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Preparation of magnetic nanodendrimers and their applications in organic reactions and biomedicine: An update

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ABSTRACT

In this review, the bioactive agents can be encapsulated into the interior of the dendrimers or chemically grafted/physically adsorbed on the dendrimer surface with the option of tailoring the carrier to the fundamental needs of the active material and its therapeutic applications. However, the high density of exo-presented surface groups allowed attachment of targeting groups or functionality that could modify the solution behavior or toxicity of dendrimers. Quite remarkably, modified dendrimers were shown to act as nano-drugs against tumors, bacteria, and viruses. Also, it was applied in medicin and agents of contrast for MRI

1. Introduction

Many Magnetic Nanodendrimer approaches have been proposed to achieve this goal, including the use of organic-based systems, polymeric nanoparticles, and dendrimers [1]. Among those, dendrimers are receiving increasing attention due to their controllable size and surface properties, which make them an attractive platform for drug delivery [2,3]. For example, it is known that polyamidoamine (PAMAM) dendrimers can adsorb small molecules noncovalently, releasing them in mildly acidic conditions, and this feature has already been exploited in the controlled delivery of fluorescent and therapeutic payloads [4]. Furthermore, dendrimer-based structures can be easily derivatized with targeting sequences such as peptides and oligonucleotides [5]. Dendrimers represent an excellent coating for metal nanoparticles, allowing the preparation of nanodevices that merge advantages of both organic and inorganic nanomaterials, such as high drug-loading capability and effective use as a contrast agent or as vector for magnetically targeted delivery. Not surprisingly, several hybrid structures composed of a metallic core and a dendrimer shell have been recently described [6,7,8], and some of them have intriguing capabilities as delivery agents. On this point, dendrimers have played a significant role due to their special physical properties which make them as suitable hosts for metal complexes and nanoparticles. Furthermore, they show excellent recyclability and reusability with maintaining their activities [9-13].

2. Biomedical application

MNPs were coated by PAMAM dendrimer until magnetite agglomeration decreased. MNPs were afforded applying co-precipitation approach. The obtained NPs were functionalized by aminopropyltrimethoxysilane to coat dendrimer. Aminosilane-functionalized MNPs were protected by PAMAM dendrimer. Features of PAMAM

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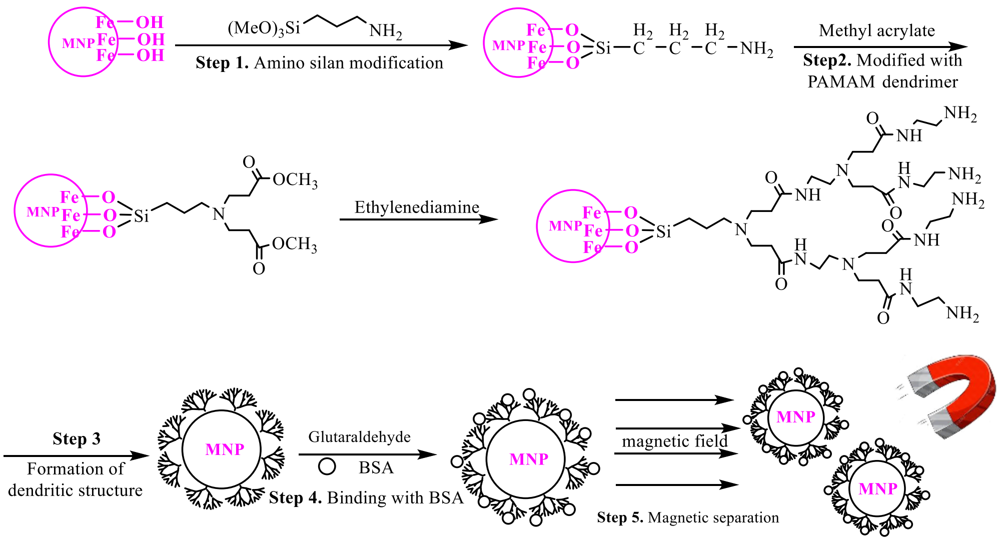
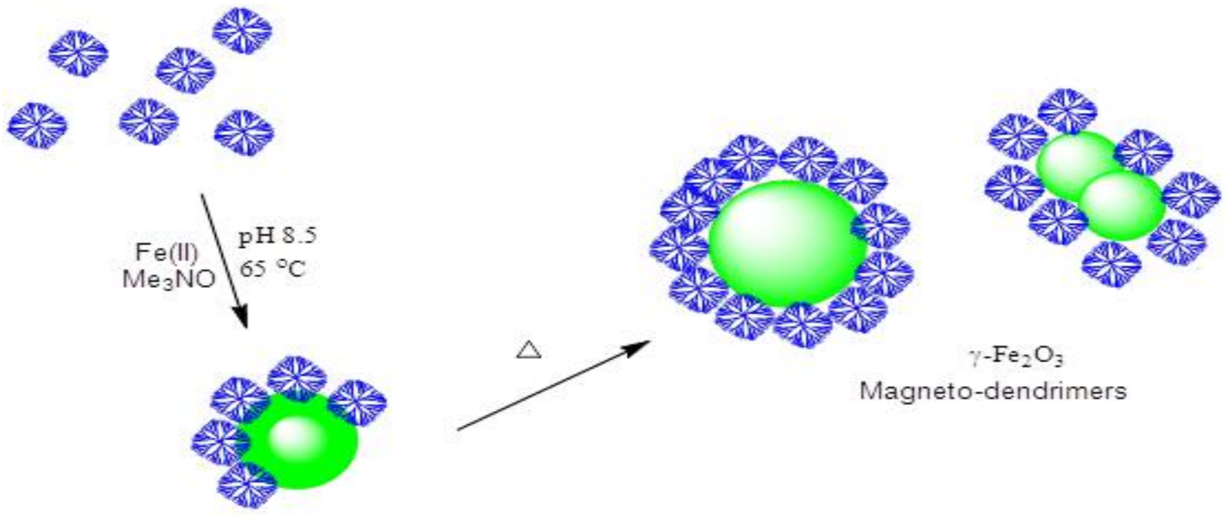
dendrimers consisted of monodisperse, hydrophilic, biocompatible and also highly flexible surface chemistry of these cascade-branched macromolecules simplified functionalization (magnetic nanoparticles = MNPs, polyamidoamine = PAMAM); nontoxic properties could be convenient nanocarriers for targeted cancer treatment by injection of different anticancer reagents and biomedical applications and drug delivery (Scheme 1) [14].

The ferrimagnetic iron oxide NPs were synthesized and stabilized (under a vast range of pH's and temperatures) by carboxylated poly(amidoamine) dendrimers that formed soluble composite materials and were characterized by TEM, SQUID magnetometry. NMR relaxation investigations of water protons showed unexpectedly high relaxation of T1 and T2, which caused these matters to be very good NPs as agents of contrast for MRI (Scheme 2) [15].

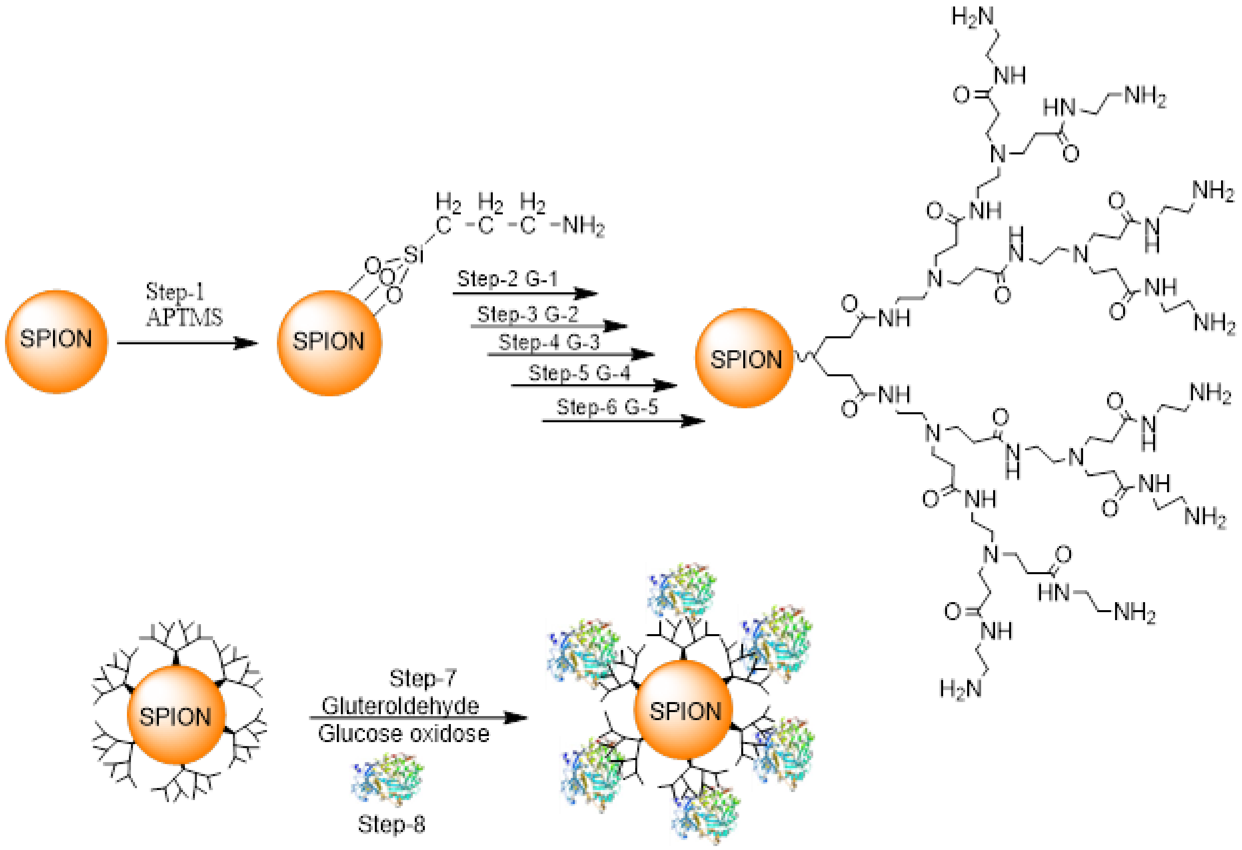
MNP was modified by polyamidoamine dendrimer for increasing invertase immobilization. Enhancing the immobilized enzyme amount onto the surface of PAMAM dendrimers grafted SPION was by 250% over SPION-G0 protected with silane. Diverse features of grafted invertase including operational stability, temperature activity, storage stability, and thermal stability were investigated. The results exhibited that the enzyme stability which was ameliorated upon immobilization, potential for biomedicine, was modified with immobilization (Scheme 3) [16].



Scheme 1. Immobilization of Fe_3O_4 with APTS and PAMAM dendrimers.



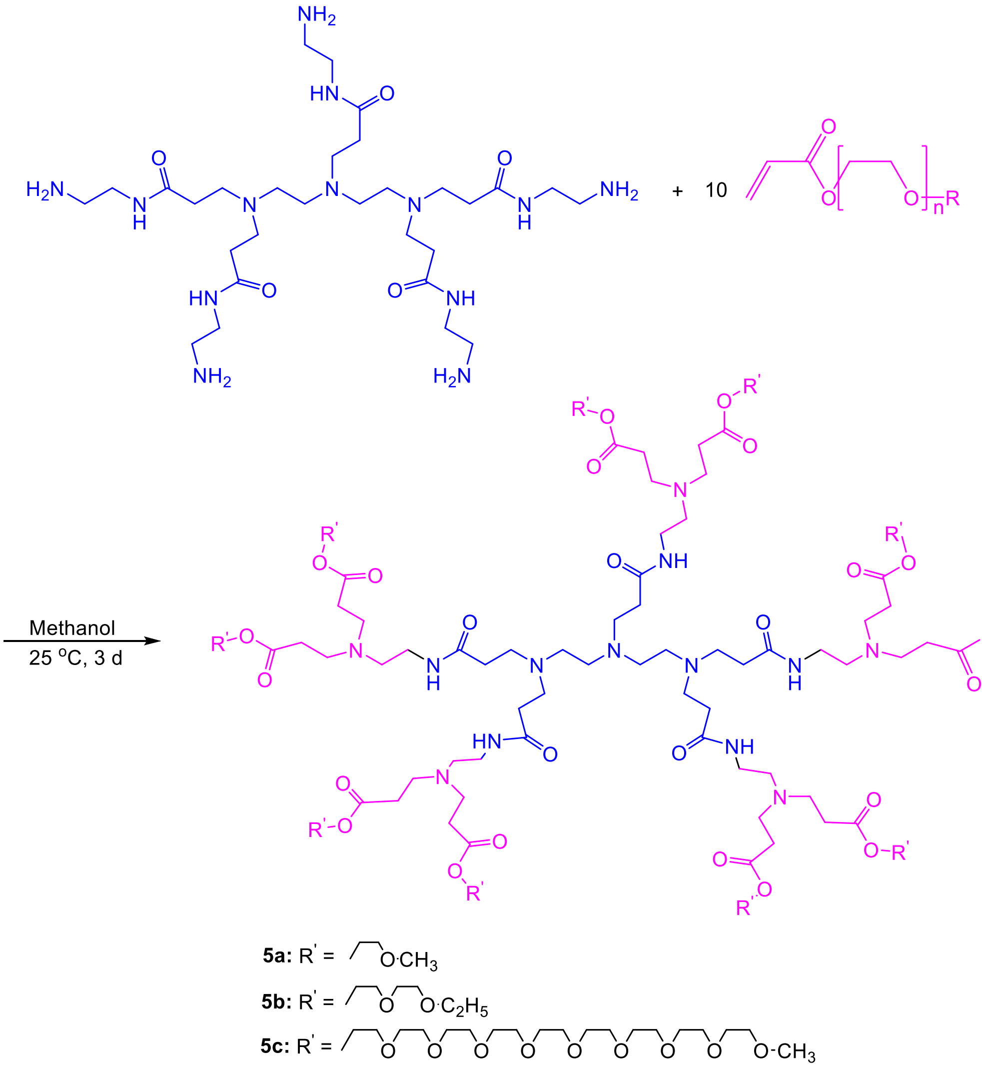
Scheme 2. Preparation of maghemite carboxylated PAMAM dendrimers



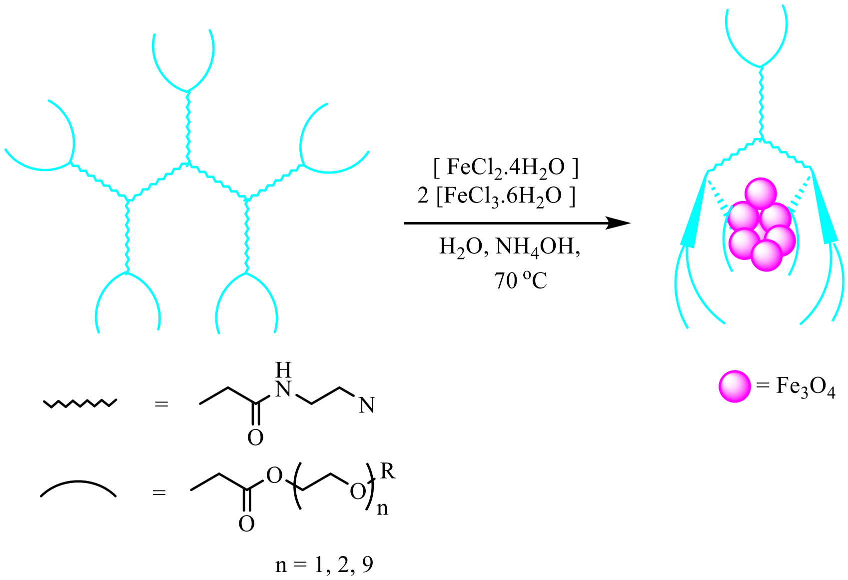
Scheme 3. Fe_3O_4 coated with PAMAM dendrimers to invertase immobilization

Fe_3O_4/PAMAM/PEG was prepared through direct and time effective chemical co-precipitation procedure [17]. Protection from coagulation of particle through creating stability to the surface of MNPs was by using easily available flexident biocompatible organic supports by EG-supported (ethylene glycol = EG) tentacles (Scheme 4). The present synthesis approach was improved to enable affording biocompatible well-defined dendrimer-encapsulated Fe_3O_4 colloids for pharmacological fields The obtained MNPs were confirmed by TG, SQUIDVSM magnetometry, XPRD, FT-IR and TEM (Scheme 5).

