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Review

Current and emerging applications of nanostructured metal–organic frameworks in cancer-targeted theranostics

Buddolla Anantha Lakshmi, Sanghyo Kim*

Department of Bionanotechnology, Gachon University, San 65, Bokjeong-Dong, Sujeong-Gu, Seongnam-Si, Gyeonggi-Do 461-701, Republic of Korea

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ABSTRACT

Nanostructured metal-organic frameworks (N-MOFs) are crystalline coordination nanopolymers in which metals are conjugated with organic and inorganic linker molecules. At present, N-MOFs have attracted significant interest owing to their intrinsically high porosity and ultrahigh surface areas, which allow them to be loaded with a broad array of materials, including drug molecules. In addition, N-MOFs possess other unique properties, such as good mobility, high reactivity, outstanding stability, real-time intracellular pH sensitivity, photosensitization, and penetration ability, which make them suitable candidates as drug delivery carriers for cancer and other targeted therapies. The opportunity for using a diverse array of chemical building components in N-MOFs facilitates the formation of structures with preferred properties for targeted therapy. In this review, we focus on the synthesis, characterization and other potential applications of N-MOFs in targeted theranostic nanodrug for cancer therapy.

1. Introduction

Nanostructured metal-organic frameworks (N-MOFs) or porous coordination polymers are hybrid materials that have self-assembled from organic bridging ligands with one-, two-, or three-dimensional structural topologies and metal-ion connecting points [1–3]. In addition, they are a class of materials with remarkable porosity, large internal surface areas, high thermal stability, and adjustable chemical functionality [4,5]. Because of their porous crystal nature, N-MOFs can be developed such molecules that can be accessed through their pores for various applications, including drug delivery, and researchers have thus aimed to use these structures to help patients by developing clinically functional formulations [6–8]. On the other hand, N-MOFs becoming the enticing material in cancer targeted therapy due to other fascinating features, that include, i) binding capacity of targeting ligands to cancer cells, ii) enhanced cytotoxicity of drug loaded N-MOFs, iii) pH-responsive drug delivery, and iv) photosensitizer- based performance [9–11]. Generally, targeted drug delivery system (DDS) requires four important steps: retain, evade, target, and release in addition to retain its components (encapsulated or associated) and allow to evade the body's defense mechanisms. Thereby, it targets the diseased site without affecting the healthy organs by releasing drugs at the diseased site [12]. In order to achieve the effective cancer drug delivery process, nanomedicine has to undergo the CAPIR cascade which includes, i) circulation within the blood stream, ii) accumulation in the tumor, iii) penetration deeply into the tumor tissue, iv) internalization into tumor cells, and v) intracellular drug release [13]. In addition, potential nanomedicine should meet the requirements of drug retention and release properties along with surface stealthy and sticky and “tumor penetration properties. Therefore, stability, surface, and size of nanoparticles are crucial for the effective action of nanomedicine in cancer therapy [14,15].

On the other hand, targeted drug delivery system by combining with chemotherapy plays a vital role in the mitigation of adverse effects that are raised in cancer [16]. Hence, for proper design and delivery of nanomedicine, we should consider the significant pharmacokinetic principle *i.e.* enhanced permeability and retention (EPR) effect. The passive targeting of nanomedicine occurs through characteristic features of solid tumors including leaky vasculature and defects in lymphatic drainage system, which permits nanomedicine to settle and accumulate within the tumor tissues. To achieve such targets, detailed investigations are necessary to assess the EPR effect of nanomedicines on the proper release of drugs in tumor tissues [17]. However, the therapeutic efficacy of anticancer drugs has remained an uncertain issue owing to their low biodistribution and unwanted side effects that occur even in healthy tissues. Because of its potential ability to overcome these issues, nanotechnology can play a vital role in achieving better therapeutic efficacy against cancer [18,19]. In recent times, N-

* Corresponding author.
E-mail address: samkim@gachon.ac.kr (S. Kim).

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MOFs are emerging as alternative nanocarrier platforms in the drug delivery [20–24]. For instance, dendrimers demonstrate hydrophobic pore cavities, which limits their physical encapsulation *i.e.* drug loading process. Comparatively, N-MOFs have the chance to enhance its drug loading process due to their proper selection of organic linkers. Further, in dendrimers, drug loading capacity is limited due to its small size. Whereas in N-MOFs, higher drug loading capacities are possible because of large pore volumes [25–27]. In addition, researchers should consider the practicality of N-MOF use in cancer treatment, given the limitations of using MOFs in the human physiological environment. Moreover, combining N-MOFs with diverse types of photosensitizers could be very advantageous in photodynamic therapy (PDT). N-MOFs with potential X-ray attenuating capabilities can induce radiotherapy (RT) and even enhance biodegradation owing to the presence of metal–ligand bonds. Thus, research has also focused on the application of a combination therapy using PDT and RT. For example, a remarkable anticancer therapeutic efficacy was observed *in vivo* using polyethylene (PEG)-coated N-MOFs comprising the X-ray attenuator hafnium (Hf^{4+}) and the photosensitizer tetrakis (4-carboxyphenyl) porphyrin (TCPP) in a "reoxygenation of tumor" process [28,29]. The present review discusses the synthesis and thorough characterization methods involved in the design of MOF-related nanoparticles. It focuses on the recently developed N-MOFs and the challenges faced in their application to the field of cancer therapy. Additionally, future aspects in the design of N-MOFs and their application in tumor-targeting therapies have been addressed.

2. Synthesis and characterization of N-MOFs

The structure of MOFs results from the coordination and self-assembly of metal cations and organic ligands/linkers. Several bonding types can be observed in a MOF crystal; namely, electrostatic interactions, hydrogen bonding, metal coordination, and pi-pi stacking [30]. The properties and structures of MOF crystals are greatly influenced by both the inorganic metal nodes (including metal ions or clusters) and the organic linkers. The linker-based tunability of the structure allows researchers to achieve the desired MOF properties, such as high surface area, meso/microporosity, and proper functionalization [31]. Some of the linkers typically used in MOF synthesis include carboxylates, phosphonates, and sulfonates. In the case of phosphonate linkers, their kinetics, protonation, and pH are the significant parameters benefiting self-assembly, whereas a dynamic nature and switchability are the two major benefits of using sulfonate linkers [32].

Traditionally, MOFs are produced using hydrothermal or solvothermal synthesis. Other methods have also been explored to improve MOF synthesis, including electrochemical, ionothermal, mechanochemical, microwave (MW)-assisted, and sonochemical techniques. The majority of MOFs are synthesized through crystallization in a solution. In most cases, solvents and other residues are trapped within the pores of the material and thus activation and purification are required. Purification is typically performed to remove impurities that might interfere with the performance of the MOFs, whereas activation is required to evacuate the trapped molecules from the pores [33]. Interestingly, Bae et al. compared two evacuation methods: $CHCl_3$ exchange, and supercritical drying. After characterization of the MOF crystals, supercritical drying was found to be the more effective method [34].

