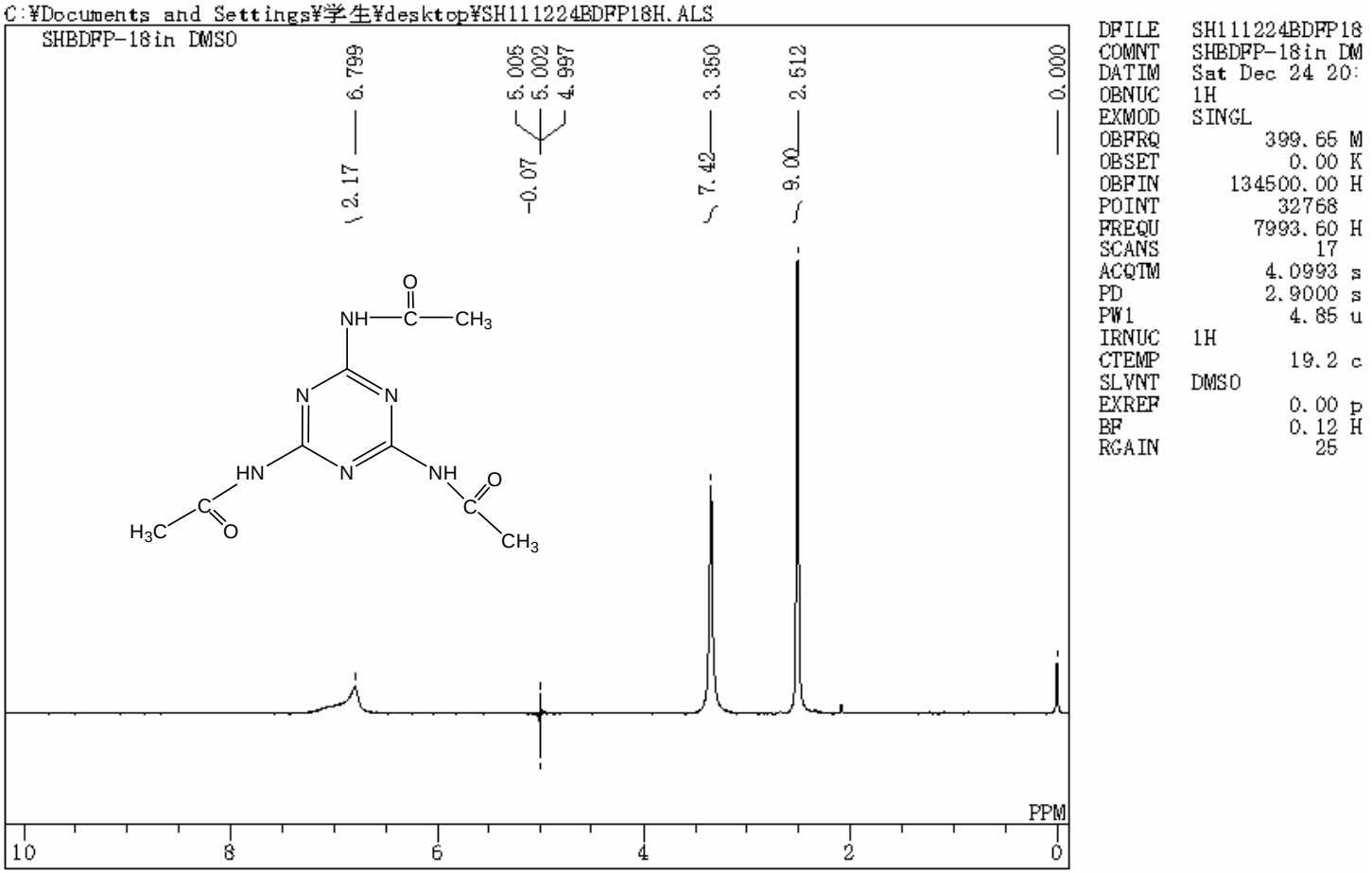


Fig. 6(a): ^{1}H NMR spectrum of the compound **12**

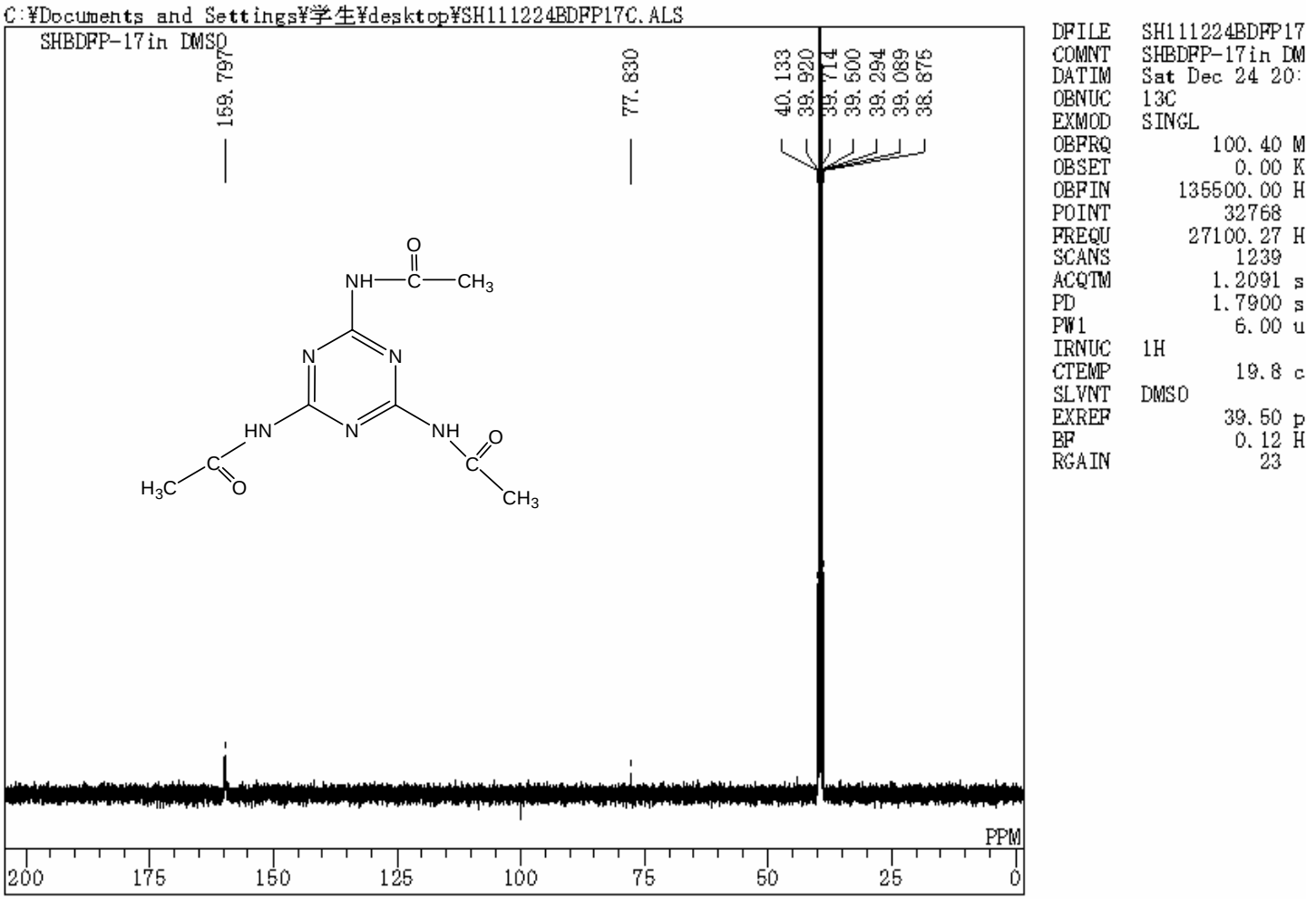


Fig. 6(b): ^{13}C NMR spectrum of the compound **12**