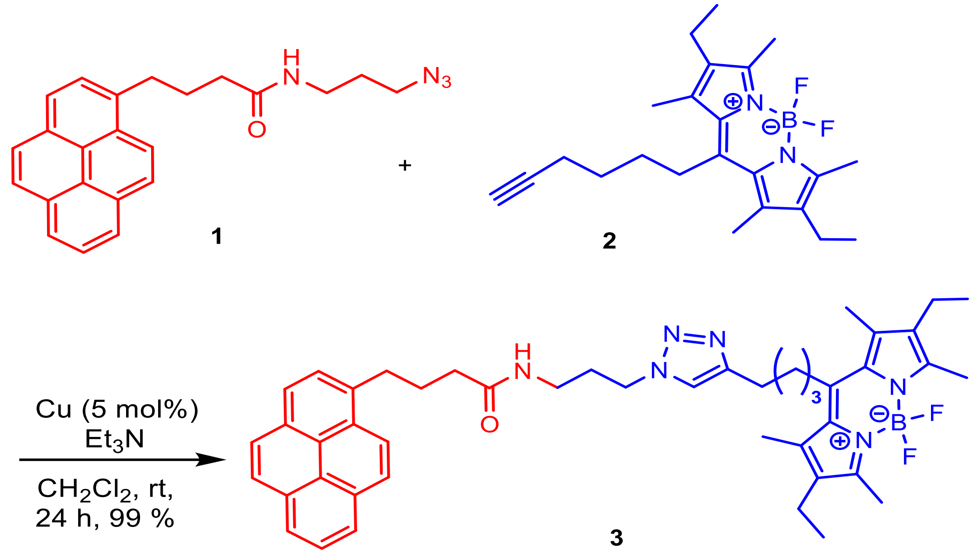
BODIPY Fluorescent dye and dendrimers immobilized on magnetically Co/C NPs were synthesized by Kainz in 2011 (Scheme 6) [18]. Magnetically graphene-supported onto Co NPs were applied for noncovalently grafted pyrene-labeled BODIPY dye using π-π interactions. As can be seen in Scheme 60, from the reaction between pyrene, azide functionalized and alkyne modified BODIPY dye as a so-called “click”-reaction, the pyrene-tagged BODIPY in the presence of opper-catalyzed azide/alkyne cycloaddition (CuAAC). In the next study, surface as a dual functionalization of graphene was investigated (Scheme 7). Then, the nanoparticles were covalently functionalized with polyester dendrons based on 2,2-bis-(hydroxymethyl) propionic acid. One of advantages of this method is that these dendrons are high multiplicity of surface sites, biocompatible. Next, to functionalized PY-labeled dye, grafting covalent on Co/C NPs was carried out noncovalent immobilization of dendrimers by diazonium for reversibly attached drugs as a nanosized carrier (Scheme 6).



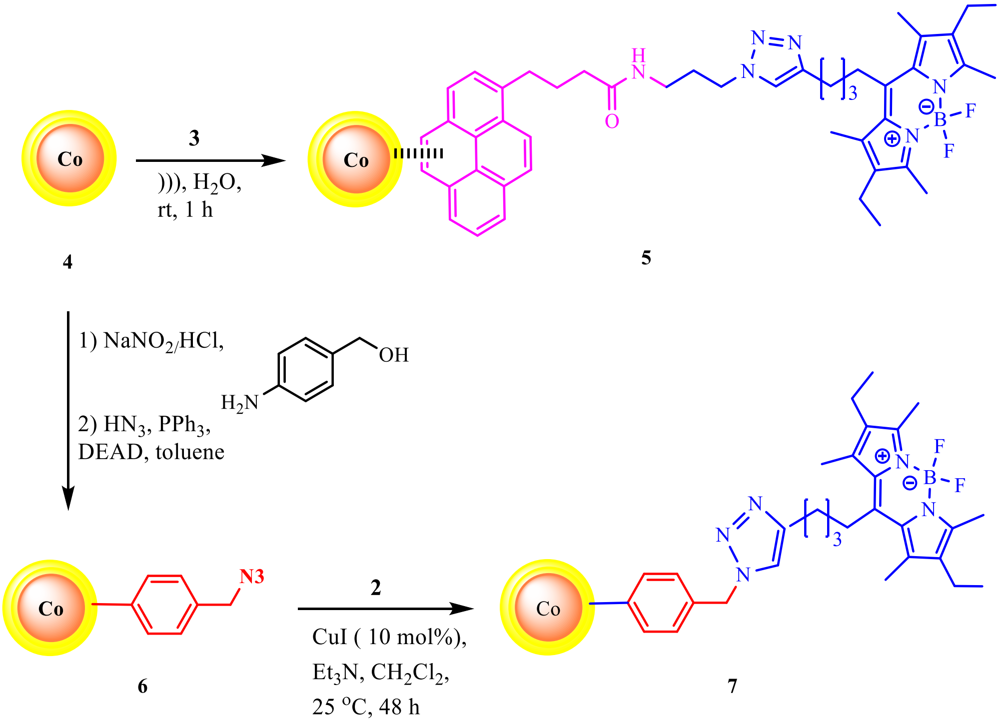
Scheme 4. Preparation of EG-modified amidoamine-based low-generation dendrimers 5a-5c



Scheme 5. Schematic of the synthesis of Fe_3O_4/PAMAM/PEG via the co-precipitation method in solution

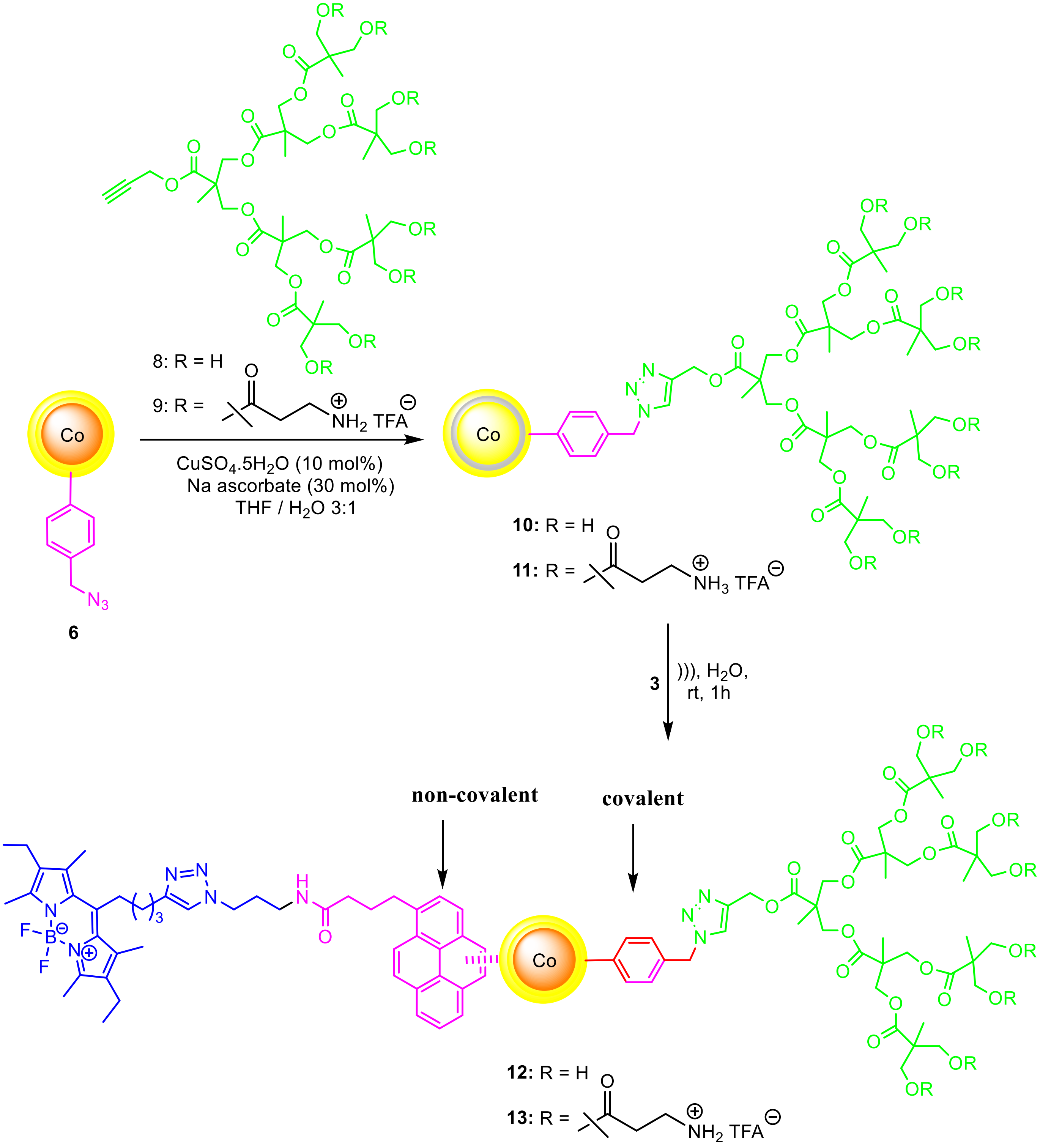


Scheme 6. Schematic of the preparation of Pyrene-immobilized BODIPY Fluorescent dye

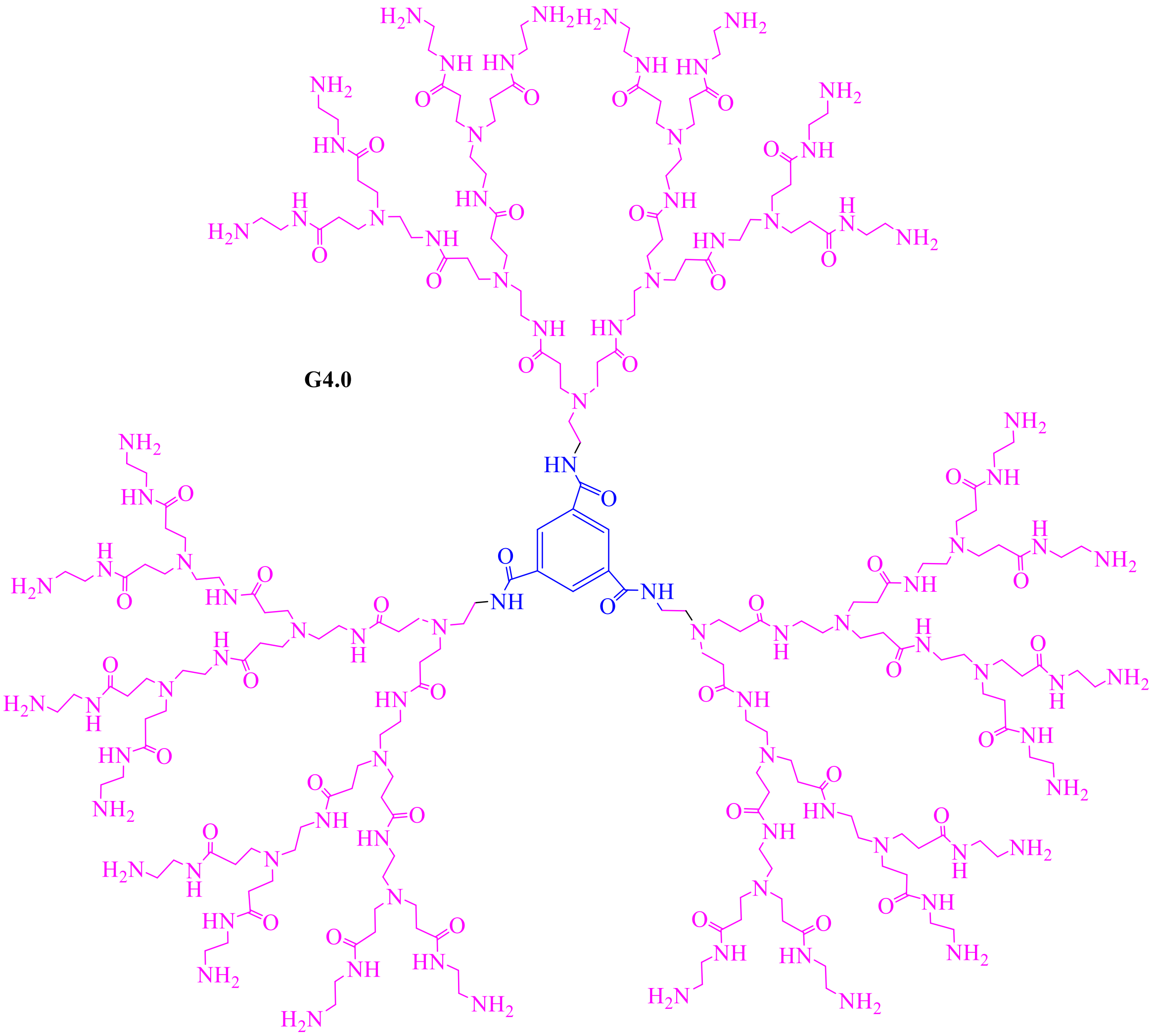


Scheme 7. Covalently and noncovalently immobilization on magnetically NPs Co/C

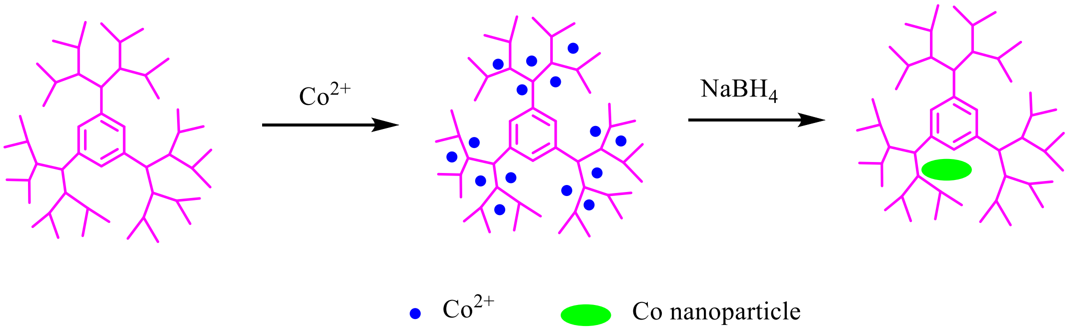
An easy approach was introduced to afford various Co NPs applying the template of dendrimers with a trimesyl core (from G3.0 to G6.0). For example, the structure of a dendrimer molecule (G4.0) is shown in Scheme 8. Along this line, the Co nanoparticles were synthesized through a two-step easily. First, coordination of dendrimers with Co^{2+} ions, and subsequent chemical reduction by $NaBH_4$ to produce Co nanoparticles were done (Schemes 9 and 10) [19]. The produced materials were studied by various . analysis such as FT-IR, TEM, XPS, X-ray and TGA. Also, their magnetic properties were examined with ZFC–FC curves and hysteresis loops. NCs (nanocomposites) exhibited superparamagnetic properties at room temperature. Co NPs represented a great T_1 MRI increment effect that could be a potential MRI contrast agent. Also, the potential of Co nanoparticles as MRI contrast agents was investigated



Scheme 8. Combined BODIPY Fluorescent dye and dendrimers immobilized covalently and noncovalently on magnetically NPs Co/C



