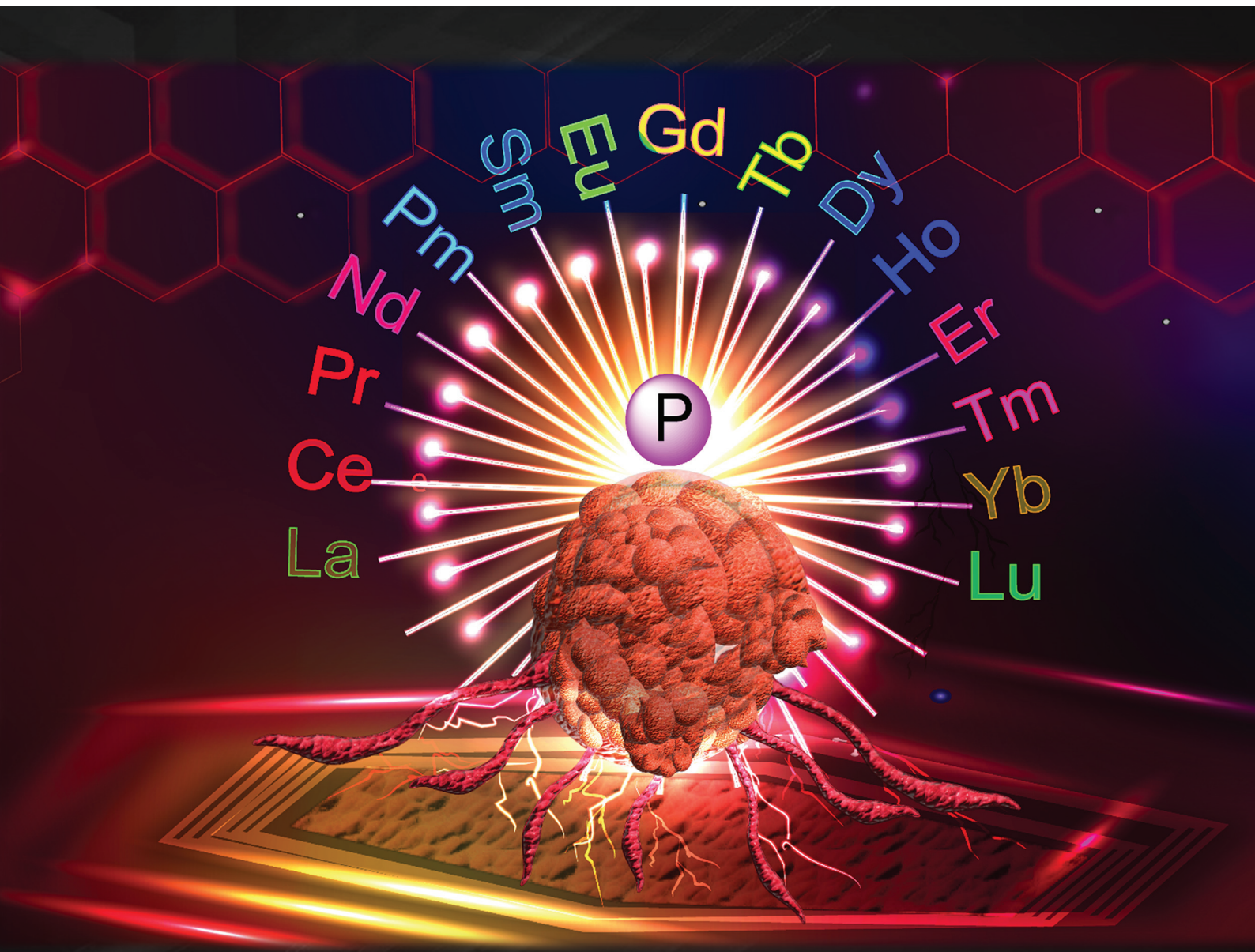


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## Next-generation therapeutics: unlocking the power of lanthanide compounds with phosphorus-containing ligands

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The continuing challenge of drug resistance and the limited efficacy of anticancer conventional therapies underlines the urgent need to develop new medicinal strategies. Metal-based compounds have appeared as promising candidates in medicine, especially in oncology, including lanthanides offering exceptional physicochemical properties such as luminescence, paramagnetism, and radiotherapeutic potential. Despite their growing obvious role in diagnostics and imaging, the biological applications of lanthanide compounds remain underexplored, although a few are used in the clinic including radiopharmaceutical, radioligand therapy, radioimmunotherapy and radioembolization device exist for specific purposes. There is a particularly low number of lanthanide complexes containing phosphorus-based ligands. That is why, this work highlights the potential of lanthanide inorganic compounds with phosphorus-based ligands, especially phosphine and phosphine oxide ligands coordinated to the metal ion as multifunctional anticancer agents. These compounds exhibit strong versatility, and ability to stabilize lower oxidation states of metal ions, enabling their use in numerous therapeutic modalities, such as chemotherapy, radiotherapy, photodynamic therapy (PDT), and theranostics. The integration of lanthanide ions with organophosphine ligands offers a promising platform for targeted drug delivery, multimodal treatment, and personalized medicine. This manuscript provides an overview of current clinical and preclinical reports and as such, highlighting the untouched potential of the combined lanthanide–phosphine class of inorganic compounds that could be developed as a next-generation therapy, especially towards cancer diseases.

