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P792: a rapid clearance blood pool agent for magnetic resonance imaging: preliminary results

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Abstract

An original MRI contrast agent, called P792, is described. P792 is a gadolinium macrocyclic compound based on a Gd-DOTA structure substituted by hydrophilic arms. The chemical structure of P792 has been optimized in order to provide (1) a high r_1 relaxivity in the clinical field for MRI: 29 $mM^{-1} \times s^{-1}$ at 60 MHz, (2) a high biocompatibility profile and (3) a high molecular volume: the apparent hydrodynamic volume of P792 is 125 times greater than that of Gd-DOTA.

As a result of this high molecular volume, P792 presents an unusual pharmacokinetic profile, as it is a Rapid Clearance Blood Pool Agent (RCBPA) characterized by limited diffusion across the normal endothelium.

The original pharmacokinetic properties of this RCBPA are expected to be well suited to MR coronary angiography, angiography, perfusion imaging (stress and rest), and permeability imaging (detection of ischemia and tumor grading). Further experimental imaging studies are ongoing to define the clinical value of this compound.

Keywords: MRI blood pool contrast agent; Gadolinium macrocycle; Chemistry; Relaxivity; Pharmacokinetics; Acute toxicity

1. Introduction

In addition to classical anatomical imaging of the human body, new accurate morphological (such as quantification of stenoses) and functional (such as quantification of perfusion or permeability in pathological tissues) data will probably play a pivotal role in modern diagnostic medicine [1].

Clinically approved nonspecific agents (NSA) present a major drawback in these new anatomical and functional applications because of their massive and rapid extravasation in the interstitial space [2]. The pharmacokinetic behavior of NSA (Fig. 1a), characterized by unrestricted interstitial diffusion and urinary excretion [3], limits their potential for MR coronary angiography, perfusion and permeability imaging. This drawback can be overcome by the development of Blood Pool Agents (BPA) characterized by limited or even no diffusion across the vascular endothelium [4,5].

However, establishing an optimal balance between blood residence time and imaging time constitutes a key issue in each clinical indication, especially with the development of ultrafast MR imaging. The pharmacokinetic concepts underlying the selection of a BPA adapted to each clinical indication may, therefore, lead to the development of different classes of intravascular agents [5–8].

Various categories of BPA are currently under investigation [5,7,8].

- Low Diffusion Agents (LDA): this original category corresponds to compounds, which can diffuse through the vascular endothelium but at a much lower rate than NSA (Fig. 1b), with free renal excretion [7,8]. Two LDA have been described, P760 [2,7,8] and MNS 60 [9].
- Rapid Clearance Blood Pool Agents (RCBPA): characterized by a limited or an absence of diffusion across normal endothelium (and consequently a limited volume of distribution), while their clearances

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are equivalent to the glomerular filtration rate (Fig. 1c) [7,8]. This category of RCBPA includes P775 [7] and Gadomer 17 [10–12].

- Slow Clearance Blood Pool Agents (SCBPA): these compounds are confined to the blood compartment, but their renal clearance is restricted (Fig. 1d). Such categories include gadolinium chelates bound covalently [13] or reversibly [14,15] to albumin, ultrasmall iron particles [6,16], and macromolecular agents [17–20].

In this article, we describe P792, a new RCBPA. The main chemical, physicochemical and toxicological properties of this monogadolinium chelate are presented to provide a brief overview of this new MRI contrast agent.

2. Materials and methods

2.1. Reference products

Gd-DOTA (0.5 M Dotarem®, Guerbet France) was used as reference product.

2.2. Chemical synthesis of P792

Two distinct routes to obtain P792 were used.

