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Review

Metal coordinated pyrrole-based macrocycles as contrast agents for magnetic resonance imaging technologies: Synthesis and applications

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ABSTRACT

The number of scientific reports on the field of imaging in biomedical sciences is rising massively, with the emergence of "noninvasive" *in vivo* imaging technologies, of which Magnetic Resonance Imaging (MRI) is considered to be among the top techniques in modern Medical Imaging. These techniques manage to detect events at molecular and cellular levels, providing a faster diagnostic evaluation to oncology patients and consequently hastening drug development processes.

Of the many contrast agents developed by Organic Chemists during the last decades, tetrapyrrolic macrocycles like porphyrins and related compounds, like phthalocyanines, represent some of the oldest, most widely studied chemical structures in biomedical applications. These macrocyclic structures display intrinsic affinity for tumor localization, and their well-described photosensitizing and photophysical features allured many scientists toward their potential use as contrast agents in a variety of *in vivo* imaging technologies, namely in the MRI technique. Furthermore, a special emphasis is put on the development of multimodal contrast agents, which may be the future of Medical Imaging.

This review intends to give an insight on developments on MRI technologies involving tetrapyrrolic-based contrast agents for cancer detection. It is a Chemist's view, regarding the synthesis of the crucial contrast agents, selecting influential milestones over the last few decades on this field, along with pertinent reflections pointing to future guidelines.

Abbreviations: AAV9, adeno-associated serotype 9 viral vector; BODIPY, boron-dipyrromethene; BSA, bovine serum albumin; C60, Buckminsterfullerene; CCMV, cowpea chlorotic mottle virus; CD, β-cyclodextrin; Cell line H1299, human non-small cell lung carcinoma cell line; Cell line HaCaT, spontaneously transformed aneuploid immortal keratinocyte cell line; Cell line HeLa, Henrietta Lacks epithelioid cervix carcinoma cell line; Cell line MDA-MB-231, human breast adenocarcinoma cell line; CMV, constitutive cytomegalovirus; GFP, green fluorescent protein; DCC, dicyclocarbodiimide; DDQ, 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone; DIEA, *N,N*-diisopropylethylamine; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; DO3A, 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DOTAC10, 1,4,7,10-tetraaza-1-(1-carboxymethylundecane)-4,7,10-triacetic acid cyclododecane; DOX, doxorubicin; DTPA, diethylenetriaminepentaacetic acid; DTTA, diethylenetriaminetetraacetic acid; Gadophrin-2, Gd-DTPA mesoporphyrin; HSA, human serum albumin; HEPES buffer, (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) buffer solution; HOP-8P, α-aqua-13,17-bis(1-carboxypropionyl) carbamoylethyl-3,8-bis(1-phenethyloxyethyl)-beta-hydroxy-2,7,12,18-tetramethyl-porphyrinato manganese(III); Mice type BALB/c, albino laboratory-bred strain of the House Mouse; Mice type ICR, Imprinting Control Region mice; Mn(II)TPPS$_4$, 5,10,15,20-tetra-(4-sulfonatophenyl)-porphyrinato manganese(II); Mn(III)THPP, Mn(III)-*meso*-tetra-(4-hydroxy)phenylporphyrinate; Mn(III)TPPP$_4$, Mn(III)-*meso*-tetra-(4-phosphatophenyl)porphyrinate; Mn(III)TPPS$_4$, 5,10,15,20-tetra-(4-sulfonatophenyl)-porphyrinato manganese(III) acetate; Mn(III)TPPS$_4$(Cl), 5,10,15,20-tetra-(4-chlorosulfonatophenyl)-porphyrinato manganese(III) acetate; Mn(OAc)$_2$·4H$_2$O, manganese(II) acetate tetrahydrate; mPEG, methoxy poly(ethylene glycol); NH$_4$Ac buffer, ammonium acetate buffer solution; PEG, poly(ethyleneglycol); PLA, poly(lactic acid); PLGA, poly(lactide-co-glycolide); PSI, polysuccinimide; SEAP, secreted enzyme alkaline phosphatase; SPION, superparamagnetic iron oxide nanoparticle; SuO-CTMIO, 5-carboxy-1,1,3,3-tetramethylisoindolin-2-yloxyl-*N*-hydroxysuccinimidyl ester; TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran; TPPS$_4$, 5,10,15,20-tetra-(4-sulfonatophenyl)-porphyrin; Tumor line EMT-6, mouse mammary sarcoma tumor line; Tumor line HT 29, Caucasian colon adenocarcinoma grade II tumor line; Tumor line LX-1, Human hepatic stellate tumor line; Tumor line KB, subline of the KERATIN-forming tumor cell line HeLa; Tumor line SCC VII, squamous cell carcinoma tumor line; Tumor line WiDr, human colon carcinoma tumor line.

