Metal-Organic Frameworks for Bioimaging: Strategies and Challenges

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Abstract

Metal-organic frameworks (MOFs), composites with metal ions and organic linkers, have become promising candidates in the biomedical field own to their unique properties, such as high surface area, pore-volume, tunable pore size, and versatile functionalities. In this review, we introduce and summarize the synthesis and characterization methods of MOFs, and their bioimaging applications, including optical bioimaging, magnetic resonance imaging (MRI), computed tomography (CT), and multi-mode. Furthermore, their bioimaging strategies, remaining challenges and future directions are discussed and proposed. This review provides valuable references for the designing of molecular bioimaging probes based on MOFs.

Key words: Metal-organic frameworks; Optical bioimaging; Magnetic resonance imaging (MRI); Computed tomography

Introduction

Metal-organic framework (MOF), a kind of coordination polymer, has drawn widespread attention since its first put forward as polymeric frameworks consisting of 3D linked rod-like segments by Robson et al. in 1989 [1]. Later, Yaghi et al. [2] reported a 2D coordination compound synthesized from a rigid organic ligand, trimesic acid (BTC), and a transition metal Co, and named it MOF in 1995. It was the first time that the concept of the metal-organic framework has been formally proposed. Over the next two decades, as an independent branch of coordination chemistry, MOF families grew at an astonishing rate. Recently, MOFs have been widely exploited in various aspects, such as storage of materials [3], separation [4-6], purification [7], catalysis [8-13], sensing [14-19], bio-imaging [20, 21], energy storage [22-27], drug delivery [28, 29], etc. MOFs are particularly promising for biomedical candidates in biological sensing and imaging due to their quenching performance and luminescence properties [30]. Since Yaghi et al. [2] improved the apparent surface area, pore-volume and stability of MOF-5 [31], the biological performance of MOF had significantly been optimized, and the scope of the application had been extensively developed. Compared with traditional materials, MOFs are equipped with many properties, such as biodegradability, biocompatible, high loading efficiency, tunable pore sizes, large specific surface area, topological diversity, easy functionalization, etc. [32] Besides, the large pores, high porosity and large specific surface area of MOFs are all beneficial to improve loading efficiency of the guest molecule. Easy to functionalize, good biocompatibility, water solubility and degradability can improve utilization and recyclability of the drug in the body. Furthermore, forces, such as hydrogen bond effect, Van der Waals forces, π-π stacking between aromatic rings exist in the MOFs [33, 34]. MOFs have been used as novel probes in the field of biosensing. In 2002, Wang et al. [35] designed the first sensor involving MOFs. Asefa and coworkers...
[36] firstly prepared biosensors based on MOF in 2008. Since then, MOFs have attracted great interest as biosensing materials. For example, the most widely used optical sensor, fluorescence, can be turned by the metal, ligand units [37], or the guest molecules [38]. Simultaneously, MOF possesses adjustable size, low toxicity, and biodegradability, which provides possibilities for applications in vivo.

Especially, benefiting from quenching and intrinsic fluorescence properties of MOF, it has been developed as a fluorescence quencher of dye-labeled aptamers, which enabled detection of various biomolecules, including biomacromolecule (nucleic acid, enzyme-activity/proteins) and small biomolecules (dopamine, amino acid, glucose, and H2O2) by a fluorescence “turn-on” progress [39]. Additionally, through a reasonable design strategy, MOFs can be integrated with intrinsic fluorescence properties, which can be affected by biomolecules and provide a light source for optical imaging. When the MOF is doped with Au [40], Mn2+ [41], Gd3+ [42], SPIO, Fe3O4 [43], Fe3+/Fe2+ [44], fluorescent dyes, upconversion nanomaterials [45] (NaYF4: Yb/Er, Gd3+ and Tm3+), quantum dots as well as other materials (graphene, dots, nanotubes) [34], MOF will equip with the function of imaging.

In recent years, the emerging functional MOFs have shown significant advantages in the field of bioimaging. Although the previous applications and challenges have been well summarized and presented, these applications are also rapidly updated with the rapid development of MOFs [46-48]. Therefore, in this review, the synthesis methods of MOFs and their unique properties, such as rational aperture design, diversity, easy to functionalize, high BET/Langmuir surface area etc., have been summarized. Meanwhile, the research progress in bioimaging applications related to MOF, the preparation of MOF probes, and its detection mechanisms are also reviewed. Furthermore, the challenges and future development directions in this field are further discussed. We hope this review will arouse broad interest and inspire readers to rationally design more biological applications based on the unique properties of MOF.

### Synthesis methods and characterization of MOF

#### Synthesis methods of NMOF

Particle size is a crucial parameter since it determines the physical and chemical properties of the particles [49]. Preparation of stable, monodispersed, and nanoscale nanoparticles is necessary. Up until now, various synthesis methods of NMOF have been developed, and the methods are summarized as follows (Fig. 1).

![Synthesis methods of MOFs](image.png)

Figure 1. The main synthesis methods of MOFs.
Hydrothermal/solvothermal

Under the reaction conditions of high temperature (60 and 300 °C) and high pressure, the insoluble reactants at standard temperature and pressure are placed together with solvent and dissolved in a sealed stainless steel reaction vessel lined with polytetrafluoroethylene. And the product is crystallized after reducing the temperature to a certain degree of saturation. These characteristics of MOFs can be adjusted by changing certain experimental parameters, including reaction temperature, reaction time, solvent type, surfactant type, and precursor type. Typically, the ZIF-n family, such as ZIF-8 (40 nm), is primarily synthesized using the solvothermal method [50]. This method is also suitable for the MIL-n family, such as flexible porous MIL-89 (50-100 nm), MIL-88A (150 nm), MIL-53 (350 nm), inflexible porous MIL-100 (200 nm), MIL-101-NH$_2$ (120 nm), etc. The method owns short synthesis time and it solves the problem of the insolubility of the precursor. The solvents used in the synthesis with different functional groups, polarities, dielectric constants, boiling points and viscosities, can significantly increase the diversity of the synthetic routes and product structures.

Microwave-assisted synthesis

Microwave-assisted MOF synthesis yields high-quality MOF crystals with reaction times from 5 seconds to 2.5 minutes, whereas conventional solvothermal and hydrothermal processes require hours or even days. In addition, the MOF material provided by the microwave-assisted method has a uniform crystal size and a well-defined shape, and the size can be adapted to a wide range of applications by controlling the reaction conditions. Typical materials include IRMOF-n (n=1, 2, 3) (100 nm) [51], dual hierarchical porous structure MIL-101(Cr) (22 nm). In this method, two-particle sizes (50 nm, 100 nm) of MIL-101 (Cr) were synthesized by Khan [52] and Zhao [53], respectively. Recently, Feng et al. [54] successfully synthesized nanoscale medi-MOF-1 with shape, controlled size and graded porosity by microwave heating and growth regulation. Microwave heating retains short reaction times, first kinetics of growing and crystal nucleation, as well as high yields of desirable products that are isolated with no or few secondary products. Advantages also include morphology control, phase selectivity, high efficiency, particle size reduction, etc.

