

A review of responsive MRI contrast agents: 2005-2014

Dina V. Hingorani¹, Adam S. Bernstein,² and Mark D. Pagel^{1,2,3,4}

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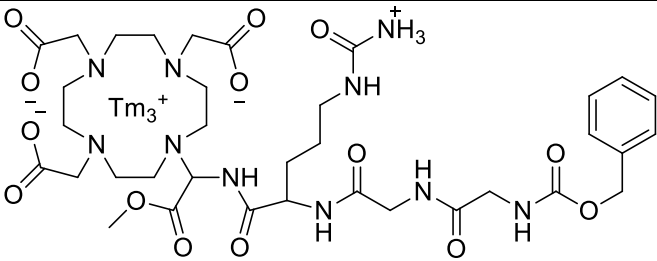
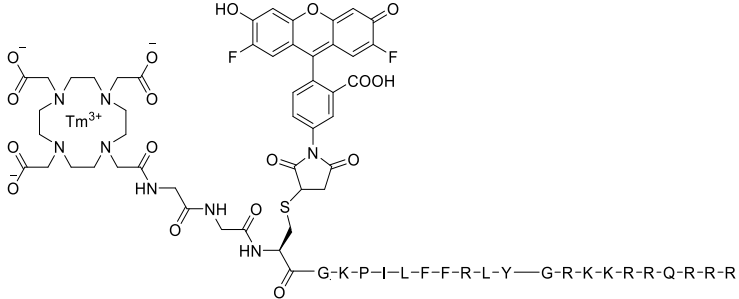
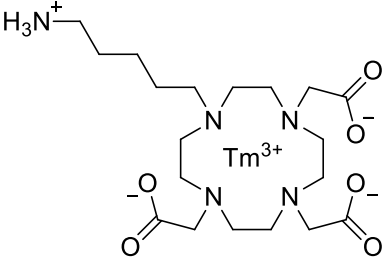
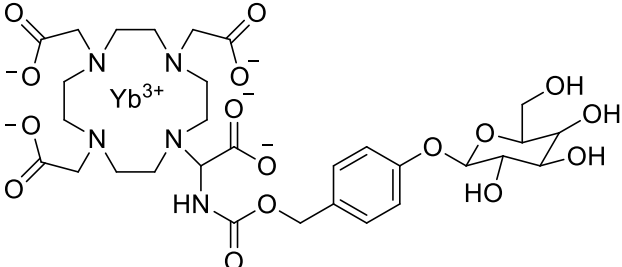
2. Department of Biomedical Engineering, University of Arizona

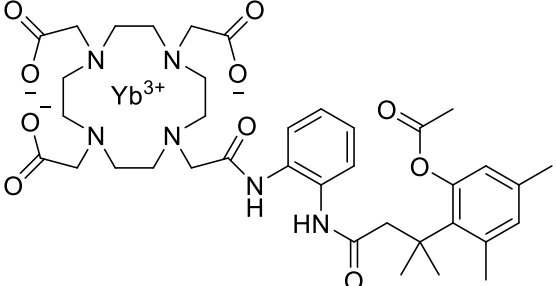
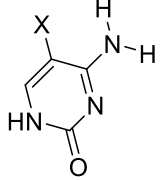
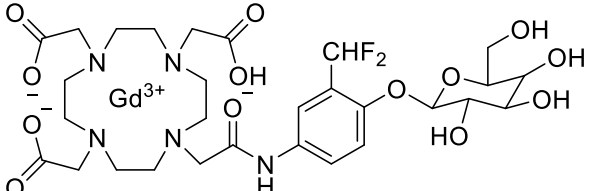
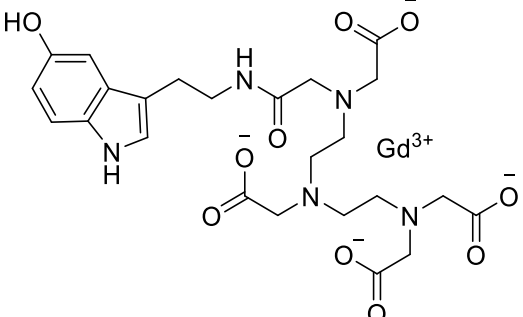
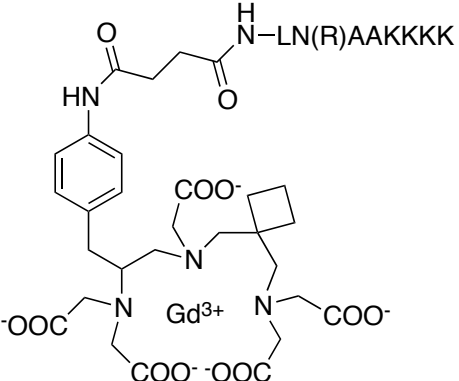
3. Department of Medical Imaging, University of Arizona

