Synthesis And Characterization Of Metallodendrimers Containing Nickel Using 2,4,6-Tri Amino Pyrimidine

By

Sadia Hoque Munia
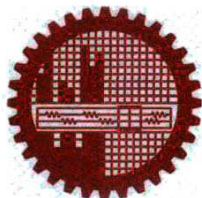
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Board of Examiners

_30.03.2019_

1. Dr. Md. Wahab Khan
Professor
Department of Chemistry
BUET, Dhaka.

Supervisor & Chairman

2. Dr. Md. Abdur Rashid
Professor & Head
Department of Chemistry
BUET, Dhaka.

Member (Ex-officio)

3. Dr. Md. Ayub Ali
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Department of Chemistry
BUET, Dhaka.

Member

4. Dr. A. M. Sarwaruddin Chowdhury
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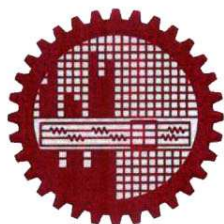
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It is hereby declared that this thesis or any part of it has not been submitted elsewhere for the award of any degree or diploma.

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SADIA HOQUE MUNIA
Student No:0413033118 F
Session: April-2013
Department of Chemistry
BUET, Dhaka-1000

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DEDICATED

TO

MY BELOVED PARENTS
&
HONORABLE SUPERVISOR

ACKNOWLEDGEMENT

IN THE NAME OF ALLAH, THE MOST GRACIOUS, THE MOST MERCIFUL.

"IF YOU GIVE THANKS I WILL GIVE YOU MORE"—QURAN 14:7

At the beginning, I humbly acknowledge my deepest gratitude to the Almighty, Allah, the most benevolent and merciful creator for His infinite mercy bestowed on me and who has enabled me in carrying out the research work presented in this dissertation.

I feel entitled to write this section with the intent of being comprehensive rather than succinct. It is the best opportunity I have to thank all of the people who have helped me throughout my M.Phil. journey.

I am extremely delighted to express my indebtedness and deepest sense of gratitude and sincere thanks to my reverend teacher and supervisor **Professor Dr. Md. Wahab Khan**, Department of Chemistry, Bangladesh University of Engineering And Technology, Dhaka, for his indispensable guidance, constant encouragement, untiring efforts, keen interest and thoughtful suggestions throughout the progress of this research work. It is obvious that his attributive contribution and efforts have greatly shaped me into what I am today. In fact I am quite lucky to be a part of his ambitious research team.

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Abstract

In the light of precedent and current developments, there is preference for the development of new bioorganometallic metallodendrimers. Dendrimers and Metallodendrimers are highly branched, globular, multivalent, monodisperse three dimensional fractal like macromolecules with synthetic resourcefulness and many promising applications ranging from catalysis to electronics and drug delivery. Because of multipurpose applications it was intended to expand a method to synthesis nickel containing metallodendrimer molecules using 2,4,6-triaminopyrimidine or Diazine.

At first, a suitable process for the synthesis of metallodendrimer compounds **7-11** was developed from the reaction of diazine (pyrimidine) with different aroylchlorides **2-6** in presence of $(Ph_3P)_2NiBr_2$ at room temperature as shown in the **scheme 1.**
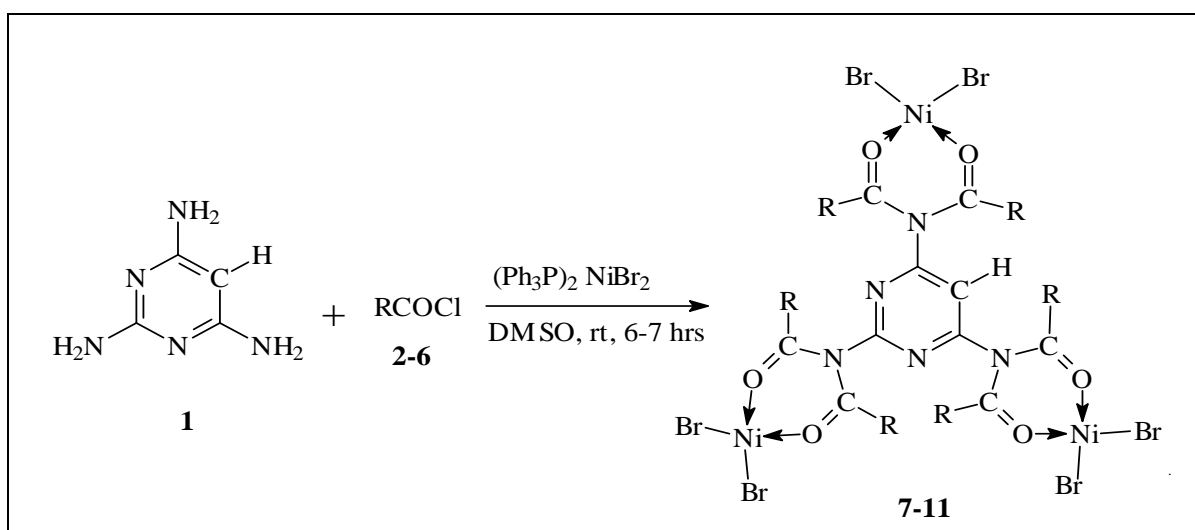
Scheme: 1

2, 7 $R = C_6H_4CH_3(p)$
3, 8 $R = C_6H_4NO_2 (p)$
4, 9 $R = C_6H_5$
5, 10 $R = C_6H_4Cl (p)$
6, 11 $R = C_6H_4OCH_3 (p)$

The synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR spectrophotometry to establish the structure. SEM was taken for analysis of surface morphology. The Compounds were found having a homogeneous and non☐homogeneous morphology with the particle size range from 100 μm to 500 μm. The particle size detected by SEM indicated that the molecule was supramolecule.

LIST OF ABBREVIATIONS

Ac	acetyl
aq.	Aqueous
b p	Boiling point
br	broad
dt	doublet
dec.	Decomposition
DMSO	*N, N*-dimethyl sulfoxide
equiv.	Equivalent
Et	ethyl
Et_2O	diethyl ether
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
rt	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/ δc	chemical shift
λ_{max}	ultraviolet absorption in nm
ν_{max}	infrared absorption in cm^{-1}

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Chapter - 1

Introduction

1.1 Dendrimers: an overview

Dendrimers, in contrast to linear polymers, are symmetrically highly branched, monodispersed three dimensional fractal like macromolecules.
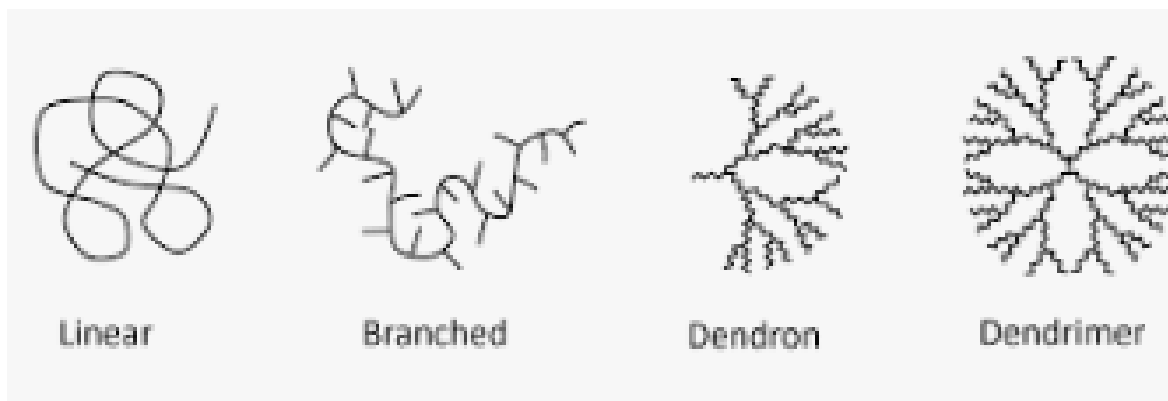
Figure 1.1: Linear, Branched polymers, Dendron and Dendrimer

These nanoparticles, similar in size (5-10 nanometers in diameter) to naturally occurring proteins were attained by an repetitive order of reaction steps producing a higher generation (G) molecule [1a-f].
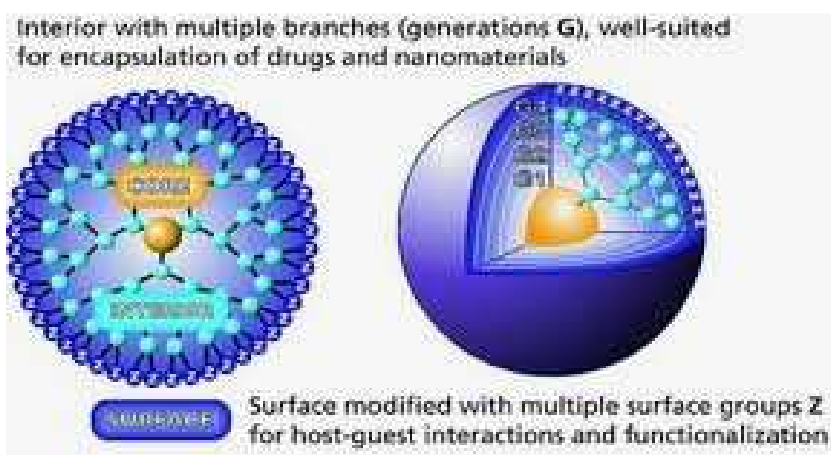
Figure 1.2 : Higher Generation Dendrimer

Large dendrimers have a tendency to assume a globular shape [1g-j].

The "Dendrimer'' word derived from two Greek words *Dendron*: "tree/branch'' and *meros*: "part'' [2].

Chemists' interest towards dendrimers is featured to the specifically determined molecular and more or less perfect structures they demonstrate when compared to usual polymers. In addition, dendrimers and linear polymers show significant differences in their physical properties [3, 4]. For instance, dendrimers have established a dissimilar solubility outline as soon as compared with their linear counter parts [5-9].
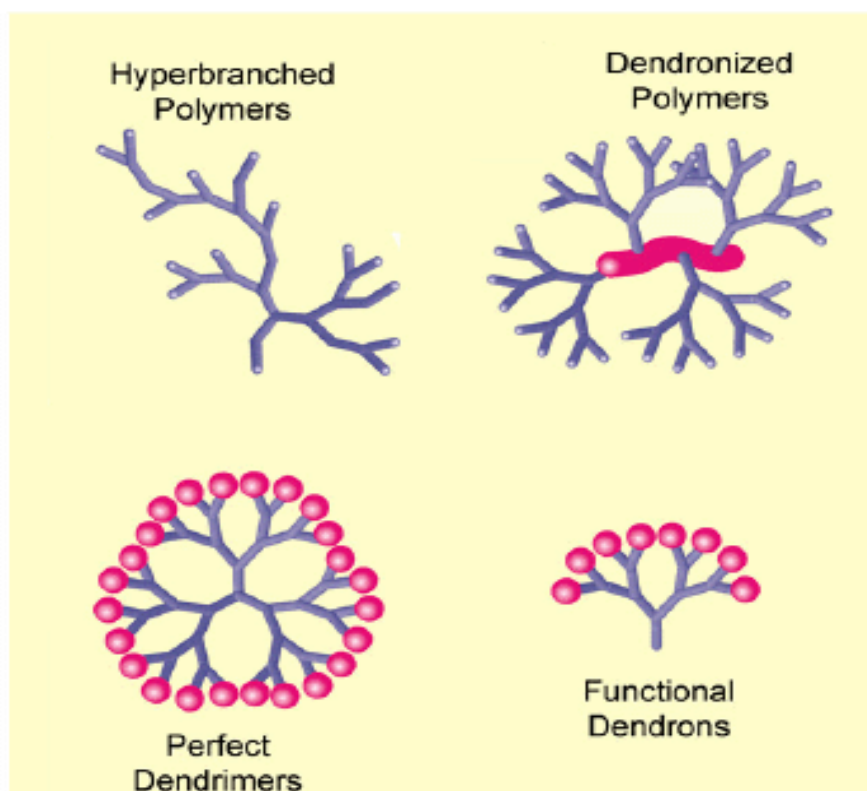
Figure 1.3: Subclasses given at the dendritic state.

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 [10a, c].

Dendrimers are a class of regularly branched mono-dispersed polymer with distinctive structural and topological features whose properties are attracting significant concern from both scientists and technologists [11].

Dendrimers are just among molecular chemistry and polymer chemistry. They relate to the molecular chemistry world by virtue of their step by step controlled synthesis, and they pertain to the polymer world due to their repetitive structure made of monomers. Contrasting classical polymers, dendrimers have a high degree of molecular regularity, narrow molecular weight allocation, definite size and shape uniqueness and a highly-functionalized terminal surface. Dendrimer oligonucleotide are delegate of a new sector of polymer science, often been referred to as the "Polymers of the 21st century" [12].

Dendrimers are a striking special set of polymers with controlled configuration.

1.2 Historical perspective

A dendrimer is both a covalently accumulate molecule and also a discrete nanoparticle. The earliest dendrimers be accomplished by divergent synthesis highly developed by Fritz Vogtle in 1978 [13], R. G. Denkewalter at Allied corporation in 1981 [14], Donald Tomalia at Dow Chemical in 1983 and by George Newkome in 1985 [15].

In 1990 a convergent synthetic approach was introduced by Jean Frechet [16]. A lot of investigation has already been concluded by studying the diverse properties and appliance of dendrimers but a lot of researchers still believe it to be in its preliminary stages.

Dendrimers are specifically defined, synthetic nonmaterials. Dendritic polymers or dendrimers offer a route to produce very distinct nanostructures suitable for drug solubilization applications, delivery of DNA and oligonucletide, targeting drug at exact receptor site, and aptitude to act as carrier for the improvement of drug delivery system.

Dendrimers are core-shell nanostructures with specific structural design and low polydispersity, which are synthesized in a layer-by-layer fashion (expressed in 'generations') around a core unit, consequential in high level of control over size, branching points and surface functionality. The ability to modify dendrimer properties to therapeutic needs makes them perfect carriers for small molecule drugs and biomolecules. Dendrimers are being considered as additives in numerous routes of administration, including intravenous, oral, transdermal, pulmonary and ocular [17].

1.3 Metallodendrimer

Dendritic and metallodendritic polymers are distinctive "ball shaped" polymeric substance, whose molecular construction 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.

Because of their exclusive properties such as solubility in water, well defined molecular architecture, and spherical shape, dendrimers and metallodendrimers have found several applications in chemical, physical and biological processes [18-20].

In recent times, metallodendrimers have been extensively investigated in diverse fields, such as molecular light harvesting, catalysts, liquid crystals, molecular encapsulation, and drug delivery [21].

In the case of poly amido amine (PAMAM) dendrimers the initiator core is an ammonia or ethylene diamine (EDA) molecule. Ammonia has three and EDA has four probable binding sites for amido amine repeating units. The primary amino groups are on the surface of molecule two new branches perhaps attached to each of them [22].

Metallodendrimer compounds have been prepared by means of click chemistry, employing [23], thiolene reactions [24] and azide - alkyne reactions [25-27].

Metallodendrimers [27], i.e. dendrimers that contain metal atoms or cations, comprise a special class of dendrimer whose redox [28], catalytic [29], ion recognition [30], sensor [31], and light harvesting [32], properties are well recognized. Additional recompense of these dendritic catalysts have been confirmed and are described in the review by ven Leeuwen [33]. Dendritic encapsulation of functional molecules allows for the separation of the active site, a structure that mimics that of active sites in biomaterials [34-36].

