PALLADIUM MEDIATED SYNTHESIS OF METALLO-DENDRIMERS BASED ON DIAZINE AND TRIAZINE

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Abstract

In the light of past and recent developments, there is precedence for the development of new bioorganometallic metallodendrimers. Dendrimers and Metallodendrimers 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 palladium mediated metallodendrimer molecules based on Triazine and Diazine.

Firstly, a convenient method for the synthesis of metallodendrimer compounds 8-17 was developed from the reaction of triazine (melamine) and diazine (pyrimidine) with different aroylchlorides 3-7 in the presence of (Ph₃P)₂PdCl₂ at room temperature as shown in Scheme 1.

Scheme 1

1, 8-12, X=N; 2, 13-17, X=CH; 3, 8, 13, R= C₆H₄CH₃(p); 4, 9, 14, R= C₆H₄Cl(p); 5, 10, 15, R= C₆H₅; 6, 11, 16, R= C₆H₄OCH₃(p); 7, 12, 17, R= C₆H₄NO₂(p)

All the synthesized compounds were characterized by analytical data obtained from IR spectra, ¹H NMR, ¹³C NMR and Mass spectrophotometry to establish the structure. The SEM was taken for the analysis of surface morphology of the synthesized compounds. EDX was also taken for metal investigation as well as elemental analysis. The compounds were found having a homogeneous as well as non-homogeneous morphology with the particle size range from 100 µm to 500 nm.
LIST OF ABBREVIATIONS

Ac    acetyl
aq.   Aqueous
b.p.  Boiling point
br    broad
d     doublet
dec.  Decomposition
DMF   N, N-dimethyl formamide
equiv. Equivalent
Et    ethyl
Et₂O  diethyl ether
EDX   Energy Dispersive X-ray spectroscopy
EtOAc ethyl acetate
h     hour
hv    light
Hz    hertz
IR    infrared (spectrum)
J     coupling constant
m     multiplet or medium
M     mass or metal
min   minutes
mmol  mili mole
mol   mole
mol % mole percent
m. p. Melting point
NMR   nuclear magnetic resonance
OAc   acetate
Ph    phenyl
PhH  benzene
ppm  parts per million
quin.  Quintet
r.t.  Room temperature
SEM  Scanning Electron Microscope
s  singlet/ strong/ second
t  triplet
T  temperature
TLC  thin layer chromatography
TMS  trimethylsilane
UV  ultra-violet
W  weak
Δ  heat/ reflux
δ_H/ δ_c  chemical shift
λ_max  ultraviolet absorption in nm
ν_max  infrared absorption in cm⁻¹
Introduction:

1.1 Dendrimers: an overview:

Dendrimers (from the Greek, dendron: tree, branch, meros: part) are defined as highly branched monodispersed three dimensional macromolecules obtained by an iterative sequence of reaction steps. Large dendrimers tend to adopt a globular shape. Chemists' attraction towards dendrimers is attributed to the precisely defined molecular and almost perfect structures they exhibit when compared to conventional polymers. In addition, dendrimers and linear polymers present considerable differences in their physical properties. For example, dendrimers have demonstrated a different solubility pattern when compared with their linear counter parts.

Convention a linear polymers are two dimensional, randomly coiled chains typically containing two reactive chain ends. Dendrimers feature a large number of functional groups at the periphery and internal cavities that can host guests of different sizes.

Dendritic and metallodendritic polymers are unique “ball shaped” polymeric substance, whose molecular architecture consists of an initial core and repeating units with branching and terminal groups. Each repeating units bears a branching point to which two or several new repeating units are attached. Owing to their unique properties such as solubility in water, well defined molecular architecture, and spherical shape, dendrimers and metallodendrimers have found numerous applications in chemical, physical and biological processes.

Recently, metallodendrimers have been widely investigated in different fields, such as molecular light harvesting, catalysts, liquid crystals, molecular encapsulation, and drug delivery. In the case of poly(amidoamine) (PAMAM) dendrimers the initiator core is an ammonia or ethylenediamine (EDA) molecule. Ammonia has three and EDA has four possible binding sites for amidoamine repeating units. The primary amino groups are on the surface of molecule two new branches may be attached to each of them.

Metallodendrimer compounds have been prepared via click chemistry, employing thiolene reactions and azide-alkyne reactions. Compounds containing S-triazine and dendrimers based on triazine have received a remarkable attention owing to their potential applications and have shown molecular recognition and self-assembly properties. Dendrimers are a class of regularly branched mono-dispersed polymer having 5-10 nanometers in diameter with unique structural and
topological features whose properties are attracting considerable interest from both scientists and technologists. Dendrimers are just in between molecular chemistry and polymer chemistry. They pertain to the molecular chemistry world by virtue of their step by step controlled synthesis, and they pertain to the polymer world because of their repetitive structure made of monomers. Unlike classical polymers, dendrimers have a high degree of molecular uniformity, narrow molecular weight distribution, specific size and shape characteristics, and a highly-functionalized terminal surface. Dendrimer oligonucleotides are representative of a new segment of polymer science, often been referred to as the “Polymers of the 21st century”.

Dendrimers are precisely defined, synthetic nonmaterial’s that are approximately 5-10 nanometers in diameter. Dendritic polymers or dendrimers provide a route to create very well-defined nanostructures suitable for drug solubilization applications, delivery of DNA and oligonucleotide, targeting drug at specific receptor site, and ability to act as carrier for the development of drug delivery system.

Dendrimers are core-shell nanostructures with precise architecture and low polydispersity, which are synthesized in a layer-by-layer fashion (expressed in “generations”) around a core unit, resulting in high level of control over size, branching points and surface functionality. The ability to tailor dendrimer properties to therapeutic needs makes them ideal carriers for small molecule drugs and biomolecules. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral, transdermal, pulmonary and ocular.

Metallodendrimers, i.e. dendrimers that contain metal atoms or cations, constitute a special class of dendrimer whose redox, catalytic, ion recognition, sensor, and light harvesting properties are well documented. Other advantages of these dendritic catalysts have been demonstrated and are described in the review by ven Leeuwen. Dendritic encapsulation of functional molecules allows for the isolation of the active site, a structure that mimics that of active sites in biomaterials. 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. The active catalytic centre in a metallodendrimer can be situated in three different areas: (a) metal atom as the dendrimer core, (b) metal atoms in the dendrimer branches
(c) metal atoms in the periphery. Diazine and Triazine core is more electrons withdrawing and possesses a larger nucleophilic susceptibility than the benzene core. These cores might also have interesting physical properties. The symmetry and electronic properties of the diazine core and the triazine core have made them valuable molecular skeleton for exploring a wide range of interesting applications such as antitumor agent and catalytic supports. But the facile and efficient methods for the synthesis of metallodendrimer still remain scarce.

1.2 Historical perspective:

As depicted in the book of Newkome, Moorefield and Vogtle, Dendrimers and Dendron’s: Concepts, Syntheses, Applications, the development of the dendrimer Chemistry can be broken down into three different periods. The first can be defined as roughly from the late 1880's to the early 1940's. At that time it was believed that Branched structures lead to in soluble and intractable materials. However, means of separation as well as characterization were too primitive to lead to relevant conclusions. Nonetheless, Zincke and Friedel and Crafts (1885) were already speculating on Polymers adopting non-linear or branched connectivity. In 1922, Ingold and Nickolls reported the preparation of the branched "methanetetraacetic acid". This work is still considered as the earliest case of deliberately constructed dendritic structure.

The second period covers four decades, from the early 1940's to the late 1970's. This period is defined by the incredible amount of work generated to prepare branched structures. The main piece of work covering this subject is attributed to Flory who introduced an alternative approach to polymer synthesis in 1952. Macromolecules generated using this synthetic strategy, were anticipated to be highly branched, entanglement-free and non-crystalline, with broad molecular weight distributions. He reported the preparation of a highly branched polymer, employing an AB₂-type monomer, without "insoluble gel formation". The third period began in the late 1970's and still continues. However, much of the work in this area only began to build momentum in the mid-1980s. A chronology of the key developments in dendritic polymers is provided in the following table.
1.3 Synthetic Strategies:

The strictly controlled structure of ideal dendrimers results from the layered assembly of branch cells surrounding the core, which is attained through sequential reaction cycles. This can be achieved in two different ways, namely by divergent (core-first) or convergent (arm-first/core-last) methods.

The divergent approach begins with a multifunctional core onto which polyfunctional monomers of the ABn-type are added. Dendrimers result when the branching multiplicity (subscript n) of the monomer unit is at least 2. Following the addition of these small molecule building blocks, the

<table>
<thead>
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<th>Year</th>
<th>Type</th>
<th>Authors</th>
</tr>
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<tbody>
<tr>
<td>1978</td>
<td>Cascade growth and dendrimers</td>
<td>Vögtle&lt;sup&gt;39&lt;/sup&gt;</td>
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<tr>
<td>1982</td>
<td>Cascade growth and dendrimers</td>
<td>Maciejewski&lt;sup&gt;40&lt;/sup&gt;</td>
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<td>1983</td>
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<td>de Gennes&lt;sup&gt;41&lt;/sup&gt;</td>
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<td>Cascade growth and dendrimers</td>
<td>Tomalia, Newkome&lt;sup&gt;43&lt;/sup&gt;</td>
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<tr>
<td>1990</td>
<td>Cascade growth and dendrimers</td>
<td>Fréchet/Hawker, Miller/Neenan&lt;sup&gt;45&lt;/sup&gt;</td>
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<td>Random hyperbranched polymers</td>
<td>Odian/Tomalia&lt;sup&gt;46&lt;/sup&gt;</td>
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<td>Dendrigraft polymers</td>
<td>Fréchet/Hawker&lt;sup&gt;48&lt;/sup&gt;</td>
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<tr>
<td>1991</td>
<td>Dendrigraft polymers</td>
<td>Möller, Gauthier, Hedstrand/Ferritto, Tomalia&lt;sup&gt;51&lt;/sup&gt;</td>
</tr>
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subsequent layer can be added after deprotection of the end groups and another monomer condensation reaction. The structure resulting after the first addition cycle is known as a generation-1(G1) dendrimer. Further reaction cycles are employed to prepare dendrimers of the desired generation, size, or molecular weight.

The convergent approach uses monomers similar to the divergent strategy and provides branched molecules with the same characteristics and predictability; however, wedge like dendrons are first synthesized and subsequently anchored on a core to complete the dendritic structure. The number of dendrons that can be coupled with a core is governed by the core functionality. Convergent growth of the dendron occurs through selective protection of one of the functional groups followed by a condensation reaction, resulting in directional growth. The dendron unit is interesting in itself, and it has been investigated as its own entity, but deprotection and coupling with a multifunctional “anchor” core is required to complete the dendrimer structure.

Scheme 1.1 Synthesis of a G2 dendrimer by (a) divergent and (b) convergent strategies.

The divergent synthesis (Scheme 1.1a) begins with an unprotected trifunctional initiating core (Nc=3). The G0 core can be coupled with a partially protected monomer, BA2(P)2, having a branching multiplicity(Nb) of 2. The G1 dendrimer results after removal of the protecting group on the A functionality(-PA). Coupling of this substrate with the protected monomer yields what is referred to as a half-generation dendrimer(G1.5), and the G2 dendrimer is obtained upon deprotection. The convergent synthesis starts by coupling a partially protected monomer, B(P)A2, with a complementary protected monomer, BA2(P)2, to yield a dendron. Deprotection of the B
group(-PB) at the focal point of the dendron allows selective coupling with the G0 core(A3) to obtain the G1.5 dendrimer. Deprotection of the terminal a functionalities provides the G2 dendrimer.

1.4 General Characteristics:

A graphical comparison of the structure of dendrons, dendrimers, hyperbranched polymers, and dendrigraft polymers is provided in Figure 1.1.

![Figure 1.1 Structure of four types of dendritic polymers: (a) Dendron, (b) dendrimer, (c) hyperbranched polymer, and (d) dendrigraft polymer.](image)

Each color in Figure 1.1 represents the branching levels derived from building blocks introduced in successive generations, these being small molecules for dendrons, dendrimers, and hyperbranched polymers (Figure 1.1(a–c), and polymeric segments for the dendrigraft polymers (Figure 1.1d). The size, shape, and molecular weight of a dendrimer depend on the molecular weight and the branching multiplicity of the monomer, as well as its generation number. Molecular weights can range from the hundreds or thousands for low generations, to over $10^5$ g/mol for generations 10 and above the corresponding diameters of these structures ranges from ca.1 to above 10 nm. Different generations of dendrimers derived from a trifunctional core are compared in Scheme 1.2.

![Scheme 1.2 Dendrimer generations derived from a trifunctional core and a monomer with a branching multiplicity of 2](image)
The three-dimensional topology of dendrimers displays a transition from ellipsoidal to spherical for increasing generations.\textsuperscript{52} The onset of the morphogenesis is reliant on the core multiplicity and the synthetic strategy (divergent or convergent) used. Increased core multiplicity (Nc = 3 or 4 vs. Nc = 2) forces a shape change at least one generation earlier. The convergent method has a similar effect due to the more perfect structure (increased crowding) attained for a particular generation. The most significant transformations occur between generations 3 and 5, after which the dendritic species adopt either spheroidal or slightly ellipsoidal geometries. An increase in generation number also brings enhanced surface group congestion, until a maximum known as the dense packing state is reached. Beyond this point only a fraction of the end-groups can participate in the next cycle of monomer addition. Targeting a specific molecular weight and number of functional groups in dendrimer synthesis is relatively easy due to the uniform structure of the molecules, in as much as complete reactions are possible.

1.5 Common Structures:

1.5.1 Dendrimers Synthesized by a Divergent Strategy

The concept of branched macromolecules derived from repetitive reaction cycles of multifunctional small molecules was first introduced in 1978.\textsuperscript{53} Vögtle thus reported a cascade-type divergent synthesis for low molecular weight polypropyleneimine by the cyanoethylation of various amines cited in Reference \textsuperscript{53}, using acrylonitrile in glacial acetic acid at reflux for 24 h. Subsequent reduction of the cyanofunctionalities with cobalt(II) chloride hexahydrate and NaBH\textsubscript{4} in methanol converted the terminal cyanoethyl groups to primary propylamine functionalities, which were subjected to further cyanoethylation and reduction reactions to obtain the upper generation cascade polymers.