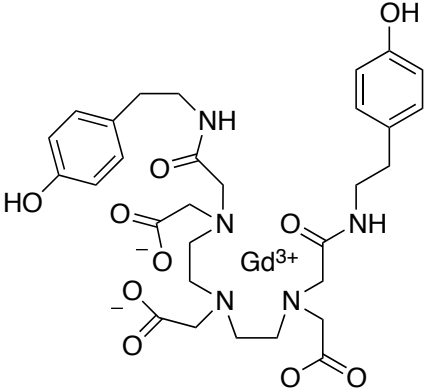
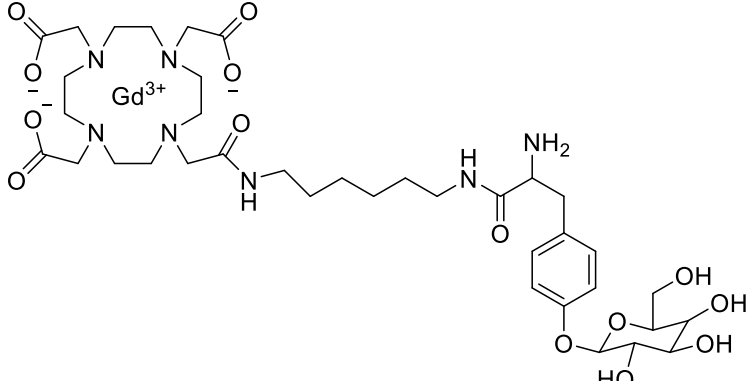
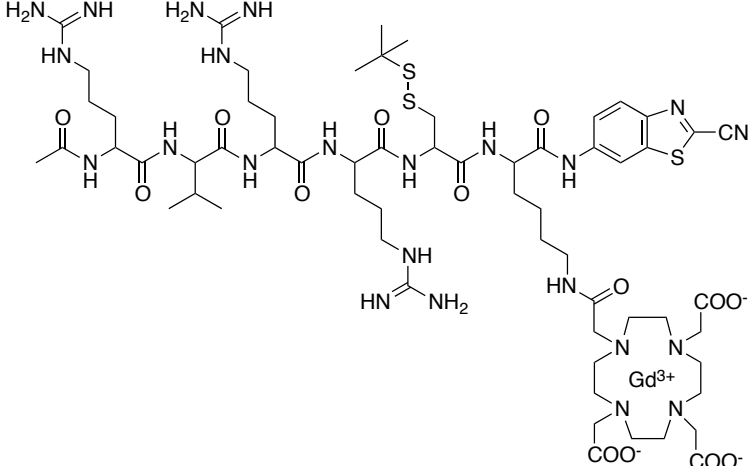
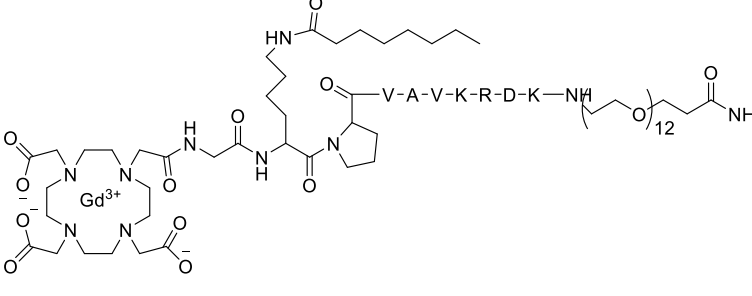
4. University of Arizona Cancer Center, University of Arizona

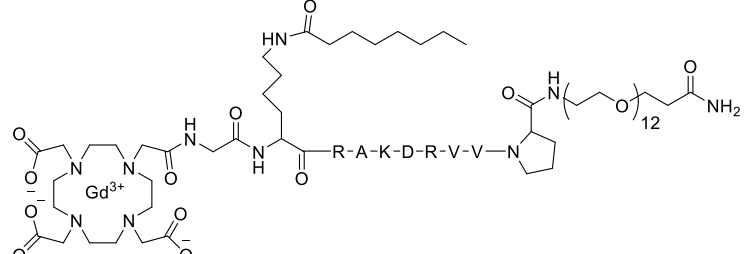
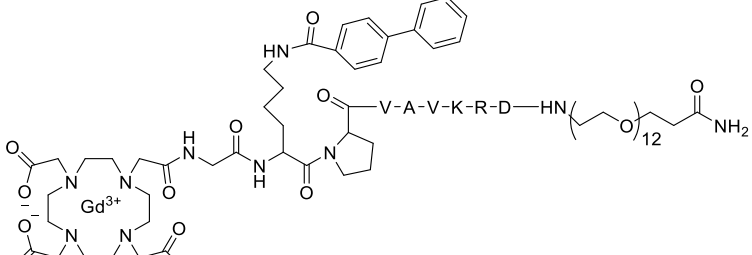
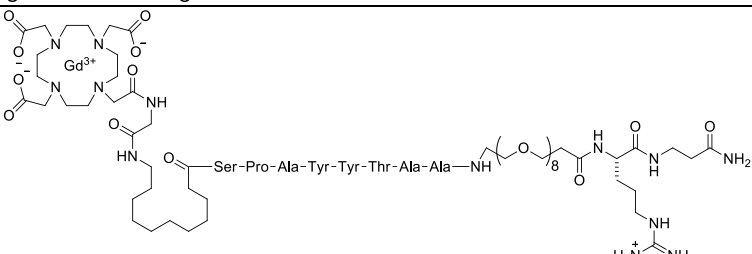
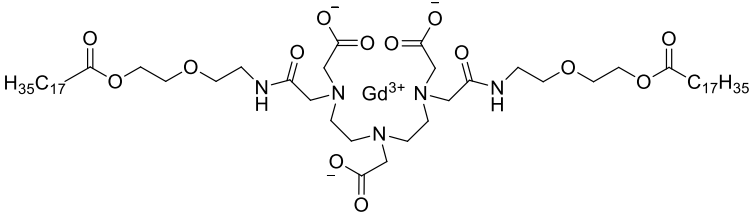
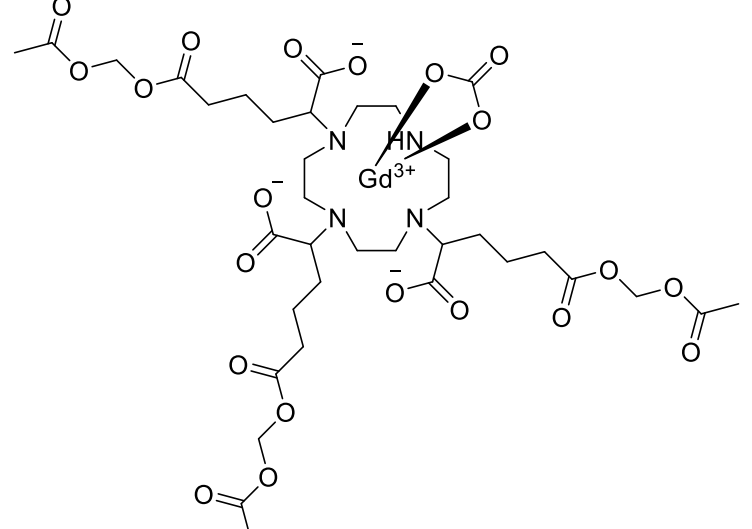
Supporting Information