Sonochemical synthesis

The mixed solution with a certain proportion of metal salt, organic ligand and an organic solvent is placed in the reaction bottle, using ultrasonic equipment to control the appropriate temperature and power. The violent reaction environment causes the molecules to collide quickly, which accelerates the reaction rate. For instance, microporous flexible MIL-100 (Fe) [55] and MIL-53 (Fe) [56] and Cu$_2$(BTC)$_2$ (10-200 nm) [57] have been obtained by the sonochemical method. Sonochemical synthesis possesses the advantages of rapidity, facility and etc. Compared with the solvothermal reaction, the reaction time is greatly reduced, and the heating and cooling rates are increased.

Electrochemical synthesis

The principle is that the metal ions are first obtained by in-situ anodization and dispersed into a solution containing organic ligands and an electrolyte. The organic ligands are deprotonated and combined with metal ions to form a MOF material. HKUST-1 was the first MOF that was synthesized by the electrochemical synthesis in 2005. Later, MIL-100 (Fe) [58] was prepared by electrochemical deposition under high pressure and high temperature. Electrochemical synthesis is superior environmentally friendly, easy operation and highly efficient synthesis compared with other synthetic methods. Furthermore, it is an effective route for the generation of heterogeneous multiphasic and multilayered MOF layers. However, the limitation of anodic electrodeposition remains.

Diffusion method

The diffusion method can be generally divided into three parts: gas-phase diffusion, liquid phase diffusion, and gel diffusion. The gas-phase diffusion method refers to the fact that the two solvents have different choices for the solubility of the target compound and the two solvents have a certain mutual solubility. When the solubility of the solvent diffuses to a solvent with high solubility, the solubility of the compound is lowered, forcing it to continue to crystallize. In the liquid phase diffusion method, a ligand and a metal salt are dissolved in two different solvents. One solution as a buffer was mixed with another solution and chemically reacted. Consequently, crystals may produce near the solution interface. In the gel diffusion method, a ligand is formulated in a gel, agar, or gelatin while a metal salt solution is placed on the gel, and the crystal begins to form when the two components slowly diffuse to the interface. The synthesis conditions are mild, and a high-quality single crystal can be obtained. However, it takes a week to several weeks or a few months.

Solvent volatilization method

The appropriate metal salt and organic ligand are selected and dissolved in a suitable solvent, and
the polymer crystals are prepared by slowly volatile-zing to cause a chemical reaction. The synthesis device of the solvent volatilization method is simple with mild working conditions and highly pure crystal. However, the synthesis takes a long time, and it is necessary to select a suitable solvent.

Besides, the synthesis methods of MOFs also include seed-mediated method [59], post-modification method [60], in situ diffusion synthesis [61], microwave-assisted coprecipitation [62], etc. It is worth noting that the synthesis will be affected by many factors, including metal center, organic ligand, reaction solvent, synthesis temperature, pH value of reaction solution, reactant ratio counterion, etc. We need to choose the appropriate method based on the existing experimental conditions and the demand for MOF quality and size.

**Characterization of MOF**

Every step of the synthesis of MOF needs to be proved, such as the morphology, pore size, specific surface area, and particle size. In this section, the main methods of characterization have been summarized in Table 1.

### Table 1. Characterization methods of MOF and functionalities

| Methods                              | Abbreviation | Functionalities                                      |
|--------------------------------------|--------------|-----------------------------------------------------|
| Single crystal X-ray diffraction     | SCXRD        | Characterization of crystal structure                |
| Powder X-ray diffraction             | PXRD         | Characterization of crystallinity and phase purity   |
| Brunauer-Emmett-Teller               | BET          | Detection of pore volume, pore size distribution    |
| Dynamic laser scattering             | DLS          | Particle size distribution                          |
| Scanning electron microscopy         | SEM          | Detecting the surface topography and size distribution of the crystal |
| Transmission electron microscopy     | TEM          | Detecting the morphology and thickness of the crystal |
| Thermogravimetric Analysis           | TGA          | Thermal stability analysis                          |
| UV-Vis Spectroscopy                  | UV-vis       | Structure identification                            |
| 1H nuclear magnetic resonance        | 1H NMR       | Determine the structure of the molecule             |
| Fourier Transform                    | FTIR         | Determination of functional groups and chemical structures of organic compounds in crystals |
| Infrared Spectroscopy                |              | Crystal space structure determination, the study of adsorption sites |
| Neutron diffraction                  |              | Specific surface area detection                      |
| N2 absorption-adsorption spectrometer| BJH          | Pore size, Porosity                                 |

**MOFs for Bioimaging**

The image modes can be divided into two categories: (1) the image providing structural information, such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound; (2) the image providing functional and molecular information, such as optical imaging, PET, SPECT, and magnetic resonance spectroscopy. Among them, MRI, CT, and optical imaging are the most common imaging methods. This section will focus on the imaging methods of the above three aspects. Of course, other imaging methods will also be involved.

### Single-modality imaging

**Optical bioimaging**

To date, MOF-based optical imaging has become a hot topic [63]. Optical imaging (mainly fluorescence imaging) includes the following aspects: (1) Fluorescent reagent doping-based “turn on” mechanism. Here, MOF is primarily used as a fluorescence quenching platform for fluorescein/dye-labeled probes and the fluorescence will “turn on” due to the binding of probes with the target molecules; (2) Non-fluorescent reagent doped optical imaging, including up-conversion fluorescence imaging and NIR PersL imaging; (3) Undoped optical imaging, in which, the MOF itself is involved in the illumination for imaging; usually, the illuminator has various forms, and the mechanisms are complicated.

**Fluorescent reagent doping-based “turn on” mechanisms**

In this part, most of them are fluorescence imaging based on fluorescent dye reagent doping. Common fluorescent doping reagents include Cathepsin B (CaB), 5-carboxyl fluorescein (5-FAM), TAMRA, rhodamine B isothiocyanate (RBITC), etc. MOF mainly acts as a quenching platform when the target material appears. The fluorescence quenching by the MOF will “turn on”.

Cathepsin B (CaB), abundantly found in the lysosome and one of the cysteine endopeptidases, plays a crucial role in the regulation of cellular metabolism [64]. Interestingly, in Shen’s group, a core-shell nanoparticle, Au-Cy3P@ZIF-8, had been designed with enzyme and pH dual-recognition switch for localized and high specificity fluorescence imaging of lysosomal CaB in living cells [65]. Under the acidic environment, the ZIF-8 shell of the nanoprobe could be disassembled and then the CaB recognized a cleavage site, exposed substrate peptide between arginine and glycine. Due to the departure of a Cy3-labeled, the fluorescence was turned on. Similarly, Liu et al. [60] designed a CPC@MOF probe with chlorine e6 (Ce6)-labeled CaB substrate peptide, camptothecin and HOOC-PEG-FA modified MIL-101-NH2 using the same mechanism, and MOF was used as a fluorescence quenching platform.

