Recent Progress in Therapeutic and Diagnostic Applications of Lanthanides

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Abstract: The biological properties of the lanthanides, primarily based on their similarity to calcium, have been the basis for research into potential therapeutic applications of lanthanides since the early part of the twentieth century. Up to date, cerium nitrate has been used as a topical cream with silver sulfadiazene for the treatment of burn wounds. A lanthanide texaphyrin complex (motexafin gadolinium) has been evaluated through Phase III clinical trials for the treatment of brain metastases in non-small cell lung cancer. Lanthanum carbonate (Fosrenol) as a phosphate binder has been approved for the treatment of hyperphosphatemia in renal dialysis patients in both the USA and Europe. This review will highlight therapeutic applications of the lanthanides for burn wounds, cancer, hyperphosphatemia, immune function, magnetic resonance imaging (MRI) contrast agents and osteoporosis, and discuss their future potential in the medical fields.

Keywords: Lanthanides, therapeutic application, burn wounds, cancer, hyperphosphatemia, immune function, MRI contrast agents, osteoporosis.

INTRODUCTION

The lanthanides consist of elements from lanthanum (Z=57) to lutetium (Z=71) plus scandium (Z=21) and yttrium (Z=39), with an electronic configuration of $[Xe]4f^{0-14}5d^{0-1}6s^2$ in the periodic table. In physiological solution, they tend to lose the "d" and "s" electrons, forming stable trivalent ions (Ln^{3+}), besides Ce and Eu which also exist as Ce^{4+} and Eu^{2+}. Ln^{3+} is easy to bind with oxygen atom through electrostatic interaction. The biological properties of the lanthanides are primarily based on their similarity to calcium. They have similar ionic radii to calcium, but higher charge, which lead to higher affinity for Ca^{2+} site on biological molecules. Ln^{3+} have excellent flexibility over coordination number range from 6-12, with a preferred coordination number of 8-9, meanwhile Ca^{2+} has a preferred coordination number of 6.

The physical properties of Lanthanides are crucial to their unique biological activities. Based on that, more attention has been given to the potential therapeutic applications of lanthanides since the early part of the twentieth century. One of the earliest therapeutic applications of lanthanides was the use of cerium oxalate as an anti-emetic. Later the lanthanides were found to have anti-coagulant and anti-atherosclerotic properties, but many of these early applications have been unsuccessful. Up to now, cerium nitrate as a topical cream with silver sulfadiazine has been used for the treatment of burn wounds. A lanthanide texaphyrin complex (motexafin gadolinium) has been evaluated through Phase III clinical trials for the treatment of brain metastases in non-small cell lung cancer. Lanthanum carbonate (Fosrenol) as a phosphate binder has been approved for the treatment of hyperphosphatemia in renal dialysis patients in both the USA and Europe. Gadolinium-based complexes as contrast agents have been used in magnetic resonance imaging (MRI) (Table **1**). This review will describe recent advances and success in the therapeutic applications of the lanthanides.

Table 1. Medical Uses of Lanthanide Compounds

Compounds	Uses	Status
Gd-Motexafin	Cancer	Clinical phase III
Fosrenol	Hyperphosphataemia	Approved
Flammacerium	Burn	Approved
Magnevist, Omniscan, OptiMARK, Vasovist, MultiHance, Gadovist, Dotarem, ProHance, Primovist	MRI contrast agents	Approved

1. BURN WOUNDS

Burns and their sequelae are responsible for significant mortality and morbidity all over the world, especially in developing countries [1]. Over the past five decades, advances in the understanding of burn pathophysiology resulted in improvements in the clinical problems of burn injured patients. As a result, burn mortality rates have declined, which may be attributed to the development of treatment modalities that including surgical excision of burn

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wounds and use of topical antimicrobial agents and systemic antibiotics [2, 3]. Bacterial and viral infections, notably herpes simplex virus (HSV) and cytomegalovirus (CMV), are the most common cause of not only wound infections but also mortality in burn patients [4, 5]. So the search for an ideal topical antiseptic agent with high antimicrobial efficacy and low toxicity was performed for decades [6].

Absorption of rare earths (RE) from the skin is known to be negligible, however, when the skin was stripped or wounded, RE seemed to be absorbed into the body to some extent [7]. The initial rationale for using cerium for the treatment of burn wounds was based on their antibacterial effects at the end of the 19th century. Several cerium (III) salts including acetate, stearate, chloride, and nitrate were reported to have antibacterial activity. Systematic studies confirmed that cerium nitrate had broad-spectrum antibacterial activity against a range of bacteria including *Pseudomonas aeruginosa* and *Staphylococcus aureus* [8]. So cerium nitrate was used for the treatment of burn wounds as a topical antiseptic agent since the 1976. It was found to be especially effective for gram-negative bacteria and fungi [9]. It represented a convenient and less expensive alternative.

Now cerium nitrate is usually administered in combination with silver sulfadiazine in the clinic. This combination as Flammacerium was manufactured commercially in Europe, and as Dermacerium in South America. Although there are several reports that the mortality is reduced by Flammacerium treatment compared with predicted death rates, the clinical benefit of cerium nitrate is unclear. It has been demonstrated that the mixture of cerium nitrate and silver sulphadiazine had greater synergistic effects on staphylococci, which was generally more resistant to silver sulphadiazine alone than other microbial species. The findings indicated that the mixture was effective in the prevention and treatment of wound infections [10]. Monafo *et al*. [11] reported that whether $Ce(NO_3)_3$ alone or combined with silver sulphadiazine had performed stupendous broad-spectrum antibacterial activity. Subsequent studies have demonstrated that cerium nitrate has little anti-bacterial activity against common burn pathogens, which suggests that there may be an alternative mechanism.

The disruption of the immune system is one of the major contributors to morbidity and mortality from major burns. In addition, dysregulation of the immune response is also a contributory factor to the systemic inflammatory immune response (SIRS) and multi-organ failure syndrome (MOFS) associated mortality [8, 12]. Deveci *et al*. reported that treatment by cerium nitrate bathing prevented the elevation of tumor necrosis factor-α (TNF-α) level in the early period after thermal injury and then might limit the severity of the inflammatory reaction [13]. Apart from direct antiseptic effects, cerium helps to prevent postburn sepsis and systemic inflammatory response by fixing burn toxins [14]. Boeckx *et al*. [15] reported that cerium nitrate led to a firm, impermeable eschar, but the eschar formed by silver sulfadiazine was typically soft, moist, uneven and macerated. It was also found that the eschar formed by cerium nitrate contained deposits of insoluble pyrophosphate and carbonate salts, and calcium. Thus the eschar acting as a biological dressing may form an impermeable crust over the wound. This covering may prevent both ingress and egress of bacteria from the wound and keep the wound in a clean and healthy state, thus it is very helpful for a skin graft [16].

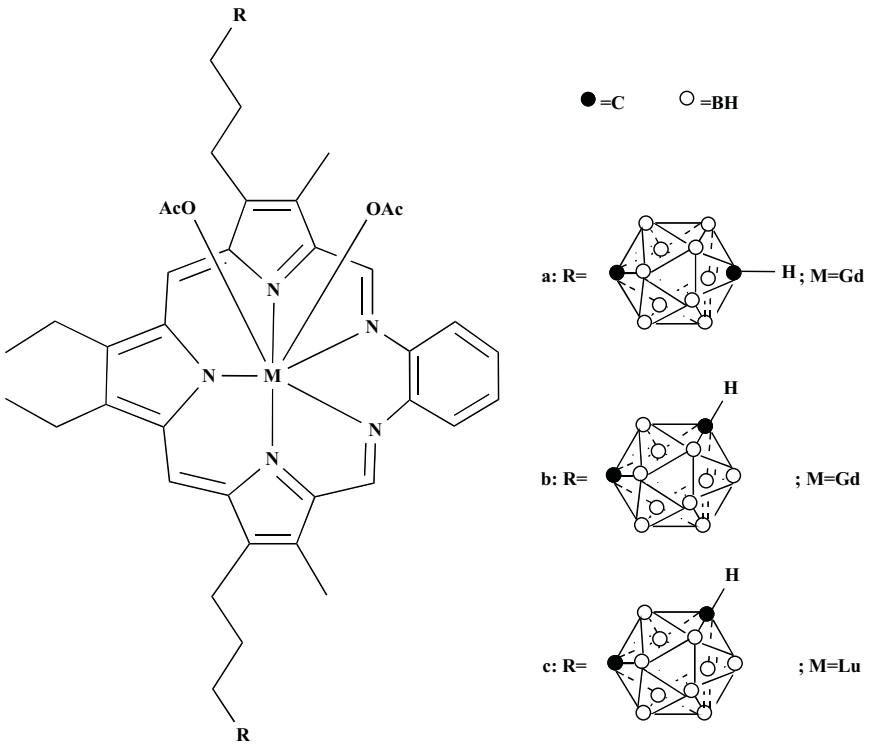
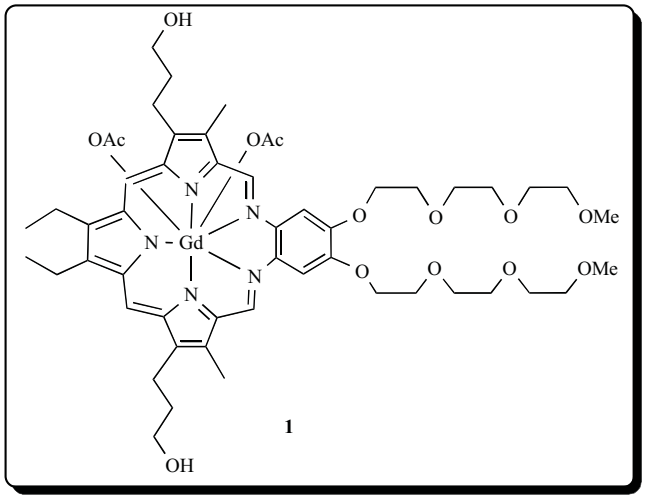


Fig. (1). Structures of GdB- and LuB-texaphyrins.

In summary, although the clinical benefit of cerium nitrate is unclear, a firm biological dressing formed by cerium nitrate treatment may provide a valuable role in burns treatment. The mechanism remains to be further studied.

2. CANCER

The development of metal-based agents for the diagnosis and therapy of cancer has greatly increased survival rates of cancer patients. RE-based compounds have also been investigated for their anticancer potential [17]. Early clinical reports indicated that cerium (III) iodide had activity against solid tumors. Recently much attention has been focused on lanthanide complexes. For example, cerium (III), lanthanum (III) and neodymium (III) complexes with ligands such as hymecromone, umbellipherone, mendiaxon, warfarin, coumachlor and niffcoumar have been synthesized. It was found that these complexes demonstrated cytotoxicity against HL-60 cell line [18, 19]. Recently, new lanthanide complexes with dihalo-substituted 8-quinolinol were reported to have high cytotoxicity of against liver cancer Bel-7402 [20]. Bandyopadhyaya *et al.* [21] reported that some novel *m*- and *p*-carboranyl GdB- and LuB-texaphyrin complexes (Fig. **1**) could kill cancer cells primarily by the induction of DNA double strand breaks. A redox active gadolinium texaphyrin complex (**1**) has been evaluated through Phase III clinical trials for the treatment of brain metastases of non-small cell lung cancer [22].



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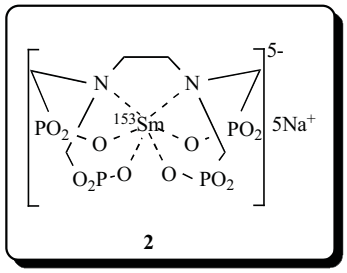
Radiopharmaceuticals containing radio nuclides are used extensively in nuclear medicine for the diagnosis or therapy of various diseases. An ideal radiopharmaceutical is one that can damage and/or destroy the target cells without affecting the normal cells [23]. Metallic radio nuclides (such as ^{68}Ga and ^{90}Y) can provide significant advantages over their nonmetal counterparts (such as ^{11}C and ^{18}F) due to their wide range of nuclear properties (type of radiation, half-life, particle energy and coordination chemistry) and thus can be used as radiopharmaceuticals [24]. The lanthanides and lanthanide-like radioisotopes, typified by ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{149}Pm, and ^{90}Y, are excellent candidates for this distinction [25-27]. Rasaneh *et al.* labeled trastuzumab with ^{177}Lu and tested their immunoreactivity and toxicity against human breast cancer cell line (MCF-7), the results indicated that the complex could be used in radio immunotherapy against breast cancer [28]. Chakraborty *et al.* compared the radiochemical properties and biological behaviors of ^{177}Lu complexes with ethylenediaminetetra-methylene phosphonic acid (EDTMP) and 1, 4, 7, 10-cyclododecyltetraamine-tetramethylenephosphonic acid (DOTMP) in bone metastasis by animal models, the latter was found to have slightly faster blood clearance along with lower retention in liver and kidney [29]. The ^{166}Ho complex with DOTMP agent was currently investigated in the treatment of multiple myeloma and leukemia *via* bone marrow ablation in combination with total body irradiation and/or high dose chemotherapy [30]. In order to find the most suitable candidate for bone therapy, numerous ^{153}Sm complexes have been synthesized and evaluated in chemical and biological systems. The ^{153}Sm complex with EDTMP (**2**) had relatively high thermodynamic stability, high and long lasting bone uptake, and rapid blood clearance for a therapeutic bone-seeking radiopharmaceutical [31]. Furthermore, ^{153}Sm which was not taken up by the skeleton was excreted primarily through the kidneys, with most of the activity found in the urine 30 minutes post-injection. This rapid urinary clearance minimized the dose received by non-target organs, while the long residence time on bone maximized the skeletal dose [32]. Recently studies showed that 1, 4, 7, 10-tetrakis(carbo-xymethyl)-1,4,7,10-tetraazacyclododecane (DOTA) was the most suitable ligand for binding scandium radionuclides ^{44}Sc and ^{47}Sc to biomolecules. The ^{13}C NMR studied have shown that Sc–DOTA formed complexes in solution with eight-coordination geometry like Lu–DOTA. ^{44}Sc has better nuclear properties, a longer half-life and forms stable radiobioconjugates with a structure similar to that of ^{90}Y and ^{177}Lu, which is important when planning radionuclide therapy. Moreover, being a low energy and carrier-free β– emitter, ^{47}Sc might be an alternative to the carrier-containing ^{177}Lu radionuclide for targeted radionuclide therapy [33].