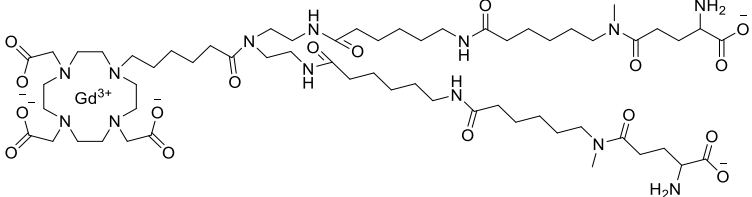
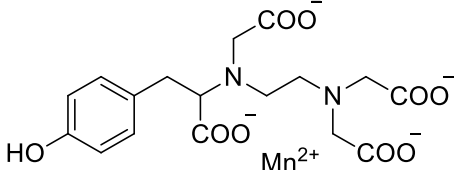
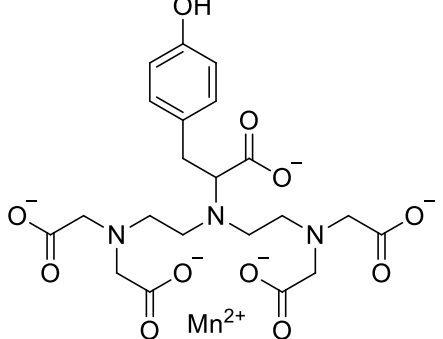
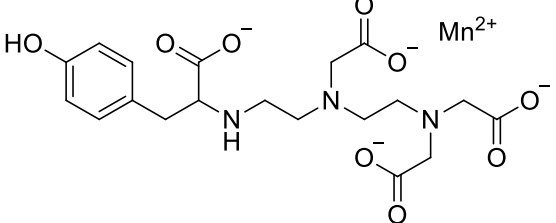
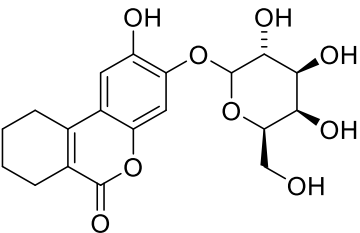
The following table lists the chemical structures, the intended biomarkers, and the references for each responsive MRI contrast agent presented in this review.

Responsive to:	Structure	Reference #:
urokinase-plasminogen activator	 <p>The structure shows a central Tm³⁺ ion coordinated by a 10-membered polyaza macrocyclic ligand with four acetate counterions. A peptide chain is attached to the macrocycle, ending in a benzyl carbamate group.</p>	51,52
cathepsin D	 <p>The structure features a central Tm³⁺ ion coordinated by a 10-membered polyaza macrocyclic ligand with four acetate counterions. A peptide chain is attached to the macrocycle, ending in a fluorinated aromatic group with a hydroxyl and a carboxylic acid substituent.</p>	53
transglutaminase	 <p>The structure shows a central Tm³⁺ ion coordinated by a 10-membered polyaza macrocyclic ligand with four acetate counterions. A long alkyl chain is attached to the macrocycle, ending in a protonated amine group (H₃N⁺).</p>	54
β-galactosidase	 <p>The structure features a central Yb³⁺ ion coordinated by a 10-membered polyaza macrocyclic ligand with four acetate counterions. A galactose sugar moiety is attached to the macrocycle via a benzyl ether linkage.</p>	55

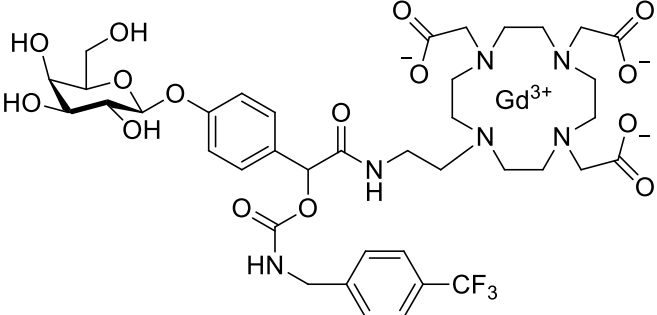
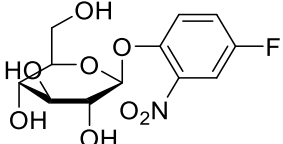
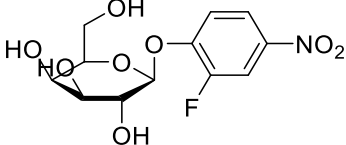
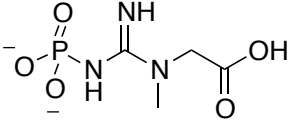
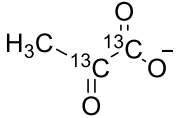
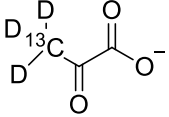
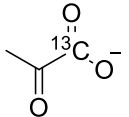
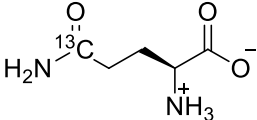
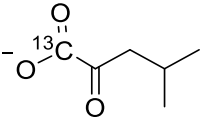
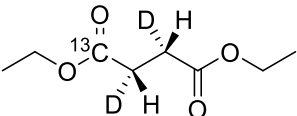
<p>esterase</p>	 <p>The structure shows a Yb³⁺ ion coordinated by a macrocyclic ligand with four nitrogen atoms. Each nitrogen is part of a side chain containing a carboxylate group. One of these side chains is further substituted with a complex organic group, including a benzamide moiety and a branched aliphatic chain with a methyl group.</p>	<p>56</p>
<p>cytosine deaminase</p>	 <p>X = H or F</p>	<p>57</p>
<p>protein kinase A</p>	<p>LRRASLG peptide</p>	<p>58</p>
<p>β-galactosidase, human serum albumin</p>	 <p>The structure shows a Gd³⁺ ion coordinated by a macrocyclic ligand with four nitrogen atoms. Each nitrogen is part of a side chain containing a carboxylate group. One of these side chains is further substituted with a complex organic group, including a benzamide moiety and a fluorinated sugar derivative (CHF₂ group).</p>	<p>59</p>
<p>myeloperoxidase</p>	 <p>The structure shows a Gd³⁺ ion coordinated by a macrocyclic ligand with four nitrogen atoms. Each nitrogen is part of a side chain containing a carboxylate group. One of these side chains is further substituted with a complex organic group, including a hydroxyindole derivative.</p>	<p>60</p>
<p>Legumain</p>	 <p>The structure shows a Gd³⁺ ion coordinated by a macrocyclic ligand with four nitrogen atoms. Each nitrogen is part of a side chain containing a carboxylate group. One of these side chains is further substituted with a complex organic group, including a hydroxyindole derivative and a peptide chain (HN-LN(R)AAKKKK).</p>	<p>61</p>