2.1. Solvothermal synthesis

In solvothermal synthesis, a mixture containing the precursors is heated to the boiling point of the solvent, resulting in high-quality crystals at higher yields. However, the drawbacks of using this conventional method are a longer synthesis time and the need for special equipment. In contrast, non-solvothermal synthesis uses lower temperatures, has no need for complex equipment, and can be performed in an open system at atmospheric pressure. Notably, it is necessary to choose the appropriate metal salt, organic linkers, solvent, and physical parameters in order to achieve crystallization [35].

Pachfule et al. carried out the solvothermal synthesis of fluorinated MOFs (F-MOFs); namely, F-MOF-4, Cu-F-MOF-4B, and Zn-F-MOF-4B, using 4,4′-(hexafluoroisopropylidene) *bis* (benzoic acid) (H_2hfbba) as the linker, 3-methyl pyridine as the co-ligand, and *N*,*N*-diethylformamide (DEF) or *N*,*N*-dimethylformamide (DMF) as the solvent. Perfluorinated polycarboxylates, like H_2hfbba, are typically used to produce F-MOFs owing to their inherent porosity and potential for added functionalities. Cu-F-MOF-4B was synthesized by heating a mixture of DEF, 3-methylpyridine, H_2hfbba, and $Cu(NO_3)_2{\cdot}3H_2O$ at 85 °C for 4 days [36]. In a different approach, McKinstry et al. investigated a continuous method for the solvothermal synthesis of MOF-5. They developed a continuous stirred tank reactor that was composed of three sections: feed, reactor, and collector. Inside the feed tanks, both solutions were stirred and heated to promote complete dissolution of the precursors. The feed tank fed the terephthalic acid and zinc nitrate solutions into the reactor, wherein the reaction took place. Products were pumped from the bottom of the reactor into glass vials. Unfortunately, certain cases of one-pot synthesis led to the formation of two or more phases, requiring phase separation, which is often challenging [37]. Xu et al. reported a fast and efficient seed-mediated approach in synthesizing phase-pure MOFs. They prepared different recipes and heated the solutions at 120 °C for 24 h in an oven. Seed crystals were added to each reaction to bypass the nucleation stage and to serve as the template for the growing MOFs. As the precursors were depleted from the solution, the formation of unnecessary growth was prevented [38].

2.2. Microwave-assisted synthesis

As a long synthesis time is a common issue among the solvothermal methods, different approaches were developed to address this problem. The use of MW as a heat source for the synthesis permits the rapid and efficient formation of MOFs. The solvents used in MW-assisted synthesis should not significantly influence the penetration depth of the MW radiation and must be able to convert the MW radiation into heat [39].

2.3. Room temperature synthesis

Several studies have indicated the possibility of MOF synthesis at room temperature, which is an ideal method for reactants with thermal sensitivity. Tranchemontagne et al. managed to synthesize MOFs with ultrahigh porosity, one-dimensional pores, and open metal sites: namely, MOF-5, MOF-74, MOF-177, MOF-199, and IRMOF-0. Based on their characterization by powder X-ray diffraction (PXRD), thermogravimetric analysis, Fourier-transform infrared (FTIR), and sorption experiments, room temperature synthesis is a viable alternative method to solvothermal synthesis, but for a shorter duration [40]. Moreover, Hu et al. investigated the synthesis of Prussian Blue analogs using the room temperature approach. This method is considerably cheaper than complex processes like the hydrothermal, MW-assisted, and sonochemical approaches. Those authors were able to produce $Cd_3[Co(CN)_6]_2{\cdot}nH_2O$ with different structures; namely, nanocubes and octahedrons. The synthesis involved the preparation of an aqueous mixture containing $K_3[Co(CN)_6]_2$, $CdCl_2{\cdot}nH_2O$, and poly(vinylpyrrolidone) (or sodium dodecyl benzenesulfonate for the octahedron). The cubic $Cd_3[Co(CN)_6]_2{\cdot}nH_2O$ had good crystallinity as suggested by PXRD analysis. Unfortunately, both structures had a lower porosity and surface area than their bulk versions owing to the presence of guest molecules trapped inside the framework [41].

2.4. Chemical vapor deposition

The catalytic applications of MOFs are often limited by certain

factors. Lower stability toward temperature, moisture, or impurities has been observed in some MOFs. Moreover, some materials have metal centers that are inaccessible for adsorption owing to their coordination with linkers. Using the chemical vapor deposition method, Zhang et al. created a Pd-based catalyst using [$Pd(C_3H_5)(C_5H_5)$] (a volatile metal–organic precursor that has a low decomposition temperature under an H_2 environment), with MOF-5 acting as a support. Samples of activated MOF-5 and [$Pd(C_3H_5)(C_5H_5)$] were mixed in a container and then subjected to the evacuation process. This was followed by Pb loading under static vacuum conditions at room temperature. Lastly, hydrogenation was employed. [$Pd(C_3H_5)(C_5H_5)$]@MOF-5 retained most of the properties of pure activated MOFs. Isotherm measurements suggested that the MOF formed was microporous. The catalytic abilities of the framework were observed to be higher in samples with a higher Pd loading [42].

2.5. Electrosynthesis

Electrochemical synthesis allows the continuous production of MOFs and offers mild conditions, simple processes, and easy cleanup. Joaristi et al. tested different parameters for the electrochemical synthesis of MOFs, using different metals (Cu, Zn, and Al) and linkers (di/tridentate carboxylic acids and imidazoles) [43]. The electrochemical synthesis resulted in a high yield of Hong Kong University of Science and Technology framework (HKUST)-1 and synthesis of zeolitic imidazolate framework (ZIF)-8 at 0 °C. The use of acidic *bis*(trichloromethyl) carbonate (BTC) and a neutral pH enabled the production of an aluminum trimesate analog of the Materials of Institut Lavoisier (MIL)-100 MOF, MIL-100(Al). In another study, Yang et al. synthesized MOF-5 (IL) *via* electrochemical method using tunable ionic liquid (IL), 1-butyl-3-methylimidazolium chloride, as a template and further used in the enhancement of photocatalytic potential of bismuth oxyhalide (BiOBr) [44].

2.6. Mechanosynthesis/solvent-free synthesis

A solvent-free approach permits rapid and high-yield MOF synthesis. A one-step activation of the materials was enough to significantly increase the specific surface area of the materials. In a mechanosynthesis reported by Tella et al. [$[Cu(NO_3)_2(bipy)_2](py)_2$] was synthesized by grinding the reagents using a mortar and pestle, following which the light green powder was purified and activated. The as-synthesized MOFs were thermally stable up to 100 °C. This process was comparatively faster than the other conventional methods, where no heating was required. More importantly, it offers a green alternative for traditional methods because fewer or no wastes are produced [45]. In one study, two bismuth-based MOFs were synthesized using either benzene-1,4-dicarboxylate or pyridine-2,5-dicarboxylate as linkers [46]. Both MOFs were produced by grinding the reactants using a ball mill. The dried slurry from the process was characterized using XRD analysis to determine the completeness of the reactions. Klimakow et al. also used the ball mill method for the mechanosynthesis of HKUST-1 and MOF-14. Liquid-assisted milling of the precursors was done for 25 min. The synthesized MOFs had PXRD patterns that were comparable to the theoretical pattern [47].