The yield of the cyanoethylation and reduction reactions in Vögtle” s work was less than ideal, varying from 76% for the zeroth generation to 35% for the G1 product. These low yields resulted in ill-defined structures and prevented the synthesis of the upper generation structures. This procedure was nevertheless improved upon in the early 1990s after optimizing the cyanoethylation and hydrogenation reactions, by working in aqueous solutions at 80°C and through hydrogenation with Raney cobalt, respectively.\textsuperscript{54, 55} In this case diaminobutane (DAB) served as multifunctional core to generate DAB-dendr-(CN)x and DAB dendr-(NH\textsubscript{2})x dendrimers after the cyanoethylation
and hydrogenation reactions respectively. Their action sequence for the divergent synthesis of poly-propylenimine dendrimers is shown in Scheme 1.3

![Scheme 1.3 Preparation of polypropylenimine dendrimers](image)

Polyamidoamine (PAMAM) dendrimers, synthesized subsequently, are likely the most widely investigated and used dendritic polymers to date. The first dendrimers commercialized in that family were the Starburst® systems. These species were developed in the mid-1980s by Tomalia, at about the same time when Newkome developed similar dendritic architectures named Arborols. A major incentive for development of these molecules was the creation of covalently bonded (unimolecular) micelles comparable to the well-known multi-or intermolecular micellar systems.

PAMAM dendrimers are versatile in that their terminal groups can be easily modified for targeted functionality or reactivity. These compounds are synthesized by the condensation of amines and acrylates. An initiating core containing one or more amine functionalities is first reacted with an excess of methyl acrylate, resulting in an alkyl ester branch addition at each amino hydrogen. This ester-terminated product is referred to as the G0.5 dendrimer. Amidation of the ester with ethylenediamine (EDA) causes branch extension with terminal amino groups. This amine-terminated dendrimer is referred to as a G1 PAMAM dendrimer. Repetitive cycles of Michael addition of the acrylate ester and amidation with EDA leads to successive generations of dendrimers. Functional group modification chemistry can also be performed on the terminal ester or amine groups. Thus treatment of the half-generation (ester-terminated) PAMAM dendrimers with alkali metal hydroxides yields carboxylate functionalities.
1.5.2 Dendrimers Synthesized by a Convergent Strategy

Hawker and Fréchet made a major contribution to the dendritic polymer chemistry field by developing a convergent approach to dendrimer synthesis in 1990. Dendritic fragments (dendrons) of benzylether were thus created by coupling phenols with benzylic halides. This approach represents a surface-to-core method, where the monomers are assembled from the peripheral units towards the core. Benzyl bromide was first coupled with dihydroxybenzyl alcohol (DHBA) in the presence of potassium carbonate and 18-crown-6 as a phase transfer catalyst in acetone as shown in scheme 1.5.
Scheme 1.5 Synthesis of a Fréchet benzyl ether dendrimer by a convergent approach

Following isolation and purification of the product, the G1 dendritic benzyl alcohol was converted to a benzylic bromide by treatment with carbon tetrabromide and triphenyl phosphine. Further cycles of DHBA monomer coupling were performed to obtain subsequent dendron generations. To obtain a symmetrical dendrimer, the dendritic wedges carrying a bromide functionality at their focal point can be coupled with a polyfunctional core such as l,l,l-tris (4’-hydroxyphenyl) ethane. A convergent strategy such as this, with only one final coupling step for the dendron wedge facilitates high yield reactions leading to well-defined structures. The symmetry of the molecules can be controlled through the functionality of the anchoring core.
In fact Newkome was really the first one to report a convergent dendron synthesis for the preparation of arborols, but the generation number and the molecular weight attained were limited. The synthesis of arborols started from a trifunctional branch cell formed by treating an alkyl halide with triethyl sodium methanetricarboxylate. Subsequent reduction of the ester with LiAlH₄ yielded a triol. The formation of the second tier through another cycle of esterification was attempted by tosylation with tosyl chloride in pyridine and treatment with the methylsodiumtriester, but the yield was very low due to inefficient nucleophilic attack at the three terminal sites as a result of steric crowding. To solve this issue, extension of the ester was performed prior to tosylation and coupling with the methylsodium trimester to afford the nonaester. The third generation of this cascade molecule, obtained through amide functionalization with tris (hydroxyl methyl) aminomethane was completely water-soluble. The reaction scheme for Newkome’s synthesis of a 27-arm arborol is shown in Scheme 1.6

Scheme 1.6 Arborol synthesis according to Newkome
1.5.3 Applications and Recent Trends:

Considering the extensive control achieved over the size, shape, and surface functionality of dendrimers, it is not surprising that these molecules have a wide range of potential applications. Upon examination of the structural features of a dendrimer, one can visualize sector specific uses as shown in Figure 1.5.3A.

The first application examined, and one of the primary motivations for dendrimer syntheses, was asunimolecular micelles. In contrast to common micellar structures formed through intermolecular association or aggregation, dendrimers are covalently bonded structures unaffected by their surrounding environment. Consequently, the ability of amphiphilic dendrimers to encapsulate guest compounds should be independent of changes in concentration, solvent, and pH, among others. A strong incentive for dendrimer micelles is in catalysis. Considering the structure and functionality control attained, catalytic sites can be introduced specifically within the core, on the periphery of dendrimers, or both, as illustrated in Figure 1.3.

Figure 1.2 Structural features and potential uses of dendrimers.

Figure 1.3 Internal (a) and peripheral (b) dendrimer functionalization.
The preparation of metallodendrimers, incorporating metallic species within their structure is a relatively facile process given the ease and versatility of dendrimer functionalization which can be tailored for metal coordination. For example, the PAMAM dendrimers discussed earlier can coordinate different transition metals through their nitrogen atoms. Metals able to coordinate with the PAMAM structure include among others Cu, Au, Pd, Pt, Ag, Co, as well as bimetallic systems such as Pd-Au and Pt-Ru. Dendritic catalyst selectivity, activity, and stability can vary on the basis of steric effects, the location of the catalyst, and the architecture of the dendritic support.

Coronal functionalization of the dendrimers with metals is typically performed by a divergent approach, i.e. with the metal binding process occurring in the final step. Catalysis on the periphery of dendrimers provides easily accessible sites; however, steric crowding of the reactants can influence the activity level observed. In theory, such a system should have a performance comparable to homogeneous (non-supported) systems. Examples of peripherally functionalized catalysts include carbosilane dendrimers with Ni at their peripheral functional sites serving in the Kharasch addition of polyhalogenoalkanes to terminal carbon-carbon double bonds, which displayed regioselectivity. Polypropyl enimine dendrimers have likewise been end-functionalized with palladium, rhodium, iridium, and Pd-Ni bimetallic catalysts for use in the Heck reaction and hydro formylation. Polyamidoamine dendrimers supported on silica were complexed with rhodium for heterogeneous catalysis in the hydroformylation of styrene and various other olefins. The highly active catalyst yielded branched chain aldehydes with high selectivity from aryl olefins and vinyl esters. The catalyst was easily recovered, and no significant loss in selectivity or activity was observed upon reuse. Core-functionalized metallodendrimer catalysts are sometimes referred to as dendrizymes by analogy to biological systems and due to the observed influence of the generation number on selectivity. Ferrocenyldiphosphine core-functionalized carbosilane dendrimers have thus been prepared as Pd ligands for the homogeneous catalysis of allylic alkylation reactions, and displayed variations in product selectivity for the largest dendrimers investigated. Fréchet-type polyether dendrons were complexed with Pt for use as SO2 sensor, and with Ni for the Kharasch addition of CCl4 to methyl methacrylate. The Dendron wedges, when functionalized at their focal point,
displayed adequate catalytic activity with easy recovery and good stability. Mimicking biological species is a major investigation area for dendrimers, particularly for PAMAM-based structures due to their similarities in size, shape, and chemical make-up with globular proteins. Thus the immunodiagnostic capabilities of dendrimers have been investigated\textsuperscript{79} as well as in vitro and in vivo gene delivery\textsuperscript{80} and gene expression.\textsuperscript{81} These species possess an exterior barrier controlled through end-group functionalization, as well as void spaces within their interior, much like liposomes. The tailored unimolecular micelle characteristics of dendrimers, with an open interior (in contrast to typical micelles), allows them to entrap guest molecules of various sizes and to selectively release them under certain conditions.\textsuperscript{82} These characteristics have led to the development of macromolecular drug delivery systems from dendrimers. In analogy to other complexation processes, drug molecules can be loaded inside or attached at the periphery of the molecules, to form dendrimer-drug conjugates. In the latter category, it has been demonstrated that PAMAM dendrimer palatinate conjugates have anti-tumor activity.\textsuperscript{83} More recently, it was shown that the encapsulation or complexation of camptothecin (a plant alkaloid known for its anti-cancer potency) with PAMAM dendrimers increased its solubility, which represents a step towards the effective delivery of this drug to cancerous cells.\textsuperscript{84} PAMAM dendrimer–glucosamine conjugates have even been shown to prevent scar tissue formation.\textsuperscript{85} Lastly, dendrimers have been investigated for light-harvesting applications.\textsuperscript{86}

1.5.4 Dendrimer Templates

Polyamidoamine(PAMAM) dendrimers were among the first dendritic macromolecules synthesized and are likely the most widely used dendritic molecules to this day.\textsuperscript{87, 88} PAMAM dendrimers offer ample opportunities for chemical functionalization given the reactivity of the amine-based building blocks used in their synthesis. Illustrated in Figure 1.4 is the branched architecture of a generation (G1) PAMAM dendrimer containing various amine and oxygen functionalities available for the coordination of various metal loading of PAMAM molecules with metals has been accomplished by various researchers, some of which will be described herein. This includes PAMAM dendrimers functionalized with different functional groups, or coupled with polymer segments to create larger templates.
Crooks and Tomalia both investigated the loading and reduction of copper salt within PAMAM dendrimer scaffolds. Crooks loaded both amine- and hydroxyl-terminated (G4) PAMAM dendrimers (G4-NH$_2$ and G4-OH respectively) with Cu$^{2+}$ using CuSO$_4$, and reduced the salt to Cu$^0$ with NaBH$_4$. It was observed that aqueous solutions of Cu-loaded G4-OH were stable in the absence of oxygen, showing no agglomeration or precipitation. The size of the Cu nanoparticles was dependent on the template characteristics. As binding only occurred within the dendrimer core, the copper nanoclusters were well shielded from each other and from the aqueous environment, resulting in soluble unmolecular micelles.

TEM analysis and UV-Vis spectroscopy both revealed ultra-fine copper particles less than 2 nm in diameter. Intradendrimer copper clusters larger than 5 nm should exhibit a Mieplasmon resonance peak around 590 nm in UV-Vis analysis, but this was not observed for the G4-OH Cu$^0$ system. For the loaded G4-NH$_2$ template, in contrast, a plasmon peak was evident after Cu$^{2+}$ reduction. This was attributed to copper complexation with the NH$_2$-functionalized corona of the dendrimers and Cu$^0$ agglomeration into larger clusters on the exterior of the dendrimer after reduction.

Tomalia found similar results in his work: Extremely stable copper-loaded PAMAM dendrimers were obtained in both aqueous and methanolic environments. Specifically, Tomalia examined copper(II)-acetate loading and its reduction with hydrazine in PAMAM dendrimers capped with TRIS[tris-(2-hydroxymethyl) methyl, (CH$_2$OH)$_3$], amino (NH$_2$), or pivalate [NHCOC(CH$_3$)$_3$] functionalities. Most samples lacked plasmon resonance in the 590 nm region, with the exception of the TRIS-capped dendrimers for which a small increase in plasmon resonance was observed after 21 h. The PAMAM structure is not limited to copper loading, as many metallic nanoparticles have been successfully templated including Au, Pd, Pt, Ag, Co, and bimetallic particles of Pd-Au and Pt-Ru. The images shown in Figure 1.5.4B are typical for the size, shape, and distribution of metal within dendrimer templates. PAMAM dendrimers can be loaded at various.
levels relative to the number of coordinating amine sites, which depends on the 6\textsuperscript{th} generation number of the dendrimer used. Thus Figure 1.5 corresponds to a G4 PAMAM dendrimer end-functionalized with hydroxyl groups and loaded with either 40 or 60 atoms per dendrimer (Figure 1.5(a) and Figure 1.5(b), respectively). The diameter of these nanoparticles was reported to be $1.4 \pm 0.2$ nm and $1.6 \pm 0.2$ nm, respectively. Figure 1.5(c) depicts dendrimers loaded with 40 atoms of Pd, having a diameter of $1.3 \pm 0.2$ nm.

Figure 1.5 TEM images for G4 PAMAM-OH loaded with (a) 40 atoms of Pt, (b) 60 atoms of Pt, and (c) 40 atoms of Pd.\textsuperscript{68}

PAMAM dendrimers can also serve as precursors for the synthesis of much larger and higher molecular weight polymers by using the terminal end groups on the periphery of the dendrimers for coupling reactions. For example, vinylsulfonyl(VS) end-functionalized poly(ethylene glycol), PEG-VS, was coupled with PAMAM dendrimers having amine end groups via Michael addition.\textsuperscript{100} The star-branched dendrimer-linear polymer hybrid obtained has a core-shell morphology and the ability to house materials within its core, while the polymer chains in the corona helped to stabilize the molecules in solvents. Metal loading into PAMAM-PEG dendrimer-star polymers was illustrated by the same group.\textsuperscript{101} The dendrimer core was thus used to template the deposition of Cd(NO\textsubscript{2})\textsubscript{3}·4H\textsubscript{2}O in methanol before its reaction with Na\textsubscript{2}S·9H\textsubscript{2}O. Zero-valent gold was also formed within the core of these dendrimer hybrids by loading HAuCl\textsubscript{4}·H\textsubscript{2}O and reduction with NaBH\textsubscript{4} in aqueous solution. The synthesis of the hybrid dendrimers and metal loading within their core is shown in Scheme 1.7.

![Scheme 1.7 Synthesis and metal loading of PAMAM-PEG dendrimer-star polymer](image_url)
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.\textsuperscript{102, 103, 104}

![Figure 1.6: Ferrocene containing dendrimer](image)

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. Metallo dendrimers can form as metal complexes with dendritic counter ions for example by hydrolysis of ester terminated PAMAM dendrimers with sodium hydroxide.