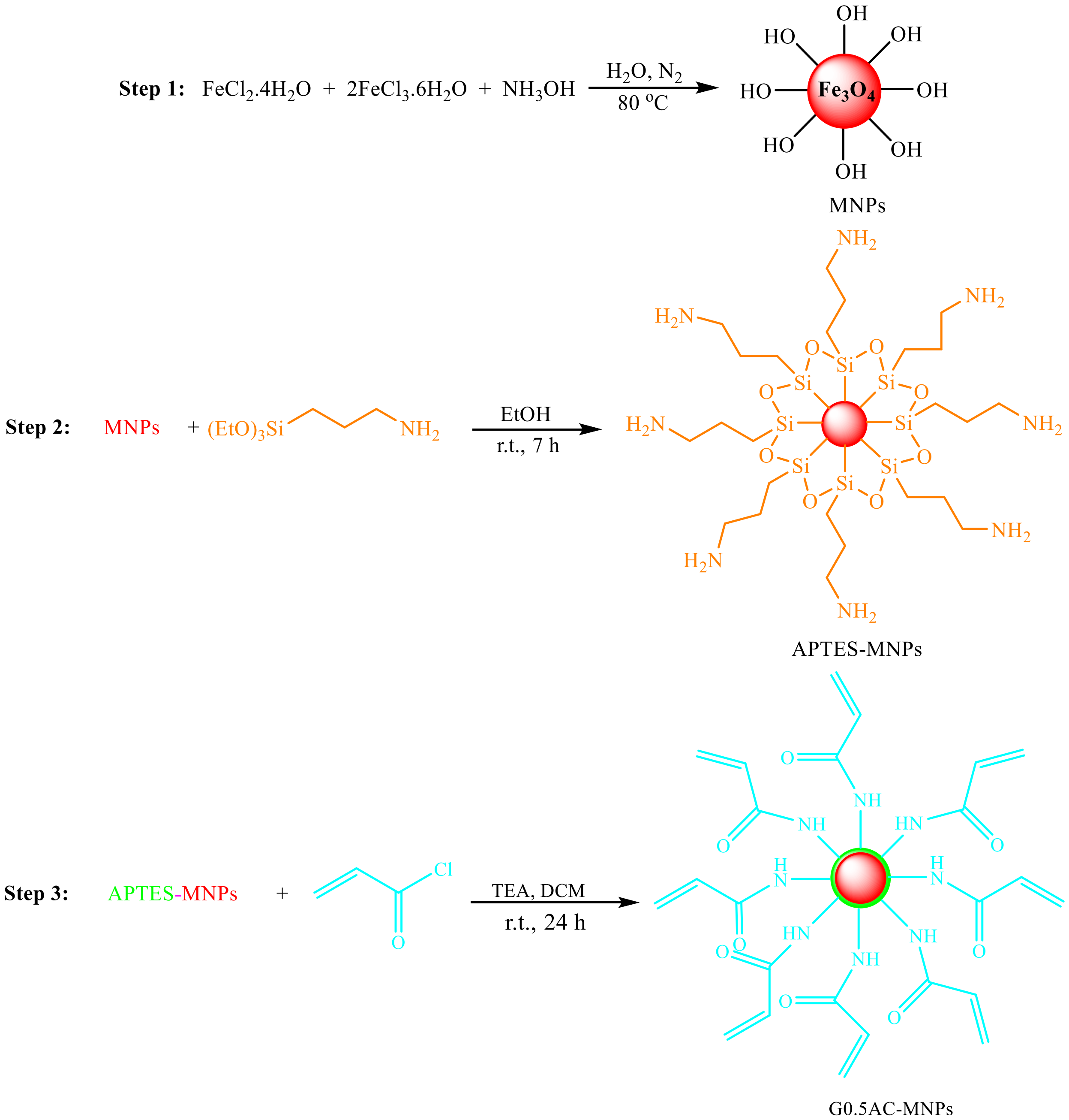
Scheme 9. Dendrimer G4.0 structure

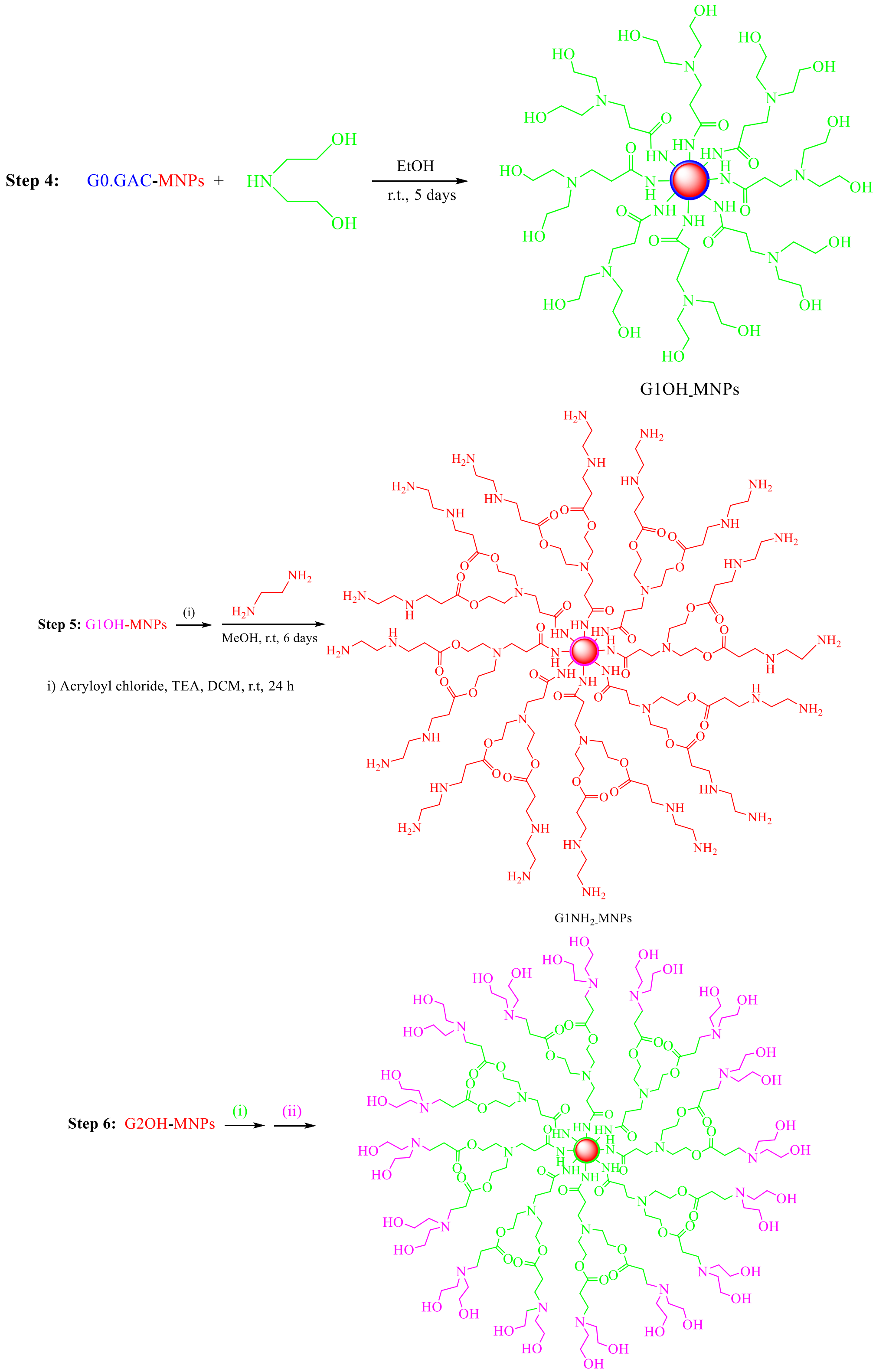


Scheme10. Synthesis of Co NPs by the dendrimers template

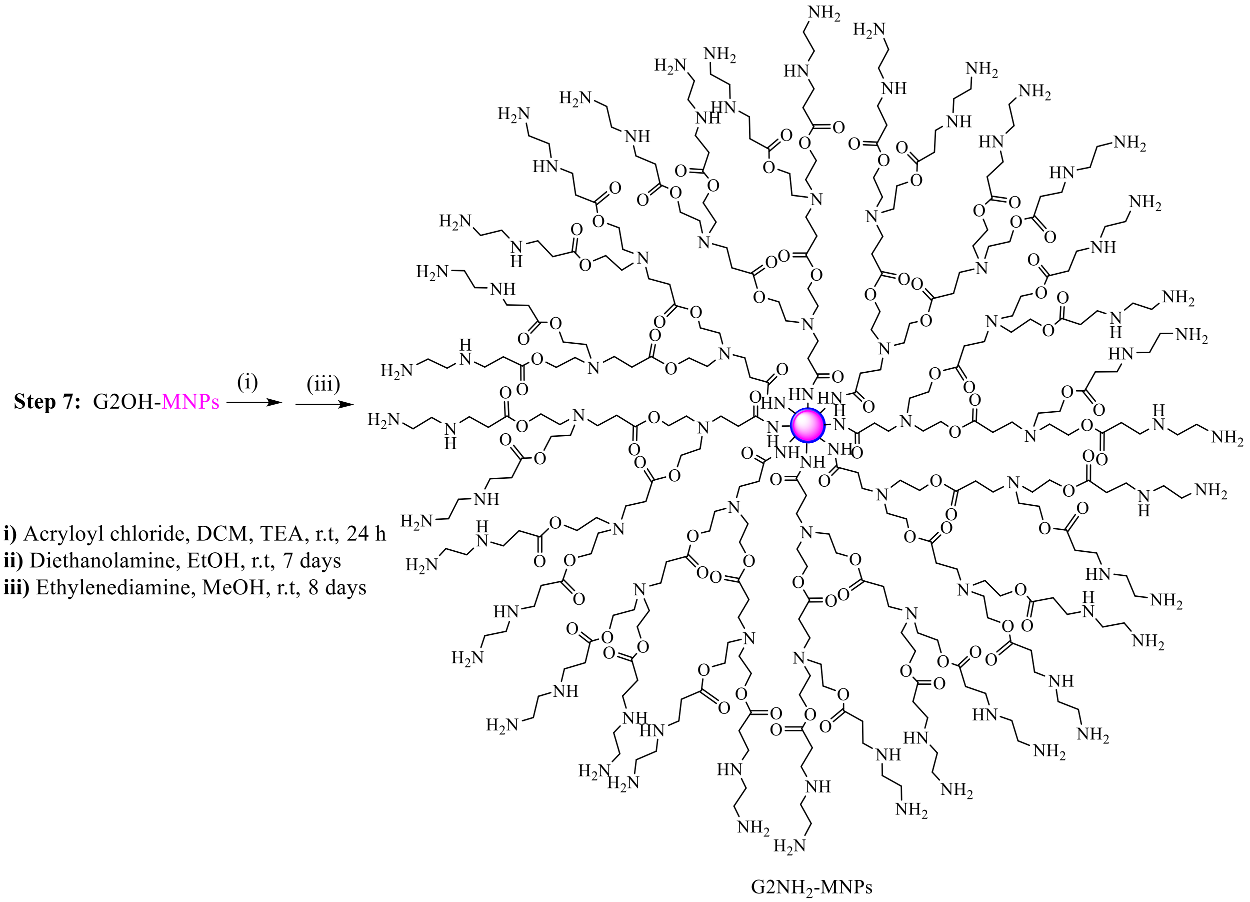
Successful preparation of novel dendrimers with functional groups of OH/NH$_2$ comprising Fe$_3$O$_4$ core supported by branches of amino ester with pH sensitive properties was reported by Dayyani et al. (2015) for effective hydrophobic drugs entrapment. Fe$_3$O$_4$ NPs were prepared via the co-precipitation approach and their surfaces were protected with APTES. The Magento Dendrimer first and second generations were afforded with OH end groups employing the necessary amounts of acrylic chloride and DEA, respectively using sequential acylation and additional Michael reactions. Dendrimer comprising amino modified groups up to the second generation was prepared applying the necessary quantities of acrylic chloride and EDA with the same procedure [20].

Fe_3O_4 grafted onto dendrimers with amine functional groups indicated encapsulation efficiency and high drug loading. The structure of G1NH_2-MNPs and G2NH_2-MNPs showed an amorphous and spherical morphology respectively; On the other hand, the G1OH-MNPs and G2OH-MNPs indicated polygon morphology (Scheme 11). Also, G1NH_2-MNPs, G2NH_2-MNPs G1OH-MNPs, and G2OH-MNPs can be highly effective carriers for cancer therapy, because they could deliver the encapsulated drug more quickly in acidic media. A profile of moderate release, low magnetic properties and rapid decomposition were perceived in buffer media (Scheme 12). The toxicology investigations demonstrated that all the NPs were biocompatible and drug-loaded NPs could deliver quercetin effectively into the cells.



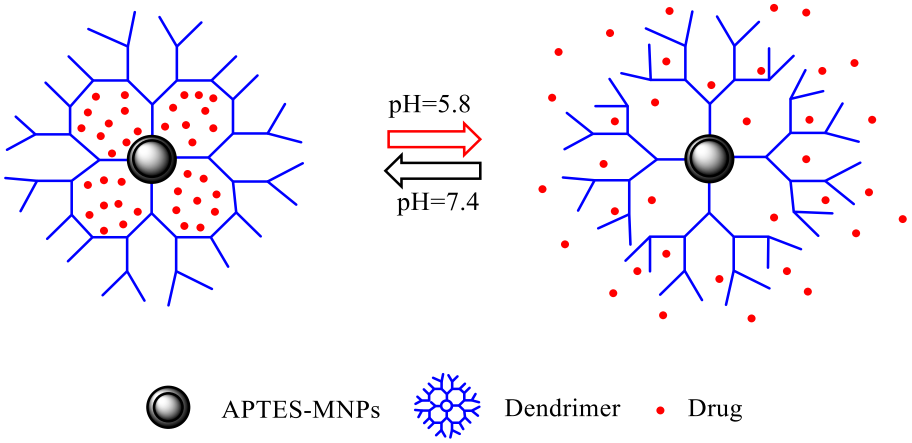

Step 4:
G0.GAC-MNPs +
HN
OH
OH
EtOH
r.t., 5 days
G1OH_MNPs
Step 5: G1OH-MNPs
(i)
H_2N
NH_2
MeOH, r.t, 6 days
i) Acryloyl chloride, TEA, DCM, r.t, 24 h
G1NH_2_MNPs
Step 6: G2OH-MNPs
(i)
(ii)

G2OH-MNPs



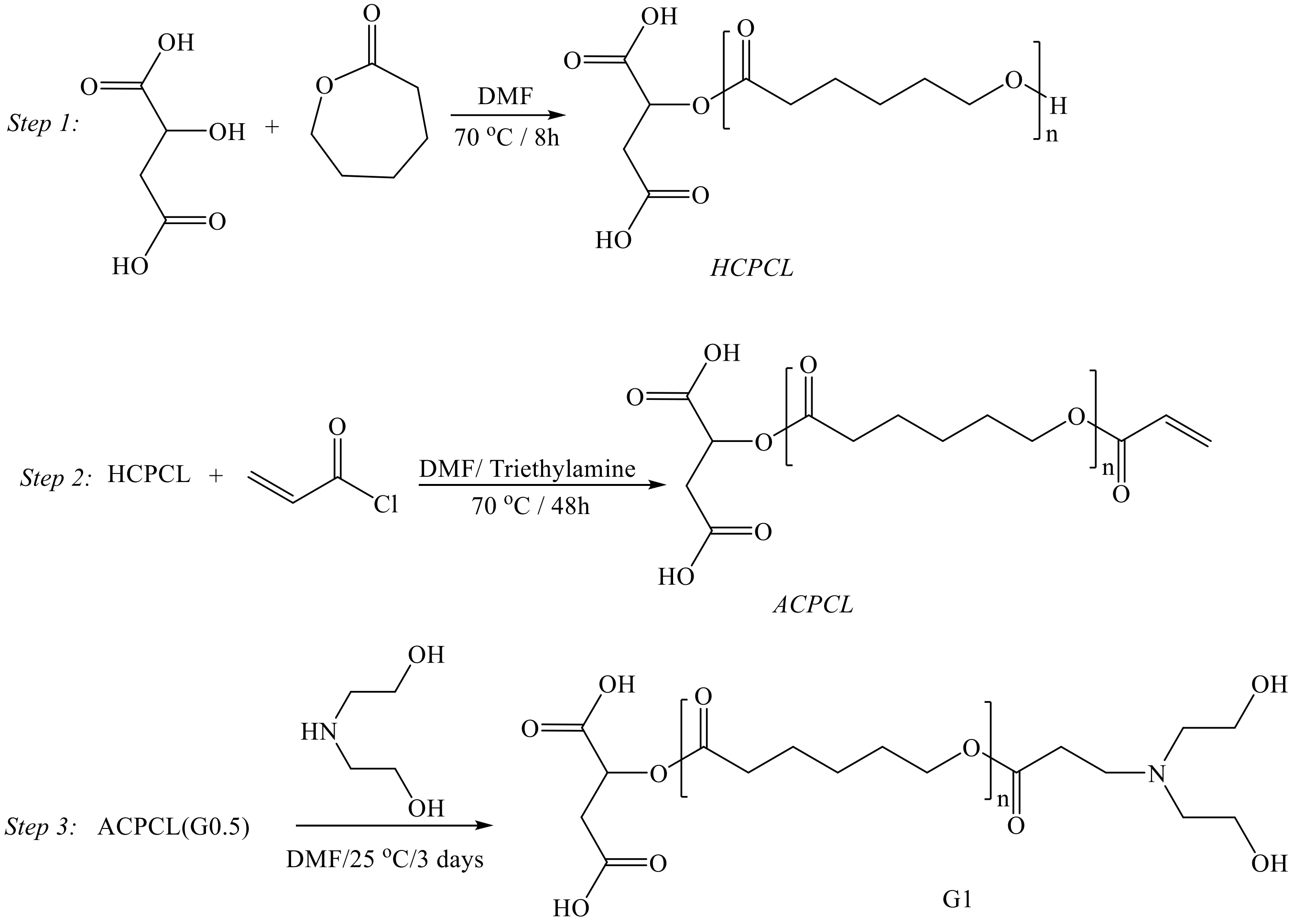
i) Acryloyl chloride, DCM, TEA, r.t, 24 h
ii) Diethanolamine, EtOH, r.t, 7 days
iii) Ethylenediamine, MeOH, r.t, 8 days