2.2.1. Route A

About 0.47 g of gadolinium oxide were introduced into a 30 ml aqueous solution of 2 g of a tetracarboxylated substituted gadoteric acid derivative (compound **1**, Fig. 2) at pH 5.5–6. After mixing at 80°C during 3 h, the crude mixture was precipitated in ethanol to obtain the gadolinium complex 2. Then 1.6 g of this gadolinium complex were introduced into 25 ml of water containing 10 g of the amino derivative (compound **3**, Fig. 2). Also 18 ml of dioxane and 1.4 g of 1-(3-dimethylaminopropyl)-3 ethylcarbodiimide were then introduced. After mixing for 2 h, the crude mixture was precipitated in 100 ml of ethanol. After purification and ultrafiltration on a 5 kDa membrane (Filtron®), 4 g of P792 (compound **4**, Fig. 2) were obtained.

2.2.2. Route B

About 0.17 g of the tetracarboxylated compound **1** (Fig. 2) was introduced into 8 ml of water containing 1.3 g of the amino derivative (compound **3**, Fig. 2) and the pH was adjusted to 5. Then 16.2 mg of 1-hydroxybenzotriazole, 200 mg of 1-(3-dimethylaminopropyl)-3 ethylcarbodiimide, and 7 ml of dioxane were introduced. After mixing for 5 h, the crude mixture was precipitated in 25 ml of ethanol. After filtration, 1.2 g of crude product was obtained. This product was purified by preparative HPLC (Purospher®, C_{18}, 120 Å, H_2O/CH_3CN) to yield 0.25 g of pure product 5. Also 52 mg of compound **5** and 4 mg of gadolinium chloride hexahydrate in aqueous solution were heated at 50°C during 2 h at a pH of 5.2 to obtain P792 after concentration.

2.3. Formulation

The P792 sodium salt solution was adjusted to a concentration of 34–38 mM and formulated with mannitol to achieve an osmolality equivalent to that of plasma (300 mOsm/kg), pH = 7.4.

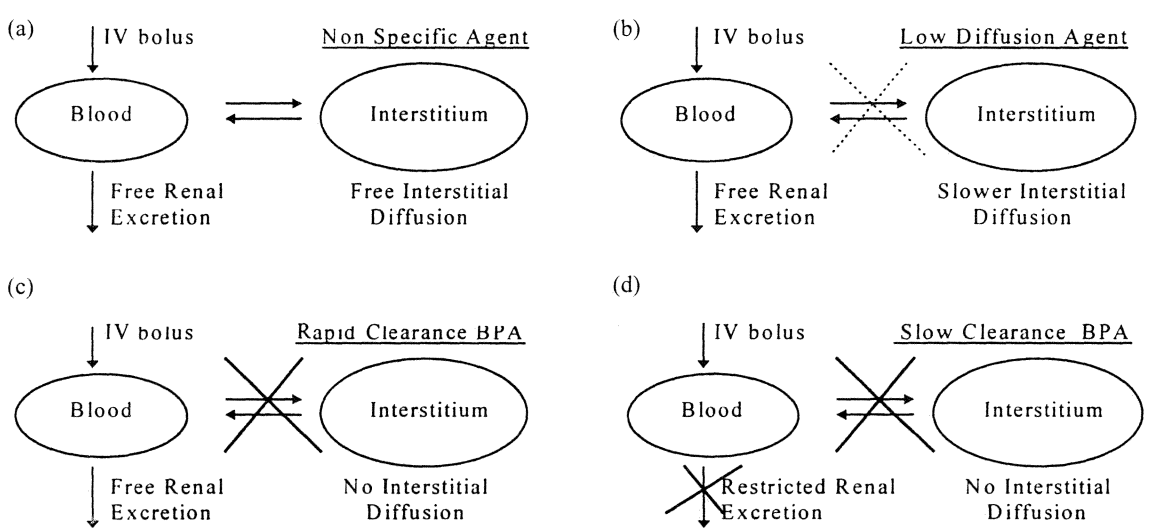

Fig. 1. Schematic compartimental pharmacokinetic representation of different classes of contrast agents: (a) Non Specific Agent (NSA example, Gd-DOTA), (b) Low Diffusion Agent (LDA example, P760), (c) Rapid Clearance Blood Pool Agent (RCBPA example, P792), (d) Slow Clearance Blood Pool Agent (SCBPA example, P717).