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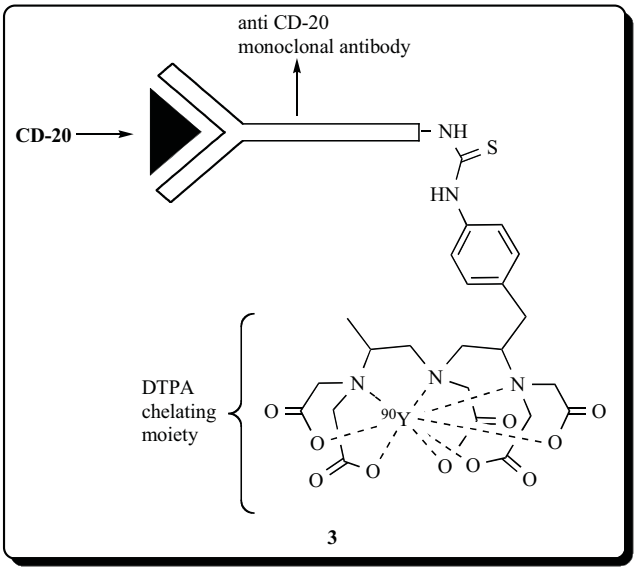
The development of target-specific lanthanide radiopharmaceuticals has gained considerable success in nuclear medicine by the conjugation of radio nuclides to biomolecules for early detection of diseases and radiotherapy of cancers. The size of the metal chelate and distance from the biomolecule, as well as the overall complex stability are important design considerations for target-specific radiopharmaceuticals [34]. The ^{177}Lu-labeled antitumor antibody was investigated and the results showed that intraperitoneal administration of ^{177}Lu-CC49 had antitumor activity with only mild or moderate side effects [35]. Now, the radio-labeled monoclonal antibody ^{90}Y-ibritumomab tiuxetan (**3**) has been approved by the FDA for the treatment of non-Hodgkin's lymphoma, and it was a significant milestone in the area of target specific radiopharmaceuticals. Diethylenetriamine pentaacetic acid (DTPA) chelated ^{90}Y

was attached to the monoclonal antibody through a linker, ensuring the tight binding of this tissue-damaging radionuclide. The antibody is directed to the antigen CD-20 which is expressed on the surface of B-cell lymphomas. The *β*-particle, emitted during ^{90}Y decay, has a mean tissue penetration distance of 5.3 mm, thus it is useful for killing tumour cells that are in close proximity to B-cell lymphomas which do not express CD-20, or those that are poorly vascularized [34, 36, 37]. Papi *et al.* further optimized the labeling of ^{90}Y-ibritumomab tiuxetan with special regard to simplicity, speed, safety and radiation protection because ^{90}Y-Zevalin labeling especially in high-dose might cause finger radiation exposure, where up to 7.4 GBq could be injected [38].



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In summary, the future development will be focused on the potential use of target-specific radiopharmaceuticals in the treatment of cancer.

3. HYPERPHOSPHATEMIA

Hyperphosphatemia which increases serum phosphate levels is one of the clinical consequences that accompany end-stage renal disease (ESRD). The pathological consequences of hyperphosphatemia are severe. Unfortunately, hyperphosphatemia cannot be controlled by normal dialysis. Although long, slow and nocturnal dialysis may be effective, it presents difficulties for the patients [39, 40]. This means that alternative treatment options are needed.

The ideal phosphate binder should have a high affinity for phosphate and be able to bind phosphate rapidly with little or no systemic absorption. In addition, it should be also non-toxic, available as a palatable oral dosage form with a low pill burden. Aluminum-based binders such as aluminum hydroxide were used in the 1970s and early 1980s, they were very effective, but aluminum absorbed was found to be toxic [41]. As a result, calcium phosphate binders replaced aluminum-based phosphate binders in the 1990s, however, calcium-based agents resulted in hypercalcemia and increased risk of cardiovascular calcification by the absorption of calcium [42]. These drawbacks have stimulated research into aluminum- and calcium-free binders. Renagel (sevelamer hydrochloride) was approved by the FDA in 1998 and also gained approval in Europe in 2000, but its high cost relative to calcium- and aluminum-based binder and high pill burden are main drawbacks. In 2004, a new phosphate binding drug based on lanthanum carbonate (Fosrenol) was approved in both the USA and Europe [43].

Preclinical studies confirmed that Fosrenol was poorly absorbed with >90% excreted in the feces, and just 0.001% absorbed when given by the oral route. No toxicity was observed in animal studies and clinic observations [44-47], for example, there was no effect on cardiovascular, central nervous system (CNS), calcium, vitamin D or parathyroid hormone (PTH) metabolism, also any direct effect on bone. Fosrenol can bind phosphate at the lower pH (pH=1) in the stomach, and at the higher pH (pH=7) in the small intestine, duodenum and jejunum. Lanthanum carbonate was as effective as aluminum hydroxide, and more effective than either Renagel or calcium carbonate at reducing urine phosphate levels. In addition, the distribution studies showed that Fosrenol had the best biodistribution profile with little or no oral absorption and tissue accumulation, and effectively complete elimination in the feces [48].

Phase III clinical studies of Fosrenol have been performed in both Europe and North America [49-52]. Fosrenol reduced and maintained phosphate levels compared with placebo group, but it was as effective as calcium carbonate. Fosrenol resulted in a decrease in the production of calcium phosphate, but had no effects on serum calcium levels compared with calcium carbonate or placebo group. PTH levels remained stable or showed an increase by Fosrenol treated patients. In addition, it was found that Fosrenol was safe and well tolerated for over 4 years and effective for most patients at doses of 1350–2250 mg per day [51]. It was reported that the side effects of Fosrenol were mild-moderate and the frequency of the side effects was also similar to those of other phosphate binders [53]. The pill burden of Fosrenol was 12 tablets, while calcium carbonate was 18 tablets [52]. In addition, Fosrenol would achieve the best effect when the tablets were taken with or immediately after food.

In summary, Fosrenol is an alternative non-aluminum, non-calcium phosphate binder. It represents a significant improvement in treatment options for patients with ESRD.

4. IMMUNE FUNCTION

The immune system is one of the most important means by which animals protect themselves from external threats, and plays a critical role in surveillance and prevention of malignancy. In recent years, immunotherapy has received more and more attention. Until now, some contradictory effects of the lanthanides on immune function have been reported. For example, $GdCl_3$ significantly reduced ED_2 expression in Kupffer cells *in vivo*, but the ED_2 expression in Kupffer cells was not affected *in vitro* [54]. $La(NO_3)_3$ suppressed the cell-mediated immunity at dose of 20 $mg \cdot kg^{-1}$, but promoted at doses of 10.0, 2.0, 0.2, and 0.1 $mg \cdot kg^{-1}$ after oral administration for 6 months [55].

The hepatoprotective effect of $GdCl_3$ towards liver damage caused by a variety of toxicants including ethanol, CCl_4, and cadmium has been reported. It was found that the hepatoprotective effect of $GdCl_3$ was primarily due to the inactivation and destruction of the Kuppfer cells, which resulted in the reduction of cytokine and reactive oxygen species (ROS) production [56, 57]. $GdCl_3$ could deplete Kuppfer cells in a model of cadmium-induced liver toxicity at low, mid and high doses [58]. In addition, the protective effect of gadolinium on hepatocytes is also related to cytochrome P450 [59].

Immunotherapy for the treatment of cancer is an active area of medical research [60, 61]. It was found that $Gd@C_{82}(OH)_{22}$ had anticancer activity arising from immunomodulatory effects observed both *in vivo* and *in vitro* [62]. $Gd@C_{82}(OH)_{22}$ nanoparticles stimulated T cells and macrophages to release significantly greater quantities of TNF-α, which played a key role in cellular immune processes. This may be caused by stimulating Th0 cells to differentiate proportionately more Th1 cells that release more TNF-α, then TNF-α triggers a series of signal pathways to promote tumor cell apoptosis.

Rheumatoid arthritis is an inflammatory disease. RE ions may be able to modulate the inflammatory process in rheumatoid arthritis. It was found that $PrCl_3$, $GdCl_3$, and $YbCl_3$ were able to reduce carrageenin-induced inflammation, $GdCl_3$ and $Ce(NO_3)_3$ could modulate the levels of the inflammatory cytokines such as interleukin-2 (IL-2) and TNF-α [63, 12]. In addition, it was also found that La^{3+} could reduce ROS production under inflammatory conditions. These results suggest that RE ions may have anti-arthritic properties by immune effects.

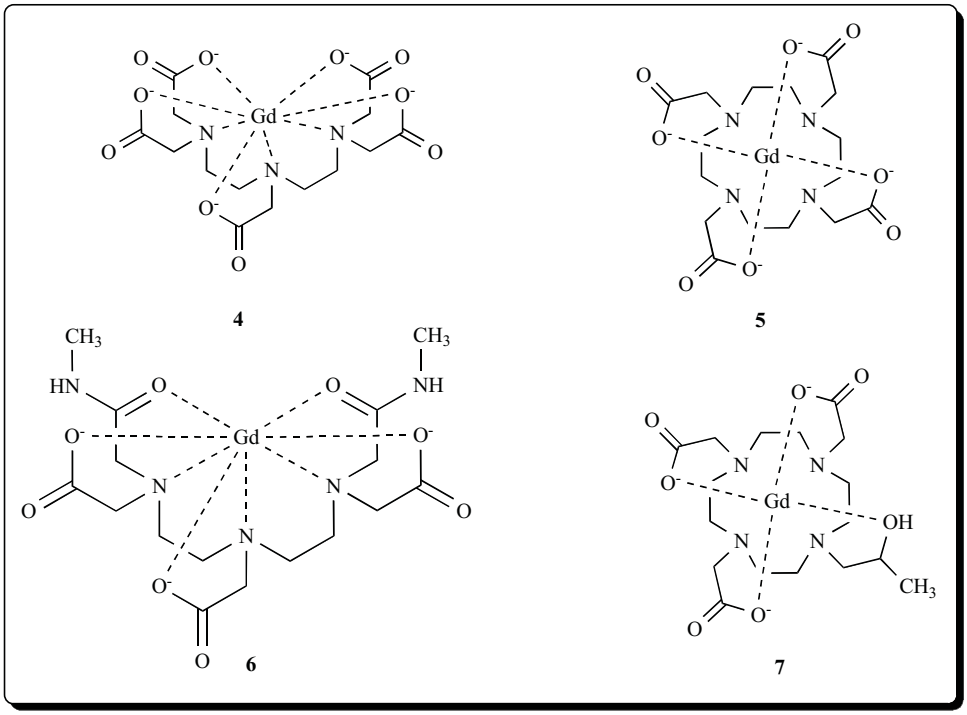
In summary, the effects of lanthanides on immune function are complicated, the therapeutic application of lanthanides on immune function remains to be further studied.

5. MRI CONTRAST AGENTS

The anionic complexes of $Gd(DTPA)^{2-}$ (**4**) and $Gd(DOTA)^{-}$ (DOTA = 1, 4, 7,10-tetrakis (carboxymethyl)-1,4,7,10-tetraazacyclododecane) (**5**) are the first complexes used in clinical practice, and Gd(DTPA-BMA) (BMA = bismethylamide) (**6**) and $Gd(HPDO_3A)$ ($HPDO_3A$ = 1-(2-hydroxypropyl)-4,7,10-tetraazacyclododecane-N,N',N''-triacetic acid) (**7**) are complexes based on the structures of the above anionic complexes. These first generation contrast agents are very useful with the rise in MRI scans being used in diagnosis, but there are some shortcomings, for example, they are nonspecific. The next generation of contrast agents should be designed to be more specific and effective, with an unusually high relaxivity, greater thermodynamic stability. The progress on lanthanides in magnetic resonance imaging was summarized as follows:

5.1. Smart Contrast Agents

The relaxivity of smart contrast agents is responsive to changes including pH, metal ion concentration or enzyme activity in physiological surroundings. In 2005, Tóth *et al*. reported a pH responsive contrast agent based on fullerenes by encapsulating metal atoms into their interior space. The availability of water-soluble gadofullerenes is potential in this area. It was found that the residence time of this complex was longer *in vivo,* but the relaxivity was lower compared with commercially available contrast agents. They further characterized the water soluble gadofullerene derivatives $Gd@C_{60}(OH)_x$ and $Gd@C_{60}[C(COOH)_2]_{10}$ (Fig. **2**) in order to elucidate the mechanism. It was observed that the relaxivity of two complexes increased considerably (a factor of 2.6 for $Gd@C_{60}(OH)_x$ and 3.8 for



$Gd@C_{60}[C(COOH)_2]_{10}$) with decreasing pH [64]. This suggests that the pH and temperature may affect the proton exchange rate or the molecular rotation rate. In addition, it was found that $Gd@C_{60}[C(COOH)_2]_{10}$ was an attractive candidate for *ex vivo* labeling and noninvasive *in vivo* tracking of any mammalian cell *via* magnetic resonance imaging [65]. Thus gadofullerene complexes as pH responsive MRI contrast agents may be ideal candidates for intercellular MRI applications.

