Component-9

Importance of Green Chemistry in the Synthesis of Nanomaterials, Supramolecules and Heterocyclic Compounds through Metal Mediated Reactions:

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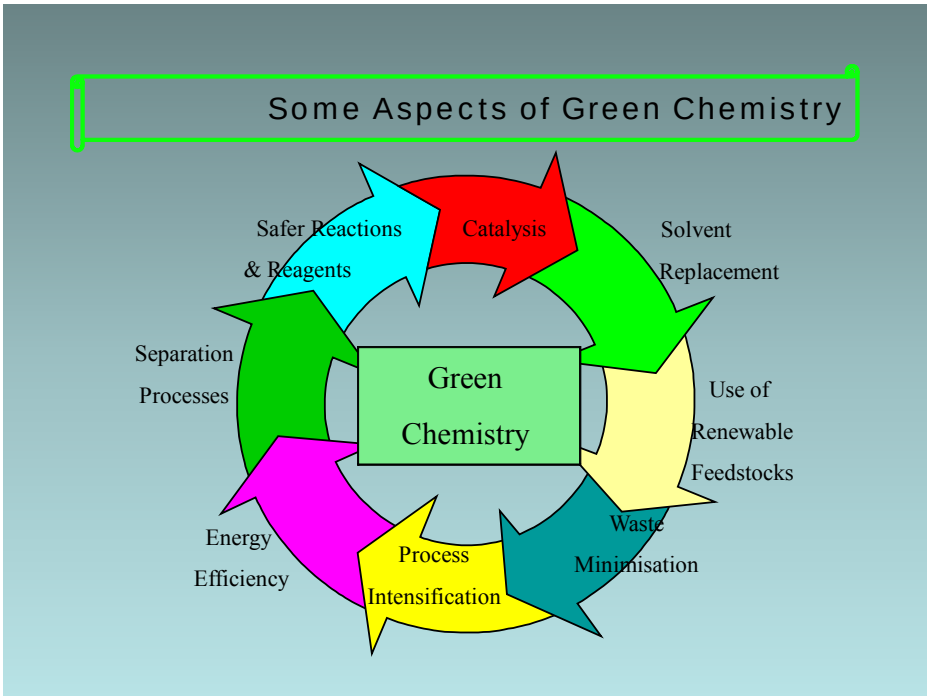
CHAPTER 1
INTRODUCTION

Green chemistry incorporates a new approach to the synthesis, processing and application of chemical substances in such a manner as to reduce threats to health and the environment. This new approach is also known as:

- Environmentally benign chemistry
- Clean chemistry
- Atom economy
- Benign-by-design chemistry

The beginning of green chemistry is frequently considered as a response to the need to reduce the damage of the environment by man-made materials and the processes used to produce them. A quick view of green chemistry issues in the past decade demonstrates many methodologies that protect human health and the environment in an economically beneficial manner. This project presents selected examples of the implementation of green chemistry principles in everyday life, in industry, the laboratory and in education.

The first principle describes the basic idea of green chemistry - protecting the environment from pollution. The remaining principles are focused on such issues as atom economy, toxicity, solvent and other media using consumption of energy, application of raw materials from renewable sources and degradation of chemical products to simple, nontoxic substances that are friendly for the environment. So, it is the top priority program of chemical community in the world to overcome these ill effects of chemical reactions and make this world a safer and cleaner place for living.



During the last decade our group has been very actively engaged in redesigning conventional procedures as well as developing new and efficient green methodologies for many useful chemical transformations. Our main focus is on the use of safer chemicals and avoidance of toxic organic solvents and catalysis.

Our group has synthesized heterocyclic compounds such as isoindolinones, isoquinolinones, benzofurans, indoles and uracil derivatives through palladium catalyst reactions in a mild and

facile condition. Now it is planned considering green chemistry to synthesize supramolecules and hetereocyclic compounds of industrial and biological importance.

Dendrimers are highly branched, globular, multivalent, monodisperse molecules with synthetic versatility and many possible applications ranging from catalysis to electronics and drug delivery. 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]

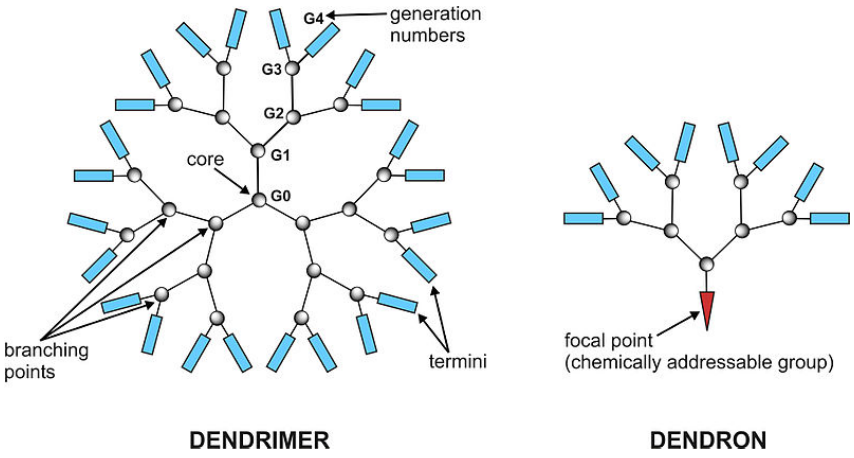


Figure 1: Dendrimer and Dendron

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,[4] R.G. Denkewalter at Allied Corporation in 1981,[5,6] Donald Tomalia at Dow Chemical in 1983[7] and in 1985,[8.9] and by George Newkome in 1985.[10] In 1990 a convergent synthetic approach was introduced by Jean Fréchet.[11] Dendrimer popularity then greatly increased, resulting in more than 5,000 scientific papers and patents by the year 2005.

Divergent Methods:

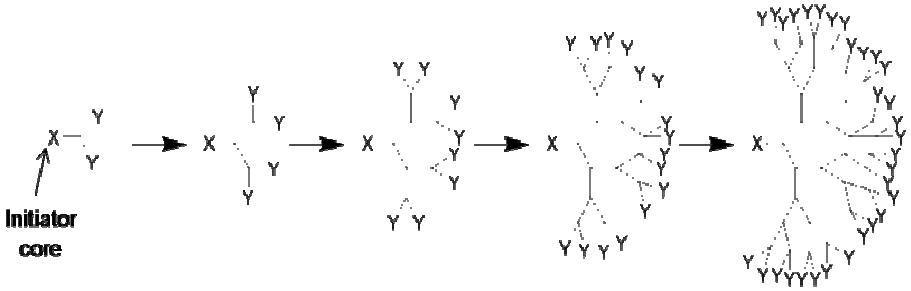


Figure 2**:** Schematic of divergent synthesis of dendrimers

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.[12]

Convergent Methods:

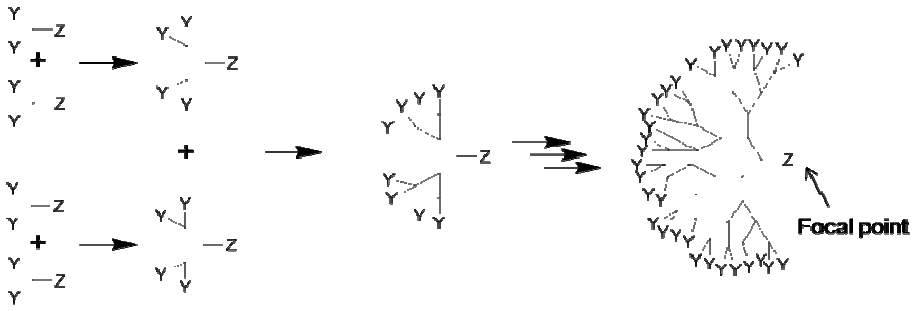
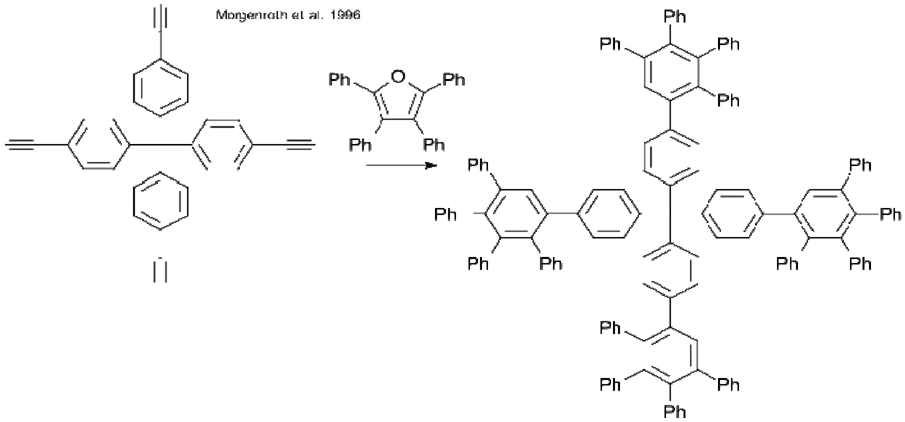


Figure 3: Schematic of convergent synthesis of dendrimers

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.[12]

Dendrimers have been prepared via click chemistry, employing Diels-Alder reactions,[13] thiol-ene reactions [14] and azide-alkyne reactions.[15,16,17] An example is the synthesis of certain polyphenylene dendrimers can be seen in figure 6.[18]

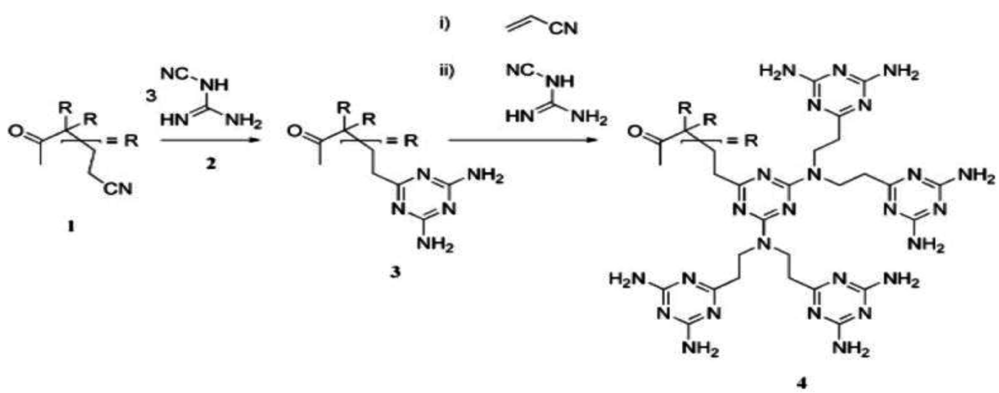


Scheme 1: Dendrimer DA reaction Mullen 1996

Some Synthetic Routes to Triazine Dendrimers:

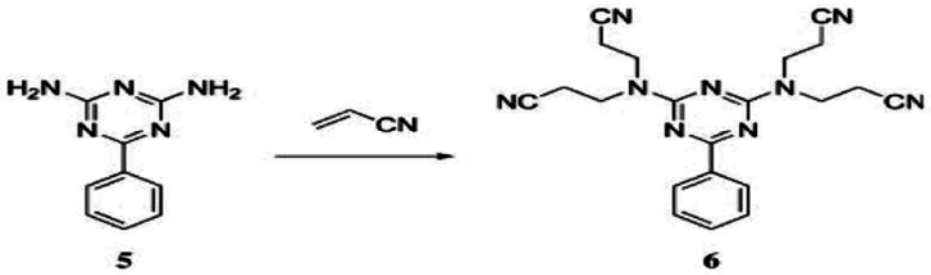
Much of the early work in the area focused on the optimization of routes for the synthesis of these species using either cycloaddition reactions or triazine substitution reactions.

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,[19] one of which was reviewed in a separate account in 1995 (Scheme: 6).[20] 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.[21] 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,[22] 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.[23]



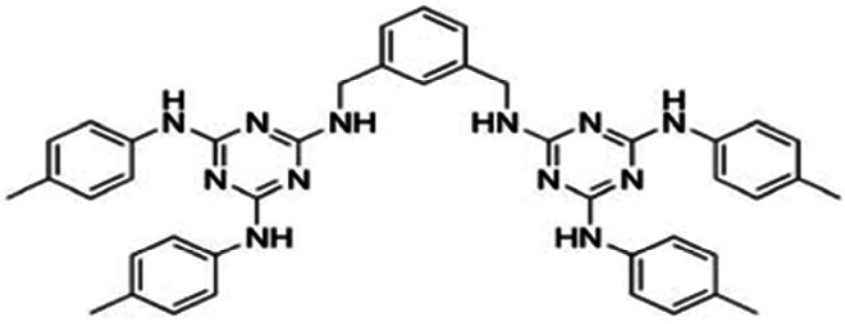
Scheme 2: Initial efforts to prepare triazine-based dendrimers employed cycloaddition methods.

A method resulting in compound **6**, with features strikingly similar to that of Vögtle's, was described in a patent by Niederhauser[24] 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.[25] 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 3 : Niederhauser's route to tetracyanoethyl benzo guanamine.

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(methylami-no)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).[26]



Scheme 4: Dendritic molecule designed for use as a chelating agent for Gd in MRI applications.

CHAPTER 2
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.[27] 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.[28]

In 1998, an early report described the use of triazine-based dendrimers as potential light-harvesting antennae.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. In 1992, Wyeth-Ayerst initiated a program to identify novel inhibitors of the human respiratory syncytial virus (RSV).