More recently, a number of dendrimers based on metal complexes have been synthesized\textsuperscript{105}. Metal complexes are characterized by a precise molecular geometry related to the characteristic
coordination number of the metal ion and can exhibit valuable properties such as absorption of visible light, luminescence and reduction and oxidation at low potentials. By using metal complexes it is possible to incorporate in the dendritic structure specific pieces of information that, when placed in suitable sites of the array, can be used to perform valuable functions. From a structural viewpoint, most of the metal-containing dendrimers can be classified according to four categories:

(i) dendrimers built around a metal complex as a core;
(ii) dendrimers containing metal complexes as peripheral units;
(iii) dendrimers containing metal complexes in the branches;
(iv) dendrimers based on metals as branching centers.

Examples of dendrimers synthesized by Balzani and coworkers, shows in some cases some complexes assembly architectures containing polypyridine metal complexes like Ru and Os. The design of such plynuclear metal complexes capable of exhibiting interesting photo physical and electrochemical properties. Using polypyridine ligands like 2,3-dpp and 2,5-dpp as bridging ligands (dpp=bis(2-pyridyl)pyrazine), Ru(II) and Os(II) as metal centers, complexes-as-metals and complexes-as-ligands synthetic strategy, Balzani has prepared a series of homo- and heterometallic di-109, tri-110, tetra-111,112, hexa-113,114, hepta-115, deca-116, trideca-117, and docosanuclear118 complexes. Such complexes, which have a dendrimer-type structure are very interesting because depending on the number and location of the metal and the ligand components, predetermined energy migration (Fig I-36 right) and redox patterns (Fig I.6a) can be obtained. The use of this kind of dendrimers as molecular-level antennas to harvest sunlight has been recently reviewed 120.
The 2,2′:6′,2″-terpyridine ligands have very interesting chemical properties due to the possible linear functionalisation at the 4′-position\textsuperscript{121,127}. In the course to synthesise molecules which are potential molecular-wire at nanoscale, the useful of 4′-substituted tpy ligand is a great interest because the bridging spacer formed after complexing with transition metal can have a linear geometry. However that is not the case with the 2,2′-bipyridine ligands which have several problems when used for devices with well-defined geometries, and after complexation and formation of heteroleptic complexes, the problem of enantiomer formation appears. Octahedral complexes [M(tpy)\textsubscript{3}]\textsuperscript{2+} are achiral and the substitution in 4′-position does not generates enantiomers. According the definition of Constable,\textsuperscript{128} metallostars are first generation metalloendrimers and it is convenient to consider...
them as a separate class because the majority of compounds of this class have been specifically prepared as first-generation species without the structural development of the ligands that would be required for the separation of a dendrimer. In the literature, the distinction between metallostars and metallodendrimers is not usually clearly made. A series of heptanuclear metallostars based upon central \{M(bpy)\}_3 motifs and bearing pendant \{M''(tpy)\}_2 units has been prepared by Constable and co-workers making extensive use of the reactions of coordinated bpy and tpy ligands. In a convergent approach, the complex (Fig 1.6b) was obtained by the reaction of 4, 4''-(HO)₂ bpy with [Ru(tpy)(tpy-Cl)]²⁺.

**Fig 1.8 Geometrical representation of dinuclear complexes containing bpy ligand and tpy ligand**

The inherent chirality of the \{M(bpy)\}_3 motif is a disadvantage when it comes to multinuclear compounds as these will be formed as mixtures of diastereoisomers unless special conditions are used to optimize stereospecificity. In contrast, \{M(tpy)\}_2 units linked through the 4''-position are achiral and are an ideal motif for the linear extension of achiral metallostars.

**Fig 1.9 Octadecanuclear Ru(II) terpyridine based metallostar^{129, 130}**
Multiinuclear oligopyridine complexes are important in metallosupramolecular chemistry and species such as rods or wires, helicates and dendrimers are well established. The investigation of photo induced energy- and electron-transfer (Metal-to-Ligand) in geometrically well defined poly-nuclear systems allows the electronic and nuclear factors governing these processes to be investigated. The exploitation of the spectroscopic (particularly luminescence) properties of transition metal-oligopyridine complexes for ion sensing, light harvesting or energy collection using high-nuclearity dendrimers is of intense current interest

![Photoinduced energy transfer through a Ru-Os Y shaped metallostar](image)

1,4,8,11-Tetraazacyclotetradecane (cyclam), which is one of the most extensively investigated ligands in coordination chemistry, in its protonated forms can play the role of host towards cyanide metal complexes. Balzani and Vögtle have investigated the acid-driven adducts formed in acetonitrile dichloromethane solution between [Ru(bpy)(CN)₄]²⁻ and 1,4,8,11-tetrakis (naphthyl methyl) cyclam and a dendrimer consisting of a cyclam core appended with 1,2,3,5 dimethoxy benzene and 16 naphtyl unit (Fig 1.11)-[Ru(bpy)(CN)₄]²⁻, with the two cyclamic ligands exhibiting characteristic absorption and emission bands that are strongly affected by addition of acid.
Fig 1.11 Structure of \([\text{Ru(bpy)(CN)}_4]^{2-}\) complex and of two cyclam-cored dendrimers

Schem 1.8 Representation of the formation of the \([\text{Ru(bpy)(CN)}_4]_2-\) (Cyclam) adduct
1.7 Application of metalloendrimer

1.7.1 Application of metalloendrimer with focus on Cancer:

Cancer is a class of disease characterized by uncontrolled cell proliferation (i.e. undergoing cell division beyond the normal limits) and the ability of these cells to invade adjacent tissue, and sometimes spreading to other locations of the body via blood or lymph. The main types of cancers (based on mortality rate) are lung, stomach, colorectal, liver and breast cancer. These cancers can be treated by several methods such as surgery, radiotherapy and most importantly chemotherapy, which is the main treatment of this disease. Chemotherapy is the treatment of cancer with anticancer drugs that target and destroy cancer cells. In the last decade, a revolution in cancer treatment has been presented by organometallic chemists.\textsuperscript{134, 135}

1.7.1a The Use of Metals as Therapeutic Agents

For the last 25 years medicinal inorganic chemistry was a new and unexplored field. However, research has flourished following the success of platinum-based anticancer agents.\textsuperscript{136} In addition to metal-based therapies, the efficacy of organic drugs can be improved by combining them with metals.\textsuperscript{136}

1.7.1b Platinum Anticancer Agents

The therapeutic properties of cis-diamminedichloroplatinum(II)\textsuperscript{(II)}(cis-[Pt(NH\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}, cisplatin) was accidentally discovered by Barnett Rosenberg,\textsuperscript{137, 138} in the late 1960s, whilst he was investigating the influence of an electric field on the growth of Escherichia coli bacteria. Cisplatin was in fact first synthesized by Michele Peyrone\textsuperscript{139} in 1844 and was known as Peyrone’s chloride. More than a century later it became the first metal-containing anticancer drug. Today, cisplatin is FDA approved, and is used in the treatment of a wide range of tumors,\textsuperscript{140} in particular ovarian\textsuperscript{141, 142} and testicular cancers.\textsuperscript{143, 144} Cisplatin is also used in combination therapy of many other solid tumors, such as head, neck, bladder and small cell lung cancers.\textsuperscript{145} Analogs of cisplatin (i.e. carboplatin and oxaliplatin), have shown great effectiveness as second-generation drugs.\textsuperscript{146} Oxaliplatin is currently a „billion-dollar” drug, primarily used to treat colorectal cancer.\textsuperscript{147}
Farrell and co-workers synthesized a Pt-based trinuclear complex with the general formula [trans, trans, trans-(NH$_3$)$_2$-Pt(Cl)(CH$_2$)$_6$NH$_2$Pt(NH$_3$)$_2$NH$_2$(CH$_2$)$_6$NH$_2$Pt-(NH$_3$)$_2$(Cl))][NO$_3$]$_4$ (BBR3464, Figure 1.12) which showed potent in vitro toxicity over cisplatin and its mononuclear analog. BBR3464 was claimed as the first platinum-based drug with a DNA binding mode different to cisplatin. Though Phase II trials of BBR3464 were not pursued further, the concept of multinuclearity may assist in the improvement of the activity of potential therapeutic agents.

![Figure 1.12](image)

**Figure 1.12** Structure of the trinuclear Pt-based anticancer agent, BBR3464.

The clinical successes of platinum-based therapies tend to be overlooked due to the severe toxic side-effects and drug-resistance of these complexes. To overcome these limitations researchers have moved their attention to compounds incorporating other metals.

### 1.7.1c Titanium Anticancer Agents

There have been two TiIV complexes explored as anticancer agents, both entered clinical trials in the 1990s. The first is a tris-acetylacetonate derivative called Budotitane (Figure 1.13) and the second, titanocene dichloride [(η5-C$_5$H$_5$)$_2$TiCl$_2$]. Both complexes are similar in structure to cisplatin, with both containing two labile chloride ligands. Though the rate hydrolysis of these Ti-complexes is much faster than cisplatin, it did however lead to complications. Bound water is more acidic, which lead to the formation of hydroxo-bridged species, which in turn lead to toxic TiO$_2$ and hence did not complete Phase I clinical trials. Titanocene dichloride had more success than Budotitane, with the completion of Phase I and II clinical trials; however it was abandoned.
Titanocene dichloride was not approved for clinical use since it did not show significant advantages over current drugs on the market. The poor water solubility and low hydrolytic stability hampered its development.\textsuperscript{153, 154}

\textbf{Figure 1.13 Structures of Ti-based anticancer agents: Budotitane}

To aid in stability of the Ti-based complexes, ansa derivatives of titanocene dichloride were developed (Figure 1.14)\textsuperscript{153} and some complexes were active against 36 human tumor cell lines.\textsuperscript{157} However, the hydrolytic stability of the complexes remained a problem, hence an alternative approach was taken. The dichloride ligands of the ansa derivatives were replaced with an oxalate ligand, generating bis[(p-methoxybenzyl)cyclopentadienyl]-titanium(IV) oxalate (oxalititanocene Y, Figure 1.14) which was found to be twice as potent as cisplatin towards pig kidney epithelial (LLC-PK) cells\textsuperscript{158} and demonstrated favorable pharmacokinetic properties.

\textbf{Fig.1.14 Structures of dichloride titanocene derivative (left) and oxalititanocene Y (right).}\textsuperscript{156, 158}
1.7.1d Gallium Anticancer Agents

There are only a handful of gallium-based complexes used as anticancer agents, namely Ganite® (gallium nitrate complex), KP46 [tris(8-quinolinolato)gallium (III)] and GaM (gallium maltolate), tris(3-hydroxy-2-methyl-4H-pyran-4-onato)gallium (Figure 1.15). Ganite® is FDA approved, and used to treat cancer-related hypercalcemia, however the drug has poor bioavailability. KP46 is an orally bioavailable drug, which has been through Phase I clinical trials for the treatment of solid tumors via S-phase cell cycle and apoptosis. Though not redox active under biological conditions, Ga(III) has similar chemistry to Fe(III) and can be transported to cells via the Fe(III) transport system (bound to serum protein transferrin).

Figure 1.15 Structures of KP46 (left) and GaM (right).

1.7.1e Tin Anticancer Agents

Sn IV complexes have become very attractive as therapeutic agents because of their attractive properties such as, increased water solubility, lower general toxicity than Pt-based drugs, better body clearance, fewer side-effects and most importantly does not develop drug resistance. Recently, a tributyl complex tri-n-butyltin(IV)lupinylsulfide hydrogen flumarate (IST-FE 35, Figure 1.16), displayed inhibition of the implanted tumors (p388 myelomonocytic leukemia and B16-F10 melanoma) in BDF1 mice. Following a single dose of the drug, IST-FE reduced the tumor volume by 96% at day 11.
Other examples of a Sn-based antitumor agents, are the trigonal-bipyrimidal anionic tin(IV) complexes recently synthesized by Kaluderovic,\textsuperscript{168} namely, triphenyltin(IV) chlorides containing N-phthaloyl-L-glycine(P-Gly), N-phthaloyl-L-alanine(P-AlaH), and 1, 2, 4-benzenetricarboxylic 1, 2-anhydride(BTCH), were tested against a series of cancer cell lines. The Sn-based complexes displayed high activity in the cancer cell lines, with some of the complexes displaying IC50 values lower than cisplatin. The most active complex of the series (50 times more potent than cisplatin) was the organotin complex, triethylammonium(N-phthaloylglycinato)triphenyltin(IV) chloride [SnPh$_3$(P-Gly)Cl] and was found to induce apoptosis via extrinsic pathways on DLD-1 cancer cells.\textsuperscript{168} Other metals have been used in the pursuit of potential therapeutic agents, such as gold\textsuperscript{169} arsenic,\textsuperscript{170} copper,\textsuperscript{171} zinc,\textsuperscript{172} bismuth,\textsuperscript{173} molybdenum.\textsuperscript{174} However, ruthenium-based complexes have shown the most promise as anticancer agents.\textsuperscript{175}

**1.7.1f Ruthenium(III) Anticancer Agents**

Soon after the discovery of the cytotoxic effects of platinum-based drugs, ruthenium compounds were investigated as potential therapeutic agents. As an alternative to platinum, ruthenium has shown favorable properties and conditions to form the basis for anticancer drug design.\textsuperscript{13} Moreover ruthenium is less toxic than platinum, with its biological activity attributed to its ability to mimic the behavior of iron, and bind to biomolecules, such as human serum albumin and transferrin.\textsuperscript{176} Two inorganic Ru(III) complexes, [ImH][transRu(DMSO)(Im)Cl$_4$] (NAMI-A, where Im=imidazole)\textsuperscript{177-179} and [IndH][trans-Ru(Ind)$_2$Cl$_4$](KP1019, where Ind=indazole)\textsuperscript{180-182} (Figure 1.18) are currently undergoing Phase II clinical trials.