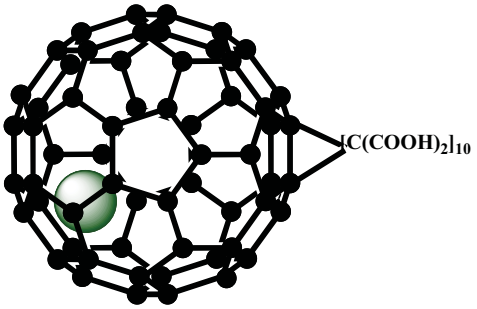


Fig. (2). Structure depiction of gadofullerene derivative $Gd@C_{60}[C(COOH)_2]_{10}$

5.2. Redox Responsive Contrast Agents

Redox responsive MRI contrast agents are very useful diagnostic tools that are used to measure the partial pressures of oxygen, which plays a role in tumor progression and metastasis, chemoresistance and radioresistance in cancer cells [66, 67]. Europium(II) complexes with macrocyclic ligands have been proposed as redox responsive contrast agents considering that these complexes do not display any proton catalyzed dissociation at physiological pH. Merbach *et al*. studied the water exchange kinetics and electronic relaxation of the three Eu(II) complexes: $[Eu(DTPA)(H_2O)]^{3-}$, $[Eu(ODDM)]^{2-}$ ($ODDM^{4-}$ = 1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane-7,16-dimalonate), and $[Eu(ODDA)(H_2O)]$ ($ODDA^{2-}$ = 1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane-7,16-diacetate) (Fig. **3**). It was found that the redox potentials of these complexes were $E_{1/2}$ = -1.35 V for Eu^{III}/Eu^{II}(DTPA), $E_{1/2}$ = -0.92 V for Eu^{III}/Eu^{II}(ODDM) and $E_{1/2}$ = -0.82 V for Eu^{III}/Eu^{II}(ODDA), this indicated that the azacrown ether complexes were more redox stable than the DTPA complex [68]. A Eu(II) complex with the ligand 4,7,13,16,21,24-hexaoxa-1,10-diazabi-cyclo[8.8.8]hexacosane (cryptand 2.2.2) (Fig. **4**) has been synthesized and found that it has high redox stability. This complex as a redox responsive contrast agent may be promising because it has characteristics such as stability against oxidation, two inner sphere coordinated water molecules, water exchange rates within the optimal rate for good relaxivity, and a macromolecular structure to allow for slow tumbling of the complex. The only problem was that the stability of the Eu(II) complex was 10^7 times higher than that of the Eu(III) complex, which meant that the Eu(III) complex might be susceptible to dissociation, further releasing toxic Eu(III) into the body [69]. In order to solve this problem, modification of the 2.2.2 cryptand yielded TETA (TETA = 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetate) and DOTA (Fig. **4**) [70]. However, the Eu(III) complex with TETA had a lower stability, this indicated that the size of the ligand and the carboxylate groups were unfavorable in the reduced state. In addition, it was also found that the TETA complex had low relaxivity, but the DOTA complex demonstrated a relaxivity rate typical to that shown for low molecular weight complexes with one exchangeable water molecule. Ratnakar *et al.* demonstrated that the water exchange kinetics and the chemical exchange saturation transfer (CEST) properties of EuDOTA–tetraamide complexes (**8**) were acutely sensitive to changes in the electronic properties of the ligand, even at a relatively remote site, providing these sites can communicate electronically with a donor atom coordinated to the metal ion. The success generating differences in CEST in a chemically reducible system suggests that it may prove possible to design redox-responsive systems applicable to biology [71]. In summary, it is important to form large macromolecules in order to slow down rotation and optimize relaxivity in the development of Europium(II) complexes as redox responsive contrast agents.

Raghunand *et al.* [72] synthesized DO3A-based thiol complexes of gadolinium (**9**). These complexes can form reversible covalent linkages with human serum albumin

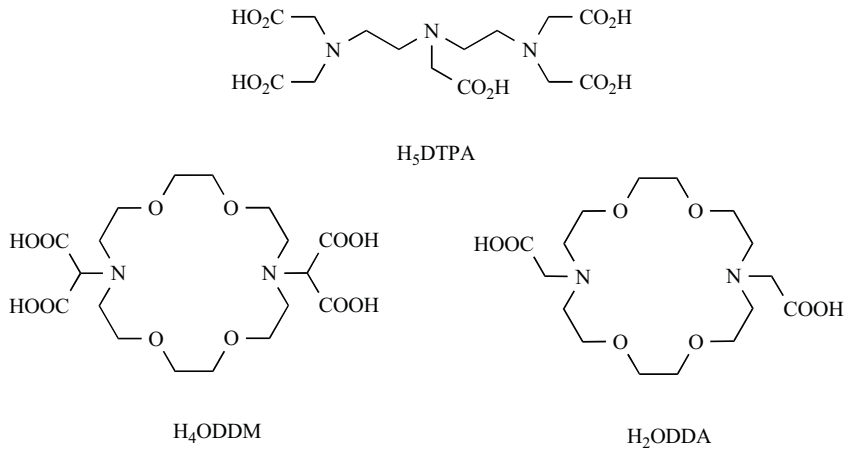
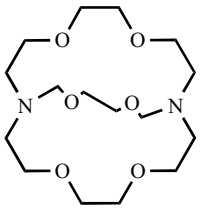
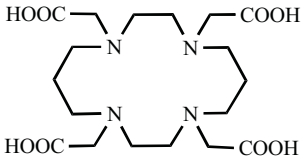


Fig. (3). The structures of the H_5DTPA, H_4ODDM and H_2ODDA.

(HSA), which contains a reactive thiol at cysteine-34. The longitudinal water-proton relaxivities of the hexyl and propyl complexes at 37°C and 4.7 T were 2.3 and 2.9 mM^{-1} s^{-1} in saline, respectively. The relaxivities of the HSA-bound forms of the hexyl and propyl complexes were calculated to be 5.3 and 4.5 mM^{-1} s^{-1}, respectively. Evidences *in vitro* and *in vivo* showed reversible redox-sensitive binding of these complexes to HSA. The results displayed the potential of Gd complexes as redox-sensitive MRI contrast agents.



cryptand 2.2.2



H_4TETA

Fig. (4). The structures of cryptand 2.2.2 and H_4TETA.

5.3. Nanoparticle-Based MRI Contrast Agents

Nanoparticle-based MRI contrast agents have the potential for application in targeted diagnostic studies and image monitored site-specific drug delivery.

In 2000, there was a report on the synthesis of nanoparticles loaded with gadolinium and the applicability as MRI contrast agents [73]. The polymeric core of the nanoparticles consisted of acidic methylacrylic acid coordinated with Gd(III), and this core was coated with a polymeric shell consisting mainly of ethylacrylate monomers (Fig. **5**). This structure allowed water to pass through, moreover, it also ensured the required rapid exchange and biocompatibility. It was found that the relaxation rate was significantly reduced compared to the free polymer or free water, but the comparison with other contrast agents was not reported.

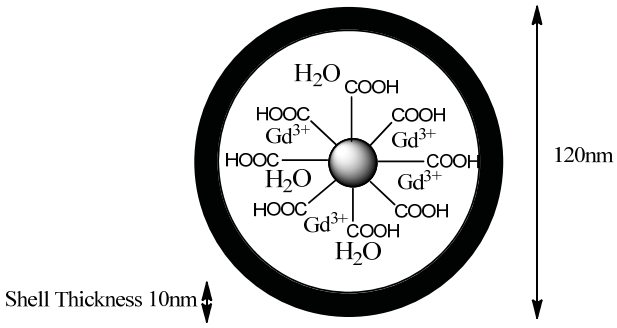
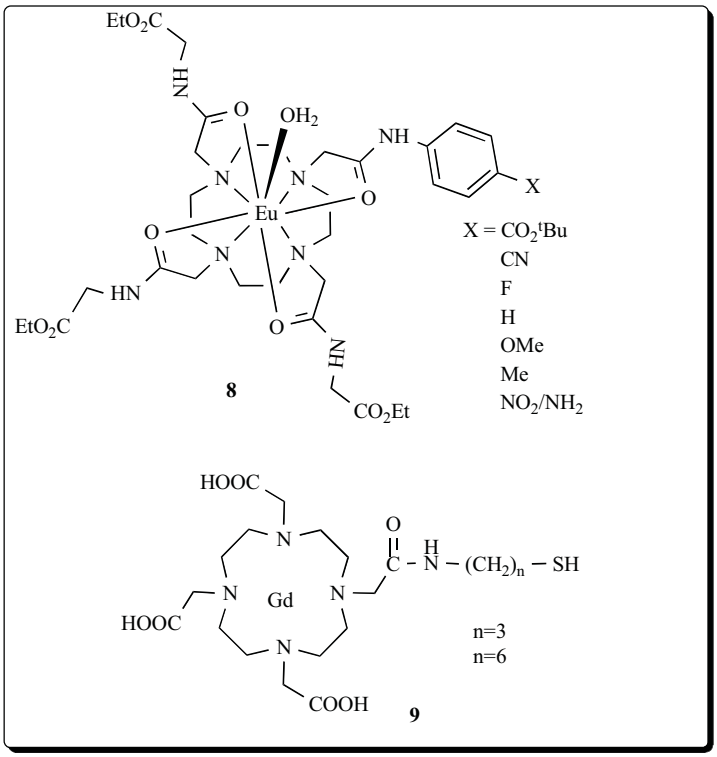
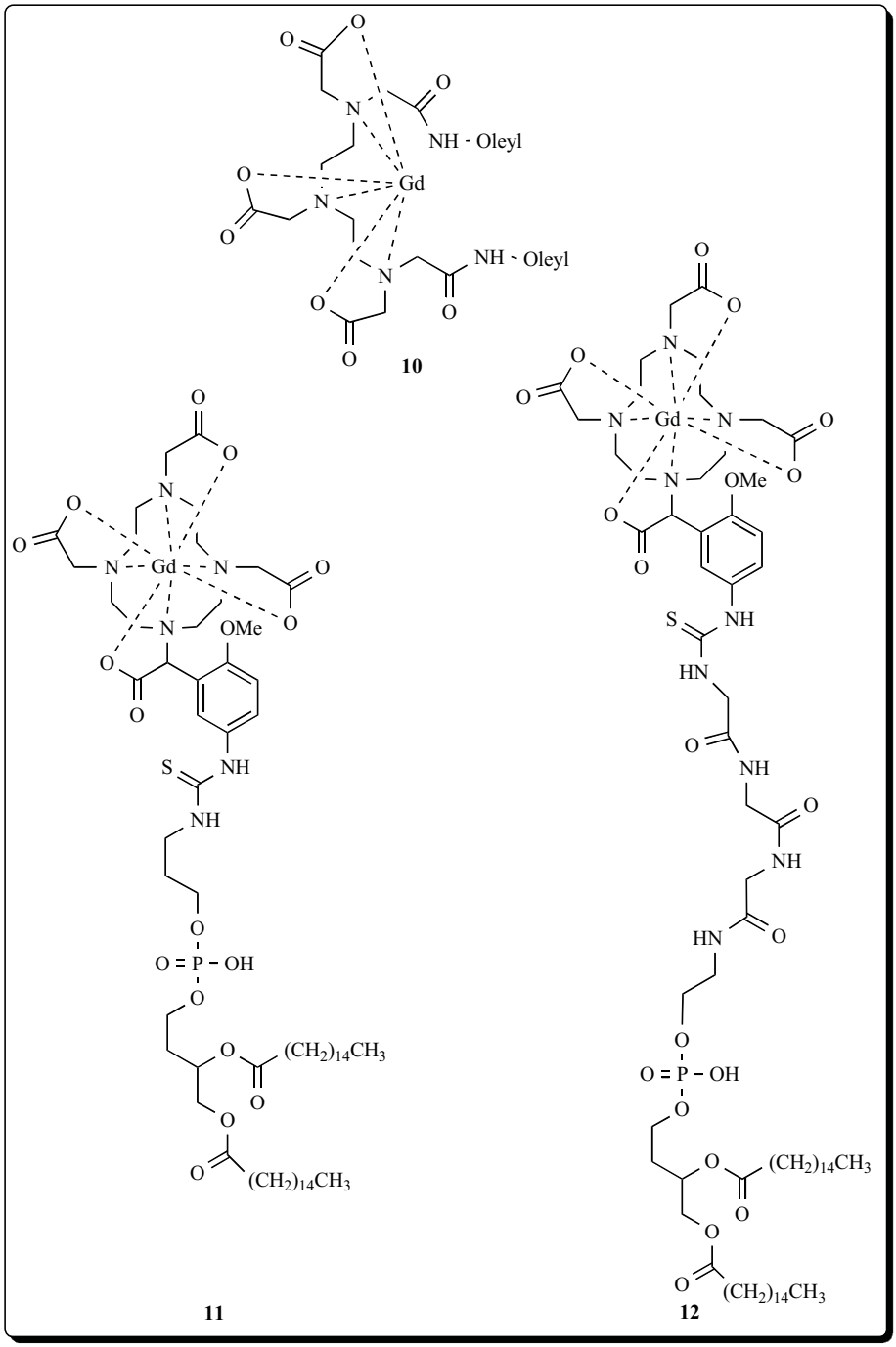


Fig. (5). Schematic representation of the Gd(III)-loaded core-shell nanoparticles.