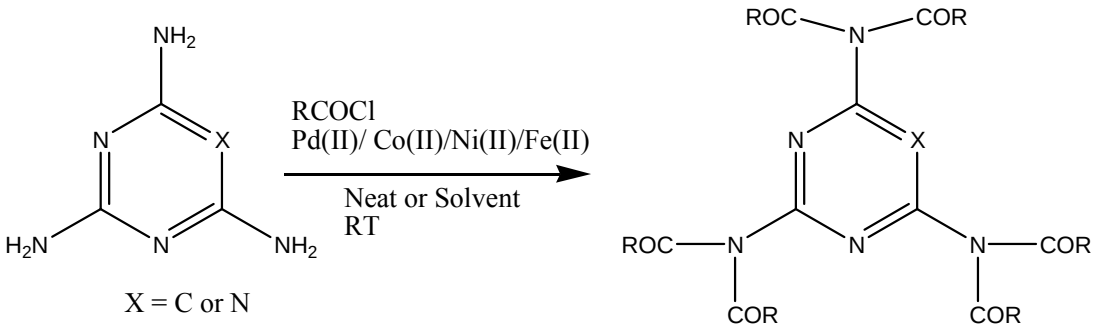
Promising triazine-based antibiotics have been developed by their examination as part of a dendrimer bound to a polystyrene resin.

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.

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. The accumulation of these data and other animal studies suggests that dendrimers based on melamine have potential for a variety of biomedical applications.

CHAPTER 3
RESULTS AND DISCUSSION

Dendrimers are highly branched, globular, multivalent, monodisperse molecules with synthetic versatility and have many possible applications ranging from catalysis to electronics and drug delivery. Due to versatile applications it was planned to develop a convenient method for the synthesis of dendrimer molecules from the reaction of triazine and diazine with different acylchlorides at variable temperatures using catalytic and non-catalytic reaction. A convenient synthesis of a series of highly functionalized dendrimers from the coupling reaction of melamine (2, 4, 6–triamino–1, 3, 5–triazine) and 2, 4, 6-triamino pyrimidine with different acylchlorides by divergent method is reported. A metal mediated synthesis of metallodendrimers from the coupling reaction of melamine and 2, 4, 6 triamino pyrimidine with acylchlorides under mild conditions is also reported. All the synthesized compounds were characterized by using analytical data obtained from ^{1}H NMR, ^{13}C NMR, IR & UV. EDX & SEM were also taken for metal investigation and to know the surface morphology.



X = C or N

R = CH_3, C_6H_4Cl-*p*, $C_6H_4CH_3$-*p*

Scheme 5

Table 1: Synthesis of 2, 4, 6 –Tris(diarylamido)-1, 3, 5-triazine from melamine:

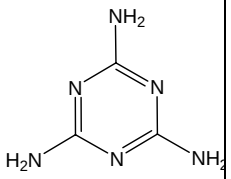
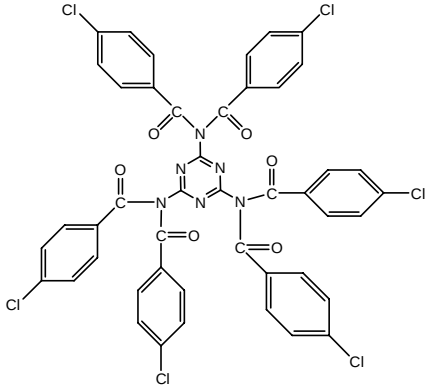
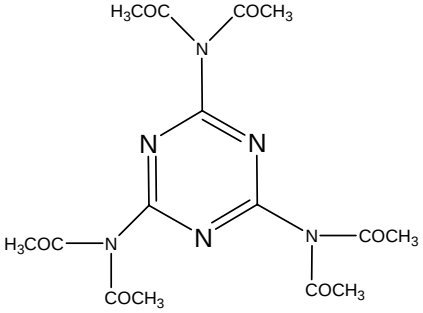
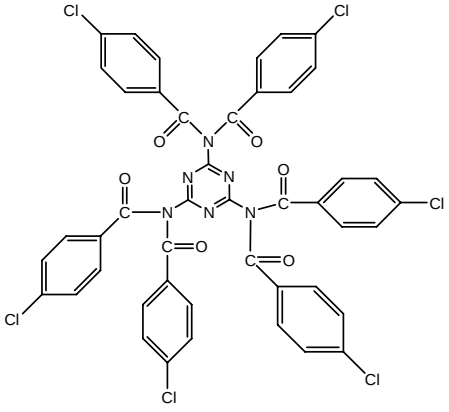
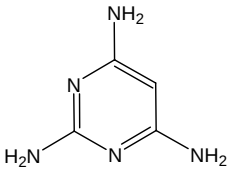
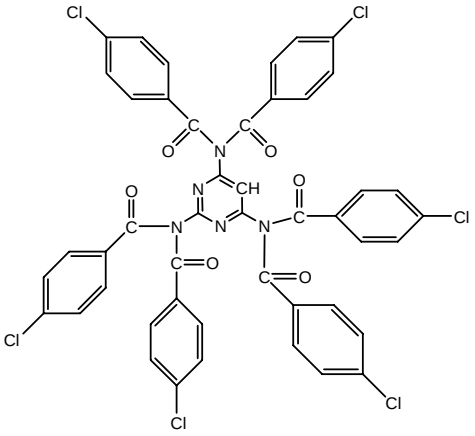
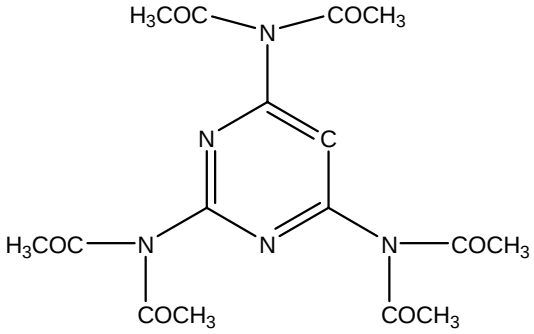
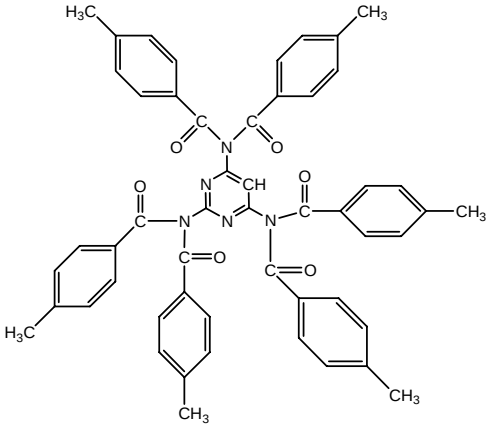
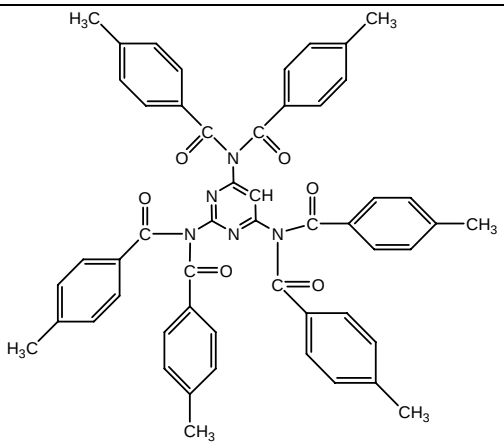
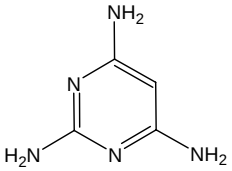
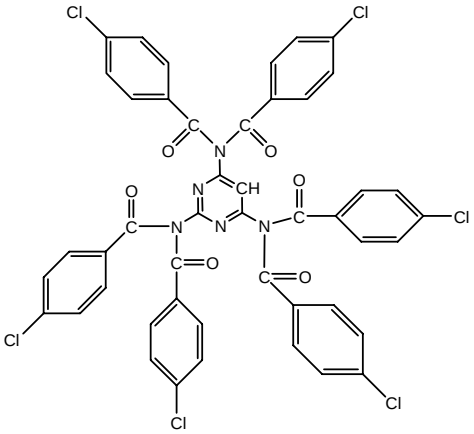
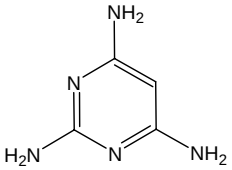
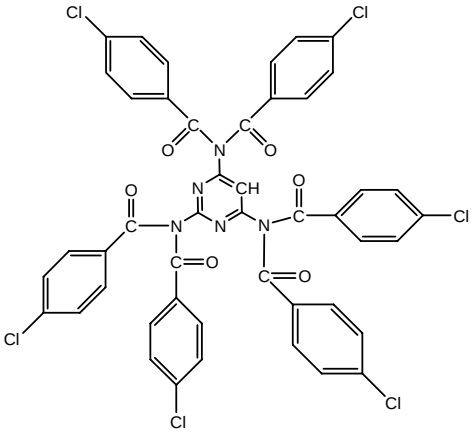
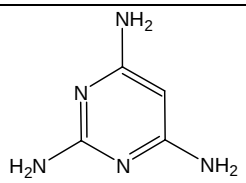
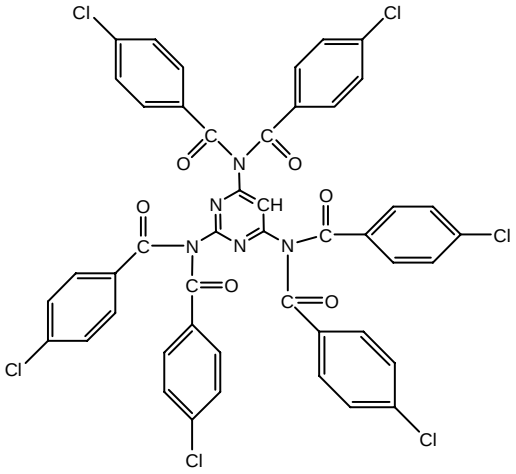
Entry	Substrate	Reagent and conditions	Product
1.	 1	p-ClC_6H_4COCl, $PdCl_2$, Ph_3P r. t, 6 hrs	 3
2.		CH_3COCl, $(Ph_3P)_2CoCl_2$, r. t., 6 hrs	 4
3.		*p*-ClC_6H_4COCl, $(Ph_3P)_2CoCl2$, r. t., 7 hrs	 5