2.7. Sonochemical synthesis

The sonochemical approach relies on the formation and collapse of cavities. Cavitation provides agitation to increase contact between the reactants. As ultrasonic waves propagate across the medium, dissolved gases are released from the liquid and create gas voids called cavities [48]. Kim et al. described the sonochemical synthesis of $Cu_3(BTC)_2$ using choline chloride/dimethylurea. A mixture of Cu(II) nitrate hydrate, H_3BTC, choline chloride, and 1,3-dimethylurea was prepared and placed in a Pyrex reactor fitted to an ultrasonic generator (VCX500). Effective activation of the material prior to the solidification of the framework significantly improved the BET values with no drastic effect on the structure itself. It was found that a synthesis time of 60 min could lead to optimal properties. However, sonication beyond 60 min caused structural deterioration [49]. Moreover, Carson et al. investigated the additive-assisted sonochemical synthesis of Cu-4,4′-hexafluoroisopropylidene-*bis*-benzoate (Cu-hfipbb) by sonicating a reaction mixture containing deionized water, H_2hfipbb, and Cu(II) nitrate hemi (pentahydrate). Unfortunately, the overall yield was considerably lower than that obtained from the other sonochemical methods. The presence of 2-propanol caused morphological changes, from long needles to isotropic particles. According to the CO_2 isotherm measurements, there was no reduction in the porosity despite the decrease in size. In addition, higher adsorption capacities were observed [50].

3. Characterization

The characterization of MOFs requires the use of different methods that are appropriate for the study of their structure, thermal stability, and surface area. The high porosity of MOFs is reported to be superior to that of other materials, such as activated carbon, silica gels, and zeolites [51]. The morphology of MOFs can be studied through microscopy. Transmission electron microscopy provides insights into the presence of internal defects. Additionally, scanning electron microscopy (SEM) and atomic force microscopy (AFM) can provide additional information on the morphology of the crystal, as demonstrated in a study by Rodenas et al. where SEM and AFM revealed the size and stacked orientation of copper 1,4-benzenedicarboxylate nanosheets [52].

X-ray diffraction analysis is generally used for investigating the crystallinity and purity of the synthesized materials [36]. MOFs with smaller crystals are characterized by PXRD, which is useful for detecting and explaining differences or similarities between products prepared under different conditions or methods [48]. Sharp peak patterns usually indicate the high crystallinity of MOFs [39]. Experimental peak patterns are usually compared with theoretical patterns to establish whether the MOF synthesis had resulted in high-quality materials. Beside from XRD, X-ray absorption spectroscopy is also used to study the structure of the crystals, and active sites within the framework [48]. Additionally, FTIR spectroscopy can be employed for identification of the presence of a compound. Zhang et al. used the Nicolet Impact 410 spectrometer to collect FTIR spectra from the samples. The spectra further confirmed the presence of trapped guest molecules inside the MOF [42]. Several studies have also used Raman spectroscopy for additional confirmation of results. Tröbs et al. compared the Raman spectra of the products with those of the starting materials to determine the completeness of the reaction [46]. Furthermore, thermogravimetric analysis can determine the thermal stability of MOFs [37]. Mass changes are monitored in response to increasing temperature. Despite their superior porosity, MOFs suffer from lower thermal stability than zeolites do [48]. Using MW-assisted synthesis, Taddei et al. were able to synthesize UiO-66 with thermal stability up to 450 °C [52].

Lastly, adsorption isotherm measurements can be employed to evaluate the pore size and storage capabilities of MOF crystals [37]. Degassing of the samples is performed prior to the adsorption experiments [52]. Moreover, the BET method, which evaluates the relationship of adsorption with pressure and temperature, can be used to determine the total surface area of a given material. In a study conducted by Pachfule et al. F-MOF samples were subjected to H_2 and CO_2 adsorption-desorption experiments using a Quantachrome Quadrasorb automatic volumetric instrument at 77 K and room temperature, respectively. It was revealed that the samples were nonporous to N_2 but were able to adsorb H_2 and CO_2. Small-angle X-ray scattering can provide supplementary data for studying the pore size of MOFs [36]. Fig. 1 presents a flowchart of the sophisticated methods associated with the fabrication of MOFs.

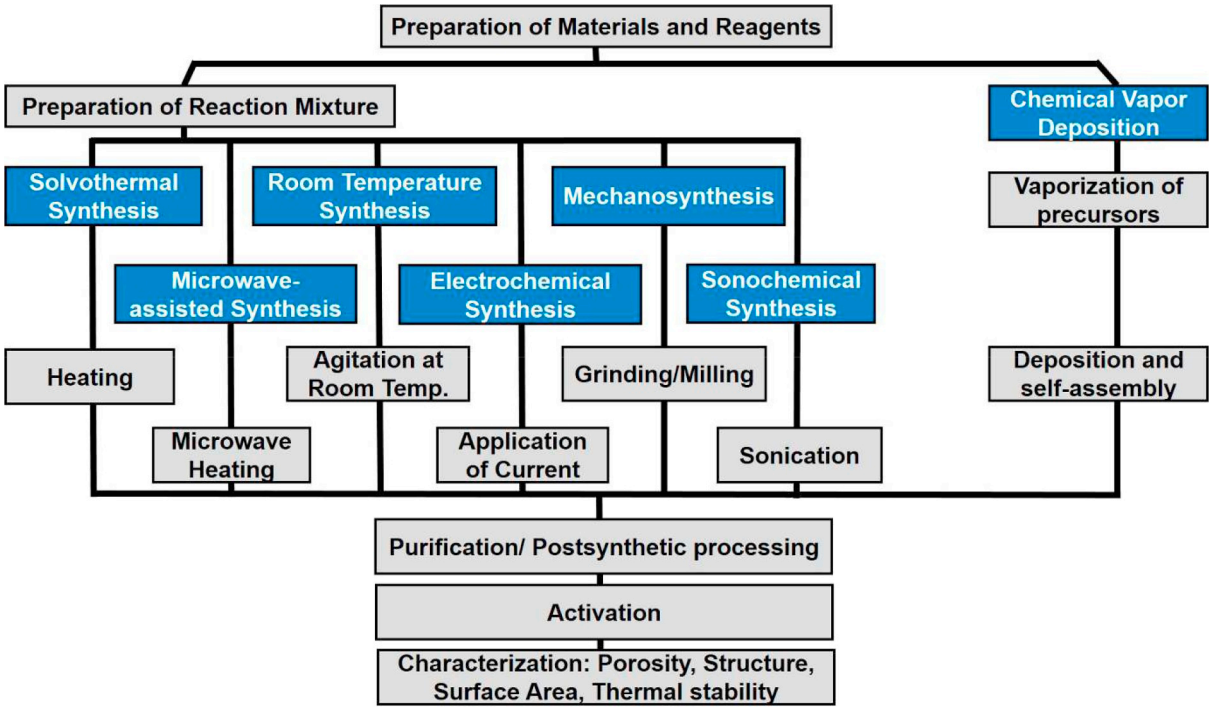

Fig. 1. A flowchart presenting the sophisticated methods associated with the fabrication of MOFs.

