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Synthesis, properties, and prospective medical applications of metal-organic frameworks

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Abstract. Researchers strive to develop novel delivery systems for therapeutic substances and new therapies. The aim is to maximize the efficacy and effectiveness of conducted therapy while maintaining controlled drug delivery profiles and minimizing the side effects of therapy. Currently, numerous methods of drug administration are in use. Simultaneously, novel potential drug cargos, such as metal-organic frameworks, quantum dots, carbon nanotubes, or dendrimers, are under vigorous investigation. This paper aims to consider metal-organic frameworks (MOFs), which are composed of metal ions/clusters coordinated to organic linkers forming one-, two-, or three-dimensional materials with unprecedentedly large specific surface areas, high porosity, and a capability of a high degree of modifications. They have found many potential applications, and due to their low toxicity, high biocompatibility, and bioavailability, they are considered materials of the "medicine of the future".

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This review constitutes a state of the art concerning the recent progress on the metal-organic frameworks, particularly on synthesis and characterization of MOFs, including their classification and possibilities of their modification. In the present paper, a recent state of the art of biomedical applications, such as innovative cancer therapy, bone regeneration, bioimaging, biosensing, and upgrade delivery system based on MOFs is provided. Furthermore, MOF's toxicity and forward-looking perspectives have been thoroughly discussed.

Keywords: metal-organic frameworks, toxicity, drug delivery system, detoxification, biomedical application

1. A BRIEF OVEREVIEW

Metal-organic frameworks (MOFs) belong to the group of highly porous materials with well-defined structures. Exemplary MOF structures are shown in Figure 1. The organic part, called ligand or linker, is made up of organic acids, mainly those containing a minimum of two carboxyl groups in their structure, but it is also possible to use heterocyclic compounds, anions of organophosphorus compounds, or salts of sulfonic acids. The ligand can be either in the form of an alkyl chain or an aromatic ring (Gangu et al., 2016; Lawson et al., 2021b; Yusuf et al., 2022a). Interestingly, MOFs constructed from linkers that are biological units are also known. Examples of such bio-linkers are peptides, amino acids, carbohydrates, or porphyrin, classified as endogenous ligands, or nicotinic acid or curcumin, known as exogenous ligands (Anderson and Stylianou, 2017; J. Liu et al., 2022; Yusuf et al., 2022a). The choice of ligand greatly influences the physicochemical properties of the material, including, for example, chemical or thermal stability (Yusuf et al., 2022a). The inorganic type of block forming the MOF structure constitutes inorganic nodes occurring as metal clusters or ions (Howarth et al., 2016). The metal should be at least divalent to create coordination bonding with surrounding ligands, i.e., cross-linking, which ensures the chemical stability of this system. The choice of the appropriate metal source creating the MOF structure should also be related to its biocompatibility, non-toxicity, and safety for humans. The commonly used metal ions forming MOF structures include Mg^{2+}, Ca^{2+}, Fe^{2+}, Fe^{3+}, and Zn^{2+}. Their median human lethal dose, defined as LD_{50} (mg/kg), is equal to 5000, 1940, 984, 450, and 100-600, respectively (Rojas et al., 2019). It was also found that MOFs containing traces of Cu, Mn, Se, Mo, Cr, and V could be beneficial for the functioning of the human body (Wiśniewska et al., 2023). In turn, metals such as Zr, Au, and Ag are attracting much attention as potential building blocks of MOFs for biomedical applications (W. Hu et al., 2024). These unique building blocks (organic and inorganic) provide control in the construction of MOFs. Moreover, the strong bond between ligand and metal gives thermal,

chemical, and even architectural stability. It is worth emphasizing that MOFs fill the gaps in reticular chemistry, especially in 2D and 3D structures. Information on the unique nature and prospective character of metal-organic frameworks can be found in the article (Gagliardi and Yaghi, 2023). A very attractive feature is the entrance of the molecule into the pores of the MOF and then observation of the phenomena occurring inside the structure. Such a phenomenon occurs when substrates (drugs, gases, organic compounds, or other reagents) bind to the atoms of the metal-organic framework. Another feature highlighting their forward-looking nature is the possibility of multi-stage synthetic MOF modification. That results in an increase in the heterogeneity and multifunctionality of the MOF structure. Multi-variant MOFs outperform their "pure, homogeneous" analogs in terms of their impact on programmed drug release, highly selective separation, and enzyme-like catalysis. Importantly, almost every aspect of MOF chemistry provides multi-variants. Moreover, given that computational chemistry is a very important field in MOF development, artificial intelligence (AI) is worth paying attention to. The integration of AI with computational chemistry has the potential to revolutionize the field, not only in reticular chemistry but also in broader chemistry, including metal-organic structures. An important aspect that would form the future of artificial intelligence computational chemistry is the reproducibility of calculations and results generated by AI. It is necessary to make an effort to provide transparency and facilitate verification and validation of computational results. (Gagliardi and Yaghi, 2023).

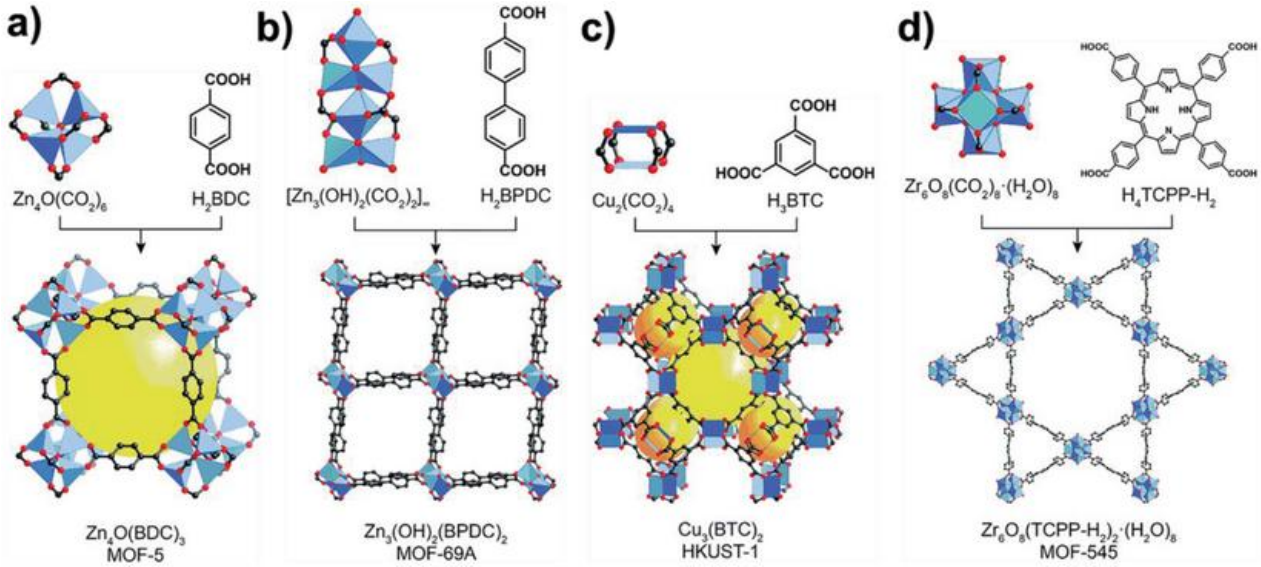

Figure 1. Exemplary MOF structures (De Villenoisy et al., 2023).

Considering the steadily growing popularity of metal-organic frameworks, there are many examples of review articles in the literature. However, very often, such papers are limited to specific issues. For example, on the application of MOF-type materials in adsorption (Akeremale et al., 2023) or degradation of organic pollutants as photocatalysts (Khan et al., 2023). There are also review articles dedicated to bio-MOFs and their applications (J. Liu et al., 2022), MOFs with superconducting properties (Gao et al., 2021) or MOF applications in the field of biotechnology (Chattopadhyay et al., 2021). In addition, a large number of articles focus on biomedical applications of metal-organic frameworks, including drug delivery systems (S. He et al., 2021) or anticancer therapies (Rojas et al., 2019). General reviews concerning the synthesis, characterization, and properties of metal-organic frameworks can also be found (Gangu et al., 2016; Yusuf et al., 2022a). Due to the very high popularity of MOFs, and thus the growing number of studies in this field, review articles should be constantly updated. The number of new synthesis methods, including ecological and economical syntheses based on Green Chemistry principles, is rising. Modification methods of metal-organic frameworks or knowledge of structural defects are also changing. The number of potential applications of MOFs is increasing every year. Therefore, frequent updating and publishing of new review articles is essential, hence, the present review constitutes a compendium of knowledge. It describes not only the methods of synthesis or characterization of metal-organic structures but also addresses issues of surface modification, structural defects, or even the toxicity of MOFs in both *in vivo* and *in vitro* systems. The presented manuscript is relevant from a biomedical application point of view. However, it focuses on bioimaging, biodetection, innovative anti-cancer therapies based on MOFs, or even bone regeneration using the mentioned materials. Drug delivery systems based on MOFs with stimulated or targeted responses and multidrug therapies also can be a reason for the production of large amounts of the review-type articles. It must be pointed out that the section on overdose problems and body detoxification systems based on metal-organic frameworks represents an innovative approach not previously described, which raises the range and unique nature of this review. In the final part of the presented article, the most important aspects of synthesis, characterization, properties, and biomedical applications were shown. Nevertheless, it refers to those less obvious but equally promising and forward-looking subjects.

1.1. Dimensions of Metal-organic Frameworks

The fundamental building blocks creating MOFs' structure are the Secondary Building Units (SBUs). They are a combination of a metal with an oxygen atom belonging to an organic linker.