Moreover, it is likely to construct dendrimers water soluble, not like most polymers, by functionalizing their outer shell with charged species or other hydrophilic groups. Other convenient   properties of dendrimers consist of toxicity, crystallinity, tecto - dendrimer formation, and chirality. The active catalytic centre in a metallodendrimer can be located 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 vulnerability than the benzene core. These cores may also contain attractive physical properties. The symmetry and electronic properties of the diazine core has made them

important molecular skeleton for exploring a wide range of interesting applications such as antitumor agent and catalytic supports [37].

But the superficial and competent methods for the synthesis of metallodendrimer still remain inadequate.
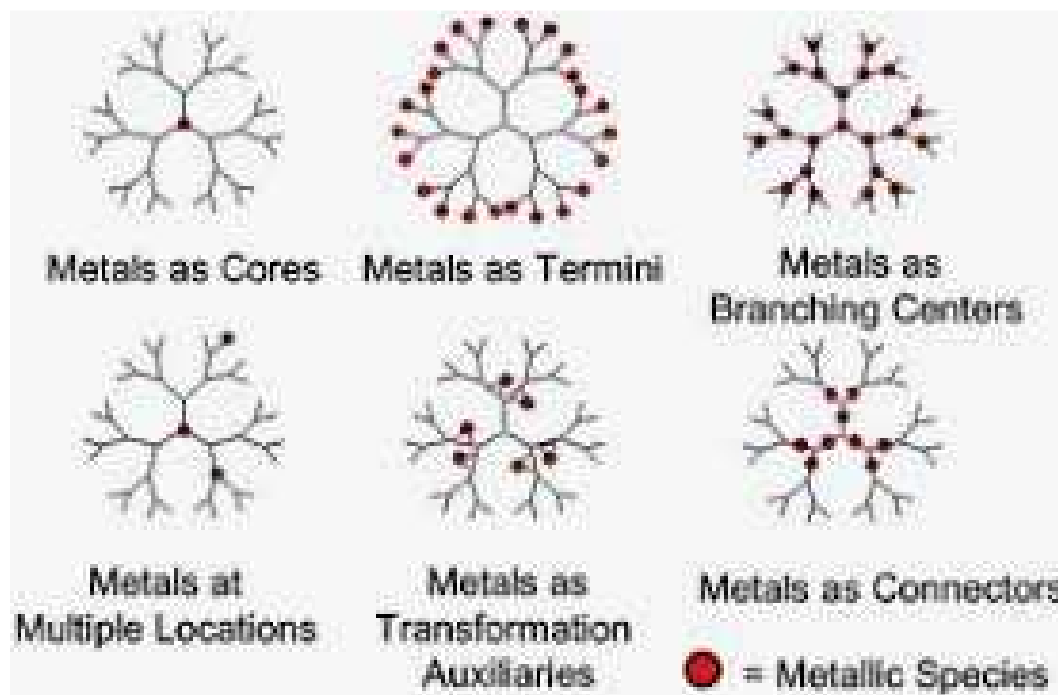
Figure 1.4: Metals' position in metallodendritic molecule

1.4 Synthesis of dendrimer and metallodendrimer compounds

Dendrimers studies cover up a variety of areas, as for example theoretical, synthesis, characterization of structures, properties and studies on its possible applications.

At present there is a incessant endeavor to advance the competence and cost reduce in these macromolecules synthesis. These materials belong to a new class of polymers with structures that really diverge from the conventional linear polymers, and are constructed from monomers called AB [38].

The dendrimers can be synthesized with high structural regularity and controlled molecular weights, where the macromolecules consisting of a central polyfuctional core are covalently bonded to layers of repeating units (generations) and to terminal functional groups.

These are inter-reliant units and form a single molecular shape, therefore representing fundamental properties to these molecules, for instance high solubility and low viscosity [39].

There are two dendrimer synthesis routes, the convergent [40] and divergent route [41].
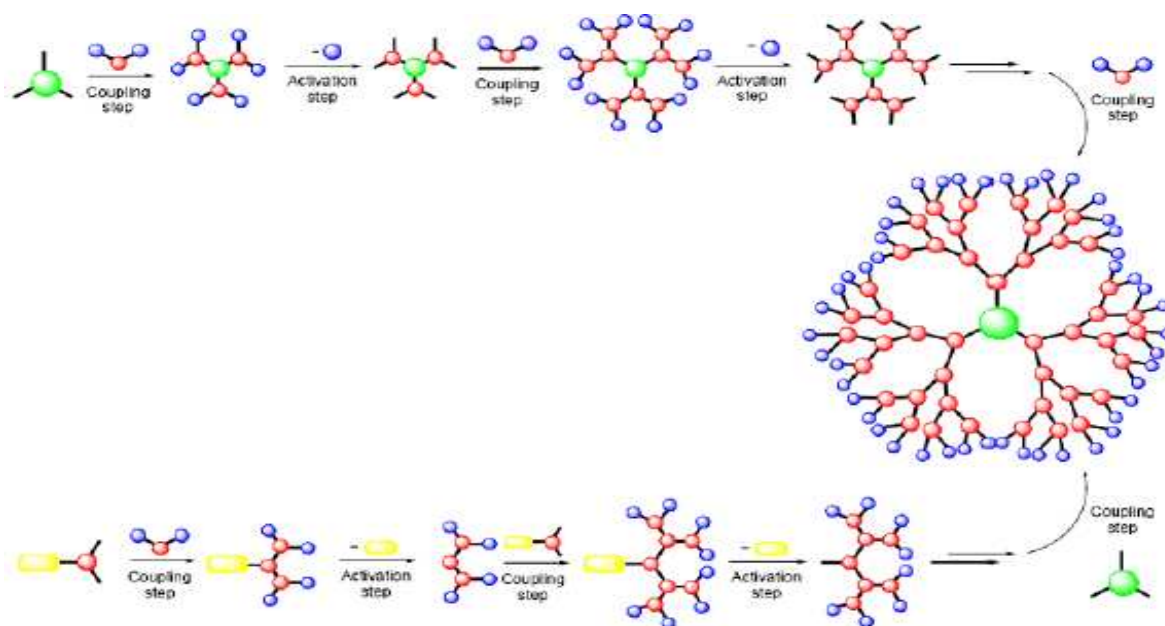
Figure 1.5: Divergent (A-top panel) and Convergent (B-bottom panel) synthesis of dendrimer.

1.4.1 Divergent growth method

The divergent synthetic approach was urbanized throughout the period between the late seventies and the early eighties with key contributions from Vögtle, Denkewalter, Tomalia and Newkome.

The principle of this scheme involves development from a central core, while branching is encouraged by means of a sequence of repetitive addition and activation steps which multiply the number of branches. This method is characterized by a swift augment in the number of reactive groups at the periphery of the increasing molecule. Therefore, expansion of the dendrimer is from the central core to the periphery.
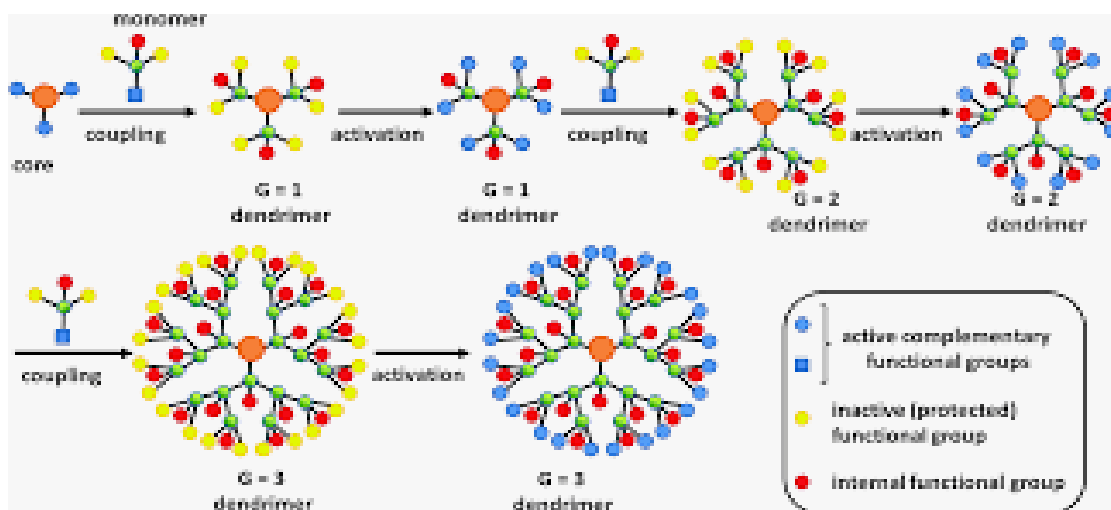
Figure 1.6: Divergent growth method

1.4.2 Convergent growth method

The convergent method reported by Fréchet and Hawker involves the superior structure of branched subunits (dendrons), which are afterward attached to a multi-functional core [42]. The convergent approach overcomes some of the problems linked with the divergent approach, mainly those related with purification owing to a dissimilarity of molecular weight between the preformed branches and the core molecule. The main drawback of dendrimer synthesis by this method is another time the steric crowding. Since the dendrimer generation increases, the reactive groups are hidden at the focal point of the dendrons, and the attachment of the preformed units to the core□fragment becomes ever more difficult.
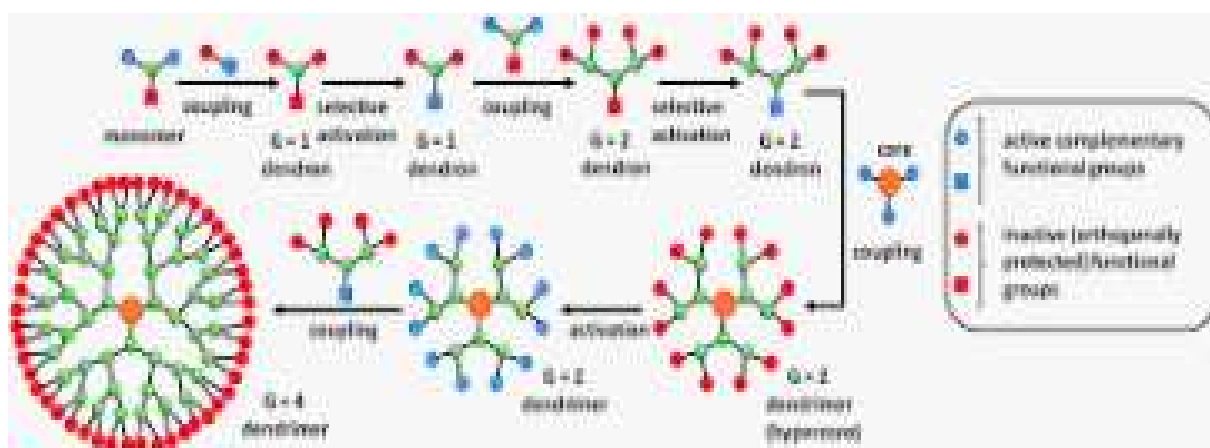
Figure 1.7: Convergent growth method

1.5 Aplication of metallodendrimer

1.5.1 Aplication of metallodendrimer with focus on Cancer

Cancer is a category of disease characterized by unrestrained cell production (i.e. undergoing cell division beyond the normal limits) and the capability of these cells to attack neighboring tissue, and at times diffusion to other locations of the body by means of 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 numerous methods for example surgery, radiotherapy and most notably chemotherapy, which is the main treatment of this disease. Chemotherapy is the treatment of cancer through anticancer drugs that target and destroy cancer cells. In the last decade, a revolution in cancer treatment has been offered by organometallic chemists [43, 44].

1.5.1a The Use of Metals as Therapeutic Agents

For the last 25 years medicinal inorganic chemistry was a fresh and unexplored field. Though, research has flourished following the achievement of platinum-based anticancer agents [45]. In addition to metal-based therapies, the efficiency of organic drugs can be better by combining them with metals [45].

1.5.1b Platinum Anticancer Agents

The therapeutic properties of cis-diamminedichloridoplatinum(II)(cis-$[Pt(NH_3)_2Cl_2$, cisplatin) was accidently revealed by Barnett Rosenberg [46, 47], in the late 1960s, at the same time he was investigating the control of an electric field on the growth of Escherichia coli bacteria. Cisplatin was actually first synthesized by Michele Peyrone [48] 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 [49], in particular ovarian [50, 51] and testicular cancers [52, 53].

Cisplatin is also used in combination therapy of many other solid tumors, such as head, neck, bladder and small cell lung cancers [54].

Analogs of cisplatin (i.e. carboplatin and oxaliplatin), have exposed immense efficacy as second-generation drugs [55].

Oxaliplatin is presently a 'billion-dollar' drug, primarily used to treat colorectal cancer [56].
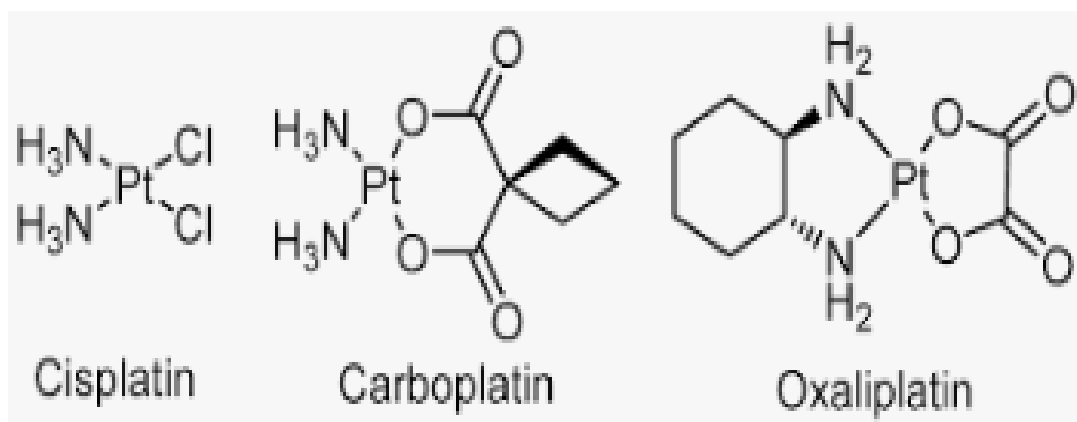
Figure 1.8: Platinum Anticancer Agents

1.5.1c 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 [57] and the second, titanocene dichloride [(η5-C_5H_5)$_2$TiCl$_2$] [58].

Both complexes are alike in structure to cisplatin, with both containing two labile chloride ligands. Although the hydrolysis rate of these Ti-complexes is much faster than cisplatin, it did however lead to complications. Bound water is more acidic, which guide to the formation of hydroxo-bridged species, which consecutively lead to toxic TiO_2 and therefore did not complete Phase I clinical trials [59, 60].