4. Recent applications of N-MOFs in cancer-targeted therapy

N-MOFs have come out as promising candidates for biomedical applications, particularly in cancer-targeted therapy as they are appropriate for the diverse administration routes. Before moving toward the applications of N-MOFs, a brief note on EPR effect is necessary. Nanomedicine-derived therapeutics has evolved as a magnificent approach in the tumor targeting therapy by eliminating specificity problems occurred from conventional chemotherapeutics. For this purpose, researchers need to recall the EPR effect. Significantly, three major benefits can be noticed with nanomedicines by avoiding the EPR effect. Those include i) lowered toxicity of chemotherapeutics, ii) anticancer drug delivery at specific site, and iii) imaging of microenvironment of tumors [53]. Following are the most recent appropriate studies that are concerning the use of N-MOFs in cancer-targeted therapy *via* controlled drug release, imaging, biocatalysis or sensing.

In a study, He et al. reported the use of N-MOFs for the co-delivery of cisplatin and pooled small interfering RNAs to intensify the therapeutic efficacy of the anticancer drug by silencing multiple drug resistance genes and resensitizing resistant ovarian cancer cells to cisplatin treatment. MIL-101, a biocompatible, degradable, and highly water-stable MOF, has been applied as a doxorubicin (DOX) delivery system in cancer therapy by means of simple surface modification [54,55]. Interestingly, N-MOFs loaded with 5-fluorouracil (5-FU) have shown efficient cytotoxic effects toward cancer cells and enhanced the intracellular uptake of nanoparticles within the cells [56]. Additionally, biodegradable core-shell dual-MOFs have been designed for chemothermal cancer treatment, *in vivo* synchronous diagnosis, and therapy monitoring applications by applying a Prussian blue MOF core surrounded by a ZIF-8 shell [57].

Wang et al. developed MOFs with polymer composites (UiO-66@CyP) using the cyanine polymer *via* Passerini reaction. The product possessed properties that could rapidly advance cancer therapy, such as size homogeneity, adjustable morphology, and outstanding dispersibility in the aqueous environment. In addition, the presence of carboxyl, aldehyde, and isocyano groups in the MOFs rendered them as potential photothermal therapy (PTT) agents for the purpose of cancer cell ablation, using low-power laser irradiation and near-infrared fluorescence imaging agents [58]. In another study, a ZnMOF was developed using free acidic groups (-COOH) and antibodies. The product provided excellent targeting efficiency and capture ability, and selectivity in the recognition of cancer cells. Furthermore, Qi et al. have developed a potential MOF-mediated immunotrapper system that enables targeted cell sequestration along with drug delivery for efficient cancer treatment [59].

Ranji-Burachaloo et al. designed a reduced iron MOF conjugated with folic acid (rMOF-FA) nanoparticles, which evolved into an interesting nanomaterial for cancer treatment, with a selectivity index of 2.45, which is comparatively higher than that of the available commercial drugs. Iron released from the rMOF-FA reacts with the hydrogen peroxide (H_2O_2) present in cancer cells, thereby increasing hydroxyl radical generation, which further results in the oxidation of lipids, DNA, and proteins to inhibit cancer cell viability [60]. In another study, aggregated gold nanoclusters were incorporated into MOFs (aAuNCs-MOFs), which demonstrated better biocompatibility and maximum luminescence. The as-prepared aAuNCs-MOFs had a faster rate of drug release, especially in acidic media (at pH 5.0 and 6.0), because ZIF-8 was very stable in media with a neutral pH (pH 7.4). Hence, the camptothecin delivered by aAuNCs-MOFs showed potential cytotoxic efficacy, and the system thereby provides a hopeful nanoplatform for the delivery of anticancer drugs into cancer cells [61]. Su et al. developed a medi-MOF-1 using Zn (II) and curcumin as the metal and linker, respectively, with ibuprofen as the model drug. The product's superior features, such as its high surface area (Langmuir model: 3002 $m^2 g^{-1}$), better degradation, suitable drug storage and release, and potential inhibition of pancreatic cancer cell growth (BxPC-3), demonstrate its promise as a pharmacological agent [62].

Another interesting development is the MOF@HA@ICG composite, in which MIL-100 (Fe) nanoparticles were conjugated with hyaluronic acid (HA) and indocyanine green (ICG). Through cancer-targeted and near-infrared image-guided drug delivery, both *in vitro* and *in vivo*, the MOF@HA@ICG nanoparticles were efficiently taken up by MCF-7 cells and prevented the growth of xenograft tumors [63]. The attractive advantages of MOFs have led to their emergence as promising cancer therapy and drug delivery candidates in recent years [64–67]. These advantages include their benefits of i) stimulus-responsive drug-

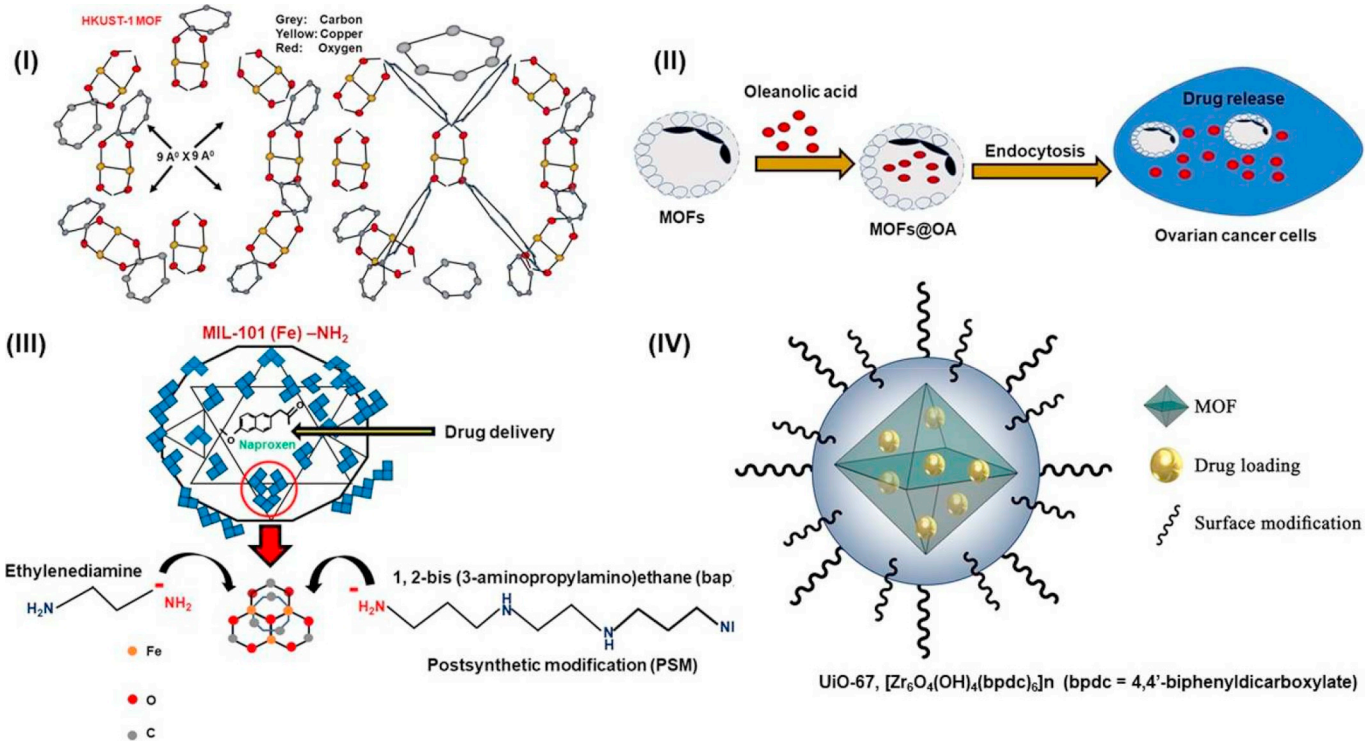

Fig. 2. Overview of recent MOFs employed in the drug delivery systems [73–76].