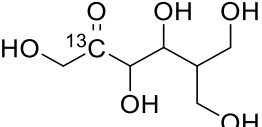
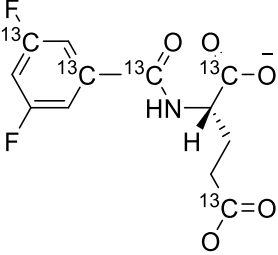
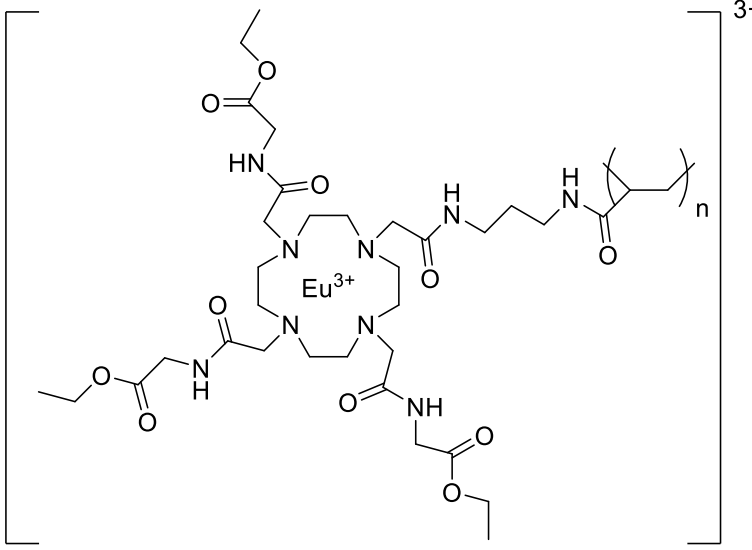
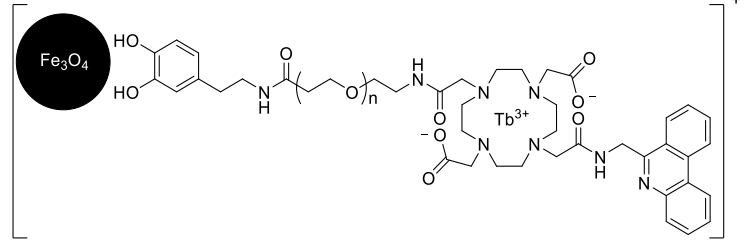
<p>tyrosinase</p>		<p>62</p>
<p>β-galactosidase</p>		<p>63</p>
<p>Furin</p>		<p>64</p>
<p>matrix metalloproteinases</p>		<p>65</p>

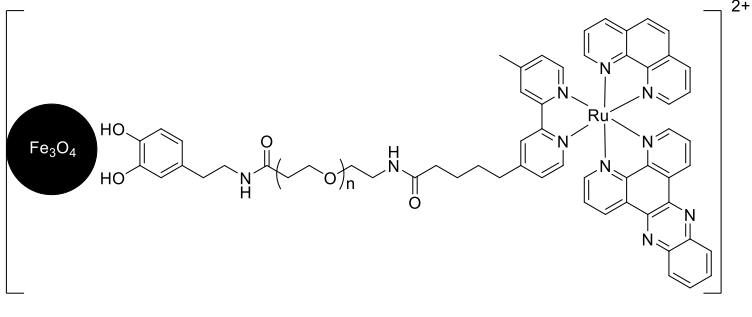
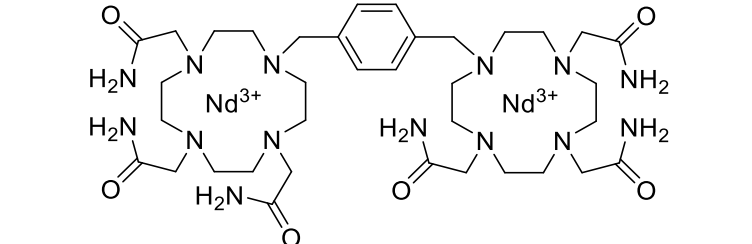
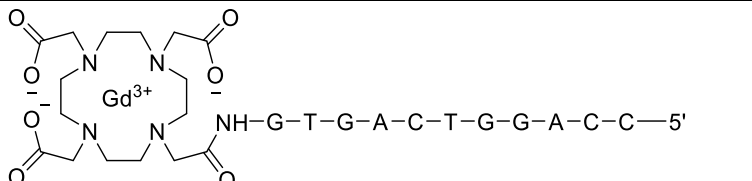
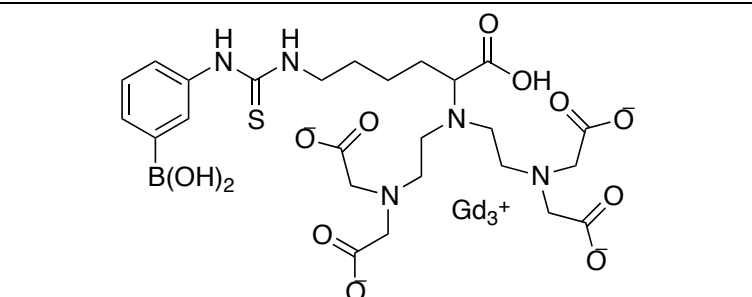
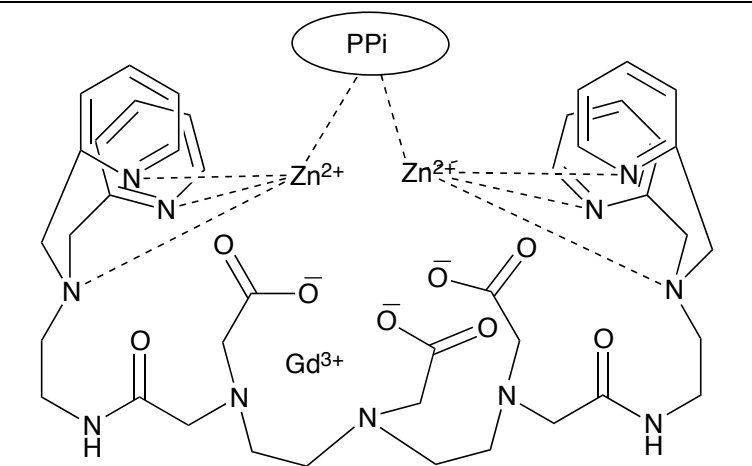
<p>Matrix metalloproteinases</p>		<p>65</p>
<p>Matrix metalloproteinases</p>		<p>65</p>
<p>matrix metalloproteinases</p>		<p>66</p>
<p>lipase</p>		<p>68</p>
<p>esterase</p>		<p>70</p>