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**Figure 1.17 Structure of Sn$^{IV}$ anticancer complex, IST-FS 35.\textsuperscript{166, 167}**

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NAMI-A, synthesized by Gianni Sava, is a tetrachlorido imidazole/DMSO-Ru(III) compound, and was the first of the two Ru(III) complexes to enter clinical trials. NAMI-A, was found to be inactive during initial in vitro testing. However, in vivo testing showed that the drug inhibits matrix metalloproteinases and prevents metastases (tumor growth)\textsuperscript{179} with little impact on primary tumors in animal models.\textsuperscript{178}

KP1019, developed by Bernhard Keppler, is administered intravenously and hence binds initially to proteins in the bloodstream. In fact, following cellular uptake of KP1019, it was primarily found bound to proteins (i.e. albumin and transferrin) and on DNA in peripheral leukocytes.\textsuperscript{181} The side-effects seen with platinum-based anticancer agents were related to their binding to serum proteins, while KP1019 binds to transferrin, an important step in its mode of action, as it aids in the transport into the cell via the transition pathway.\textsuperscript{180, 183, 184}

In recent years the focus on Ru(III) complexes has shifted towards the development of Ru(II) complexes, as in both cases (i.e. NAMI-A and KP1019) the active drug is considered a Ru(II) species. Moreover, the Ru(III) agents are “activated” upon entering the cancerous cell, by reduction to the Ru(II) species which coordinate more rapidly to biomolecules.\textsuperscript{185, 186}
1.7.1g Ruthenium(II) Compounds as Anticancer Agents

Ru(III)-based anticancer drugs such as NAMI-A, KP1019 and their derivatives, pioneered as alternatives to Pt-based therapeutic agents. However, with the +2 oxidation state proposed as the active ruthenium species, several investigations into the development of Ru (II) compounds as anticancer agents have been pursued.187-189

1.7.1h Organometallic Ruthenium-Based Antitumor Compounds

In organometallic complexes, it is the metal-carbon bond which endows these coordination complexes with their unique properties. The lability of the metal-ligand bond can greatly be influenced by the presence of metal-carbon bonds, as these complexes have high trans-effects and trans-influences. Moreover, the π-bonded arene and cyclopentadienyl (Cp) ligands can act as both electron donors and π-acceptors. Similarly to Ru(III) complexes, Ru(II) complexes have been extensively studied as anticancer agents.187-189 The most widely studied organoruthenium compounds are the ruthenium-arene and ruthenium-cyclopentadienyl half-sandwich compounds, also referred to as „piano-stool“ complexes.190 The term „piano-stool“ is derived from the orientation of the coordinating ligands around the metal centre. All these pseudo-octahedral complexes have either a Cp (η5) or arene (η6) ring (i.e. the „seat“ of the „piano-stool“), and coordinating ligands (i.e. the „legs“ of the „piano-stool“). There are three forms of binding in which the coordinating ligands can coordinate around the d6 metal [Ru(II), Os(II), Ir(III) or Rh(III)]. Depending on the nature of the ligand, binding can occur in a monodentate (Z), bidentate(X-Y) or tridentate (X-Y-Z) manner, in-turn generating neutral or charged (isolated as salts) complexes. The different types of coordinating ligands (X, Y, Z and arene/Cp) dictate the reactivity (labile or inert) of the complexes. The π-donor ability of the arene/Cp ligand protect the metal centre from oxidation.1

The first half-sandwich organoruthenium antitumor agent was 1-β hydroxyethyl-2-methyl-5-nitroimidazole (metronidazole) coordinated to a ruthenium(II)-benzene dichlorido moiety. The Ru-complex is more active in vitro than its base-ligand, metronidazole.191
1.7.1i Multinuclear Ruthenium-Arene Compounds as Anticancer Agents

The trinuclear Pt-based anticancer agent, BBR3464, is 2-6 orders of magnitude more active than cisplatin in cisplatin-resistant cell lines.\textsuperscript{192} Hence, the use of multinuclear complexes as potential therapeutic agents has since been considered.

In order to improve the activity of the ruthenium-arene complexes, Keppler and co-workers, synthesized water-soluble dinuclear ruthenium-arene complexes, based on 3-hydroxy-2-methyl pyridinone with varied alkyl spacers (Figure 1.19).\textsuperscript{193} The dinuclear ruthenium-arene complexes were compared against Pt-based antitumor agents (i.e. cisplatin, carboplatin and oxaliplatin), in a series of human tumor cell lines.\textsuperscript{193} In particular, one of the dinuclear complexes has similar activity to oxaliplatin, with the mononuclear derivative (Figure 1.19) inactive in the same cell line.

Figure 1.19 dinuclear (with varying spacer lengths, right) ruthenium-arene antitumor complexes\textsuperscript{193}

Stringer et al. prepared a series of mononuclear and dinuclear ruthenium-arene complexes based on benzaldehydethiosemicarbazone (Figure 1.20).\textsuperscript{194} The thiosemicarbazone moiety is known for its potent enzyme inhibition (in particular ribonucleotide reductase) and is capable of interrupting DNA replication.\textsuperscript{195} The dinuclear complex showed enhanced biological activity (IC50=8.96 μM) in the oesophageal cancer cell line (WHCO1), over its mononuclear derivative (IC50 >200 μM, WHCO1).\textsuperscript{194}
A tetranuclear ruthenium-arene complex with general formula \([((p\text{-cymene})_4\text{Ru}_4\text{Cl}_6\text{R}_1\text{Cl}_2]\) (where R1=1,2-bis(di-N-methylimidazol-2-ylphosphine)ethane) was prepared by Noffke and co-workers (Figure 1.21).\(^{196}\) However, the cytotoxicity of the complexes are poor in several cancer cell lines (Hct116, Huh7, H411E and A2780 cells).

**Figure 1.20** Ruthenium-arene thiosemicarbazone-based antitumor agents, mononuclear and dinuclear\(^{194}\)

**Figure 1.21** novel tetranuclear ruthenium-arene complex synthesized by Noffke et al.\(^{196}\)
1.7.1j Ferrocene in Cancer Research

Ferrocene was first discovered in 1951, however the structure was elucidated afterwards independently by Wilkinson, Fischer and Pfab. The benzene inspired name „ferrocene” was coined by Woodword and co-workers in 1952. Scientists wasted no time in developing new strategies in synthesizing ferrocene and its derivatives. Owing to its ease of functionalization and favorable electronic properties, a wide range of applications for these sandwich complexes were explored. Stability of ferrocene in aqueous and aerobic media, the large variety of derivatives and the favorable electronic properties made ferrocene and its derivatives attractive as potential biological agents.

1.7.1k Ferrocene in Medicine: With Focus on Ferrocenyl-Based Derivatives as Therapeutic Agents

Many ferrocenyl compounds display good in vivo or in vitro activity as antitumor, antimalarial, antifungal and antiretroviral (ARV) agents, and show DNA-cleavage activity. Brynes et al. reported the first ferrocene-based anticancer complex in the late 1970s, with the compounds bearing amine or amide groups tested against leukemia P-388 cells. The ferrocenyl-derived compounds were administered to mice and the activity of these complexes were low but showed an improvement compared to the starting ligand. This report clearly suggests, the incorporation of ferrocene into an appropriate biomolecule or carrier molecule, could provide the compound with enhanced anticancer activity.

Jaouen and co-workers developed a series of ferrocenyl derivatives and studied their activity in cancer cells. The ferrocenyl derivatives, called ferrocifens (Figure 1.22), were derived from the anticancer drug tamoxifen (Figure 1.22), where one of the phenyl rings was replaced with ferrocene moiety. Derivatives of the active metabolite, hydroxytamoxifen (Figure 1.22) were also synthesized and the antiproliferative activity of these ferrocenyl derivatives investigated against breast cancer cells (MCF-7, hormone independent and MDA-MB231, hormone dependent). The ferrocifens exhibited strong biological activity in both cell lines, though some were comparable to hydroxyl-tamoxifen, others were slightly better. The authors attribute the activity to the greater lipophilicity of ferrocifens and the cytotoxicity induced by the redox-active ferrocene moiety. Furthermore, these results show that ferrocifens are the first molecules to show activity in both hormone-dependent and hormone-independent human breast cancer lines.
Figure 1.22 Structures of parent drugs tamoxifen and hydroxytamoxifen (left) and the ferrocenyl-based derivatives, ferrocifens (right).\textsuperscript{213, 214}

The extended π-system plays an important role on the mode of action of the ferrocenyl-derived anticancer agents, with authors reporting a correlation between cytotoxicity and electron transfer capacity of these complexes.\textsuperscript{215} The mode of action is said to originate from a series of redox processes on the ferrocenyl moiety, which results in the generation of reactive oxygen species (ROS).\textsuperscript{215}

It has been shown that tethering the ferrocenyl moiety onto biologically active compounds increases their potency. The increase in activity has been attributed to the combined action of the organic drug and the Fenton chemistry of the Fe centre.\textsuperscript{216}

1.7.1 Heterometallic and Multinuclear Ferrocenyl-Derived Anticancer Agents

Ferrocene has been linked to both platinum\textsuperscript{121-124} gold\textsuperscript{125} and ruthenium\textsuperscript{126, 127} in an effort to achieve a synergistic effect between the two biologically active centres. Nieto and co-workers synthesized a series of heterometallic Pt(II) compounds with β-aminoethylferrocenes. The compounds were tested against four cancer cell lines (HBL-100 (breast), HeLa (cervix), SW1573 (lung), WiDr (colon)). One of the β-aminoethylferrocenes-Pt(II) compounds (Figure 1.23) displayed good cytotoxicity in all four cell lines (IC50=1.7 - 2.3 μM), with activity in the colon cancer cell line better than the benchmark drug (cisplatin).
Recently, Dyson and co-workers prepared heterometallic phosphinoferrocene amino conjugates, incorporating the biologically active ruthenium-arene moiety (Figure 1.24). These systems show moderate to good in vitro antitumor activity towards both the sensitive and cisplatin resistant human ovarian cancer cell lines (A2780, IC50 = 4.1 μM; A2780cisR, IC50 = 6.9 μM).

1.7.2 Metallodendrimers: Metal Decorated Dendrimers for Oncology

The term metallodendrimers is derived from the name given to metal functionalized highly branched macromolecules known as dendrimers. The term dendrimer is built from the Greek words “dendros” meaning tree, and “meros” meaning part. These complex macromolecules have well-defined shape, are highly branched and are built from a central core. Compared to linear polymers, dendrimers can be synthesized reproducibly with low polydispersity, which is a highly discernible feature for drug delivery agents. A wide range of functionalities can be included throughout the dendritic framework (on the periphery, at the core or interspersed) which give them a wide range of applications in medicinal chemistry, host-guest chemistry.
1.7.3 Applications of Metalloendrimers: With Focus on Nanomedicine

The well-defined and ordered molecular structure of dendrimers and their unique properties such as the high density and highly flexible design, the reactivity of the functional groups on the periphery, as well as the possible aqueous solubility and low toxicity offers dendrimer applications in a variety of fields. These fields include catalysis, biosensors, adhesives, magnetic resonance imaging, and nanomedicine. Moreover in catalysis, the catalytically active complex can be located throughout the dendritic framework. The multinuclearity approach affords greater activity and efficiency of the the concept of multinuclearity could lead to improved activity of metallo drugs. Hence, another application of metalloendrimers is the delivery of drugs. Several approaches have been used:

i. physical encapsulation of the drugs into the void spaces (drawbacks, fast and uncontrolled delivery of drugs)

ii. electrostatic binding between the ionic peripheral groups of the dendrimer and the drug

iii. hydrogen bonding between the peripheral functional groups and the drug

iv. and covalent linkage of the drug to the dendritic periphery or surface (known as the pro-drug approach)

Notably, in nanomedicine, the concept of multinuclearity can be applied to improve the potency of chemotherapeutic drugs. By exploiting the enhanced permeability and retention effect (EPR effect) dendrimers can be used to selectively target drug-targets.

The EPR effect is a phenomenon in which macromolecules (such as metalloendrimers), can exploit the physiological patterns of solid tumors (Figure 1.25). Metalloendrimers can accumulate at the tumor site due to an increase in blood vessel permeability (porous endothelial layer) within the cancerous cells over healthy tissues. The healthy endothelial layer surrounding blood vessels, restricts the size of molecules that can diffuse from the blood stream into the cells. In contrast, the endothelial layer of cancerous tissues is more porous, providing access to the surrounding tissue. Furthermore, diseased tissues have an impaired lymphatic drainage system, thus once macromolecules have entered the cancerous site they are retained for longer periods (increase in bio-availability). A tetraruthenium cluster is highly active against the polio virus, without effecting healthy cells.
The use of dendrimers in the field of medicine is highly developed, with a number of dendrimer conjugates reported. However, the use of metallodrugs conjugated to dendritic frameworks is sparse, with only a handful of reports as antitumor agents or antimalarial agents.

Following the successes of cisplatin and its analogs, in particular the trinuclear Pt-based complex (BBR3464) mentioned earlier. Researchers have pursued the idea of functionalizing metallodrugs onto dendritic scaffolds in an effort to improve the activity of the metallodrug. There are only a handful of metallodendrimer specifically developed to target cancerous cells and are highlighted in a recent review.

It should come to no surprise that the first metallodendrimer synthesized to target cancer cells, was a tetranuclear Pt-based compound. The platinum-functionalized metallodendrimer DAB(PA-tPt-Cl)$_4$ (where DAB=diaminobutane, PA=polyamine) is based on the first-generation poly(propylene) (PPI) dendritic scaffold.

The Pt-metalloendrimer was synthesized to overcome problems associated with cisplatin resistance in cancer cells:

i. Deactivation of the Pt-species by intracellular thiolates and
tii. Improved repair of crosslinks with DNA.
With the severe side-effects of platinum-based drugs, researchers shifted their attention to other metals. Hence, Zhao and co-workers synthesized tetranuclear (Pt-based) and hexanuclear (Cu-based) PAMAM metallodendrimers (Figure 1.26), with the biological activity of these complexes investigated (in cisplatin-sensitive, MOLT-4, and cisplatin-resistant, MCF-7, breast cancer cells).

Figure 1.26 Structure of G1tetranuclearPt-(left) and Cu-functionalized (right) metallodendrimer.

The ligands showed no activity against the cancer cells, whilst the multinuclear complexes showed enhanced activity over their mononuclear derivatives. Moreover, the copper analogs displayed greater activity to their platinum analogs, with the authors attributing the low toxicity of the Pt-complexes to poor solubility in the testing medium and ability of the complexes to self-assemble (seen through SEM experiments).