controlled release, ii) maximum drug-loading capacity, and iii) suitable biodegradability, owing to their versatile morphology, high porosity, and extremely high surface area as well as weak coordination bonds. Lian et al. developed an enzyme-MOF nanoreactor, in which a prodrug would activate and produce a cytotoxic substance. This system prevented cell proliferation and demonstrated efficient apoptotic/necrotic behavior by inducing oxidative stress in the cells [68]. MOFs have been applied as suitable vehicles of payloads in drug delivery systems and incorporated into therapeutic nanoreactors, where very low acute toxicity was observed. Notably, the systematic design of biocompatible and biodegradable MOFs for *in vivo* conditions is always appreciable [69].

Yang et al. used Mn^{2+}, the near-infrared dye IR825, and a shell coating of polydopamine (PDA) to produce Mn-IR825@PDA-PEG N-MOPs by the self-assembly process. These demonstrated potential therapeutic capabilities, such as i) efficient tumor homing, ii) better tumor-targeted imaging, iii) strong near-infrared absorbance, iv) rapid renal excretion rates, v) time-dependent biodistribution, vi) excellent biodegradability, and vii) excellent photothermal behavior and safety *in vivo*. More importantly, the above advantages provide increased hope regarding the real-world translation of MOFs from preclinical testing to clinical drug development against cancers [70]. The combination of both PTT and chemotherapy has shown tremendous results in the killing of cancer cells. In this regard, the polypyrrole (PPy)-based PPy@MIL-100-DOX composite has exhibited excellent therapeutic efficacy [71].

Since potential cancer drugs can be delivered *via* MOFs, it is important to functionalize the drugs by tuning the various nanomaterials. Microporous MOFs were designed using 5-FU as the model cancer drug, with results in the HepG2 human hepatoblastoma cell line and MDA-MB-435S human breast ductal carcinoma cell line showing better drug-loading capacities and drug release profiles [72]. Chen et al. successfully synthesized stable HKUST-1 MOFs for the controlled drug release of pharmaceutical products such as ibuprofen, anethole, and guaiacol. In a study, Zhang et al. successfully designed hollow N-MOF as a superior drug delivery vehicle, which demonstrated enhanced drug loading capacity and sustained release. In another study, zirconium N-MOFs were developed with advanced features such as low toxicity, aqueous stability, and stimuli-responsive drug release [73–76]. Some of the recent MOFs employed in drug delivery were depicted in Fig. 2.

4.1. N-MOFs in pH-responsive tumor-targeted drug delivery

3-MA@ZIF-8 nanoparticles comprising the autophagy inhibitor 3-methyladenine (3-MA) were developed. They have shown promising advantages such as outstanding stability, biocompatibility, and a uniform shape and size. Interestingly, these 3-MA@ZIF-8 nanoparticles achieved pH-sensitive tumor-targeting drug delivery with controlled drug release [77]. In another study, polyacrylic acid (PAA)-based PAA@ZIF-8 nanoparticles were shown to be promising anticancer material for their maximum drug-loading capacity and pH-sensitive drug release characteristics, where selective release of the encapsulated drug in tumors was possible owing to the pH-responsive behavior [78]. Yan et al. designed (polyacrylic acid sodium salt) (PAAS)-based PAAS@ZIF-8 nanocomposites (30–200 nm in size) with superior features, such as high drug-loading capacity, pH sensitivity, and good release kinetics, making them promising as drug delivery vehicles and suitable N-MOFs in cancer therapy [79]. The curcumin (CCM)-loaded CCM@NZIF-8 nanoparticles developed by Min et al. showed excellent high biocompatibility and enhanced stability in physiological conditions, making them an optimal carrier for cancer drug delivery. Interestingly, the anticancer properties of the CCM@NZIF-8 nanoparticles were beneficial in achieving antitumor activity both *in vitro* and *in vivo* [80]. The Zr- and UiO-66 nanoparticle-based MOFs have also shown better drug-capturing abilities and pH-sensitive drug release, providing effective antitumor activity in the MCF-7 and HepG2 cell lines [81]. Zhuang et al. developed ZIF-8 nanospheres (70 nm in size) with better cellular uptake and control of the behavior of small-molecule loading, which resulted in easy tuning of the physicochemical properties and pH-responsive disintegration of the ZIF-8 framework. Such versatile nature of ZIF-8 nanospheres will have potential impact in cancer treatment [82]. Liang et al. constructed pH responsive core@shell

nanocomposite using BSA/DOX nanoparticles as cores and ZIF-8 as a shell. In this DDS, drug release can be facilitated at low pH (5.0–6.0), which is the favorable environment for tumor growth. However, ZIF-8 as a shell providing the safety in storing DOX at physiological pH 7.4 and overcomes its release. Interestingly, ZIFs provide the huge number of positive charges to the BSA/DOX nanoparticles and can enhance the cellular uptake because of the negatively charged cell membranes [83]. Interestingly, Zheng et al. developed pH induced one-pot process for the encapsulation of DOX and three organic dyes (rhodamine B, methyl orange, methylene blue) into the ZIFs with highest loadings (14–20 wt %). The above pH-responsive DDS using ZIFs have shown controlled drug release in the pH range (5.0–6.5). But no drug release was observed at physiological (PBS, pH 7.4) [84]. A detailed list of MOFs used in cancer drug delivery is presented in Table 1. In a different and novel approach, Wuttke et al. designed N-MOFs that were coated by a bilipid layer, which resulted in their excellent uptake by cancer cells. These lipid layers allowed the MOFs to store various imaging, diagnostic, and drug moieties. Hence, these MOF@lipid nanoparticles could be used in both drug delivery and diagnostics [85]. Generally, hypoxic cancer cells possess higher amounts of H_2O_2, but conversion of the H_2O_2 to O_2 through the Fenton reaction minimizes the hypoxia. In this regard, N-MOFs (Fe-tributyl phosphate nano rice) were fabricated to overcome the hypoxic conditions so that PDT would be more effective, as well as to progress cancer immunotherapy. The combination of PDT with immune checkpoint blockade would provide antitumor immunity in the systemic circulation [86]. Lu et al. briefly described such a novel tumor therapy strategy, where they combined radiotherapy-radiodynamic therapy (enhanced by N-MOFs treated with low-dose X-rays) with checkpoint blockade immunotherapy [87]. A simplified overview of novel N-MOFs that have emerged in cancer therapy is illustrated in Fig. 3.