Scheme 11. Synthesis of MNPs, APTES-MNPs, G0.5AC-MNPs, G1OH-MNPs, G1NH$_2$-MNPs, G2OH-MNPs, and G2NH$_2$-MNPs

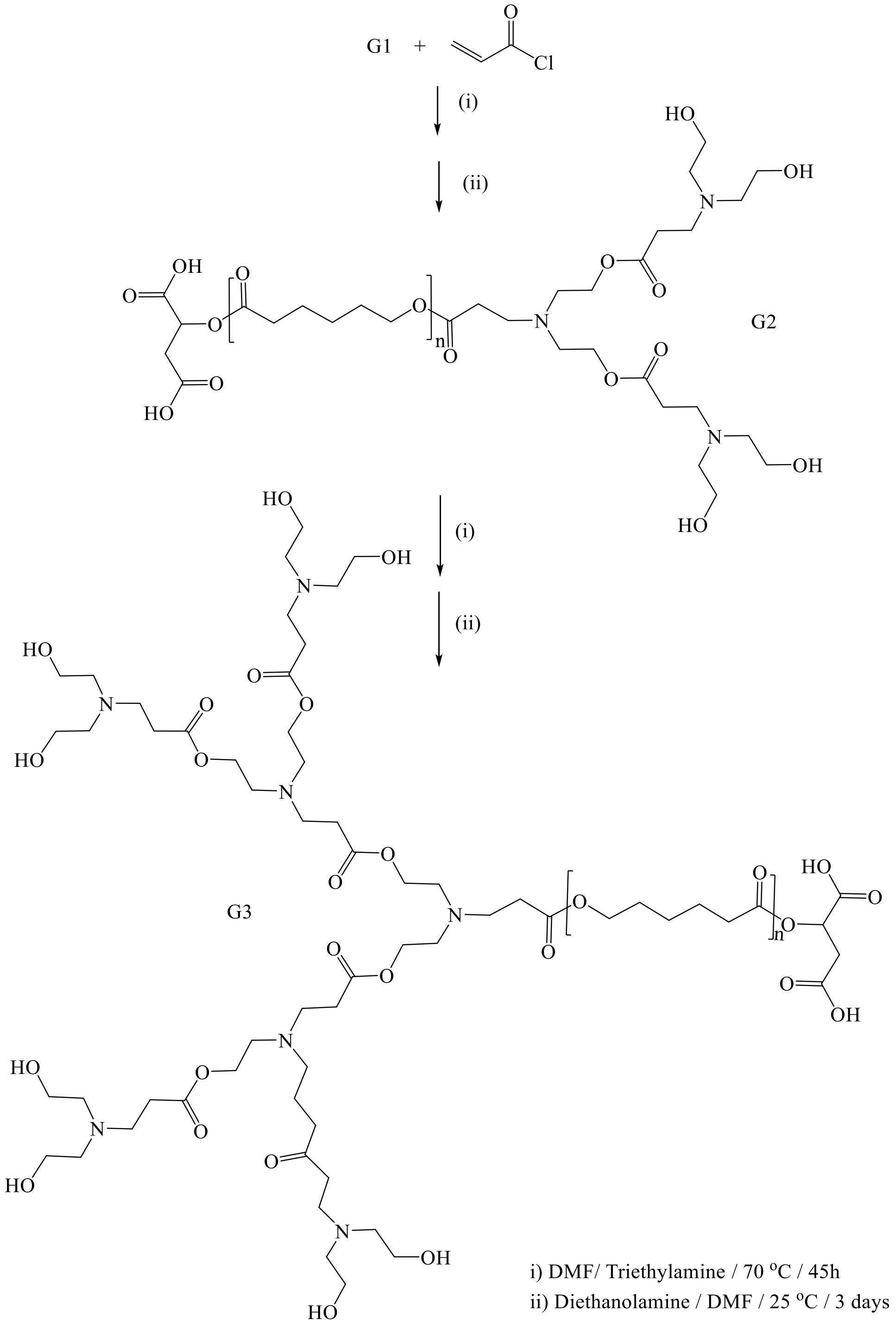


Scheme 12. The drug release from magneto dendrimer via changing buffer media *p*H

Khoee and Hemati prepared G1, G2 and G3 dendrons by sequential acrylation and Micheal addition reactions [21]. G1 dendrons was produced from HCPCL and acryloyl chloride and finally diethanolamine. G2 was produced from G1 dendrons and acryloyl chloride in DMF and triethylamine. Also, G3 dendrons was produced by G2 dendrons and acryloyl chloride in DMF and trimethylamine (Schemes 13 and 14). These amphiphilic dendrons were produced easily mPEG-adipoyl chloride with hydroxyl group of G1, G2 and G3 (Scheme15). NPs comprising Fe_3O_4 supported by amphiphilic dendrimers coated onto copolymers of PCL/PEG were designed to effectively entrap hydrophobic drugs. Amphiphilic dendrons containing hydrophobic inner shell of poly ε-caprolactone, conical poly (amino-ester) and hydrophilic corona of m-PEG were fabricated. Adsorption of malic acid-terminated dendrons on the surface of pre-coated NPs of Fe_3O_4 to oleic acid was performed trough approach of ligand exchange to form convergent dendrimers. The variability of the Copolymer deposition onto the SPIONs surface could be possible with changes in the dendritic scopes' generation, in convergent dendrimers; the most effective of factor in dendrons adsorbing capability on the MNPs surface was their spatial structure (Scheme 16). Seemingly, increasing drug entrapment was possible with enhancing the generation, while G2 seemed to perform well in this competition. Excellent HLB and Ultra-low CMC in these NPs hindered them from accumulation. This generation could be propounded as a convenient nanocarrier, due to low polydispersity, reasonable release profile, small particle size, excellent magnetic properties and excellent encapsulation performance. A significant factor that made it possible for these NPs to put in the smart carrier's category was Its *p*H-sensitivity (Scheme 17).



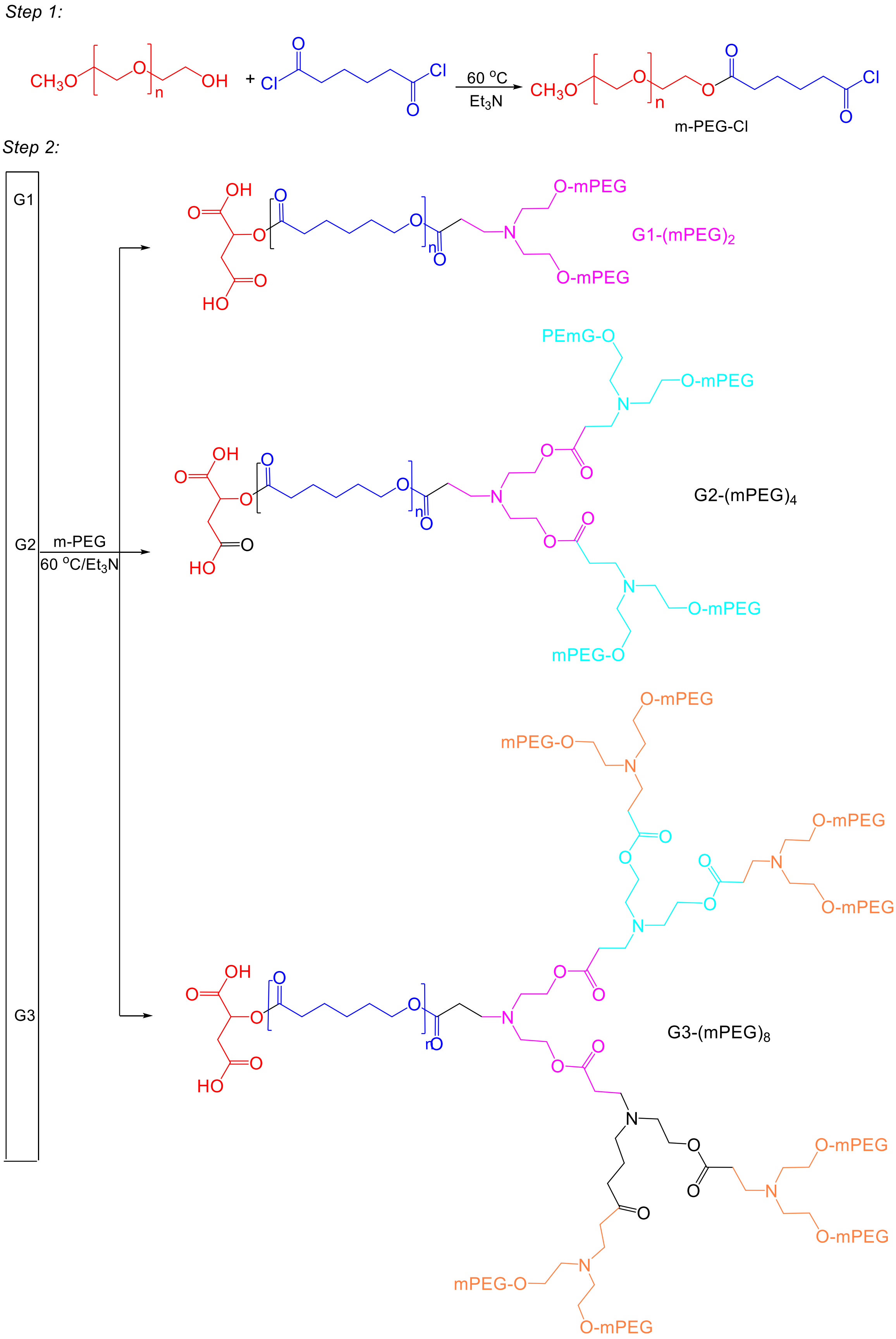
Scheme 13. Synthesis of G1 from sequential reaction between HCPCL, acryloyl chloride and diethanolamine