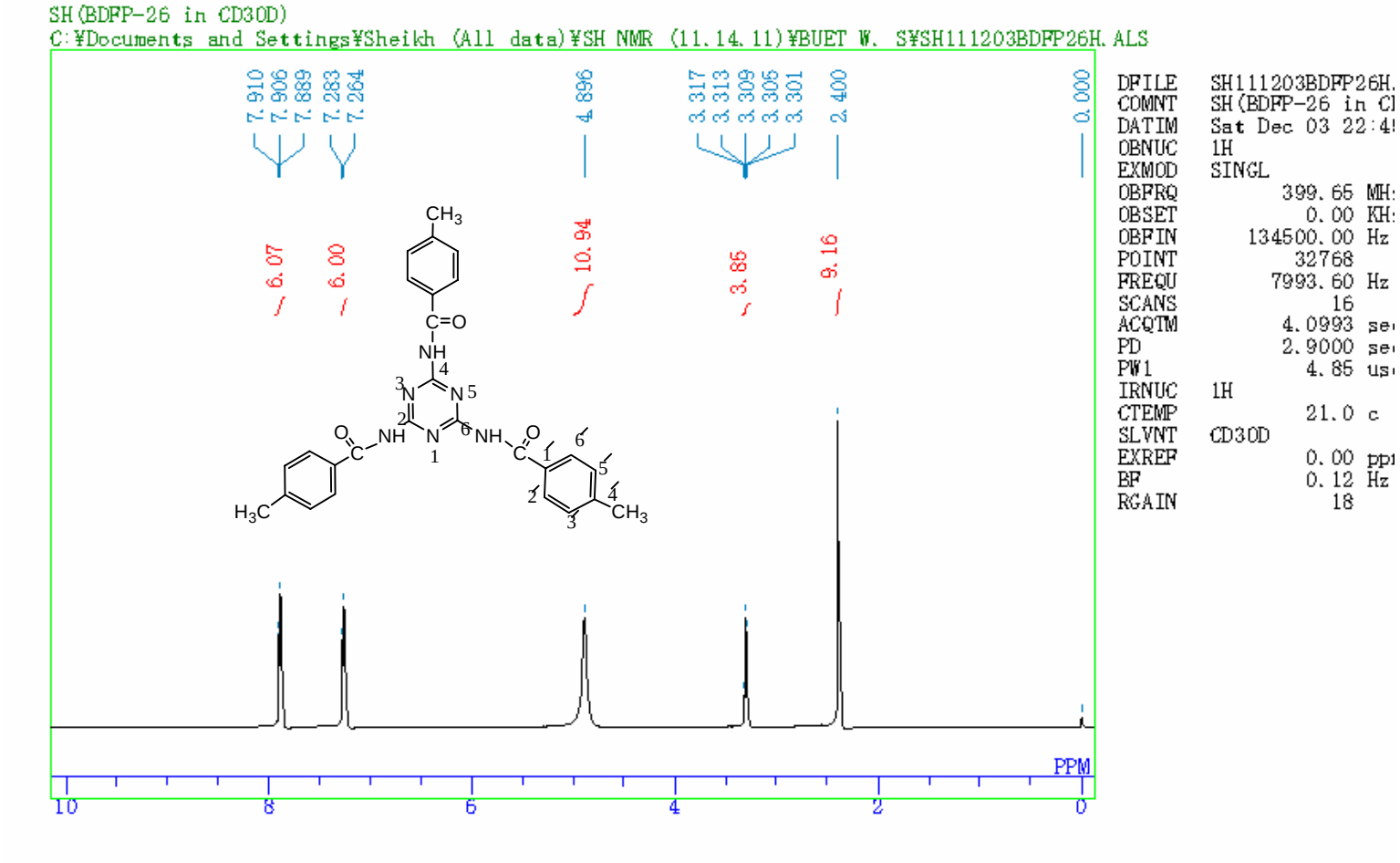


Fig. 7(a): ^{1}H NMR spectrum of the compound **13**

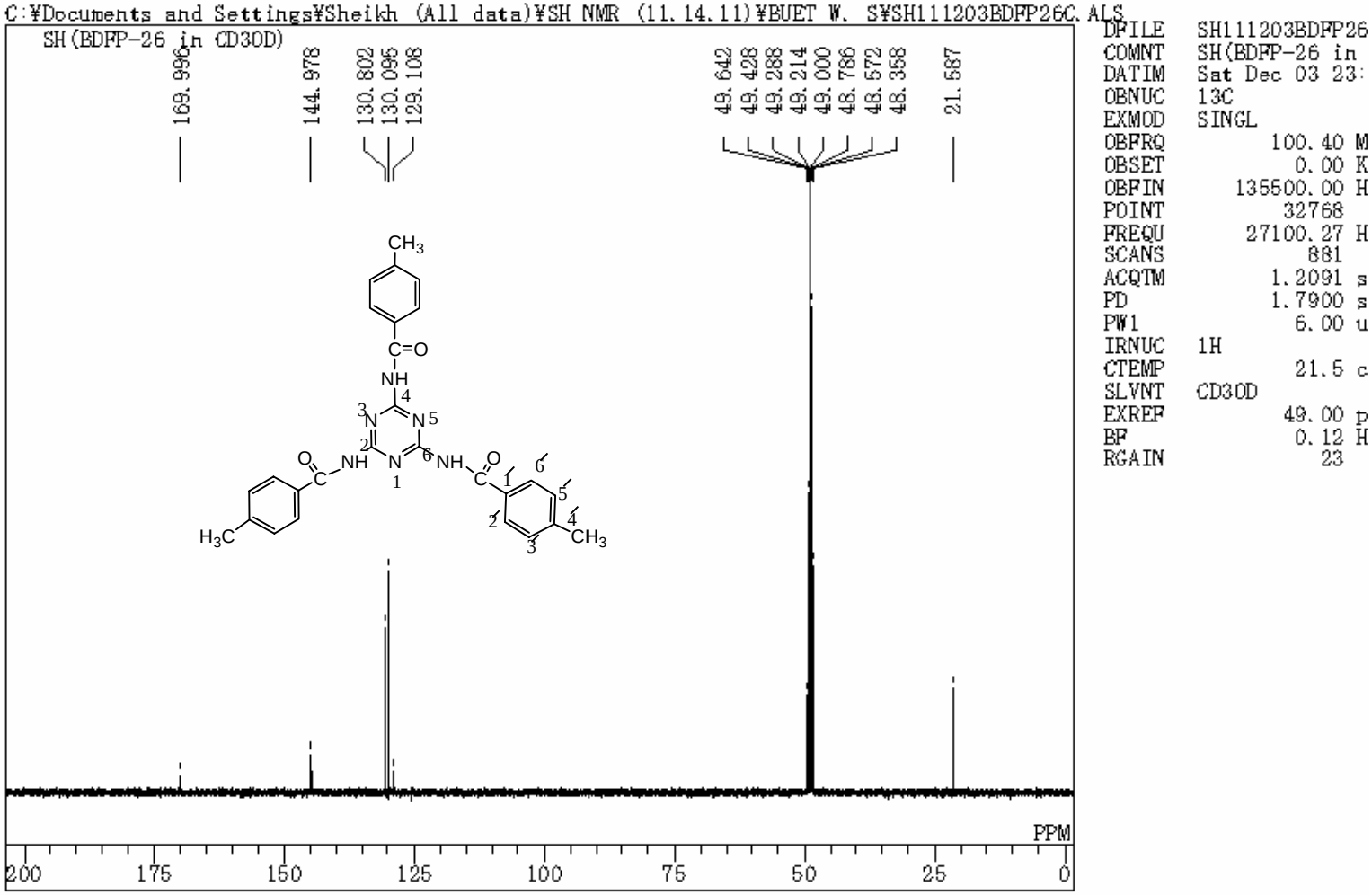


Fig. 7(b): ^{13}C NMR spectrum of the compound **13**