4.2. Recent photosensitizer-based N-MOFs in cancer treatment

Given that effective strategies are always crucial in cancer research; MOFs have been designed using materials more suited for loading novel photosensitizers for use in PDT. Metal-functionalized N-MOFs that are activated by hydrogen sulfide (a signaling molecule in tumor cells) and that release singlet oxygen ($^1O_2$) in a controlled manner have already been constructed. These N-MOF photosensitizers have demonstrated excellent tumor removal capabilities (*in vivo* results) and maximum photosensitizer-loading capacity [88]. Recently, platinum-nanozyme-decorated MOFs (PCN-224–Pt nanoconjugates) were found to offer possible PDT efficiency, excellent stability, and catalase-like behavior *via* the formation of O_2 in the hypoxic tumor regions, thereby providing a potential platform for cancer therapy [89]. Novel N-MOFs have been constructed as multifunctional nanoprobes, using cathepsin B as a potential PDT agent, with high specificity and efficiency in cancer therapy. Furthermore, the reduction of side effects, retardation of multidrug resistance, and reduction of the low efficiency of PDT in hypoxic (reduced oxygen condition) cells have made MOFs potential agents in cancer therapy [90]. Bůžek et al. designed PCN-222/MOF-545 nanoparticles, which induce cancer cell apoptosis by means of oxidative stress. Interestingly, that research group proposed some interesting phenomena related to the photosensitizing behavior of the N-MOFs, in that it depended on their morphology, size, and application attributes [91]. Kan et al. designed a UiO-66 type of N-MOF using *S*-ethylthiol ester monosubstituted metal-free porphyrin (TPP-SH) by means of post-synthetic modification. The resultant TPP-SH@UiO-66 composite showed superior photodynamic activity, making it a potential PDT agent in cancer therapy [92]. Park et al. synthesized size-controlled PCN-224 nanoparticles using Zr (IV)-based porphyrinic MOFs and H2TCPP (an organic linker). The PCN-224 nanoparticles were synthesized at different sizes (*i.e.*, 30, 60, 90, 140, and 190 nm), among which the 90-nm nanoparticles demonstrated the maximum Zr uptake in cells and a significantly higher uptake of TCPP by the MOF structure. Moreover, active targeting and enhanced PDT efficacy were observed [93]. Recently, photoactive porphyrin-porous organic polymers (H_2P-POPs) were coated onto the surface of amine-containing UiO-66 MOFs to produce MOFs@POP nanocomposites. These so-called “UNM” composites ensured better PDT efficacy by generating $^1O_2$ in the cancer cells and inducing cell apoptosis [94]. Park et al. demonstrated an energy-transfer-based $^1O_2$-controlled PDT mechanism by employing Zr-MOFs as nanocarriers, where the photosensitizing system incorporated in the MOF pores regulated $^1O_2$ generation with the aid of a photochromic switch. Facile tuning of the ratios between the photosensitizer and the switch molecule enabled the control of $^1O_2$ generation, thereby providing improved PDT efficacy in cancer treatment [95]. A brief outline of recent photosensitizer-based N-MOFs used in cancer PDT is summarized in Fig. 4.

4.3. Biocompatible and water resistance MOFs

Currently, non-toxic and biocompatible MOFs draw more attention in the pharmaceutical and biomedical applications. Whereas, previously reported MOFs, which were designed using different metals such as Co, Ni, and Cr were non biocompatible. In order to overcome the toxicity problem, Horcajada et al., designed non-toxic iron (III) carboxylate MOFs including MIL-53, MIL-88A, MIL-88Bt, MIL-89, MIL-100, and MIL-101_NH_2. These MOFs are biocompatible and prepared using biologically benign water or ethanol as a medium by avoiding other organic solvents. In addition, C. O. Tavra et al. developed Zr-based MOF, in which anticancer drug *i.e.* α-cyano-4-hydroxycinnamic acid (α-CHC) was loaded and evaluated their controlled drug delivery release. Interestingly, these MOFs are biocompatible and effectively able to penetrate the cells. It demonstrates that MOFs are suitable DDS for cancer therapy [96]. Biocompatible MOFs were synthesized from γ-cyclodextrin (γ-CD), which are highly nontoxic and stable in nature [97]. In one study, Horcajada et al. designed two MOFs by employing fumarate and galactarate for effective loading and release of drugs. Significantly, their degradation clearly indicates that MOFs are low toxic and even biocompatible [7]. In addition, water-sensitivity is the major obstacle for MOFs to use in industrial and bio-applications. To solve this issue, several researchers synthesized a variety of water stable or hydrophobic MOFs. C. Wang et al. defined the water stable MOFs as MOFs which do not demonstrate structural breakdown after exposure to the water. In general, water stable MOFs can be classified into three types *i.e.* i) metal carboxylate frameworks with high-valence metal ions, ii) metal azolate frameworks consisting nitrogen-donor ligands, and iii) MOFs surface functionalized by hydrophobic pores. In the last decade, numerous water stable MOFs have been designed. (i) Zr-based PCN-228-230, PCN-521, PCN-777, NU-1000, NU-1105, MOF-808, MIL-160, MIL-163, FJI−H6, $[Zr_6O_4(OH)_4(btba)3](DMF)x(H_2O)y$, (ii) Hf-based PCN-523,22 FJI-H7; (iii) lanthanide element-based $[La(pyzdc)1.5(H_2O)2]2H_2O$, $([Dy(Cmdcp)(H_2O)3](NO_3)2H_2O)n$,$[Eu(HL)(H_2O)2]n2H_2O$,Tb-DSOA,$[Tb(L)(OH)].x(solv)$, $([Tb(L1)1.5(H_2O)]3H_2O)n$, (iv) Al-based MIL-121,CAU-10, and (v)In-based JLU-Liu18,InPCF-1 [98]. W. Zhang et al. designed MOFs using polydimethylsiloxanes (PDMS) as a hydrophobic layer for enhancing their water stability [99]. Generally, hydrophobicity of MOFs is classified based on the contact angles (CAs) with water. Contact angles between 90 and 150 are termed as hydrophobic. Whereas CAs > 150 are called as superhydrophobic and CAs much > 150 are referred as ultra-hydrophobic. In this context, few hydrophobic and superhydrophobic MOFs were developed including IRMOFs and MIL-53(Al)-NH_2, respectively by incorporating hydrophobic alkyl chains through PSM by Cohen et al. [100,101].

5. Challenges in using N-MOFs in cancer-targeted therapy

Despite the fascinating benefits associated with N-MOFs in biomedical applications, few challenges are still faced by their evolution into clinical nanotheranostics. Critical factors for the use of N-MOFs as a

Table 1
Drug delivery by recent metal–organic frameworks in cancer treatment.