In another study, in 2018, Gao et al. [66] obtained a multifunctional system, UIO-66-NH2-FA-5-FAM/5-FU, for cancer treatment and fluorescence imaging. After the target drug, 5-FU was adsorbed on MOF, the fluorescence imaging agent 5-carboxyl fluorescein (5-FAM) and the targeted reagent folic acid (FA) were...
covalently grafted. Predictably, this system displayed good fluorescence imaging in vitro based on 5-FAM and due to the targeting effect of folic acid, fluorescence can be enhanced and can target liver cancer cells HePG-2. The difference from the previous two examples is that the imaging system uses FA as a targeting agent to enhance the imaging effect.

Also using targeted mediated imaging, Liu et al. [67] revealed Zr-based MOF nanoparticles modified with DNA aptamers through strong coordination between zirconium and phosphate for photodynamic therapy and target-induced imaging. Note here that, target-induced imaging is achieved based on the structural change of the aptamer after binding with the target; not only that, the conjugation of Zr-MOF with DNA aptamer results in fluorescence quenching of TAMRA (fluorescent dyes), then target-induced imaging is achieved (Figure 2A).

MOF-based living cells pH imaging in a broad range is a problem to be solved. Chen et al. [68] constructed a valid dual-emission fluorescent MOF nanocomposite probe (RB-PCN) for broad-range (pH=1-11) and sensitive pH fluorescence imaging, RB-PCN was prepared with DBI-PEG-NH2 functionalized Fe3O4 as the core and Zr-MOF as a shell and then further reacted with rhodamine B isothiocyanate (RBITC). RB-PCN exhibited two emissions at 641 nm for PCN-224 in response to the alkaline range (red) and at 575 nm for RBITC in response to the acidic range (green) under the single-excitation. In essence, the system was also a fluorescence turn-on strategy caused by the pH-responsive property of the fluorescence reagent RBITC.

Figure 2. A) Illustration of phosphate-terminal DNA aptamer conjugation to a Zr-MOF nanoparticle quencher for target-induced imaging and photodynamic therapy. Reproduced with permission. [67] Copyright 2018, Royal Society of Chemistry. B) Schematic illustration of the synthetic procedure, drug loading and receptor-mediated endocytosis pathway of the targeted UCNPs@MOF core-shell NCs. The insets have expanded the view of the porous cavities of MIL-100 (Fe) and part coordination structure, respectively. Reproduced with permission. [70] Copyright 2015, Science. C) In vivo NIR PersL imaging. a) Mice were intravenously injected with ZGO@ZIF-8 (0.2 mL, 1 mg/mL in PBS) and radiated at 254 nm for 5 min b) 661 nm LED recharging for 2 min and c) 10 min apart. d) Ex vivo NIR PersL imaging. e) Total luminescence of main organs of mice after 24 h of administration. Reproduced with permission. [74] Copyright 2019, American Chemical Society. D) Depth fluorescence images of probe 1 (100 µg/mL) in rat liver tissue. The change of fluorescence intensity with scan depth was determined by spectral confocal multi-photon microscopy. Reproduced with permission. [77] Copyright 2019, American Chemical Society.
Non-fluorescent reagent doped optical imaging

Doping fluorescent reagents in MOF is a common fluorescence imaging strategy. In addition, non-fluorescent reagents, such as up-conversion materials and PersL nanoparticles, can also be doped in MOF for fluorescence imaging.

**Up-conversion fluorescence imaging:**

Contrary to ordinary down-conversion illuminating mechanisms, upconversion nanoparticles (UCNPs) used the anti-Stokes effect. It is favored by researchers due to its ability to convert near-infrared radiation into visible light and the properties of high fluorescence efficiency, good stability, and high resolution [69]. The introduction of up-conversion luminescent particles also gives the MOF a new development direction.

Deng et al. [70] obtained core-shell nanocarriers, UCNPs@MOF-DOX-AS1411, with MIL-100 (Fe) as shell and β-NaYF4: Yb3+/Er3+ (UCNPs) as core via a two-step approach. The mechanism was that after UCNPs equipped with the aptamers, AS1411, were targeted to the tumor cell surface, nanocarriers exhibit satisfactory up-conversion green emission UC luminescent imaging when exposed to 980 nm laser. (Figure 2B) Similarly, Chowdhuri et al. [71] synthesized nanoplatform (UCNPs@ZIF-8/FA) with folic acid (FA) packed by a one-post method for targeting, fluorescence imaging, and pH-responsive drug release. In this research, ZIF-8 with folic acid encapsulated was directly coated on UCNPs (NaYF4: Er3+, Yb3+) to form a monodispersed core-shell structured nanocomposite.

Compared with the former, their work was based on MOF, both using the up-conversion particles NaYF4: Er3+, Yb3+ as optical imaging elements and had higher resolution images. Both of them were core-shell structures and took pH-sensitive MOFs as the shell. Although they were receptor-mediated endocytosis, there are differences in the types of target ligands, the former used AS1411 and the latter employed FA.

**NIR PersL imaging:**

Persistent luminescence (PersL) is a unique optical phenomenon wherein light is able to last for hours or seconds after absent the excitation source [72]. Up to now, near-infrared (NIR) PersL nanoparticles (PLNPs) have aroused curiosity among researchers since they can serve as optical probes bioimaging systems with preponderances of low irradiation damage, auto-fluorescence-free, and deep tissue penetration [73]. Remind that this principle of optical imaging is different from ordinary fluorescent or phosphorescent.

Recently, a multifunctional nanoplatforms, ZGO@ZIF-8-DOX, which took chromium (Cr)-doped zinc gallogermanate (ZGGO) NIR PLNPs as a core and ZIF-8 as a shell for dual functionalities of pH drug delivery (LC = 93.2%) and auto-fluorescence-free NIR PersL imaging had been reported [74] (Figure 2C). Most importantly, the PL phenomenon in ZGGO NP was attributed to the 4A2→2E transition of Cr3+. Compared with other imaging methods, the resolution of this platform was higher and could achieve deep tissue penetration. However, the combination of PLNPs and MOF was currently in infancy. Even so, NIR PersL imaging as a special imaging method provided a new idea for optical imaging systems. Compared to the previous fluorescent reagent doping, non-fluorescent reagents doped optical imaging is mainly based on the mechanism of illumination under specific near-infrared light (NIR).

Undoped optical imaging

**Single-photon fluorescence bioimaging:**

Compared to the imaging mechanism involved in fluorescent reagents, the imaging involved in non-fluorescent reagents is mainly based on the reaction between MOF and target molecules leading to light-on. For example, peroxynitrite (ONOO−), a member of the ROS, while an excessive concentration exists in the organism causes diseases such as diabetes [75]. Mostakim SK and coworkers [76] synthesized boronic acid-functionalized Hafnium (Hf)-based MOF, Hf-Uio-66-B(OH)2 as a fluorescent turn-on probe for selective sensing and imaging of ONOO−. The fluorescent turn-on reaction of the probe to peroxynitrite could be attributed to the oxidative cleavage of the boronic acid group to the corresponding hydroxyl group.