Table 2: Synthesis of 2, 4, 6-tri(diarylamido)-1,3-diazine from 2, 4,6 triaminopyrimidine:

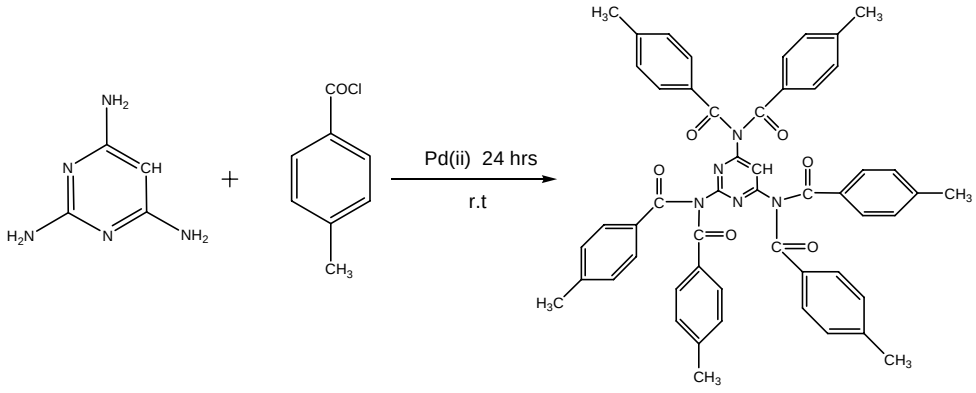
1	 **2**	*p*-ClC_6H_4COCl, $PdCl_2$, r. t., 6 hrs	 **6**
2		CH_3COCl, Mohr's salt, r. t., 6 hrs	 **7**
3		*p*-$CH_3C_6H_4COCl$ Solvent DMSO, r. t., 24 hrs	 **8**

3		*p*-$CH_3C_6H_4COCl$, $(Ph_3P)_2PdCl_2$, r. t., 6 hrs	 **9**
4	 2	*p*-ClC_6H_4COCl, CuI, r. t., Neat, 24 hrs	 10
5	 2	*p*-ClC_6H_4COCl, $[FeSO_4.(NH_4)_2SO_4.6H_2O]$, r. t., Neat, 24 hrs	 11

6	 2	*p*-ClC_6H_4COCl, ZnO , DMF, r. t., 24 hrs	 12

Experimental:
Melting points of the synthesized compounds were determined by open capillary tubes in melting point apparatus (Model BUCHI, B-540). IR spectra were recorded on a SHIMADZU FTIR spectrophotometer. NMR spectra were taken on BRUKER DPX–400 spectrophotometer using tetramethylsilane as an internal standard. SEM images were taken in a Scanning Electron Microscope (Model F-3400).

Synthesis of 2,4,6-Tris(di-4-methylbenzamido)-1,3-diazine[6] through Bis(triphenylphosphine)Palladium(II)chloride:
The mixture of 0.01 g pyrimidine, 0.43 ml *p*- toluoylchloride, 3 mol% bis(triphenylphosphine) Palladium(II)chloride catalyst in 2 ml DMSO was stirred at room temperature for about 24 hours in a 100 ml flask. The progress of the reaction was monitored by tlc. At the starting of the reaction, the mixture was turned into a clear solution and gradually it turned into white solid. After 24 hours the reaction was stopped by adding distilled water. Then the reaction mixture was extracted with $CHCl_3$. After the removal of solvent the product was crystallized by using ethanol and the desired compound was obtained.