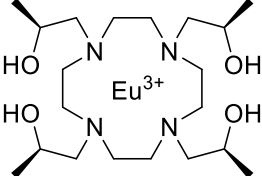
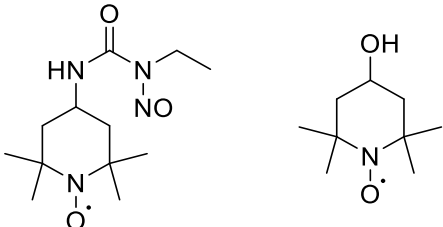
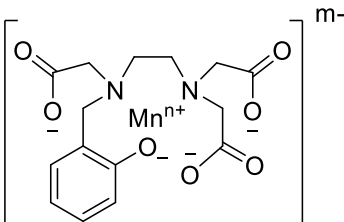
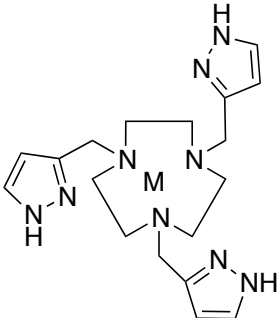
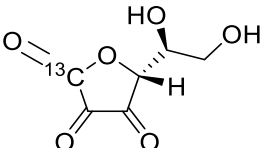
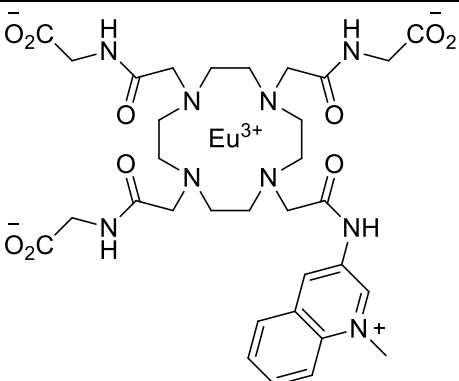
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tyrosinase		72
tyrosinase		72
tyrosinase		72
β-galactosidase		73,74

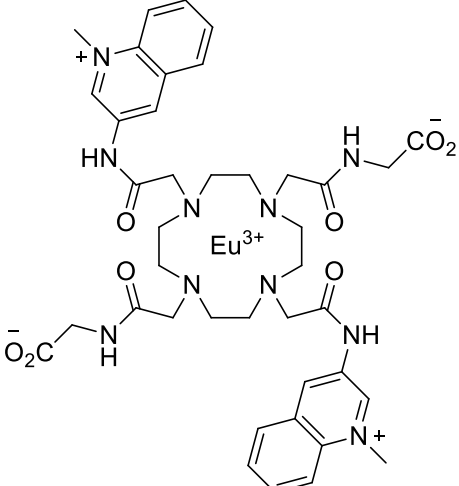
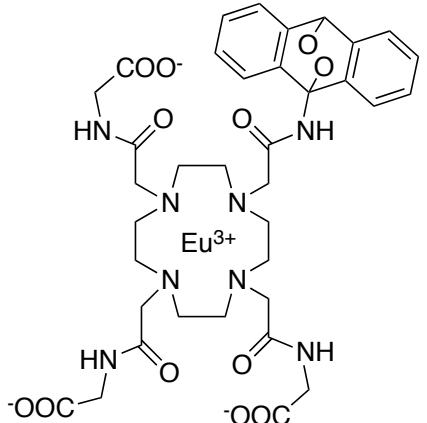
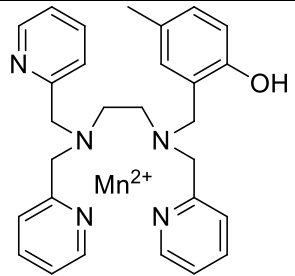
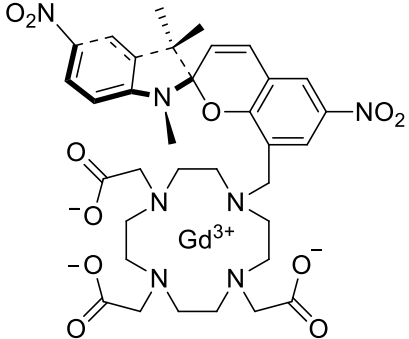
<p>matrix metalloprotease-2</p>		<p>77</p>
<p>secreted alkaline phosphatase</p>		<p>80</p>
<p>caspase-3</p>		<p>82</p>
<p>β-Lactamase</p>		<p>83</p>