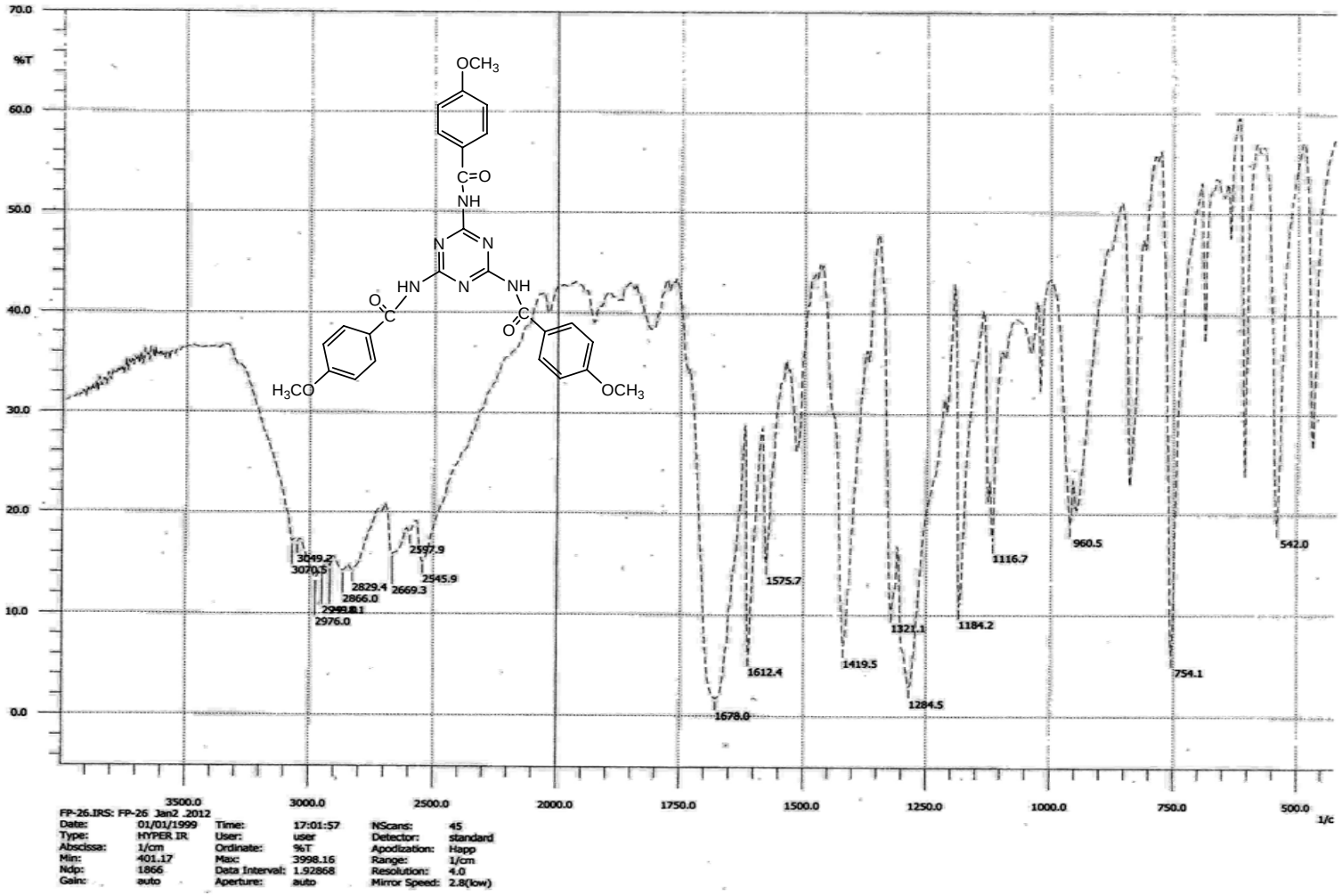
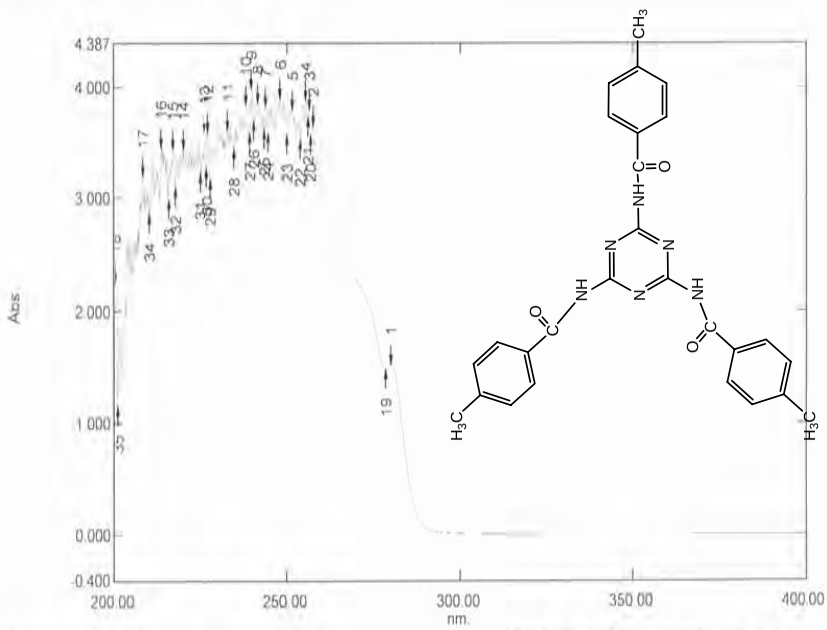


Fig. 7(c): IR spectrum of the compound **13**

Spectrum Point Pick Report

03/14/2012 02:43:42 PM

Data Set: FP-26.spc - RawData



Measurement Properties	
Wavelength Range (nm.)	200.00 to 400.00
Scan Speed	Fast
Sampling Interval	0.1
Auto Sampling Interval	Disabled
Scan Mode	Single

Instrument Properties	
Instrument Type	UV-1800 Series
Measuring Mode	Absorbance
Slit Width	1.0 nm
Light Source Change Wavelength	340.8 nm
S/R Exchange	Normal