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### Introduction

A promising approach in anticancer drug design involves the use of metal-based compounds because of their ability to inhibit abnormal and uncontrolled proliferation characteristic of some aggressive malignant tumours.<sup>1–85</sup> As oncology is evolving, the identification of tumour-specific biomarkers enables more precise and varied chemotherapeutic treatment procedures including dose adjustments and variation in treatment regimens.<sup>86–88</sup> However, chemotherapy resistance remains a major problem for effective cancer treatment, underscoring the urgent need to develop new therapeutic approaches including the use of combination therapies,<sup>89</sup> interventions targeting the tumour microenvironment, innovative drug delivery technologies,<sup>90–92</sup> and the implementation of personalized medicine.<sup>93</sup> Since cisplatin discovery by Barnett Rosenberg in 1965, this inorganic compound (known since 1845 as *Peyrone's*

*salt*) has become a cornerstone of cancer treatment, paving the way for the development of numerous platinum (Pt)-based derivatives aimed at overcoming the toxicity and limitations associated with the original drug.<sup>11,13,14,94</sup>

Many other transition metals have shown promising results, although most remain at the pre-clinical stage. Metal complexes such as those of osmium (Os), along with various other metal ions, are actively being explored by numerous research groups in the field of medicine. Here we mention specifically the results with Ru-based<sup>5,7</sup> and Cu-based<sup>6,8</sup> drugs that have had not only success at the pre-clinical level but also show recent promise to reach the level of use in the clinics. Perhaps less commonly known is the fact that approvals exist for applications of lanthanides as radiopharmaceutical, radioligand therapy, radioimmunotherapy and radioembolization device exist for specific cancers<sup>95</sup> and fuel the topic of this perspective article. However, only a few studies have investigated the therapeutic anticancer potential of lanthanide compounds, such as inorganic lanthanide complexes containing organophosphorus or phosphine ligands. However, few inorganic lanthanide phosphonate ligands have been successful and are currently in the clinic highlighting the potential of combining phosphorus ligands with lanthanide ions as a potential prom-

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ising strategy in the development of new anticancer drugs the topic of this review.<sup>96–99</sup>