SBUs occur in triangle, square, octahedron, or tetrahedron shape, and it is crucial to determine the structure of the MOF. A further step in the construction of the metal-organic backbone is the linking of multiple SBUs through ligand bonding, in which the ligand binds to two metal centers. In this way, an internal lattice of the MOF is formed, known as the third level of the MOF's framework. At this stage, pores and cages of a certain size are formed. Furthermore, the external morphology of the metal-organic framework crystals, including their shape, size, and orientation, is determined. The fourth level of the MOF construction depends on the internal growth of the framework. To some extent, the building blocks of MOFs are the so-called coordinatively unsaturated metallic centers (CUSs). They act as acidic Lewis sites enabling the incorporation of molecules (also therapeutic) into MOFs and leading to the functionalization of MOF surfaces (Hyjek and Jodłowski, 2023; Lawson et al., 2021b). The metal-organic framework can also occur in the form of one-, two-, or three-dimensional units. In a 1D unit, the metal-ligand coordination bond extends in one direction. In 2D units, the resulting layers bond together in an edge-to-edge or layer-by-layer pattern, accompanied by the generation of weak interactions between the layers. Hence, it is possible to introduce a "guest" molecule (e.g., drugs) in the void between the layers or the same MOF layer. In turn, a 3D unit is a stable and highly porous framework where coordination bonds extend into three dimensions (Yusuf et al., 2022b). The levels of MOF structure are shown in Figure 2.

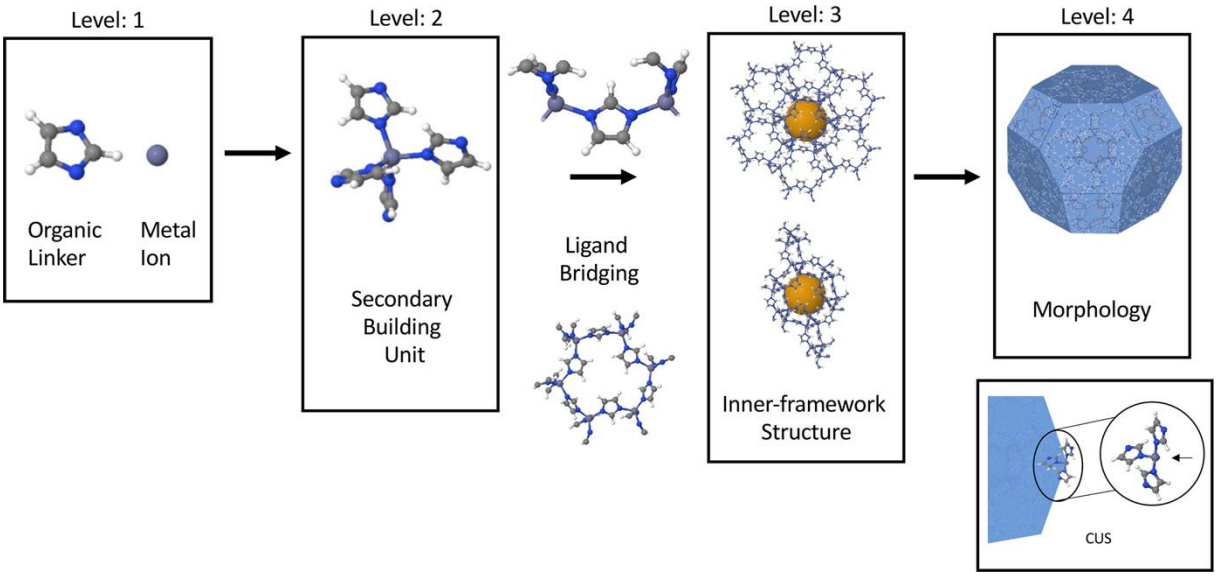

Figure 2. The levels of metal-organic frameworks structure (Lawson et al., 2021a).

The building units that form the backbone, i.e., inorganic nodes and organic linkers, can be modified by chemical reactions or external impulses to induce an alteration. This change can

occur at a specific location, such as in a point (non-dimensional system), along a specific 1D pathway, over molecules lying on a 2D flat surface, or throughout the crystal, which is referred to as a 3D structure. The metal-organic framework by itself is responsible for the orientation, geometries, and resulting molecules' spatial arrangement. Therefore, to a certain extent, it is possible to control the final structure of the molecule arising from the skeleton. On the other hand, by choosing certain building units, their influence on the change of the resulting molecule at the level of its geometry, spatial arrangement, and orientation is also possible. The molecules' lattice, resulting in large systems such as MOFs (metal-organic frameworks) or COFs (covalent organic frameworks), can be used as catalysts in many reactions without deterioration of their either crystallinity or porosity. It must be underlined that the ability to change the building units provides rotation of specific bonds with organic linkers, which ensures the formation of free spaces of specific dimensions and, thus, high selectivity. It is feasible to adsorb a guest molecule, which modifies many physicochemical characteristics of the structure. Thus, control of the structure, including the selection of appropriate building units, gives control over the properties, as well as propagation in a specific dimension. It is these features of MOF structures that are called addressability. This emphasizes the wide possibilities of changing, modifying, and adapting the framework. Another important feature of MOFs is their rigidity, providing the ability to pack or release a guest molecule without breaking the strong bonds forming the backbone. Additionally, it allows for maintaining the pore size regardless of the environment, making possible the separation of difficult-to-separate molecules. As highlighted by Yaghi et al. (Yaghi, 2019) MOFs extend coordination chemistry and organic chemistry from 0D and 1D dimensions to 2D and 3D while adding previously unknown structural diversity and multiplicity (Yaghi, 2019).

1.2. Porous properties of metal-organic frameworks

Metal-organic frameworks are materials capable of structural modifications, which makes them attractive in many potential applications. Interestingly, the first polymeric framework was discovered by the team of Hoskin and Robson in 1998 (Hoskins and Robson, 1989), but in 1995, Yaghi was the first to successfully synthesize, characterize, and name metal-organic frameworks (Yaghi et al., 1995). The number of discovered and synthesized MOF structures is still increasing, and by 2023, more than 100,000 different metal-organic structures have been discovered (Glasby et al., 2023). These materials are characterized by high chemical and thermal stability, synthesis simplicity, low density, well-defined porosity, and ordered structure. Both the porous properties and high accessibility make MOFs effective adsorbents, and even

high molar mass molecules, such as drugs or other therapeutic molecules, can be easily and efficiently absorbed (Rocío-Bautista et al., 2019). In this regard, some MOF structures can perfectly serve as future drug delivery systems (DDS). Specifically desirable features of MOFs are the large specific surface area and the ability to modify the outer and inner surfaces, which can contribute to drug stability, biodistribution, or targeted drug release. In addition, it is possible to achieve gradual and controlled drug release profiles, avoiding the sudden drug ejection known as the "burst effect" and a safe biodegradation of the carrier. The potential biomedical applications of MOFs are thoroughly described in the literature (Awasthi et al., 2022; Chedid and Yassin, 2018; Sun et al., 2020; Valizadeh Harzand et al., 2023).

Due to the broad spectrum of inorganic nodes and organic ligands, it is possible to obtain materials with different pore diameters. Metal-organic frameworks may exhibit a wide range of porosity that can be adjusted depending on their potential application (Abazari et al., 2018). The porous composition of MOFs depends on the coordination of the metal, the extent of the linker, and the number of functional groups, and even the method of their synthesis (Butova et al., 2016; Valizadeh Harzand et al., 2023). Modification of porosity in MOFs is also achieved through the use of modulators. As acids, they compete with the organic linker for the metal node space and subsequently induce structural defects (Butova et al., 2016). The influence of the coordination of metallic node bonded with the same ligand on the active surface and porosity of MOF is illustrated in Figure 3.

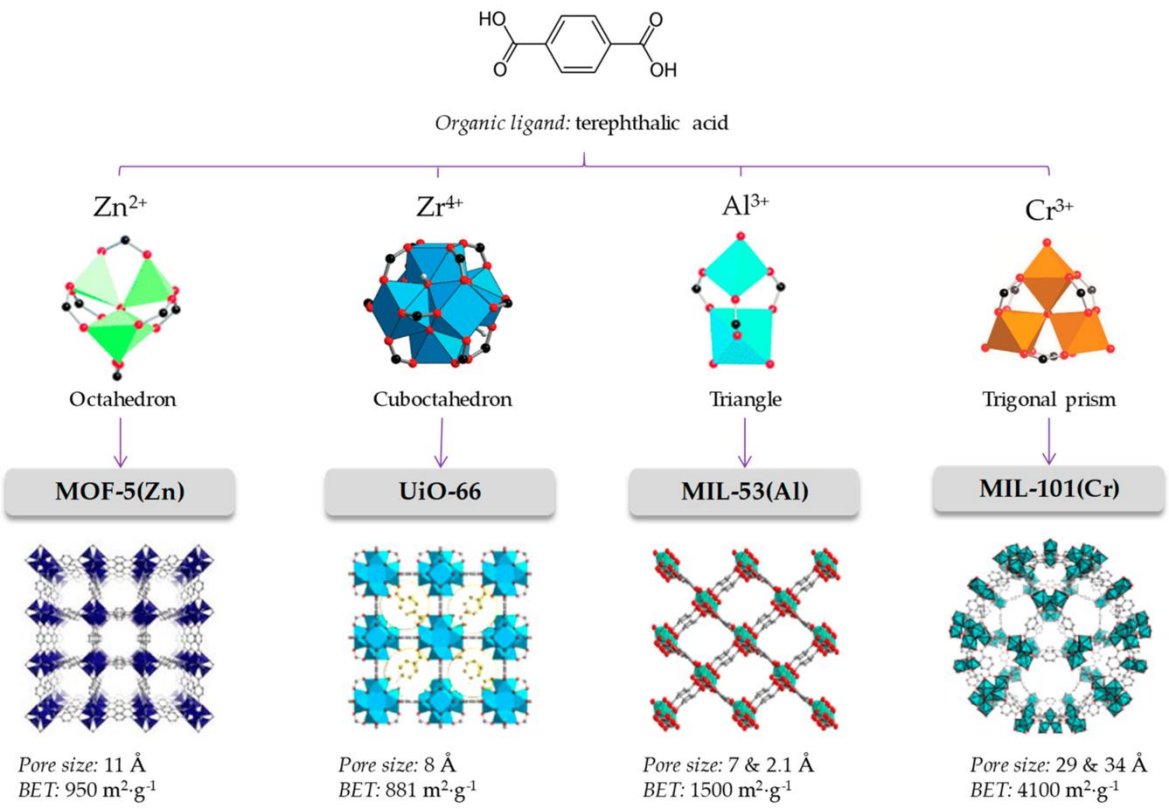

Figure 3. Diverse metal-organic framework based on a common ligand (Rocío-Bautista et al., 2019).