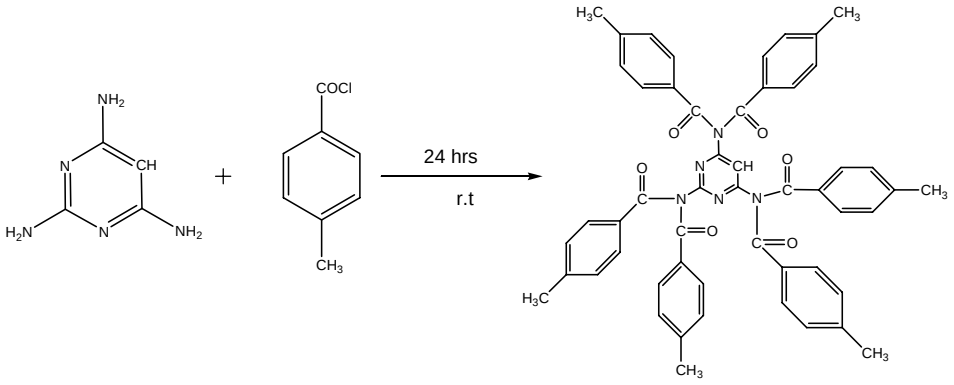


2 **6**

MF: $C_{52}H_{43}N_5O_6$,
MW: 833.38

Physical Properties: Yellowish white powdered solid, mp. 167 – 169 ^{o}C, odorless and 93% of yield.
IR (KBr): ν_{max} 3300, 3070.2, 2977.9, 1683.7, 1612.4, 1419.5, 756.0 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.4 (s,3H, Ar-CH_3), 7.37 (d, 2H, Ar-H, J= 8.8 Hz), 4.017 (d, 2H, Ar-H, J= 8.8Hz).
^{13}C NMR (125.77 MHz, $CDCl_3$): δ_C 171.92, 144.20, 129.80, 128.76, 126.15, 21.81.

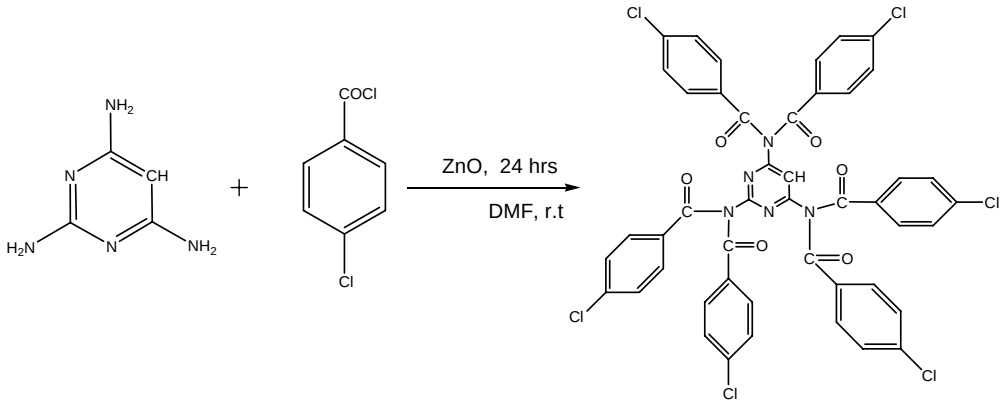
Synthesis of 2,4,6-Tris(di-4-methylbenzamido)-1,3-diazine [8] (without catalyst):
The mixture of 0.01 g pyrimidine, 0.43 ml *p*- toluoylchloride in 2 ml DMSO was stirred at room temperature for around 24 hours in a 100 ml round bottle flask. The progress of the reaction was monitored by tlc. At the starting of the reaction, the mixture was turned into a clear solution and gradually it turned into white solid. After 24 hours the reaction was stopped by adding distilled water. Then the reaction mixture was extracted with $CHCl_3$. After the removal of solvent the product was crystallized by using ethanol and the required compound was obtained.



2 **8**

MF: $C_{52}H_{43}N_5O_6$
MW: 833.38
Physical Properties: Yellowish white powdered solid, mp: more than 250 ^{o}C, odorless and 52 % yield.
IR (KBr): ν_{max} 3658.7, 3290.3, 2979.8, 1683.7, 1612.4, 1323.1, 756.0, 545.8 cm^{-1}
^{1}H NMR (400 MHz, DMSO): δ_H 3.25 (s, 3H, Ar-CH_3), 7.32 (d, 2H, Ar-H, J=7.60 Hz), 7.83(d, 2H, Ar-H, J=4.0Hz).
^{13}C NMR (125.77 MHz, DMSO): δ_C 167.29, 143.02, 127.99, 129.37, 129.17, 21.12.

Synthesis of 2,4,6-Tris(di-4-chlorobenzamido)-1,3-diazine [12] by Zinc oxide or Zinc(II) chloride:
The mixture of 0.01 g pyrimidine, 1 ml *p*-chlorobenzoylchloride, 8 mol% of $ZnO/ZnCl_2$ in 2 ml DMF was stirred at room temperature for around 24 hours in a 100 ml round bottle flask. The desired compound was obtained after usual workup and crystallization from ethyl acetate.

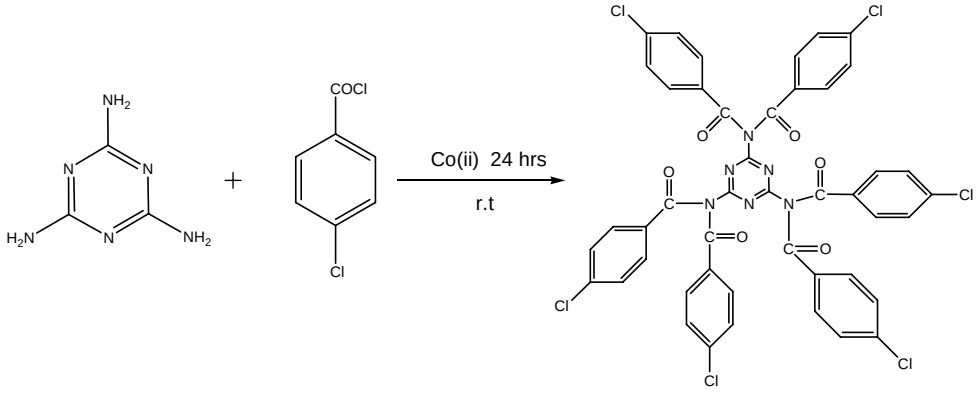


2 **12**

MF: $C_{46}H_{25}N_5O_6Cl_6$
MW: 961.24
Physical properties: White crystalline needle shaped solid, mp: 226-228 ^oC, odorless and 80 % of yield
IR (KBr): ν_{max} 3645.65, 3095.5, 1685.7, 1652.9, 1593.1, 1095.5, 761.8 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.44 (s, C-5, py),

Synthesis of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine [5]by bis (triphenylphosphine Cobalt(II)chloride:

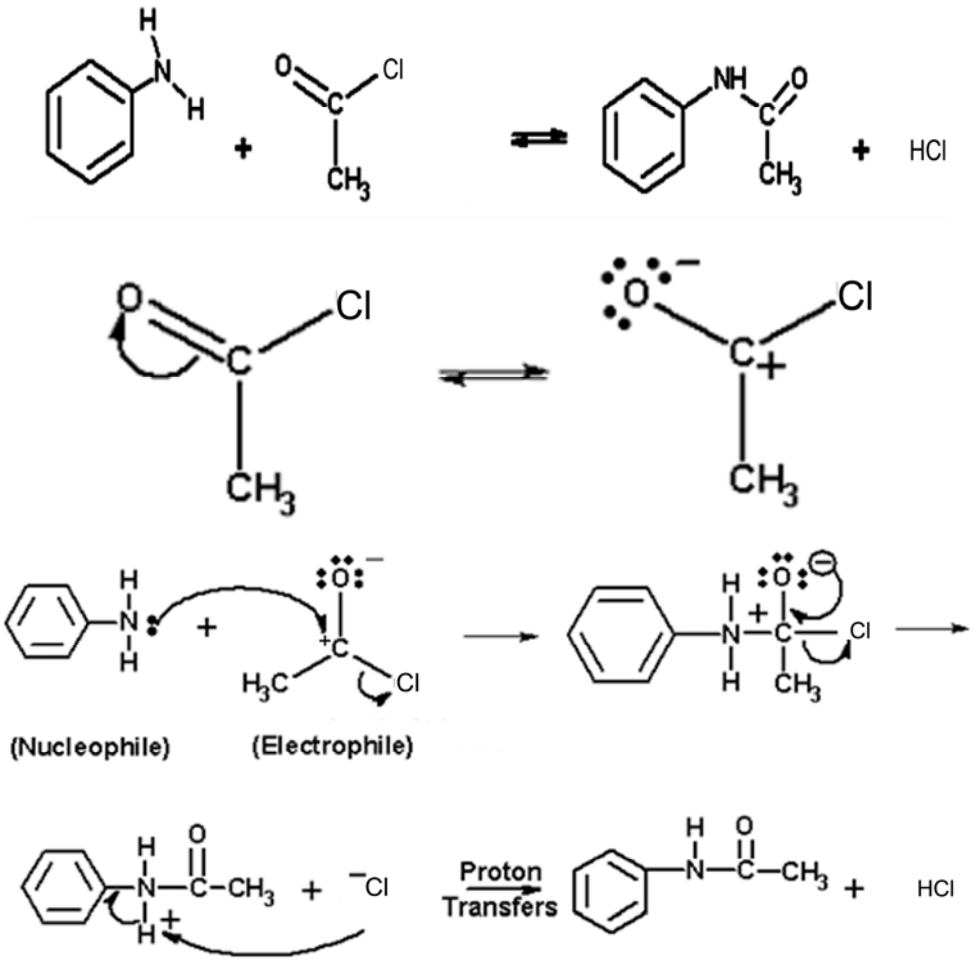
The mixture of 0.01g malamine, 2 ml *p*-chlorobenzoylchloride and 3 mol% of bis (triphenylphosphine) Cobalt(II)chloride catalyst was stirred at room temperature for around 24 hours in a 100 ml round bottle flask. After usual workup and crystallization by using ethyl acetate the desired compound was obtained.



1 **5**

MF: $C_{45}H_{24}N_6O_6Cl_6$
MW: 957.23
Physical properties: White crystalline solid, mp: 176-178 ^oC, odorless and 85 % of yield
IR (KBr): ν_{max} 3649.1, 3095.5, 1683.7, 1593.1, 1323.1, 1093.6, 761.8 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46 (d, 2H, Ar-H, J=8.0 Hz), 6.04 (d, 2H, Ar-H, J=8.0 Hz).
^{13}C NMR (125.77 MHz, $CDCl_3$): δ_C 161.30, 141.42, 131.87, 131.55, 129.36, 128.87, 127.06.
Mechanism:

Nucleophilic Acyl Substitution (addition / elimination) reaction:



Scanning Electron Microscopic (SEM) analysis:

Scanning Electron Microscopic (SEM) analysis is employed to get a clear insight about the surface morphology. SEM is known to the best choice because of its potential in precise analysis of a solid surface. 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 15.0 KV with magnifications ranging from 400-5000 with non-destructive methods.

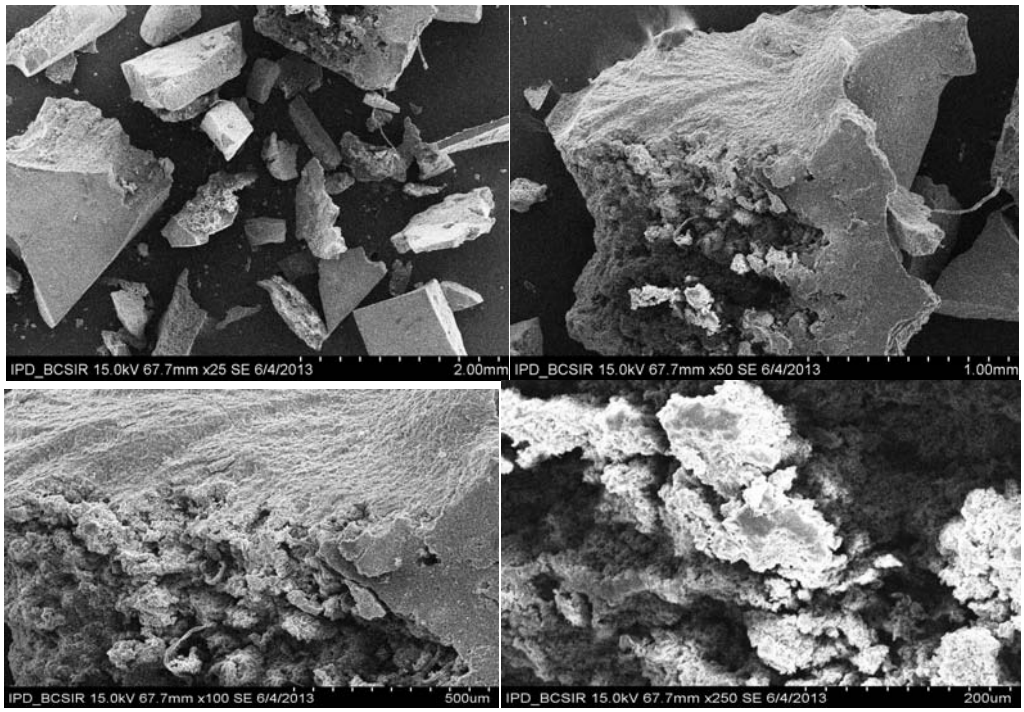


Fig. 1: SEM micrographs of 2,4,6-Tris(di-4-methylbenzamido)-1,5-diazine without catalyst

Figure 1 shows the SEM images of 2, 4, 6-Tris(di-4-methylbenzamido)-1,5-diazine without catalyst. 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.