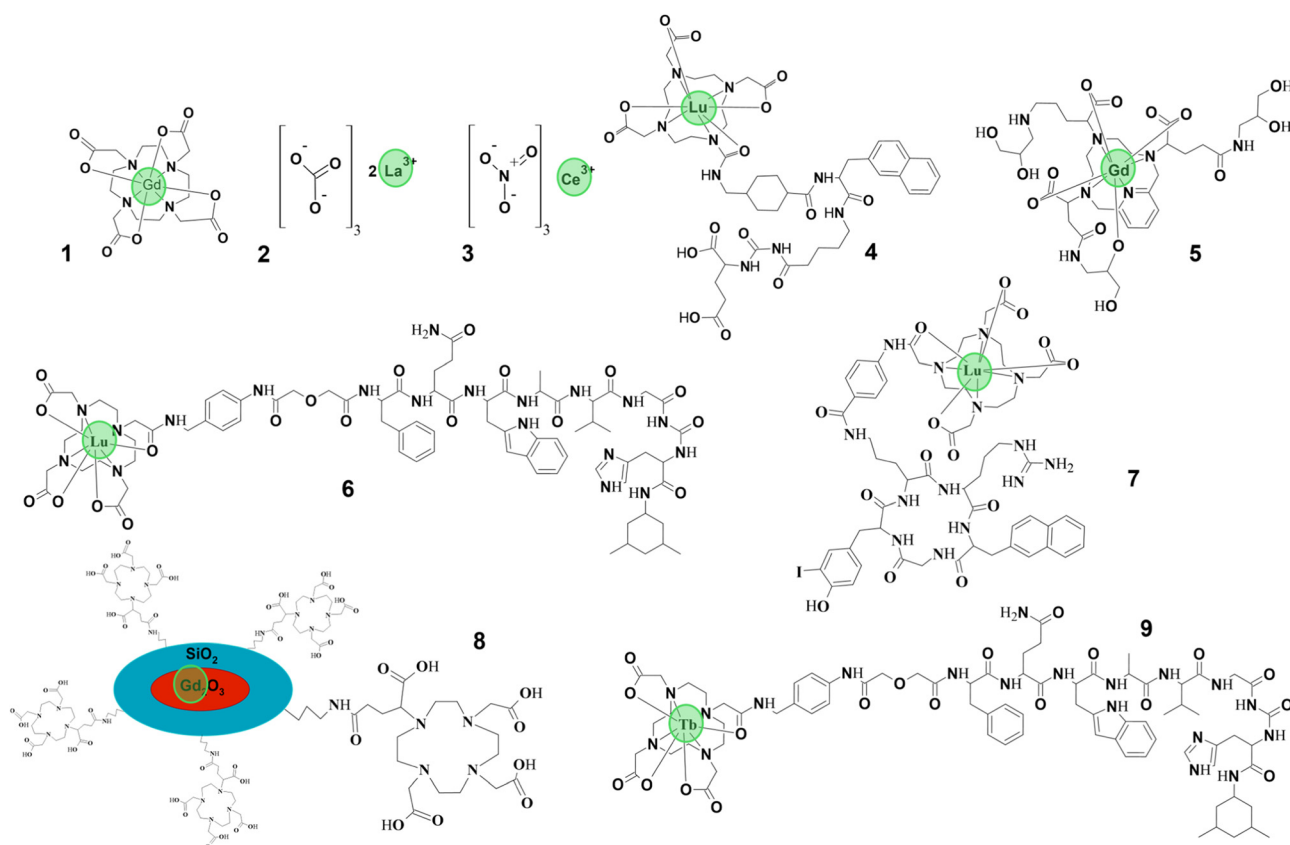
## Lanthanides compounds

In recent years, rare earth elements (REEs) particularly the lanthanides, a group of fifteen metallic elements ranging from lanthanum (atomic number 57) to lutetium (atomic number 71) have become key players in biomedicine. Their unique chemical and physical properties have enabled the development of advanced diagnostic and therapeutic tools. For example, gadolinium-based compounds are now widely used in MRI imaging,<sup>96,100,101</sup> (Scheme 1, compound 1 and Table 1), lanthanum carbonate (Fosrenol)<sup>102,103</sup> (Scheme 1, compound 2 and Table 1) and cerium nitrate<sup>102,104,105</sup> (Scheme 1, compound 3 and Table 1) have received clinical approval for the treatment of kidney disease and burns, respectively. The field of theragnostic, which combines therapy and diagnostics, has embraced lanthanides for their dual functionality. A breakthrough came in 2022 when the FDA approved lanthanide-based drugs: Pluvicto (<sup>177</sup>Lu-PSMA-617) (Scheme 1, compound 4 and Table 1), a radiopharmaceutical targeting PSMA-expressing prostate cancer cells, delivers beta radiation to destroy tumors.<sup>102,106</sup> Gadoplicenol (Scheme 1, compound 5 and Table 1), a highly stable gadolinium-based contrast agent,<sup>102,107,108</sup>

has been approved for use in magnetic resonance imaging (MRI) in both adults and children. Additionally, there are rising number of examples of lanthanide compounds in the clinic or in clinical trials (Table 1 and Scheme 1).

For example, lutetium (<sup>177</sup>Lu)-Neobomb1, also known as [<sup>177</sup>Lu]-NeoB (Scheme 1, compound 6 and Table 1), is an innovative radiopharmaceutical being investigated in clinical trials for the treatment of advanced solid tumors.<sup>112–114</sup> [<sup>177</sup>Lu] Pentixather (Scheme 1, compound 7 and Table 1) is another compound currently in Phase I/II clinical trials, being examined for the treatment of several CXCR4-positive cancers, particularly hematologic malignancies and selected solid tumors.<sup>115</sup> In addition to examples from medicine and clinical research, lanthanide complexes are widely studied in pre-clinical studies, and this research is expanding significantly year by year.<sup>111,122–133</sup> These findings highlight the growing potential of rare earth elements in healthcare, and ongoing research is expanding their role in diagnostics, targeted therapy, and imaging.<sup>99,103–108,111–132,231,233</sup> As their applications continue to expand, REEs have the potential to become an even more integral part of both technological innovation and medical advancement.

Within the framework of the hard and soft acids and bases (HSAB) theory, REE ions are classified as hard acids more than transition metal ions and therefore show a strong preference for binding to hard Lewis bases, particularly those containing



**Scheme 1** Schematic view of selected lanthanide-based compounds currently in clinical trials or approved for medical use see Table 1.

**Table 1** Selected lanthanide-based compounds currently in clinical trials or approved for medical use

Lanthanide based compound	Purpose	Availability, year	Literature
(Gd) Gadolinium-based contrast agents (GBCAs), Scheme 1, compound 1	Magnetic resonance imaging (MRI)	Approved	102, 109 and 110
(La) Fosrenol; Scheme 1, compound 2	Phosphate binder used primarily in the treatment of hyperphosphatemia in patients with end-stage renal disease (ESRD)	Approved, 2004	102 and 103
(Ce) Cerium nitrate; Scheme 1, compound 3	An antiseptic for burns	Approved, 1976	104 and 105
( <sup>177</sup> Lu) Pluvicto ( <sup>177</sup> Lu-PSMA-617); Scheme 1, compound 4	Designed to treat patients with prostate-specific membrane antigen (PSMA) positive metastatic castration-resistant prostate cancer (mCRPC)	Approved, 2022	102 and 106
(Gd) Gadopiclenol; Scheme 1, compound 5	Contrast agent (GBCA), for use in adult and pediatric patients aged 2 years and older	Approved, 2022	102,107,108
( <sup>153</sup> Sm) <sup>153</sup> Sm-EDTMP (Sm-153-EDTMP, Quadramet®); Scheme 4, compound 30	For the palliation of pain in patients with osteoblastic bone metastases	Approved, 1997	200 and 201
( <sup>153</sup> Sm) samarium-153 with docetaxel; Scheme 4, compound 31	Resistant metastatic prostate cancer	A Phase I trial, 2007	99 and 111
( <sup>177</sup> Lu) Lutetium ( <sup>177</sup> Lu)-Neobomb1; Scheme 1, compound 6	Radiopharmaceutical for the treatment of advanced solid tumours	A Phase I/II trial, 2016	112–114
( <sup>177</sup> Lu) [ <sup>177</sup> Lu]Pentixather; Scheme 1, compound 7	CXCR4-positive hematologic malignancies (AML, ALL)	A Phase I/II trial, 2024	115
(Gd) AGuIX NPs; Scheme 1, compound 8	Brain metastasis, lung and pancreatic cancer	A Phase I/II trial, 2021	116–118
( <sup>161</sup> Tb) <sup>161</sup> Tb-labeled radiopharmaceuticals; Scheme 1, compound 9	Prostate cancer and selected neuroendocrine tumours	A Phase I/II trial	119–121