A lipid encapsulated, perfluorocarbon nanoparticle featured a Gd-DTPA-BOA (BOA = bis-oleate) complex (**10**) was reported and used for the specific and sensitive detection of fibrin and the molecular signature of angiogenesis [74-76]. It was found that the relaxivity was much higher for each gadolinium ion than free Gd-DTPA contrast agents. The payload is often in excess of 50,000 gadolinium ions per nanoparticle, which gives particle based relaxivities of around 1, 000, 000 mM^{-1} s^{-1} [76]. In order to avoid the loss of two coordination bonds to the gadolinium(III) ion for lipid attachment, the paramagnetic chelate for Gd-DTPA-PE (PE = phosphatidyl-ethanolamine) was developed and found to have a relaxivity twice as large as the previously reported compound (33.7 mM^{-1} s^{-1}), but the transmetallation effects





were not considered [77]. Another development in this area was the incorporation of Gd-MeO-DOTA (MeO = methoxy) (**11**) and Gd-MeO-DOTA-triglycine-PE (**12**). They demonstrated high relaxivity (29.8 mM^{-1} s^{-1} and 33.0 mM^{-1} s^{-1} for **11** and **12** respectively) [76]. For these nanoparticulate contrast agents, there was an improved retention of gadolinium within the nanoparticle. In addition, the transmetallation effects were reduced by using the MeO-DOTA chelates.

Bunzli *et al.* reported the synthesis of luminescent lanthanide(III) and gadolinium(III) complexes with a podate ligand (Fig. **6**) as spherical nanoparticles [78]. The relaxivity of this species is a magnitude higher than clinically approved contrast agents. This was attributed to the porous structure of aggregates which allowed water to freely circulate around the contrast agent. In addition, the experimental results also indicated that the relaxivity could be controlled depending on the physical properties of the nanoparticles.

Fayad *et al.* synthesized a high density lipoprotein-like nanoparticulate contrast agent Gd(DTPA-DMPE) (DMPE = l,2-dimyristoyl-sn-glycero-3-phosphoethanolamine) (**13**) in order to target atherosclerotic plaques [79]. It was found that the relaxivity was independent of gadolinium concentration, and accumulation was observed locally to the plaque. The

specificity of this nanoparticulate contrast agent may be used for the diagnosis and characterization of atherosclerosis without invasion.

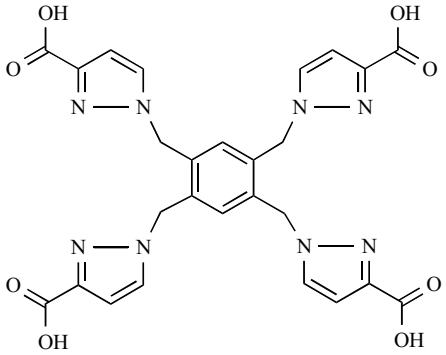
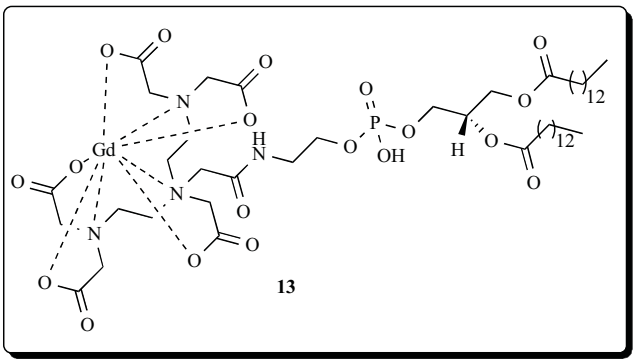
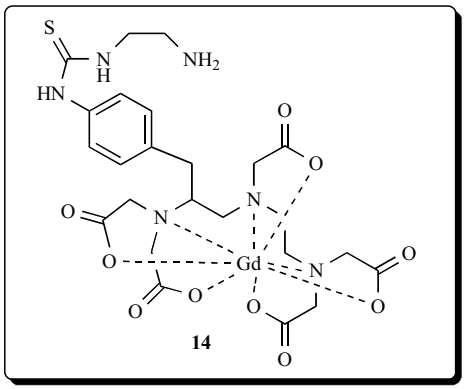


Fig. (6). The structure of the podate ligand.



Wooley *et al.* [80, 81] reported non-immunogenic and non-toxic shell-crosslinked knedel-like nanoparticles (SCKs) with gadolinium chelates as MRI active structures. The shell may act as a reservoir for water molecules because it is heavily hydrated, this provides readily exchangeable water molecules for their potential application as MRI agents. The shell layer consists of amines, amides and ether functional groups which may be used to coordinate to the gadolinium centre. But this is not viable in biological systems of the gadolinium ion due to the toxicity [82]. Thus, a DTPA analogue (**14**) was synthesized; it was found that this DTPA analogue had high molecular relaxivity and a large loading capacity [83]. Further biological assessments have not been reported yet.



A NaY zeolite was reported for imaging of the digestive tract, the Na^+ was partially exchanged for Gd^{3+} in this compound (Fig. **7**). Zeolites are chemically and thermally stable aluminosilicates with well-defined pore structures [84]. Peters *et al.* found that destruction of the zeolite structure enlarged the cages, and these zeolites were more efficient with increasing the longitudinal relaxation of water proton. There is a dramatic decrease in diffusion rate of water in zeolites when zeolites have smaller pore sizes. These results indicated that these materials had potential as T_1 contrast agents at low field, and as T_2 contrast agents at high fields [85].

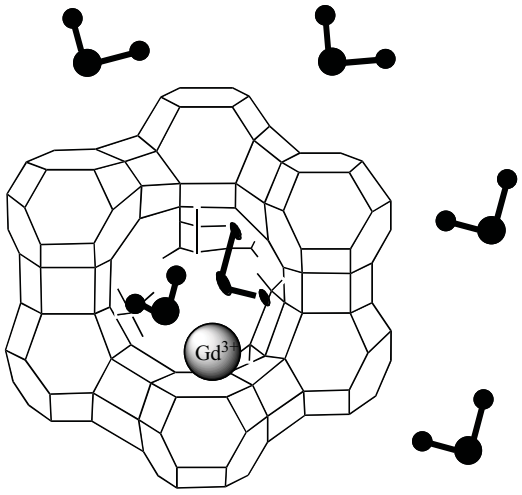


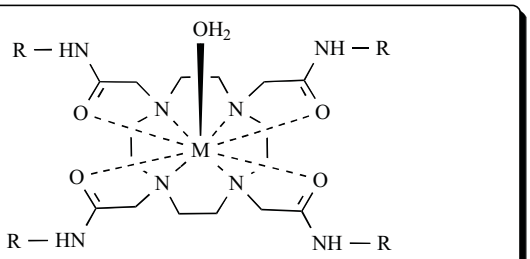
Fig. (7). Structure depiction of a NaY zeolite.

Quantum dots are nanoparticulate clusters of semiconductor material with quantum confinement effects. This means that the optical properties of these nanoparticles are controlled by their size, rather than their composition, which makes them useful for optical imaging agents [86]. Mulder *et al*. [87] have reported that the relaxivity per Mm of quantum dots coated with paramagnetic and pegylated lipids was of nearly 2000 $mM^{-1}s^{-1}$. The quantum dots were functionalized by covalently linking αvβ3-specific Arg-Gly-Asp (RGD) peptides, and the specificity was confirmed by endothelial cells. The biocompatible chitosan nanobeads incorporating quantum dots and Gd(DTPA) have been synthesized [88]. These compounds can be used as multifunctional biomarkers for cell labeling by their paramagnetic and fluorescent properties. The quantum dots and gadolinium chelate are electrostatically attracted to the positively charged chitosan backbone, which forms a three dimensional mesh [88]. It was found that the encapsulated gadolinium chelate would not be released from mesh-like structure, the T_1 values dropped as the concentration of the gadolinium chelate increased, consequently the signal in images increased. In addition, it was also found that r_1 values of these nanobeads were lower than that of free Gd(DTPA), but there was no significant difference.

5.4. PARACEST Contrast Agents

The use of paramagnetic lanthanide complexes as CEST named PARACEST contrast agents is favorable as the paramagnetic ion induces a large shift in the resonance of the nuclei surrounding it, which then causes a more efficient transfer of the magnetization.

Aime *et al*. reported that the Eu[DOTAM]$^{3+}$ complexes (DOTAM = 1,4,7,10-tetrakis (carbamoylmethyl)-1,4,7,10-tetraazacyclododecane) exhibited an NMR signal for the water bound to the metal centre at low temperatures in deuterated acetonitrile [89]. Based on these results, Zhang *et al*. demonstrated that the resonance of the bound water of a similar DOTA-tetra(amide) derivative could be observed at temperatures up to 40 ºC. They postulated that the reagent might be a useful PARACEST contrast agent by the large NMR shift between bound and bulk water in the system [90]. The europium(III) or terbium(III) complexes with the same DotamGLY ligand (**15**) was further studied [91]. They have two pools of exchangeable protons—the coordinated water protons and the amide protons [92]. It was found that irradiation at 50 ppm from the bulk water resonance detected a response from the europium agent, whilst switching to irradiation at 600 ppm from bulk water detected the terbium agent. When the rat heptoma tumor cells were treated, and then the same irradiation process was repeated, irradiation at 600 ppm caused exclusive detection of the terbium complex containing cells and at 50 ppm the europium containing cells. These results further expanded MR imaging to the field of cell tracking in *vivo* [91].



DOTAM-Gly, R=Glycine; DOTAM-Gly-Phe, R=Glycine-Phenyla

M = Eu(III), Tb(III)

15

5.5. Site-Specific Contrast Agents

Commonly used blood-pool contrast agents are not specific to a type of tissue. Recently, MRI contrast agents have been rapidly developed to specifically target different type of tissue [93, 94]. Gd-chelate-based MR contrast agents speed up longitudinal relaxation by shortening tissue T_1 values, resulting in positive enhancement in T_1-weighted MR imaging. Nanoparticle probes detecting inflammation, apoptosis, extracellular matrix, and angiogenesis may provide tools for assessing the risk of progressive vascular dysfunction and heart failure. Various nanoparticles containing Gd chelates are promising for imaging cardiovascular targets [95]. Lukes *et al*. reported the properties and synthesis of trivalent lanthanide complexes with a DOTA-like ligand (4- {[(bis-phosphonomethyl)carbamoyl]methyl}-7,10-bis-(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)-acetic acid (BPAMD) (Fig. **8**) in order to apply this complex to bone imaging [96]. It was found that the relaxivity was higher than that of Gd-DOTA with a larger rotational correlation time (88 ps). The potential for bone targeting was measured by a sorption experiment with hydroxyapatite as the model for bone. The uptake was found to be 95% within an hour and reversible within about three days. In addition, after binding to the apatite, the rotational correlation time further lengthens, thus increasing the relaxivity again to 24.0 $mM^{-1}s^{-1}$ at 20 MHz [96]. Recent studies showed that the Lu-177 complexes with BPAMD had a high affinity for bones, particularly for growth plates and teeth with a prolonged retention [97]. These experimental results suggest that this complex may be a suitable for the MRI of bone tissue.