**Two-photon fluorescence bioimaging:**

Single-photon excitation leads to a low signal-to-noise ratio and photobleaching problems. By contrast, two photons fluorescent probes exhibit effective intracellular deep tissue imaging. Yang’s group developed a two-photon metal-organic framework (TP-MOF) employing click chemistry for depth fluorescence bioimaging with a penetration of 130 μm in rat liver tissue [77]. (Figure 2D) Furthermore, TP organic moiety presented selectivity, photostability, biocompatibility, as well as fluorescence responsive properties. Specifically, unlike other optical imaging, this fluorescence comes from the MOF itself, which acts as the light source in which the components of the MOF participate in the reaction and emit an optical signal under external stimulation. This unique optical signal comes from a specific design of MOF. Significantly, this molecular design concept can be
extended to other MOF-based bioimaging, laying a foundation for further research.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) distinguishes abnormalities in tissues due to changes in nuclear relaxation rate and/or water density through variation in NMR water proton signals. MRI is widely used in clinical imaging because of its non-invasiveness, high spatial resolution, and deep penetration, which can diagnose diseases by changing the longitudinal (T1) and transverse (T2) relaxation rates of water protons. A contrast agent is an imaging enhancement reagent used to shorten imaging time and improve imaging contrast and sharpness. MRI contrast agents are divided into three types: (1) Paramagnetic substances (Gd, Mn, Fe), affects surrounding water molecules and shortens T1 time; (2) Ferromagnetic substances (Fe-Co); (3) Super-paramagnetic substances (SPIO, Fe3O4, Fe3+, Fe2+), by interfering with the local magnetic field of the human body, it shortens the T2 time, the lesion shows a high signal, while the normal tissue shows a low signal. Typically, high paramagnetic metal ion compounds such as Gd3+, Mn2+ and Fe3+/Fe2+ are widely used as nuclear magnetic resonance agents. Here, we introduce MRI contrast agents using metal MOFs.

Paramagnetic substances (Gd-based/Mn-based)

As an excellent MRI contrast agent, Gd has been fully recognized in imaging due to it can shorten the T1 time and achieve better imaging results. Hatakeyama et al. [42] synthesized nanoscale Gd-MOF for PDT and MRI with a high relaxation rate of 40.8 mM⁻¹s⁻¹ due to the enhanced rotation-related time and the reduced distance between the proton of Gd3+ and hydrogen atoms, also, the increased diffusion time of H2O. In addition, McLeod and coworkers incorporate Gd(III) complexes into Zr-MOFs (nano NU-1000, micro NU-1000, NU-901) through solvent-assisted ligand incorporation (SALI) and study the effect of pore shape and particle size on proton relaxation. The results show that Gd nano NU-1000 achieved the best proton relaxivity of 26±1 mM⁻¹s⁻¹ at 1.4 T [78].

Coincidentally, also combined with porphyrins, Zhang et al. [79] firstly developed nanoscale Mn-porphyrin MOF probe, NMOF-SNO, with biocompatible Zr4+ ions as the coordination center, Mn-porphyrin as a bridging ligand, and S-nitrosothiol (SNO) functionalized for MRI-guided nitric oxide (NO) detection and synergistic photothermal therapy (PTT). NMOF provided a high molar extinction coefficient, strong T1-weighted MR contrast, and adequate photothermal stability after Mn2+ inserting into the porphyrin ring successfully.

Besides, Qin et al. [80] designed and synthesized two water-stable 3D Mn-based MOF (1) and Gd-based MOF (2) as high-efficiency contrast agents for MRI. Furthermore, in vitro MRI demonstrated that the relaxation r1 of 1 and 2 was 17.50 mM⁻¹·S⁻¹ and 13.46 mM⁻¹·S⁻¹, respectively, which are higher than the r1 (4.87 mM⁻¹·S⁻¹) of similar Gd-DTPA (DTPA = diethylenetriamine pentaacetate). Compared with 2, 1 existed lower cytotoxicity and higher r1 relaxivity and revealed excellent kidney-positive signal aggrandizement. MOF 1 was a potential MRI candidate (Figure 3A).

Actually, the principle of action is the same whether it is Gd or Mn: shortening the T1 relaxation time. In addition to Gd3+ and Mn2+, more other types of MOFs are also used as contrast agents.

Ferromagnetic substances (Fe-based)

In addition, Fe-based MOF is also gaining attention. In 2018, Zhang et al. [44] designed a Fe-based nanocomposite, AuNS@MOF-ZD2, with a TNBC-targeted peptide (ZD2) modified and a gold nanostar (AuNS) coated within MIL-101-NH2 (Fe) to achieve T1-weighted MRI and photothermal therapy (PTT) for targeting toward triple-negative breast cancer (TNBC). As a result, nanocomposites present favorable T1-weighted magnetic resonance (MR) relaxivity and biocompatibility and efficient photothermal conversion ability (40.5%). In vitro and in vivo experiments demonstrated satisfactory T1-weighted PTT and MRI performance under a low power density of 808 nm laser, and an excellent hot cathode effect was obtained in TNBC. Another example, Huang et al. [81] proposed a multifunctional probe, PPy@MIL-53, by a combination of MIL-53 and polypyrrole (PPy) for MRI-guided PTT of tumors in vivo.

Shu et al. [82] in 2018 synthesized a hyaluronic acid (HA), a widely reported targeting molecule [83], conjugated ZIF-8 for both targeted and pH-responsive drug delivery and magnetic resonance imaging of prostate cancer PC-3 cells. In this work, DOX@ZIF-8 was formed by the one-pot method, then coated with polydopamine (PDA), sequentially chelated with Fe3+, and bound with hyaluronic acid (HA) to form a multifunctional ZIF-8 nanocarrier (DOX@ZIF-HA). Note here that, PDA chelating Fe3+ made DOX@ZIF-HA a good contrast agent for MR. More importantly, this was the first time that HA had been combined with ZIF-8 (Figure 3B).

Recently, Xu and others reported Fe-based MOF composed of Fe(III) ions and hematoporphyrin monomethyl ether, loaded with DOX, DOX@FeCPs was used in MR imaging-guided deep tumor
sonodynamic chemotherapy combination therapy. T2-weighted MRI in vivo was performed on a CT26 tumor-bearing mouse via injecting FeCPs saline and the results demonstrated that FeCPs have passive targeting effects on tumors [84].

Undoubtedly, the superparamagnetic iron ion is the imaging element of MRI in the above cases. The basic principle is to shorten the T2 time by interfering with the local magnetic field of the human body. The lesion shows a high signal, while the normal tissue shows a low signal. It’s different from Gd3+ and Mn2+ in the mechanism. Most of the above are 1H MRI, which was achieved by affecting the surrounding water molecules.