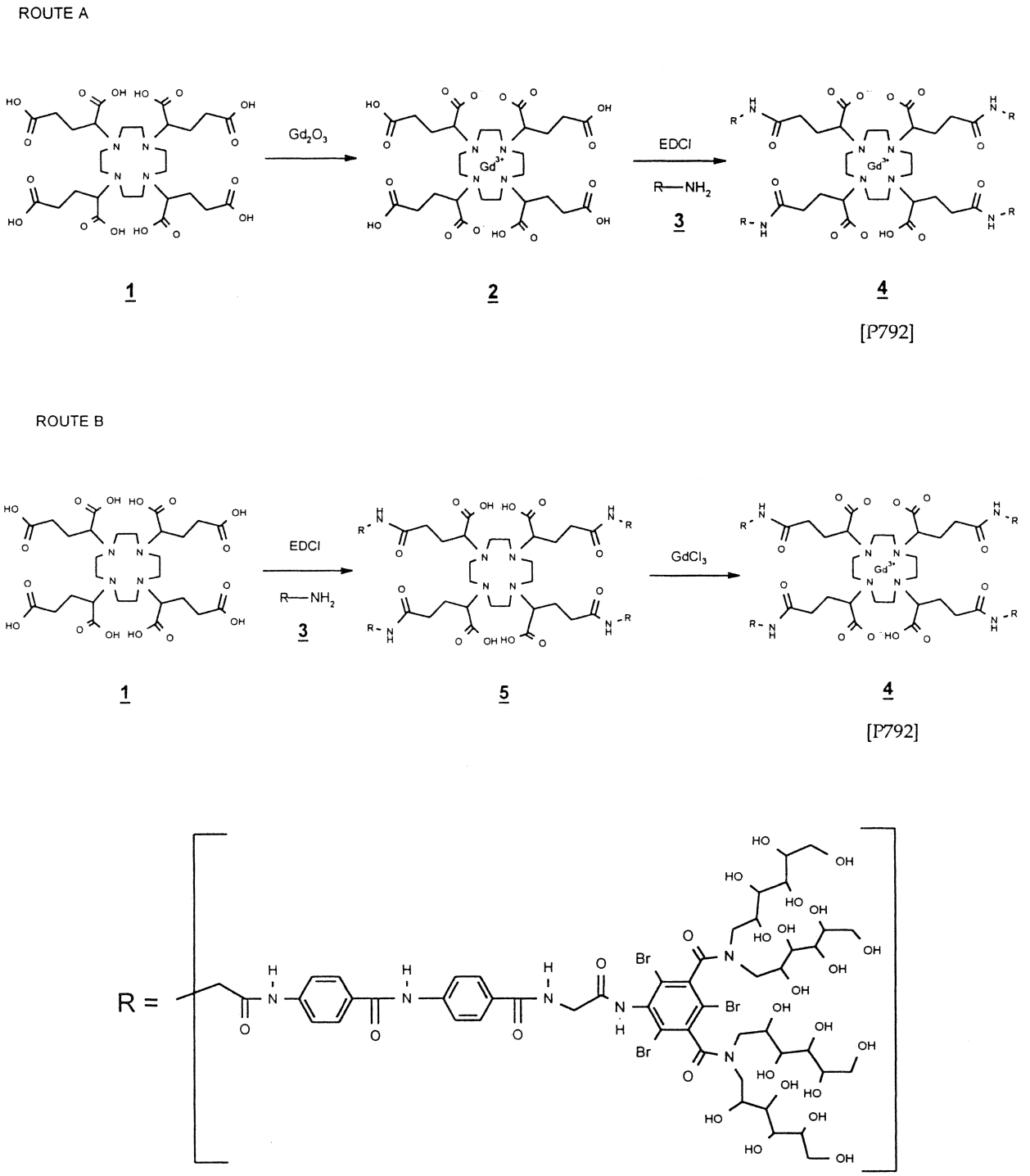

Fig. 2. Chemical synthesis of P792.