An unquestionable advantage of MOFs is the simplicity of modifying their porosity, which influences their use as drug carriers. A sufficiently small particle size can provide much deeper penetration of therapeutic particles, increase biodistribution, and prevent embolism, which is particularly important for intravenous administration. An average particle size diameter of 1-100 nm is the most recommended for drug carriers, contrast agents, or sensitive probes (Rojas et al., 2019). If injectable routes of administration are being considered, MOFs should be characterized by particle size not exceeding 200 nm (Rojas et al., 2019). In the case of gastrointestinal therapies, recommended particle size ranges within 50-1800 nm, which is related to the intestinal mucosa, which acts as a sieve conditioning the passage and absorption of delivered particles (Rojas et al., 2019).

1.3. Classification and nomenclature of MOFs

The nomenclature and classification of metal-organic frameworks can be determined by the name referring to the type of framework, the name of the institution where the material was first synthesized, or its potential application. Some examples of MOF nomenclature regarding their construction are described below. For instance, isoreticular frameworks are classified as

materials built of octahedral units with micropores. Their building unit is $[Zn_4O]^{6+}$ surrounded by aromatic, carboxyl ligands (e.g., IRMOF-3). Another common group of MOFs is the so-called ZIFs, which stands for Zeolitic Imidazolate Frameworks. In their structure, the angle between the imidazolium derivative and the metal node is about 145°, which is similar to the angle in the Si-O-Si bond that forms molecular sieves (e.g., ZIF-8, ZIF-67). Other groups are stereo-octahedral materials, creating a three-dimensional structure in the form of a hole-cage-hole (Sundararaman et al., 2024). This group is classified as porous coordination frameworks (PCNs), which is particularly important in electrochemical applications (e.g., PCN-222, PCN-333). The next group with a similar name is porous coordination polymers (PCPs). In this case, SBUs are formed by transition metal ions coordinated by linkers in the form of carboxylic acids or pyridines. These materials are of great importance in heterogeneous catalysis (Butova et al., 2016; Hyjek and Jodłowski, 2023; Yusuf et al., 2022b). In the concept of nomenclature related to building blocks, it is worth noting the relatively new Bio-MOF group, meaning biological metal-organic frameworks. Some of its building blocks are bio-elements such as adenine, nitrogenous bases, saccharides, or amino acids. This group exhibits great biomedical potential (Anderson and Stylianou, 2017; J. Liu et al.). Passing to the nomenclature based on the place of discovery of MOFs, it is worth highlighting a few examples. The well-known UiO group - Universitetet i Oslo (University of Oslo), based on zirconium centers and dicarboxylic ligands (L. Hao et al., 2018), MIL - Materials Institute Lavoisier (Souza et al., 2020), NU - Northwestern University (Webber et al., 2020), POST - Pohang University of Science and Technology (Seo et al., 2000), DUT - Dresden University of Technology (Grünker et al., 2014), NOTT - University of Nottingham (S. Yang et al., 2012), HKUST - Hong Kong University of Science and Technology (Baheri et al., 2021), CAU - Christian-Albrechts-University (Ahnfeldt et al., 2009), and JUK – Jagiellonian University in Kraków (Roztocki et al., 2020). Other criteria for the classification of metal-organic frameworks are the types of metallic nodes and organic ligands resulting in differentiated topology, dimensionality, cages, functional groups, and supermolecules. The topology-based group assigns MOFs based on their framework and structure, distribution, and connection of metallic nodes (e.g., UiO-66 or MIL-53). The subsequent group is based on the number of dimensions in which the structure grows. Hence, 0D structure denotes clusters or isolated metallic sites, 1D are chains, 2D is formed by layers, whereas 3D constitutes porous structures. The unusual classification refers to the functional groups occurring in organic ligands. Their presence significantly affects the reactivity of the framework, its stability, or its adsorption capacity. The most common existing groups are carboxylate, pyrazolate, imidazolate, phosphonate, amine, or hydroxyls. Classification based

on supermolecules plays a significant role in the design of new MOFs and the understanding of their performance in a variety of applications. It is based on the presence of hydrogen bonds, as well as interactions between π-π, host-guest, or coordination interactions between metal nodes and guest molecules. Knowledge of the metal-organic framework, the size of the cages, the dimensionality of the framework, as well as interconnections and interactions between MOF's building blocks, allows not only to design materials for specific applications but also to more profound understand their behavior, and potential benefits and risks associated with their potential medical application (Wiśniewska et al., 2023). Examples of different MOF structures are illustrated in Figure 4. Most of them were previously described by Lillerud et al. (Cavka et al., 2008) and Hao et al. (L. Hao et al., 2018). Inorganic building blocks for MOFs were contained in papers. It is worth emphasizing that this inorganic unit, especially the geometry and coordination of metal ions, had a great influence on creating frameworks.

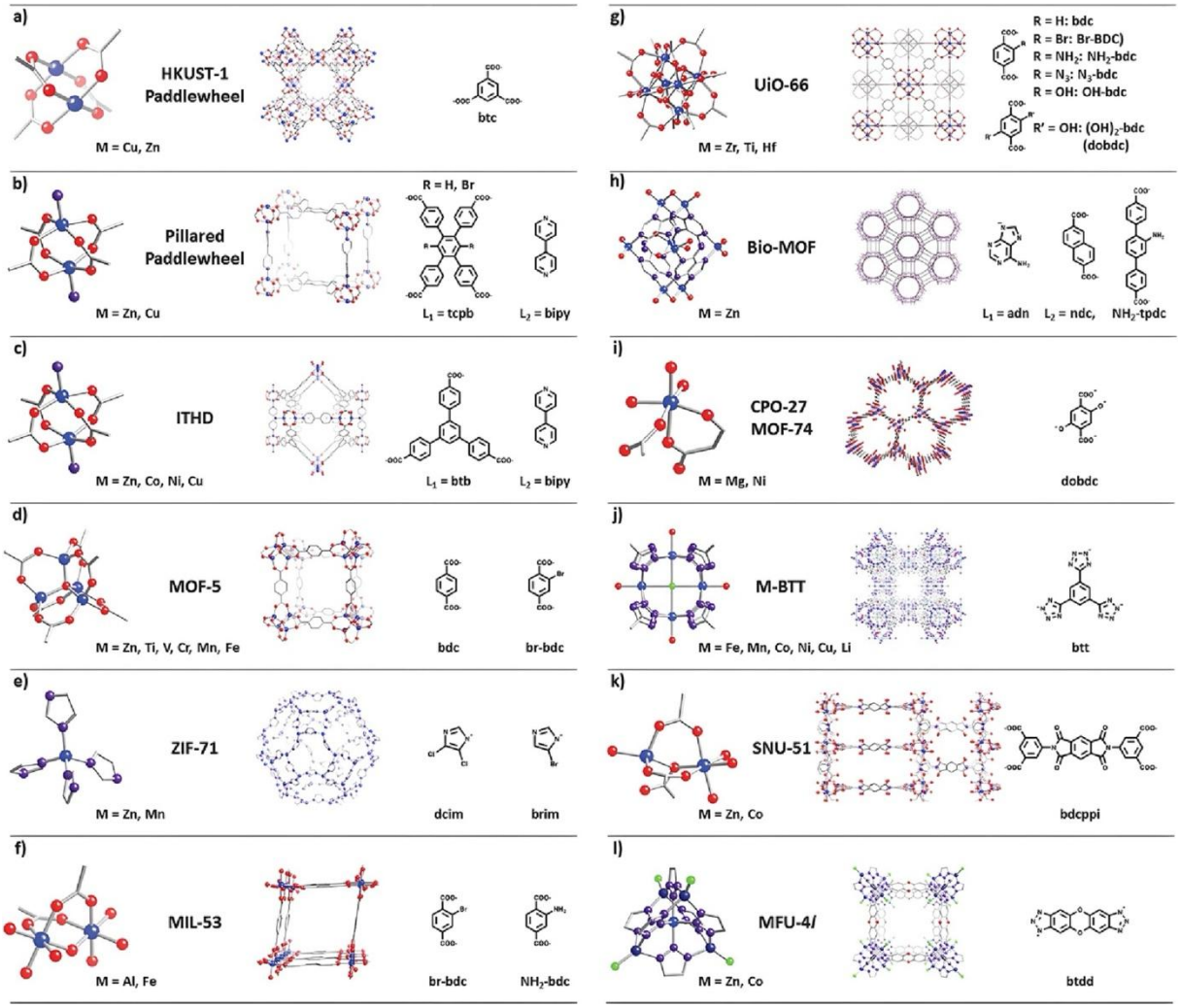

Figure 4. Framework structures (center) and the corresponding secondary building units (SBUs) of some of the most commonly used MOFs (Deria et al., 2014).

2. METAL-ORGANIC FRAMEWORKS – METHODS OF SYNTHESIS AND CHARACTERIZATION

Currently, numerous methods of metal-organic framework synthesis can be distinguished. Some of them are based on conventional techniques without the necessity of using specialized equipment, whereas others require conditions of elevated temperature and pressure to promote the formation of crystalline framework (D. Ma et al., 2023). Furthermore, modern methods based on "green chemistry" like microwave radiation, ultrasound irradiation, or mechanochemical forces are currently under vigorous investigation (Rocío-Bautista et al., 2019). In turn, Gangu et al. (Gangu et al., 2016; Lawson et al., 2021b) reported that the choice of the synthesis pathway, the type of solvent, temperature, or the power of radiation influenced not only the synthesis yield but also the crystallinity of the final form of a product. Exemplary descriptions of the selected MOF synthesis techniques, including their physicochemical characterization, are listed below.

2.1. Methods of MOFs synthesis

In order to simplify the review of the most common techniques currently used to obtain metal-organic structures, in addition to brief descriptions, their graphical representation is provided in Figure 5.