19F MRI

1H MRI occupies a dominant position in clinical magnetic resonance technology, but it still faces the challenge because of its strong water background signals in vivo and low signal-to-noise ratio. On the contrary, 19F MRI has attracted the attention of researchers owing to its high signal-to-noise ratio and lower background signal than 1H MRI.

Guo et al. [85] used it as a pH-responsive switch to turn on the MRI signal. They fabricated pH-sensitive 19F MRI nanoprobe, FNP-PEG, by partly replacing the 2-methylimidazole of the ZIF-8, of which the strong 19F MRI signal revealed an interesting pH-determined property. Moreover, the contrast agent for pH-responsive (7.4 to 5.5) imaging with low background and high penetration depth. When the surface of PEG was cleaved under acidic conditions, the internal ZIF-8 was cleaved, and the 19F-containing TFMIM(4(5)-(trifluoromethyl)imidazole) was released, therefore, resulting in imaging. Interestingly, T2 would decrease as the pH increases due to the coordination between zinc and the organic ligand of N-donor in the MOF matrix restricts the movement of 19F molecules, resulting in a short T2 relaxation time and weak 19F signal (Figure 3C). Recently, Zhou and others fabricated Zr-based MOF nanoparticles (UiO-66-F NPs) by a solvothermal method as tumor micro-environment responsive 19F MRI contrast agent, enhancing 19F MRI signal under acidic conditions but maintain stability under neutral conditions. Importantly, this design concept provides a new concept for future MRI design.

Figure 3. A) (a) 1/T1 plot of MOFs 1, 2 and Gd-DTPA concentration. (b) Dynamic MR signal intensity study of a normal kidney after intravenous injection of MOF 1. Reproduced with permission. [80] Copyright 2017, American Chemical Society. B) Schematic diagram for the preparation of DOX@ZIF-HA and the Fe3+-mediated coordination interaction between HA and PDA. Reproduced with permission. [82] Copyright 2018, Royal Society of Chemistry. C) Schematic illustration for the application and preparation of 19F MRI probes. Reproduced with permission. [85] Copyright 2018, Royal Society of Chemistry.
Computed tomography (CT)

Computed tomography (CT), one of the most prevalent imaging techniques in the clinic due to its cost-effective, anatomical imaging ability, and wide availability, provides high-resolution 3D tomography anatomical information. In the body, the contrast agent enhances the distinction between organs and tissues of similar density. Nevertheless, the non-specific distribution and fast clearance of the contrast agent in vivo limit its clinical application. With the development of nanotechnology, some MOF-based contrast agents have been used to improve CT imaging ability and efficacy.

Zhang et al. [86] reported a kind of iodine-boron-dipyrromethene (BODIPY) containing NMOF, UiO-PDT, as CT contrast agents. The results of in vivo animal experiments and in vitro toxicity analysis showed that there was no apparent toxicity even at a high dose of 100 mg kg⁻¹. That is to say, the bioavailability of UiO-PDT was favorable. What’s more, in vivo CT imaging results showed that UiO-PDT nanoparticles could be preferentially clustered in the tumor site of liver cancer rates. However, no aggregation was observed in the organs and non-surrounding connective tissue. After 24 h, the best CT imaging performance was achieved. All of these results suggest that the UiO-PDT may be a promising candidate for future CT imaging (Figure 4A) [87].

More recently, Robison et al. [20] solvothermal synthesized a bismuth-based MOF (Bi-NU-901) as a contrast agent for X-ray computed tomography (X-ray CT). Most importantly, in vivo research showed that Bi-NU-901 provided ~7 times better contrast intensity compared to Zr-MOF, which possess the same topology, and ~14 times better than a commercial CT contrast agent. Besides, Zhang et al. [88] designed two probes, including DOX@Gd-MOFs-Glu and Yb-MOFs-Glu, for tumor-specific targeting pH-responsive drug delivery and CT imaging. This platform showed good biocompatibility. That means the platform achieved a multifunctional strategy of “three birds with one stone”.

Except for MOF itself as a contrast agent, modifying the surface of the MOF with a contrast agent or encapsulating the contrast agent in the MOF is also a strategy. Su et al. used a one-pot method to prepare ZIF-8/DOX, then coated with the contrast agent ZrO₂ and loaded with an ionic liquid to form a nanocomposite material ZIF-8/DOX@ZrO₂@IL, which is used for chemo-microwave thermal therapy of tumors. ZrO₂ coating not only reduced toxic side effects and exhibited biocompatibility but also enhanced the efficacy of CT imaging. It is worth noting that such a MOF complex provided a promising platform for CT imaging (Figure 4B) [89].
53-NH₂ was used for MRI (T2-magnetic response) and as a reagent for fluorescent imaging, while Fe-MIL-FAM/5-FU, for targeted drug delivery and multimode imaging, which has been widely studied as one of the most common imaging modes in years. It is unlikely to be used for comprehensive diagnostic information [93]. Different imaging modes can often simultaneously enhance contrast on T1- and T2-weighted MRI and fluorescence imaging. In addition, PAM/PAT reflects fluorescence, photoacoustic (PA), and positron emission tomography (PET).

Table 2. Summary of clinical imaging modalities and related nanomaterials as contrast agents

| Modality                        | Measured signals | Resolution | Depth | Related nanomaterials                                                                 |
|---------------------------------|------------------|------------|-------|-------------------------------------------------------------------------------------|
| Magnetic resonance imaging (MRI) | Magnetic field variations | 25-100 μm | No limit | SPIO, Fe₃O₄, Fe₃⁺, Fe₂⁺ [44] nanoparticles (T₂), Mn(II) [41] and Gd(III) [42] doped nanoparticles (T₁) |
| Optical imaging                 | Light            | 1-3 mm     | < 2 mm | Dye-loaded nanoparticles [65], upconversion nanomaterials (NaYF₄:Yb/Er, Gd³⁺ and Tm³⁺), quantum dots, modified carbon-based materials (grapheme, dots, nanotubes) [34] |
| Computed tomography (X-ray CT)  | X-ray            | 50 μm      | No limit | Iron oxide-doped nanomaterials, iodinated nanoparticles, high-Z elements (e.g., Hf and Zr) [90] |
| Single photon emission computed tomography (SPECT) | γ-ray            | 1-2 mm     |       | Nanomaterials with radioisotopes such as ⁹⁰Tc and ¹¹¹In [91]                          |
| Positron Emission Tomography (PET) | Positron from radioactive nuclides | 1-2 mm |       | Nanoparticles with radioisotopes such as ¹⁹F, ¹²⁵I, ⁶⁸Ga, and ¹³¹I                           |
| Photacoustic imaging (PA) | Photoacoustic signal | ~1 mm      | 50 mm | Near-infrared dye-loaded (Cypate, indocyanine green) [92], upconversion nanoparticles (UCNPs), carbon nanomaterials, gold nanorods |
| Fluorescence reflectance imaging (FR) | Light            | < 1 cm     | < 1 cm | -                                                                                     |
| UM/UI                           | Sound            | 50 μm      | mm to cm | Microbubbles, emulsions, polystyrene beads                                           |
| PAM/PAT                         | -                | mm to cm   | mm to cm | Gold nanomaterials, carbon nanotubes, dye-loaded nanomaterials                        |

Multimode bioimaging

Generally speaking, due to the inherent limitations of the single-imaging technique, it is unlikely to be used for comprehensive diagnostic information [93]. Different imaging modes can often complement each other, which requires the fusion of different imaging modes. As a result, “multimode imaging technology” has developed rapidly in recent years.