Stability of anticancer agents in solution is a key aspect before consideration for biological and clinical applications. Rodrigues and co-workers monitored the degradation and stability of low generation ruthenium-based poly (alkylideneamine)-nitrile metallodendrimers (Figure 1.27) by \(^{31}\)P-NMR spectroscopy. The metallodendrimers containing the [Ru (Cp)(PPh\(_3\))]\(^{2+}\) moiety was unstable at physiological temperature, as there is a release of the Ru half-sandwich. However, the metallodendrimer containing the [Ru (dppe)\(_2\)Cl]\(^{+}\) is stable over 4 h in solution, revealing the potential of the complexes for biological applications.
Figure 1.27 Structure of poly(alkylideneamine)-nitrile metalloendrimer functionalized with [Ru(dppe)$_2$Cl]+ or [Ru(Cp)(PPh$_3$)$_2$]+. Metalloendrimers have also shown promise as potential photodynamic therapy (PDT) agents, with the synthesis of a 32-armed ruthenium-polypyridyl functionalized PAMAM metalloendrimer, by Velders and co-workers. The positively charged derivative shows promise as a PDT agent, whilst the negatively charged derivative shows promise for diagnostic fluorescence assays.

Figure 1.28 A positively and negatively charged PAMAM polypyridylruthenium metalloendrimer.
2. Present work: Synthesis & characterization of Palladium mediated metallodendrimer compounds based on diazine and triazine.

2.1 Rationale:
Dendrimers, which are highly branched macromolecules that emanate from a central core with a well-defined structure, have attracted considerable attention from a fundamental viewpoint and their development is rapidly expanding in many applications (e.g., OLEDs, sensors, and lasers). The incorporation of transition metals or lanthanides into dendritic macromolecules leads to a new class of materials called “metallodendrimers”.

The active catalytic centre in a metallodendrimer can be situated in three different areas: (i) metal atom as the dendrimer core; (ii) metal atoms in the dendrimer branches; (iii) metal atoms in the periphery. The synthesis of the third type of metallodendrimer may be envisaged by two strategies. Firstly, it is possible to build the dendrimer and then incorporate the metal atoms in the final stage or, secondly, the metal atoms can be incorporated within the molecular fragments used to build the dendrimer. Regardless of the choice of route, it is necessary to obtain appropriate dendrons that have the ability to coordinate the catalytically active metal atom.

Research on metallodendrimers has received significant attention in recent years owing, in part, to their potential applications in homogenous catalysis, sensing and light harvesting. Metallodendrimer compounds have been prepared via click chemistry, employing Diels-Alder reactions, thiol-ene reactions and azide-alkyne reactions. Compounds containing S-triazine and dendrimers based on triazine have received a remarkable attention owing to their potential applications and have shown molecular recognition and self-assembly properties.

In view of remarkable importance of dendrimer and metallodendrimer compounds in the field of biological and medicinal chemistry and metal mediated approaches still remain scarce for their synthesis. The aim of the present study was to synthesize dendrimer and metallodendrimer based on diazine and triazine. It is planned to develop a simple and efficient method for the synthesis of metallodendrimer compounds from the reaction of triazine and diazine with different aroylchlorides at variable temperatures in presence of bis-triphenylphosphine palladium(II) chloride. It is expected that the synthesized compounds would be biologically active and they might be used as an intermediate products and catalyst for the synthesis of heterocyclic compounds as well as drugs. It might also be applicable in chemical, physical and biological processes.
2.2 Results and Discussion:

2.2.1 Synthesis of 2,4,6-Tris (di-amido)-1,3,5-triazine Palladium(II) chloride 8-12

The compounds, 8-12 were synthesized by treating melamine with different aroylchlorides in the presence of (Ph₃P)₂PdCl₂ in different solvents at room temperature for 6-7 hours as shown in Scheme 2.1 and Table 1

3, 8 R = C₆H₄CH₃(p)  
4, 9 R = C₆H₄Cl(p)  
5, 10 R = C₆H₄OCH₃(p)  
6, 11 R = C₆H₅  
7, 12 R = C₆H₄NO₂(p)
<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Substrate</th>
<th>Reagents and conditions</th>
<th>Products (8-12)</th>
<th>m. p. (°C)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate Image 1" /></td>
<td>$p$-CH$_3$C$_6$H$_4$COCl, DMSO r.t, 6-7 h (Ph$_3$P)$_2$PdCl$_2$</td>
<td><img src="image" alt="Product Image 8" /></td>
<td>328-330</td>
<td>90</td>
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<tr>
<td>2</td>
<td><img src="image" alt="Substrate Image 2" /></td>
<td>$p$-ClC$_6$H$_4$COCl, DMSO r.t, 6 h (Ph$_3$P)$_2$PdCl$_2$</td>
<td><img src="image" alt="Product Image 9" /></td>
<td>310-312</td>
<td>90</td>
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<td>3</td>
<td><img src="image" alt="Substrate Image 3" /></td>
<td>$p$-CH$_3$OC$_6$H$_4$COCl, DMSO r.t, 6 h (Ph$_3$P)$_2$PdCl$_2$</td>
<td><img src="image" alt="Product Image 10" /></td>
<td>320-322</td>
<td>95</td>
</tr>
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<td></td>
<td>Structure</td>
<td>Reagents</td>
<td>Yield</td>
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<tr>
<td>4</td>
<td><img src="image1" alt="Structure" /></td>
<td>C₆H₅COCl, DMF, r.t., 6 h, (Ph₃P)₂PdCl₂</td>
<td>290-292</td>
<td>90</td>
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<tr>
<td>5</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-NO₂C₆H₄COCl, DMSO, r.t, 6 h, (Ph₃P)₂PdCl₂</td>
<td>304-306</td>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>

**N. B:** Yield % was calculated on the basis of (Ph₃P)₂PdCl₂.
2.2.2 Synthesis of 2,4,6-Tris(di-amido)-1,5-diazine Palladium(II) chloride 13-17

The compounds 13-17 were synthesized by treating pyrimidine (0.2 g) with different aroylchlorides in the presence of (Ph₃P)₂PdCl₂ in different solvents at room temperature for 6-7 hours as shown in Scheme 2.2 and Table 2.

3, 13 R = C₆H₄CH₃(p)
4, 14 R = C₆H₄Cl(p)
5, 15 R = C₆H₄OCH₃(p)
6, 16 R = C₆H₅
7, 17 R = C₆H₄NO₂(p)
Table 2:

<table>
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<tr>
<th>Sl. No</th>
<th>Substrate</th>
<th>Reagents and conditions</th>
<th>Products (13-17)</th>
<th>m. p. (°C)</th>
<th>Yield %</th>
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</thead>
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<tr>
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<td>315-317</td>
<td>96</td>
</tr>
</tbody>
</table>
| 3 | \[
\begin{array}{c}
\text{C}_6\text{H}_5\text{COCl} \\
\text{DMF} \\
r.t., 6-7 \text{ h} \\
(\text{Ph}_3\text{P})_2\text{PdCl}_2
\end{array}
\] | 280-282 | 90 |
|---|---|---|---|
| 4 | \[
\begin{array}{c}
p-\text{NO}_2\text{C}_6\text{H}_4\text{COCl} \\
\text{DMSO} \\
r.t, 6-7 \text{ h} \\
(\text{Ph}_3\text{P})_2\text{PdCl}_2
\end{array}
\] | 305-307 | 92 |

**N. B:** Yield % was calculated on the basis of (Ph$_3$P)$_2$PdCl$_2$. 
2.3 Mechanism of the reactions:
2.4 Characterization:

2.4.1 Characterization of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8

The compound was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of p-methyl benzoyl chloride by stirring at room temperature for 6-7 hours in the presence of (Ph₃P)₂PdCl₂ and solvent (DMF).

The structure of the compound was established by various spectral data.

In IR spectrum of the compound the absorption band was found at 3134.1 cm⁻¹ due to the C-H (aro) stretching absorption, whereas a broad band at 3085.9 cm⁻¹ stretching absorption represents the (C=H) aliphatic group. Absorption band at 1720.4 cm⁻¹ display keto (C=O) group. Stretching absorption $\nu_{\text{max}}$ 1664.5, 1575.7, 1288.4 and 488.72 cm⁻¹ stretching bands indicated the presence of C=N, aromatic C=C,C-N and Pd-Cl respectively.

In $^1$H NMR spectrum of compound 8, the chemical shift at $\delta_H$ 2.46 (s, 6×3H, Ar-CH₃) was found as a singlet for the hydrogen atoms in six CH₃ groups. Chemical shift at $\delta_H$ 7.24 (d, 6×2H, Ar-H, J=8.0 Hz) showed a doublet for aromatic protons of C-3′, C-5′ carbon of six phenyl rings and $\delta_H$ 7.91 (d, 6×2H, Ar-H, J=8.5 Hz) showed another doublet for similar protons of C-2′, C-6′ carbon of six phenyl rings.

In the $^{13}$C NMR spectral data of compound 8, the chemical shift $\delta$ 21.86 indicated the presence of six identical carbons in six methyl groups (Ar-CH₃).The chemical shift at $\delta$ 130.36 and 129.31 was found for the two carbons (C-1′, C-4′) of phenyl rings. The peak at $\delta$ 126.71 represent aromatic carbons of C-2′, C-6′ and carbons of C-3′, C-5′ of six phenyl rings respectively. The chemical shift at $\delta$ 144.75 was obtained for the carbons C-2, C-4 and C-6 of melamine ring. The chemical shift at $\delta$ 172.64 was obtained for carbonyl carbon (C=O).

Mass spectrometry data indicated the proposed structure of metallodendrimer compound 8, Positive-molecular ion mass peak (M+) 1363.08 indicated the molecular ion of the compound.
2.4.2 Characterization of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine palladium(II) chloride 9

The compound was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of p-chlorobenzoyl chloride by stirring at room temperature for 6-7 hours by using (Ph₃P)₂PdCl₂ in presence of DMSO.

The structure of the compound was established by various spectral data. In IR spectrum of the compound, the absorption band was found at 3095.4 cm⁻¹ due to the C-H (aro) stretching absorption, whereas a broad band at 1683.7 cm⁻¹ represents the keto (C=O) group. Strong absorption band at 1593.1 cm⁻¹ displays strong C=N stretching absorption. \( \nu_{\text{max}} \) 1323.1 cm⁻¹ stretching bands indicated the presence of C=C in phenyl ring and \( \nu_{\text{max}} \) 1093.6 cm⁻¹ indicated the presence of aromatic C-N stretching and strong absorption band in 761.8 and 472.92 cm⁻¹ display C-Cl and Pd-Cl stretching absorption.

In \(^1\)H NMR spectrum of compound, chemical shift at \( \delta_H \) 7.46 (d, 6×2H, Ar-H, J=7.5 Hz) showed a doublet for aromatic protons of C -3', C-5' of six phenyl rings and \( \delta_H \) 8.04 (d, 6×2H, Ar-H, J=7.0 Hz) showed another doublet for similar protons of C-2', C-6' carbon of six phenyl rings.

In the \(^13\)C NMR spectral data of the compound, the chemical shift at \( \delta \) 127.0 and 128.87 was found for the two tertiary carbons C -1' and C -4' of phenyl rings. The peak at \( \delta \) 129.36 and 131.35 represent the aromatic carbons of C -2', C-6' and C -3', C-5' of six phenyl rings respectively. The chemical shift at \( \delta \) 141.47 was obtained for the carbons C-2, C-4 and C-6 of melamine ring. The chemical shift at \( \delta \) 161.30 was obtained for carbonyl carbon (C=O). Mass spectrometry data indicated the proposed structures of metalloendrimers compound 9. Positive-molecular ion mass peak (M⁺) 1481.58 indicated the molecular ion of the compound.
2.4.3 Characterization of 2,4,6-Tris(di-4-methoxybenzamido)-1,3,5-triazine palladium(II) chloride 10

The compound was synthesized from 2,4,6-triamino-1,3,5-triazine (melamine) with the reaction of p-methoxybenzoyl chloride by stirring at room temperature for 6-7 hours in the presence of (Ph₃P)₂PdCl₂ and solvent (DMF).

The structure of the compound was established by various spectral data.

In IR spectrum of the compound the absorption band was found at 3014.5 cm⁻¹ due to the C-H (aro) stretching absorption, whereas a broad band at 2984.85 cm⁻¹ stretching absorption represents the (C=H) aliphatic group. Absorption band at 1608.39 cm⁻¹ display keto (C=O) group. Stretching absorption νmax 1304.84, 1288.4 and 1027.13 cm⁻¹ stretching bands indicated the presence of C=N, aromatic C=C and C-N respectively.

In ¹H NMR spectrum of compound 10, the chemical shift at δH 3.79 ppm (s, 6×3H, Ar-OCH₃) was found as a singlet for the hydrogen atoms in six -OCH₃ groups. Chemical shift at δH 6.99 ppm (m, 6×2H, Ph-H) showed a doublet for aromatic protons of C -3’, C-5’ carbon of six phenyl rings and δH 7.923 ppm (6×2H, Ph-H) showed another doublet for similar protons of C-2’, C-6’ carbon of six phenyl rings.

In the ¹³C NMR spectral data of compound 10, the chemical shift δC 55.406 indicated the presence of six identical carbons in six methyl groups (Ar-OCH₃). The chemical shift at δC 123.037 ppm and δC 113.798 ppm was found for the two carbons (C-1’, C-4’) of phenyl rings. The peak at δC 131.355 ppm represent aromatic carbons of C-2’, C-6’ and carbons of C-3’, C-5’ of six phenyl rings respectively. The chemical shift at δC 162.86 ppm was obtained for the carbons C-2, C-4 and C-6 of melamine ring. The chemical shift at δC 167.047 ppm was obtained for carbonyl carbon (C=O).
2.4.4 Characterization of 2,4,6-Tris(di-4-benzamido)-1,3,5-Triazine palladium(II) chloride 11

Compound 11 was synthesized from 2,4,6-triamino-1,3,5-triazine (malamine) with the reaction of benzoyl chloride and DMF by stirring at room temperature for 6-7 hours in presence of \((\text{Ph}_3\text{P})_2\text{PdCl}_2\).

The structure of the compound was established by various spectral data.

In IR spectrum of compound 11, the absorption band was found at 3072.4 cm\(^{-1}\) due to the C-H (aro) stretching absorption, whereas a broad band at 1683.7 cm\(^{-1}\) represents the keto (C=O) group. Strong absorption band at 1675.5 cm\(^{-1}\) displays strong C=N stretching absorption. \(\nu_{\text{max}}\) 1585.4 cm\(^{-1}\) stretching bands indicated the presence of C=C in phenyl ring and \(\nu_{\text{max}}\) 1294.1 cm\(^{-1}\) indicated the presence of aromatic C-N stretching.