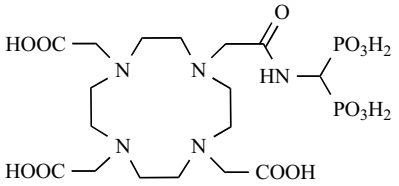


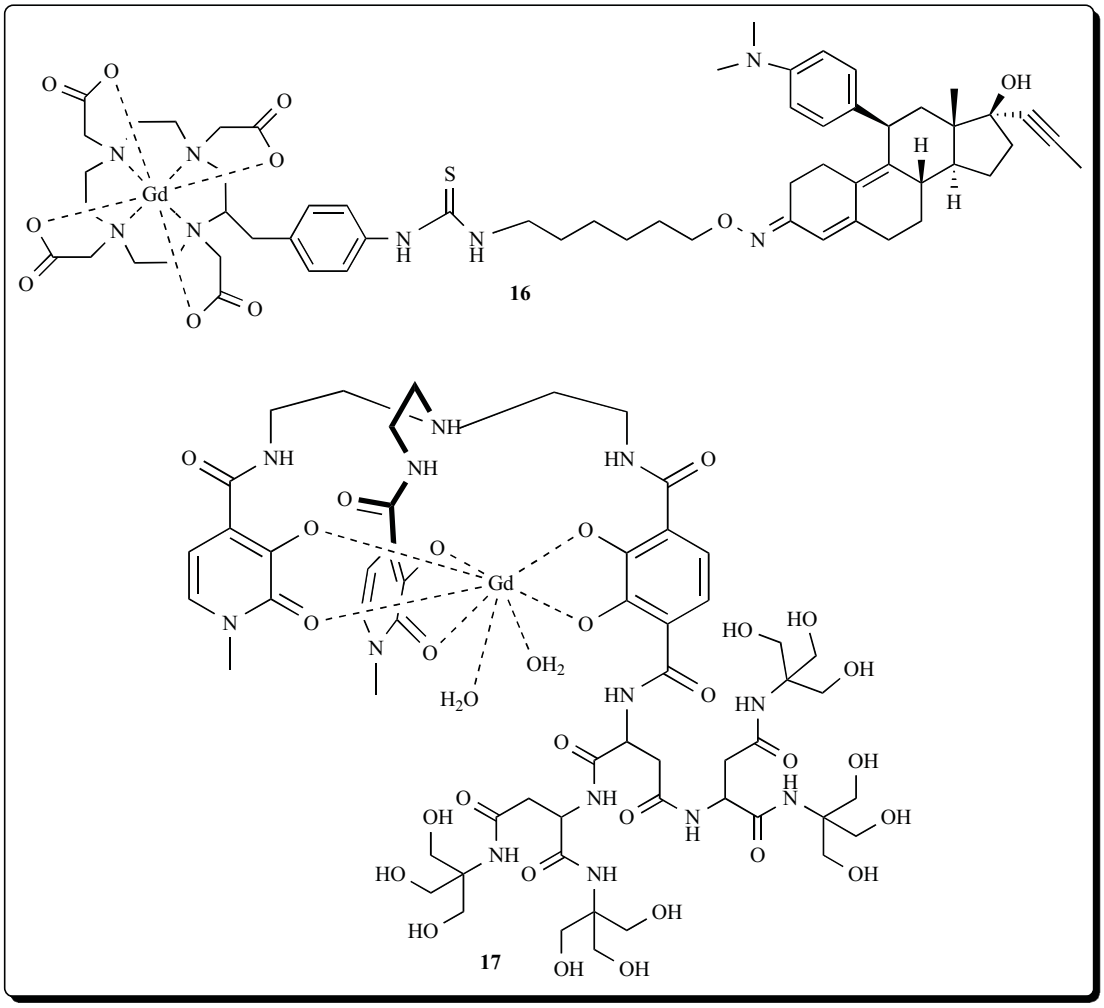
Fig. (8). The structure of BPAMD.

In addition, a steroid conjugated contrast agent (**16**) was reported to bind selectively to a receptor that causes a gene expression pathway. Meade *et al*. covalently attached the steroid RU-486 (mifepristone) by an aminooxy-functionalized linker to a Gd-DOTA analogue [98]. The binding of the mutated progesterone receptor to RU-486 triggers a signal transduction cascade by activating transcription of lac-Z, the target reporter gene. This gene switch system is particularly useful for tracking the cell signaling *in vitro* and *in vivo* with an appropriate imaging strategy. The relaxivity of this compound was 8.5 $mM^{-1} s^{-1}$, higher than the relaxivity of commercial Gd(III) analogues. This may be caused by the hydrophobic nature of the steroid, further increase the rotational correlation time and relaxivity. This study is currently under further development to optimize the linker and chelate in order to provide a useful MRI contrast agent that can specifically track certain cell line through the body.

5.6. Relaxivity-Enhancing Contrast Agents

The ability of an agent to affect T_1 and T_2 is characterized by the concentration-normalized relaxivities r_1 and r_2 respectively. The aim of a contrast agent is to maximize this value, and there are a number of parameters that can be changed to do that. It is thought that the relaxivity of complex with more water molecules in the inner sphere would be higher, but the overall complex less stable, with the gadolinium less shielded from the environment and more likely to transmetallate. In fact, the majority of Gd(III) based contrast agents only have one water molecule attached, which hampers the ability to demonstrate good relaxivity.

Hydroxypyridinone(HOPO)-based chelates with higher relaxivity and high stability were reported, in the complexes, two water molecules were coordinated to the metal centre. Raymond *et al*. [99] reported Gd(HOPO)-based chelate attached to a dendron containing 12 hydroxyl functional groups (**17**) to impart aqueous solubility to the molecule. It was found that the relaxivity of the compound was three times that of the commercially available Gd(DO_3A). It was one of the first published reagents with a fast water exchange and a high relaxivity at the high magnetic fields which was used in the new generation of scanners. An analogous Gd(III) complex with the octadentate ligand H(2,2)-1,2-



HOPO (Fig. **9**) has also been developed, this complex has one coordinated water molecule and shows better relaxometric properties than the complexes of ligands based on the DOTA or DTPA skeleton [100].

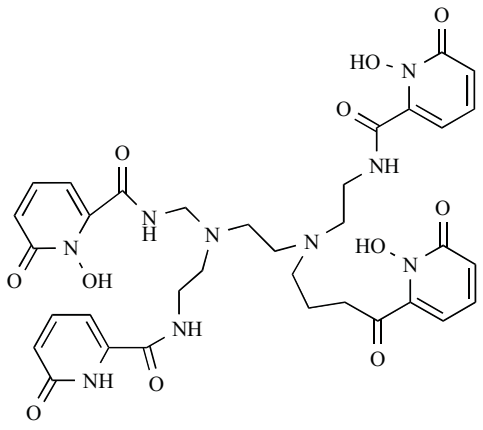


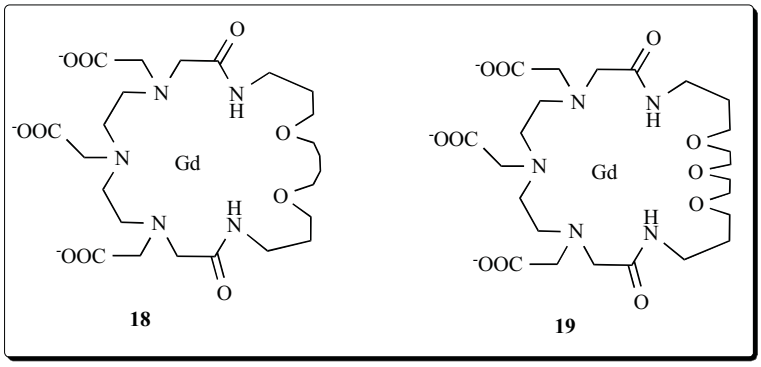
Fig. (9). The structure of H(2,2)-1,2-HOPO ligand.

Another method of enhancing relaxivity is the use of larger complexes to reduce the rotational tumbling time of the molecule. Wong *et al.* reported the synthesis and relaxivity of the contrast agents (**18, 19**) by using a variation on polyaminocarboxylate macrocycles. These compounds had relaxivity values of 5.87 $mM^{-1}s^{-1}$ and 6.14 $mM^{-1}s^{-1}$ at 20 MHz and 25 ºC, significantly higher than Gd-DOTA (4.74 $mM^{-1}s^{-1}$), this was attributed to their larger size which caused lengthening of τ_R. However, it was found that the water exchange rate was slow, which caused a limitation upon the relaxivity, indicating that the compounds need to be optimized before application [101].

5.7. High-Field Contrast Agents

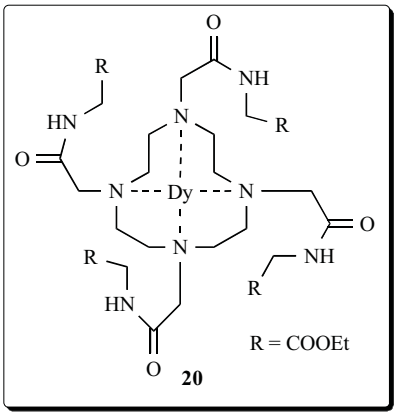
Clinical MRI is moving towards to the use of high magnetic fields, but commercial Gd(III) based contrast agents display poor water relaxivity. It was found that dysprosium complexes had potential application as negative contrast agents at high magnetic fields due to their efficient transverse relaxivity.

Muller *et al.* have demonstrated that the transverse relaxivity can be limited by lengthening the residence time of water by Dy-DOTA-4AmCE46 (**20**) [102]. It was found that the transverse relaxivity of complex with fast exchange of water protons increased with the square of the magnetic field and the residence time. A residence time of greater than 1 ms restricts the relaxivity for dysprosium complex at high magnetic fields, whereas residence times of less than 100 ns limits the relaxivity at both low and high magnetic fields.



Therefore, it is very important to have optimum r_2 at the high magnetic fields. In addition, the residence time needs to be optimized between 0.1 and 1 μs [102].

In summary, it is crucial to design of a suitable molecular structure for dysprosium(III) complexes as negative contrast agents. In addition, Fine tuning the residence times of the water protons and the relaxivity may lead to promising contrast agents for high field magnetic resonance imaging. This field is still fairly new and remains to be studied.



5.8. Luminescent Contrast Agents

The trivalent lanthanide ions have been used for luminescence studies. Europium(III) and terbium(III) are the most commonly used ions because of their characters, for example, they emit in the visible spectrum, in the red and green regions respectively. In addition, they possess long luminescent lifetimes and this means that background fluorescence from tissues can be rejected by temporal gating. This will aid to the development of new luminescent-based contrast agents.

Li *et al*. [103] designed a range of lipophilic chelates based on the ligand DTPA-PDA (PDA = 2,6-pyridinedimethaneamine) (Fig. **10**) for MRI and fluorescence imaging. The idea of design was to tag the cell membrane with the contrast agent in contrast to the more common hydrophilic chelates used in aqueous conditions. This is not possible in human studies as maintaining a gadolinium complex within the body, even if well encapsulated would not be recommended based on the toxicity of free gadolinium ions [104]. The addition of these lipophilic gadolinium complexes to Hela cells resulted in rapid uptake into the cell membrane and increase in the intensity of T_1 weighted images. The mechanism of uptake was studied using diffusion enhanced fluorescence resonance energy transfer (DEFRET) with the terbium (III) complex analogue. Trivalent terbium and europium are efficient energy donors in DEFRET imaging, thus they can be used to identify localization of the complexes within biological systems [103].

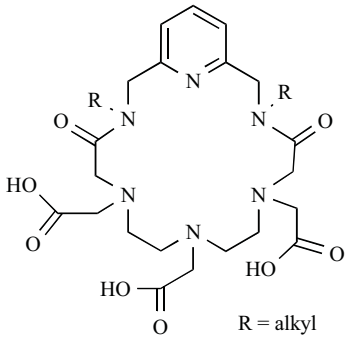


Fig. (10). The structure of DTPA-PDA.

In summary, up to date, gadolinium(III) remains the dominant starting material for contrast agent design, but other lanthanide ions are also being increasingly investigated as alternatives to gadolinium(III). With the current efforts devoted to the development of structure–activity relationships, it will be fascinating to see how much more chemists and their collaborators can achieve in the near future.

6. OSTEOPOROSIS

Osteoporosis is a systemic skeletal disease and characterized by low bone mass and the microarchitectural deterioration of bone tissue [105]. The loss of bone mass in osteoporosis is due to an imbalance between the formation and resorption of bone, which, in turn, depends on the interactions between osteoblasts (OBs) and osteoclasts (OCs) [106].

Owing to the similarity of RE ions and Ca^{2+} in the physical and chemical properties, rare earth ions are reported to be involved in the pathogenesis of osteoporosis. Available evidences suggest that rare earth elements show versatile effects in the process of bone remolding *in vitro* [107, 108]. Quarles *et al*. reported that Gd^{3+} could stimulate DNA

synthesis of MC3T3-E1 OBs in a dose-dependent manner in *vitro*. This was related to Gd^{3+}-activated G-proteins in OB membranes [109]. Hartle *et al.* found that Gd^{3+} inhibited Prostaglandin E (PGE)-stimulated cyclic adenosine monophosphate (cAMP) accumulation, but potentiated p*arathyroid hormone* (PTH)-stimulated cAMP production [110]. Using the model of UMR106 (a rat osteosarcoma cell line), we studied the effects of $LaCl_3$, $SmCl_3$, $ErCl_3$, $NdCl_3$, $GdCl_3$ and $DyCl_3$ on the proliferation, differentiation and mineralized function of OBs *in vitro* [111]. The results indicated that all of them inhibited the proliferation of OBs at a high concentration of 1.00×10^{-4} mol/L. At concentrations of 1.00×10^{-9}~1.00×10^{-5} mol/L, all of them stimulated the proliferation of osteoblasts. As to alkaline phosphatase activity, all of them significantly improved alkaline phosphatase activity at concentrations of 1.00×10^{-7} and 1.00×10^{-5} mol/L. $LaCl_3$ promoted the transition of cell cycle from G_0/G_1 phase to S phase and stimulated mineralized function at concentrations of 1.00×10^{-8} and 1.00×10^{-9} mol/L. Wang *et al.* reported that La^{3+} exposure enhanced OB differentiation in *vitro* and the effect depended on extracellular signal-regulated kinase (ERK) phosphorylation *via* pertussis toxin (PTx)-sensitive Gi protein signaling [112]. It was found that effects of $CeCl_3$, YCl_3 and $DyCl_3$ on the proliferation, differentiation, adipocytic transdifferentiation and mineralized function of primary OBs depended on the concentration, culture time and ion species [113-115].