oxygen or nitrogen atoms with available lone ion pairs.<sup>102</sup> For this reason, most lanthanide compounds with biological activity, reported in the literature, possess donor ligands containing nitrogen (–N), oxygen (–O) and sometimes sulphur (–S),<sup>111,124–133,230,232</sup> while examples involving donor ligands containing phosphorus (–P) remain relatively rare,<sup>134,135</sup> which can be attributed to synthetic challenges, in addition to the fact that f-element–phosphorus chemistry is still maturing.<sup>136</sup> Despite this, the literature contains some examples of lanthanides complexes containing phosphines and especially phosphine oxides that exhibit luminescent,<sup>98,137–162</sup> magnetic,<sup>135,163–181</sup> and catalytic<sup>182–193</sup> properties. However, application of these compounds remains limited and their potential in medicine has only recently been recognized.<sup>96,97</sup>

## Phosphorus-containing compounds

Phosphorus-containing compounds represent a structurally diverse and chemically rich class of molecules which when the phosphorus atoms are in the +III or +V oxidation state encompasses a wide variety of derivatives. Compounds with phosphorus(III) include phosphite esters, phosphonites, phosphines, phosphorothioites, phosphorodithioites, and phosphoamidites. Compounds with phosphorus(V) include phosphonium ylides, phosphates, phosphoamidates, phosphonates, phosphine oxides, phosphorothioates, phosphorofluoridates, thiophosphates, phosphoric anhydrides, and bisphosphonates.

Phosphines with the phosphorus in oxidation state III constitute a class of compounds which deserve special attention

due to their low cost, structural versatility, and ability to form stable coordination compounds with transition metal ions.<sup>82,96,97</sup> Importantly, phosphines can stabilize metal centres in lower oxidation states, a valuable property in the design of metal-based drugs.<sup>82</sup> Phosphine metal complexes are also used as catalysts and exhibit photophysical and photochemical properties, such as capability of emission.<sup>198–204</sup> The broad scope of phosphorus compounds justifies their widespread use in medicinal chemistry, materials science, and catalysis (Table 2 and Scheme 2).

Phosphorus-containing drugs constitute a significant class of therapeutic agents with broad clinical relevance across a wide range of disease areas (Table 2). Their development continues to attract significant interest from the pharmaceutical industry due to their structural versatility.<sup>96,97</sup> A historical example is menadiol sodium diphosphate, a vitamin K<sub>4</sub> derivative developed by Roche and approved in 1941 for the prevention of bleeding disorders.<sup>205</sup> Since then, numerous phosphorus-based compounds have entered clinical use, underscoring their continuing importance in modern medicine (Table 2 and Scheme 2).<sup>96</sup> A particularly interesting example is fosazepam<sup>96,194</sup> (Scheme 2, compound 10 and Table 2), a drug belonging to the benzodiazepine class, known primarily for its anxiolytic and sedative-hypnotic effects. Fosazepam is a water-soluble derivative of diazepam, modified by the addition of a dimethylphosphoryl group to increase its solubility in aqueous media (Table 2). Other important examples of phosphine oxide-based drugs include Brigatinib,<sup>96,100,101</sup> (Scheme 2, compound 11 and Table 2) that acts as a dual inhibitor of anaplastic lymphoma kinase (ALK) and the epidermal growth factor receptor (EGFR), making it effective in targeted cancer therapy

**Table 2** Selected phosphorus (with oxidation state) compounds currently in clinical trials or approved for medical use and their properties

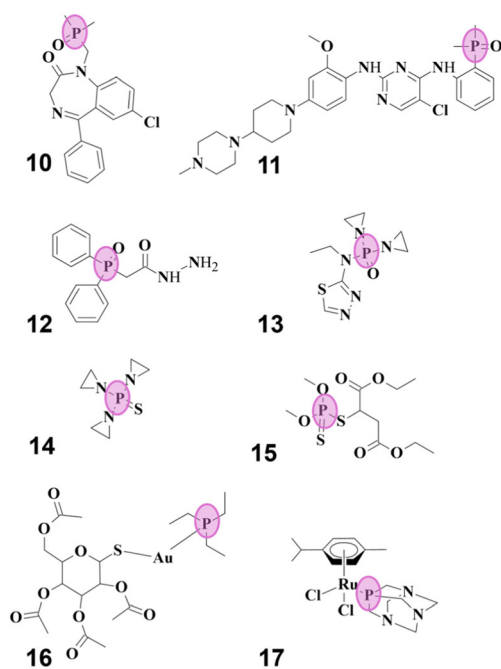
Phosphorous based compound	purpose	Availability, year	Literature
Fosazepam (P <sup>V</sup> ); Scheme 2, compound 10	Anti-anxiety and sedative-hypnotic agent	Approved, 1978	96 and 194
Brigatinib (P <sup>V</sup> ); Scheme 2, compound 11	Small-molecule targeted cancer therapy acting as both an anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR) inhibitor	Approved, 2017	96, 100 and 101
Fosfenazide (P <sup>V</sup> ); Scheme 2, compound 12	Tranquilizer with notable central nicotinic-cholinolytic, antiadrenergic, and antiserotonin effects	Approved, 1986	96 and 195
Azetepa (P <sup>V</sup> ); Scheme 2, compound 13	An anti-cancer drug and a type of alkylating agent that works by damaging and crosslinking DNA, thereby inhibiting cell growth	Approved, 1967	96, 196 and 197
Thiotepa (P <sup>V</sup> ); Scheme 2, compound 14	Treatment of gastrointestinal tumour, mammary, bladder, and ovarian cancer	Approved, 1959	85, 96 and 97
Malathion (P <sup>V</sup> ); Scheme 2, compound 15	Inhibitor of acetylcholinesterase (AChE) for treating head louse	Approved, 1956	84 and 96
Auranofin (P <sup>III</sup> ); Scheme 2, compound 16	Nonsteroidal anti-inflammatory and analgesic drug	Approved, 1985	83, 84 and 96
RAPTA-C (P <sup>III</sup> ); Scheme 2, compound 17	Antimetastatic and cytostatic properties	A Phase I/II trial, 2017	80, 81 and 96