S. No.	MOFs	Preparation strategy	Anticancer drug (or) cargo	Cell lines	Drug-loading capacity (wt%)	Drug-loading efficiency (wt%)	Drug release	Ref.
1	Microporous MOF [Zn8(O)2(CDDB)6(DMF)4(H_2O)]	Solvothermal method	5-FU	Human hepatoblastoma cell line (HepG2) and human breast ductal carcinoma cell line (MDA-MB-435S)	53.3%	–	64.9% (in PBS) 81.9% (in DI water)	72
2	3-MA@ZIF-8 NPs	ZIF-8 NPs encapsulated with 3-MA	3-MA	HeLa cells	19.8%	–	< 70% (in PBS pH 7.4) ≈ 40% (in PBS pH 6.0)	77
3	UiO N-MOFs	Encapsulation and surface coordination	Cisplatin/siRNAs	Ovarian cancer cell line (SKOV-3)	12.3 ± 1.2%	81.6 ± 0.6%	–	54
4	PAA@ZIF-8 NPs	Ion-exchange between Zn^{2+} and Na^{+}	DOX	Breast cancer cell line (MCF-7)	1.9 g DOX g^{-1} NPs	95%	35.6% (in PBS pH 7.4) 75.9% (in PBS pH 5.5)	78
5	ZIF-8	–	5-FU	–	45.4%	–	50% (in PBS pH 7.4)	107
6	ZIF-8-PAAS nanocomposites	Soft-template method	Doxorubicin	HeLa cells	385%	22%	–	79
7	CCM@NZIF-8 NPs	Nanoprecipitation	Curcumin	U14 Cervical cancer cells and HeLa cells	12.7%	88.2%	15.6% (in PBS pH 7.4) 43.4% (in PBS pH 5.5)	80
8	UiO-66 NPs	Solvothermal method	Alendronate	MCF-7 and HepG2 cells	51.4%	–	42.7% (in pH 7.4) > 59% (in pH 5.5)	81
9	ZIF-8 nanospheres	Encapsulation	Camptothecin	Breast cancer cell line (MCF-7)	2%	30%	–	82

3-MA: 3-methyladenine; CCM, curcumin; CDDB: 4,4′-(9-H carbazole-3,6-diyl) dibenzoic acid; DI: deionized; DMF: *N*, *N*-dimethylformamide; DOX: doxorubicin; N-MOF: nanostructured metal–organic framework; NPs: nanoparticles; PAA: polyacrylic acid; PAAS: poly (acrylic acid sodium salt); PBS: phosphate-buffered saline; siRNAs: small interfering RNAs; ZIF: zeolitic imidazolate framework.

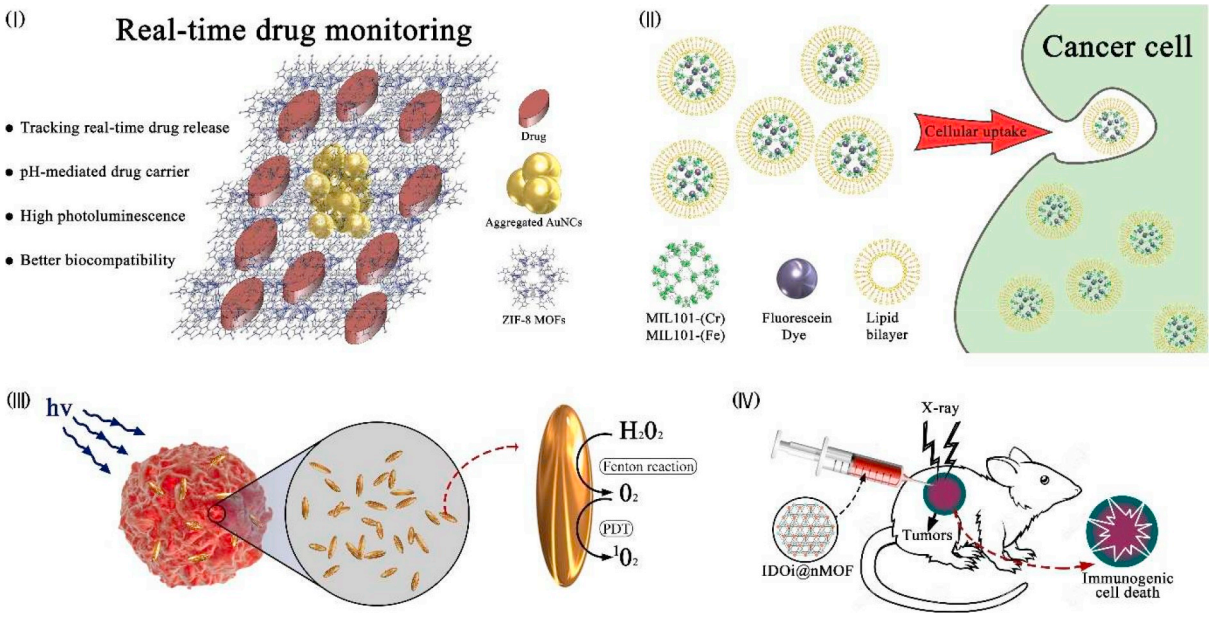

Fig. 3. A simplified overview of novel N-MOFs used as cancer therapeutic agents [61,81–83].

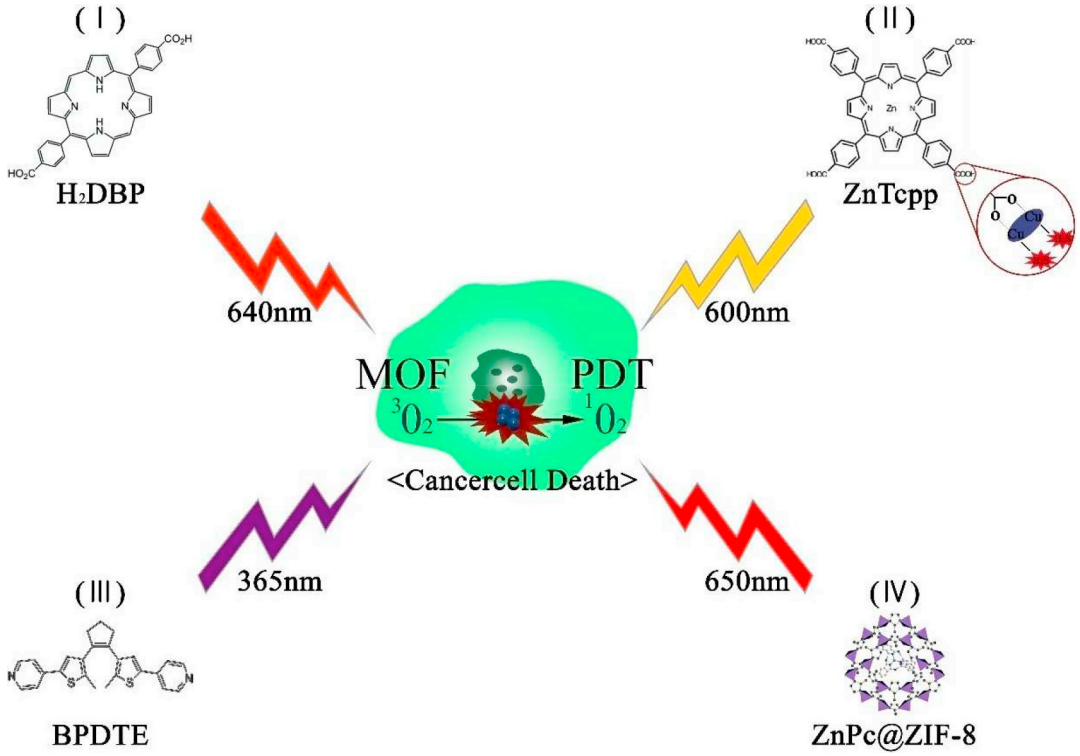

Fig. 4. A brief outline of recent photosensitizer-based MOFs used in cancer photodynamic therapy (PDT).