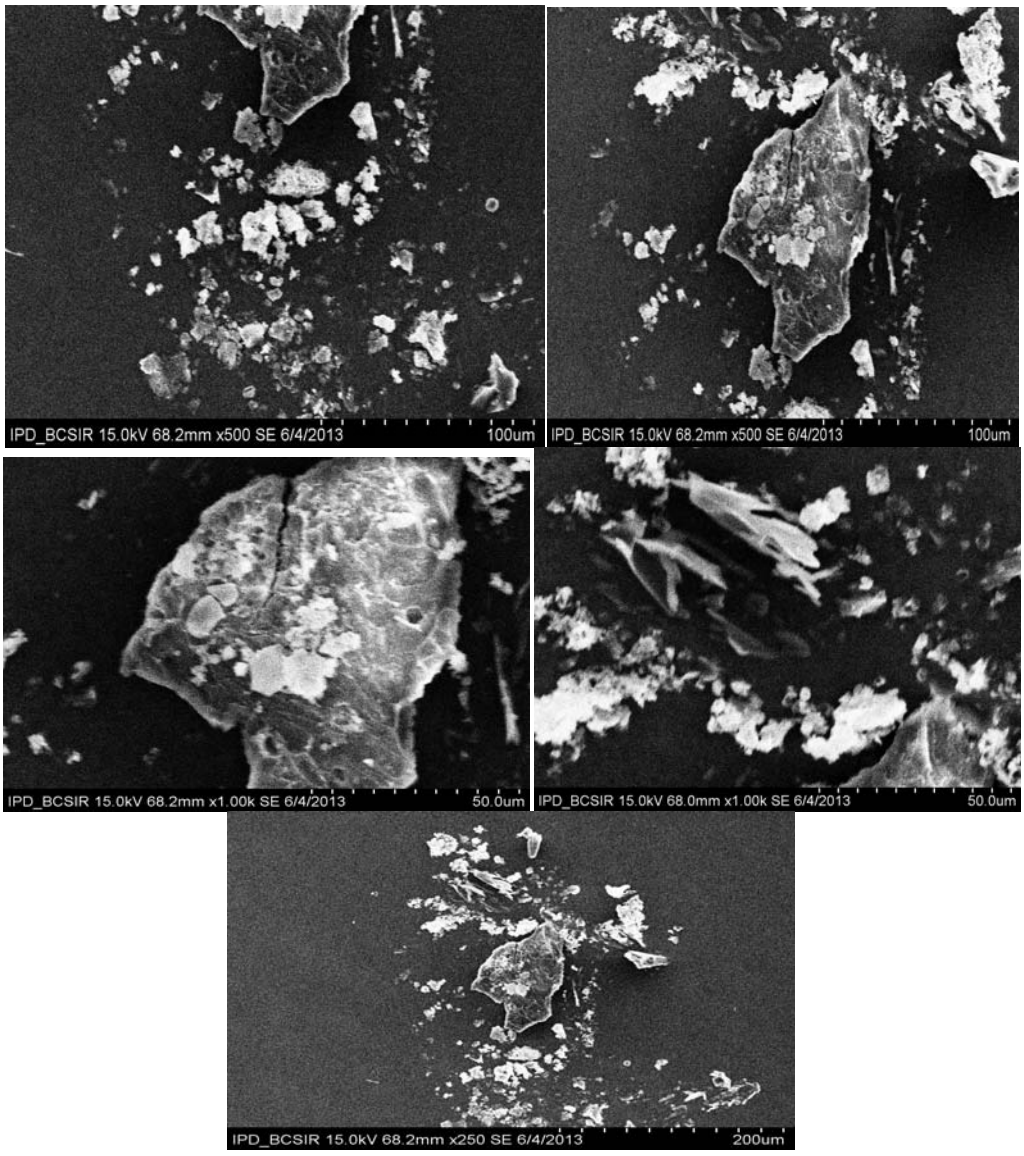


Fig. 2: SEM micrographs of 2, 4, 6-Tris(di-4-methylbenzamido)-1,5-diazine prepared by bis(triphenylphosphine)Palladium(II)chloride

Figure 2 shows SEM images for the product of 2,4,6-Tris(di-4-methylbenzamido)-1,5-diazine prepared by bis(triphenylphosphine)Palladium(II)chloride. These images show that 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. Pd-metal was involved with this structure.

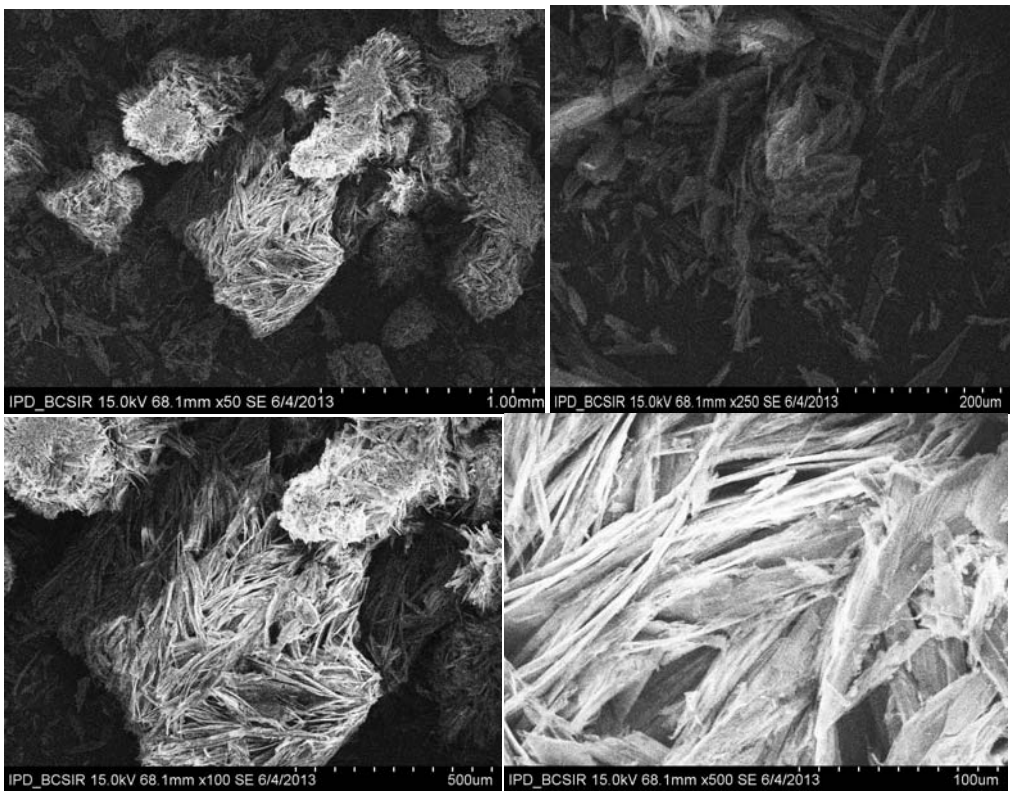


Fig.3 SEM micrographs of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine prepared by Copper(I)iodide.

Figure 3 shows the SEM image of product 2, 4, 6-Tris(di-4-chlorobenzamido)-1,3,5-triazine prepared by Copper(I)iodide. These images show the fibrous morphology. In this case, surface of the particles are fibrous 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.