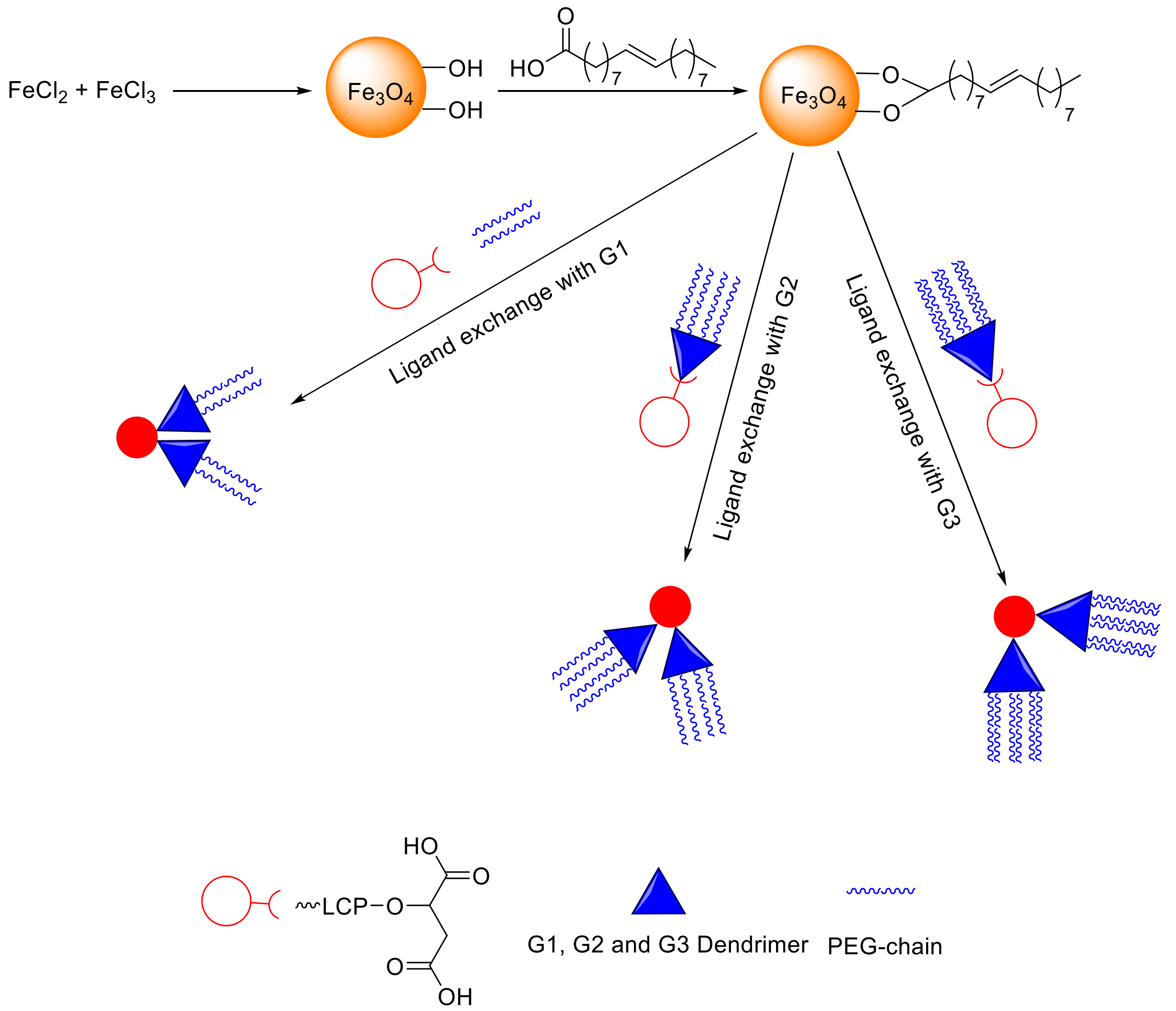
i) DMF/ Triethylamine / 70 °C / 45h

ii) Diethanolamine / DMF / 25 °C / 3 days

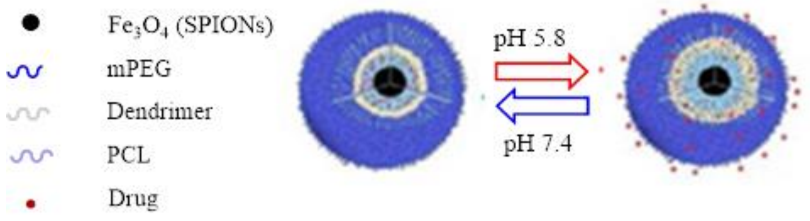
Scheme 14. G2 and G3 dendrons synthesis



Scheme 15. Coupling reactions of dendrons with various generations and mPEG-Cl

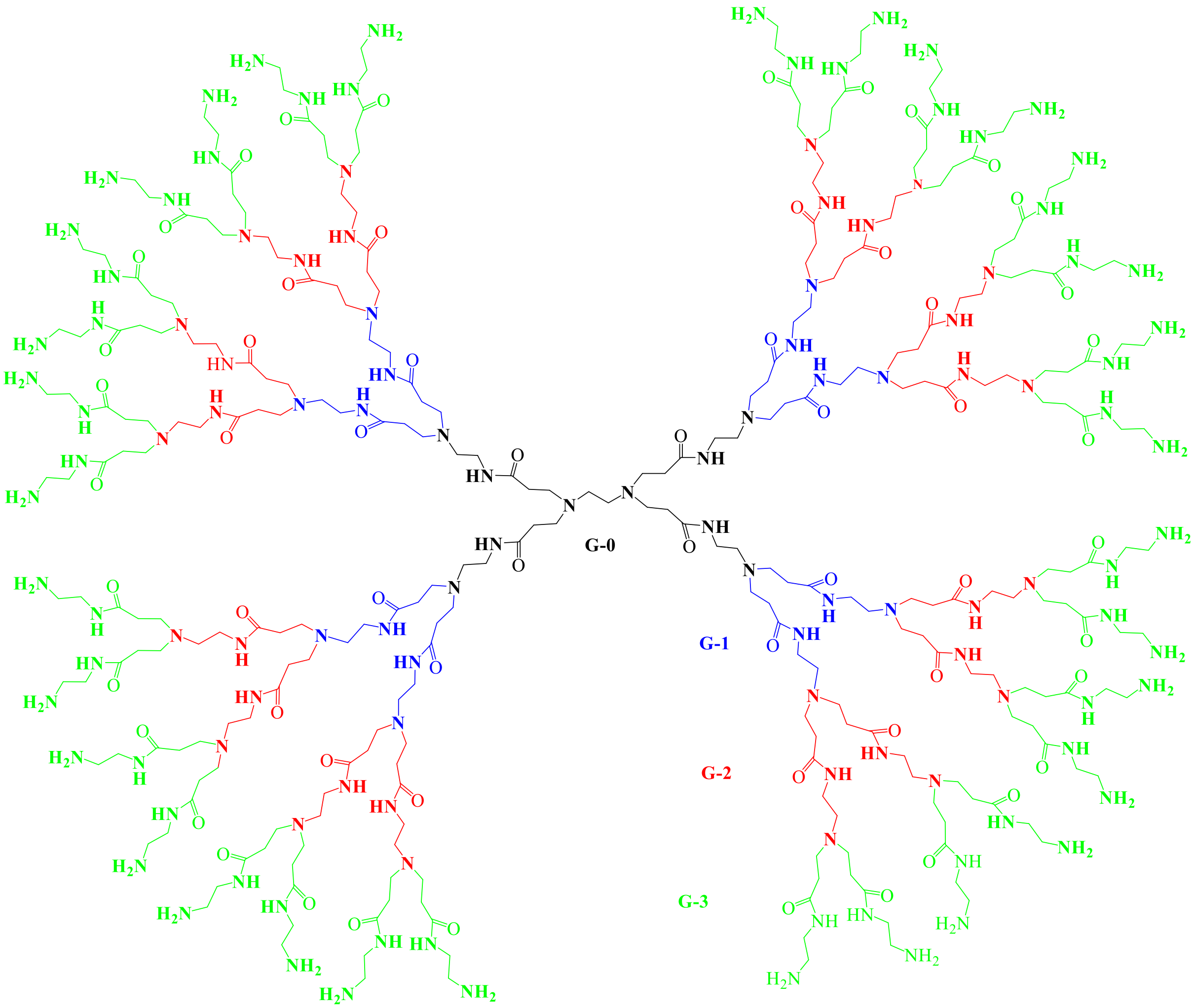


Scheme 16. Schematic of the synthesis of copolymer-stabilized MNPs using ligand exchange method



Scheme 17 Release of drug from amphiphilic dendrimer via changing in the buffer medium pH

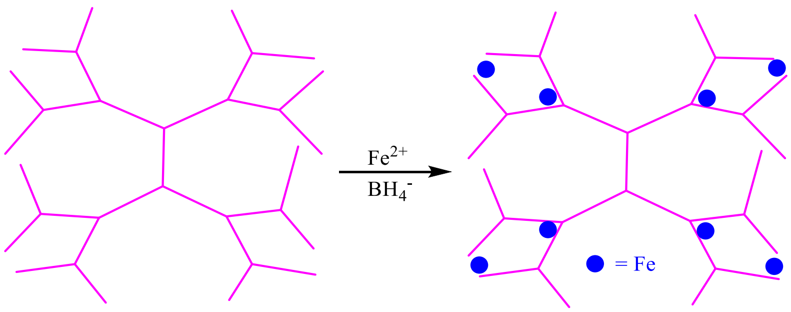
Baykal et al. synthesized various dendrimers (G0-G3) that can be seen in Scheme 18 [22]. Also, their characteristics and abbreviations are presented in Table 1. In this study, a series of Fe comprising NPs were fabricated by applying PAMAM, templates of dendrimers with various generations (G0-G3) and a reducing agent $NaBH_4$ (Scheme 19). XRD analysis showed obtained particles low crystallinity within the dendrimers; however, with developing generation of dendrimers, crystallinity of the NPs was expanded. They applied MRI contrasting for molecular imaging or cell, diagnostic, biomedicine applications, and molecular imaging or cell.



Scheme 18. The G0-G3 dendrimers structure

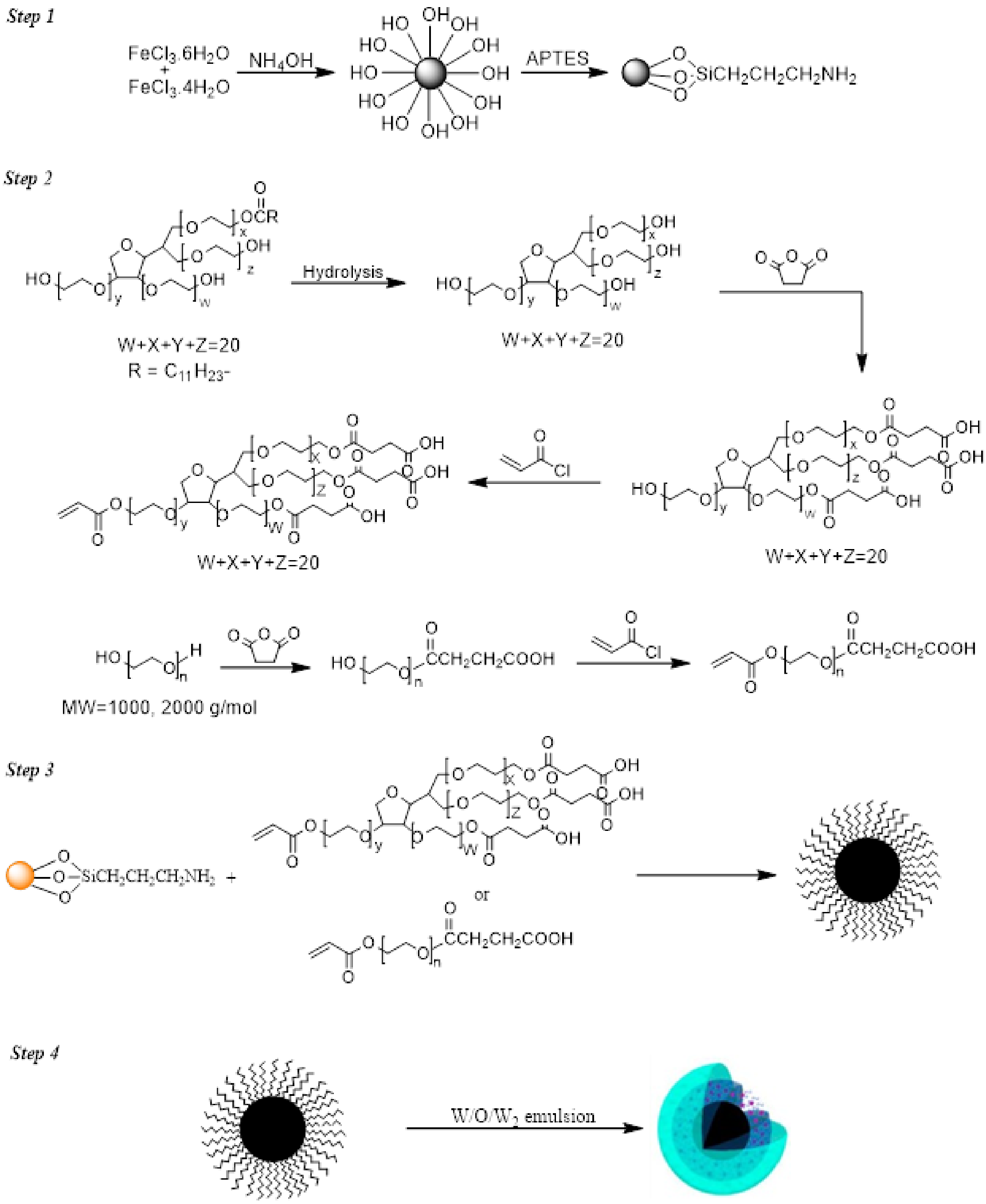
Table 1. DE-encapsulated Fe-NPs denotation

Generation	Fe Metal/dendrimer molar ratio			
	10:1	20:1	30:1	40:1
G0	F010	F020	F030	F040
G1	F110	F120	F130	F140
G2	F10	F220	F230	F240
G3	F310	F320	F330	F340



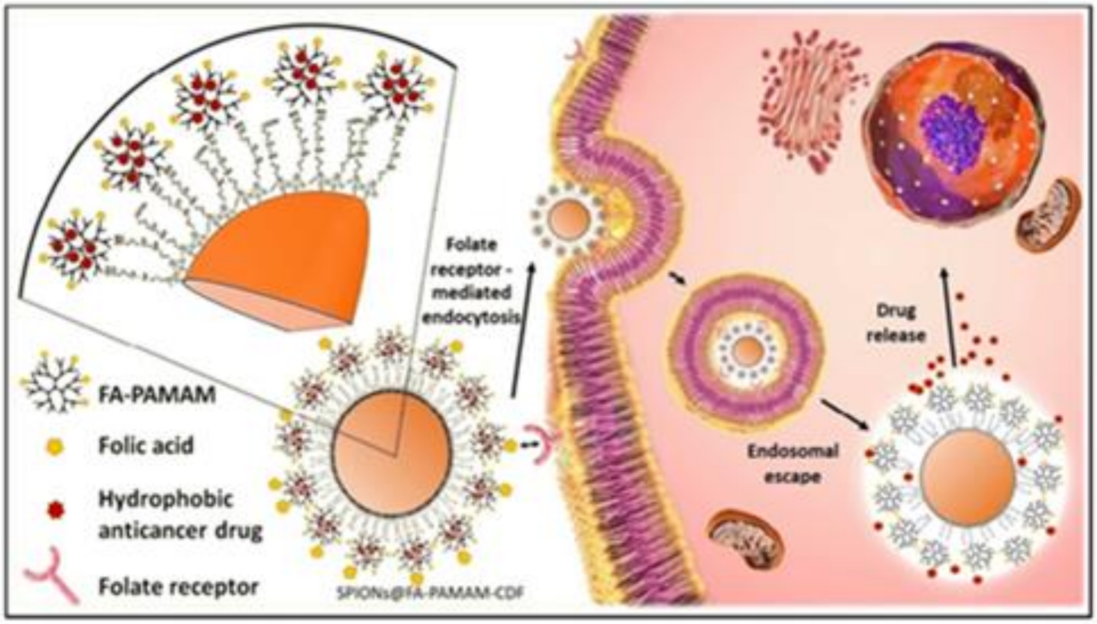
Scheme 19. Generation of dendrimer supported Fe NPs

Khoee and co-workers reported ultrasound-assisted synthesis of *p*H-responsive nanovector based on PEG/chitosan coated MNPs (Fe_3O_4@Cs-PEG nanoparticles) [23]. In this study, Fe_3O_4 NPs were produced employing coprecipitation procedure and modified by three kinds of PEG utilizing ultrasound irradiation. PEG laded particles were functionalized by CS shell via ultrasound waves double emulsion approach (Scheme 20). Various techniques confirmed that the *p*H-responsive shell was successfully grafted on the Fe_3O_4. Carrier of pH-sensitive MNPs were suggested for 5-FU delivery. Synthesized nanoparticles chemico-physical properties were examined. The results showed that pure Fe_3O_4 had a regular spherical shape and mean diameter of 20 nm which increased after step of modification depending on the type of PEG.



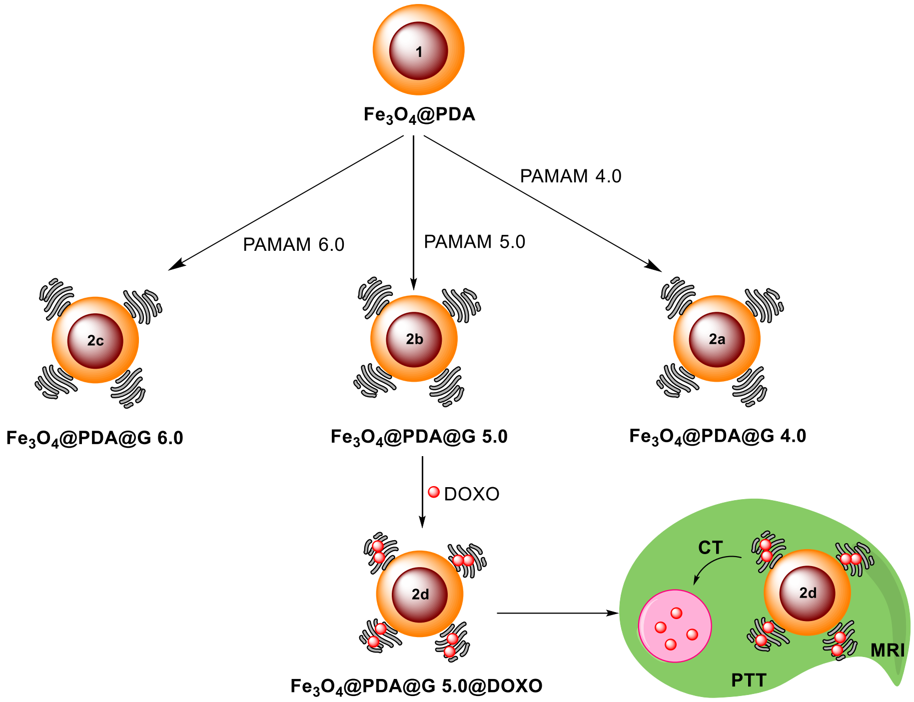
Scheme 20. Synthesis of Fe_3O_4@Cs-PEG

In 2017, Luong and co-workers developed a novel method for the synthesis of theranostic nanoparticles (SPIONs@FA-PAMAM). They used theranostic nanoparticles as therapy and simultaneous cancer imaging with SPIONs as core supported by FA-PAMAM dendrimers surface. Further 3,4-difluorobenzylidene-curcumin (CDF) as an agent of highly potent hydrophobic anticancer was co-loaded to improve its solvability and evaluate its treatable potentials in dendrimer of FA-PAMAM. The obtained NPs (SPIONs@FA-PAMAM-CDF) displayed excellent MR-contrast. When evaluated onto folate receptor overexpressing cervical (HeLa) and ovarian (SKOV3) cancer cells, the CDF loaded targeted NPs exhibited higher agglomeration with a better anticancer activity as compared with the non-targeted counterparts, because of multivalent interaction between folate receptor binding and cell overexpressing the target. The results were confirmed via observing a larger population of cells undergoing apoptosis due to up regulation of caspase 3, tumor suppressor phosphatase and tens is homolog, and NF-κB inhibition in groups treated by the targeted formulations, which further supported the multivalent the nanos tic NPs capability for simultaneous therapy and imaging of cancers (Scheme 21) [24].