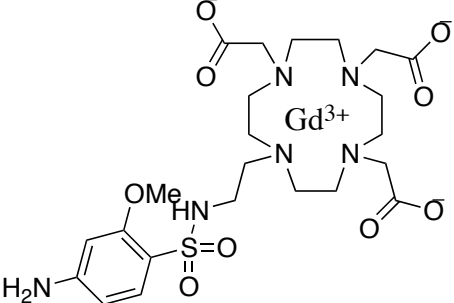
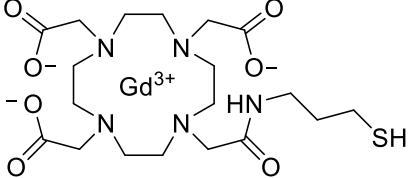
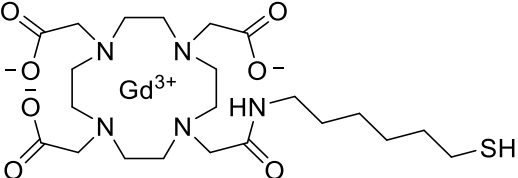
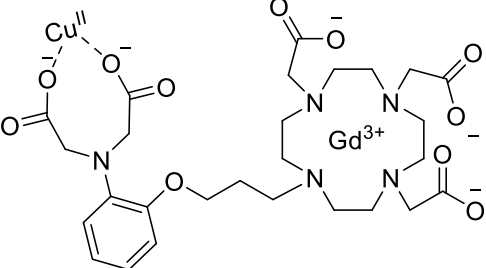
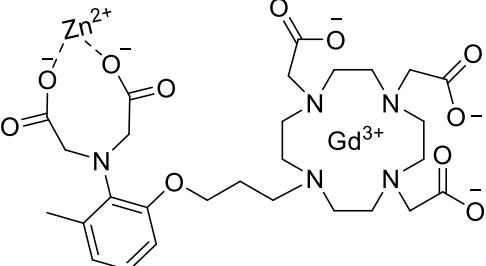
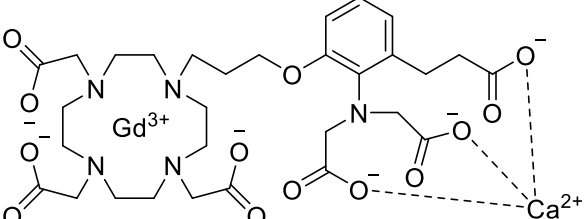
β-galactosidase		84
β-galactosidase		85
β-galactosidase		85
creatine kinase		86
pyruvate dehydrogenase, Krebs cycle metabolism, pH,		87
alanine transaminase		88
carbonic anhydrase, mitogen-activated protein kinase, pyruvate dehydrogenase, lactate dehydrogenase		89-95
glutaminase		96
Branched chain amino acid transaminase		97
succinate dehydrogenase		98

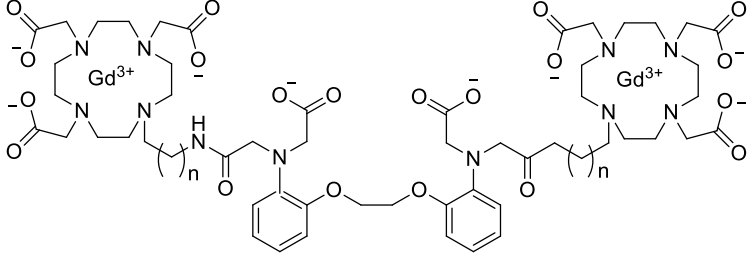
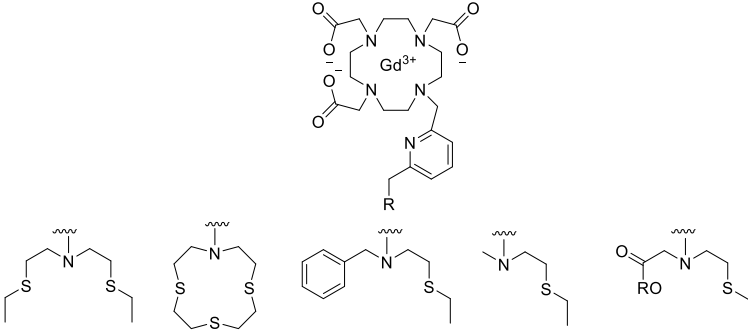
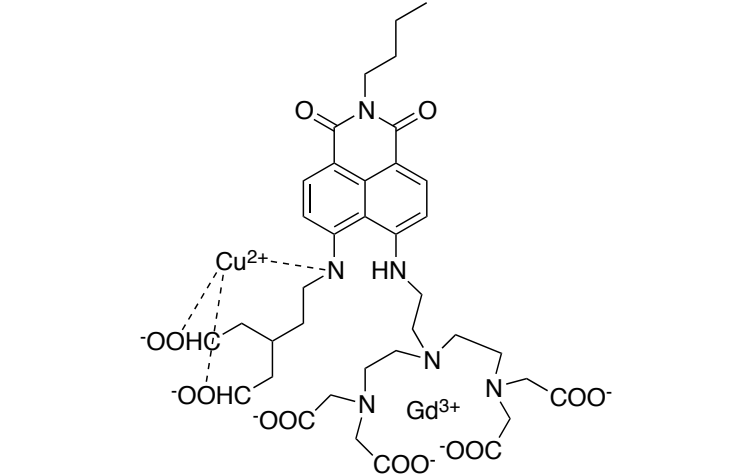
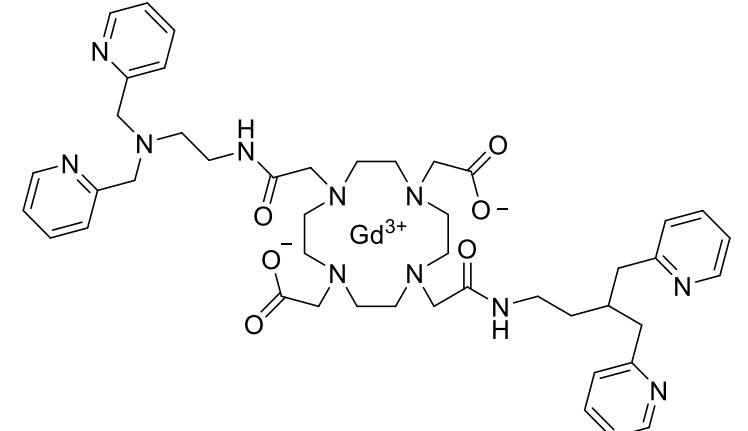
hexokinase		99
carboxypeptidase G2		100
DNA	 <p style="text-align: center;">n = 17 (average)</p>	104
DNA		105