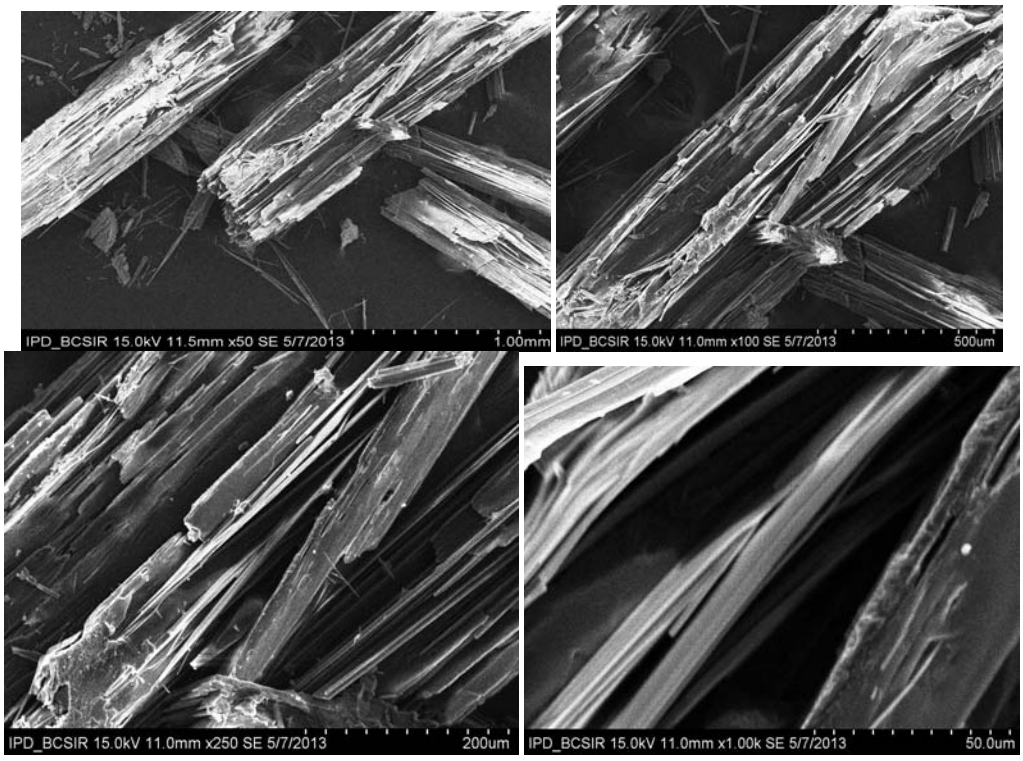


Fig.4 : SEM micrographs of 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine by Zinc oxide or Zinc(II) chloride:

Figure 4 shows the SEM images of 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine by Zinc oxide or Zinc(II) chloride. From these images it can be seen that the particles have fiber like shape. Closed viewing of the high magnification SEM image 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. These particles already exceed the nanometer level. In this structure Zn-metal was involved.

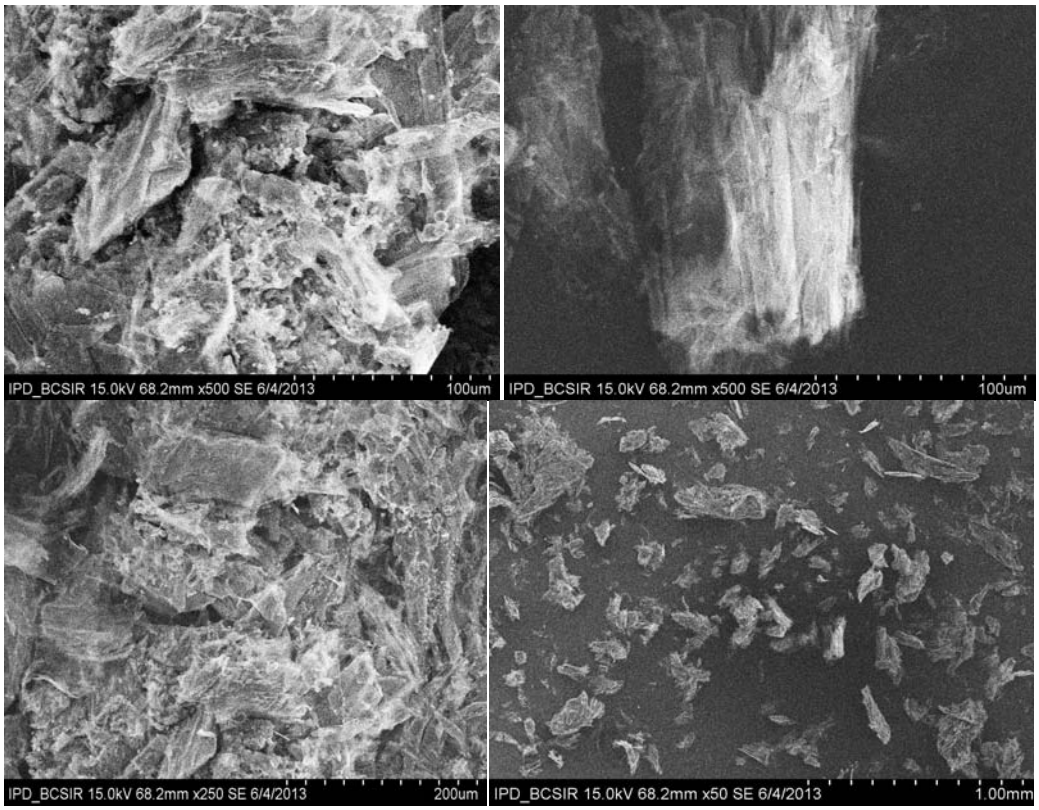


Fig. 5: SEM micrographs of 2, 4, 6-Tris (di-4-chlorobenzamido)-1,3-diazine prepared by Mohr's salt.

Figure 5 shows the SEM image for the product 2, 4, 6-Tris(di-4-chlorobenzamido)-1,3-diazine prepared by Mohr's salt. From these images it can be seen that the particles appeared to be granular particle and well distributed. The agglomerated structure was constructed by granular particle with a size of about 1 μm. Fe- metal was involved with this structure.

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 (Pd^{2+}, Zn^{2+}, Cu^{2+} and Fe^{2+}). Moreover, particles size investigation by SEM indicated that all synthesized molecules were supramolecules. So, from morphological analysis it can be concluded that, metal ion (Zn^{2+}, Cu^{2+}) from $ZnCl_2$ or CuI initially coordinated onto the surface of non-metallodendrimers, resulting fibre particles and metal ion (Pd^{2+}, Fe^{2+}) from $(Ph_3P)_2PdCl_2$ and Mohr's salt resulting granular particle.

CHAPTER 4
CONCLUSION

- In this project, 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) and 2, 4,6- triaminopyrimidine with different acylchlorides.

- Secondly, we have described another convenient method for synthesis of metallodendrimer from the neat reaction of melamine and 2, 4, 6- triaminopyrimidine with acylchloride and metal catalyst.

- Moreover, another method was demonstrated using melamine and 2, 4, 6-triaminopyrimidine with 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, 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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