MRI/OI, MR/fluorescence dual-mode imaging as one of the most common imaging modes in multimode imaging, which has been widely studied [94]. Wang et al. [95] prepared Gd and Eu Co-doped T₁-T₂ dual-mode probes, Eu₃(III)-MOF@SiO₂, for simultaneously enhancing contrast on T₁- and T₂-weighted MRI and fluorescence imaging. In addition, Gao et al. [96] designed a Fe-based and smart multifunctional platform, Fe-MIL-53-NH₂-FAM/5-FU, for targeted drug delivery and fluorescence/MR dual-mode imaging. 5-FAM serves as a reagent for fluorescent imaging, while Fe-MIL-53-NH₂ was used for MRI (T₂-magnetic response) and encapsulating the drug. Meanwhile, the FA acted as the targeted reagent. In vitro cell experiment verifies that the platform possesses better imaging performance and can produce better toxicity to MGC-803 cells with the release of 5-FU. Besides, the same year, Wang et al. [97] reported a biodegradable core-shell dual-MOFs, CSD-MOFs, with Prussian blue (PB) as the core and ZIF-8 as the shell for both fluorescence imaging (FI) and MRI dual-mode imaging. Xie et al. [98] presented a fresh multifunctional nano-drug carrier UC@mSiO₂-RB@ZIF-O₂-DOX-PEGFA (URODF) with pH-responsive chemotherapy. Most importantly, NaYF₄:Yb/Er@NaYbF₄:Nd@NaGdF₄ nanoparticles (UC) were exploited as both MR/upconversion imaging matrices. In addition, Mn(III) sealed MOF with porphyrin as an organic ligand was synthesized by Zhang’s team, which reacted with the over-expressed GSH of tumor cells to generate Mn(II) and free porphyrin. With the consumption of GSH, Mn(II)-based MRI and porphyrin-based optical imaging were activated. As shown in Figure 5A, compared with a control group, T₁ relaxation rates (r₁) increased nearly 2.3 times in the presence of GSH (2.5 mM) [41].

MRI/PAI, the combination of MOF and other carrier materials simultaneously, also opens a way for the development of imaging. In Chen’s group [99], molecularly organic/inorganic hybridized nano-platforms (HMONs-PMOF) were synthesized by merging with a polydopamine (PDA) interlayer and hollow mesoporous organosilica nanoparticles (HMONs). Benefiting from ICG confined in MOF and the Fe coordinated on PDA, nanocomposites were equipped with photoacoustic (PA) and magnetic resonance (MR) dual-modality imaging. In the process, the two types of MOF play a synergistic role (Figure 5B).

MRI/CT, as described in single-mode imaging, CT has excellent performance of imaging, however, due to the similar electron density of CT, it has a poor resolution in soft tissue [100]. Whereas MRI has the ability of deep penetration and high spatial resolution, which provides good contrast for soft tissue, but has relatively low sensitivity. Therefore, combining the advantages of several imaging methods may be achieved to provide more accurate and complex diagnostic information. Tian et al. [101], for the first time, designed GdMOF-PAA-Au hybrid system as imaging contrast agents for MRI and CT by using poly (acrylic acid), also known as PAA, as a bridge between the AuNPs and Gd-MOF. Note here that, AuNPs provided the ability of CT, while the addition of Gd-MOF was the source of MRI. The results showed that the r₁ of MRI was 4.9 mM⁻¹s⁻¹ which is approximately equal to Gd-MOF without...
modification ($\gamma = 4.5 \text{ mM}^{-1}\text{s}^{-1}$) and better than Magnevist which is a kind of MRI contrast agent used in clinical. At the same time, experiments have proved that Gd-MOF-PAA-Au hybrid nanocomposites can enhance the contrast of CT imaging even when the Au concentration is as low as 1.66 mg/mL (Figure 5C).

**MRI/PTI**, take advantage of the particular advantages of ultrathin 2D MOF, Li et al. [102] reported ultrathin 2D Cu-based MOF nanosheets, Cu-TCPP (TCPP = tetrakis (4-carboxyphenyl) porphyrin), with a facile method of solvothermal for MR/IR thermal imaging and photodynamic therapy (PDT) and photothermal therapy (PTT). As a result, due to the ultrathin properties and the d-d band transition of Cu$^{2+}$, it has excellent NIR capacity and photothermal conversion performance. Meanwhile, the sheet can produce singlet oxygen due to the inherent properties of TCPP. Furthermore, copper is capable of MRI because it has three pairs of unpaired electrons.

**Triple-mode imaging:**

Based on the targeted mediated imaging, the imaging mode gradually changes from dual-modal to three modal [103].

**MRI/OI/PAI**, in the group of Cai [104], MOF@HA@ICG NPs were obtained based on MIL-100 (Fe) for cancer theranostics and multimodal imaging, including PAI, T$_2$-weighted MRI, and FL. The result showed a high loading of indocyanine green (ICG, 40%) which was the only NIR organic dye, photostability and strong NIR absorbance. Furthermore, in vivo and in vitro data demonstrated that the MOF@HA@ICG NPs could be facile uptaken by CD44-positive MCF-7 cells and accumulated in xenograft tumors which were benefit from their targeting capability based on hyaluronic acid (HA).

**MRI/CT/PAI**, photoacoustic imaging (PAI), which is based on the photoacoustic effect, is a promising biomedical imaging method with significant spatial resolution and imaging depth and can make up for the deficiency of CT and MRI. Shang et al. [105] synthesized a star-shaped core-shell structure nanoprobe, Au@MIL-88 (Fe), multifunctional imaging of glioma, including MRI, CT, and PAI. The results showed that Au@MIL-88 (Fe) provided high contrast and demonstrated negligible cytotoxicity, in vivo and in vitro experiments showed that Au@MIL-88 (Fe) exhibited a better performance in various diagnostic imaging methods, especially in terms of CT radiological exposure level (Figure 6A).

**NIRF/PAI/MRI**, transferrin (Tf), a tumor-targeting agent, achieves Tf receptor-mediated endocytosis. For targeted precision imaging, Yang et al. [106] designed nanoparticles, cypate@MIL-53-Tf nanoparticles (denoted as CMNP-Tf), based on MIL-53 with NIR dye to achieve multimodal-imaging (NIRF/PA/MR) and guided phototherapy. T1-weighted MRI contrast property was ascribed to...
the Fe<sup>3+</sup> contribution to the longitudinal relaxivity of MRI and NIRF/PA imaging due to the inherent nature of near-infrared dye (Cypate). Hence, it opened a new way to develop a multifunctional nanoplatforam for bio-applications (Figure 6B).