In \(^1\text{H}\) NMR spectrum of compound 11, Chemical shift at \(\delta_{\text{H}}\) 7.45 (t, 6×2H, Ar-H, J=7.5 Hz) was found for the two carbons (C-1', C-4') of phenyl rings, 7.62 (t, 6×1H, Ar-H, J=6.5 Hz) showed a doublet for aromatic protons of C-3', C-5' carbon of six phenyl rings and \(\delta_{\text{H}}\) 8.15 (d, 6×2H, Ar-H, J=7.0 Hz) showed another doublet for similar protons of C-2', C-6' carbon of six phenyl rings.

In \(^{13}\text{C}\) NMR spectral data of compound 11, the peak at \(\delta\) 130.34 was found for two the carbons (C-1', C-4') of phenyl ring chemical shift at \(\delta\) 128.60 and \(\delta\) 129.46 represent the aromatic carbons of C-2', C-6' and carbons of C-3', C-5' of six phenyl rings respectively. The chemical shift at \(\delta\) 133.94 ppm was obtained for the carbons C-2, C-4 and C-6 of malamine ring and at \(\delta\) 172.77 was obtained for carbonyl carbon (C=O).

![Structure of 2,4,6-Tris(di-4-benzamido)-1,3,5-Triazine palladium(II) chloride 11](image)
2.4.5 Characterization of 2,4,6-Tris(di-4-nitrobenzamido)-1,3,5-triazine palladium(II) chloride 12

The compound 12 was synthesized from 2,4,6-triamino-1,3,5-triazine (malamine) with the reaction of 4-nitrobenzoyl chloride and DMF by stirring at room temperature for 6-7 hours in presence of (Ph3P)2PdCl2.

The structure of the compound was established by various spectral data.

In IR spectrum of the compound, the absorption band was found at 3080.21 cm⁻¹ due to the C-H (aro) stretching absorption, whereas a broad band at 1758.10 cm⁻¹ represents the keto (C=O) group. Strong absorption band at 1592.13 cm⁻¹ displays strong C=N stretching absorption. νmax 1322.23 cm⁻¹ stretching bands indicated the presence of C=C in phenyl ring and νmax 1092.67 cm⁻¹ indicated the presence of aromatic C-N stretching.

In ¹H NMR spectrum of compound, chemical shift at δH 8.104 (6×2H, Ar-H) showed a doublet for aromatic protons of C -3’, C-5’ of six phenyl rings and δH 8.297 ppm (6×2H, Ph-H) showed another doublet for similar protons of C-2’, C-6’ carbon of six phenyl rings.

In the ¹³C NMR spectral data of the compound, the chemical shift at δC 123.688 ppm and δC 136.455 ppm was found for the two tertiary carbons C -1’ and C-4’ of phenyl rings. The peak at δC 130.684 ppm represent the aromatic carbons of C -2’, C-6’ and C-3’, C-5’ of six phenyl rings. The chemical shift at δC 150.012 ppm was obtained for the carbons C-2, C-4 and C-6 of melamine ring. The chemical shift at δC 165.819 ppm was obtained for carbonyl carbon (C=O).
2.4.6 Characterization of 2,4,6-Tris(di-4-methylbenzamido)-1,5-diazine Palladium(II) chloride 13

The compound 13 was synthesized from 2,4,6-triamino-1,5-diazine (pyrimidine) with reaction of p-methyl benzoic chloride and DMSO by stirring at room temperature for about 6-7 hours in presence of (Ph₃P)₂PdCl₂.

The structure of the compound was established by various spectral data.

In IR spectrum of compound 13, the absorption band was found at 3052.29 cm⁻¹ and 2976.31 cm⁻¹ due to the C=H (aro) and C-H (ali) stretching absorption respectively, whereas a broad band at 1710.20 cm⁻¹ represents the keto (C=O) group. Strong absorption band at 1611.69 cm⁻¹ displays strong C=N stretching absorption. \( \nu_{max} \) 1418.69 cm⁻¹ stretching bands indicated the presence of C=C in phenyl ring, 468.72 and 1360.20 cm⁻¹ indicated the presence of Pd-Cl and aromatic C-N stretching.

In \(^1\)H NMR spectrum of compound, chemical shift at \( \delta_H \) 8.104 (6×2H, Ar-H) showed a doublet for aromatic protons of C ‘-3’, C-5’ of six phenyl rings and \( \delta_H \) 8.297 ppm (6×2H, Ph-H) showed another doublet for similar protons of C-2’, C-6’ carbon of six phenyl rings.

In the \(^{13}\)C NMR spectral data of compound 13, the chemical shift \( \delta \) 21.63 ppm indicated the presence of carbons in three methyl groups (Ar-CH₃). The chemical shift at \( \delta \) 131.28 ppm and \( \delta \) 129.71 ppm was found for two tertiary carbons (C-1’, C-4’) of phenyl rings. The peak at \( \delta \) 130.50 ppm represents the aromatic carbons of C’ -2’, C-6’ and carbons of C’-3’, C-5’ of six phenyl rings respectively. The chemical shift at \( \delta \) 144.63 ppm was obtained for the carbons C-2, C-3, C-4 and C-6 of pyrimidine ring and \( \delta \) 172.33 ppm was obtained for carbonyl carbon (C=O).

Mass spectrometry data indicated the proposed structure of metallodendrimer compound, 13. Positive-molecular ion mass peak (M+) 1369.44 indicated the molecular ion of the compound.
2.4.7 Characterization of 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine palladium(II) chloride 14

The compound 14 was synthesized from 2,4,6-triamino-1,5-diazine (pyrimidine) with reaction of p-chlorobenzoyl chloride in presence of solvent DMSO by stirring at room temperature for about 6-7 hours in presence of (Ph₃P)₂PdCl₂.

The structure of the compound was established by various spectral data.

In IR spectrum of compound 14, the absorption band was found at 3094.89(s) cm⁻¹ due to the C=H (aro) stretching absorption, whereas a broad band at 1620.20 cm⁻¹ represents the keto (C=O) group. Strong absorption band at 1592.29(s) cm⁻¹ displays strong C=N stretching absorption. 𝜈_{max} 1424.48(m-w) cm⁻¹ stretching bands indicated the presence of C=C in phenyl ring, 𝜈_{max} 1092.71(s) and 460 cm⁻¹ indicated the presence of aromatic C-N and Pd-Cl stretching.

In ^1H NMR spectrum of compound 14, chemical shift at 𝛿_H 8.01 ppm (d, 6×2H, Ar-H) showed a doublet for aromatic protons of C -3́, C-5́ of six phenyl rings and 𝛿_H 7.27 ppm (d, 6×2H, Ar-H) showed another doublet for similar protons of C -2́, C-6́ carbon of six phenyl rings. The chemical shift at 𝛿_H 4.96 ppm (s, 1H, -C-H) was obtained for the proton (-CH) of carbon (C-3) of pyrimidine ring.

In the ^13C NMR spectral data of compound 14, the chemical shift at 𝛿 129.73 ppm and 130.67 ppm was found for the two tertiary carbons (C-1́ and C-4́) of phenyl ring. The peak at 𝛿 132.34 ppm represents the aromatic carbons of C -2́, C-6́ and carbons C -3́, C-5́ of six phenyl rings respectively. The chemical shift at 𝛿 140.24 ppm was obtained for the carbons C-2, C-3, C-4 and C-6 of pyrimidine ring. The chemical shift at 𝛿 16.71 ppm was obtained for carbonyl carbon (C=O).

Mass spectrometry data indicated the proposed structure of metallodendrimer compound 14. Positive-molecular ion mass peak (M+) 1479.55 indicated the molecular ion of the compound.
2.4.8 Characterization of 2,4,6-Tris(di-4-methoxybenzamido)-1,5-diazine Palladium(II) Chloride 15

Compound 15 was synthesized from 2,4,6-triamino-1,5-diazine (pyrimidine) with reaction of \( p \)-methyl benzyol chloride and DMSO by stirring at room temperature for 6-7 hours in presence of \((\text{Ph}_3\text{P})_2\text{PdCl}_2\).

The structure of the compound was established by various spectral data.

In IR spectrum of compound 15, the absorption band was found at 3052.29 cm\(^{-1}\) and 2976.31 cm\(^{-1}\) due to the C=H (aro) and C-H (ali) stretching absorption respectively, whereas a broad band at 16083.91 cm\(^{-1}\) represents the keto (C=O) group. Strong absorption band at 1304.84 cm\(^{-1}\) displays strong C=N stretching absorption. \( v_{\text{max}} \) 2664.75 cm\(^{-1}\) and 2645.16 cm\(^{-1}\) stretching bands indicated the presence of C=C in phenyl ring and \( v_{\text{max}} \) 1027.13 cm\(^{-1}\) indicated the presence of aromatic C-N stretching.

In \(^1\text{H NMR}\) spectrum of compound 15, the chemical shift at \( \delta_{\text{H}} \) 3.8 ppm (s, 6×3H, Ar-\text{OCH}_3) was found as a singlet for the hydrogen atoms in six aromatic methyl (-\text{OCH}_3) groups. Chemical shift at \( \delta_{\text{H}} \) 7.8 ppm (6×2H, Ph-H) showed a doublet for aromatic protons of C -3', C-5' carbons of six phenyl rings and \( \delta_{\text{H}} \) 6.9 ppm (d, 6×2H, Ar-H) showed another doublet for similar protons of carbons C-2', C-6' of six phenyl rings. The chemical shift at \( \delta_{\text{H}} \) 3.3 ppm (s, 1H, -C-H) was obtained for the proton (-\text{CH}) of carbon (C-3) of pyrimidine ring.

In the \(^{13}\text{C NMR}\) spectral data of compound 15, the chemical shift \( \delta_{\text{C}} \) 55.406 ppm indicated the presence of carbons in three methyl groups (Ar-\text{OCH}_3). The chemical shift at \( \delta_{\text{C}} \) 122.947 ppm and \( \delta_{\text{C}} \) 113.732 ppm was found for two tertiary carbons (C-1', C-4') of phenyl rings. The peak at \( \delta_{\text{C}} \) 131.287 ppm represents the aromatic carbons of C -2', C-6' and carbons of C-3', C-5' of six phenyl rings respectively. The chemical shift at \( \delta_{\text{C}} \) 162.803 ppm was obtained for the carbons C-2, C-3, C-4 and C-6 of pyrimidine ring and \( \delta_{\text{C}} \) 166.957 ppm was obtained for carbonyl carbon (C=O).
2.4.9 Characterization of 2,4,6-Tris(di-benzamido)-1,5-Diazone palladium(II) chloride 16

The compound 16 was synthesized from 2,4,6-triamino-1,5-diazone (pyrimidine) with the reaction of benzoyl chloride and DMF by stirring at room temperature for 6-7 hours in presence of (Ph₃P)₂PdCl₂.

The structure of the compound was established by various spectral data.

In IR spectrum of compound 16, the absorption band was found at 3072.4 cm⁻¹ due to the C-H (aro) stretching absorption, whereas a broad band at 1691.4 cm⁻¹ represents the keto (C=O) group. Strong absorption band at 1683.7 cm⁻¹ displays strong C=N stretching absorption. \( \nu_{\text{max}} \) 1585.4 cm⁻¹ stretching bands indicated the presence of C=C in phenyl ring and \( \nu_{\text{max}} \) 1294.1 cm⁻¹ indicated the presence of aromatic C-N stretching.

In \(^1\)H NMR spectrum of compound 16, Chemical shift at \( \delta_H \) 7.45 (t, 6×2H, Ar-H, J=7.5 Hz) was found for the two carbons (C-1’, C-4’) of phenyl rings, 7.62 (t, 6×1H, Ar-H, J=6.5 Hz) showed a doublet for aromatic protons of C-3’, C-5’ carbon of six phenyl rings and \( \delta_H \) 8.15 (d, 6×2H, Ar-H, J=7.0 Hz) showed another doublet for similar protons of C-2’, C-6’ carbon of six phenyl rings.

In \(^13\)C NMR spectral data of compound 16, the peak at \( \delta \) 130.34 was found for two the carbons (C-1’, C-4’) of phenyl ring. Chemical shift at \( \delta \) 128.60 and \( \delta \) 129.46 represent the aromatic carbons of C-2’, C-6’ and carbons of C-3’, C-5’ of six phenyl rings respectively. The chemical shift at \( \delta \) 133.94 ppm was obtained for the carbons C-2, C-4 and C-6 of ring of pyrimidine ring, chemical shift at \( \delta \) 144.75 ppm was obtained for the carbons C-3 of pyrimidine ring and at \( \delta \) 172.77 was obtained for carbonyl carbon (C=O).
2.4.10 Characterization of 2,4,6-Tris(di-4-nitrobenzamido)-1,5-diazine palladium(II) chloride 17

The compound 17 was synthesized from 2,4,6-triamino-1,5-diazine (pyrimidine) with reaction of 4-nitrobenzoyl chloride and DMF by stirring at room temperature for 6-7 hours in presence of (Ph₃P)₂PdCl₂.

The structure of the compound was established by various spectral data.

In IR spectrum of the compound, the absorption band was found at 3080.21 cm⁻¹ due to the C-H (aro) stretching absorption, whereas a broad band at 1758.10 cm⁻¹ represents the keto (C=O) group. Strong absorption band at 1592.13 cm⁻¹ displays strong C=N stretching absorption. ν_max 1322.23 cm⁻¹ stretching bands indicated the presence of C=C in phenyl ring and ν_max 1092.67 cm⁻¹ indicated the presence of aromatic C-N stretching.

In ¹H NMR spectrum of compound, chemical shift at δ_H 8.043 (6×2H, Ar-H) showed a doublet for aromatic protons of C-3’, C-5’ of six phenyl rings and δ_H 8.221 ppm (6×2H, Ph-H) showed another doublet for similar protons of C-2’, C-6’ carbon of six phenyl rings and δ_H 7.544 ppm for 1H of pyrimidine ring.