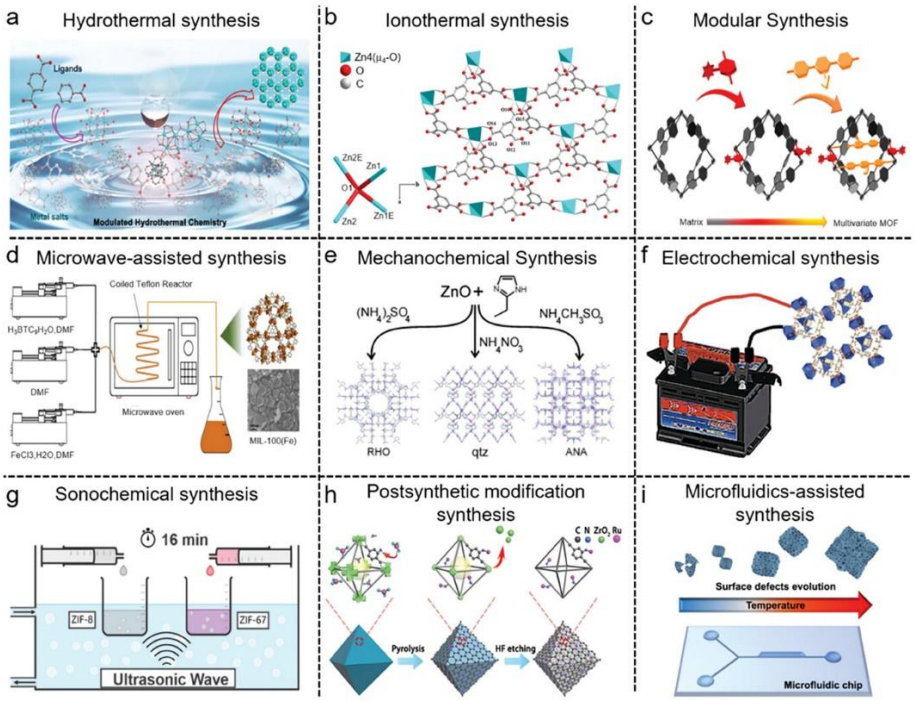

Figure 5. Graphical representation of the most currently used techniques in the preparation of metal-organic frameworks (D. Li et al., 2024).

2.1.1. Solvothermal methods

Solvothermal synthesis of metal-organic frameworks is one of the most utilized due to its simplicity and easy accessibility. The method provides highly crystalline products and very high yields. This technique is based on a metallic precursor and an organic ligand dissolution in a protic (methanol, ethanol, water) or aprotic solvent (DMF, DMA, DMSO, acetonitrile). The synthesis is usually conducted in stainless-steel autoclaves or glass vessels at a temperature exceeding the normal boiling point of the solvent and at elevated pressure (solvothermal conditions). This method leads to the development of products with large crystals due to slow crystallization (Gangu et al., 2016; Lawson et al., 2021b; D. Ma et al., 2023).

2.1.2. Microwave radiation-assisted technique

Microwave (MW) radiation is often applied in organic syntheses to facilitate the formation of nanocrystals. Heat is generated by the interaction of an electromagnetic wave with the charge of a polar solvent, or, more precisely, with the permanent dipole moment of the solvent molecules. That leads to the growth of the solvent temperature followed by the reaction between mixture components. Both the applied energy (300-300,000 MHz) and the solvent are crucial for the physicochemical properties of the resulting product. The method provides very fast crystallization and is particularly popular for producing nanoparticles, e.g., for MOF-based catalysts (Couzon et al., 2022; X. Ma et al., 2019; Mao et al., 2022; Rocío-Bautista et al., 2019).

2.1.3. Sonochemical method

In this method, an inorganic precursor in the form of salt and an organic linker are mixed in a liquid solvent. The whole mixture undergoes ultrasonic cavitation (a phenomenon based on the development of cavitation bubbles and their subsequent collapse under the influence of ultrasonic irradiation, forming spots of very high temperature of 4000-5000 K and a pressure exceeding 1000 bar) (Yusuf et al., 2022b). The method results in the very rapid crystallization of MOF materials. This technique was used for the first time in MOF synthesis in 2008 (Qiu et al., 2008), and its popularity is still increasing, e.g., in the syntheses of MOF-5 (Son et al., 2008) or Hf-MIL-140A and Zr-MIL-140A (Jodłowski, Kurowski, et al., 2023).

2.1.4. Mechanochemical method

This solvent-free technique is characterized by its simplicity and eco-friendliness. It is based on grinding inorganic salts and organic ligands in a ball mill or mortar. During milling agents, an evaporation of the volatile components and water formed as a by-product takes place. This method easily enables a high-scale production of MOFs (Užarević et al., 20113).

2.1.5. Electrochemical method

In this method, the source of metal is deposited on the anode, whereas an organic linker is dissolved in a liquid medium. With the application of suitable voltage, the metal dissolves and reacts with the linker, forming MOF close to the electrode immersed in the solution. The reaction usually does not reach as high yields as competitive techniques (Martinez Joaristi et al., 2012).

There are also many other alternative methods for MOF production, such as diffusional, ionothermal (using ionic liquids), solvent evaporation, and spray-drying methods. These techniques are rarely used, but their interest is growing (Hyjek and Jodłowski, 2023; Yusuf et al., 2022b).

2.2. Characterization of metal-organic frameworks

Synthesized metal-organic frameworks undergo physicochemical characterization. One of the features of prepared MOF-type materials is their crystallinity determined by the powder X-ray diffraction technique (PXRD). The comparison of the PXRD patterns of the synthesized material with the PXRD patterns available in the literature allows for the determination of the reproducibility of the MOF preparation method (Chattopadhyay et al., 2021; Lawson et al., 2021b). However, due to a high electron density of the inorganic nodes or large parameters of units, neutron diffractometry can be considered an alternative technique. The main disadvantages are the large amounts of studied material required for this analysis and the need for the exchange of hydrogen by deuterium atoms in the organic ligand, which generates high costs. Another solution is using a single-crystal X-ray diffraction (Butova et al., 2016). Exemplary diffractograms are depicted in Figure 6. The local atomic and electron structure of the investigated materials can be obtained from X-ray absorption near edge (XANES) and extended X-ray absorption structure (EXAFS) analysis (Jodłowski, Kurowski, et al., 2023).

The subsequent characterization of MOFs is to recognize their surface area and porosity. Fundamental parameters are specific surface area, pore sizes, and their distribution. The adsorption isotherm measurements can be analyzed using the Langmuir and the Brunauer-Emmett-Teller methods, which postulate the monolayer and multilayer adsorption, respectively. The porosity parameters of the studied sample are determined based on the content of N_2 adsorbed on the surface of the material at a specific temperature and pressure.

To characterize the porous structure of the prepared MOF-based materials, many other specialized techniques can also be used, including Atomic Force Microscopy or gas adsorption thoroughly described in (Chattopadhyay et al., 2021; Dymek et al., 2024; Jodłowski, Kurowski,

et al., 2023). Exemplary results from the porosity measurements of MOF samples are given in Figure 7.

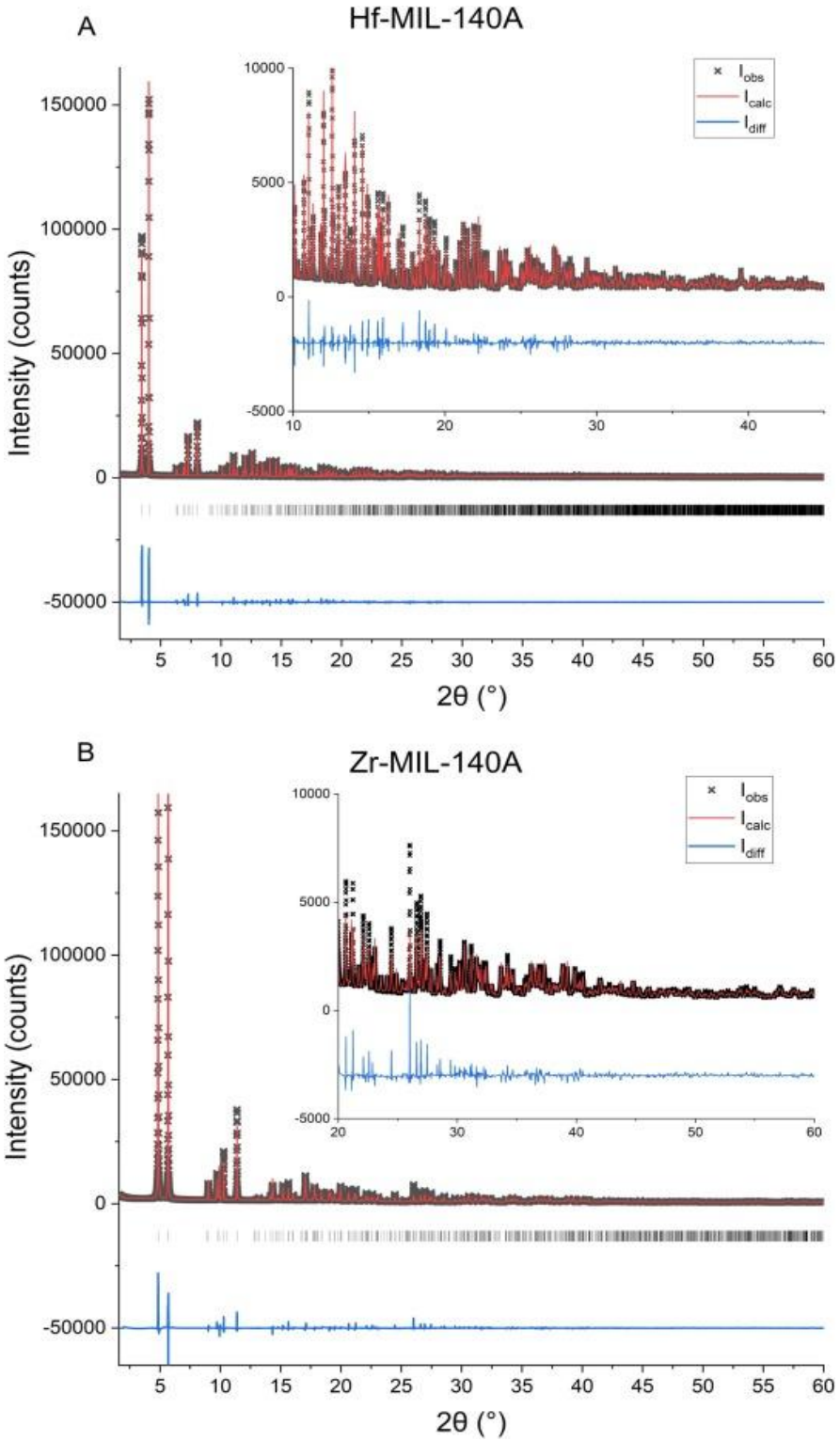

Figure 6. Rietveld plots for MIL-140A with Hf and Zr as a metallic node (Jodłowski, Kurowski, et al., 2023).