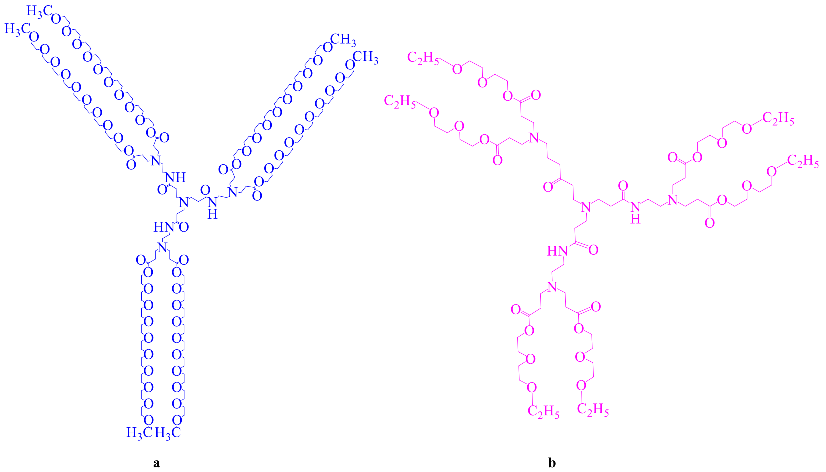
Scheme 21. The pictorial representation of the folate receptor mediated endocytosis followed through drug release of the targeted the nanos tic formulation SPIONs@FA-PAMAM-CDF in cancer cells overexpressing folate receptors. Reprinted with permission from Ref. [11], Copyright (2017) American Chemical Society

Jędrzaka et al. (2019) carried out the synthesis various of PAMAM dendrimers (G 4.0, 5.0 and 6.0) modified MNPs grafted with polydopamine (PDA) and introduced their application in therapy of advanced cancer (Scheme 22) [25]. In addition, it was represented that nanocarriers modified by G 5.0 could be successfully employed in CT-PTT (combined chemo- and photothermal therapy = CT-PTT) of the liver cancer cells. The result showed that the cooperative effect of the above-mentioned methods led to more deaths cancer cells in proportion to their individual performance. Also, the usage of dual therapy by in vitro studies caused the desired cell death mechanism-apoptosis. Furthermore, the afforded material had the properties of MRI Contrast and were promising smart drug delivery system for therapy of cancer.



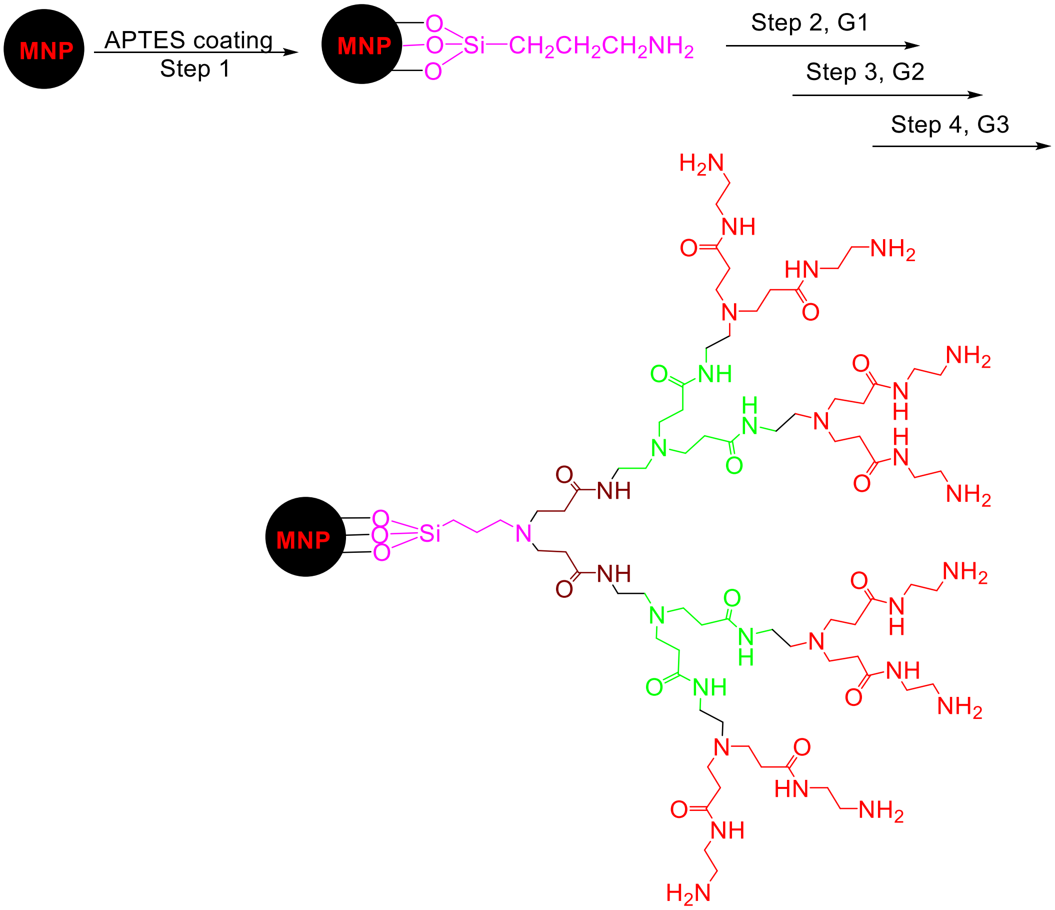
Scheme 22. The preparation of nanoplatform immobilized on the Fe_3O_4@PDA@G 4.0-6.0 NP and its application in CT-PTT therapy onto HepG2 cells

Kirschning et al. (2015) reported two various chain lengths of PEG@PAMAM dendrimers [26]. They synthesized the S6@PEG@PAMAM with six end-coated ethylene glycolether-tentacles of type $CH_2CH_2C(O)O(CH_2CH_2O)_9CH_3$, and S6-PEG-PAMAM with six end-grafted ethylene glycolether-tentacles of type $CH_2CH_2C(O)O(CH_2CH_2O)_2C_2H_5$, and characterized by microstructural and different spectroscopic analysis (Scheme 23). The multiple s-donor ability of these dendrimers led to their use to stabilize the MNPs. These NPs were tested for their potential use in cancer drugs, DOX (doxorubicin), because they were superparamagnetic and mesoporous. Achieving excellent drug-loading performance by controllable release was the main challenge in the developed drug delivery system. The variation in potential of zeta and fluorescence intensity quenching suggested chemical interaction of DOX with NPs. The efficiency of loading was computed to be more than 95% by a temperature sensitive release and sustained *p*H. In addition, enzyme cathepsin B was utilized to destroy the dendritic shell to stimulate release of sustained drug in the proximity of tumor cells.



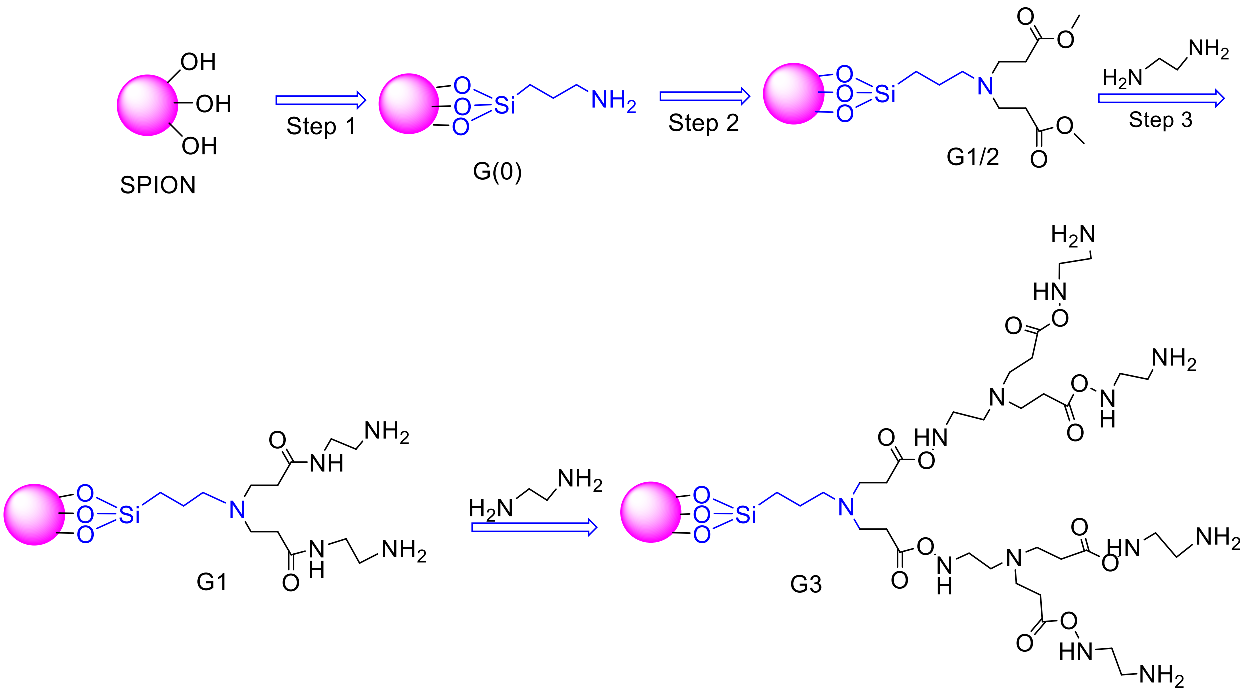
Scheme 23. Dendrimer’s structure: (a) long branch or L6@PEG@PAMAM (b) short branch or S6@PEG@PAMAM

Fe_3O_4 were utilized in different biomedical applications such as MRI contrast agent, drug delivery, hyperthermia and biosensors. Surface functionalizing the NPs by a biocompatible section was required to prevent their accumulation and enable them to target the defined area. The dendrimers attracted considerable interest due to their small size, well-defined globular shape, monodispersed and relative ease incorporation of targeting ligands. In the study, the superparamagnetic iron oxide was synthesized by coprecipitation method and modified by APTES, and then PAMAM caoted MNPs were fabricated (Scheme 24) [27]. Biocompatibility of NCs (nanocomposites) was confirmed even at high concentrations of NPs, 100 µg / ml by cytotoxicity assay. Dendrimer modified MNPs were able to act as hyperthermia mediators of magnetic fluid and agents of contrast for MRI. MRI results displayed that the fabricated NCs were a desired option for MRI contrast agent.



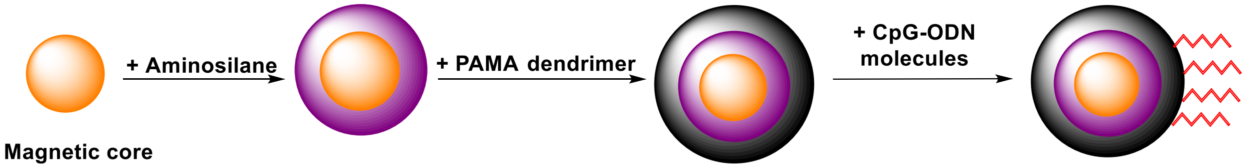
Scheme 24. Immobilization of iron oxide with PAMAM dendrimer

Khosroshahi et al. (2016) investigated fluorescent dendronized magnetic nanoparticles (FDMNPs), for potential applications in imaging and drug delivery [28]. Briefly, they synthesized FDMNPs and evaluated the effect of polyamidoamine (PAMAM) dendrimer and then fluorescein isothiocyanate (FITC) and its direct anchoring onto superparamagnetic iron oxide nanoparticles (Scheme 25). The cytotoxicity assays of nanostructures were carried out at various concentrations from 10 to 500 µg/mL via MCF-7 and L929 cell lines. In MTT assay, IC_{50} was 201.88 µg/mL for DMNP incubated MCF-7 and IC50 was 201.88 µg/mL for DMNP incubated MCF-7 cell lines, while the cell viability for FDMNPs did not decrease to 50%. The results represented that conjugation of FITC reduced the toxicity of DMNPs mainly due to the surface charge decrease. It seems that DMNP was cytotoxic for both cell lines at the concentration levels. On the other hand, at all concentrations, FDMNPs exhibited more biocompatibility and cell viability of L929 and MCF-7 cell lines. The fluorescence microscopy of fluorescent dendronized MNPs incubated by MCF-7 cells demonstrated a successful localization of cells showing their ability for applications such as a magnetic fluorescent probe in imaging purposes and cell studies. T2 relativity measurements indicated the synthesized nanostructures applicability as the agents of contrast in differential evaluation of tissue by changing their relaxation times.

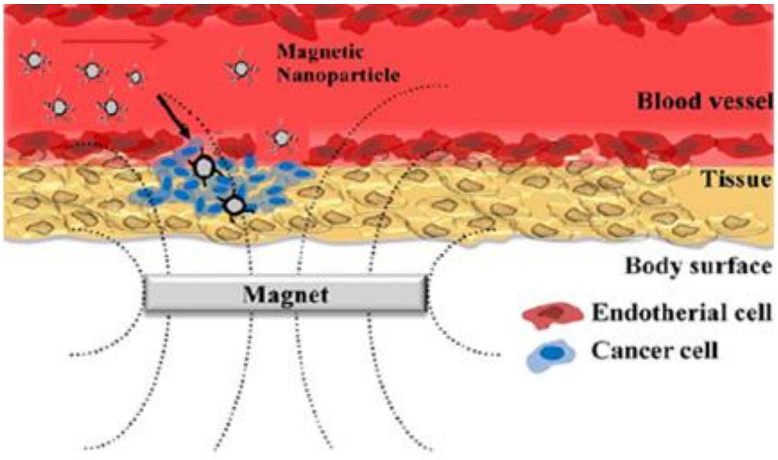


Scheme 25. Preparation of Fe_3O_4@PAMAM

One significant application of nanotechnology in therapy of cancer included designing NPs to deliver oligonucleotides, genes and drugs. NPs should be engineered so that they could target and demolish tumor cells with minimal damage to tissues of healthy. This study aimed to create convenient and efficient nanocarrier with the ability to interact with and delivery CpG-oligodeoxynucleotides (CpG-ODNs) was performed to tumor cells. Toll-like receptor 9 was activated by CpG-ODNs, which created a signal cascade for cell death. CpG-ODNs activate Toll-like receptor 9 (TLR9), which can generate a signal cascade for cell death. Three layers of MNPs consisting of a Fe_3O_4 magnetic core, a interlayer of APTS (aminesiline) and a cationic PAMAM (poly amidoamine) dendrimer were used (Scheme 26). This novel targeted delivery system is to enhance the accumulation of CpG-ODN molecules in tumor cells (Scheme 27) [29]. The results demonstrated that the prepared DcMNPs having very positive charges onto their surface could link to molecules of CpG-ODN applying electrostatic means. These NPs with the average sizes of 10-40 nm attached to CpG-ODN molecules effectively and induced cell death in MDA-MB231 and SKBR3 tumor cells and could be considered an appropriate targeted delivery system for CpG-ODN in biomedical applications. The magnetic core of these NPs showed a potential for selective drug targeting as they could be concentrated and held in position employing means of a simple magnet.