2.4. Physicochemical characterization of P792

2.4.1. Mass spectrometry

Electrospray Ionization Mass Spectrometry (ESI-MS) analysis was performed with a Quatro II mass spectrometer (Micromass, Manchester, UK). Acquisition and processing of raw data were performed with MassLynx software. Ten scans (15 s per scan) were acquired in negative mode over the mass range (m/z) 500–2000.

2.4.2. HPLC experiments

The HPLC analytical profile of P792 was obtained using a Waters or Hewlett Packard system with diode

array detectors, on a column (250 × 4.6 mm) with a C_{18}-5 μm stationary phase (Platinum® EPS-Alltech), $\lambda = 230$ nm with gradient elution at a flow rate of 1 ml/min. The mobile phase consisted of [H_2O] and [CH_3CN].

2.4.3. Relaxivity measurements

Water proton relaxation measurements were performed with a Bruker Minispec PC 120 instrument (Bruker, France) at 20 MHz (0.47 T), 37°C, pH 7.4, on solutions with a concentration range between 0.1 and 0.8 mM in sterile water. Spin-lattice relaxation times, T_1, were measured by the usual inversion-recovery method [21]. Relaxivities, r_1, were calculated from the slope of the regression line of $[1/T_1^p]$ (s^{-1}) versus concentration (mmol/l) with a least-squares method. Experiments at 60 MHz were performed with an experimental relaxometer using a concentration of 1 mM.

2.5. Animal studies

All studies were performed in strict accordance with the European Economic Community Directive (86/609/EEC) on animal welfare.

2.6. Pharmacokinetics and biodistribution

2.6.1. Plasma pharmacokinetics of P792 in rats

Anesthetised rats (Sprague–Dawley) received an intravenous (i.v.) bolus injection of either P792 ($n = 2$) at a dose of 13 μmol/kg (corresponding to the expected clinical dose) or Gd-DOTA ($n = 2$) at a dose of 0.1 mmol/kg. Blood samples were taken from the caudal artery at different time-points for 120 min. Pharmacokinetic data were analyzed on Siphar/win software (Simed S.A.). Elimination half-life (T1/2), volume of distribution (Vd), and clearance (Cl) were determined. To compare the pharmacokinetic parameters of the two products, concentrations were divided by the theoretical plasma concentration C0 (considered to be the injected dose instantaneously homogenized in the plasma compartment of 40 ml/kg).

2.6.2. Rat biodistribution studies

The biodistribution of P792, 1 and 7 days post-injection, was assessed by gadolinium assays in urine, faeces, lymph nodes, and liver. Six male rats (Sprague–Dawley) were kept in metabolic cages and received a caudal i.v. bolus of P792 at a dose of 50 μmole/kg. Three rats were sacrificed at 24 h and the remaining three rats were sacrificed at 7 days. Results are expressed as the percentage of the dose injected.

2.6.3. Gadolinium assays

Total gadolinium concentrations in these animals were determined by ICP-AES (Perkin Elmer-Optima 3300 RL). Hematocrits were measured on each sample to take into account hemodilution caused by collection of numerous blood samples. The plasma levels determined were then corrected for variations of hematocrit.

Table 1
Relaxivities of P792 in water, 37°C at 20 and 60 MHz

Magnetic field	Relaxivity ($mM^{-1} \times s^{-1}$)
20 MHz	$r_1 = 39.0 \pm 1.5$
60 MHz	$r_1 = 29.0 \pm 1.0$

2.7. Acute toxicity studies

2.7.1. Intracerebral injection

Male mice (Swiss OF1, Iffa Credo) were anesthetized and received a slow injection over several seconds using three different doses. Mice (five per dose) were housed together with free access to food and water and were observed for 1 week. For ethical reasons, a small number of animals were selected in order to obtain an approximated evaluation of the acute toxicity. The lethal dose 50% (LD_{50}) was calculated according to Reed and Muench [22].