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Contents

1. Introduction

Pyrrole-based macrocycles, including porphyrins and phthalocyanines are, without any doubt, considered some of the most extensively studied chemical structures for many purposes, of which is reputed their applicability in optoelectronics and catalysis [1–27] and in biomedical applications [28–44].

These chemical entities may find particular interest in biomedical applications, as they hold several favorable features, including modular photophysical properties, such as possible long wavelength absorption and emission at appropriate wavelength range (especially in the near infrared region, avoiding tissue autofluorescence), straightforward functionalization, preferential uptake in tumors and reportedly low *in vivo* toxicity.

Given this, of the possible applications that porphyrins and phthalocyanines may find in biomedicine, molecular imaging is definitely a logical target purpose. This interdisciplinary field has enjoyed a significant growth in the 21st century, resulting from the intersection of the molecular biology and *in vivo* imaging areas. With the aid of fundamental disciplines as Physics and Chemistry, the potential of the molecular imaging field is very high, as *in vivo* medical imaging enjoys a steady interest and growth over last decade, mainly due to the developments in the engineering of software and imaging devices and instruments, but also on the chemistry of imaging probes. As proof of the growth from which medical imaging is benefiting, several modalities are currently being utilized, including Magnetic Resonance Imaging (MRI), X-ray Radiography and Computed Tomography (CT), radionuclide imaging using single photons and positrons (Single-Photon Emission Computed Tomography – SPECT, and Positron Emission Tomography – PET), Fluorine Nuclear Magnetic Resonance – ^{19}F-NMR, Ultrasonography, Fluorescence Imaging, Fluorescence Reflectance Imaging, Optical imaging and Photoacoustic Tomography [41].

With the clear emergence of "non-invasive" *in vivo* imaging technologies, Magnetic Resonance Imaging (MRI) may be considered among the top techniques in modern medical imaging. This technique, with its outstanding spatial resolution, manages to detect events at molecular and cellular levels, consequently hastening drug development processes. The focus of this review puts emphasis on MRI technological developments, involving tetrapyrrolic-based contrast agent for malignancy detection.

Moreover, the medical community states that the future of imaging techniques should be based on new molecules possessing multiple functionalities, comprising several of the essential conditions for explicit images, such as: i) spatial resolution; ii) tissue penetration depth; iii) tissue contrast; iv) time necessary for image capture; and v) cost. Multimodal imaging may permit visualization in a single examination of early stage tumors and pharmacokinetic processes, drug action mechanisms and tumor growth processes, taking advantage of the strengths of each modality, by using a single multifunctional compound.

To praise the remarkable work that has been produced over the years in this field of knowledge, several reviews have been published, scrutinizing developments on MRI technologies [45–60]. For the reader who wishes to have a different view on the field, these contributions should be eagerly considered.

1.1. Basic considerations on MRI technology

The primordial MRI intent was to provide a non-invasive diagnosis means and Mendonça-Dias and Lauterbur [61] were the first to demonstrate the benefits of using contrast agents to improve tissue discrimination in MRI by enhancing sensitivity and/or specificity.

Since then, the categorization of contrast agents has evolved and nowadays they can be randomly grouped as ferromagnetic, superparamagnetic, diamagnetic and paramagnetic materials [62]. Briefly, ferromagnetic materials usually contain iron, nickel, or cobalt and possess a large positive magnetic susceptibility resulting from magnetic alignment of their different magnetic domains in the presence of a magnetic field. Superparamagnetic materials contain multiple elements that have ferromagnetic properties in bulk, mainly of iron sources, but consist of nanoparticles which are single-domain, *i.e.* composed of a single magnetic domain, and they have lower magnetic susceptibility than ferromagnetic materials. Paramagnetic materials include oxygen and ions of various metals like Fe, Mn, and Gd. These ions have unpaired electrons, resulting in a positive magnetic susceptibility, which is <0.001 times of that of ferromagnetic materials. Diamagnetic materials have no intrinsic atomic magnetic moment, but when placed in a magnetic field, they weakly repel the field, resulting in a small negative magnetic susceptibility.

Of these materials, paramagnetic and superparamagnetic contrast agents are the most commonly used in MRI. Paramagnetic contrast agents consist of Gd(III) or Mn(II) chelates of polyaminocarboxylate ligands, causing a reduction both in the T_1 and T_2 relaxation times of water protons in solution; however T_1 reduction is more important. They are classified as positive contrast agents, *i.e.*, generate bright images on MRI, caused by increased signal intensity on T_1 weighted images. The superparamagnetic contrast agents consist of iron oxide nanoparticles, resulting in shorter T_1 and T_2 relaxation times. The larger nanoparticles are considered negative agents, appearing dark on T_2 weighted