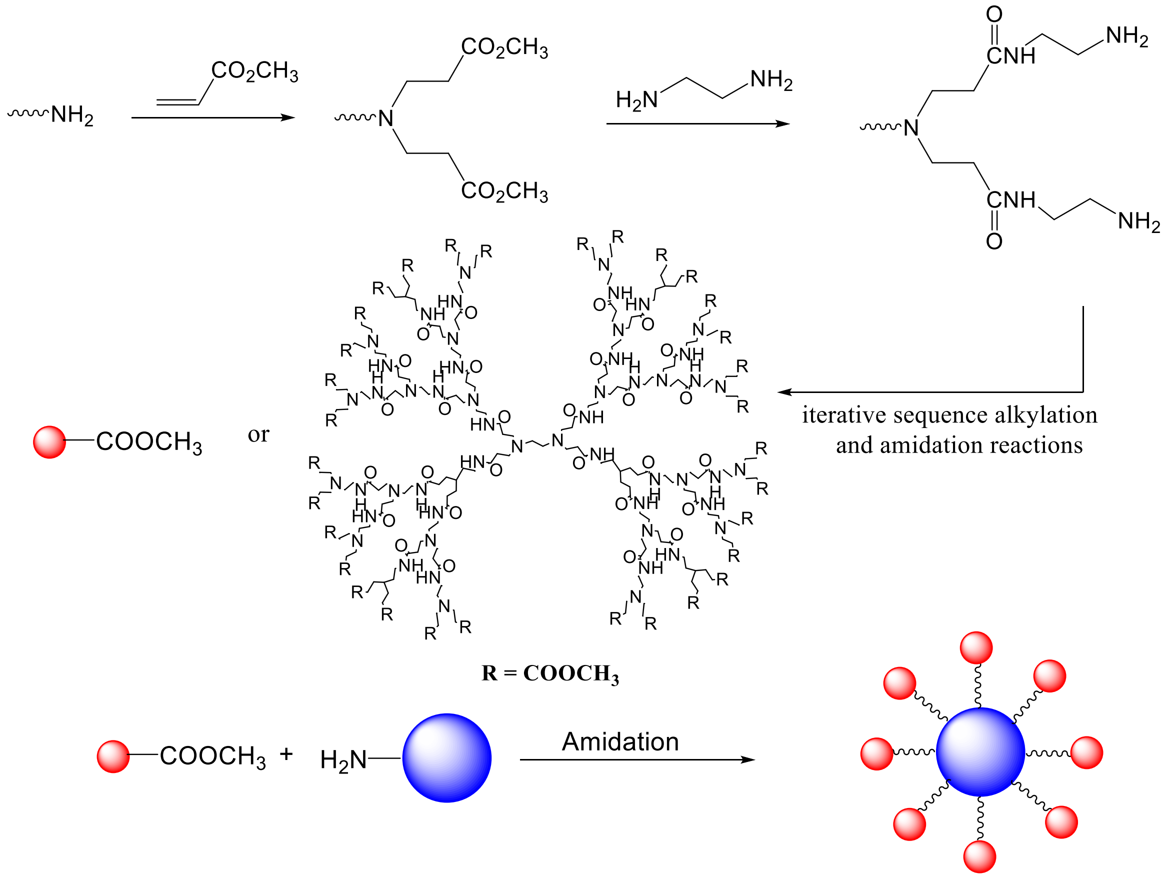


Scheme 26. PAMAM dendrimer-coated magnetic nanoparticles



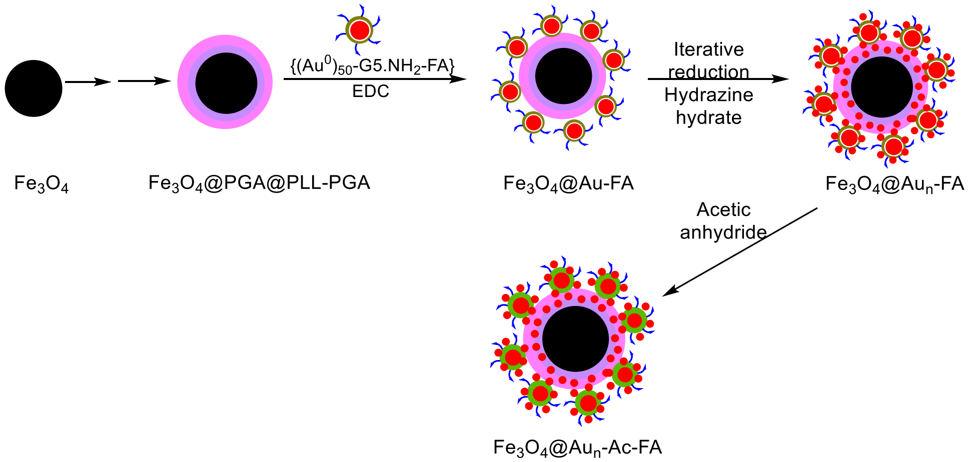
Scheme 27. The effect of external magnetic field on drug delivery system. Reprinted with permission from Ref. [30], Copyright (2016) Elsevier

PAMAM dendrimer with 3.5 generation from ethylenediamine as the primary core and methyl acrylate was afforded. Also, Fe_3O_4 NPs as magnetic ones were functionalized through APTES ((3-aminopropyl) triethoxysilane) to prepare amine-modified magnetic NPs (Fe_3O_4@APTES). Then, 3.5GD dendrimer was immobilized by Fe_3O_4@APTES to yield Fe_3O_4@3.5GD NPs (dendrimer-immobilized magnetic nanoparticles) (Scheme 28) [30]. We applied in vitro cellular cytotoxicity to measure the biocompatibility of fabricated structures and assess the cytotoxic impact of immobilized dendrimer via HeLa cells.



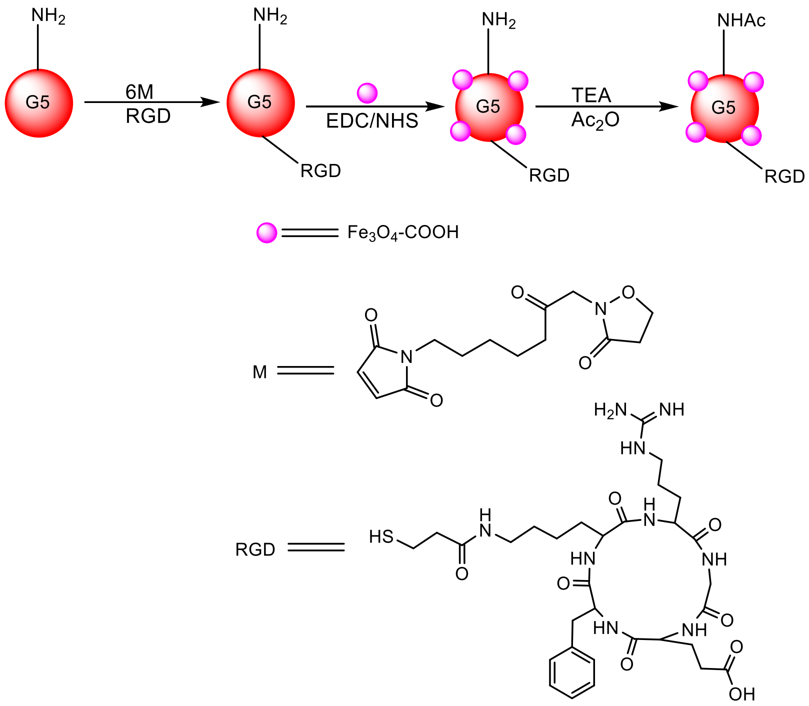
Scheme 27. Preparation of MNPs immobilized 3.5GD

Cai et al. (2015) reported the synthesis of Fe_3O_4@Au NCPs (Nanocomposite particles) for targeted dual mode CT/MR (computed tomography / magnetic resonance) imaging of tumors [31]. In this procedure, Fe_3O_4 NPs were assembled by multilayers of PGA/poly(L-lysine)/PGA/FA-functionalized dendrimer-entrapped Au NPs applying a technique of layer-by-layer self-assembly. The 1-ethyl 3-(3-dimethylaminopropyl) carbodiimide was used as a the crosslinked for interlayers. Then, Au core NPs were used for subsequent seed-mediated growth of Au shells through repetition Au salt reduction process. Next, Fe_3O_4@Au_n.Ac-FA NCPs with a exactly molar ratio of Au/Fe_3O_4 was obtained from the remaining amines acetylation of dendrimers (Scheme 28). Importantly, with the FA-mediated targeting, the Fe_3O_4@Au_n.Ac-FA NCPs were able to be specifically up taken via cancer cells overexpressing receptors of FA, and be utilized as an effective nanoprobe for targeted dual mode CT/MR imaging of a xenografted tumor model. With the versatile dendrimer chemistry, the improved Fe_3O_4/Au NCPs may be variously modified, thereby prepared a unique platform for diagnosis and therapy of different biological systems.



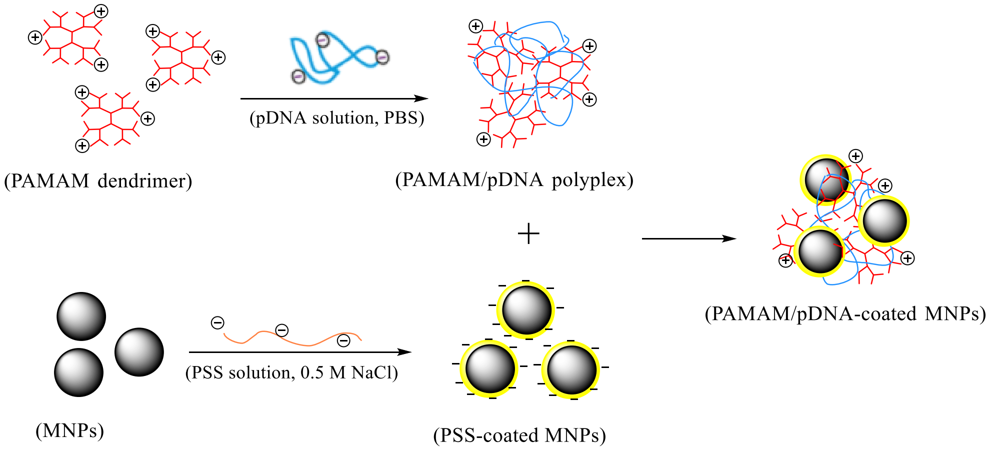
Scheme 28. Synthesis of Fe_3O_4@Au NCPs (Nanocomposite particles)

Yang and co-workers introduced a novel method to the synthesize Fe_3O_4 NPs linked with RGD (Arg-Gly-Asp= RGD)-functionalized dendrimers (G5. NHAc@RGD@Fe_3O_4 NPs) as a platform for targeted MRI (magnetic resonance imaging) of C6 glioma cells . Fe_3O_4 NPs prepared utilizing a solvothermal route were grafted with RGD peptide functionalized generation-5 PAA (poly(amidoamine) = PAA) dendrimers (G5.NH_2-RGD) (Scheme29) [32]. Subsequently, the acetylation of the dendrimer terminal amines was carried out to prepare of G5. NHAc@RGD@Fe_3O_4 NPs. The researchers also indicated that on the basis of the cell morphological observation, cell viability assay and also hemolysis assay, the G5. NHAc-RGD-Fe_3O_4 NPs catalyst could accelerate excellent hemocompatibility and cytocompatibility over the studied concentration range. In addition, RGD grafted on the Fe_3O_4 NPs allowed for the effective targeting of the Ps to C6 cells that overexpressed receptors of αvβ3, which was investigated using in vitro cell MR imaging and cellular uptake. Finally, the G5. NHAcRGD@Fe_3O_4 NPs were applied in the targeted MR imaging of C6 glioma cells in mice. The results yielded from the study exhibited that the improved G5. NHAc@RGD@Fe_3O_4 NPs proposed important potential for employ as agents of contrast in the targeted MR imaging of various types of tumors.



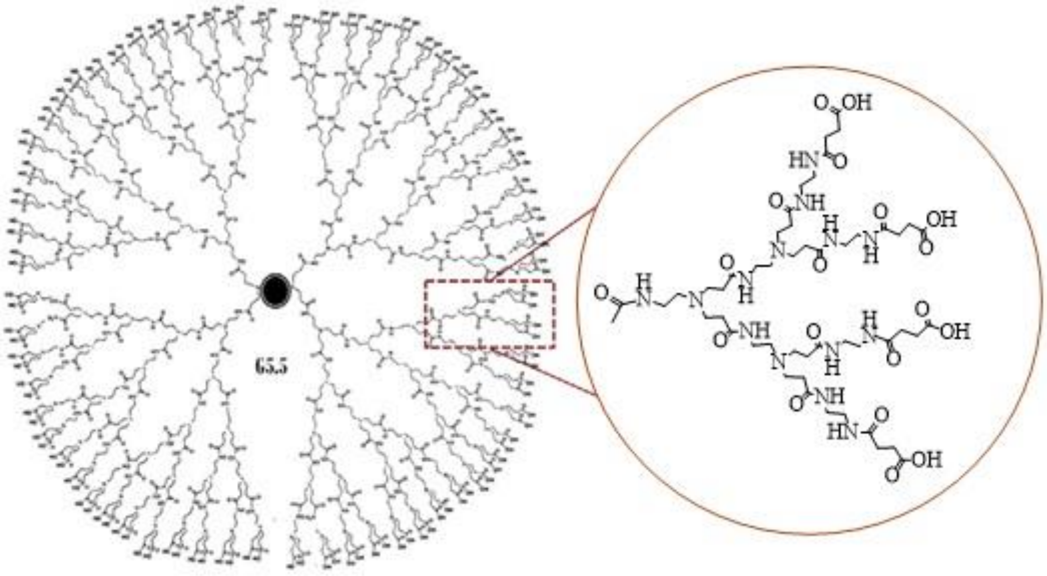
Scheme 29. The synthesis of Fe_3O_4 coated with G5. NHAc-RGD NPs

An ingenious and easy approach was introduced to modify MNPs with plasmid DNA (*p*DNA) to afford nanohybrid systems compatible for nucleic acid treatment. The nanohybrids were synthesized via blending complexes of *p*DNA (dendriplexes) and dendrimers and poly(styrene) sulfonate-supported MNPs using electrostatic interactions (Scheme 30). The effects of the dendrimer 2, 4 and 6 and the amine to phosphate group (N/P) ratio on the hydrodynamic diameter, cell viability, zeta potential, transfection efficiency and cellular internalization of the nanohybrids were systematically examined at various transfection conditions including presence or absence of an external magnetic field, *p*DNA concentration, incubation time and presence or absence of fetal bovine serum. Satisfactory results were obtained when the nanohybrids were able to transfect NIH 3T3 cells. Also, the level of gene expression was strongly dependent on the generation of dendrimer, the *p*DNA concentration and the N/P ratio. Xiao et al. (2015) reported the preparation of novel dendriplex-supported MNPs. The reaction proceeds with Fe_3O_4 grafted within a silica shell with a bulky NHC ligand framework through a surfactant-directed self-assembly method. In summary, a coherent set of results was obtained demonstrating the potential of the improved nanohybrids as efficient gene delivery nanomaterials [33].



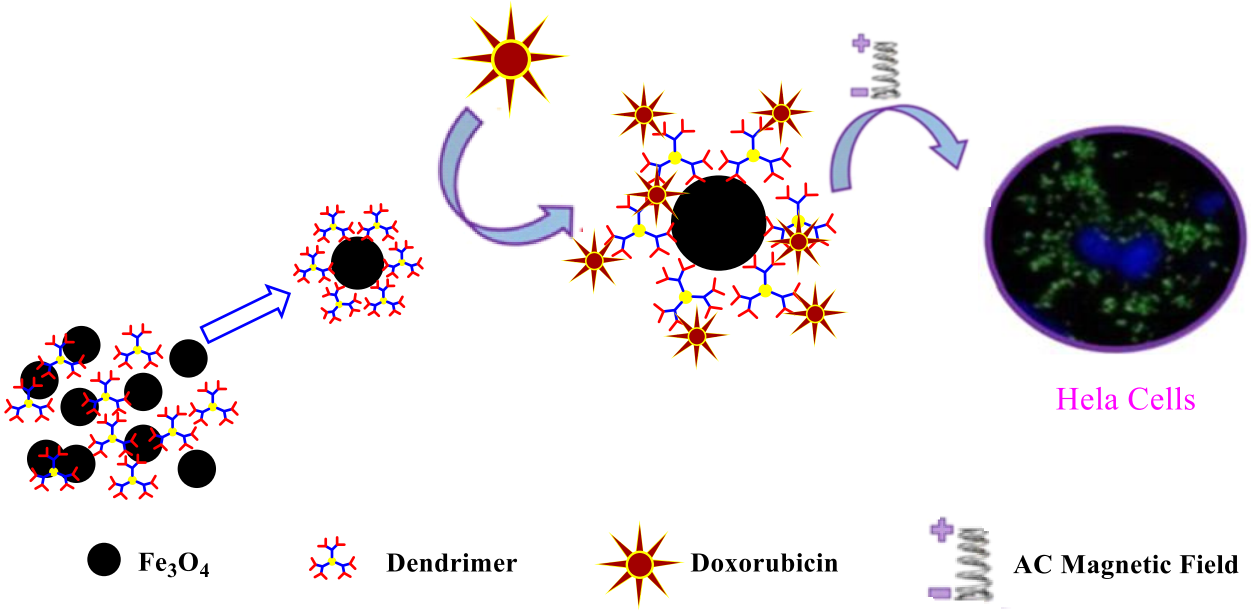
Scheme 30. Synthesis of MNPs coated by PAMAM/Pdan using electrostatic interactions

The usage of magnetic nanoparticles (MNPs) as a Tumor-specific delivery of anticancer drugs have received great attention due to reducing systemic toxicity and minimizing side effects. An advantage for selective drug targeting was provided by the magnetic core of these NPs as they could be targeted to the tumor site and aggregated in cancer cells via an external magnetic field. MNPs could be supported by PAMAM dendrimer and loaded with drugs. However, due to polyamidoamine dendrimers toxicity in relation to their multiple cationic charges for terminal -NH_2 groups, their biomedical applications were limited. Functionalizing the groups of positively charged end with groups of negatively charged -COOH, was a satisfactory strategy for affording dendrimers of less toxic polyamidoamine. Gemcitabine as a deoxycytidine analogue was an efficient anticancer drug. Gunduz and co-workers obtained an efficient, less toxic targeted delivery system for Gemcitabine [33]. Half generations, between G4.5 and G7.5, of polyamidoamine dendrimer supported MNPs (DcMNPs) were prepared and grafted with Gemcitabine. Gemcitabine was efficiently grafted on half generations surface of PAMAM dendrimer supported MNPs (Scheme 31). Gemcitabine did not efficiently graft to Generations G4 and G5. The most excellent drug loading was the yield for dendrimer supported MNPs by Generation 5.5. Empty NPs indicated no considerable cytotoxicity on MCF-7 and SKBR-3 cells. On the other hand, Gemcitabine loaded NPs in MCF-7 cell were 3.0 times more toxic and in SKBR-3 cell were 6.0 times more toxic compared with free Gemcitabine. Gemcitabine loaded onto Generation 5.5 dendrimer supported MNPs indicated a higher stability than free Gemcitabine. About 94% of the drug was maintained over six weeks with a pH of 7.2. Due to their stability, cellular uptake, toxicity, targetability under magnetic field and size distribution characteristics of the dendrimeric NPs afforded could be useful as a delivery system for Gemcitabine in therapy of cancer.