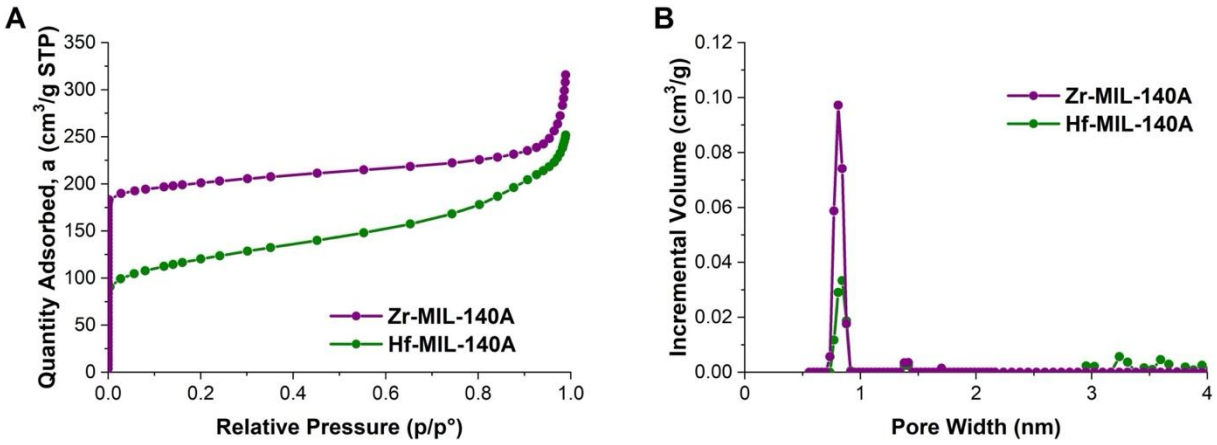

Figure 7. N_2 adsorption isotherms (A) and DFT pore size distribution of MIL-140A samples (B) (Jodłowski, Kurowski, et al., 2023).

The existence of functional groups in MOF materials can be confirmed using Fourier Transform Infrared Spectroscopy (FTIR). Concerning infrared spectroscopy, several IR measurement techniques are crucial for the complementary characterization of metal-organic frameworks. One of them is the Attenuated Total Reflectance (ATR) technique, which allows for the rapid characterization of both pure MOFs and composite materials (Dymek et al., 2024). Another method is related to transmission measurements, where a thin wafer (with or without KBr addition) is prepared. It must be pointed out that studied samples are usually thermally pretreated to remove any impurities from the sample surface to receive spectra free of bands stemming from contamination (Hyjek et al., 2024). Another FTIR-based method is Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFT). This type of IR measurement may be performed in a flow of inert or reaction gas, leading to the recording of spectra appropriate for highly sensitive surface analysis of the material, e.g., after the sorption process. For example, if a MOF sample is used as a catalyst in a reaction where adsorbed probe molecules are reagents, the DRIFT technique is used to explain at least a partial mechanism of the catalyzed reaction at the catalyst surface (Chattopadhyay et al., 2021; Dymek et al., 2021). As a complementary method to FTIR spectroscopy, Raman spectroscopy (RS) is usually performed.

MOF thermostability is usually determined by thermo gravimetric analysis (TGA). The factor under study is the decrease in sample weight as a function of increasing temperature. Thermal analysis provides information on the potential degradation of the MOF over a range of temperatures studied. Directly combining thermal analysis with mass spectrometry can make it

possible to determine the mechanism of structure decomposition (Butova et al., 2016; Hyjek et al., 2024).

In turn, the purity of the MOF samples, the presence or absence of solvent in the pores of the MOF, or the unreacted ligands can be determined by the Nuclear Magnetic Resonance technique (NMR). The limitations of this method are related to the very low solubility of MOFs in most solvents (Butova et al., 2016; Jodłowski, Dymek, et al., 2023).

The morphology and surface topology of the MOF can be observed by microimaging using Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), or Atomic Force Microscopy (AFM) (Dymek et al., 2024; Hyjek et al., 2024; Jodłowski, Kurowski, et al., 2023). Exemplary microphotographs illustrating the studied MOF by the SEM technique are presented in Figure 8.

Apart from the physicochemical characterization of the prepared samples, theoretical calculations, e.g., using Density Functional Theory (DFT), are usually utilized to determine the nature and energetics of host-guest interactions at the molecular level (Jodłowski, Dymek, et al., 2023; Jodłowski et al., 2024). DFT is a method of choice for solid-state systems comprising both organic fragments and the transition metal atoms (Piskorz and Zasada, 2019). The calculations can be performed with or without the influence of the polarizable solvent and, hence, can give insight into the kinetics of the desorption or dissolution of the guest molecules from the MOF frameworks. The computational methods can also help attribute the IR or RS bands with accuracy close to the experimental spectroscopy, even in the so-called "fingerprint" regions of the spectra where the number of bands overlap and cannot be distinguished and attributed separately without modelling.

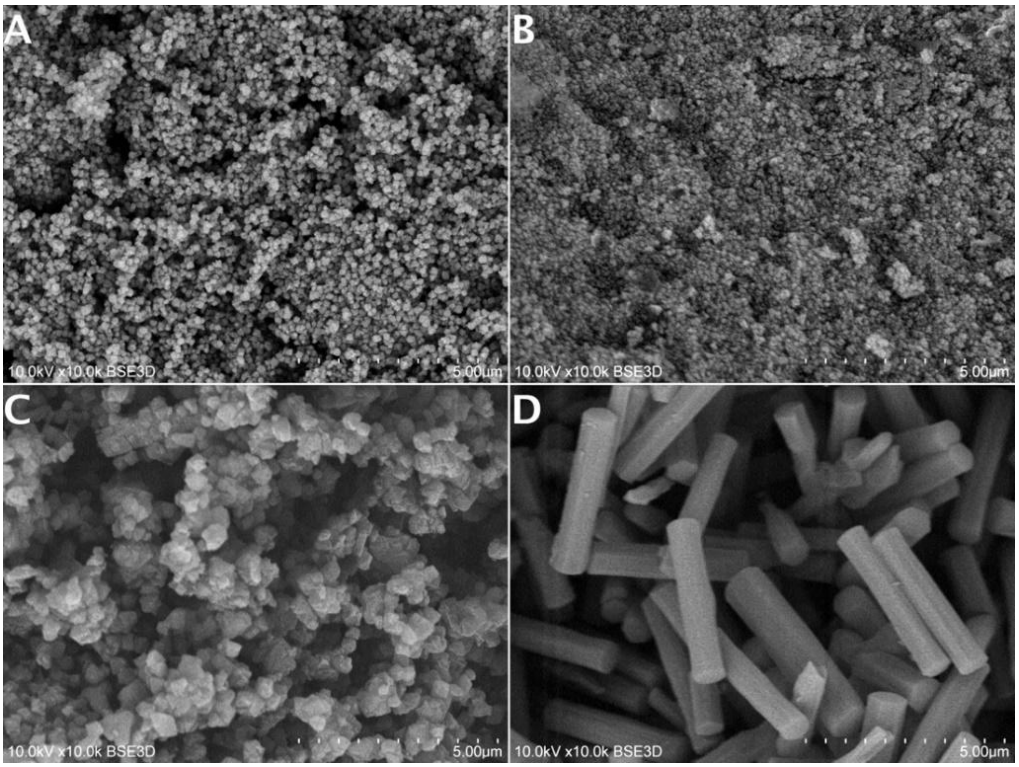

Figure 8. SEM microphotographs of composites acriflavine@MOF: ACF@MOF-808 (A), ACF@UiO-66 (B), ACF@UiO-67 (C), ACF@NU-(D) (Jodłowski et al., 2022).

2.3. Defect engineering and structure modification

Metal-organic frameworks, similar to other crystalline materials, are characterized by the occurrence of some kind of structural defects. Their presence was first noted by Behrens et al. (Schaate et al., 2011) who observed changes in the crystallinity of the UiO-66 framework as a result of the addition of monocarboxylic acid terminating linker chains. Subsequent studies confirmed that the addition of various acids affected not only the crystallinity and porosity but also the stability or reactivity of the MOF structure. Structural defect-inducing acids added during MOF synthesis are referred to modulators. The positive effects of defective structures on their catalytic, adsorption, or conductivity properties were reported in (Y. Feng et al., 2019; Shearer et al., 2016). The current classification of defects in MOFs distinguishes two types: missing linker or missing cluster (node), as shown in Figure 9. However, it must be pointed out that those effects usually coexist in the MOF structure (L. Liu et al., 2019).

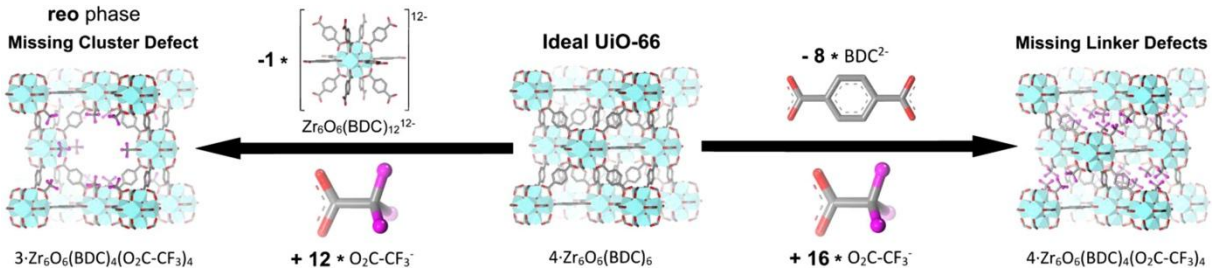

Figure 9. Diagram illustrating the structure and composition differences between ideal and defective UiO-66 unit cells (Shearer et al., 2016).