2.7.2. Intravenous injection

Conscious mice received an i.v. injection of the test substance in the caudal vein at a rate of 2 ml/min. A geometric progression of three doses was injected. The maximal volume able to be injected in mice was 50 ml/kg (large volume has been already used for the evaluation of acute toxicity of contrast media in mice) [23]. Male mice (five per dose) were housed together with free access to food and water and were observed for 1 week. The lethal dose 50% was calculated according to Reed and Muench [22].

The Safety Index was calculated as the ratio of the i.v.-LD_{50}/clinical dose (0.013 mmol Gd/kg for P792 and 0.1 mmol Gd/kg for Gd-DOTA).

3. Results

P792 is obtained by a peptidic-type coupling onto a tetracarboxylic substrate derived from Gd-DOTA (Fig. 2).

Optimization of the chemical conditions resulted in a monodispersed compound. The structure of P792 is characterized by the mass spectrum (Electrospray Ionization, negative mode), characteristic masses $m/z =$ 1617 and 1293 (molecular mass of P792, 6473 g/mol).

The r_1 relaxivities measured in water, at two magnetic fields (20 and 60 MHz) are indicated in Table 1.

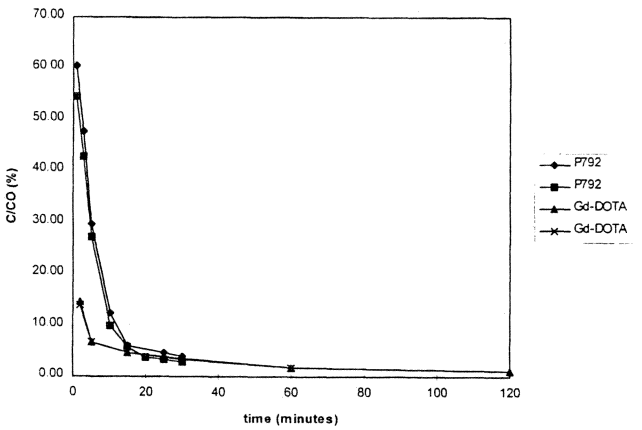

Fig. 3. Plasmatic pharmacokinetic profiles of P792 versus Gd-DOTA in rats.

Table 2
LD_{50} i.v. and i.c. of P792 in comparison to Gd-DOTA

	P792	Gd-DOTA
i.v.-LD_{50} mmol/kg	>1.88	13.1
Safety index	>144	131
i.c.-LD_{50} mmol/kg	0.19	0.25
Safety index	14.6	2.5

The pharmacokinetic profiles of P792 compared with Gd-DOTA in rats are illustrated in Fig. 3. The plasma P792 concentration, standardized to the theoretical plasma concentration C0, was significantly higher than the Gd-DOTA concentration during the first 10 min post-injection, the C5/C0 ratio of P792 (29%) was threefold higher than that of Gd-DOTA (7%). The elimination half-life, steady-state volume of distribution and total clearance (Table 3) were determined from analysis of the pharmacokinetic curves (no statistical analysis was performed in view of the small number of animals).

The biodistribution results at 24 h and 7 days in rats showed that the predominant route of elimination is the kidneys (Table 4).

Acute toxicity results are indicated in Table 2. No mortality was observed following i.v. injection of the maximum injectable volume (50 ml/kg) for P792 and the i.v. LD_{50} could, therefore, not be determined (> 1.88 mmole/kg). The i.c. LD_{50} of P792 was similar to that of commercially available non-specific agents [24].

4. Discussion

P792 is a derivative of the polyaminocarboxylic macrocycle Gd-DOTA substituted by very large hydrophilic arms on nitrogen atoms.

The Gd-DOTA macrocycle was selected because of its excellent kinetic stability [25] and thermodynamic properties [26–28], as well as its relaxometric properties particularly adapted to the preparation of products with a high relaxivity [29]. The structure of this new DOTA type of molecule has been studied in detail by NMR and crystallography [30]. The specific structure of the hydrophilic arms results in an optimization of the molecular volume and biocompatibility of the prototype.