(Table 2) and Fosfenazide,<sup>96,195</sup> (Scheme 2, compound 12 and Table 2) currently prescribed for the treatment of alcohol use.<sup>87,88</sup> Despite the mentioned above phosphorus-containing drugs in medicine and clinical research, numerous examples of inorganic compounds containing P-ligands have been reported in scientific papers (Scheme 2 and Table 2). These compounds exhibit diverse biological properties, including promising anticancer activity, and represent a growing area of interest in inorganic medicinal chemistry. Among the most reported compounds demonstrating anticancer activity are phosphine complexes of copper,<sup>56–68</sup> iridium,<sup>69–76,78–80</sup> ruthenium,<sup>48–55,71,72,75,78,81,206</sup> osmium,<sup>41–44,46,47</sup>

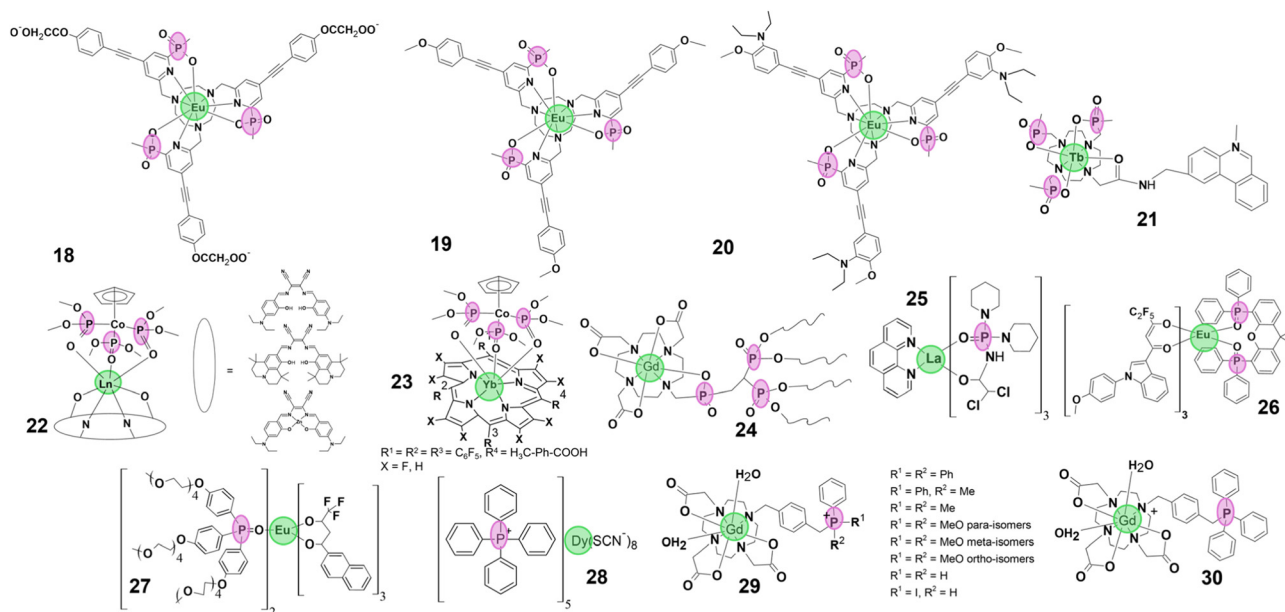
platinum,<sup>33,34,36–40</sup> palladium,<sup>29–32,34,37,38</sup> gold,<sup>19–28,207</sup> and silver.<sup>16–18,208,209</sup> These metal-based complexes have demonstrated promising therapeutic potential due to their ability to interact with biological targets and modulate cellular processes involved in cancer progression but have not yet reached clinical explorations.