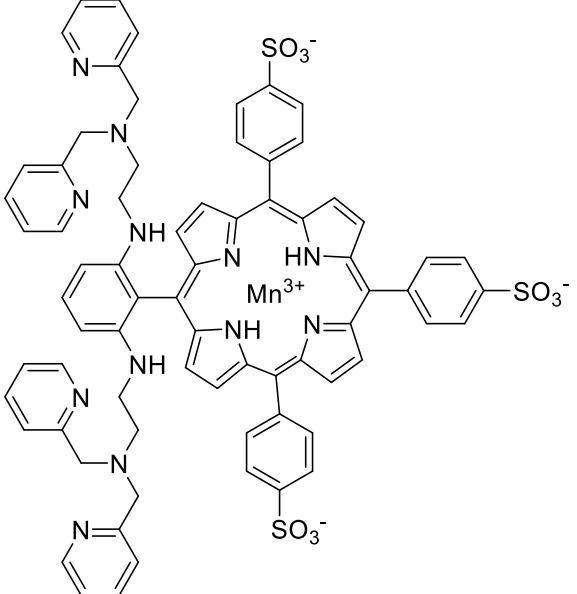
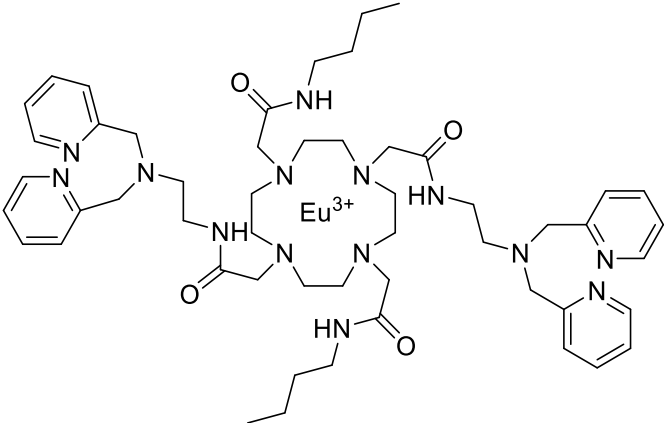
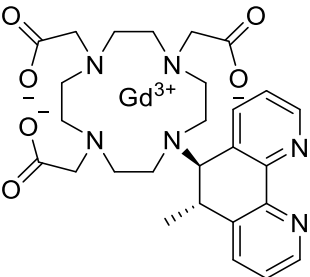
DNA	 <p>The structure shows an Fe_3O_4 nanoparticle (black circle) attached to a polymer chain. The polymer chain consists of a hydroxybenzyl group, a poly(ethylene glycol) (PEG) linker of length n, and a terminal amide group. This amide group is linked to a complex ligand system that includes a Ruthenium (Ru) center coordinated to two terpyridine-like ligands and a phenyl ring.</p>	105
DNA	 <p>The structure shows two Nd³⁺ ions coordinated to two separate macrocyclic ligands. Each macrocycle has four nitrogen atoms and two amide groups. The two macrocycles are linked together via a central phenylene ring.</p>	106
adenosine	 <p>The structure shows a Gd³⁺ ion coordinated to a macrocyclic ligand with four nitrogen atoms and four amide groups. The ligand is attached to a DNA strand at the 3' position, with the sequence NH-G-T-G-A-C-T-G-G-A-C-C-5'.</p>	107
carbohydrates	 <p>The structure shows a Gd³⁺ ion coordinated to a macrocyclic ligand with four nitrogen atoms and four amide groups. The ligand is attached to a DNA strand at the 3' position, with the sequence NH-G-T-G-A-C-T-G-G-A-C-C-5'. A boronic acid group (B(OH)₂) is also present, which can interact with the DNA strand.</p>	119
pyrophosphate	 <p>The structure shows a Gd³⁺ ion coordinated to a macrocyclic ligand with four nitrogen atoms and four amide groups. The ligand is attached to a DNA strand at the 3' position, with the sequence NH-G-T-G-A-C-T-G-G-A-C-C-5'. Two Zn²⁺ ions are coordinated to the DNA strand, and a pyrophosphate (PPi) group is coordinated to both Zn²⁺ ions.</p>	120

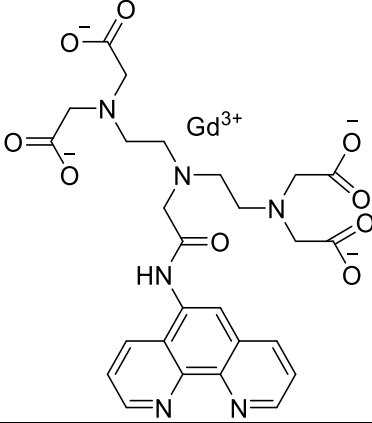
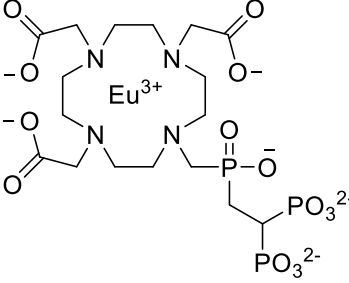
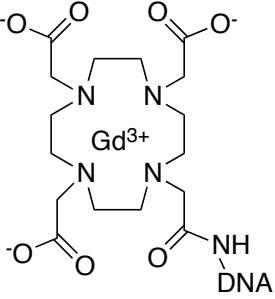
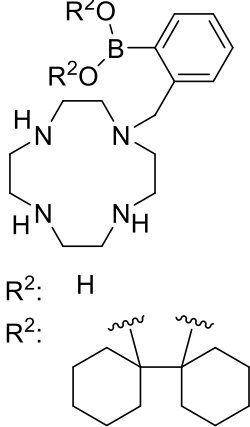
phosphate esters		123
Redox State		126
Redox State		127
Redox State	 <p data-bbox="755 1228 950 1270">M= Co²⁺ or Co³⁺</p>	128
Redox State		129
Redox State		131