Titanocene dichloride had more accomplishment than Budotitane, with the completion of Phase I and II clinical trials; nevertheless it was abandoned [61].
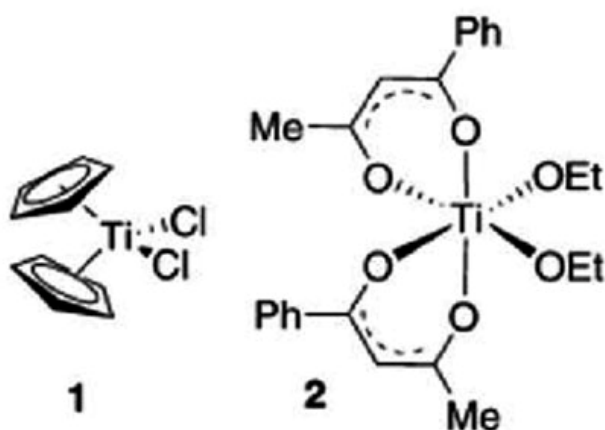
Figure 1.9: Titanium Anticancer Agents

Titanocene dichloride was not permitted for clinical use as it did not demonstrate noteworthy advantages above current drugs on the market. The poor water solubility and low hydrolytic stability held back its progress [59, 60].

To assist in stability of the Ti-based complexes, ansa derivatives of titanocene dichloride were developed [59] and some complexes were vigorous against 36 human tumor cell lines [62].

However, the hydrolytic stability of the complexes remained a setback, for this reason an substitute 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) which was found to be twice as strong as cisplatin towards pig kidney epithelial (LLC-PK) cells [63] and established constructive pharmacokinetic properties.

1.5.1d Gallium Anticancer Agents

There are just a handful of gallium-based complexes used as anticancer agents [64], namely Ganite® (galliumnitrate complex) [64], KP46 [tris(8-quinlinolato)gallium (III)] [65] and GaM (galliummaltolate), tris(3-hydroxy-2-methyl-4H-pyran-4onato)gallium) [66].

Ganite® is FDA permitted, and used to treat cancer-correlated hypercalcemia, but the drug has poor bioavailability [64].

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 [65].

Although not redox active under biological environment, 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) [67].
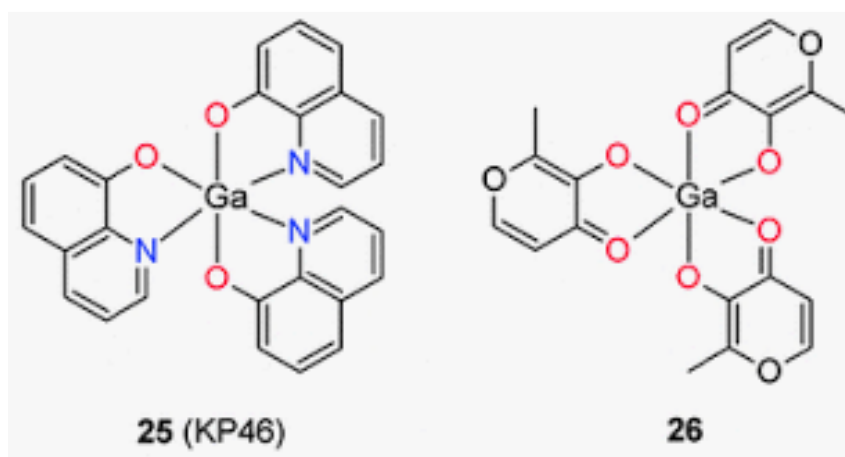
Figure 1.10: Structures of KP46 (left) and GaM (right)

1.5.1e Tin Anticancer Agents

Sn IV complexes have become very striking as therapeutic agents because of their attractive properties for example augmented water solubility, lower general toxicity than Pt-based drugs, better body clearance, fewer side-effects and most importantly does not develop drug resistance [68,69].

In recent times, a tributyl complex tri-n-butyltin(IV)lupinylsulfide hydrogen flumarate (IST-FE 35), displayed inhibition of the implanted tumors (p388 myelomonocytic leukemia and B16-F10 melanoma) in BDF1 mice [70, 71].

Following a single dose of the drug, IST-FE 168 abridged the tumor volume by 96 % at day 11 [70,71].
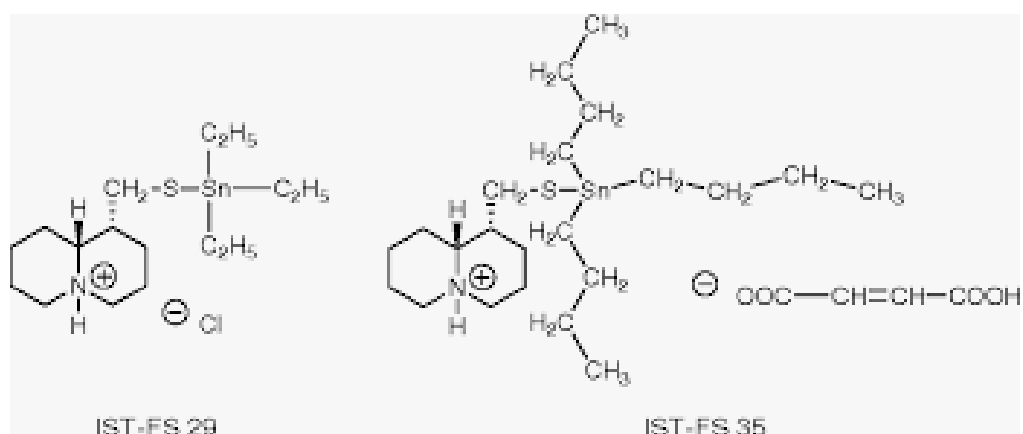
Figure 1.11: Structure of Sn IV anticancer complex, IST-FS 35.

Additional examples of a Sn-based antitumor agents, are the trigonal-bipyrimidal anionic tin(IV) complexes lately synthesized by Kaluderovic [72], 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 powerful 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 [72].

Other metals have been used in the search of possible therapeutic agents, such as gold [73], arsenic [74], copper [75], zinc [76], bismuth [77], molybdenum [78].

However, ruthenium-based complexes have revealed the most pledge as anticancer agents [79].

1.5.1f Ruthenium (III) Anticancer Agents

Soon after the innovation of the cytotoxic effects of platinum-based drugs, ruthenium compounds were investigated as potential therapeutic agents. As an substitute to platinum, ruthenium has shown constructive properties and circumstances to form the basis for anticancer drug design.13 Furthermore ruthenium is less toxic than platinum, with its

biological activity ascribed to its aptitude to imitate the behavior of iron, and bind to biomolecules, for example human serum albumin and transferrin [80].

Two inorganic Ru(III) complexes, [ImH][transRu(DMSO)(Im)Cl4] (NAMI-A, where Im=imidazole) [81-83] and [IndH][trans-Ru(Ind)$_2$Cl$_4$](KP1019, where Ind=indazole) [84-86] are now undergoing Phase II clinical trials.
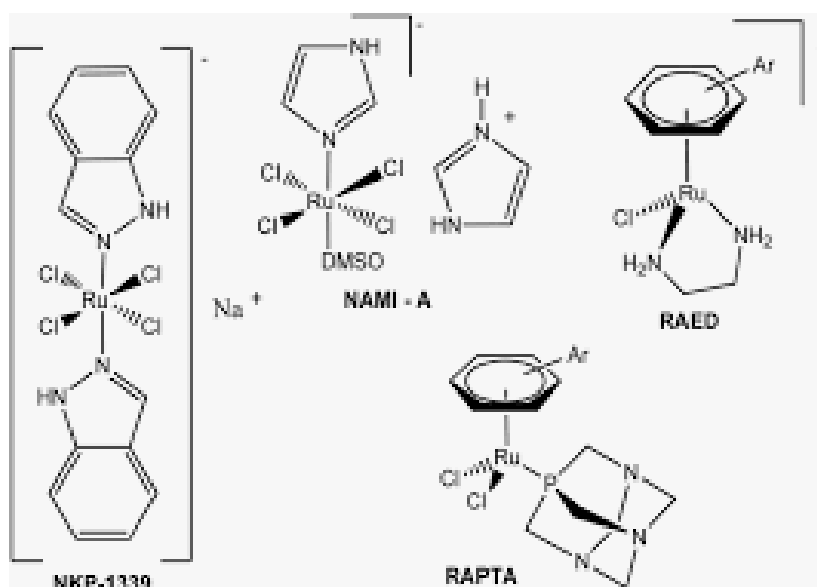
Figure 1.12: Ru(III)-anticancer compounds, NAMI-A (left) and KP1019 (right), currently undergoing clinical trials.

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 stationary during initial in vitro testing. Yet, in vivo testing showed that the drug inhibits matrix metallo - proteinases and prevents metastases (tumor growth) [83] with little impact on primary tumors in animal models [82].

KP1019, developed by Bernhard Keppler, is administered intravenously and hence binds initially to proteins in the blood stream. Actually, following cellular uptake of KP1019, it was primarily found bound to proteins (i.e. albumin and transferrin) and on DNA in peripheral leukocytes [85].The side-effects seen with platinum-based anticancer agents were connected 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 [84, 87, 88].

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. Likewise, the Ru (III) agents are activated upon entering the cancerous cell, by reduction to the Ru (II) species which synchronize more rapidly to biomolecules [89, 90].

1.5.1g 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. Nonetheless, with the +2 oxidation state proposed as the active ruthenium species, numerous investigations into the expansion of Ru (II) compounds as anticancer agents have been pursued. [91-93]
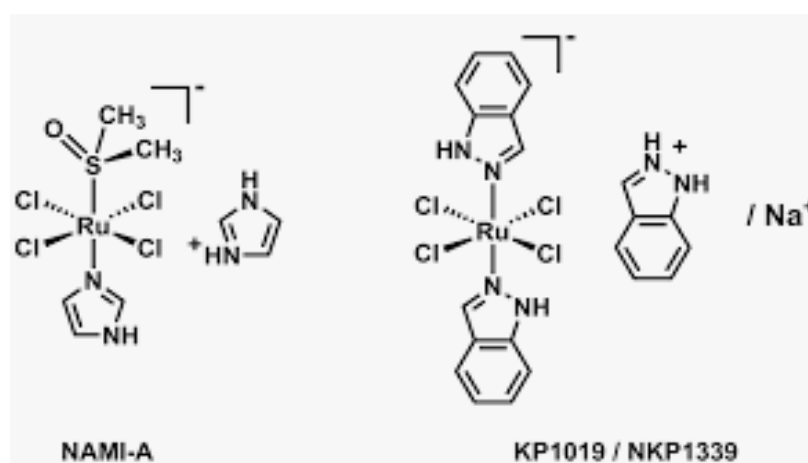
Figure 1.13: Organometallic Ruthenium-Based Antitumor Compounds

In organometallic complexes, it is the metal-carbon bond which endows these coordination complexes with their exceptional properties. The lability of the metal-ligand bond can really be predisposed by the attendance of metal-carbon bonds, as these complexes have high trans-effects and trans-influences. Besides, the π-bonded arene and cyclopentadienyl (Cp) ligands can perform as both electron donors and π-acceptors. Similarly to Ru (III) complexes, Ru (II) complexes have been comprehensively considered as anticancer agents [91-93].

The most extensively studied organoruthenium compounds are the ruthenium-arene and ruthenium-cyclopentadienyl half-sandwich compounds, also referred to as 'piano-stool' complexes. [94]

The term 'piano-stool' is resulting 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 organize around the d6 metal [Ru(II), Os(II), Ir(III) or Rh(III)]. Depending on the nature of the ligand, binding can arise in a monodentate (Z), bidentate(X-Y) or tridentate (X-Y-Z) manner, in-turn generating neutral or charged (secluded as salts) complexes. The different types of coordinating ligands (X, Y, Z and arene/Cp) order the reactivity (labile or inert) of the complexes. The π-donor ability of the arene/Cp ligand defend the metal centre from oxidation.1 The first half-sandwich organoruthenium antitumor agent was 1-β hydroxyethyl-2-methyl-5-nitro imidazole (metronidazole) synchronized to a ruthenium(II)-benzene dichlorido moiety. The Ru-complex is more active in vitro than its base-ligand, metronidazole. [95]

1.5.1i 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. [96]

For this reason, the use of multinuclear complexes as potential therapeutic agents has since been measured. In order to advance 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. [97]

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. [97]

Especially, one of the dinuclear complexes has similar activity to oxaliplatin, with the mononuclear derivative inactive in the same cell line.
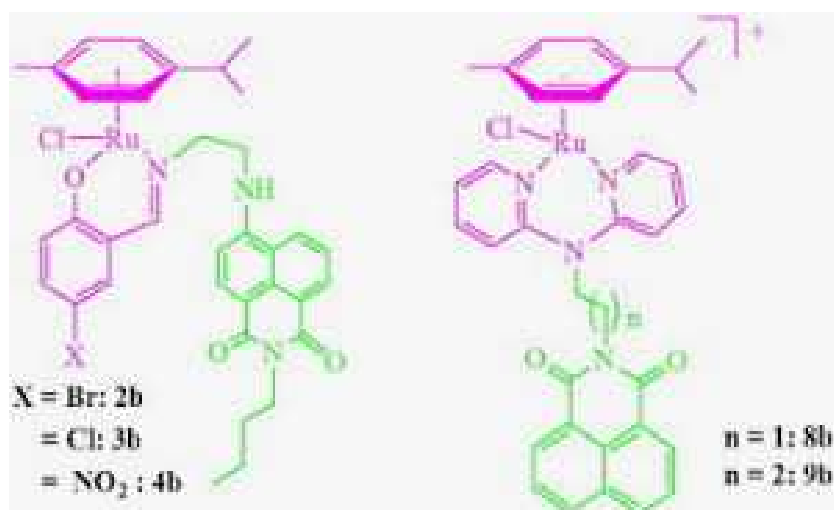
Figure 1.14: Dinuclear (with varying spacer lengths, right) ruthenium-arene antitumor complexes

Stringer et al. prepared a series of mononuclear and dinuclear ruthenium-arene complexes based on benzaldehyde thiosemicarbazone [98].

The thiosemicarbazone moiety is known for its effective enzyme inhibition (in particular ribonucleotide reductase) and is competent of interrupting DNA replication [99].

The dinuclear complex showed improved biological activity (IC50=8.96 μM) in the oesophageal cancer cell line (WHCO1), over its mononuclear derivative (IC50 >200 μM, WHCO1) [98].

A tetranuclear ruthenium-arene complex with general formula [(p-cymene)$_4$Ru$_4$ (R1)Cl$_6$]Cl$_2$ (where R1=1,2-bis(di-N-methylimidazol-2-ylphosphine)ethane) was prepared by Noffke and co-workers [100].
However, the cytotoxicity of the complexes are poor in several cancer cell lines (Hct116, Huh7, H411E and A2780 cells).

1.5.1j Ferrocene in Cancer Research

Ferrocene was first discovered in 1951, [101,102] conversely the structure was elucidated afterwards separately by Wilkinson, Fischer and Pfab [103,104].

The benzene encouraged name 'ferrocene' was coined by Woodword and co-workers in 1952 [105].

Scientists shattered no time in developing new strategies in synthesizing ferrocene and its derivatives [106].

Due to its simplicity of functionalization and favorable electronic properties, a wide range applications for these sandwich complexes were explored [107].

Stability of ferrocene in aqueous and aerobic media, the large diversity of derivatives and the favorable electronic properties made ferrocene and its derivatives striking as potential biological agents [108,109].

1.5.1k Ferrocene in Medicine: With Focus on Ferrocenyl-Based Derivatives as Therapeutic Agents

Many ferrocenyl compounds exhibit good in vivo or in vitro activity as antitumor [110], antimalarial [111], antifungal [112] and antiretroviral (ARV)[113] agents and demonstrate DNA-cleavage activity [114].

Brynes*et al.* reported the first ferrocene-based anticancer complex in the late 1970s, with the compounds bearing amine or amide groups experienced against leukemia P-388 cells [114].

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 [115].