successful cancer-targeted therapy include i) the design of effective and functional building blocks for use in antitumor imaging and therapeutics, ii) the development of N-MOFs with ultra-small sizes, which will allow the sufficient integration of biomolecules, iii) improved stability, dispersibility, and surface modification of N-MOFs in order to achieve prolonged blood circulation, better tumor-targeting capacity, and induced cellular uptake, and iv) the development of biocompatible N-MOFs with low toxicity that are able to mitigate the adverse effects encountered in cancer [102]. The optimal *in vitro* and *in vivo* performances of N-MOFs should be thoroughly investigated according to their biodegradation and stability. In addition, deep studies related to the metabolic pathways involved and the mechanisms of N-MOFs as nanocarriers are crucial in the *in vivo* modalities. Other recent challenges have included the control of drug loading and drug release by the N-MOFs. To solve these issues, Wuttke et al. fabricated MOFs with lipid bilayers in which the drugs were encapsulated. Although these N-MOFs have potential benefits in imaging and efficient drug delivery, the cumulative accumulation of MOFs within the human body can become a considerable challenge owing to their heavy metal components, which leads to improper cancer treatment [103]. In the same vein, combination therapies using PTT/chemotherapy with gene therapy, radiotherapy, and immunotherapy have also shown critical challenges, such

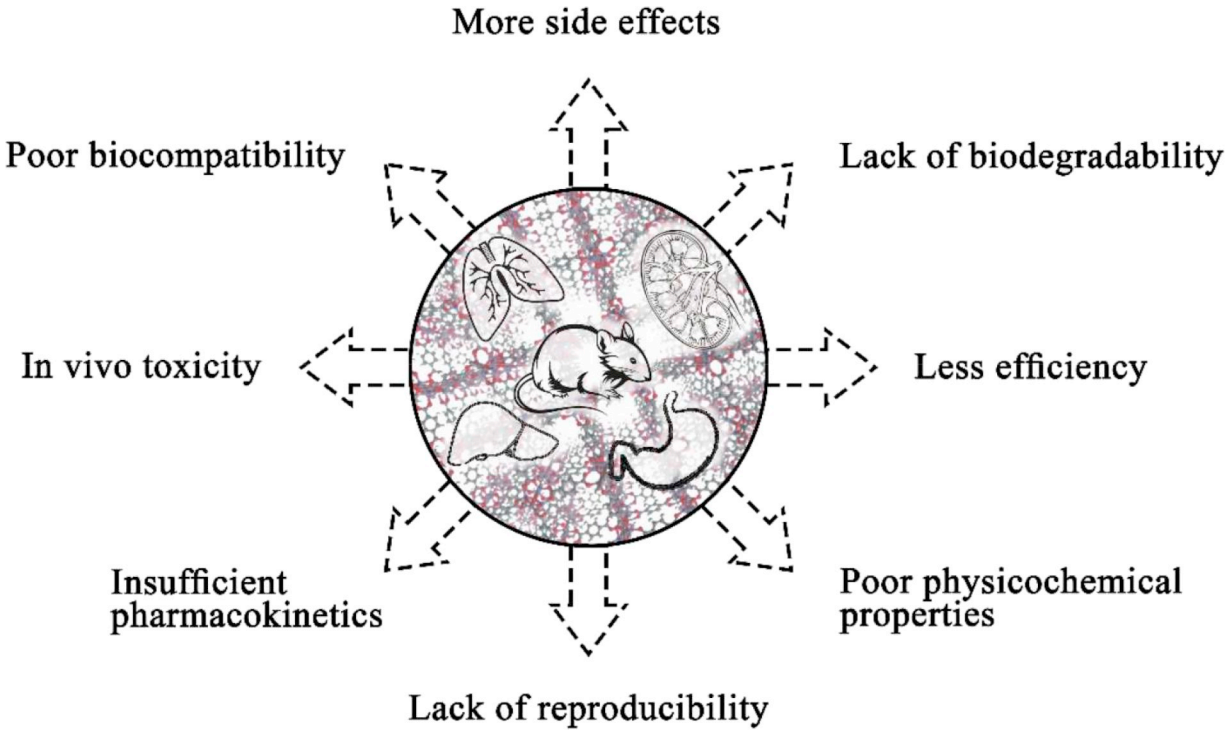

Fig. 5. Significant challenges regarding the use of N-MOFs in cancer-targeted therapy.

as low drug dosages and low laser power applied in cancer therapy [104–107]. Unfortunately, the clinical applicability of N-MOFs is in the preliminary stage regarding aspects such as their pharmacokinetics (loading with potential drugs), efficiency, and *in vivo* toxicity [108]. Furthermore, researchers need to focus on the critical issues raised in the potential drug delivery function of MOFs, including their biodegradability under human body physiological conditions, diffusion of the drug through the MOF pores, and both drug–solvent and drug–matrix interactions [109]. Lack of valuable, reproducible, and enough data regarding the efficacy and absorption, digestion, metabolism, and excretion parameters pertaining to the deployment of MOFs for drug delivery is one of the significant concerns in cancer treatment [110]. Other concerns include their i) surface modification, ii) size distribution, iii) colloidal stability, iv) morphological characteristics, and v) synergistic effects. All these above-mentioned physicochemical properties play vital roles in the determination of an effective theragnostic option for cancer [111]. More importantly, N-MOFs still have few challenges that make significant interest, especially toward cancer-targeted therapy. For the purpose of thorough understanding, these major challenges have been illustrated in Fig. 5.

6. Conclusion and future perspectives

In conclusion, N-MOFs show outstanding features, such as high drug-loading capacities, controllable cargo release, and flexible pH responsiveness, making them promising candidates as drug delivery systems for cancer therapy. Notably, recently developed N-MOFs have provided an optimistic platform for use in the treatment of cancers. Despite the critical challenges remaining in their real-world use, such as their biodegradability, *in vivo* toxicity, and biocompatibility, some N-MOFs are expected to evolve as “nano hotspots” in the cancer field owing to their demonstrated enhancement of PDT efficacy and active targeting modalities, among other advantages. In the future, other potential cancer drugs can be effectively loaded into N-MOFs for targeted delivery; furthermore, control over the physicochemical properties of N-MOFs, including their pH and temperature sensitivity, will be advantageous for cancer treatment. Future research should focus on reducing the side effects of N-MOFs and on using *in vivo* models to study their applicability for cancer therapy.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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