#### Lanthanide compounds with phosphorus-containing ligands

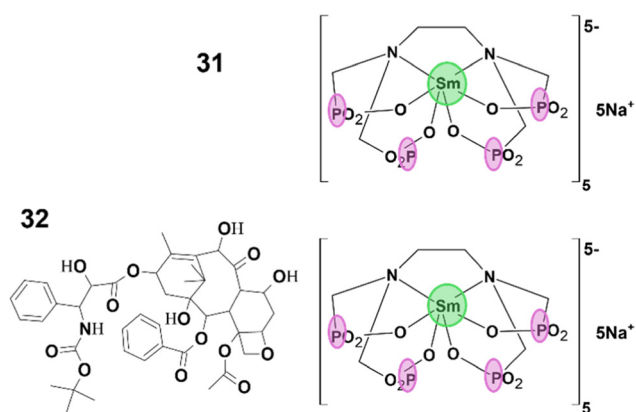
Despite the potential beneficial properties of both lanthanides and phosphorus-based ligands, their combination into coordination compounds remains underexplored, with only a limited number of reported examples. To date, only a limited number of lanthanide complexes with phosphorus-based ligands have been reported in the context of biological applications.<sup>210–218</sup> These include systems containing phosphinates, phosphonates, phosphoramides, phosphonium salts, and phosphine oxides. Lanthanides offer unique photophysical and magnetic properties, such as strong luminescence, MRI-relevant magnetism, and redox/photochemical activity, making them attractive for imaging, photodynamic therapy (PDT), and theranostic applications. Phosphorus-containing ligands (*e.g.*, phosphines, phosphine oxides, phosphonates, phosphonium salts, phosphinates) allow for excellent design control with tunable lipophilicity and charge for cellular uptake, and, in some cases, intrinsic bioactivity or abilities for targeting specific organelles. These features make P-ligands promising tools for the design of functional lanthanide-based anticancer and diagnostic drugs. In this chapter, we briefly discuss representative examples of such complexes, highlighting their structural features and functional significance in imaging, therapy, and theranostics (Scheme 3 and 4). Below we describe reported lanthanide complexes with P-containing ligands organized according to the type of P-ligand that have been tested for their biological properties. We show their structures in Schemes 3 and 4. The major lanthanide complexes reported are found to bind to an oxygen and/or nitrogen atom on the phosphorus, however, a few compounds are isolated as salts



**Scheme 2** Schematic view of selected phosphorus compounds currently in clinical trials or approved for medical use. See Table 2.



Scheme 3 Schematic view of lanthanide compounds with phosphorus-containing ligands.



Scheme 4 Samarium ( $^{153}\text{Sm}$ ) lexidronam.

where there are ionic interactions between the lanthanide and the P-ligand.

**Lanthanide compounds with phosphinates.** Parker and co-workers synthesized a series of Eu(III) complexes (Scheme 3, exemplary compounds 18–20) based on a triazacyclononane or *N*-functionalized 1,4,7-triazacyclononane core containing three pyridylmethylphosphinate groups functionalized with highly absorbing arylalkynyl.<sup>219–221</sup> These complexes demonstrated excellent cellular uptake and distinct subcellular localization, which allowed monitoring of their intracellular distribution by fluorescence microscopy and time-gated spectral imaging.<sup>220,221</sup> Their use as cellular imaging agents was demonstrated by selective staining of mitochondria, lysosomes, and endoplasmic reticulum in various mammalian cell lines.<sup>219</sup> The same group synthesized a variety of cationic terbium complexes (Scheme 3; example compounds 21),

bearing an *N*-methylphenanthridinium chromophore functionalized with three pyridylmethylphosphinate groups as an oxygen bio-sensors.<sup>222,223</sup> Understanding oxygen gradients in biological samples is crucial to understanding many biological processes, including aerobic energy metabolism. This requires the development of sensitive, selective, non-invasive, and real-time detection methods.<sup>223</sup>

**Lanthanide compounds with phosphonates.** Another group of compounds are these synthesized using the tripodal Kläui ligand  $[\text{Na}(\eta^5\text{-C}_5\text{H}_5)\text{Co}\{\text{P}(\text{=O})(\text{OMe})_2\}_3]^{2-}$ .<sup>215,220,222,224,233,234</sup> The synthesis, excited state dynamics, and biological applications of luminescent lanthanide complexes characterized by sandwich-type structures and containing metals such as Ln: Lu(III), Gd(III), Eu(III), and Yb(III), coordinated with salen-type ligands (*N,N'*-bis(salicylidene)ethylenediamine) were described. Importantly, Jun-Long Zhang and coworkers discovered that the Lu(III) complex (Scheme 3, example of lanthanides complexes 22) exhibit extremely intense fluorescence centered around the ligand, with a quantum yield of up to 62%, despite the proximity of the metal center to the chromophoric ligand.<sup>233,234</sup> Importantly, Lu-based compounds have been used as molecular platforms for constructing fluorescent probes with organelle specificity for live-cell imaging. Preliminary *in vivo* imaging studies using a mouse model further demonstrate the potential of lanthanide coordination complexes for bioimaging applications beyond the *in vitro* or cellular environment.<sup>220,223,224,234</sup> Furthermore, the same research group led by Jun-Long Zhang published results on the synthesis of biocompatible Yb<sup>3+</sup> complexes (Scheme 3, example of lanthanides complexes 23) for near-infrared (NIR) live-cell imaging.<sup>225,233,234</sup> They found out that when excited in the visible (Soret band) or red (Q band) range,  $\beta$ -fluorinated Yb<sup>3+</sup> complexes exhibit strong luminescence in the near-infra-

red (NIR), with quantum yields of up to 23% in dimethyl sulfide and 13% in aqueous media. These complexes also exhibit enhanced stability and extended luminescence lifetimes (up to 249 ms) compared to their  $\beta$ -nonfluorinated analogues. This makes  $\beta$ -fluorinated  $\text{Yb}^{3+}$  complexes a promising new class of optical probes for both steady-state and time-resolved fluorescence lifetime imaging. Confocal near-infrared (NIR) fluorescence microscopy revealed strong and specific intracellular  $\text{Yb}^{3+}$  luminescence signals after biocompatible complexes were taken up by living cells.<sup>220,222,225,233,234</sup> In literature we can find more examples of Ln complexes with phosphonate ligands like Gd(III) with bis(phosphonate) containing DOTA analogue (Scheme 3, example compound 24).<sup>217,218</sup> Therefore, it may be concluded that this compound has potential as a positive MRI contrast agent for bone and for other calcified tissues. This complex shows a high affinity for divalent cations resulting in the formation of coordination oligomers and polymers, which is accompanied by a significant increase of the relativity due to the decrease of the molecular tumbling rate. This phenomenon may be applied in the development of *in vitro* and *in vivo* responsive contrast agents for these ions.<sup>218</sup>