This report clearly suggests, the integration of ferrocene into an appropriate biomolecule or carrier molecule, could offer the compound with enhanced anticancer activity.

1.5.1l Heterometallic and Multinuclear Ferrocenyl-Derived Anticancer Agents

Ferrocene has been connected to both platinum [116-119] gold [120] and ruthenium [121, 122] in an attempt to attain 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 experienced against four cancer cell lines (HBL-100 (breast), HeLa (cervix), SW1573 (lung), WiDr (colon)). One of the β-aminoethylferrocenes-Pt(II) compounds 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).

1.5.2 Metallodendrimers: Metal Decorated Dendrimers for Oncology

The term metallodendrimers is resulting from the name given to metal functionalized highly branched macromolecules known as dendrimers. The term dendrimer is built from the Greek words "dendrons" meaning tree, and "meros" meaning part. These complex macromolecules have distinct shape, are extremely branched and are built from a central core [82].

Compared to linear polymers, dendrimers can be synthesized reproducibly with low polydispersity, which is a highly noticeable feature for drug delivery agents.

A wide range of functionalities can be incorporated throughout the dendritic framework (on the periphery, at the core or interspersed which give them a wide range of applications in medicinal chemistry [83, 84], host-guest chemistry [85,86].

Chapter - 2

Results & Discussion

2.0 Present work : Synthesis and characterization of metallodendrimers containing nickel using 2,4,6-tri amino pyrimidine.

2.1 Rationale

Dendrimers, which are symmetrically highly branched, monodispersed, three dimensional fractal like macromolecules that originate from a central core with a well-defined structure, have involved significant concentration from a basic point of view and their progress is hastily increasing in many applications (e.g. OLEDs, sensors, and lasers).

The inclusion 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 located 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 perhaps envisaged by two strategies.

Firstly, it is possible to build the dendrimer and then include the metal atoms in the final stage or, secondly, the metal atoms can be included within the molecular fragments used to build the dendrimer.

Apart from of the choice of route, it is obligatory to attain proper dendrons that have the skill to coordinate the catalytically active metal atom. Additionally, dendrons have to put up with different functional groups as focal points.

In terms of complex development or the coordination of metal atoms, the azoles are excellent candidates because of the presence of lone pairs on the nitrogen atoms and the chance of alteration into nucleophilic carbenes.

Metal complexes demonstrate a variety of functionalities caused by the tunable reduction and oxidation levels of the metal ions.

Metallodendrimers are novel molecules that combine metallic speciesinto a dendrimer scaffold. The dendritic structure of metallodendrimers produces that are discrete from those of small molecule inorganic complexes.

Moreover, dendrimers afford exceptional advantages for tuning metal centers by given that well☐controlled positioning of metallic species amid the dendrimer complexes.

The position of metallic species inside the interior of a dendrimer provides a structure with several metallic species dispersed throughout a restricted space and avert metallic species from further assembly.

Research on metallodendrimers has acknowledged noteworthy concentration in recent years due, in part, to their probable applications in homogenous catalysis, sensing and light harvesting.

Metallodendrimer compounds have been prepared through click chemistry, employing Diels-Alder reactions, thiol-ene reactions and azide-alkyne reactions.

Compounds containing S-diazine and dendrimers based on diazine have established incredible interest owing to their potential applications and have exposed molecular detection and self-assembly properties.

Since outstanding importance of dendrimer and metallodendrimer compounds in the field of biological and medicinal chemistry and metal mediated approaches still remain inadequate for their synthesis.

The aspire of the present study was to synthesize dendrimer and metallodendrimer based on diazine. It is premeditated to develop a simple and efficient method for the synthesis of metallodendrimer compounds from the reaction ofdiazine with different aroylchlorides at changeable temperatures in existence of bis-triphenylphosphinenickel(II) chloride.

It is anticipated that the synthesized compounds would be biologically active and they might be used as a transitional products and catalyst for the synthesis of heterocyclic compounds and drugs. It might also be pertinent in chemical, physical and biological processes.

2.2 Results and Discussion:

2.2.1 Synthesis of 2,4,6-Tris (di-amido)-1, 3-diazine Nickel(II) Bromide 7-11

The compounds, **7-11** were obtained by treating 2, 4, 6-triamino pyrimidine (0.1g) with different aroyl chlorides in presence of $(Ph_3P)_2NiBr_2$ as catalyst at room temperature for 6-7 hours of stirring followed by heating for 30-60 min by using solvent DMSO as shown in the **scheme 1** and **table1** in good yield % .

Scheme: 1
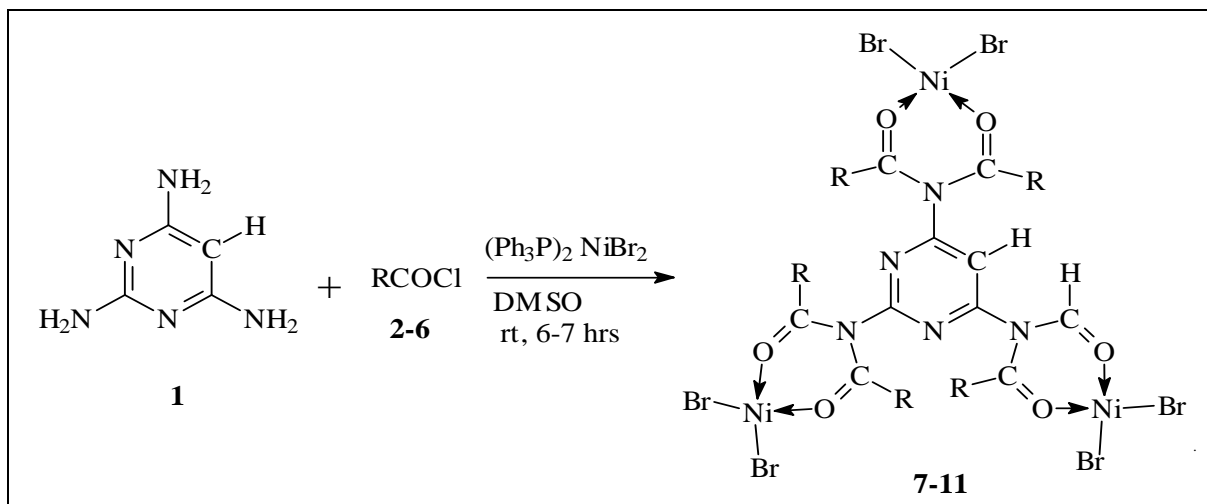
2, 7 $R = C_6H_4CH_3(p)$
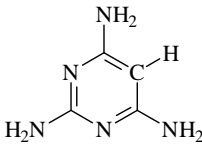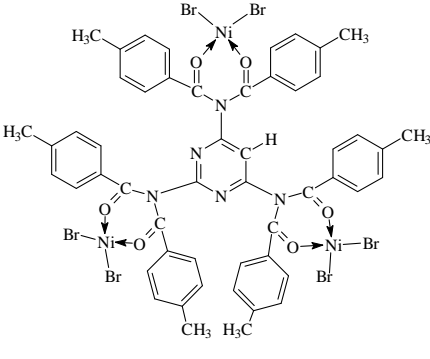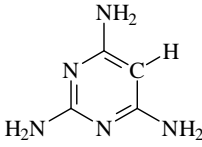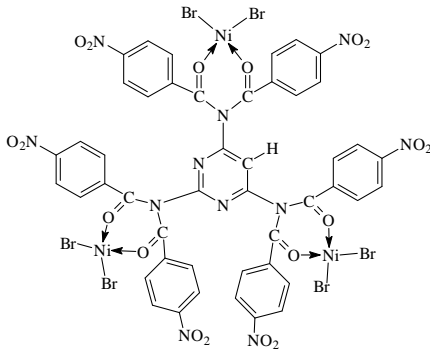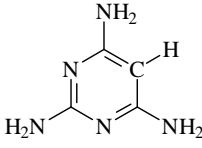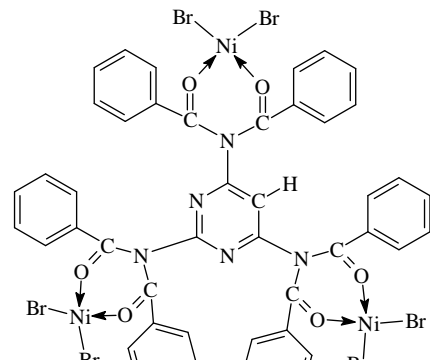
3, 8 $R = C_6H_4NO_2$ (p)
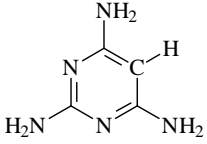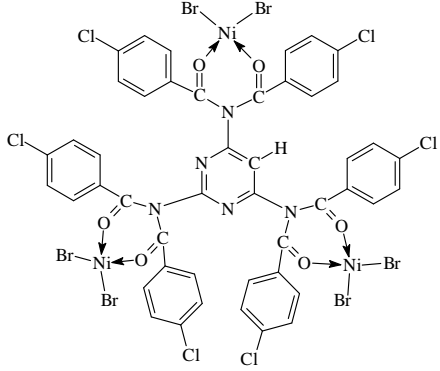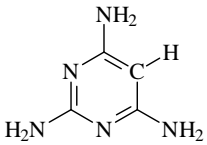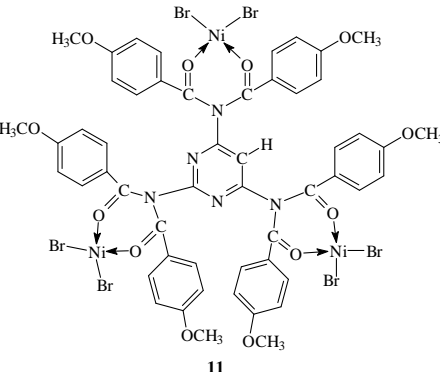
4, 9 $R = C_6H_5$

5, 10 $R = C_6H_4Cl$ (p)

6, 11 $R = C_6H_4OCH_3$ (p)

Table: 1

Sl. No	Substrate	Reagents and Conditions	Products (7-11)	m.p (°C)	Yield (%)
1.	**1**	*p*-CH$_3$C$_6$H$_4$COCl DMSO, rt, 6-7 hrs, (Ph$_3$P)$_2$NiBr$_2$ **2**	**7**	180-182	85
2.	**1**	*p*-NO$_2$C$_6$H$_4$COCl DMSO, rt, 6-7 hrs, (Ph$_3$P)$_2$NiBr$_2$ **3**	**8**	239-245	89
3.	**1**	*p*-C$_6$H$_5$COCl DMSO, rt, 6-7 hrs, (Ph$_3$P)$_2$NiBr$_2$ **4**	**9**	120-125	90

Sl. No	Substrate	Reagents and Conditions	Products (7-11)	m.p (°C)	Yield (%)
4.	**1**	*p*-ClC$_6$H$_4$COCl DMSO, rt, 6-7 hrs, (Ph$_3$P)$_2$NiBr$_2$ **5**	**10**	240-242	88
5.	**1**	*p*-CH$_3$OC$_6$H$_4$COCl DMSO, rt, 6-7 hrs, (Ph$_3$P)$_2$NiBr$_2$ **6**	**11**	180-185	92

Yield % was calculated on the basis of pyrimidine (diazine).

2.2.2 Synthesis of 2, 4, 6-Tris (di-4-methylbenzamido) -1, 3 -diazine nickel (II) chloride 12

The compound, **12** is derived from the synthesis of pyrimidine (0.1 g) with p-$CH_3C_6H_4COCl$ in the presence of $NiCl_2$ as catalyst at room temperature for 6-7 hours of stirring by using solvent DMSO.
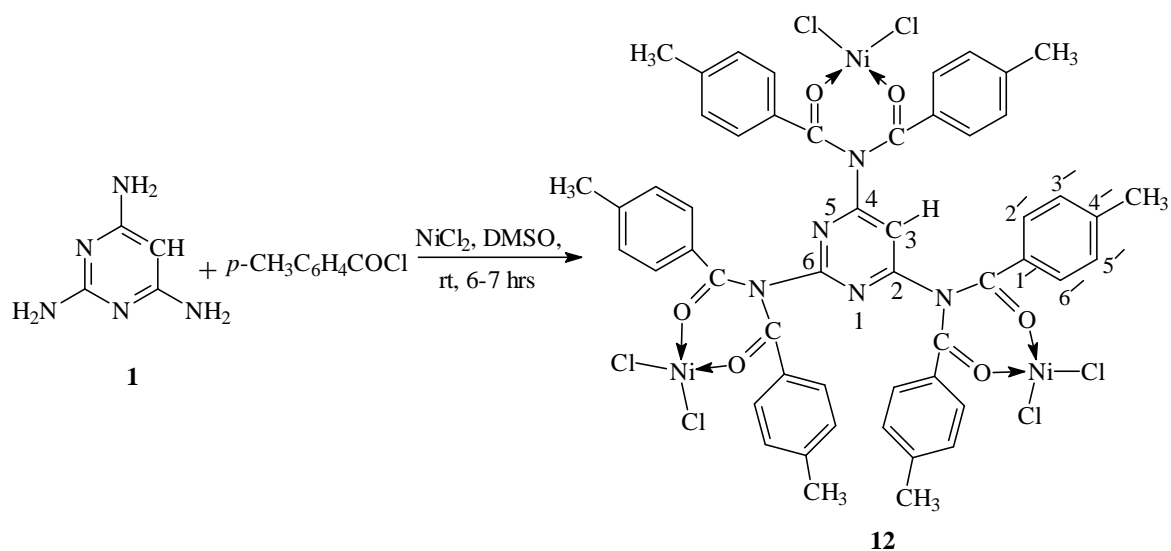
Table:2

Sl. No	Substrate	Reagents and Conditions	Products (12)	m.p (°C)	Yield (%)
1.		p-$CH_3C_6H_4COCl$ DMSO, rt, 6-7 hrs, $NiCl_2$		180-185	95

2.3.1 Characterization of 2,4,6-Tris (di-4-methylbenzamido)-1,5-diazine Nickel (II) Bromide 7

The compound **7** was synthesized from 2,4,6-triamino-1,5-diazine (pyrimidine) with reaction of *p*-methyl benzoyl chloride and DMSO by stirring at room temperature for about 6-7 hours in presence of $(Ph_3P)_2NiBr_2$.

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

In IR spectrum of compound **7**, the absorption band was found at 3380.36 cm^{-1} and 2927.08 cm^{-1} due to the C-H (aro) and C-H (ali) stretching absorption respectively, whereas a broad band at 1705.13 cm^{-1} represents the keto (C=O) group. Strong absorption band at 1608.69 cm^{-1} displays strong C=N stretching absorption. v_{max} 1416.76 cm^{-1} stretching bands indicated the presence of C=C in phenyl ring, and v_{max} 1348.29 cm^{-1} indicated the presence of aromatic C-N stretching.

In ^{1}H NMR spectrum of compound **7**, the chemical shift at δ_H 2.357 (s, 6×3H, Ar-CH$_3$) is found as a singlet for the hydrogen atoms in six CH$_3$ groups. Chemical shift at δ_H 7.29 (dt, 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 δ_H 7.84 (dt, 6×2H, Ar-H, *J*=8.0 Hz) showed another doublet for similar protons of C-2′, C-6′, carbon of six phenyl rings.