In the ¹³C NMR spectral data of the compound, the chemical shift at δ_C 123.614 ppm and δ_C 130.677 ppm was found for the two tertiary carbons C-1’ and C-4’ of phenyl rings. The peak at δ_C 137.040 ppm and δ_C 149.921 ppm represent the aromatic carbons of C-2’, C-6’ and C-3’, C-5’ of six phenyl rings. The chemical shift at δ_C 149.921 ppm was obtained for the carbons C-2, C-4 and C-6 of pyrimidine ring. The chemical shift at δ_C 161.163 ppm (C-3 of pyrimidine ring) and δ_C 166.20 ppm was obtained for carbonyl carbon (C=O).
Scanning Electron Microscope (SEM) and Energy Dispersive X-ray (EDX) Spectroscopic Analysis of the compounds (8, 9, 13 and 14)

2.5 General Discussion:

**Scanning electron microscope (SEM)** is a type of electron microscope that produces images of a sample by scanning it with a focused beam of electrons. The electrons interact with atoms in the sample, producing various signals that can be detected and that contain information about the sample's surface topography and composition. 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 10 KV with magnifications ranging from 50.00-1.00 µm. The sphericity of the micrographs was found good.

**Energy-dispersive X-ray spectroscopy (EDS, EDX, or XEDS),** sometimes called energy dispersive X-ray analysis (EDXA) or energy dispersive X-ray microanalysis (EDXMA), is an analytical technique used for the elemental analysis or chemical characterization of a sample. It relies on an interaction of some source of X-ray excitation and a sample. Its characterization capabilities are due in large part to the fundamental principle that each element has a unique atomic structure allowing unique set of peaks on its X-ray spectrum. The number and energy of the X-rays emitted from a specimen can be measured by an energy-dispersive spectrometer. As the energy of the X-rays is characteristic of the difference in energy between the two shells, and of the atomic structure of the element from which they were emitted, this allows the elemental composition of the specimen to be measured. Metal detection or investigation of metallodendrimer has been performed by employing Energy Dispersive X-ray or EDX method. The EDX spectrum was taken by selecting a zone or area of a specific particle of the sample. EDX makes use of the X-ray spectrum emitted by a solid sample bombarded with a focused beam of electrons to obtain a localized chemical analysis. All elements from atomic number 4 (Be) to 92 (U) can be detected in principle, though all instruments are equipped for light elements (Z< 10). The details of the SEM images and EDX spectra of some of the synthesized compounds are shown below-
2.5.1a SEM images and EDX spectrum of compound 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8

The SEM images of the compound 8 were taken in a Scanning Electron Microscope and described as the following way. 2.5.1 shows the SEM image of different magnification range of compound 8 synthesized as described in chapter-3. This image represented as “blooming flower”

By applying from 10 kv 10.3mmx800 SE(M) to 10 kv 10.3mmx40 k SE(M), the range of particle size of the compound were found 50.0 µm to 1.00 µm.

like structure.
2.5.1b EDX spectrum of compound 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8

<table>
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<th>O</th>
<th>Cl</th>
<th>Pd</th>
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<tr>
<td>Max.</td>
<td></td>
<td>61.31</td>
<td>22.73</td>
<td>15.55</td>
<td><strong>0.24</strong></td>
<td><strong>0.17</strong></td>
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<tr>
<td>Min.</td>
<td></td>
<td>61.31</td>
<td>22.73</td>
<td>15.55</td>
<td><strong>0.24</strong></td>
<td><strong>0.17</strong></td>
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</tbody>
</table>

Processing option: All elements analysed (Normalised)

All results in atomic%
From EDX analysis, the presence of metal (Palladium) was well observed and it was 1.39% of weight and 0.17% of atomic of the compound. From EDX analysis chlorine was found to be 0.64% of weight and 0.24% of atomic of the compound. So it can be said that palladium metal was present as palladium chloride in our synthesized compound and the reaction was successful for the preparation of the required metallodendrimer.

<table>
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Spectrum processing:
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Processing option: All elements analyzed (Normalised)
Number of iterations = 3

Standard:
C  CaCO3  1-Jun-1999 12:00 AM

2.5.2a SEM images and EDX of compound of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine palladium(II) chloride 9

The SEM images of the compound 9 were taken in a Scanning Electron Microscope and described as the following way. 2. 5. 2 shows the SEM image of different magnification range of compound 9 synthesized. This image represented as “leafs of tree” like structure.
2.5.2a SEM images of compound of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine palladium(II) chloride

By applying from 10 kv 10.3 mm x300 SE(M) to 10 kv 10.2mmx1.0 k SE(M), the range of particle size of the compound were found 100.0 µm to 50.00 µm.
2.5.2b EDX of compound of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine palladium (II) chloride 9

<table>
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<th>Weight%</th>
<th>Weight% Sigma</th>
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Processing option: All elements analyzed (Normalised)
Number of iterations = 3

Standard:
C  CaCO3  1-Jun-1999 12:00 AM
From EDX analysis, the presence of metal (Palladium) is well observed and it is .54% of weight and 0.07 % of atomic of the compound. In our synthesized compound 9, there was chlorine atom but from EDX analysis the amount of chlorine was found to be high as compared to required amount of the dendrimer and was 0.64% of weight and 0.24% of atomic of the compound. So it can be said that palladium metal was present as palladium chloride in our synthesized compound and so it can be said that the reaction was successful for the preparation of the required metallodendrimer.

2.5.3a SEM images of compound of 2,4,6-Tris(di-4-methylbenzamido)-1,5-diazine palladium(II) chloride 13

The SEM images of the compound 13 were taken in a Scanning Electron Microscope and described as the following way. 2.5.3 shows the SEM image of different magnification range of compound 13. This image represented as “branches of tree without leafs” like structure. By applying from 10 kv 10.1mmx400 k SE(M) to 10 kv 10.1 mmx110 k SE(M), the range of particle size of the compound were found 100 µm to 500 nm.
2.5.3a SEM images of compound of 2,4,6-Tris(di-4-methylbenzamido)-1,5-diazine palladium(II) chloride 13
2.5.3b EDX of compound of 2,4,6-Tris(di-4-methylbenzamido)-1,5-diazone palladium(II) chloride 13

Spectrum processing:
Peaks possibly omitted: 0.800, 0.935, 2.065, 8.04keV
Processing option: All elements analyzed (Normalised)
Number of iterations = 2

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N   Not defined   1-Jun-1999 12:00 AM

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</table>
From EDX analysis, the presence of metal (Palladium) is well observed and it was 4.10% of weight and 0.056 % of atomic of the compound. From EDX analysis chlorine was found to be 0.82% of weight and 0.33% of atomic of the compound. So it can be said that palladium metal was present as palladium chloride in our synthesized compound and the reaction was successful for the preparation of the required metallodendrimer.

2.5.4a SEM images and EDX of compound 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine palladium chloride(II) 14

The SEM images of the compound 14 were taken in a Scanning Electron Microscope and described as the following way. 2.5.4a shows the SEM image of different magnification range of compound 14. This image represented as like structure “rectangular fiber.” Each chain stacked with neighboring chain by π-π stacking interaction and formed fibrical morphology. The fibers are stabilized by π-stacking of the aromatic core of the ligands. By applying from 10 kv 10.1mmx500 k SE(M) to 10 kv 10.1mmx7.0 k SE(M), the range of particle size of the compound were found 100 µm to 5 µm.
2.5.4a SEM images of 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine palladium(II) chloride 14
2.5.4b EDX of compound 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine palladium(II) chloride 14

From EDX analysis, the presence of metal (Palladium) is well observed and it is 0.25% of weight and 0.04% of atomic of the compound. From EDX analysis the amount of chlorine was found to be high as compared to required amount of the dendrimer and was 29.81% of weight and 13.06% of atomic of the compound. So it can be said that palladium metal was present as palladium chloride in our synthesized compound and the reaction was successful for the preparation of the required metallodendrimer.
3. General discussion

Unless otherwise noted, all reagents were reagent grade and were used without purification. Dehydrated DMF, DMSO were used as reaction solvent. These solvents were purchased from Aldrich and used as received. De-ionized water was used in the experiment where required. The melting point of the synthesized compounds were determined by open capillary tubes by a melting point apparatus (Model BUCHI, B-540). The IR specrtra were taken on a Shimadzu FTIR 8400S Fourier Transform. Infrared Spectrophotometer (400-4000 cm⁻¹) with KBr pellets. ¹H-NMR and ¹³C-NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a JEOL AL 300/BZ instrument. Chemical shifts were given relative to TMS. Mass spectra (MS) were measured by using AXIMA-CFR, Shimadzu/Kratos TOF Mass spectrometer. Analytical thin layer chromatography (TLC) were Merck aluminium oxide 60 F254 neutral or silica gel 60 F254 coated on 25 TCC aluminium sheets (20 × 20 cm). Flash column chromatographic. All reagents were purchased from Sigma Aldrich and were directly used without further purification.

3.1 Synthesis of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8

The mixture of 0.2 g (0.00158 mol) melamine, 3 mL p-methylbenzoylchloride and 8 mol% of bis-triphenyl phosphine Palladium (II) chloride was added in 5 mL of DMF and the reaction mixture was stirred at room temperature for around 5-6 hours in a 250 mL round bottom flask. 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 6 hours the reaction was stopped by adding distilled water. After a while it was filtered under suction on a Buchner funnel and washed with sufficient distilled water, washed with sodium bicarbonate to remove completely any remaining acid. Finally the product was crystallized by using ethyl acetate and the required compound was obtained which was white crystalline solid.
MF: C_{51}N_{62}O_{6}Pd_{3}Cl_{6}
MW: 1366.8938

Physical analysis: white crystalline solid, m. p: 328-330 °C, odorless and 90 % of yield.

Analytical analysis:
IR (KBr): ν_{max} (cm^{-1}) 3010.43 (C-H aro.), 1760.21 (C=O), 1612.52 (C=N), 1416.23 (C=C aro.), 1288.46 (C-N), 1332.46 (CH_{3}), 488.72 (Pd-Cl) cm^{-1}.

^{1}H NMR (300 MHz, CD_{3}OD): δ_{H} 2.39 ppm (s, 6×3H, Ar-CH_{3}), δ_{H} 7.28 ppm (6×2H, Ph-H) and δ_{H} 7.923 ppm (6×2H, Ph-H).

^{13}C NMR (75 MHz, CD_{3}OD): δ_{C} 21.634 (6C of 6CH_{3}), δ_{C} 129.07 ppm (C-1 of benzene ring) δ_{C} 130.506 ppm (C-2, C-6, C-3, C-5 of benzene ring), δ_{C} 131.28 ppm (C-4 of benzene ring), δ_{C} 144.37 ppm (C-2, C-4, C-6 of melamine ring) and δ_{C} 170.02 ppm (C=O).

3.2 Synthesis of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine palladium(II) chloride 9
The mixture of 0.2 g (0.00158 mol) melamine, 3 mL p-chlorobenzoylchloride and 8 mol% of bis-triphenyl phosphine Palladium (II) chloride was added in 5 mL of DMSO in a round bottle flask and the reaction was carried out by a similar procedure described by compound 8.
MF: C_{45}N_{6}H_{54}O_{6}Pd_{3}Cl_{12}

MW: 1489.4047

Physical analysis: White crystalline solid, m. p: 310-312° C, odorless and 90 % of yield.

Analytical analysis:

IR (KBr): $\nu_{\text{max}}$ (cm$^{-1}$) 3080.21 (C-H aro.), 1758.1 (C=O), 1592.13 (C=N aro.), 1322.23 (C=C aro.), 1092.67 (C-N aro.), 472.92 (472.92) cm$^{-1}$.

$^1$H NMR (300. MHz, CD$_3$OD): $\delta$H 7.27 ppm (6×2H, Ph-H) and $\delta$H 7.92 ppm (6×2H, Ph-H).

$^{13}$C NMR (75 MHz, CD$_3$OD): $\delta$C 129.73 ppm (C-1 of benzene ring), $\delta$C 132.34 ppm (C-2, C-6, C-3, C-5 of benzene ring), $\delta$C 130.67 ppm (C-4 of benzene ring), $\delta$C 140.24 ppm (C-2, C-4, C-6 of melamine ring) and $\delta$C 168.71 ppm (C=O).

3.3 Synthesis of 2,4,6-Tris(4-methoxybenzamido)-1,3,5-triazine palladium(II) chloride 10

The mixture of 0.2 g (0.00158 mol) melamine, 3 mL $p$-methoxybenzoylchloride and 8 mol% of bis-triphenyl phosphine Palladium (II) chloride was added in 5 mL of DMSO in a 250 ml round bottle flask. The reaction was carried out by a similar procedure described by compound 8.
MF: C_{51}N_{6}H_{42}O_{12}Pd_{3}Cl_{6}

MW: 1462.8902

Physical analysis: White crystalline solid, m. p: 320-322°C, odorless and 95 % of yield.

Analytical analysis:

IR (KBr): ν_{max} (cm^{-1}) 3014.5, 2984.85, 2844.13, 2664.75, 2645.16, 16083.91, 1304.84, 1027.13 and 844.85 cm^{-1}

H NMR (300 MHz, CD_{3}OSCD_{3}): δ_{H} 3.79 ppm (s, 6×3H, Ar-OCH_{3}), δ_{H} 6.99 ppm (m, 6×2H, Ph-H) and δ_{H} 7.923 ppm (6×2H, Ph-H).

C NMR (75 MHz, CD_{3}OD): δ_{C} 55.406 (6C of 6OCH_{3}), δ_{C} 113.798 ppm (C-4 of benzene ring), δ_{C} 131.355 ppm (C-2, C-6, C-3, C-5 of benzene ring), δ_{C} 123.037 ppm (C-1 of benzene ring), δ_{C} 162.86 ppm (C-2, C-4, C-6 of melamine ring) and δ_{C} 167.047 ppm (C=O).

3.4 Synthesis of 2,4,6-Tris(di-benzamido)-1,3,5-triazine palladium(II) chloride 11

The mixture of 0.2 g (0.00158 mol) melamine, 3.5 ml benzoylchloride and 8 mol% of bis-triphenyl phosphine palladium (II) chloride was added in 6 mL DMF in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound 8.
MF: C₄₅N₆Ho₈Pd₃Cl₆

MW: 1282.7343

Physical analysis: White crystalline solid, m. p: 290-292°C, odorless and 90% of yield.

Analytical analysis:

IR (KBr): νmax (cm⁻¹) 3072.4, 1691.5, 1683.7, 1585.4 and 1294.1 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δH 7.45 (t, 6×2H, Ar-H, J=7.5 Hz), 7.62 (t, 6×1H, Ar-H, J=6.5 Hz), δH 8.15 (d, 6×2H, Ar-H, J=7.0 Hz).