The missing cluster (node) defects can be generated using formic acid during the synthesis of UiO-66, evidenced in the *reo* topology. The charge imbalance is compensated by formate anions, which allows for preservation of the geometry of $Zr_6(OH)_6O_4(CO_2)_{12}$ in the UiO-66 framework. In turn, the missing ligand defect occurs when acetic acid is used for the preparation of UiO-66. Similar observations were reported in the case of trifluoroacetic acid (Shearer et al., 2016). It was found that the application of monocarboxylic acid influenced the physicochemical properties of the obtained defective MOFs, particularly acidity and crystallinity, e.g., the type and the concentration of defects in the UiO-66 structure. Both types of defects affect the MOF's physicochemical properties, but the effect of the missing node is responsible for increased catalytic activity on a higher scale than the effect of the missing ligand. Other positive aspects of the presence of defects in the UiO-66 structure were reported (L. Liu et al., 2019; Shearer et al., 2016). Among others, the resulting defects contribute to the exposition of unsaturated Zr atoms as active sites, increasing the population of Brønsted or Lewis acidity. Another effect of defecting is a rise in the absorbance of visible light, as well as an increase in hydrophilicity. Research on defective metal-organic frameworks was performed for UiO-66, MOF-808, MOF-802, and NU-1000 by Taddei et al. (Y. Feng et al., 2019; Taddei, 2017). The most commonly used defecting agents were hydrochloric acid, hydrofluoric acid, formic acid, acetic acid, di- and trifluoroacetic acid, and benzoic acid (Vermoortele et al., 2013; L. Zhang et al., 2016).

The use of a single type of organic or metal SBU linker in the MOF results in a material with uniform chemical and physical properties. However, multiple types of organic linkers can be used to create a compositionally aperiodic MOF with the same topology as a compositionally periodic MOF. Such materials are defined as multivariate MOFs (MTV-MOFs) (Osborn Popp and Yaghi, 2017). The difference between MTV-MOF and MOF is shown in Figure 10. Apart from the synthesis of defective metal-organic frameworks, it is possible to enrich existing

MOFs (both defective and pristine) with functional groups, *e.g.*, -COOH (Custelcean and Gorbunova, 2005), -NH_2 (Hashemzadeh et al., 2021; Mocniak et al., 2015), -SO_3H (Mortazavi et al., 2020; T. Xu et al., 2020), and -OH (X. B. Yin et al., 2022). The beneficial effect of incorporating the mentioned functional groups into the MOF's structure on its sorption properties and improved catalytic properties was emphasized (Ghorbani-Vaghei et al., 2016; Jrad et al., 2019). On the other hand, a decrease of thermal stability and porosity was observed in -amino functionalized MOFs. Regarding biomedical applications, a slower release of the therapeutical substances from functionalized MOFs was indicated (Hashemzadeh et al., 2021). For instance, higher levels of drug incorporation into the MOF structure were indicated by Hashemzadeh (Hashemzadeh et al., 2021), whereas the successful synthesis of UiO-66 with -Br, -H, -NO_2, -Cl, -CH_3, and -2CF_3 functional groups was reported in (Cunha et al., 2013; Molavi et al., 2020).

The introduction of functional groups can occur during so-called *de novo* synthesis or in post-synthetic processing. Functional groups attached in this way decorate the pores, and while it is easy to determine the functionality of such materials, their spatial structure is hard to establish (Kong et al., 2013). Wang and Zhou et al. (L. Feng et al., 2018) described the possibility of creating multivariant arrangements, not only in terms of functional groups but also MOF-on-MOF arrangements. A MOF-on-MOF arrangement refers to a structure in which a MOF is surrounded by another MOF, where each MOF has its variable functionalities (Yaghi, 2019).

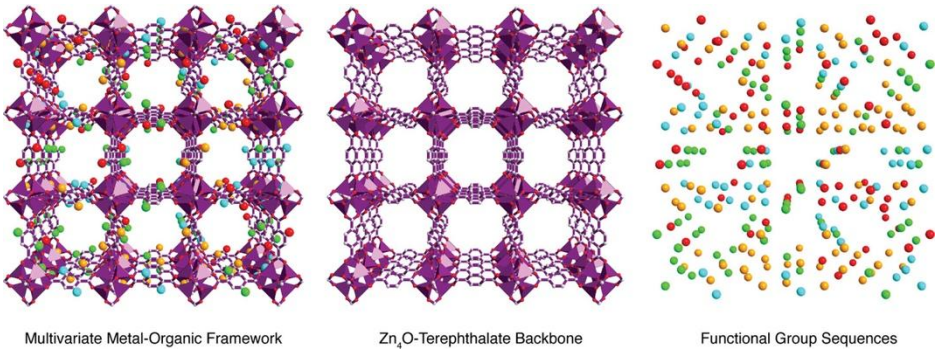

Figure 10. MTV-MOF-5 decomposed into a compositionally and structurally periodic backbone (violet) and an aperiodic decoration of the backbone by four different hypothetical functional groups (red, blue, green, and yellow spheres) (Osborn Popp and Yaghi, 2017).

3. THE APPLICATION OF METAL-ORGANIC FRAMEWORKS FOR MEDICAL PURPOSES

Metal-organic frameworks can be potentially applied for medical purposes in many aspects. It is commonly known that the medical or pharmaceutical market is highly flexible and thus

allows for much higher prices of the final products, especially in the context of specialized therapies, than for their usage in, *e.g.*, water purification or gas separation. Other advantageous factors are small doses of precursors needed to produce MOF-based materials used in medicine (in the range of milligrams), as well as their high purity, which makes the whole procedure more economically effective. Furthermore, the applied materials should demonstrate non-toxic character, adequate metabolism, biocompatibility, and bioavailability. The scientific value of the research dedicated to the medical applications of metal-organic frameworks is still increasing. The undertaken studies refer to the synthesis of the advanced MOF systems connected with their detailed characterization, including their effectiveness, and toxicity in the context of their possible medical applications (Filippousi et al., 2016; X. Liu et al., 2021; Saeb, Rabiee, Mozafari, and Mostafavi, 2021).

3.1. Diagnosis and treatment of diseases with MOF assistance

3.1.1. Biosensing

One of the promising biomedical MOF applications is biosensing. Biomedical sensors are designed to determine the presence and quantity of a selected biological agent. They should be characterized by exceptionally high sensitivity, selectivity, and thermal or chemical stability. Other desired properties are non-toxicity and rapid biodegradation in the human body. All the mentioned requirements are fulfilled by the metal-organic frameworks. The MOFs act as biosensors in various ways. Usually, the detection of a given molecule by electrochemical, luminescent, electroluminescent, or calorimetric methods takes place. The former technique involves the use of an electrode made of conductive or semiconducting materials, also known as a transducer. It is immersed in an electrolyte solution in which the potentially present molecule can be detected. Subsequently, the chemical energy of the sensing molecule binding to the electrode is converted into electrical energy. The second technique is based on the color change induced by a physical or chemical stimulus. The luminescent method can be based on chemiluminescence, thermo-chemiluminescence, or electrochemiluminescence reactions. Most often, luminescent biosensors are used to record images (Tran et al., 2023). MOFs can be used for the biodetection of a wide range of molecules. For instance, the detection of proteins and enzymes can be realized by using the well-known zirconium-based PCN-222 framework. In this way, research detects alpha-casein protein (G. Zhang et al., 2016). Another example is the ytterbium-based framework as a detector of protein S of the SARS-CoV-2 virus. The minimum protein detection sensitivity was 72 ng/L, making MOFs extremely sensitive sensors (Rojas et

al., 2019). Furthermore, the performance of MOFs as DNA and RNA detectors was investigated, which is relevant for identifying many viruses. Another groundbreaking discovery was the use of zinc MOFs as detectors of HIV-1 based on its DNA, whereas Cu-MOFs were used as detectors of HBV virus (X. Zhu et al., 2013).

3.1.2. Bioimaging

Bioimaging, being one of the branches of medicine, is one of the most important techniques for diagnosis or prevention of many diseases where metal-organic frameworks have also found their potential application. They can be used to find and identify many diseases and to induce the corresponding image or increase the contrast of tissue images (Munawar et al., 2023). The most widely used techniques are magnetic resonance imaging (MRI), positron emission tomography (PET), and computer tomography (CT). The MRI technique is based on the finding of the nuclear spins changing their orientation in a magnetic field. Metal-organic frameworks can also be given as a kind of contrast agent (Saeb, Rabiee, Mozafari, Verpoort, et al., 2021b). Another way to obtain MOF-based contrast agents is to encapsulate superparamagnetic nanoparticles in their structure. Gd-based MOFs are of particular interest. They have a relaxation value much higher than those currently available on the market. The possibility of using Gd-MOF-808 and Fe-MIL-53 as contrast agents has been explored, and the results have been highly satisfactory. Bioimaging can be realized using the PET method based on radioactive ions emitting positrons, which then decay into easily detectable γ-ray photons, creating a very clear and accurate 3D image. Hence, the application of MOFs leads to adding a radioisotopic element required for safe and stable imaging (Demir Duman and Forgan, 2021). The application of UiO-66 based on ^{89}Zr as a metal center as an imaging agent was reported in (Dekrafft et al., 2012). The half-life of this MOF was 72 h, which was significantly higher than for the currently used ^{19}F (2 h) and in the case of ^{64}Cu MOF (12.7 h) (D. Chen et al., 2017). In turn, the CT technique involves exposing the patient to X-rays, using different angles of incidence, and collecting and combining the images. In this technique, the use of MOFs containing elements of high atomic number is particularly valuable. Zhao (D. Zhao et al., 2022a) demonstrated that MOFs applied *in vivo* experiments accumulate on the tumor surface, enhancing image contrast. This effect was observed for gold nanoparticles on the surface of MOFs, improving the quality of the obtained images. The use of the aforementioned techniques and combining them with the capabilities of MOFs offers many possibilities for bioimaging (D. Zhao et al., 2022b). Thus, MIL-88 (Fe) with introduced gold particles has been selected as a means for glioma imaging with MRI, PET, and CT techniques (S. He et al., 2021). Moreover, it was indicated that UiO-66 stopped the fluorescence of peptide nucleic acids being microRNAs of cancer cells (Zheng

et al., 2021). A graphical representation illustrating all the above-mentioned techniques using MOFs is shown in Figure 11.