7

2.3.2 Characterization of 2,4,6-Tris (di-4-nitrobenzamido)-1,5-diazine Nickel (II) Bromide 8

The compound **8** was synthesized from 2,4,6-triamino-1,5-diazine (pyrimidine) with the reaction of 4-nitrobenzoylchloride and DMSO by stirring at room temperature for 6-7 hours in presence of $(Ph_3P)_2NiBr_2$.

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

In IR spectrum of the compound **8** , the absorption band was found at 3115.14 cm^{-1} due to the C-H (aro) stretching absorption, whereas a broad band at 1704.17 cm^{-1} represents the keto (C=O) group. Strong absorption band at 1543.10 cm^{-1} displays strong C=N stretching absorption. ν_{max} 1350.22 cm^{-1} stretching bands indicated the presence of C=C in phenyl ring and ν_{max} 1102.35 cm^{-1} indicated the presence of aromatic C-N stretching.

In ^{1}H NMR spectrum of compound **8**, chemical shift at δ_H 8.106 (dt, 6×2H, Ar-H) showed a doublet for aromatic protons of C -3′, C-5′ of six phenyl rings and δ_H 8.277 ppm (dt, 6×2H, Ph-H) showed another doublet for similar protons of C-2′, C-6′ carbon of six phenyl rings and δ_H 7.25 ppm for H of pyrimidine ring.

8

2.3.3 Characterization of 2,4,6-Tris(di-benzamido)-1,5-diazine Nickel(II) Bromide 9

Compound **9** was synthesized from 2,4,6-triamino-1,5-diazine (pyrimidine) with the reaction of benzoyl chloride and DMSO as solvent under reaction condition stirring at room temperature for 6-7 hours in presence of $(Ph_3P)_2NiBr_2$.

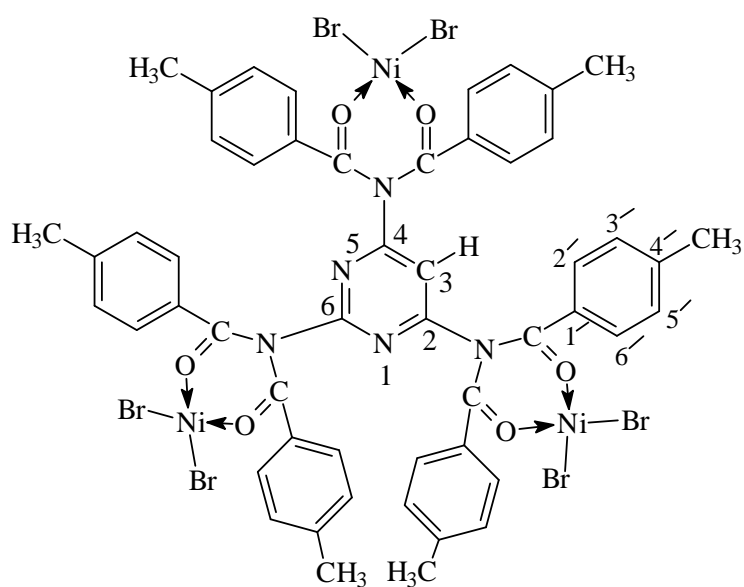The structure of the compound was established by various spectral data.

In IR spectrum of compound **9**, the absorption band was found at 3072.71 cm^{-1} due to the CH (aro) stretching absorption, 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. ν_{max} 1584.57 cm^{-1} stretching bands indicated the presence of C=C in phenyl ring and ν_{max} 1292.35 cm^{-1} indicated the presence of aromatic C-N stretching.

In ^{1}H NMR spectrum of derived compound **9**, Chemical shift at δ_H 7.521 (t, 6×2H, Ar-H, J=7.5 Hz) was found for the two carbons (C-1′, C-4′) of phenyl rings, δ_H 7.622 (t, 6×1H, Ar-H, J=7.6 Hz)showed triplet for aromatic protons of C-3′, C-5′carbon of phenyl rings and δ_H 7.946 (dt, 6×2H,Ar-H, J=8.0 Hz) showed doublet for similar protons of C-2′, C-6′carbon of six phenyl rings.

In ^{13}C NMR spectral data of synthesized compound **9**, the peak at δ_C 134.67 was found for two carbons (C-1′, C-4′) of phenyl ring, chemical shift at δ_C 130.39 and δ_C 130.91 represent the aromatic carbons of C-2′, C-6′ and C-3′, C-5′ of six phenyl rings in respective order. The chemical shift at δ_C 132.66 ppm was indicating the carbons C-2, C-4 and C-6 of pyrimidine ring and at δ_C 169.21 was for carbonyl carbon (C=O).

9

2.3.4 Characterization of 2, 4, 6-Tris (di-4-chlorobenzamido)-1, 5-diazine Nickel (II) Bromide 10

The compound **10** was derived from 2, 4, 6-triamino-1, 5-diazine (pyrimidine) with the reaction of *p*-chlorobenzoyl chloride under reaction condition stirring at room temperature for 6-7 hours with (Ph$_3$P)$_2$NiBr$_2$ in presence of DMSO as solvent.

The structure of the compound **10** was established by various spectral data.

In IR spectrum of the compound **10**, the absorption band is found at 3072.71 cm^{-1} due to the C-H (aro) stretching absorption and a broad band at 1686.81 cm^{-1} represents the keto (C=O) group. Strong absorption band at 1602.90 cm^{-1} displays strong C=N stretching absorption. v_{max} 1326.10 cm^{-1} stretching bands indicated the presence of C=C in phenyl ring and v_{max} 1027.13 cm^{-1} indicated the presence of aromatic C-N stretching and strong absorption band in v_{max} 811.09 cm^{-1} shows C-Cl stretching absorption.

In ^{1}H NMR spectrum of compound **10**, chemical shift at δ_H 7.85 (dt, 6×2H, Ar-H, J=8.0 Hz) showed a doublet for aromatic protons of C-3′, C-5′of six phenyl rings and δ_H 7.96 (dt, 6×2H, Ar-H, J=8.4 Hz) showed another doublet for similar protons of C-2′, C-6′carbon of six phenyl rings.
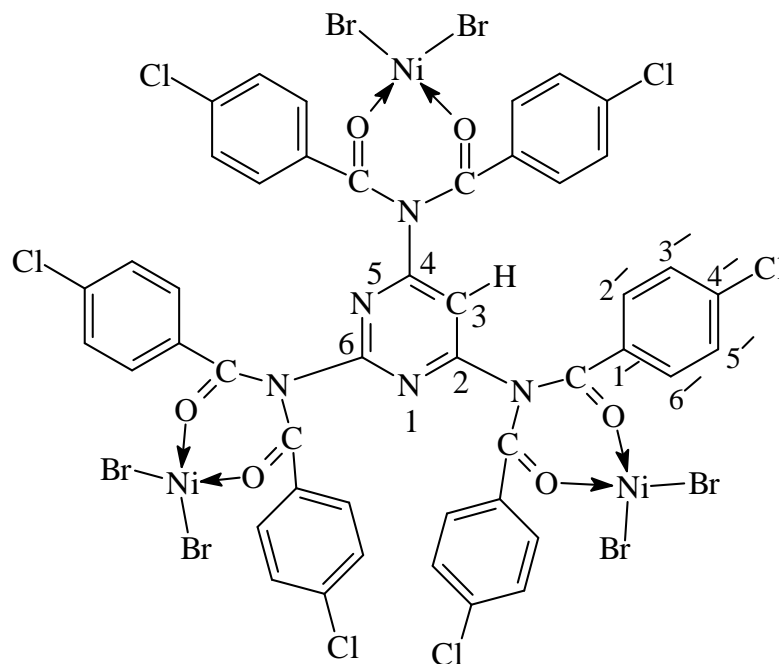
10

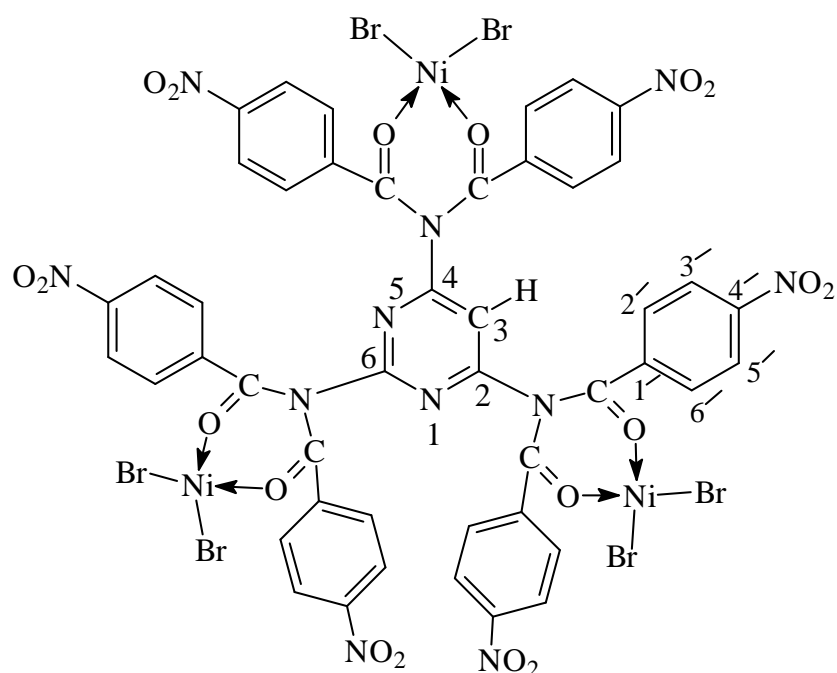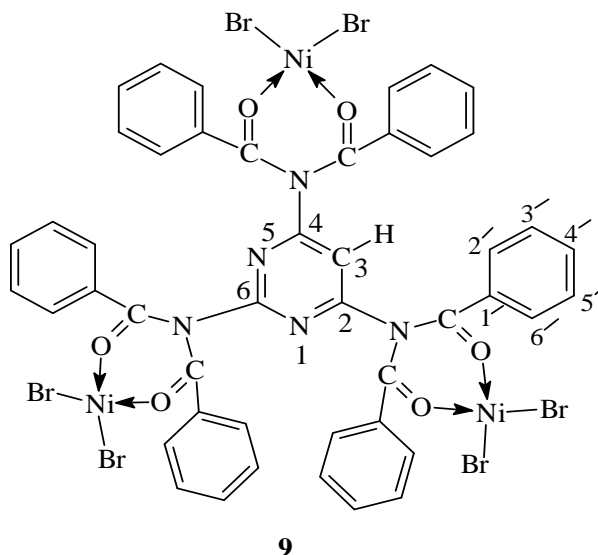## 2.3.5 Characterization of 2, 4, 6-Tris (di-4-methoxybenzamido)-1, 5-diazine nickel (II) Bromide 11

The compound **11** was derived from 2,4,6-triamino-1,5-diazine (pyrimidine) with the reaction of p-methoxybenzoyl chloride under reaction condition of stirring at room temperature for 6-7 hours in the presence of $(Ph_3P)_2NiBr_2$ and solvent (DMSO).

The structure of the compound **11,** was established by various spectral data

In IR spectrum of the compound **11,** the absorption band was found at 3114.18 cm^{-1} due to the C-H (aro) stretching absorption and a broad band at 2854.74 cm^{-1}is for stretching absorption represents the (C=H) aliphatic group. Absorption band at 1607.72 cm^{-1} displays keto (C=O) group. Stretching absorption v_{max} 1350.22, 1255.70 and 1107.18 cm^{-1} stretching bands indicated the presence of C=N, aromatic C=C and C-N in the order.

In ¹H NMR spectrum of compound **11,** the chemical shift at δ_H 2.54 ppm (s, 6×3H, Ar-OCH$_3$) is found as a singlet for the hydrogen atoms in six -OCH3 groups. Chemical shift at δ_H 8.17 ppm (dt, 6×2H, Ph-H) showed a doublet for aromatic protons of C-3′, C-5′carbon of six phenyl rings and δ_H 8.31 ppm (dt, 6×2H, Ph-H) showed another doublet for similar protons of C-2′, C-6′ carbon of six phenyl rings. The chemical shift at δ_H 3.39 ppm (s, 1H, -C-H) was obtained for the proton (-CH) of carbon (C-3) of pyrimidine ring.
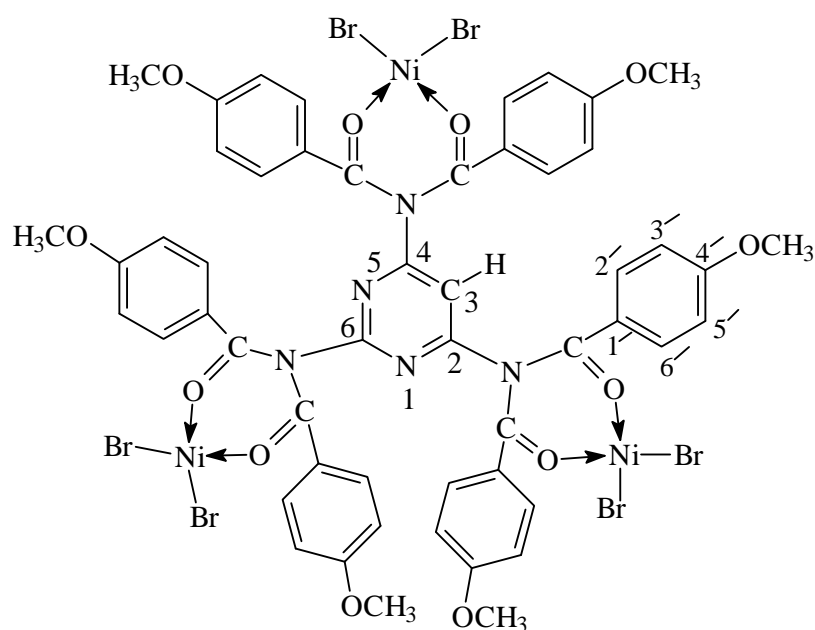
11

2.3.6 Characterization of 2, 4, 6-Tris (di-4-methylbenzamido)-1, 5-diazine nickel (II) Chloride 12

The compound **12** is the product from the synthesis of 2, 4, 6-triamino-1, 5-diazine (pyrimidine) with the reaction of *p*-methyl benzoyl chloride. Reaction condition was stirring at room temperature for 6-7 hours in presence of NiCl$_2$ and solvent (DMSO).

The structure of the compound **12** was established by various spectral data.

In IR spectrum of the synthesized compound **12** the absorption band at 3444.02 cm^{-1} is found due to the C-H (aro) stretching absorption and another broad band at 2977.23 cm^{-1} stretching absorption represents the (C=H) aliphatic group. Absorption band at 1817.00 cm^{-1} is for keto (C=O) group. Stretching absorption ν_{max} 1612.54, 1516.10 and 1286.56 cm^{-1} stretching bands indicated the presence of C=N, aromatic C=C and C-N are in the order.