¹³C NMR (75 MHz, CDCl₃): δC 128.60, 129.46, 130.34, 133.94, 144.75 and 172.77 ppm.

3. 5 Synthesis of 2,4,6-Tris(di-4-nitrobenzamido)-1,3,5-triazine palladium(II) chloride 12

The mixture of 0.2 g (0.00158 mol) melamine, 1.8 g p-nitrobenzoylchloride and 8 mol% of bis-triphenyl phosphine Palladium (II) chloride was added in 5 mL of DMF in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound 8.
MF: C_{45}N_{12}H_{24}O_{18}Pd_{3}Cl_{6}

MW: 1552.7196

Physical analysis: White crystalline solid, m. p: 304-306° C, odorless and 89% of yield.

Analytical analysis:

IR (KBr): $\nu_{\text{max}}$ (cm$^{-1}$) 3080.21 (C-H aro.), 1758.1 (C=O), 1592.13 (C=N aro.), 1322.23 (C=C aro.), 1092.67 (C-N aro.) cm$^{-1}$.

$^1$H NMR (300 MHz, CD$_3$OD): $\delta_H$ 8.104 ppm (6×2H, Ph-H) and $\delta_H$ 8.297 ppm (6×2H, Ph-H).

$^{13}$C NMR (75 MHz, CD$_3$OD): $\delta_C$ 123.688 ppm (C-1 of benzene ring), $\delta_C$ 130.684 ppm (C-2, C-6, C-3, C-5 of benzene ring), $\delta_C$ 136.455 ppm (C-4 of benzene ring), $\delta_C$ 150.012 ppm (C-2, C-4, C-6 of melamine ring) and $\delta_C$ 165.819 ppm (C=O).

3.6 Synthesis of 2,4,6-Tris(di-4-methylbenzamido)-1,5-diazine Palladium(II) chloride 13

The mixture of 0.1 g (0.00159 mol) Triaminopyrimidine, 3 mL p-toluylchloride and 8 mol% in presence of (Ph$_3$P)$_2$PdCl$_2$ in 8 mL of DMSO in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound 8.
MF: C₅₂N₅₅H₄₈O₆Pd₃Cl₆

MW: 1365.9057

Physical analysis: White crystalline solid, m. p. 324-326 C, odorless and 90 % yield.

Analytical analysis:
IR (KBr): ν max (cm⁻¹) 3052.29 (C=H aro.), 2976.31 (C-H ali.), 1710.20 (C=O), 1611.69 (C=N), 1418.69 (C=C), 1360.20 (C-N aro.), 468.72 (Pd-Cl) cm⁻¹.

¹H NMR (300 MHz, CD₃OD): δ_H 2.3 ppm (s, 6×3H, Ar-CH₃), δ_H 7.23 ppm (d, 6×2H, Ar-H), δ_H 7.80 ppm (d, 6×2H, Ar.-H ) and δ_H 4.96 ppm (s, 1H, C-H) ppm.

¹³C NMR (75 MHz, CD₃OD): δ_C 21.63 ppm (C of CH₃), 129.28 ppm (C4 of benzene ring), 130.50 ppm (C2, C6, C3, C5 of benzene ring), 131.28 ppm (C1 of benzene ring), 144.63 ppm (C2, C3, C4, C6 of pyrimidine ring) and 172.33 (C=O) ppm.

3.7 Synthesis of 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine Palladium(II) chloride 14

The mixture of 0.2 g (0.00159 mol) 2, 4, 6 triaminopyrimidine, 3mL p-chlorobenzoylchloride and 8 mol% of bis-triphenyl phosphine Palladium (II) chloride (Ph₃P)₂PdCl₂ was added in 10 mL DMF in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound 8
MF: C_{46}N_{5}H_{25}O_{6}Pd_{3}Cl_{12}

MW: 1488.4166

Physical analysis: White crystalline solid, m. p: 308-310 C, odorless and 90 % of yield.

Analytical analysis:
IR (KBr): $\nu_{\text{max}}$ (cm$^{-1}$) 3094.89 (C=H aro.), 1680.20 (C=O), 1592.29 (C=N), 1424.489 (C=C aro.), 1092.71 (C-N), 460 (Pd-Cl).

$^1$H NMR (300 MHz, CD$_3$OD): $\delta$H 4.96 ppm (s, 1H, -C-H), $\delta$H 8.01 ppm (d, 6×2H, Ar-H.), And $\delta$H 7.27 ppm (d, 6×2H, Ar-H).

$^{13}$C NMR (75 MHz, CD$_3$OD): $\delta$C 129.73 ppm (C-1 of benzene ring), 130.67 ppm (C-4 of benzene ring), 132.34 ppm (C-2, C-6, C-3, C-5 of benzene ring), 140.24 ppm (C-2, C-3, C-4 and C-6 of pyrimidine ring), and 168.71 (C=O) ppm.

3.8 Synthesis of 2,4,6-Tris(4-methoxybenzamido)-1,5-Diaizine palladium(II) chloride

The mixture of 0.2 g (0.00159 mol) 2, 4, 6 triaminopyrimidine, 3mL $p$-chlorobenzoylchloride and 8 mol% of bis-triphenyl phosphine Palladium (II) chloride ($\text{Ph}_3\text{P})_2\text{PdCl}_2$ was added in 10 mL DMF in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound 8.
**MF:** C$_{52}$N$_5$H$_{43}$O$_{12}$Pd$_3$Cl$_6$

**MW:** 1461.9012

**Physical analysis:** White crystalline solid, m. p: 315-317 °C, odorless and 96% of yield.

**IR (KBr):** $\nu_{\text{max}}$ (cm$^{-1}$) 3014.5, 2984.85, 2844.13, 2664.75, 2645.16, 16083.91, 1304.84, 1027.13 844.85 cm$^{-1}$

$^1$H NMR (300 MHz, CD$_3$OSCD$_3$): $\delta_H$ 3.8 ppm (s, 6×3H, Ar-OCH$_3$), $\delta_H$ 6.9 ppm (6×2H, Ph-H), $\delta_H$ 7.8 ppm (6×2H, Ph-H) and $\delta_H$ 3.3 ppm (1H of pyrimidine ring).

$^{13}$C NMR (75 MHz, CD$_3$OD): $\delta_C$ 55.406 (6C of 6OCH$_3$), $\delta_C$ 113.732 ppm (C-4 of benzene ring) $\delta_C$ 131.287 ppm (C-2, C-6, C-3, C-5 of benzene ring), $\delta_C$ 122.947 ppm (C-1 of benzene ring), $\delta_C$ 162.803 ppm (C-2, C-3, C-4, C-6 of pyrimidine ring) and $\delta_C$ 166.957 ppm (C=O).

3.9 **Synthesis of 2,4,6-Tris(di-benzamido)-1,5-Diazine palladium palladium(II) chloride**

The mixture of 0.2 g (0.00159 mol) melamine, 3.2 ml benzoylchloride and 8 mol% of bis-triphenyl phosphine palladium (II) chloride was added in 10 mL DMF in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound 8.
MF: C₄₅N₆H₃₀O₆Pd₃Cl₆

MW: 1281.7462

Physical analysis: White crystalline solid, m. p: 280-282°C, odorless and 90% of yield.

Analytical analysis:

IR (KBr): $\nu_{\text{max}}$ (cm$^{-1}$) 3072.4, 1691.5, 1683.7, 1585.4 and 1294.1 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta_H$ 7.45 (t, 6×2H, Ar-H, J=7.5 Hz), 7.62 (t, 6×1H, Ar-H, J=6.5 Hz), $\delta_H$ 8.15 (d, 6×2H, Ar-H, J=7.0 Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta_C$ 128.60, 129.46, 130.34, 133.94, 144.75 and 172.77 ppm.

Synthesis of 2,4,6-Tris(di-4-nitrobenzamido)-1,5-Diazine palladium(II) chloride

The mixture of 0.2 g (0.00159 mol) melamine, 1.8 g $p$-nitrobenzoylchloride and 8 mol% of bis-triphenyl phosphine Palladium (II) chloride was added in 5 mL of DMSO in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound 8.
MF: C_{46}N_{11}H_{25}O_{18}Pd_{3}Cl_{6}

MW: 1551.7316

Physical analysis: White crystalline solid, m. p: 305-307°C, odorless and 92% of yield.

Analytical analysis:

IR (KBr): \nu_{\text{max}} (\text{cm}^{-1}) 3080.21 (\text{C-H aro.}), 1758.1 (\text{C=O}), 1592.13 (\text{C=N aro.}), 1322.23 (\text{C=C aro.}), 1092.67 (\text{C-N aro.}) \text{ cm}^{-1}.

^{1}H NMR (300 MHz, CD_{3}OD): \delta_{\text{H}} 8.043 \text{ ppm} (6\times2\text{H}, \text{Ph-H}), \delta_{\text{H}} 8.221 \text{ ppm} (6\times2\text{H}, \text{Ph-H}). \delta_{\text{H}} 7.544 \text{ ppm} 1\text{H of pyrimidine ring.}

^{13}C NMR (75 MHz, CD_{3}OD): \delta_{\text{C}} 123.614 \text{ ppm} (\text{C-4 of benzene ring}), \delta_{\text{C}} 137.040 \text{ ppm} (\text{C-3, C-5 of benzene ring}), \delta_{\text{C}} 149.921 \text{ ppm} \text{C-2, C-6 of benzene ring, } \delta_{\text{C}} 130.677 \text{ ppm} (\text{C-1 of benzene ring}), \delta_{\text{C}} 161.163 \text{ ppm} (\text{C-3 of pyrimidine ring}) \text{ and } \delta_{\text{C}} 166.208 \text{ ppm} (\text{C=O}).
IR spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8

\[ \text{IR spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8} \]

\[ \text{\textsuperscript{1}H NMR spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8} \]
$^{13}$C NMR spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8

Mass spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 8
IR spectra of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine palladium(II) chloride

\[ \text{IR spectra} \]

\[ \text{1H NMR spectra} \]
$^{13}$C NMR spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-triazine palladium(II) chloride 9

Mass spectra of 2,4,6-Tris(di-4-chlorobenzamido)-1,3,5-triazine palladium(II) chloride 9
IR spectra of 2,4,6-Tris(di-4-methoxybenzamido)-1,3,5-triazine palladium(II) chloride 10

1H NMR spectra of 2,4,6-Tris(di-4-methoxybenzamido)-1,3,5-triazine palladium(II) chloride 10
$^{13}$C NMR spectra of 2,4,6-Tris(di-4-methoxybenzamido)-1,3,5-triazine palladium(II) chloride 10
IR spectra of 2,4,6-Tris(di-4-benzamido)-1,3,5-triazine palladium(II) chloride 11

$^1$H NMR spectra of 2,4,6-Tris(di-benzamido)-1,3,5-triazine palladium(II) chloride 11
$^{13}$C NMR spectra of 2,4,6-Tris(di-benzamido)-1,3,5-triazine palladium(II) chloride 11

IR spectra of 2,4,6-Tris(di-4-nitrobenzamido)-1,3,5-triazine palladium(II) chloride 12
\(^1\)H NMR spectra of 2,4,6-Tris(di-4-nitrobenzamido)-1,3,5-triazine palladium(II) chloride 12

\(^{13}\)C NMR spectra of 2,4,6-Tris(di-4-nitrobenzamido)-1,3,5-triazine palladium(II) chloride 12
IR spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,5-Diazine palladium(II) chloride

$^1$H NMR spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,5-Diazine palladium(II) chloride
$^{13}$C NMR spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,3,5-Diazine palladium(II) chloride 13

Mass spectra of 2,4,6-Tris(di-4-methylbenzamido)-1,5-Diazine palladium(II) chloride 13
IR spectrum of the compound 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine palladium(II) chloride 14

$^1$H NMR spectrum of the compound 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine palladium(II) chloride 14
$^{13}$C NMR spectrum of the compound 2,4,6-Tris(di-4-chlorobenzamido)-1,5-diazine palladium(II) chloride 14

Mass spectrum of the compound 2,4,6-tris(di-4-chlorobenzamido)-1,5-diazine palladium(II) chloride 14
IR spectra of 2,4,6-Tris(di-4-methoxybenzamido)-1,5-Diazine palladium(II) chloride 15

1H NMR spectra of 2,4,6-Tris(di-4-methoxybenzamido)-1,5-Diazine palladium(II) chloride 15
$^{13}$C NMR spectra of 2,4,6-Tris(di-4-methoxybenzamido)-1,5-Diazone palladium(II) chloride 15

$^1$H NMR spectra of 2,4,6-Tris(di-4-nitrobenzamido)-1,5-Diazone palladium(II) chloride 17
$^{13}$C NMR spectra of 2,4,6-Tris(di-4-nitrobenzamido)-1,5-Diazine palladium(II) chloride
Conclusion:
The following points can be concluded from the research work-

- A facile method for the synthesis of some highly functionalized dendrimer compounds from the reaction of commercially available 2,4,6-triamino–1,3,5–triazine (melamine) and 2,4,6-triamino–1,5-diazine (pyrimidine) with different aroylchlorides has been developed.
- The synthesis of metallodendrimer compounds was also carried out by using synthesized dendrimer in the presence of \((\text{Ph}_3\text{P})_2\text{PdCl}_2\) in DMF under room temperature.
- The surface morphology and particle size of the compounds were studied by Scanning Electron Microscope (SEM) and all the synthesized compounds were found to excellent morphology and the particle size range from 100 µm to 500 nm. The structure were found like blooming flower (compound 8), leafs of tree (compound 9), branches of tree without leaf (compound 13), rectangular fiber (compound 14).
- The presence of the elements of the synthesized compounds were detected by EDX.
- The polar aprotic solvents (DMF, DMSO) were found to the good solvent for this method.
- These synthesized compounds would be important ligands and the metallodendrimers would be potent catalyst which is under study.
- The most important features of these methods were that, the readily available inexpensive materials were used under relatively mild conditions and got relatively higher yield.
Therefore, this methodology could be utilized to synthesize the biologically important metallodendrimers mild conditions.
References:


11. Percec, V., Johansen, G., Unger, G. and Zhou, J., “Fluorophobic effect induces the selfassembly of semifluorinated tapered monodendrons containing crown ethers into