**Lanthanide compounds with phosphoramides.** Niloufar Dorosti and research group synthesised La(III) complexes using derivatives of phosphoramides.<sup>216</sup> They obtained two octa-coordinated lanthanum(III) complexes of deprotonated azaphosphor  $\beta$ -diketone and diimine ligands (Scheme 3, example compound 25). Given the potential therapeutic properties of phosphoryl-metal complexes, particularly their anticancer and antibacterial effects, the authors investigated their interactions with DNA to better understand the underlying binding mechanisms and the factors influencing them. These compounds were found to induce secondary structural damage to the DNA double helix. Based on the calculated binding constants, it was further concluded that all complexes exhibited stronger binding affinity for DNA compared to their corresponding free ligands.<sup>216</sup>

**Lanthanide compounds with phosphine oxides.** Next group of lanthanides complexes with phosphorus-based ligands are these containing phosphine oxide ligands. Reddy together with research group reported a novel lysosome targetable luminescent bio-probe derived from a europium coordination compound (Scheme 3, compound 26), namely Eu( $\text{pfpH}_3\text{OCH}_2\text{IN}$ )<sub>3</sub>(DDXPO)<sub>4</sub> [where  $\text{H}_3\text{pfpH}_3\text{OCH}_2\text{IN} = 4,4,5,5,5$ -pentafluoro-3-hydroxy-1-(4-methoxyphenyl)-1*H*-indol-3-yl)pent-2-en-1-one and DDXPO = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene oxide].<sup>215</sup> Therefore, the synthesized europium complex was evaluated for live cell imaging using a mouse preadipocyte cell line (3T3-L1). Colocalization studies using the commercial lysosome-GFP marker confirmed the specific lysosomal localization of the designed bio-probe, obtaining a high colocalization index. Importantly, the bio-probe demonstrated excellent cellular permeability, photostability, and low cytotoxicity, making it a promising candidate for lysosome-targeted imaging applications.<sup>215,220</sup> Another example of lanthanide-phosphine oxide system has been presented by Yasuchika Hasegawa and coworkers.<sup>223,231</sup> They

demonstrated a human cancer grade probing system (GPS) using a new water-soluble and structure-changeable Eu(III) complex for early brain tumour diagnosis (Scheme 3, compound 27). The designed Eu(III) complex, containing  $\beta$ -diketonates with increased atomic number  $\pi$  and triphenylphosphine oxides functionalized with tetraethylene glycol methyl ether, forms micellar aggregates that remain stable in DMEM cell culture medium. The complex demonstrates high cellular activity, characterized by rapid uptake by 3T3-L1 cells, facilitating the transition from aggregated to monomeric forms through changes in the Eu(III) coordination environment. Furthermore, intracellular components can induce further conformational changes in the Eu(III) complex. This structure-responsive luminescent Eu(III) GPS, offers a novel diagnostic strategy for assessing the malignancy of human brain tumors.<sup>214</sup>

**Lanthanide compounds phosphonium salts.** A final group of lanthanide compounds containing phosphorus ligands includes those containing phosphonium salts in their structures. Warner and co-workers have synthesized a particularly intriguing class of multifunctional phosphonium-lanthanide complexes (Scheme 3, example compound 28) that simultaneously exhibit paramagnetic properties, luminescence, and targeted accumulation in tumour mitochondria.<sup>213</sup> The  $\text{IC}_{50}$  values of these compounds, measured against the normal breast cell line Hs578B, were significantly higher than those obtained for the corresponding breast cancer cell line Hs578T, clearly indicating their selective tumour-targeting properties. Furthermore, these compounds demonstrated potential as fluorescence imaging markers in live cell cultures, including human pancreatic cancer (MIAPaCa-2) and human breast cancer (MDA-MB-231) cell lines.<sup>213</sup> Rendina and coworkers synthesised a series of Gd(III) complexes (Scheme 3, example compounds 29 and 30) covalently bounded to arylphosphonium cations possessing a varying degree of delocalisation at the phosphonium centre is presented.<sup>210,211</sup> The effect of electronic delocalization at the phosphonium center was investigated on *in vitro* cytotoxicity, cellular gadolinium (Gd) uptake, tumour cell selectivity, and intracellular localization in human glioblastoma multiforme (T98G) and human glial (SVG p12) cell lines. Cellular uptake and selectivity studies demonstrated that reduced delocalization at the phosphonium center enhanced Gd uptake in SVG p12 cells, thereby reducing overall tumour selectivity. Elemental mapping of the Gd distribution revealed the presence of discrete high-intensity spots, consistent with mitochondrial localization of the complexes.<sup>211</sup> The authors noticed that no significant trends were observed in cell uptake when various phosphonium targeting vectors were used.<sup>210</sup> Selected Gd(III) complexes are potential candidates for further investigation as theranostic agents.<sup>210,211</sup>