The usefulness of the convergent method of synthesis of P792 is illustrated by the acquisition of a monodispersed compound with a high molecular mass.

The r_1 relaxivity of P792 at 20 MHz is very high (39 $mM^{-1} \times s^{-1}$ in water) compared with that of Gd-DOTA (3.5 $mM^{-1} \times s^{-1}$ at 20 MHz) [31]. However, an even more interesting finding was the very high relaxivity at 60 MHz (clinical imager fields) in pure water (Table 1), 29 $mM^{-1} \times s^{-1}$.

The high relaxivity of P792 in pure water is probably due inpart to the choice of the Gd-DOTA skeleton, which gives P792 an appropriate electronic relaxation time [29,32], and by its increased molecular weight, which induces slowing of the rotational movement in solution (increased rotational correlation time t_R) [7,24,33].

The pharmacokinetic study in rats confirmed that P792 is a RCBPA (Fig. 3, Table 3). The normalized plasma concentration from 0 to 10 min is much higher than that of Gd-DOTA (at time 5 min post-injection, the plasma P792 concentration was three times higher than that of Gd-DOTA) reflecting compartmentalization of P792 in the vascular space, while the decrease of this plasma concentration reflects unrestricted glomerular filtration. These data are confirmed by the parameters obtained by modeling of these pharmacokinetic curves. The volume of distribution of P792 is limited compared with that of Gd-DOTA, while the total clearance of P792 is equivalent to that of Gd-DOTA. This demonstrates that the increased molecular volume of P792 considerably limits its diffusion across the vascular endothelium without decreasing its glomerular filtration.

Table 3
Pharmacokinetic parameters of Gd-DOTA and P792 in rats

Product	Animal number	C_5/C_0 (%)	T 1/2 (min)	Vd (ml/kg)	Cl (ml/min/kg)
P792	1	30	26	151	4
	2	27	14	118	6
Gd-DOTA	$n=2$	7	36	269	6.7

Table 4
Biodistribution of P792 in rats at 24 h and 7 days

	Urine (%)	Feces (%)	Lymph nodes (%)	Liver (%)	Total (%)
24 h	83	2	0.58	4.2	90
7 days	93	8	0.18	1.9	103

Hepatic retention was low (1.9% at 7 days) and the exact site of P792 uptake in the liver has not been determined. A low uptake by lymph nodes was demonstrated (Table 4), which could be potentially useful for imaging [34].

The results of biodistribution of P792 at 24 h and 7 days (Table 4) indicate mainly renal elimination (83% at 24 h) and a low fecal excretion (8% at 7 days).

The intracerebral and intravascular acute toxicity results (Table 2) show that the i.c. LD_{50} and i.v. LD_{50} safety indices are considerably higher than those of non specific contrast agents [24] and MS325 [14].

5. Conclusion

The chemical structure of P792 results in an MRI contrast agent characterized by:

- a high relaxivity r_1 at 60 MHz: 29 $mM^{-1} \times s^{-1}$ in pure water,
- an original RCBPA pharmacokinetic profile,
- a satisfactory toxicology profile.

The high relaxivity and the RCBPA pharmacokinetic profile of P792 should have a very positive impact in:

- *Anatomical vascular imaging* (*angiography*, *coronary angiography*): the absence of extravasation should increase the contrast of vessels (no enhancement of the parenchyma) and allow the use of post-bolus imaging [35] to increase spatial resolution and distality especially in MR coronary angiography [36,37].
- *Perfusion imaging*: the absence of first-pass extravasation and its high relaxivity make P792 the ideal prototype to quantify perfusion [5,20].
- *Permeability imaging*: the pharmacokinetics of RCBPA should allow differentiation between benign and malignant tumors, characterized by an intense angiogenic activity [11,38], as well as visualization of ischemic zones [5].

Experimental and clinical studies are underway to confirm the potential of P792 in MRI.

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