We previously studied the effects of $LaCl_3$, $SmCl_3$, $ErCl_3$, $NdCl_3$, $GdCl_3$ and $DyCl_3$ on bone resorbing function of OCs by primary rabbit OCs on bone slices [116]. The results indicated that the effects of RE ions on osteoclastic bone-resorbing activity exhibited a concentration-dependent duality, and various rare earth compounds could behave differently. $LaCl_3$, $SmCl_3$ and $ErCl_3$ at a concentration of 1.00×10^{-8} mol/L promoted bone resorption function, but the effect was attenuated and turned to be inhibitory with increasing concentration. $NdCl_3$, $GdCl_3$ and $DyCl_3$ did not influence osteoclastic bone resorption function at a concentration of 1.00×10^{-8} mol/L, promoted bone resorption at a concentration of 1.00×10^{-7} mol/L, and with further increasing concentration, they inhibited bone resorption function. At a concentration of 1.00×10^{-8} mol/L, the stimulatory effects of $LaCl_3$, $SmCl_3$ and $ErCl_3$ were more effective than those of $NdCl_3$, $GdCl_3$ and $DyCl_3$, but at a concentration of 1.00×10^{-7} mol/L, $LaCl_3$, $SmCl_3$ and $ErCl_3$ had weaker effects than $NdCl_3$, $GdCl_3$ and $DyCl_3$. All of the six REs exhibited inhibitory effects at concentration up to 1.00×10^{-6} mol/L. As we known, cytosolic free calcium ($[Ca^{2+}]_i$) affects cytoskeleton and the adhesion properties of OCs, we studied the effect of La^{3+} on $[Ca^{2+}]_i$ in isolated rabbit mature OCs, with the employment of fluo-3/AM as an intracellular calcium-sensitive fluorescent probe by using a confocal laser scanning microscope [117]. The results indicated that La^{3+} didn't alter basal $[Ca^{2+}]_i$ levels and cell spread area at the concentration of 1.00×10^{-8} mol/L. However, La^{3+} at higher concentrations (1.00×10^{-5} and 1.00×10^{-7} mol/L) decreased $[Ca^{2+}]_i$ levels and cell spread area and greater decreases were observed for the higher concentrations of La^{3+}. Our results seemed to suggest that La^{3+} inhibited bone resorption by decreasing $[Ca^{2+}]_i$ in rabbit mature OCs.

In addition, the effects of RE on bone metabolism *in vivo* have been reported. Jha *et al.* [118] found that Pr_6O_{11} and Nd_2O_3 promoted bone resorption by an animal model. Li *et al*. [119] reported that long-term of oral $La(NO)_3$ supplementation at a low dose to rats caused lanthanum accumulation in the bone tissue, reduced Ca/P ratio, decreased bone density, changed microstructure of bone and increased bone crystallinity. Huang *et al*. [120] examined the effects of La on the femur bone mineral of male Wistar rats after administration of $La(NO_3)_3$ by gavages at the dose of 2.0 mg $La(NO_3)_3\cdot kg^{-1}\cdot day^{-1}$ over a 6-month period. Chemical analysis confirmed La accumulation in bone and loss in bone mineral. Thermogravimetric analysis showed a decrease in the mineral-to-matrix ratio and an increase in carbonate content. Fourier-transform infrared spectrometry revealed elevation in the contents of labile carbonate and acidic phosphate. The synchrotron radiation small-angle X-ray scattering study presented a smaller mean thickness of the mineral crystals in the bone of La-treated rats. The synchrotron radiation-extended X-ray absorption fine structure analysis indicated that the $La(NO_3)_3$ treatment resulted in a lowered disorder in the crystals. These findings suggest that La retards bone maturation of rats.

In summary, the effects of RE on the proliferation, differentiation, and mineralized function of primary OBs and OCs depend on the concentration and culture time and rare earth species. Moreover, they may be pivotal factors for switching the effects of rare earth compounds on bone metabolism. This suggests RE may have antiosteoporosis activity, but the mechanism remains to be further studied.

7. OUTLOOK

Recent advances in medicinal inorganic chemistry demonstrate significant prospects for the utilization of lanthanide compounds as drugs, presenting a flourishing arena. The future development of lanthanide based drugs requires an understanding of the physiological processing of lanthanide compounds, to provide a rational basis for the design of new lanthanide based drugs. Application of new methodologies will be also beneficial for the development of lanthanide based drugs. In summary, with the rapid advance in molecular biology, combined with innovation, it is possible that new lanthanide based drugs will be materialized in the near future.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

MRI = Magnetic resonance imaging

HSV = Herpes simplex virus

CMV = Cytomegalovirus

RE = Rare earth

SIRS = Systemic inflammatory immune response

MOFS = Multi-organ failure syndrome

TNF-α = Tumor necrosis factor-α

EDTMP = Ethylenediaminetetra-methylene phosphonic acid

DOTMP = 1, 4, 7, 10-cyclododecyltetraaminetetra-methylenephosphonic acid

DTPA = Diethylenetriamine pentaacetic acid

ESRD = End stage renal disease

CNS = Central nervous system

PTH = Parathyroid hormone

ROS = Reactive oxygen species

IL-2 = Interleukin-2

DOTA = 1, 4, 7, 10-tetrakis(carboxymethyl)-1,4,7, 10-tetraazacyclododecane

BMA = Bismethylamide

HPDO3A = 1-(2-hydroxypropyl)-4,7,10-tetraazacyclododecane-N,N',N''-triacetic acid

$ODDM^{4-}$ = 1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane-7,16-dimalonate

$ODDA^{2-}$ = 1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane-7,16-diacetate

cryptand 2.2.2 = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane

TETA = 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetate

CEST = Chemical exchange saturation transfer

HSA = Human serum albumin

BOA = Bis-oleate

PE = Phosphatidyl ethanolamine

MeO = Methoxy

DMPE = l,2-dimyristoyl-sn-glycero-3-phosphoethanolamine

SCKs = Shell-crosslinked knedel-like nanoparticles

RGD = Arg-gly-asp

PARACEST = Paramagnetic chemical exchange saturation transfer

DOTAM = 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane)

BPAMD = 4-{[(bis-phosphonomethyl)carbamoyl] methyl}-7,10-bis-(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)-acetic acid

HOPO = Hydroxypyridinone

PDA = 2,6-pyridinedimethaneamine

DEFRET = Diffusion enhanced fluorescence resonance energy transfer

OBs = Osteoblasts

OCs = Osteoclasts

PGE = Prostaglandin E

cAMP = Cyclic adenosine monophosphate

ERK = Extracellular signal-regulated kinase

PTx = Pertussis toxin

REFERENCES

[1] Agbenorku, P.; Akpaloo, J.; Farhat, B.F.; Hoyte-Williams, P.E.; Yorke, J.; Agbenorku, M.; Yore, M.; Neumann, M. Burn disasters in the middle belt of Ghana from 2007 to 2008 and their consequences. *Burns*, **2010,** *36*(8), 1309-1315.

[2] Bloemsma, G.C.; Dokter, J.; Boxma, H.; Oen, I.M.M.H. Mortality and causes of death in a burn centre. *Burns,* **2008,** *34*(8), 1103-1107.

[3] Rose, J.K.; Herndon, D.N. Advances in the treatment of burn patients. *Burns*, **1997**, *23*(s1), 19-26.

[4] D'Avignon, L.C.; Hogan, B.K.; Murray, C.K.; Loo, F.L.; Hospenthal, D.R.; Cancio, L.C.; Kim, S.H.; Renz, E.M.; Barillo, D.; Holcomb, J.B.; Wade, C.E.; Wolf, S.E. Contribution of bacterial and viral infections to attributable mortality in patients with severe burns: An autopsy series. *Burns,* **2010,** *36*(6), 773-779.

[5] Keen-III, E.F.; Robinson, B.J.; Hospenthal, D.R.; Aldous, W.K.; Wolf, S.E.; Chung, K.K.; Murray, C.K. Incidence and bacteriology of burn infections at a military burn center. *Burns*, **2010,** *36*(4), 461-468.

[6] Kremer, T.; Hernekamp, F.; Riedel, K.; Peter, Ch.; Gebhardt, M.M.; Germann, G.; Heitmann, Ch.; Walther, A. Topical application of cerium nitrate prevents burn edema after burn plasma transfer. *Microvasc. Res.,* **2009,** *78*(3), 425-431.

[7] Hirano, S.; Suzuki, K.T. Exposure, metabolism, and toxicity of rare earths and related compounds. *Environ. Health Perspect.*, **1996**, *104*(s1), 85-95.

[8] Fricker, S.P. The therapeutic application of lanthanides. *Chem. Soc. Rev.*, **2006,** *35*(6), 524-533.

[9] Monafo, W.W; Tandon, S.N; Ayvazian, V.H; Tuchschmidt, J; Skinner, A.M; Deitz, F. Cerium nitrate: a new topical antiseptic for extensive burns. *Surgery,* **1976,** *80*(4), 465-473.

[10] Rosenkranz, H.S**.** A synergistic effect between cerium nitrate and silver sulphadiazine. *Burns,* **1979,** *5*(3), 278-281.

[11] Monafo, L. The use of topical certain nitrate-silver sulfadiazine in major burn injuries. *Pan. Med.*, **1983,** *25*, 151-154.

[12] Garner, J.P.; Heppell, P.S.J. Cerium nitrate in the management of burns. *Burns*, **2005,** *31*(5), 539-547.

[13] Deveci, M.; Eski, M.; Sengezer, M.; Kisa, U. Effects of cerium nitrate bathing and prompt burn wound excision on IL-6 and TNF-a levels in burned rats. *Burns,* **2000**, *26*(6), 41-45.

[14] Jakupec, M.A.; Unfried, P.; Keppler, B.K. Pharmacological properties of cerium compounds. *Rev. Physiol. Biochem. Pharmacol.,* **2005,** *153*, 101-111.

[15] Boeckx, W.; Blondeel, P.N.; Vandersteen, K.; De Wolf-Peeters, C.; Schmitz, A. Effect of cerium nitrate-silver sulphadiazine on deep

dermal burns: a histological hypothesis. *Burns,* **1992,** *18*(6), 456-462.

[16] Murphy, K.D.; Lee, J.O.; Herndon, D.N. Current pharmacotherapy for the treatment of severe burns. *Expert Opin. Pharmacother.,* **2003**, *4*(3), 369-384.

[17] Kostova, I. Lanthanides as anticancer agents. *Curr. Med. Chem. - Anti-Cancer Agents*, **2005,** *5*(6), 591-602.

[18] Kostova, I.; Kostova, R.; Momekov, G.; Trendafilova, N.; Karaivanova, M. Antineoplastic activity of new lanthanide (cerium, lanthanum and neodymium) complex compounds. *J. Trace Elem. Med. Biol.,* **2005**, *18*(3), 219-226.

[19] Kostova, I.; Manolov, I.; Momekov, G.; Tzanova, T.; Konstantinov, S.; Karaivanova, M. Cytotoxic activity of new cerium (III) complexes of bis-coumarins. *Eur. J. Med. Chem.,* **2005,** *40*(12), 1246-1254.

[20] Chen, Z.F.; Song, X.Y.; Peng, Y.; Hong, X; Liu, Y.C.; Liang, H. High cytotoxicity of dihalo-substituted 8-quinolinolato-lanthanides. *Dalton Trans.*, **2011**, *40*(8), 1684-1692.

[21] Bandyopadhyaya, A.K.; Narayanasamy, S.; Barthb, R.F.; Tjarks, W. Synthesis of novel texaphyrins containing lanthanides and boron. *Tetrahedron Lett.*, **2007,** *48*(26), 4467-4469.

[22] Meyers, C.A.; Smith, J.A.; Bezjak, A.; Mehta, M.P.; Liebmann, J.; Illidge, T.; Kunkler, I.; Caudrelier, J.M.; Eisenberg, P.D.; Meerwaldt, J.; Siemers, R.; Carrie, C.; Gaspar, L.E.; Curran, W.; Phan, S.C.; Miller, R.A.; Renschler, M.F. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J. Clin. Oncol.,* **2004,** *22*(1), 157-165.

[23] Liu, S.; Edwards, D.S. Bifunctional chelators for therapeutic lanthanide radiopharmaceuticals. *Bioconjugate Chem.,* **2001,** *12*(1), 7-34.

[24] Fani, M.; André, J.P.; Maecke, H.R. 68Ga-PET: a powerful generator-based alternative to cyclotron-based PET radiopharmaceuticals. *Contrast Media Mol. Imaging,* **2008**, *3*(2), 67-77.

[25] Li, W.P.; Ma, D.S. ; Higginbotham, C.; Hoffman, T.; Ketring, A.R.; Cutler, C.S.; Jurissona, S.S. Development of an *in vitro* model for assessing the *in vivo* stability of lanthanide chelates. *Nucl. Med. Biol.*, **2001**, *28*(2), 145-154.

[26] Tarkanyi, F.; Hermanne, A.; Takacs, S.; Ditroi, F.; Kiraly, B.; Kovalev, S. F.; Ignatyuk, A.V. Experimental study of the ^{165}Ho(p,n) nuclear reaction for production of the therapeutic radioisotope^{165}Er. *Nucl. Instrum. Methods Phys. Res., Sect. B,* **2008**, *266*(15), 3346-3352.

[27] Kremer, C.; Torresa, J.; Domınguez, S.; Mederos, A. Structure and thermodynamic stability of lanthanide complexes with amino acids and peptides. *Coord. Chem. Rev.*, **2005,** *249*(5-6), 567-590.

[28] Rasaneh, S.; Rajabi, H.; Babaei, M.H.; Daha, F.J.; Salouti, M. Radiolabeling of trastuzumab with 177Lu *via* DOTA, a new radiopharmaceutical for radioimmunotherapy of breast cancer. *Nucl. Med. Biol.*, **2009,** *36*(4), 363-369.

[29] Chakraborty, S.; Das, T.; Sarmab, H.D.; Venkatesha, M.; Banerjee, S. Comparative studies of 177Lu–EDTMP and 177Lu–DOTMP as potential agents for palliative radiotherapy of bone metastasis. *Appl. Radiat. Isotopes.* **2008**, *66*(9), 1196-1205.