In ^{1}H NMR spectrum of compound **12,** the chemical shift at δ_H 2.368 (s, 6×3H, Ar-CH3) is found as a singlet for the hydrogen atoms in six CH$_3$ groups. Chemical shift at δ_H 7.309 (dt, 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 δ_H 7.849 (dt, 6×2H, Ar-H, J=8.0 Hz) showed another doublet for similar protons of C-2′, C-6′ carbon of six phenyl rings.
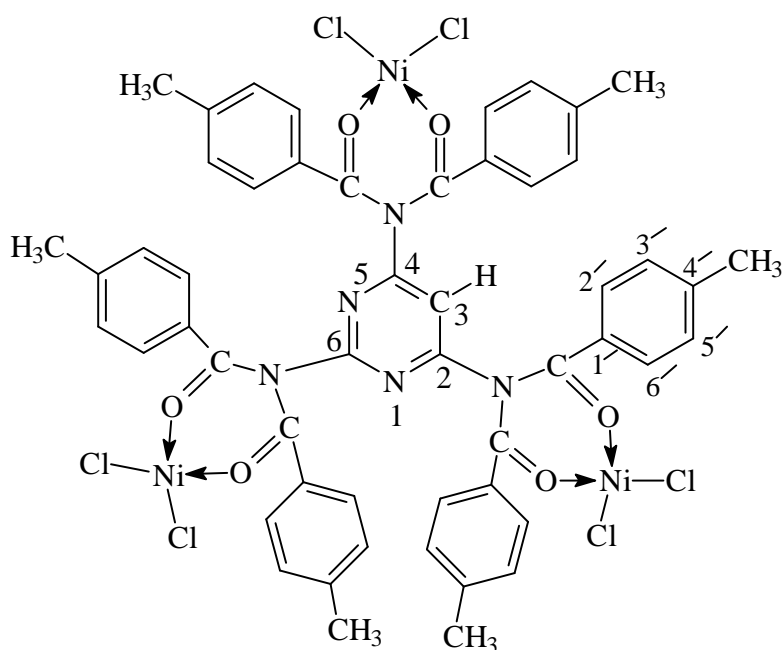
12

## Scanning Electron Microscope (SEM) Spectroscopic Analysis of the compound 8

2.4 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.

The details of the SEM images of one of the synthesized compounds is shown below-

2.4.1 SEM image of compound 2,4,6-Tris(di-4-nitrobenzamido)-1,5-diazine nickel(II) chloride 8

The SEM images of the compound **8** were taken in a Scanning Electron Microscope and described as the following way. Figure shows the SEM image of different magnification range of compound **8** synthesized as described in chapter-3. This image represented as "rectangular fiber" like structure.
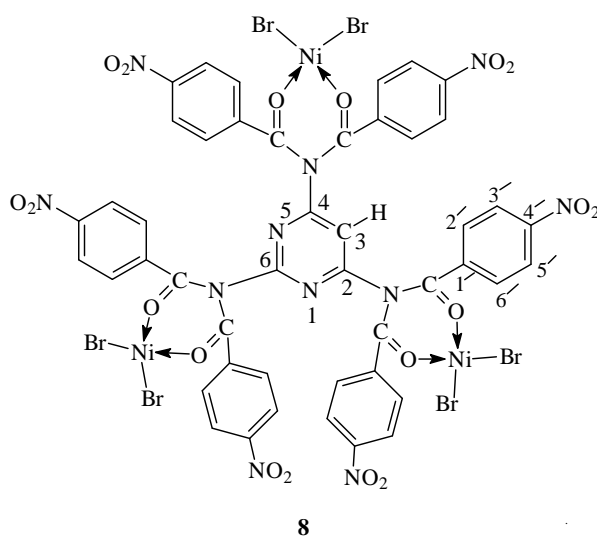
8

Figure 2.1: SEM image of compound 2,4,6-Tris(di-4-nitrobenzamido)-1,5-diazine nickel(II) chloride 8

Figure 2.1: SEM image of compound 2,4,6-Tris(di-4-nitrobenzamido)-1,5-diazine nickel(II) chloride 8

49
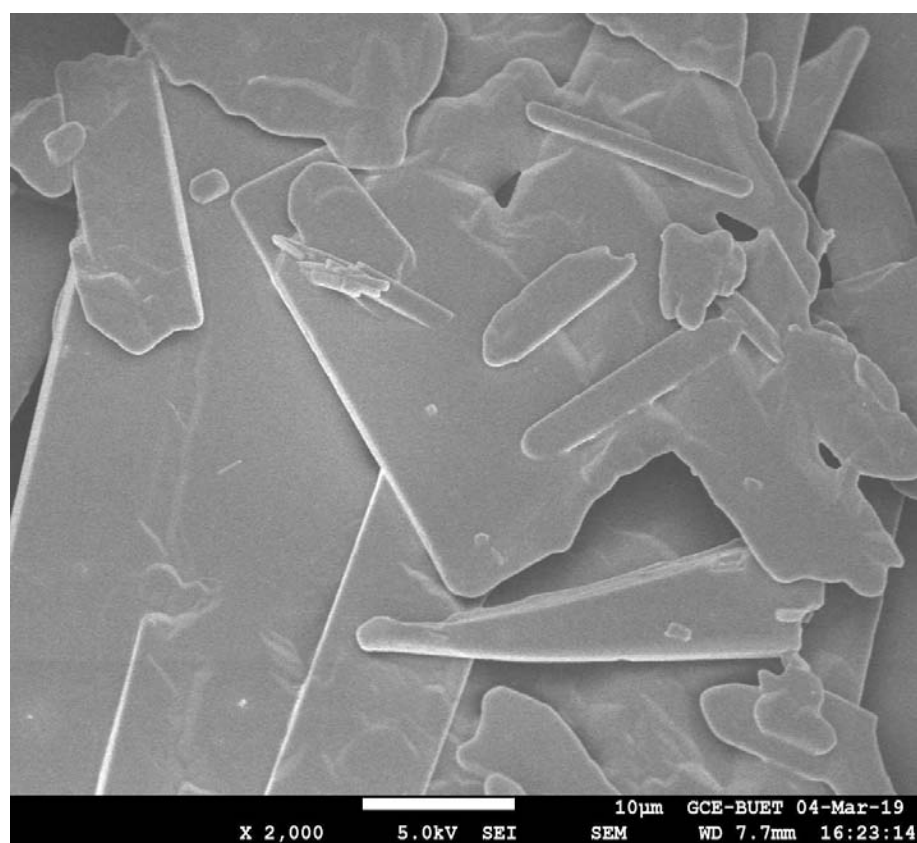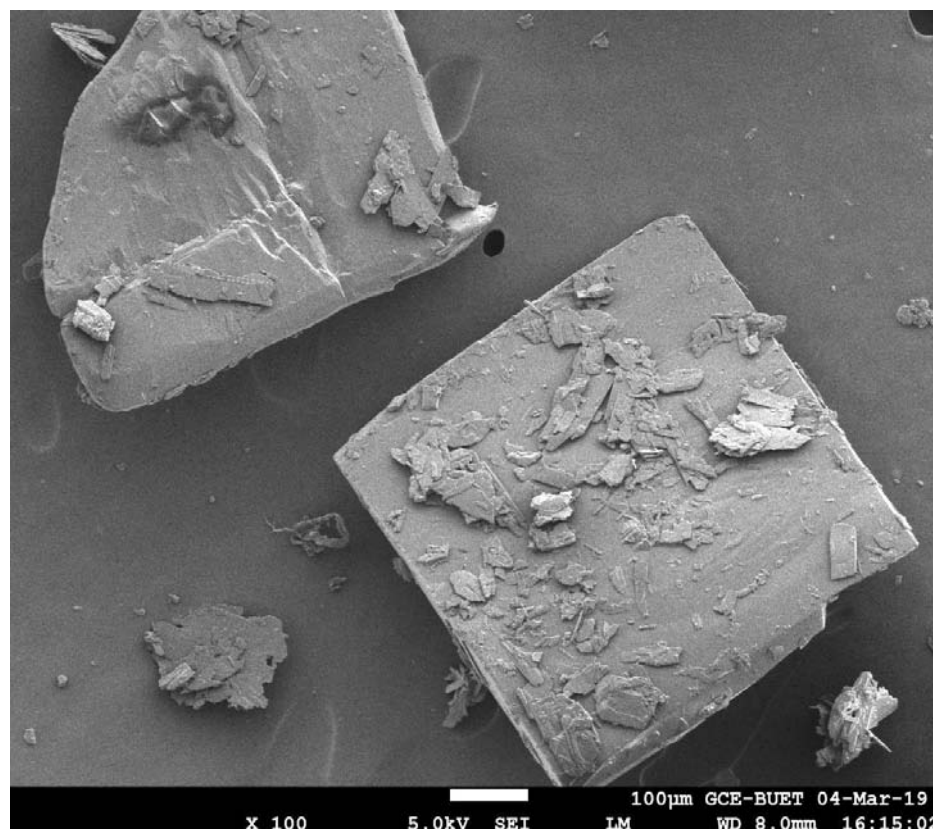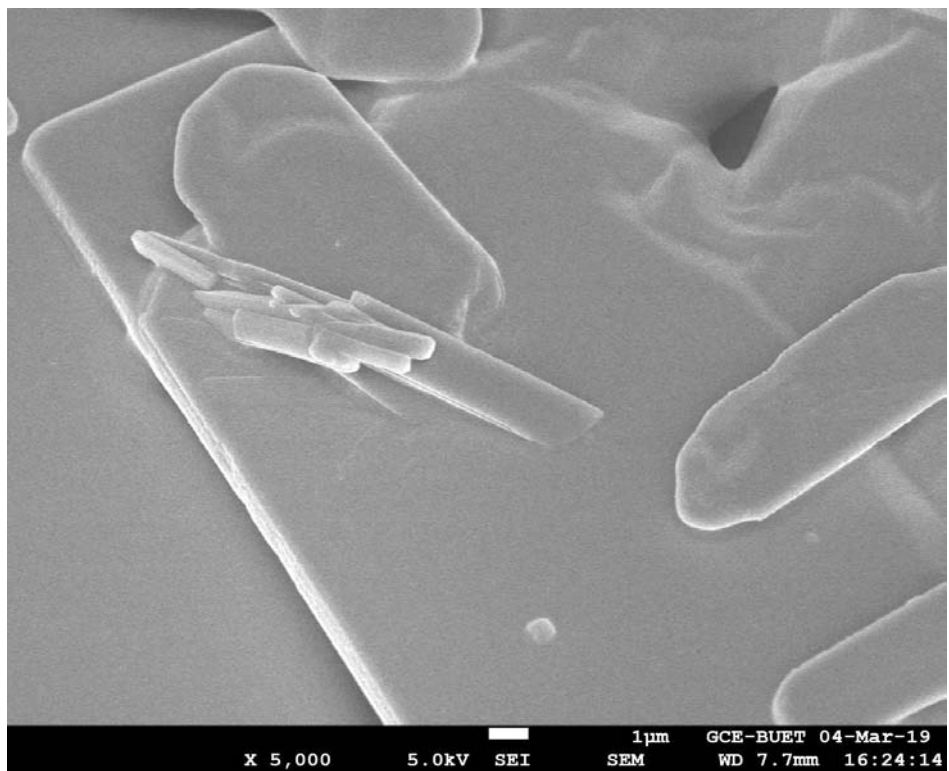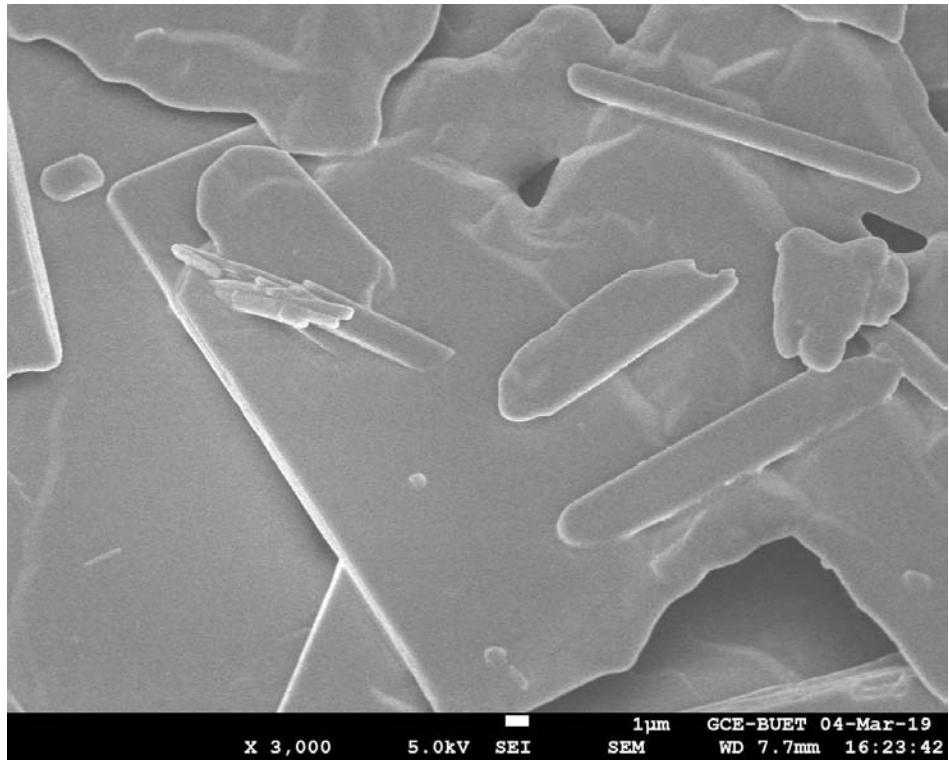
By applying from 10 kv 10.3 mm x 800 SEM to 10 kv 10.3 mm x 40 k SEM, the range of particle size of the compound were found 50.0 μm to 1.00 μm.
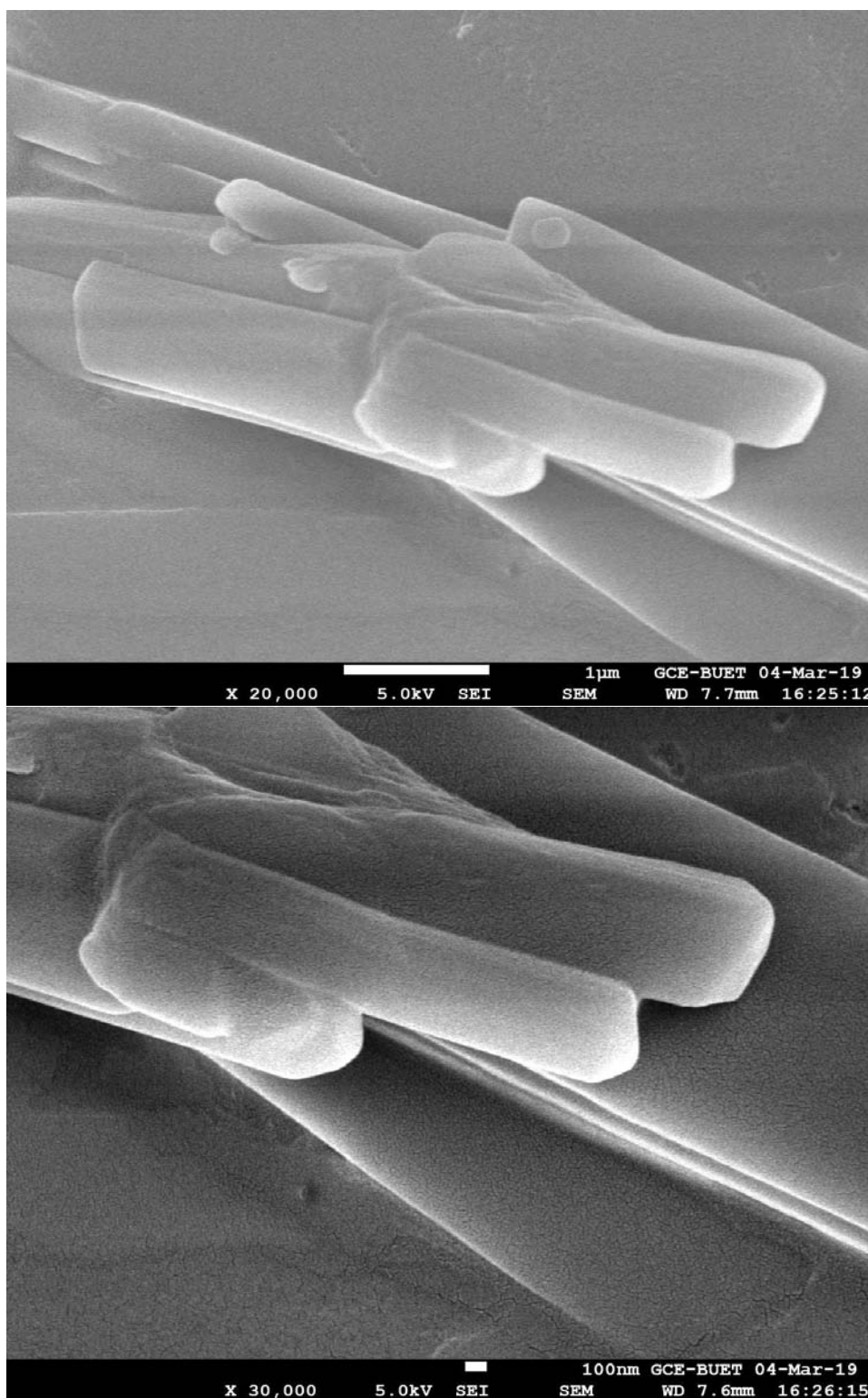
2.5 : <u>Reaction Mechanism:</u>
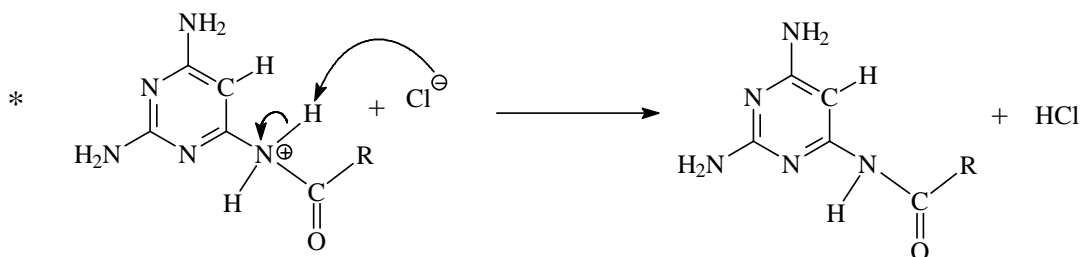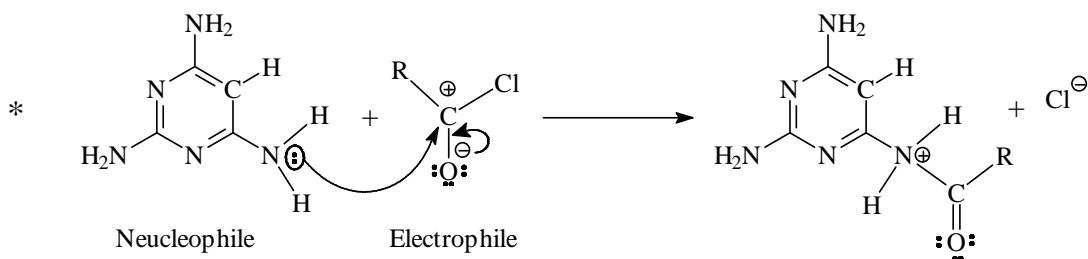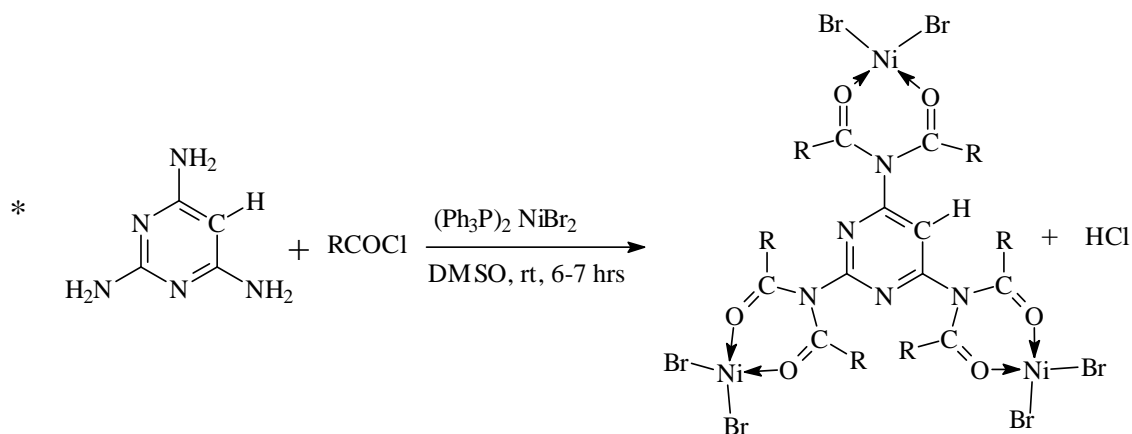
Explanation:

This is an SN^1 type reaction, where the carbonyl carbon of aroyl chloride is the electrophile and the nitrogen of amino group of diazine is the neucleophile. At the beginning, the neucleophile attacks the electrophile and attached with it. In this ligand making process, from amino group, H^+ is extracted and Cl^- is extracted from carbonyl carbon group of aroyl chloride and HCl is produced. Similarly, another hydrogen of amino group is substituted by another aroyl group and final product metallodendrimer is produced after $NiBr_2$ is attached with the ligand.

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Chapter - 3

Experimental Data

Experimental Data

3.1 Materials and Methods:

If otherwise noted, all reactions were carried out in room temperature; all reagents were reagent grade and were directly used without further purification. Dehydrated DMSO was used as reaction solvent.All the solvents and chemicals were purchased from Sigma Aldrich and used as received. De-ionized water was used in the experiment where required.

After synthesizing the compounds, melting points were determined by open capillary tubes by a melting point apparatus (Model BUCHI, B-540). The IR specrtra were recorded by a Shimadzu FTIR 8400S Fourier Transform. Infrared Spectrophotometer (400 - 4000 cm^{-1}) with KBr pellets.

^{1}H-NMR and ^{13}C-NMR spectra were taken at 300 MHz and 75 MHz, respectively, on BRUKER DPX-400 spectrophotometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts were given relative to TMS.

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). SEM was recorded in JEOL JSM -7600F Field Emission Scanning Electron Microscope.

3.2 General procedure for the synthesis of Metallodendrimers

3.2.1 Synthesis of 2,4,6-Tris (di-4-methylbenzamido)-1,5-diazine Nickel (II) Bromide 7

For this synthesis, required compounds are 0.1 g (0.0007928 mol) 2, 4, 6-triaminopyrimidine (Diazine), *p*-methyl benzoyl chloride (6.2 eqv), 8 mol% of bis-triphenyl phosphine Nickel (II) bromide and 7 mL of DMSO as solvent.

All these measured compounds were added in a 250 mL round bottom flask. The reaction mixture was stirred at room temperature for around 6 - 7 hours. The progress of the reaction was monitored.

At the beginning of the reaction, the mixture was turned into a clear "Green" solution (presence of Ni) and after 6-7 hours later reaction mixture was kept additional ½ /1 hour with constant stirring at 80°C for best results.
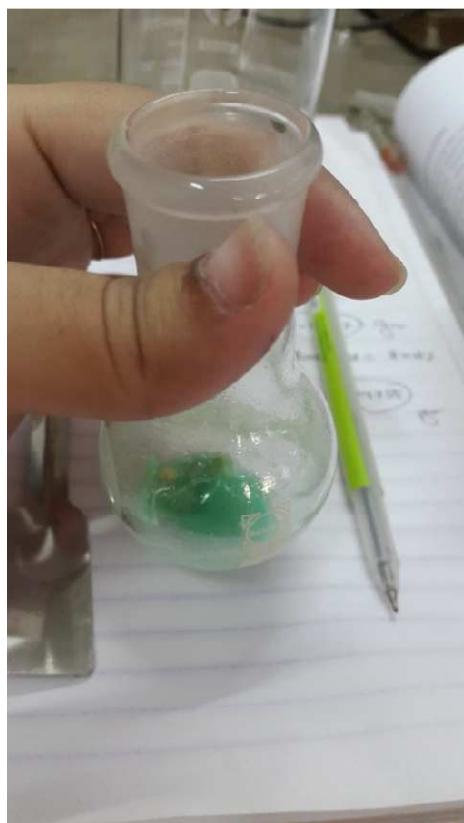
Figure 3.1 : Different stages of synthesis.

Reaction process was stopped by adding distilled water and then gradually it turned into white "curd'' like mixture, 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 hot EtOH and the required compound was formed as white shinny crystalline solid.
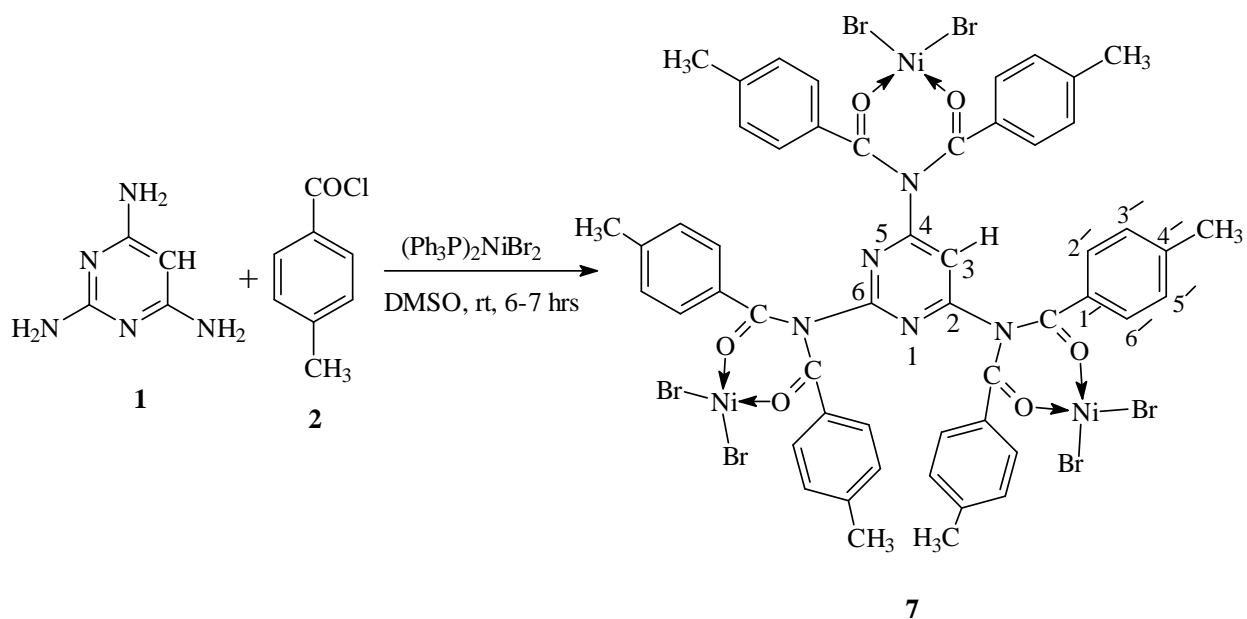
MF: $C_{52}N_5H_{43}O_6Ni_3Br_6$

MW: 1169.81

Physical analysis: White crystalline solid, m. p. 180-182°C, odorless and 85 % yield.

Analytical analysis:

IR (KBr): v_{max} (cm^{-1}) 3380.36 (C-H aro) , 2927.08 (C-H ali), 1705.13 (C=O), 1608.69 (C=N), 1416.76 (C=C), 1348.29 (C-N aro) .

^{1}H NMR (300 MHz, DMSO): δ_H 2.357 (s, 6×3H, Ar-CH$_3$), δ_H 7.29 (d, 6×2H, Ar-H,), δ_H 7.84 (d, 6×2H, Ar-H).

3.2.2 Synthesis of 2, 4, 6-Tris(di-4-nitrobenzamido)-1, 5-diazine nickel (II) bromide 8

The mixture of 0.1 g (0.0007928 mol) 2, 4, 6-triamino pyrimidine (Diazine) , 0.9203 g *p*-nitrobenzoyl chloride and 8 mol% of bis-triphenyl phosphine Nickel (II) bromide was added in 7 mL of DMSO in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound **7**
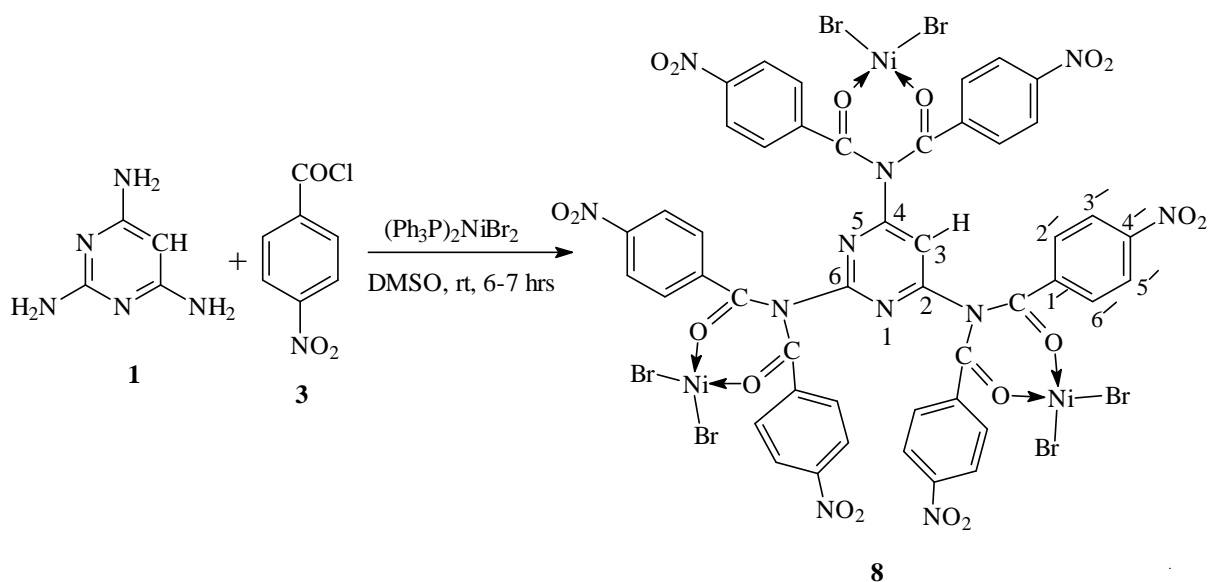
MF: $C_{46}N_{11}H_{25}O_{18}Ni_3Br_6$

MW: 1675.25

Physical analysis: White crystalline solid, m. p: 239-245 □C, odorless and 85 % of yield.

Analytical analysis:

IR (KBr): v_{max} (cm^{-1}) 3115.14 (C-H aro.), 1704.17 (C=O), 1543.10 (C=N aro.), 1350.22 (C=C aro.), 1102.35 (C-N aro.) cm^{-1}.

¹H NMR (300 MHz, DMSO): δ$_H$ 8.106 (6×2H, Ph-H), δ$_H$ 8.27 (6×2H, Ph-H). δ$_H$ 7.25 H of pyrimidine ring.