**MRI/OI/PA/PTI** Fan et al. synthesized the ICG-CpG®MOF nano-platform with MIL 101-NH<sub>2</sub> as the core carrier and double-modified with ICG and CpG ODN, which is used for multimodal imaging-guided photo-immunotherapy. Among them, ICG as a donor of photoacoustic and fluorescence imaging applied for photoacoustic, photothermal and fluorescence imaging, and MIL101(Fe) is used for T2-weighted MRI (Figure 6C) [92].

In conclusion, the ultimate goal of bioimaging is to perform ultrasensitive detection of some biomolecules by probes to high resolution, signal stable images. Complementarity between the multimode imaging, cooperate with each other to achieve the ultimate purpose of bioimaging. Considering, only a tiny part of single-mode imaging and multimode imaging are mainly introduced. Other common imaging modes are listed in Table 3 below.

### Table 3. Bioimaging applications of MOFs

| Probes | Imaging agent | MOFs | Imaging applications | Detection objects | Refs. |
|--------|---------------|------|----------------------|-------------------|-------|
| HI-NMFO@SiO<sub>2</sub>/PEG | HI | Zr@UiO | CT | spleen and liver | [107] |
| Fe-MIL-53-NH<sub>2</sub>/FA-S-FAM/5-FU | Fe | Fe-MIL-53-NH<sub>2</sub> | OI and MRI | MGC-803/HASMC | [96] |
| RecnMFO@801 | R6G | MOF-801 | OI | FL83B | [108] |
| RhB@IL-MOF/5-FU/TCH | RhB | AI-MOF | OI | HASMC/MGC-803 | [109] |
| MCM@PEG/CO-DOX | CO | MIL-100 | MRI and PAI | HCT116 | [110] |
| MCH NPs | MIL-100 | PAl | HeLa | | [111] |
| TCPC-UoO | HI | Hi-UiO-66 | CT/thermal/photoacoustic | H<sub>2</sub>O | [112] |
| Gd/Tm-MOFs@mSiO<sub>2</sub>-FA | Gd | Gd/Tm-MOFs | UCL/MRI | MCF-7 | [113] |
| cal-TFP@DCAS-Uio(M6) | calcein | Uio-66 | OI | MCF-7 | [114] |
| NUS 27-29@SiO<sub>2</sub>/ZIF-8 | NUS 27-29 | ZIF-8 | OI | HeLa/MCF-7/231/NIH-3T3 | [115] |
| FeO<sub>2</sub>/RhB@Al-MOFs | FeO<sub>2</sub>/RhB | Al-MOFs | OI | Mg<sup>2+</sup> | [116] |
| UiO-68-R6G | UiO-68-R6G | OI | Mg<sup>2+</sup> | | [117] |
| UiO-66-NH<sub>2</sub>/N-CNDs | UiO-66-NH<sub>2</sub>/N-CNDs | OI | AS49 | | [118] |
| NaLm8@MOF-Ln | Eu<sup>3+</sup>, Tm<sup>3+</sup>/Yb<sup>3+</sup> | NaYF4, MOF<sуб>Y</sub> | OI | HeLa | [45] |
| FeO<sub>2</sub>/Uio-66-NH<sub>2</sub>/graphdiyne | DOX | FeO<sub>2</sub>/Uio-66-NH<sub>2</sub>/ (FU) | OI | HeLa | [34] |
| UiO-66@DOPA-LB | IR-800 | UiO-66 | OI | 4T1 | [119] |
| PdH-MOF | PdH-MOF | Pd-MOF | PAl | 4T1 | [120] |
| PCN-Cu5-F-A-ICG | ICG | PCN-224 | OI and thermal imaging | MDA-MB-231 | [121] |
| DNA amplifier-MOF | Uio-66 | OI | mRNA | | [122] |
| DNA@Cu-MOF | Uio-66 | OI | mRNA | | [123] |
| FZIF-8/DOX-MIPs | FZIF-8 | DOX | ZIF-8 | OI | MCF-7 | [124] |
| RhB@F2O<sub>2</sub>/ZIF-8 | RhB | ZIF-8 | OI | HePeG-2 | [125] |
| Bismuth-Nu901 | Bismuth-Nu901 | CT | | | [20] |
| ZIF-8/DOX@ZrO<sub>2</sub>/ZIF-8 | ZrO<sub>2</sub> | ZIF-8 | CT | | [89] |
| Gd-MOFs/Glu/Yb-MOFs-Glu | Gd<sup>3+</sup>/Yb<sup>3+</sup> | Gd-MOFs/Yb-MOFs | MRI/CT | Kidneys, liver/gastrointestinal tract | [21] |
| Zn/TCP®PPEG NPs | Zn-TCP® | Zn-TCP® | SPECT | Liver, heart, muscle and tumor | [91] |
| HUC-PEG | Hf | Hi-Uio-66 | CT/photothermal | | [126] |
| Hf@HC-PCN-PEG | Hf@HC-PCN-PEG | PCN-224 | SPECT | | [90] |
| PCN-222(Mn) | Mn | PCN-222(Mn) | MRI | | [127] |
| APT-MnZIF-90 | Mn | ZIF-90 | MRI | MCF-7 | [128] |
| FeO<sub>2</sub>/ZIF-8 | FeO<sub>2</sub>/ZIF-8 | ZIF-8 | MRI | Tumor and liver | [33] |
| DOX/Fe@G<sub>8</sub> | Fe | ZIF-8 | MRI | MCF-7 cells | [129] |
| Mn-ZIF-8 | Mn | ZIF-8 | MRI | U87-MG | [130] |
| FeO<sub>2</sub>/Bio-MOF | FeO<sub>2</sub>/FeO<sub>4</sub> | FeO<sub>4</sub>@Bio-MOF | MRI | MDA-MB-231 | [131] |
| DOX@PCN@MnO<sub>2</sub>/PAH | Mn<sup>2+</sup> | PCN-222 | MRI | 4T1 | [132] |
| Mn(II)-TCP® | Mn(III)-TCP® | Mn(III)-TCP® | MRI/OI | 4T1 | [41] |
| MCOOP-C6 | Mn<sup>2+</sup>/C6 | Mn<sub>2+</sub>/C6 | MRI/OI | 4T1 | [133] |
| INH-MOF | Fe | Fe-MIL-101-NH<sub>2</sub> | MRI | Lungs | [134] |
| Gd-ZMOF | Gd@III | Gd-ZMOF | MRI | 4T1 | [135] |
| FA-PPSM | Mn<sup>2+</sup> | Zr(IV) porphyrin MOF | MRI | Tumor | [136] |
| MIL-CuP® | Fe | MIL-88B | MRI | Liver and tumor | [137] |
| FeO<sub>2</sub>/ALA-Zn MOF | FeO<sub>2</sub>/ALA-Zn MOF | MRI | | | [138] |
| Hep(Rapi@MOF)/PCl | Fe | (MIL)-103(Fe) | MRI | | [139] |
| Gd@III-Functionalized Zr-MOFs | Gd@III | Zr-MOFs | MRI | | [78] |
| Au@Fe(BTC)@H<sub>2</sub>O<sub>3</sub> | Fe | Fe-MOF | MRI | MDA-MB-231 | [140] |
| Cu@Fe-MOF | Cu@Fe-MOF | MRI | CT26 | | [141] |
| FeO<sub>2</sub>/C-PVP@DOX | FeO<sub>2</sub>/C-PVP@DOX | Fe-MOF | MRI | | [43] |
| DOX@FeP<sub>3</sub>s | Fe | Fe-HMME | MRI | CT26 | [84] |