[30] Bayouth, J.E.; Macey, D.J.; Kasi, L.P.; Garlich, J.R.; Mamillan, K.; Dimopoulos, M.A.; Champlin, R.E. Pharmacokinetics, dosimetry and toxicity of holmium-166-DOTMP for bone marrow ablaion in multiple myeloma. *J. Nucl. Med.,* **1995,** *36*(5), 730-737.

[31] Ali, B.S.; Mohammad, G.M.; Amir, R.J.; Moein, M.; Simindokht, S.A.; Sedigheh, M. Production, quality control and biological evaluation of ^{153}Sm-EDTMP in wild-type rodents. *Iran. J. Nucl. Med.*, **2009,** *17*(2), 12-19.

[32] Goeckeler, W.F.; Edwards, B.; Volert, W.A.; Troutner, D.E.; Holmes, R.A.; Simon, J.; Wison, D. Skeletal localization of Sm-153 chelates: potential therapeutic bone agents. *J. Nucl. Med.,* **1987,** *28*(4), 495-504.

[33] Majkowska-Pilip, A.; Bilewicz, A. Macrocyclic complexes of scandium radionuclides as precursors for diagnostic and therapeutic radiopharmaceuticals. *J. Inorg. Biochem.,* **2011**, *105*(2), 313-320.

[34] Storr, T.; Thompson, K.H.; Orvig, C. Design of targeting ligands in medicinal inorganic chemistry. *Chem. Soc. Rev.*, **2006,** *35*(6), 534-544.

[35] Meredith, R.F.; Partridge, E.E.; Alvarez, R.D.; Khazaeli, M.B.; Plott G; Russell, C.D.; Wheeler, R.H.; Liu, T.; Grizzle, W.E.; Schlom, J.; LoBuglio, A.F. Intraperitoneal radioimmunotherapy ofovarian cancerwith lutetium- 177-CC49. *J. Nucl. Med.,* **1996,** *37*(9), 1491-1496.

[36] Sharkey, R.M.; Goldenberg, D.M. Perspectives on cancer therapy with radiolabeled monoclonal antibodies. *J. Nucl. Med.*, **2005,** *46*(s1), 115-127.

[37] Frederic, P.; Antoine, I.; Xavier, F.; Isabelle, P.; Antoine, T. Retreatment with ^{90}Y-labelled ibritumomab tiuxetan in a patient with follicular lymphoma who had previously responded to treatment. *Lancet Oncol.,* **2007,** *8*(9), 849-850.

[38] Papi, S.; Martanoa, L.; Garaboldi, L.; Rossi, A.; Cremonesi, M.; Grana, C.M.; Paolucci, D.; Sansovini, M.; Paganelli, G. Marco chinol radiolabeling optimization and reduced staff radiation exposure for high-dose 90Y-ibritumomab tiuxetan (HD-Zevalin). *Nucl. Med. Biol.*, **2010,** *37*(1), 85-93.

[39] Albaaj, F.; Hutchison, A.J. Hyperphosphataemia in renal failure: causes, consequences and current management. *Drugs*, **2003**, *63*(6), 577-596.

[40] Albaaj, F.; Hutchison, A.J. Lanthanum carbonate for the treatment of hyperphosphatemia in renal failure and dialysis patients. *Expert Opin. Pharmacother.*, **2005,** *6*(2), 319-328.

[41] Salusky, I.B.; Foley, J.; Nelson, P.; Goodman, W.G. Aluminum accumulation during treatment with aluminum hydroxide and dialysis in children and young adults with chronic renal disease. *N. Engl. J. Med.,* **1991**, *324*, 527-531.

[42] Malluche, H. H.; Mawad, H. Management of hyperphosphataemia of chronic kidney disease: Lessons from the past and future directions. *Nephrol. Dial. Transplant.,* **200**2, *17*(7), 1170-1175.

[43] Persy, V.P.; Behets, G.J.; Bervoets, A.R.; De Broe, M.E.; D'Haese, P.C. Lanthanum: a safe phosphate binder. *Semin. Dial.,* **2006**, *19*(3), 195-199.

[44] Bervoets, A.R.; Behets, G.J.; Schryvers, D.; Roels, F.; Yang, Z.; Verberckmoes, S.C.; Damment, S.J.; Dauwe, S.; Mubiana, V.K.; Blust, R.; De Broe, M.E.; D'Haese, P.C. Hepatocellular transport and gastrointestinal absorption of lanthanum in chronic renal failure. *Kidney Int.,* **2009**, *75*(4), 389-398.

[45] Muller, C.; Chantrel, F.; Faller, B. A confusional state associated with use of lanthanum carbonate in a dialysis patient: a case report. *Nephrol. Dial. Transplant.,* **2009,** *24*(10), 3245-3247.

[46] Isakova, T.; Gutiérrez, O.M.; Chang, Y.; Shah, A.; Tamez, H.; Smith, K.; Thadhani, R.; Wolf, M. Phosphorus binders and survival on hemodialysis. *J. Am. Soc. Nephrol.,* **2009**, *20*(2), 388-396.

[47] Damment, S.; Secker, R.; Shen, V.; Lorenzo, V.; Rodriguez, M. Long-term treatment with lanthanum carbonate reduces mineral and bone abnormalities in rats with chronic renal failure. *Nephrol. Dial. Transplant.,* **2010,** doi: 10.1093/ndt/gfq682

[48] Persy, V.P.; Behets, G.J.; De Broe, M.E.; D'Haese, P.C. Management of hyperphosphatemia in patients with end-stage renal disease: focus on lanthanum carbonate. *Int. J. Nephrol. Renovasc. Dis.*, **2009**, *2*, 1-8.

[49] Finn, W.F.; Joy, M.S.; Hladik, G. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis. *Clin. Nephrol.,* **2004**, *62*(3), 193-201.

[50] Joy, M.S.; Finn, W.F. Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. *Am. J. Kidney Dis.,* **2003**, *42*(1), 96-107.

[51] Finn, W.F.; Joy, M.S. A long-term, open-label extension study on the safety of treatment with lanthanum carbonate, a new phosphate binder, in patients receiving hemodialysis. *Curr. Med. Res. Opin.*, **2005**, *21*(5), 657-664.

[52] Hutchison, A.J.; Maes, B.; Vanwalleghem, J.; Asmus, G.; Mohamed, E.; Schmieder, R.; Backs, W.; Jamar, R.; Vosskuhler, A. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized, comparative trial versus calcium carbonate. *Nephron. Clin. Pract.*, **2005**, *100*(1), 8-19.

[53] Swainston, H.T.; Scott, L.J. Lanthanum carbonate. *Drugs,* **2004**, *64*(9), 985-996.

[54] Lee, C.M.; Yeoh, G.C.; Olynyk, J.K. Differential effects of gadolinium chloride on Kupffer cells *in vivo* and *in vitro*. *Int. J. Biochem. Cell Biol.,* **2004**, *36*(3), 481-488.

[55] Liu, J.M.; Chen, D.; Wang, X.M. Effect of lanthanum nitrate on morphology of spleen and IL-2 and IFN-C levels secreted by splenocytes in rats. *J. Jilin Univ. (Med. Ed.),* **2002**, *28,* 121-123.

[56] Roberts, R.A.; Ganey, P.E.; Ju, C.; Kamendulis, L.M.; Rusyn, I.; Klaunig, J.E. Role of the Kupffer cell in mediating hepatic toxicity and carcinogenesis. *Toxicol. Sci.,* **2007,** *96*(1), 2-15.

[57] Wang, K.; Cheng, Y.; Yang, X.G.; Li, R.C. Cell responses to lanthanides and potential pharmacological actions of lanthanides. *Met. Ions Biol. Syst.,* **2003**, *40,* 707-751.

[58] Harstad, E.B.; Klaassen, C.D. Gadolinium chloride pretreatment prevents cadmium chloride-induced liver damage in both wild-type and MT-null mice. *Toxicol. Appl. Pharmacol*., **2002,** *180*(3), 178-185.

[59] Hirasawa, F.; Kawagoe, M.; Wang, J.S.; Arany, S.; Zhou, X.P.; Kumagai, A.; Koizumi, Y.; Koyota, S.; Sugiyama, T. Gadolinium chloride suppresses styrene-induced cytochrome P450s expression in rat liver. *Biomed. Res.,* **2007***, 28*(6), 323-330.

[60] Morgan, R.A.; Dudley, M.E.; Wunderlich, J.R.; Hughes, M.S.; Yang, J.C.; Sherry, R.M.; Royal, R.E.; Topalian, S.L.; Kammula, U.S.; Restifo, N.P.; Zheng, Z.L.; Nahvi, A.; de Vries, C.R.; Rogers-Freezer, L.J.; Mavroukakis, S.A.; Rosenberg, S.A. Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science,* **2006**, *314*(5796), 126-129.

[61] Kepp, O.; Tesniere, A.; Schlemmer, F.; Michaud, M.; Senovilla, L.; Zitvogel, L.; Kroemer, G. Immunogenic cell death modalities and their impact on cancer treatment. *Apoptosis,* **2009,** *14*(4), 364-375.

[62] Liu, Y.; Jiao, F.; Qiu Y.; Li, W.; Lao, F.; Zhou, G.Q.; Sun, B.Y.; Xing, Z.M.; Dong, J.Q.; Zhao, Y.L.; Chai, Z.F.; Chen, C.Y. The effect of $Gd@C_{82}(OH)_{22}$ nanoparticles on the release of Th1/Th2 cytokines and induction of TNF-a mediated cellular immunity. *Biomaterials*, **2009**, *30*(23-24), 3934-3945.

[63] Strande, J.L.; Routhu, K.V.; Hsu, A.; Nicolosi, A.C.; Baker, J.E. Gadolinium decreases inflammation related to myocardial ischemia and reperfusion injury. *J. Inflamm.*, **2009**, *6*, 34.

[64] Tóth, E.; Bolskar, R.D; Borel, A.; González, G.; Helm, L.; Merbach, A.E.; Sitharaman, B.; Wilson, L.J. Water-soluble gadofullerenes: toward high-relaxivity, pH-responsive MRI contrast agents. *J. Am. Chem. Soc.,* **2005,** *127*(2), 799-805.

[65] Sitharaman, B.; Tran, L.A.; Pham, Q.P.; Bolskar, R.D.; Muthupillai, R.; Flamm, S.D.; Mikos, A.G.; Wilson, L.J. Gadofullerenes as nanoscale magnetic labels for cellular MRI. *Contrast Media Mol. Imaging*, **2007,** *2*(3), 139-146.

[66] Jonas, C.R.; Gu, L.H.; Nkabyo, Y.S.; Mannery, Y.O.; Avissar, N.E.; Sax, H.C.; Jones, D.P.; Ziegler, T.R. Glutamine and KGF each regulate extracellular thiol/disulfide redox and enhance proliferation in Caco-2 cells. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **2003**, *285*(6), 1421-1429.

[67] Rehman, F.; Shanmugasundaram, P.; Schrey, M.P. Fenretinide stimulates redox-sensitive ceramide production in breast cancer cells: potential role in drug-induced cytotoxicity. *Br. J. Cancer,* **2004**, *91*(10), 1821-1828.

[68] Burai, L.; Tóth, E.; Seibig, S.; Scopelliti, R.; Merbach, A.E. Solution and solid-state characterization of EuII chelates: a possible route towards redox responsive MRI contrast agents. *Chem.-Eur. J.,* **2000**, *6*(20), 3761-3770.

[69] Burai, L.; Scopelliti, R.; Tóth, E. EuII-cryptate with optimal water exchange and electronic relaxation: a synthon for potential pO2 responsive macromolecular MRI contrast agents. *Chem. Commun.,* **2002**, *20*, 2366-2367.

[70] Burai, L.; Tóth, E.; Moreau, G.; Sour, A.; Scopelliti, R.; Merbach, A.E. Novel macrocyclic Eu(II) complexes: fast water exchange related to an extreme M——O water distance. *Chem.-Eur. J.,* **2003**, *9*(6), 1394-1404.

[71] Ratnakar, S.J.; Woods, M.; Lubag, A.J.; Kovacs, Z.; Sherry, A.D. Modulation of water exchange in europium(III) DOTA-tetraamide complexes *via* electronic substituent effects. *J. Am. Chem. Soc.,* **2008**, *130*(1), 6-7.

[72] Raghunand, N.; Jagadish, B.; Trouard, T.P.; Galons, J.P.; Gillies, R.J.; Mash, E.A. Redox-sensitive contrast agents for MRI based on reversible binding of thiols to serum albumin. *Magn. Reson. Med.,* **2006**, *55*(6), 1272-1280.

[73] Reynolds, C.H.; Annan, N.; Beshah, K.; Huber, J.H.; Shaber, S.H.; Lenkinski, R.E.; Wortman, J.A. Gadolinium-loaded nanoparticles: new contrast agents for magnetic resonance imaging. *J. Am. Chem. Soc.*, **2000**, *122*(37), 8940-8945.

[74] Yu, X.; Song, S.K.; Chen, J.; Scott, M.J.; Fuhrhop, R.J.; Hall, C.S.; Gaffney, P.J.; Wickline, S.A.; Lanza, G.M. High-resolution MRI characterization of human thrombus using a novel fibrin-targeted paramagnetic nanoparticle contrast agent. *Magn. Reson. Med.,* **2000**, *44*(6), 867-872.