Attachment Properties	
Attachment	None

Sample Preparation Properties	
Weight	
Volume	
Dilution	
Path Length	
Additional Information	

No.	Wavelength	Absorbance	Description
1	239.80	3.988	
2	248.10	3.902	
3	255.30	3.894	
4	280.30	1.517	
5			

Fig. 7(d) : UV spectrum of the compound **13**

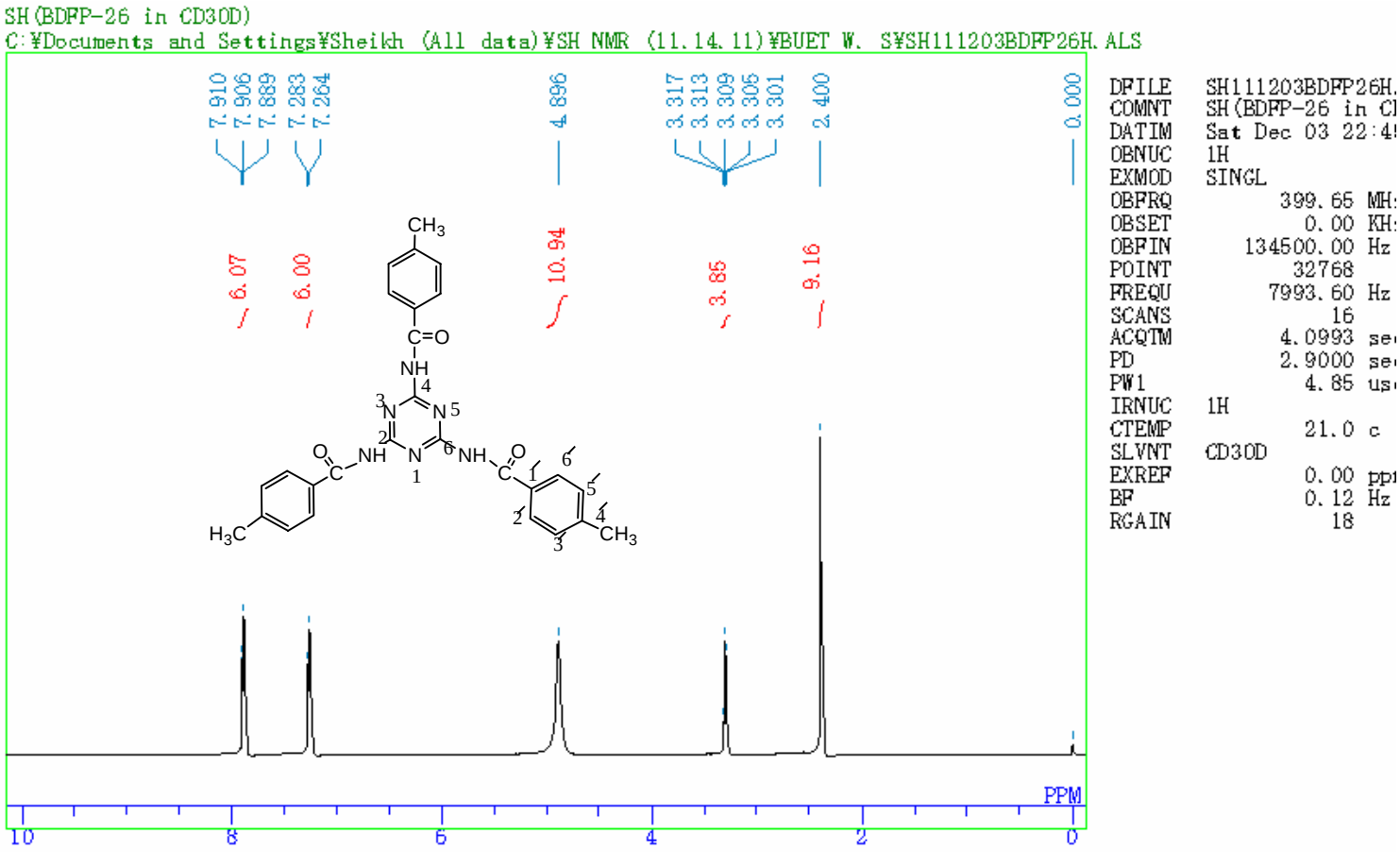


Fig. 8(a): ^{1}H NMR spectrum of the compound **14**

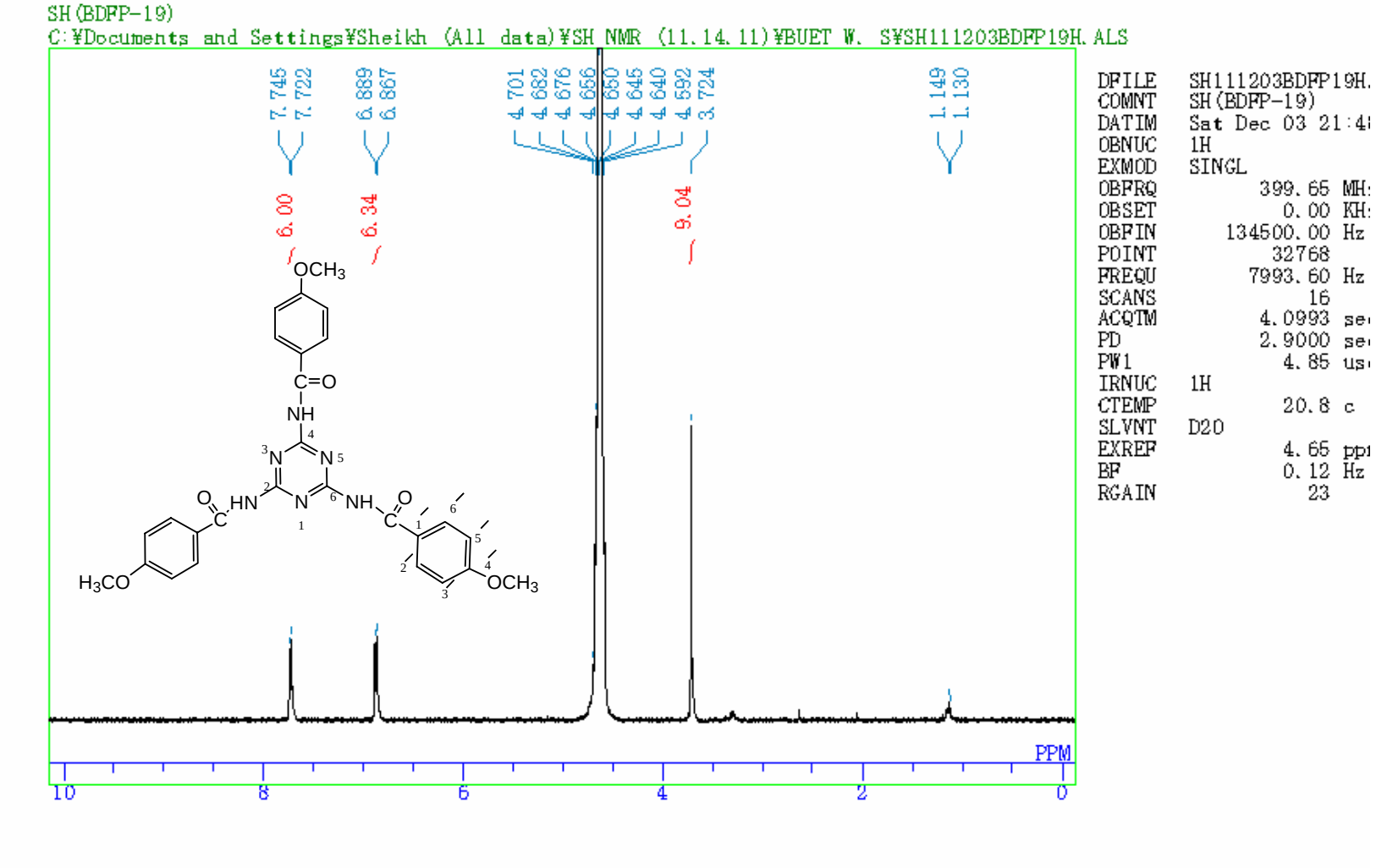


Fig. 9(a): ^{1}H NMR spectrum of the compound **15**

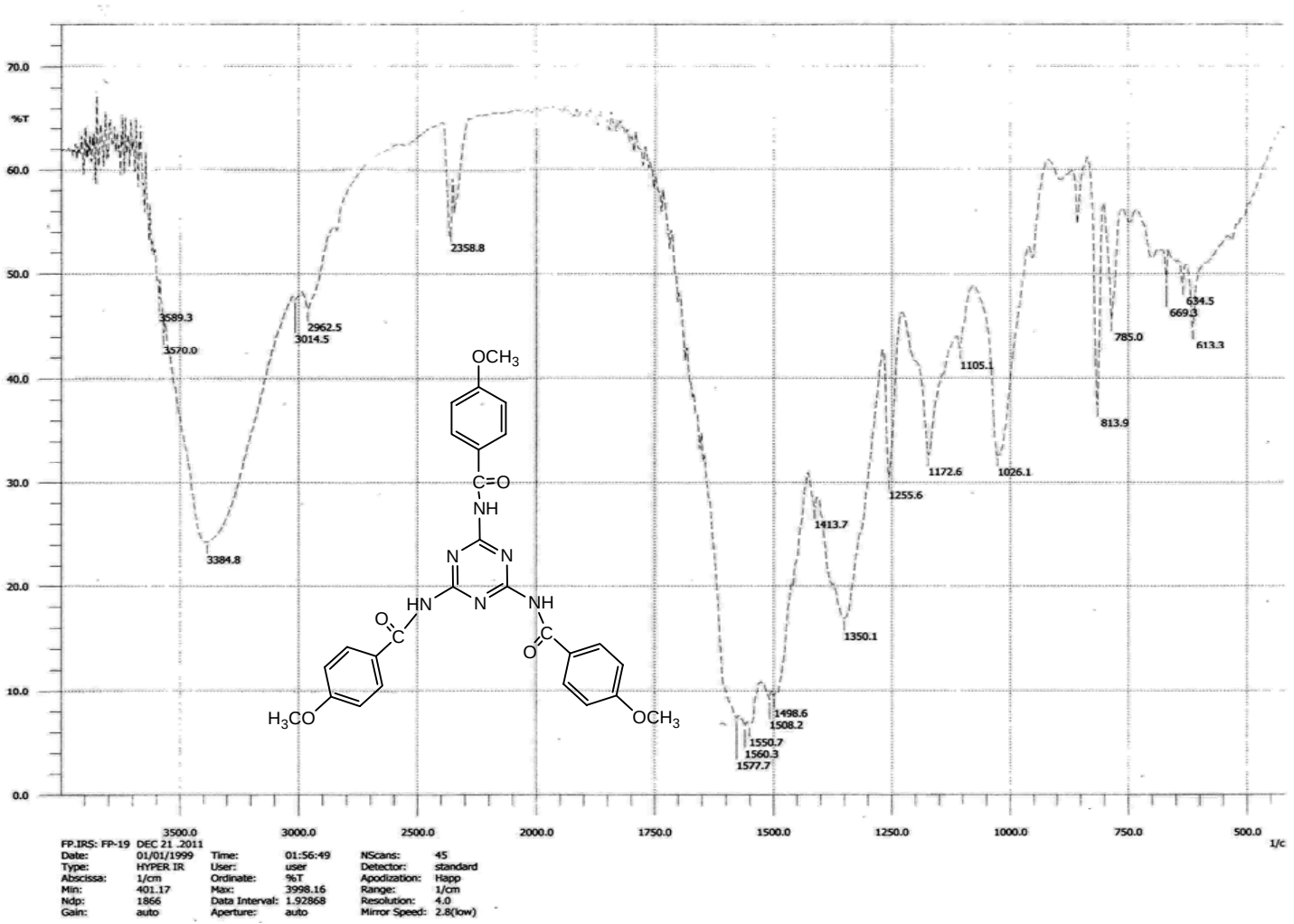


Fig. 9(b): IR spectrum of the compound **15**

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Conclusion

- In this thesis, we have synthesized a series of highly functionalized dendrimers from the neat reaction of commercially available melamine (2,4,6–triamino–1,3,5–triazine) with different acylchlorides.

- Secondly, we have described another convenient method for synthesis of metallodendrimer from the neat reaction of melamine, acylchloride and metal chlorides.

- Moreover, another method was demonstrated using melamine, acylchloride and solvent to synthesis dendrimer.

- The most important features of the synthesis were that, readily available inexpensive material was used under relatively mild conditions and relatively good yields.

- No toxic and hazardous compounds were produced by this synthesis. A variety of functional groups can be introduced by this procedure.

- Finally, EDX was taken for the metallodendrimers (**11,12,13,14**) and SEM was taken for most of the dendrimers to know the surface morphology and particle size.

- Therefore, this methodology could be utilized to synthesize the biologically important derivatives and will be attractive to both organic and medicinal chemists.

- We are currently investigating the application of these compounds as catalytic agents.

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