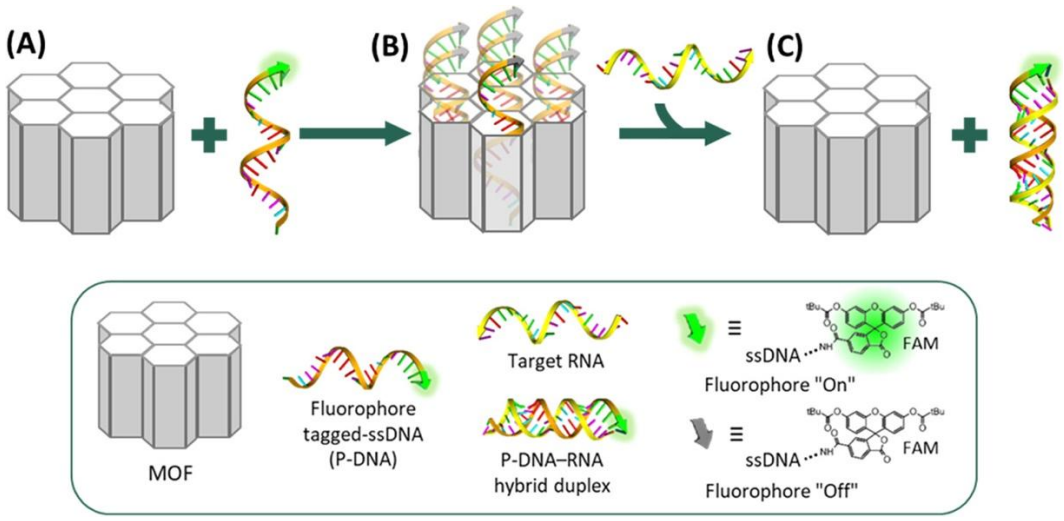

Figure 11. Scheme of the fluorescence quenching-regeneration mechanism of viral RNA detection using a MOF-based sensing platform. Reprinted with permission from (Hadynski et al., 2023). Copyright 2023 American Chemical Society.

3.2. Innovative cancer therapy based on metal-organic frameworks

Undoubtedly, one of the most problematic and timeless medical issues is efficient cancer treatment. Scientists from all over the world are striving to achieve the highest possible effectiveness of treatment while minimizing the side effects of therapy. Apart from conventional forms of treatment, new techniques are proposed; the degree of healing of patients, however, is still not satisfactory. In the context of novel technologies against cancer, metal-organic frameworks could constitute a promising remedy through the use of MOFs in photothermal (PTT), photodynamic (PDT), and chemo-photothermal therapies. In the latter kind of therapy, the drug as a chemotherapeutic agent is released from a carrier upon the irradiation of light with a specific wavelength (Deng et al., 2020; J. C. Yang et al., 2017). Shang et al. (Shang et al., 2020) synthesized a MOF that incorporated two chemotherapeutics (doxorubicin and gemcitabine). Afterward, they functionalized the MOF's surface with an arginine-glycine-aspartic acid peptide (RGD). This peptide revealed a high affinity for intergene αvβ3 occurring on the surface of tumor cells. In the undertaken studies, the formed composite Zr-Fc MOF (Fc = 1,1′-ferrocenedicarboxylic acid [$Fc(COOH)_2$]) underwent exposure to a near-infrared beam followed by the measurements of drug release from MOFs. The antitumor rate of this

synergistic chemo-phototherapy was 82% with high biocompatibility and no toxicity (Shang et al., 2020). The experiment is summarized in Figure 12.

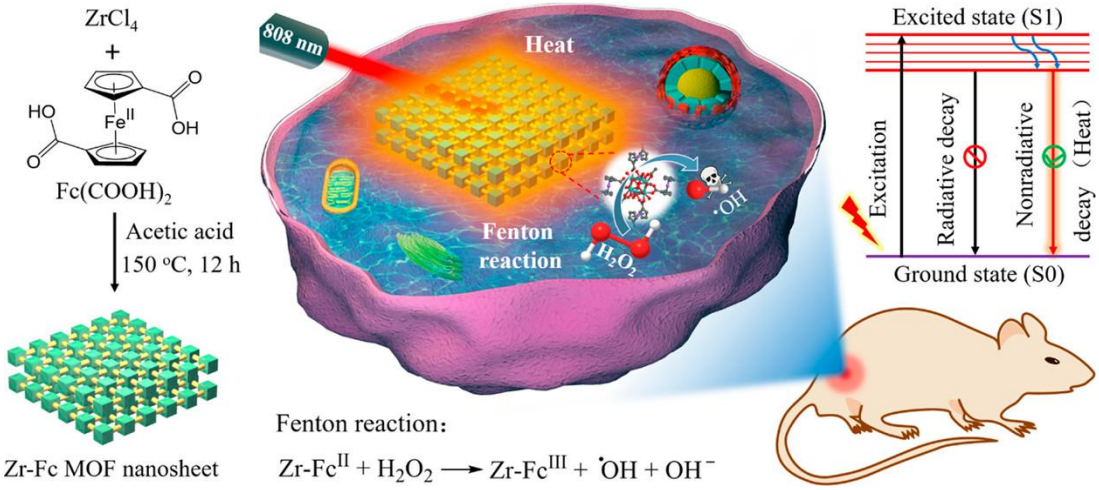

Figure 12. Illustration on the synthesis of the Zr-Fc MOF nanosheet synergetic PTT and Fenton reaction-based CDT. Reprinted with permission from (Deng et al., 2020). Copyright 2020 American Chemical Society.

Another example was the introduction of sorafenib into the ZIF-8 structure, which was then modified with polydopamine. Polydopamine is an agent that absorbs NIR radiation, making it applicable to the PTT technique and reducing the toxicity of ZIF-8. On the other hand, ZIF-8 is sensitive to a low pH environment. The combination of polydopamine and ZIF-8 properties facilitates receiving a dual drug delivery system, which can be controlled by light of a certain wavelength and low pH prevailing in the environment of the cancer cell. Experimental results evidenced the high efficacy of the therapy against HepG2 cancer in a mouse model (Q. Hu et al., 2023).

One of the PDT experiments focused on the synthesis of MOFs in which photosensitizer (PS) was the ligand. The functionalized surface enabled the MOF to create bonds with the cancer cells. Subsequently, LED light irradiation caused the release of reactive oxygen species (ROS), destroying the cancer cells. It also reported the research on combining PTT and PDT with other forms of cancer treatment, such as immunotherapy and radiation therapy (Hyjek and Jodłowski, 2023).

3.3. Bone regeneration with metal-organic frameworks

A particularly interesting application of MOFs is innovative bone regeneration therapy. The topic is timely due to an increasing number of accidents, diseases, and postoperative complications that still take place. Currently conducted therapies are expensive, time-consuming, and often mentally and physically exhausting. Thus, the remedy for improving this branch of medicine could be the introduction of MOFs as materials used in the process of bone regeneration. This idea can be supported by the high susceptibility of MOFs to modifications, taking into account their porous structure, crystallinity, and chemical composition followed by their chemical and thermal stability (Ghovvati et al., 2024). The MOF structures can be composed of elements such as Ca^{2+} and Sr^{2+}, promoting the formation of new bone tissue or restoring the function of mesenchymal stem cells. In turn, MOFs based on Mg^{2+} can improve angiogenesis during bone repair. The metallic part of MOF structures may influence bone regeneration by promoting osteoblast activity, enhancing bone formation, and supporting structural integrity (Y. Zhao et al., 2024). An idea related to the potential use of metal-organic frameworks in bone regeneration is depicted in Figure 13.

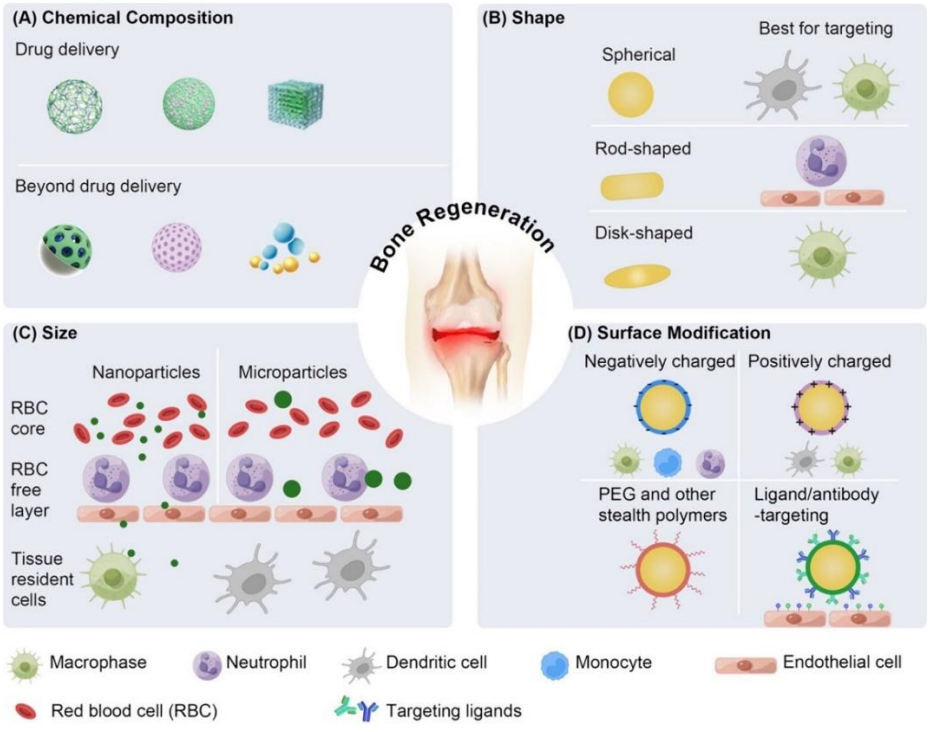

Figure 13. Various optimization strategies of MOF-based nanosystems developed for bone regeneration. Reprinted with permission from (Y. Zhao et al., 2024). Copyright 2024 American Chemical Society.