One notable example of a lanthanide compound with a phosphorus-containing ligand that has been approved for the treatment of painful metastatic bone disease is <sup>153</sup>Sm-EDTMP (Table 1 and Scheme 4, Quadramet®, compound 31).<sup>226,227,236–238</sup> Samarium-153 EDTMP is a chelated complex of a radioisotope of the element samarium with EDTMP or

ethylenediamine tetra(methylene phosphonic acid). Samarium-153 is produced by neutron irradiation of isotopically enriched  $^{152}\text{Sm}_2\text{O}_3$  in a nuclear reactor. In its soluble ionic form ( $^{153}\text{Sm}^+$ ), the radionuclide has minimal affinity for bone tissue following intravenous administration. However, when chelated with aminophosphonate ligands such as EDTMP,  $^{153}\text{Sm}$  can be efficiently targeted to the skeletal system, allowing its use in bone-targeted therapies.<sup>226–228,235</sup>

Currently in Phase I trial is a  $^{153}\text{Sm}$ -EDTMP (Samarium<sup>153</sup>) combined with docetaxel for patients with hormone-refractory prostate cancer (Table 1, Scheme 4, compound 32).<sup>229</sup> Early clinical trials in patients with metastatic castration-resistant prostate cancer suggested that combining chemotherapy with a bone-targeted radiopharmaceutical may provide improved outcomes compared with chemotherapy alone. To refine this therapeutic approach and incorporate a bone-targeted radiopharmaceutical at repeated doses into a modern chemotherapy regimen, the authors conducted a Phase I trial evaluating the combination of docetaxel and samarium-153 ( $^{153}\text{Sm}$ ) leixidronam.<sup>229</sup>

Integrating phosphorus-containing ligands with lanthanide ions has proven to be a highly effective strategy for developing multifunctional complexes for biomedical applications. These systems exhibit excellent properties, such as organelle-specific fluorescence imaging, oxygen sensing, DNA interaction, and tumour targeting. Notable examples include Eu(III), Lu(III), and Yb(III) complexes with phosphinate, phosphonate, and phosphine oxide ligands, which exhibit high quantum yield, cellular permeability, and photostability. Furthermore, Gd(III) and Sm(III) complexes with phosphorus ligands show promise as contrast agents for magnetic resonance imaging (MRI) and radiopharmaceuticals. The versatility and biocompatibility of phosphorus-based ligands make them ideal for improving the efficiency and specificity of lanthanide-based probes and therapies.

## Conclusion

The combination of lanthanide ions with phosphine ligands represents a promising strategy for the future development of the novel class anticancer drugs. Lanthanides, recognised for their unique electronic configurations and geometries, show electronic and spectroscopic signatures such as luminescence, paramagnetism, and radioactivity, which are extremely beneficial in both diagnostic and therapeutic contexts resulting in compounds with potential theranostics properties. In addition, when combined with phosphorous-based ligands, the resulting complexes gain increased solubility, stability, and biocompatibility which are critical features for clinical applications. However, it is clear from the systems described in this work, the potential of phosphorus(III) ligands remains largely untapped. Specifically, so far there is no example of biologically active lanthanide complexes with metal ion-phosphorus bonds. Phosphorus(III) ligands, such as *e.g.* aminomethylphosphines, trialkylphosphines and arylphosphines, offer

distinct advantages that could open new possibilities in the design of lanthanide-based anticancer drugs and theranostics, where lanthanide ion is coordinated directly to phosphorus from P-ligand:

- The soft donor properties of P(III) enable the stabilization of lanthanides in unusual coordination environments, potentially increasing reactivity and selectivity toward biological targets.
- Greater electronic tunability allows for precise control of ligand–metal interactions, which can be exploited to modulate luminescence, redox reactions, and catalytic activity.
- Improving the lipophilicity and membrane permeability of P(III) ligands can enhance cellular uptake and biodistribution, which is crucial for drug delivery and imaging.
- The potential for conjugation with biomolecules and nanocarriers remains high, enabling targeted delivery and combination therapies.

This opens the door to a wide range of potential anticancer therapeutics, highlighting the following features:

- Lanthanide–phosphine complexes can exert cytotoxic effects through interaction with DNA, redox modulation, or enzyme inhibition with potential cytotoxic properties in chemotherapy.
- Radioactive lanthanides' isotopes such as  $^{177}\text{Lu}$  and  $^{161}\text{Tb}$ , chelated by phosphine ligands, can serve as targeted radiopharmaceuticals capable of delivering radiation to tumour sites.
- The luminescent properties of certain lanthanide complexes enable light-triggered production of reactive oxygen species, selectively inducing apoptosis in tumour cells showing promise in photodynamic therapy (PDT).
- Functionalized phosphine ligands enable conjugation with biomolecules, enabling selective delivery to tumour-specific receptors in targeted drug delivery.
- Lanthanide–phosphorus inorganic compounds can be incorporated into nanocarriers such as liposomes or dendrimers, facilitating their co-administration with other drugs or immunomodulators in various combination therapy platforms.

Given the growing number of lanthanide-based compounds entering clinical trials and the demonstrated therapeutic versatility of phosphorus-containing drugs, combining these two fields offers a promising path to multimodal, personalized cancer treatment. This approach not only overcomes the limitations of conventional therapies but also aligns with the evolving paradigm of precision oncology.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

This is a perspective article based on publications in the literature on the topics of lanthanides and phosphorus containing ligands. No primary research results, software or code, have

been included. Thus, no new data other than the analysis and perspectives described in this manuscript were generated.

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