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Table 1. Probes, Imaging agents, MOFs, Imaging applications, Detection objects, and Refs.

| Probes                  | Imaging agent | MOFs       | Imaging applications | Detection objects | Refs |
|-------------------------|---------------|------------|----------------------|-------------------|------|
| Fe3O4@PDA@Au@MIL101-NH2| Fe3O4         | MIL-101    | MRI                  | Hela cells        | [142]|
| MIL-101(Fe)@io4         | Fe            | MIL-101    | MRI                  | HepG2             | [143]|
| Mn2+-DOX@MOF            | Mn2+         | UiO-66(Zr) (COOH)2 | MRI | 4 T1 | [144]|
| UiO-66-F/PEG-NPs        | F+           | UiO-66-F   | MRI                  | 4 T1 | [145]|
| Fe-Dox@Gd-MOF-ICG       | Gd, ICG      | Gd-MOF     | MRI/PAI/PTI          | 4T1              | [146]|
| UPPF                    | UCNPs/F+      | PCN-224(Fe) | MRI/OI              | U14              | [147]|
| Gd-PDA-Ce6@Gd-MOF       | Gd2+/PDA     | Gd-MOF     | MRI/PAI              | 4T1              | [148]|
| RhB@Gd-MOFs             | Gd2+/RhB     | Gd-MOF     | MRI/OI               | HepG2             | [149]|
| ICG@Mn/Cu/Zr-MOF@MnO2   | Mn2+/ICG     | ZIF-90     | MRI/OI/PTI           | U87              | [150]|
| Gd/Trm-FB@ZIF-8/PDA     | Gd2+         | ZIF-8      | MRI/OI/PTI           | 4T1              | [151]|
| PCN-224(Cu@GOD@MnO2)    | Mn2+/porphyrin| PCN-224   | MRI/OI              | U14              | [152]|
| Fe@Por-MOFs              | Fe/Pt        | MIL-101(Fe)| MRI/CT              | 4T1              | [153]|
| UCMOF@Do3               | UCNPs        | UCMOFs     | MRI/OI(UCL)          | HeLa             | [153]|
| ZIF-8/DMPP              | Mn2+/PDA     | ZIF-8      | MRI/PAI              | PC-3             | [154]|
| FA-Hf-Mn-NMOF           | Hf/Mn2+      | Mn-TCPP    | MRI/CT/PAI           | SI80             | [103]|
| CM-MMNPs                | Mn2+/porphyrin| Zr-TCPP    | MRI/OI               | HeLa             | [155]|
| IL8-MIL-101(Fe)@BSA-AuNCs| Fe/AuNs     | MIL-101(Fe)| MRI/OI              | H22              | [40]  |
| Fe/La-MOFs               | Fe2+/DOX     | La-MOFs    | MRI/OI               | 4T1              | [156]|
| Fe-MOF-5-NH2-F@5-FAM/5-FU| FeIII/5-FAM  | Fe-MOF     | MRI/OI               | HepG-2           | [157]|
| FA-NPMOFs               | Gd2+/porphyrin| Gd-MOF     | MRI/OI               | HepG-2           | [158]|

Magnetic resonance imaging (MRI); photoacoustic imaging (PAI); polydopamine (PDA); photoactive tetratopic chlorin (TCPP); optical bioimaging (OI); photothermal imaging (PTI).

Figure 6. A) a) Schematic diagram of the synthesis and biological application of Au@MIL-88(Fe) nanostars. b, c) CT images of mice; d, e) T2-weighted MR images of mice; f, g) in vivo PA imaging of tumors in mice; h) quantified MRI and CT signals of tumors from mice; i) bioluminescent imaging of tumor. Reproduced with permission.[105] Copyright 2017, Wiley. B) Schematic illustration of the preparation and its bio-application for multimodal imaging-guided phototherapy of Cypate@MIL-53/PEG-Tf (denoted as “CMNP-Tf”) nanoparticle. Reproduced with permission. [106] Copyright 2019, American Chemical Society. C) Schematic diagram of preparation and multimodal imaging-guided photo-immunotherapy of ICG-CpG@MOF. Reproduced with permission.[92] Copyright 2021, Elsevier.
Discussion and Prospectives

In this review, a systematic introduction of the MOF-based imaging system was presented, and several common sensors and the mechanisms of sensing were summarized. The imaging models were divided into single modal imaging and multimodal, depending on whether it is for single or multiple imaging. In the single-mode imaging section, some common imaging modes, such as optical imaging, MRI, and CT were highlighted. To the best of our knowledge, the optical imaging section has seldom been classified and described according to the doping situation. For the multimode imaging part, several of the most recent typical imaging modes have been introduced, such as MRI/optical imaging.

The current achievements exhibited the promising future of MOF for bioimaging. However, there are still many challenges that cannot be ignored. For example, MOF as a hybrid material containing metals and organics, biotoxicity and biocompatibility are the biggest challenges limiting the further clinical applications of MOF. Secondly, the poor colloidal stability and solubility of MOFs in biological media greatly limit their application for in vivo biological imaging. Thus, green synthetic routes and the “from source design” strategy should be adopted.

As far as bioimaging is concerned, the challenges are mainly in the following aspects: (1) Designing high resolution, signal stability, intelligent targeted and extend fluorescence lifetime imaging systems; (2) Reducing biotoxicity and increases biodegradability. Take MRI as an example, the toxicity of Gd³⁺, Mn²⁺ has limited its widespread clinical use due to their irreversible and tight binding to the serum proteins [159], also, Gd³⁺ may cause deposits in the brain [160]. (3) Reducing the amount of contrast agent when maintaining the same effect is needed to decrease the side effects.

Conclusion

In this review, the unique properties of MOF, such as rational aperture design, diversity, easy to functionalization, high BET/Langmuir surface area, etc., were highlighted, showing the incomparable charm of MOF. Meanwhile, the review also summarizes and discusses the bioimaging applications based on MOF, indicating MOF is a quite promising platform for bioimaging. Biotoxicity and lacking clinical studies are major problems for MOF-based bioapplications. Although MOF is still in its infancy, with the overcome of weaknesses, MOF-based bioimaging platforms are promising in the future.

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Competing Interests

The authors have declared that no competing interest exists.

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