[75] Kaneda, M.M.; Caruthers, S.; Lanza, G.M.; Wickline, S.A. Perfluorocarbon nanoemulsions for quantitative molecular imaging and targeted therapeutics. *Ann. Biomed. Eng.,* **2009,** *37*(10), 1922-1933.

[76] Winter, P.; Athey, P.; Keifer, G.; Gulyas, G.; Frank, K.; Fuhrhop, R.J.; Robertson, J.D.; Wickline, S.A.; Lanza, G.M. Improved paramagnetic chelate for molecular imaging with MRI. *J. Magn. Magn. Mater.,* **2005,** *293*(1)*,* 540-545.

[77] Winter, P.M.; Caruthers, S.D.; Yu, X.; Song, S.K.; Chen, J; Miller, B.; Robertson, J.D.; Gaffney, P.J.; Wickline, S.A.; Lanza, G.M. Improved molecular imaging contrast agent for detection of human thrombus. *Magn. Reson. Med.,* **2003,** *50*(2), 411-416.

[78] Fatin-Rouge, N.; Toth, E.; Perret, D.; Backer, R.H.; Merbach, A.E.; Bunzli, J.C.G.. Lanthanide podates with programmed intermolecular interactions: Luminescence enhancement through association with cyclodextrins and unusually large relaxivity of the gadolinium self-aggregates. *J. Am. Chem. Soc.,* **2000**, *122*(44), 10810-10820.

[79] Frias, J.C.; Williams, K.J.; Fisher, E.A.; Fayad, Z.A. Recombinant HDL-like nanoparticles: a specific contrast agent for MRI of atherosclerotic plaques. *J. Am. Chem. Soc.,* **2004**, *126*(50), 16316-16317.

[80] Turner, J.L.; Pan, D.P.J.; Plummer, R.; Chen, Z.Y.; Whittaker, A.K.; Wooley, K.L. Synthesis of gadolinium-labeled shell-crosslinked nanoparticles for magnetic resonance imaging applications. *Adv. Funct. Mater.,* **2005,** *15*(8), 1248-1254.

[81] Becker, M.L.; Bailey, L.O.; Wooley, K.L. Peptide-derivatized shell-cross-linked nanoparticles. 2. Biocompatibility evaluation. *Bioconjugate Chem.,* **2004**, *15*(4), 710-717.

[82] Tweedle, M.F.; Kumar, K. Magnetic resonance imgaging (MRI) contrast agents. In *Metallopharmaceuticals II. Diagnosis and Therapie*; Clarke, M. J., Sadler, P. J., Eds.; Springer: Berlin, Heidelberg, New York, **1999**; p 23.

[83] Corson, D.T.; Meares, C.F. Efficient multigram synthesis of the bifunctional chelating agent (S)-1-p-isothiocyanatobenzyl-diethylenetriaminepentaacetic acid. *Bioconjugate Chem.*, **2000**, *11*, 292-299.

[84] Bresinska, I.; Balkus, K.J. Studies of Gd(III) exchanged Y type zeolites relevant to magnetic resonance imaging. *J. Phys. Chem.,* **1994,** *98*(49), 12989-12994.

[85] Csajbok, E.; Banyai, I.; Elst L.V.; Muller, R.N.; Zhou, W.Z.; Peters, J.A. Gadolinium(iii)-loaded nanoparticulate zeolites as potential high-field MRI contrast agents:relationship between structure and relaxivity. *Chem.-Eur. J.,* **2005,** *11*(16), 4799-4807.

[86] Alivisatos, A.P. Semiconductor clusters, nanocrystals, and quantum dots. *Science,* **1996,** *271*(5251), 933-937.

[87] Mulder, W.J.M.; Koole, R.; Brandwijk, R.J.; Storm, G.; Chin, P.T.K.; Strijkers, G.J.; Donega, C.d.M.; Nicolay, K.; Griffioen, A.J. Quantum dots with a paramagnetic coating as a bimodal molecular imaging probe. *Nano. Lett.,* **2006,** *6*(1), 1-6.

[88] Tan, W.B.; Zhang, Y. Multifunctional quantum-dots-based magnetic chitosan beads. *Adv. Mater.,* **2005,** *17,* 2375-2380.

[89] Aime, S.; Barge, A.; Botta, M.; Sousa, A.S.D.; Parker, D. Direct NMR spectroscopic observation of a lanthanide-coordinated water molecule whose exchange rate is dependent on the conformation of the complexes. *Angew. Chem. Int., Ed. Engl.,* **1998,** *37*(19), 2673-2675.

[90] Zhang, S.R.; Winter, P.; Wu, K.; Sherry, A.D. A novel europium(III)-based MRI contrast agent. *J. Am. Chem. Soc.,* **2001,** *123*(7), 1517-1518.

[91] Aime, S.; Carrera, C.; Castelli, D.D.; Crich, S.G.; Terreno, E. Tunable imaging of cells labeled with MRI-PARACEST agents. *Angew. Chem. Int. Ed.,* **2005**, *44*(12), 1813-1815.

[92] Terreno, E.; Castelli, D.D.; Cravotto, G.; Milone, L.; Aime, S. Ln(III)-DOTAMGly complexes: a versatile series to assess the determinants of the efficacy of paramagnetic chemical exchange saturation transfer agents for magnetic resonance imaging applications. *Invest. Radiol.,* **2004**, *39*(4), 235-243.

[93] Jacques, V.; Desreux, J.F. In *Contrast Agents I. Magnetic Resonance Imaging*; Krause, W. Ed.; Springer-Verlag: Berlin, **2002**; Vol. 221, pp. 123-164.

[94] Weinmann, H.J.; Ebert, W.; Misselwitz, B.; Schmitt-Willich, H. Tissue-specific MR contrast agents. *Eur. J. Radiol.*, **2003**, *46*(1), 33-44.

[95] Chen, W.; Cormode, D.P.; Fayad, Z.A.; Mulder, W.J. Nanoparticles as magnetic resonance imaging contrast agents for vascular and cardiac diseases. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.,* **2011**, *3*(2), 146-161.

[96] Kubícek, V.; Rudovský, J.; Kotek, J.; Hermann, P.; Elst, L.V.; Muller, R.N.; Kolar, Z.I.; Wolterbeek, H.T.; Peters, J.A.; Lukes, I. A bisphosphonate monoamide analogue of DOTA: a potential agent for bone targeting. *J. Am. Chem. Soc.*, **2005**, *127*(47), 16477-16485.

[97] Vitha, T.; Kubícek, V.; Hermann, P.; Elst, L.V.; Muller, R.N.; Kolar, Z.I.; Wolterbeek, H.T.; Breeman, W.A.; Lukes, I.; Peters, J.A. Lanthanide(III) complexes of bis(phosphonate) monoamide analogues of DOTA: bone-seeking agents for imaging and therapy. *J. Med. Chem.,* **2008,** *51*(3), 677-683.

[98] Lee, J.; Zylka, M.J.; Anderson, D.J.; Burdette, J.E.; Woodruff, T.K.; Meade, T.J. A steroid-conjugated contrast agent for magnetic resonance imaging of cell signaling. *J. Am. Chem. Soc.,* **2005**, *127*(38), 13164-13166.

[99] Pierre, V.C.; Botta, M.; Raymond, K.N. Dendrimeric gadolinium chelate with fast water exchange and high relaxivity at high magnetic field strength. *J. Am. Chem. Soc.,* **2005**, *127*(2), 504-505.

[100] Jocher, C.J.; Botta, M.; Avedano, S.; Moore, E.G.; Xu, J.; Aime, S.; Raymond, K.N. Optimized relaxivity and stability of $[Gd(H(2,2)\text{-}1,2\text{-}HOPO)(H_2O)]^-$ for use as an MRI contrast agent. *Inorg. Chem.,* **2007**, *46*(12), 4796-4798.

[101] Chan, K.W.; Barra, S.; Botta, M.; Wong, W. Novel gadolinium(III) polyaminocarboxylate macrocyclic complexes as potential magnetic resonance imaging contrast agents. *J. Inorg. Biochem.,* **2004**, *98*(5), 677-682.

[102] Elst, L.V.; Zhang, S.; Sherry, A.D.; Laurent, S.; Botteman, F.; Muller, R.N. Dy-complexes as high feld T2 contrast agents: influence of water exchange rates. *Acad. Radiol.,* **2002**, *9*(s2), 297-299.

[103] Zheng, Q.; Dai, H.; Merritt, M.E.; Malloy, C.; Pan, C.Y.; Li, W.H. A new class of macrocyclic lanthanide complexes for cell labeling and magnetic resonance imaging applications. *J. Am. Chem. Soc.,* **2005,** *127*(46), 16178-16188.

[104] Crich, S.G.; Biancone, L.; Cantaluppi, V.; Duo, D.; Esposito, G.; Russo, S.; Camussi, G..; Aime, S. Improved route for the visualization of stem cells labeled with a Gd-/Eu-chelate as dual (MRI and fluorescence) agent. *Magn. Reson. Med.,* **2004,** *51*(5), 938-944.

[105] Zhang, J.C.; Liu, D.D.; Sun, J.; Zhang, D.W.; Shen, S.G.; Yang, M.S. Effect of Dy^{3+} on osteogenic and adipogenic differentiation of mouse primary bone marrow stromal cells and adipocytic trans-differentiation of mouse primary osteoblasts. *Chinese Sci. Bull.,* **2009**, *54*(1), 66-71.

[106] Riggs, B.L. Pathogenesis of osteoporosis. *Am. J. Obstet. Gynecol.,* **1987**, *156*(5), 1342-1346.

[107] Wang, K. The analogy in chemical and biological behavior between non-essential ions compared with essential ions. *South Afr. J. Chem*., **1997,** *50*(4), 232-239.

[108] Zhang, J.C.; Wang, P.; Sun, J.; Liu, C.L.; Chen, H.; Huang, J. Viewing safety of rare-earth-based drugs from effect of rare earth on bone metabolism. *Prog. Chem.,* **2009**, *21*(5), 919-928.

[109] Quarles, L.D.; Hartle, J.E.; Middleton, J.P.; Zhang, J.; Arthur, J.M. Aluminum-induced DNA synthesis in osteoblasts: Mediation by a G-protein coupled cartion sensing mechanism. *J. Cell. Biochem.*, **1994**, *56*(1), 106-117.

[110] Hartle, J.E.; Prpic, V.; Siddhanti, S.R.; Spurney, R.F.; Quarles, L.D. Differential regulation of receptor-stimulated cyclic adenosine monophosphate by polyvalent cations in MC3T3-E1 osteoblasts. *J. Bone Miner. Res.,* **1996**, *11*(6), 789-799.

[111] Zhang, J.C.; Li, X.X.; Xu, S.J.; Wang, K.; Yu, S.F.; Lin, Q. Effects of rare earth on proliferation, differentiation and function expression of cultured osteoblasts *in vitro*. *Prog. Nat. Sci.*, **2004**, *14*(4), 404-409.

[112] Wang, X.; Yuan, L.; Huang, J.; Zhang, T.L.; Wang, K. Lanthanum enhances *in vitro* osteoblast differentiation *via* pertussis toxin-sensitive gi protein and ERK signaling pathway. *J. Cell Biochem.,* **2008**, *105*(5), 1307-1315.

[113] Zhang, J.C.; Yang, K.N.; Sun, J.; Li, Y.P. Effects of $DyCl_3$ on the proliferation, differentiation and mineralization function of primary mouse osteoblasts *in vitro*. *Chinese J. Inorg. Chem*., **2010**, *26*(10), 1856-1862.

[114] Zhang, J.C.; Liu, C.L.; Li, Y.P.; Sun, J.; Wang, P.; Di, K.Q.; Zhao, Y.Y. Effect of cerium ion on the proliferation, differentiation and mineralization function of primary mouse osteoblasts *in vitro*. *J. Rare Earths*, **2010**, *28*(1), 138-142.

[115] Zhang, J.C.; Liu, C.L.; Li, Y.P.; Sun, J.; Wang, P.; Di, K.Q.; Chen, H.; Zhao, Y.Y. Effect of yttrium ion on the proliferation, differentiation and mineralization function of primary mouse osteoblasts *in vitro*. *J. Rare Earths*, **2010,** *28*(3), 466-470.

[116] Zhang, J.C.; Xu, S.J.; Wang, K.; Yu, S.F. Effects of rare earth ions on bone resorbing activity of osteoclasts *in vitro*. *Chinese Sci. Bull.*, **2003,** *48*(16), 1767-1771.

[117] Zhang, J.C.; Zhang, T.L.; Xu, S.J.; Wang, K.; Yu, S.F.; Yang, M.S. Effect of lanthanum(II) on cytosolic free calcium in isolated rabbit mature osteoclasts. *J. Rare Earths,* **2005**, *23*(5), 580-583.

[118] Jha, A.M.; Singh, A.C. Clastogenicity of lanthanides-induction of micronuclei in root tips of vicia faba. *Mutat. Res*., **1994,** *322*(3), 169-172.

[119] Li, R.C.; Yang, H.W.; Wang, K. La accumulation and microstructure change of leg bones of rats fed with $La(NO_3)_3$ in low dosage for a long term. *J. Peking Univ. (Health Sci.),* **2003**, *35*(6), 622-624.

[120] Huang, J.; Zhang, T.L.; Xu, S.J. Effects of lanthanum on composition, crystal size and lattice structure of femur bone mineral of Wistar rats. *Calcif. Tissue Int.,* **2006**, *78*(4), 241-247.

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