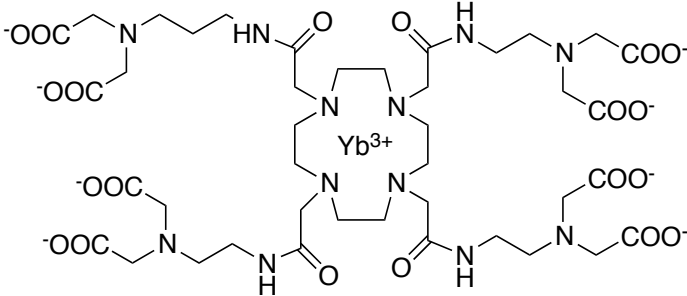
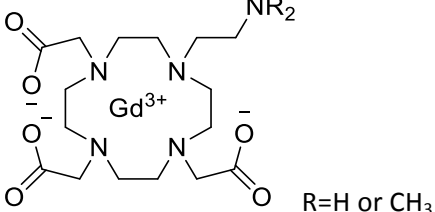
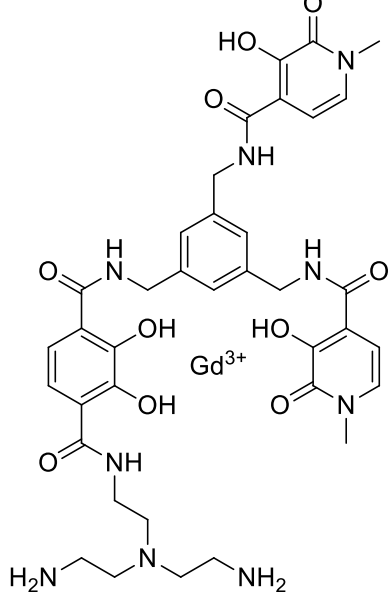
Redox State		131
Redox State		132
hydrogen peroxide		133
Visible Light, Redox State, Temp		134

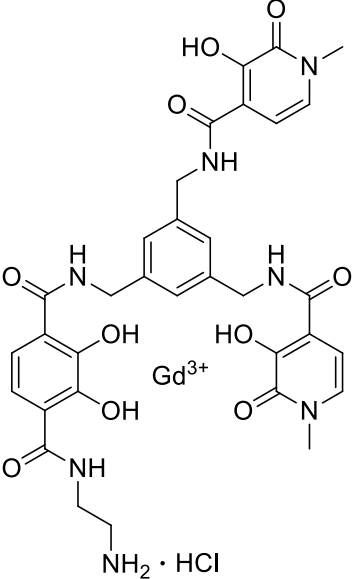
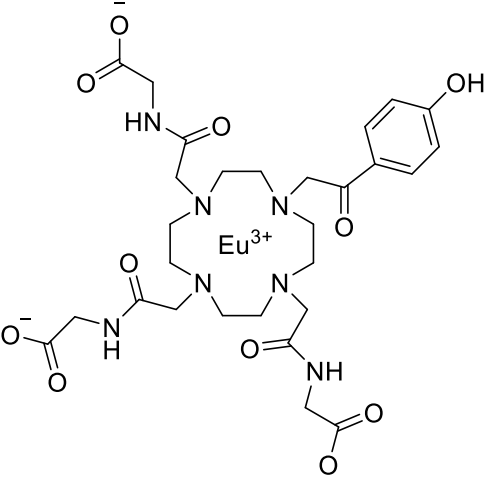
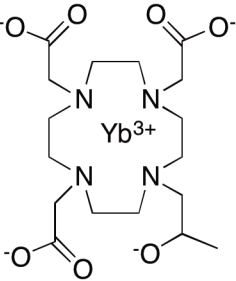
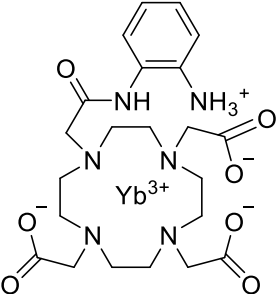
Redox State		135
Redox State		137
Redox State		137
copper ions		141
zinc ions		142
calcium ions		143

calcium ions	 <p style="text-align: center;">$n = 1 \text{ or } 2$</p>	144
copper ions		145
copper ions		146
zinc ions		147

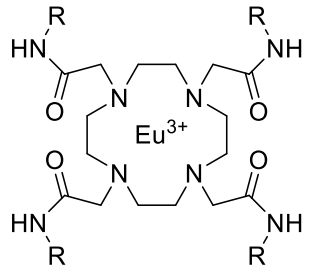
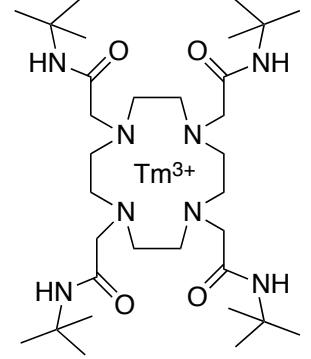
zinc ions		149
zinc ions		150
manganese ions		151

iron ions		152
calcium and magnesium ions		153
uranium ions		154
Metal ions	 <p>R²: H</p> <p>R²:</p>	156

calcium ions		157
pH		169
pH		170

pH		170
pH		171
pH		172
pH		173,174

pH		175
pH		176
pH		177
pH		178
pH		46
Temperature	<p>R = H or CH₂COO⁻</p>	184

	Ln = Dy or Eu	
Temperature	 <p>R = Glycine or Glycine-Phenylalanine</p>	185
Temperature		186