3.2.3 Synthesis of 2,4,6-Tris(di-benzamido)-1,5-diazine nickel(II) bromide 9

The mixture of 0.1 g (0.007928 mol) 2, 4, 6-triaminopyrimidine (Diazine), 0.6972g benzoyl chloride and 8 mol% of bis-triphenyl phosphine nickel (II) bromide was added in 7 mL of DMSO in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound **7.**
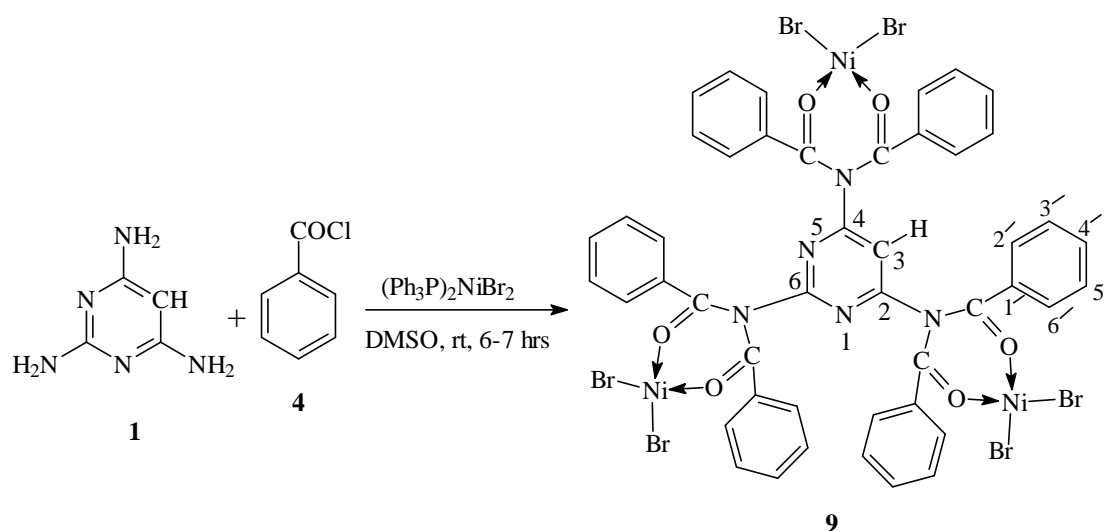
MF: C$_{45}$N$_5$H$_{31}$O$_6$Ni$_3$Br$_6$

MW: 1405.27

Physical analysis: White crystalline solid, m. p: 120-125 °C, odorless and 90 % of yield.

Analytical analysis:

IR (KBr): ν$_{max}$ (cm^{-1}) 3072.71 (C-H aro), 1683.7 (C=O), 1675.5 (C=N aro), 1584.57 (C=C aro) and 1293.35 (C-N aro) cm^{-1}.

¹H NMR (300 MHz, DMSO): δ$_H$ 7.521 (t, 6×2H, Ar-H, J=7.5 Hz), δ$_H$7.622 (t, 6×1H, Ar-H, J=7.6 Hz), δ$_H$ 7.946 (d, 6×2H, Ar-H, J=8.0 Hz).

^{13}C NMR (75 MHz, DMSO): δc 130.39 (C-4′of benzene ring),δc 134.40 (C-2′, C-6′, C-3′,C-5′of benzene ring), δc 132.66 (C-1′ of benzene ring), δc 132.66 (C-2,C-3, C-4 and C-6 of pyrimidine ring) and δc 169.21 ppm (C=O).

3.2.4 Synthesis of 2, 4, 6-Tris (di-4-chlorobenzamido)-1, 5-diazine nickel (II) bromide 10

The mixture of 0.1 g (0.007928 mol) 2, 4, 6-triaminopyrimidine (Diazine), 0.8680g p-chlorobenzoyl chloride and 8 mol% of bis-triphenyl phosphine nickel (II) bromide was added in 7 mL of DMSO in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound **7.**
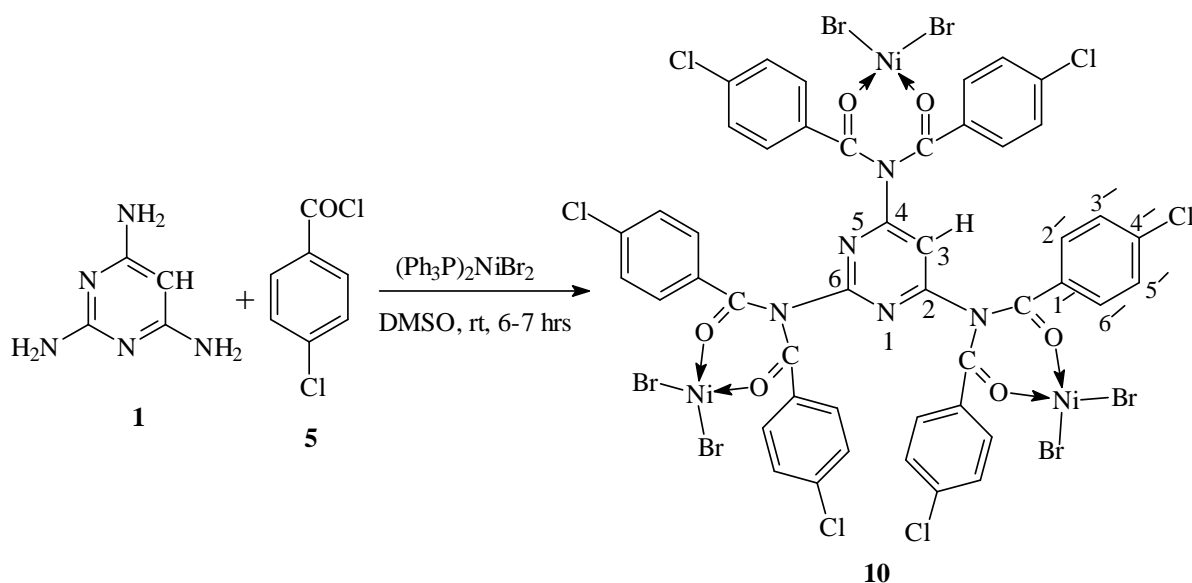
MF: $C_{46}N_5H_{25}O_6Ni_3Br_6$

MW: 1399.22

Physical analysis: White crystalline solid, m. p: 240-245°C, odorless and 88 % of yield.

Analytical analysis:

IR (KBr): v_{max} (cm^{-1}) 3072.71 (C=H aro.), 1686.81 (C=O), 1602.90 (C=N), 1326.10 (C=C aro.), 1027.13 (C-N), 811.09 (C-Cl).

¹H NMR (300 MHz, DMSO): δ_H4.96 (s, 1H, -C-H), δ_H7.85 (d, 6×2H, Ar-H,) And δ_H 7.96 (d, 6×2H, Ar-H).

3.2.5 Synthesis of 2, 4, 6-Tris (di-4-methoxybenzamido)-1, 5-diazine nickel (II) bromide 11

The mixture of 0.1 g (0.007928 mol) 2, 4, 6-triaminopyrimidine (Diazine), 0.8461 g p-methoxybenzoyl chloride and 8 mol% of bis-triphenyl phosphine nickel (II) bromide was added in 7 mL of DMSO in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound **7.**
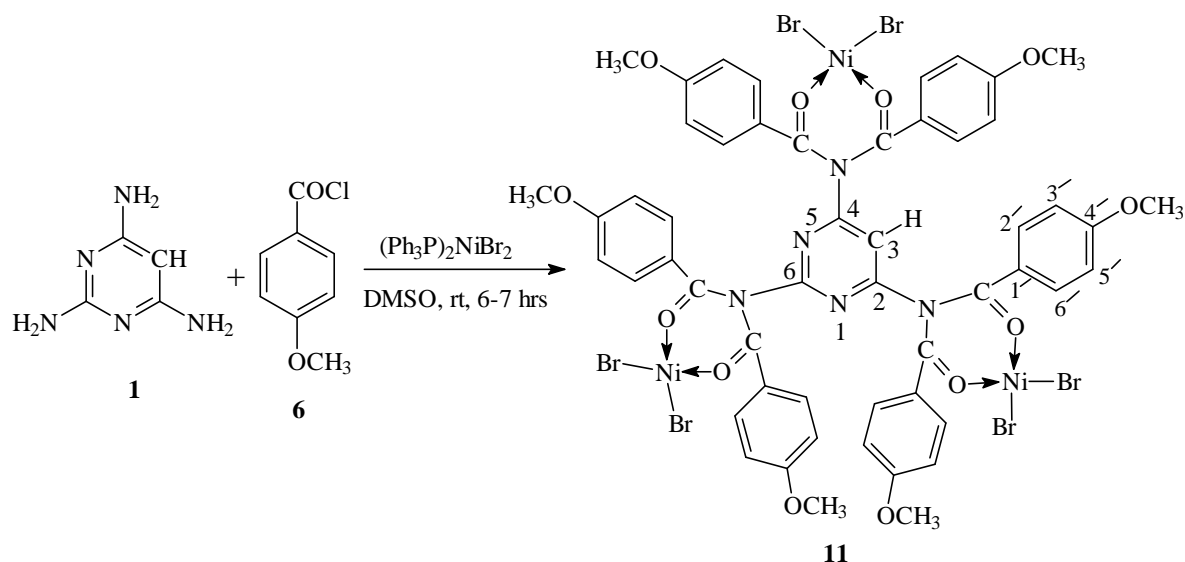
MF: $C_{52}N_5H_{43}O_{12}Ni_3Br_6$

MW: 1585.42

Physical analysis: White crystalline solid, m. p: 180-185°C, odorless and 92% of yield.

Analytical analysis:

IR (KBr): ν_{max}(cm⁻¹) 3114.18, 2854.74, 1607.72, 1350.22, 1255.70 and 1107.18 cm⁻¹

¹H NMR (300 MHz, DMSO): δ$_H$2.54 (s, 6×3H, Ar-OCH3), δ$_H$8.17 (6×2H, Ph-H), δ$_H$8.31 (6×2H, Ph-H) and δ$_H$ 3.39 (1H of pyrimidine ring).

3.2.6 Synthesis of 2, 4, 6-Tris (di-4-methylbenzamido)-1, 5-diazine nickel (II) Chloride 12

The mixture of 0.1 g (0.007928 mol) 2, 4, 6-triaminopyrimidine (Diazine), 0.7667g *p*-methyl benzoyl chloride and 8 mol% of bis-triphenyl phosphine nickel (II) chloride was added in 7 mL of DMSO in a 250 ml round bottle flask and the reaction was carried out by a similar procedure described by compound **7**.
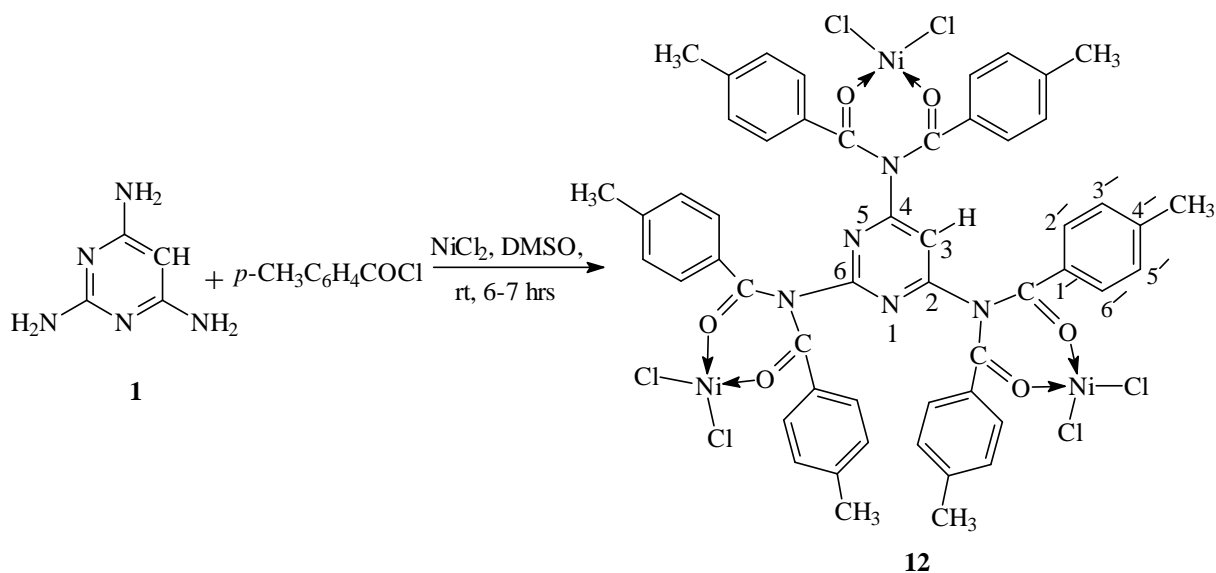
MF: $C_{52}N_5H_{43}O_6Ni_3Cl_6$

MW: 1222.72

Physical analysis: White crystalline solid, m. p: 180-185°C, Odorless and 95% of yield.

Analytical analysis:

IR (KBr): ν$_{max}$ (cm^{-1}) 3444.12 (C-H, aro), 2977.23 (C=H), 1817.00 (C=O), 1612.54 (C=N), 1516.10 (C=C), 1286.56 (C-N)

^{1}H NMR (400 MHz, DMSO): δ_H2.349 (s, 6×3H, Ar-CH3), δ_H7.230 (d, 6×2H, Ar-H), δ_H 7.90 (d, 6×2H, Ar-H).

Conclusion

Conclusion

The following points can be concluded from the research work-

★ In this thesis, a convenient method has been developed for the synthesis of a series of highly funtionalized metallodendrimers from the neat reaction of commercially available pyrimidine (2,4,6- triamino -1,3-diazine) with different aroylchlorides.

★ A facile method for the synthesis of metallodendrimers from the reaction of pyrimidine with different aroylchlorides using bis-triphenylphosphine Nickel(II) Bromide has been established under different conditions.

★ The synthesis of metallodendrimer compounds was also carried out by using synthesized dendrimer in the presence of $(Ph_3P)_2NiBr_2$ as legand in DMSO under room temperature.

★ The surface morphology and particle size of the compound were studied by taking Scanning Electron Microscope (SEM) and the synthesized compound was found to be supramolecule. SEM was taken 5-10 Kv at magnification ($\times$ 100-30000) of different range of particle size of the compound was found 1 μm to 100 μm and the shapes of the compounds were found as rock shaped. The structure were found like (compound **8**), rectangular fiber.

★ To ensure the presence of required metal such as nitrogen and halogen, elementary test (Lassaigne test) was done.

★ The required structures of the synthesized compounds was proved by IR, ^{1}H, ^{13}C.

★ At the time of synthesizing the compounds, the reactions were carried out in different solvents like DMF, DMSO and MeOH. And good result was found in case of polar aprotic solvent DMSO.

★ The most important feature of the synthesis were that the readily available inexpensive materials were used under relatively mild conditions and with higher yield.

★ A variety of functional groups can be introduced through this procedure. Moreover, no toxic and hazardous compounds were produced during the synthesis of compounds, so it is environment friendly.

★ These synthesized compounds would be important ligands and the metallodendrimers would be potent catalyst which is under study.

★ The synthesized compounds would be used as anti cancer agent, anti tumor agent and drug carrier during chemotherapy.

So reviewing those entire highlights, in conclusion it is established that this methodology could be utilized to synthesize the biologically important derivatives and will be attractive to both organic and medicinal chemists

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