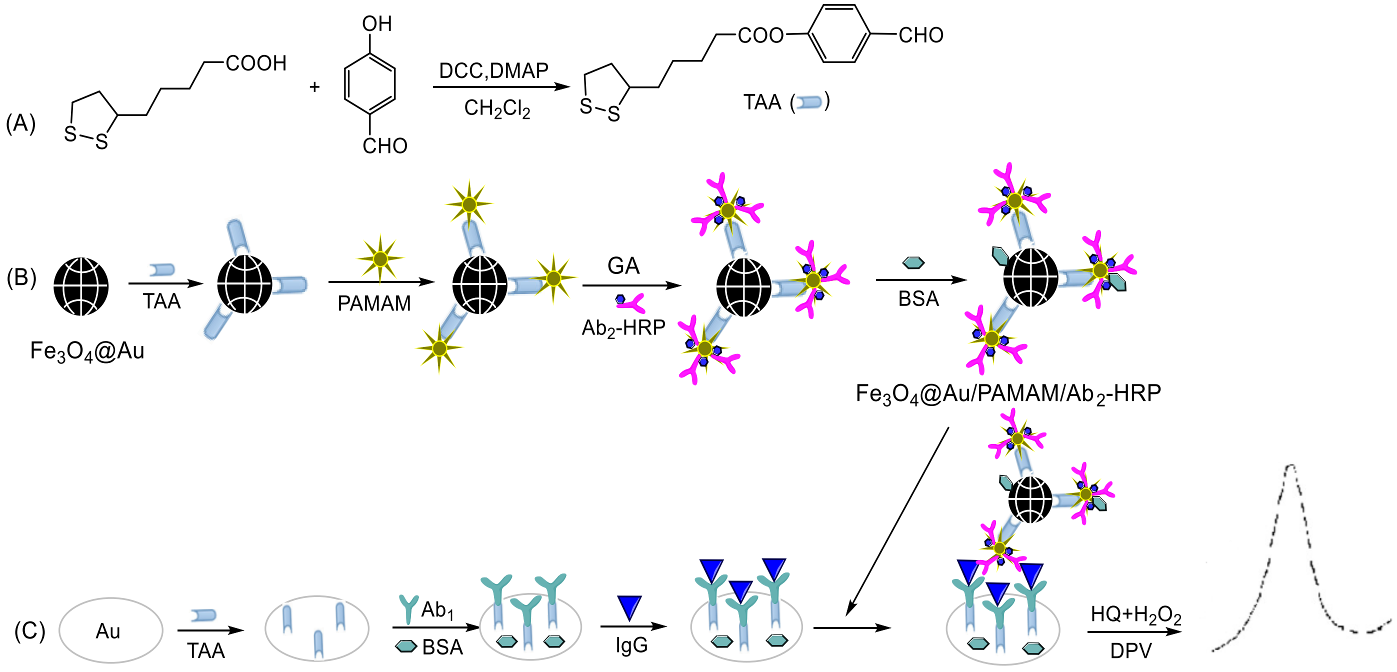
Scheme 31. The structure of 5.5 PAMAM dendrimer magnetic nanoparticle with carboxyl end group

Nigam and Bahadur presented the synthesis of a novel group of biocompatible, cationic, peptide dendrimers, which were then utilized to stabilize and modify MNPs for cancer combinatory treatment [34]. One advantage of the peptide dendrimers rather than PAMAM dendrimers was that the synthesized peptide dendrimers had an edge over the widely used PAMAM dendrimers. Synthesized peptide dendrimers had low cytotoxicity and better biocompatibility of their degradation products. It was found that peptide dendrimer was as effective as polyamidoamine dendrimers in drug carrying capacity, while profiles of drug release considerably exceeded those of PAMAM's. In this work, a dose-dependent study was performed to survey their half maximal inhibitory concentration in vitro with different cancer cell lines. Dendrimer-conjugated iron oxide nanoparticles were successfully incubated to ACMF (alternating current magnetic field) to cervical cancer cell class (Scheme 32). The results proved peptide dendrimer as an effective alternative to polyamidoamine, which could be utilized successfully in biomedical applications.



Scheme 32. Application of MNPs modified nanocatalyst for cancer therapy

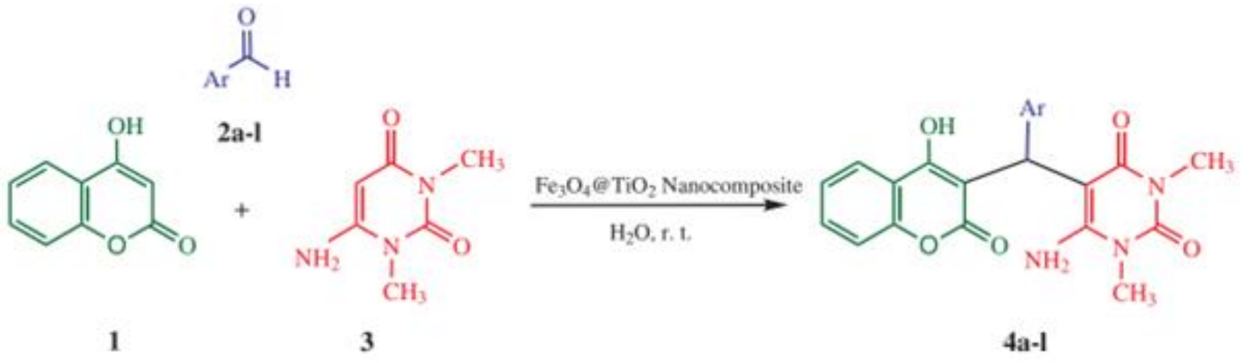
In 2015, a new thiol aromatic aldehyde was prepared by Zhang and co-workers (Scheme 33A) [35]. It could be employed as a substrate to straight immobilize antibodies onto an Au electrode, for which additional chemical cross-linker was not required. The author demonstrated that thiol aromatic aldehyde as a linker can be functionalized with Fe_3O_4@Au and then, treatment with multiple enzymes and many functional groups of the PAMAM dendrimer to corresponding Fe_3O_4@PAMAM@Ab_2-HRP (Scheme 33B, 33C). The fabricated multiple enzymes greatly enhanced the signal of detection. In optimal conditions, the proposed electrochemical immunosuppressant displayed desired performance for IgG detection in the range of 0.005-50 ng ml^{-1} with a detection limit of 3 *pg* ml^{-1} based on a signal-to-noise ratio of 3. It had a very good potential application in the clinical analysis area.



Scheme 33A, B, C. Schematic illustration of Fe_3O_4@PAMAM@Ab_2-HRP

3. Organic Reactions

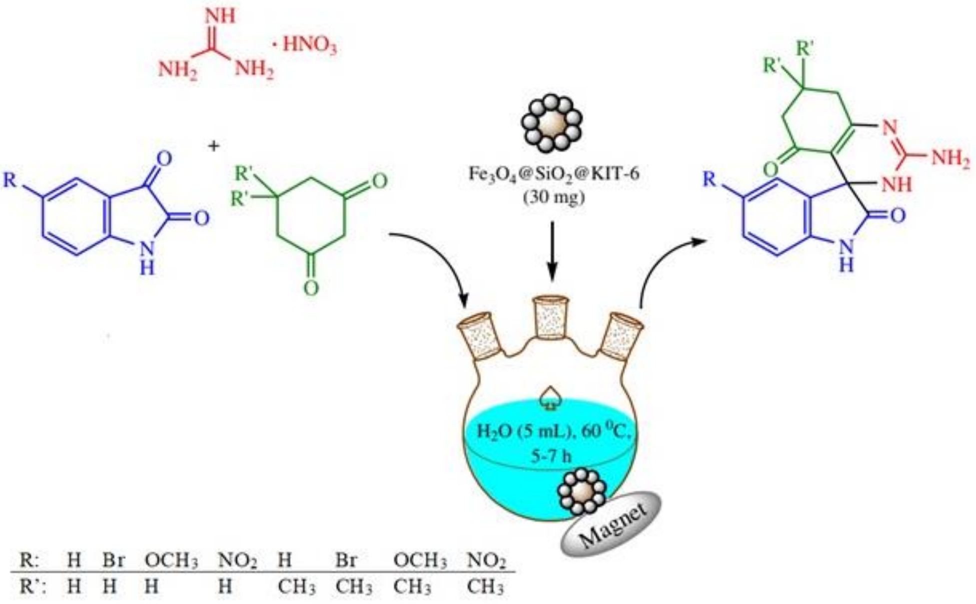
In 2018-2020, S. Abdolmammadi and coworkers presented the synthesis of a novel group of biocompatible nanocatalyst for an efficient methodology dealing with the Fe_3O_4@TiO_2 nanocomposite-catalyzed direct condensation reaction of 4-hydroxycoumarin, aromatic aldehydes, and 6-amino-1,3-dimethyluracil in aqueous media at room temperature is reported (Scheme 34) [36-37, 40].



1a, 4a Ar = C_6H_5, **1b, 4b** Ar = 4-Br-C_6H_4, **1c, 4c** Ar = 4-Cl-C_6H_4, **1d, 4d** Ar = 2,4-Cl_2-C_6H_3, **1e, 4e** Ar = 4-NC-C_6H_4, **1f, 4f** Ar = 3-HO-C_6H_4, **1g, 4g** Ar = 4-CH_3O-C_6H_4, **1h, 4h** Ar = 4-CH_3-C_6H_4, **1i, 4i** Ar = 3-O_2N-C_6H_4, **1j, 4j** Ar = Furan-2-yl, **1k, 4k** Ar = Pyridin-4-yl, **1l, 4l** Ar = Thiophen-3-yl

Scheme 34. Application of Fe_3O_4@TiO_2 nanocomposite in condensation reaction

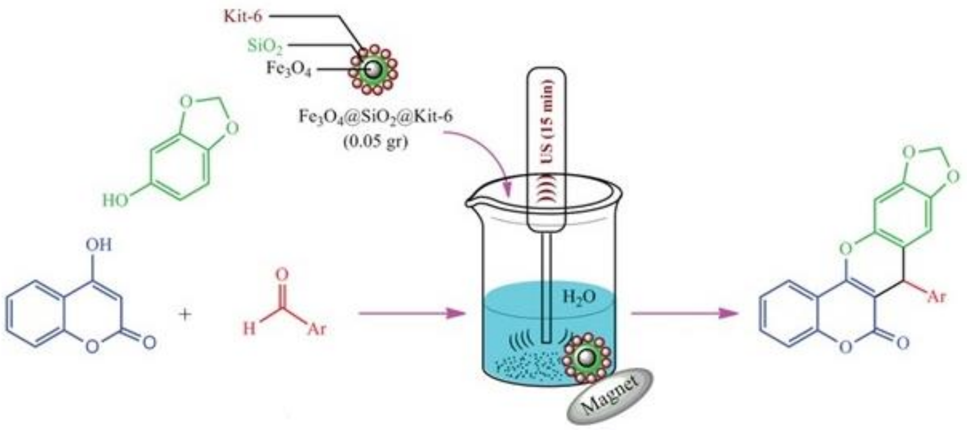
In continue of research works, a series of eight new spiro[3,4′]1,3-dihydro-2*H*-indol-2-one-2′-amino-4′,6′, 7′,8′-tetrahydro-2′,5'(1'*H*,3'*H*)-quinazoline-diones were successfully synthesized through a three-component reaction of 1*H*-indole-2,3-diones (isatins), guanidine nitrate, and 1,3-cyclohexanediones, by use of Kit-6 mesoporous silica coated Fe_3O_4 nanoparticles (Fe_3O_4@SiO_2@KIT-6) as a highly efficient magnetically separable nanocatalyst in aqueous media at 60°C (Scheme 35) [37, 40].



R:	H	Br	OCH3	NO2	H	Br	OCH3	NO2
R':	H	H	H	H	CH3	CH3	CH3	CH3

Scheme 35. Schematic illustration Fe_3O_4@SiO_2@KIT-6 for preparation of quinazoline-diones

A new effective approach to synthesize a series of 7-aryl-6*H*,7*H*-[1] benzopyrano[4,3-b][1,3]dioxolo[4,5-g][1]benzopyran-6-ones was reported using $Fe_3O_4@SiO_2@Kit-6$ as heterogeneous catalyst at room temperature under ultrasonic irradiation in aqueous media (Scheme 36) [38, 40]. Also, there are similar methods for application of heterogenization of catalysts with magnetic supports for important organic reactions [41-43].



Ar: C_6H_5, 4-BrC_6H_4, 4-NCC_6H_4, 3-OHC_6H_4, 4-$CH_3OC_6H_4$, 2-$CH_3C_6H_4$, 3-$O_2NC_6H_4$

Scheme 36. Schematic illustration $Fe_3O_4@SiO_2@KIT-6$ for preparation of benzopyran-6-ones

4. Conclusions

The heterogenization of catalysts with magnetic supports are a new method for modern organic chemistry, which allows the efficient isolation, reuse, and recycling of precious catalysts or reagents. Magnetic separation reduces the costs of production but it also prevents the generation and accumulation of toxic waste. These reasons account for the development of magnetically separable nanocatalysts, with uses in sustainable and benign chemical transformations. The high-surface area and cost-effective solid supports are important features, but the main problem when using MNPs is the unwanted aggregation of tiny magnetic particles. This problem has been mitigated by immobilizing catalyst species onto pre-synthesized MNPs, as well as by the functionalization and modification of MNPs with suitable ligandsand coating or encapsulating with stabilizing mate, rials such as silica, ionic liquids, polymers and carbon. The application of magnetically supported catalysts may affect most types of organic reactions, such as cyclo-addition, oxidation, reduction, and coupling, including their asymmetric equivalents. We have emphasized the use of different dendrons, with diverse chemical structure and size, to functionalize diverse various substrates like linear polymers, and plane and curved inorganic surfaces. Apart from this, the review also demonstrates that self-assembly shows an ideal approach to create well-defined hyperbranched surfaces and includes some discussion about the ability of both organic and inorganic building blocks to direct this process. Finally, the use of magnetic nanocatalysts in continuous flow synthesis needs to be exploited. The automated recycling of magnetic nanocatalysts needs to be studied to demonstrate their usefulness as supports for use in parallel and high-throughput synthesis.

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