4. DRUG DELIVERY SYSTEM BASED ON MOFs

The use of MOFs as novel drug carriers for various therapies seems attractive and is, thus, one of their most thoroughly studied applications. MOF-based drug delivery systems indicate many unique features related to their design, modifiability, and functionalization. The very slow and gradual release of drugs from MOFs reduces the side effects of therapy, as well as the so-called burst effect (S. He et al., 2021). In addition, the drug-releasing at the target site, *e.g.*, in the tumor cell environment, eliminates the drug-transfer effect and increases the effectiveness of the therapy. Drugs are released from metal-organic frameworks for a long time so that the therapeutic dose persists in the patient's bloodstream throughout this period. That reduces the need for frequent dosing and minimizes the risk of the patient skipping a dose (intentionally or by accident), which is a common problem in mental illness. The above-mentioned features of MOFs connected with their high susceptibility to various modifications allow for the use of metal-organic frameworks as Drug Delivery Systems and adjust them to the chosen "personalized" applications (Sun et al., 2020; Valizadeh Harzand et al., 2023).

4.1. Targeted drug delivery systems

Targeted drug delivery systems intend significant growth in therapy effectiveness. It is realized by the coating of the MOF surfaces with molecules oriented in a specific direction. The most often applied solutions are folic, lactobionic, or glyceric acids, which provide targeted drug release in the cancer environment. For example, there are folates on the surface of cancer cells, which have an affinity for folic acid (Abazari et al., 2019; Dong et al., 2018). If the surface of the MOF framework is functionalized with this acid, its molecule directs the carrier in the cancer environment, and drug release occurs there. It was evidenced by an experiment in which 5-fluorouracil, doxorubicin, and curcumin were introduced into a metal-organic framework, and their delivery efficiency was studied after the functionalization of the MOF surface with folic acid (Alves et al., 2021). Another molecule used for such purposes was poly(acrylic acid-mannose acrylamide) (PAAMAM) (Demir Duman et al., 2022). Duman et al. (Demir Duman et al., 2022) coated the surface of MOF-808 with two chemotherapeutics, noticing a synergistic effect between floxuridine and carboplatin. They observed a very high cytotoxicity against HepG2 human liver cancer cells (Demir Duman et al., 2022). In other studies, Mugaka et al. (Mugaka et al., 2021) synthesized a zinc MOF containing modified histidine acting as a linker (Bio-MOF series). The prepared system was functionalized with the Fmoc-His-Asp-Gly-Arg peptide, and doxorubicin was incorporated into its structure. That allowed the MOF-based carrier to attach to the cancer cell and migrate into the cell interior, leading to drug release and

making the proposed therapy direct and thus extremely effective (Mugaka et al., 2021). A scheme illustrating the work of the designed system is given in Figure 14.

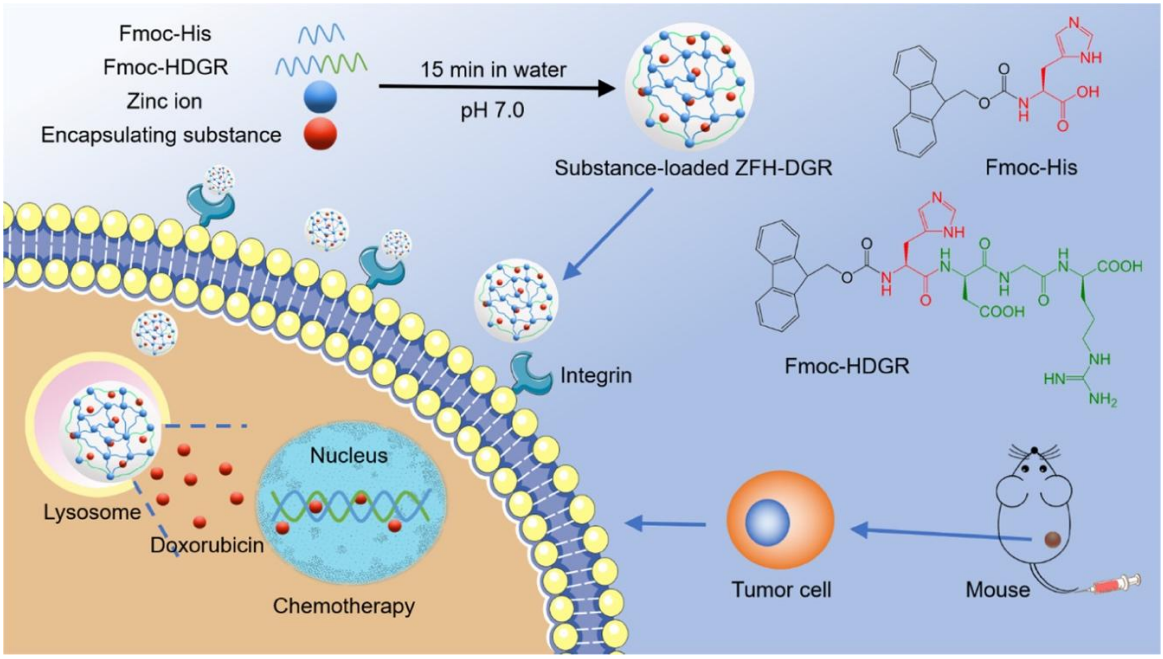

Figure 14. One-Pot Preparation of ZFH-DGR/Cargos and Their Targeted Delivery for Precise Therapy of Tumor. Reprinted with permission from (Mugaka et al., 2021). Copyright 2021 American Chemical Society.

Another research is related to the functionalization of the MOF surface with L-α-phosphatidyl-ethanolamine (DOPE) or hyaluronic acid in the therapy against leukemia (M. Cai et al., 2020). The use of those modifiers for MOF's functionalization turned out to be particularly important. It enabled offsetting the disadvantages of the therapies proposed and known so far, fighting against limitations and leading to enormous growth in the therapy effectiveness, which was connected directly with the enhancement of the patient's comfort (H. Zhang et al., 2018).

4.2.Stimulated-response drug delivery system

Metal-organic frameworks differ in crystallinity, porous structure, and chemical and thermal stability. Their sensitivity to certain external conditions, such as pH, temperature, or the presence of specific chemicals, makes them useful as stimulated drug carriers. This means that the drug can be released from the metal-organic framework due to the presence of external factors such as elevated temperature. This is due to the degradation of the structure under the

influence of factors to which it is sensitive. The crucial issue is a correct selection of the MOF structure to ensure its stability under conditions occurring in the human body with simultaneous degradation in the microenvironment of the diseased cell, tissue, or organ (Akbar et al., 2022; W. Cai et al., 2019; Y. Wang et al., 2020).

In the case of pH-stimulated responses, the use of MOFs unstable under acidic conditions is particularly important for the development of cancer therapies. Several MOF structures seem to be good candidates for this purpose. For example, the MOF-74 (Zn) was modified with arsenic trioxide, and for the prepared system, the drug release profiles in media with different environmental pH levels were determined. The optimal results were obtained for a pH equal to 6.0. The proposed solution is expected to be used in the therapy against leukemia (Schnabel et al., 2020). A similar situation occurred for ZIF-8, revealing a highly pH-stable structure. The ZIF-8 can be used in the treatment of breast cancer (MCF-7 cell line). Moreover, the ZIF-8 framework is sensitive to H_2S occurring in the tumor environment.

Another possibility of the use of metal-organic frameworks refers to the drug release under redox reaction conditions known as redox-responsive release (H. Zhao et al., 2021). This phenomenon often takes place in the presence of glutathione (GSH), glucose, or selected enzymes. Cancer tissues are characterized by GSH concentrations from 100 to 1000 times higher than in healthy tissues or the extracellular matrix. GSH is a highly reducing agent that simply undergoes oxidation. The presence of disulfide bonds in metal-organic frameworks facilitates the oxidation of GSH, reduction of the MOF, and release of the drug (Y. Wang et al., 2020). An example of the MOF containing the aforementioned bond is DTBA, consisting of a Zr node and the linker in the form of 4,4′-dithiobisbenzoic acid, which constitutes an ideal material for GSH-stimulated response (Lei et al., 2018). In turn, for glucose-sensitive carriers, the simulated response involves the oxidation of glucose to gluconic acid and H_2O_2. Hydrogen peroxide generates acidification of the environment, followed by the degradation of MOF and the drug release. This solution is helpful for insulin tuning based on glucose oxidase. Suitable MOFs for such types of purposes are MIL-100 (Fe) (L. Zhang et al., 2018) and ZIF-8 (Y. Zhang, Lin, et al., 2019).

The application of MOFs is also possible in the case of enzyme-stimulated responses. However, the encapsulation of the metal-organic frameworks in hyaluronic acid or pectin can turn out to be necessary. For instance, the MOF envelope is degraded in the human body, and the drug is released very slowly. It was found that PCN-224 encapsulated in hyaluronic acid was functionalized and revealed high effectiveness in cancer therapy.

Another effect was elevated MOF stability, allowing it to remain stable under the conditions occurring in the human body, whereas the acid degraded minimalizing sudden drug release at a non-target site (Y. Wang et al., 2020). A simulated response can also occur under the presence of adenosine triphosphate (ATP), which is a highly energetic molecule commonly existing in living organisms. The formation of ATP complexes with DNA and RNA can occur, which promotes the release of the drug directly into their structure, as well as a coordinated response if there are free electron pairs in solution, originating from the imidazole ring, benzene, or amino groups. Other examples are the ion-stimulated response, as well as simulated drug release affected by physical factors such as light, pressure, or temperature.

For light- or temperature-dependent responses, light-sensitive materials such as PCN-222 (Kim et al., 2019), PCN-224 (D. Feng et al., 2012), or USTC-8M should be used (W. Xu et al., 2015). They are proposed for photodynamic therapies due to their good oxidative properties. Metal-organic frameworks have also found application in transferring NO molecules for medical purposes, including cancer or cardiac therapies (D. Zhao et al., 2022a). Metal-organic frameworks unstable at elevated temperatures are also used as carriers for treatment, mainly for anti-cancer therapies, which are associated with the temperature prevailing around the tumor. In this case, the weakening of the host-guest interaction takes place, which is directly affected by entropy values. The □-□ stacking interaction is cleaved as the temperature increases (Y. Zhang et al., 2020). Such a phenomenon was observed in ZJU-801 (Ke et al., 2016). The effect of pressure was also investigated. Jiang *et al.* (Ke et al., 2016) observed a significant time prolongation of the drug release with rising pressure. An example of a MOF-based stimulated DDS response is depicted in Figure 15.

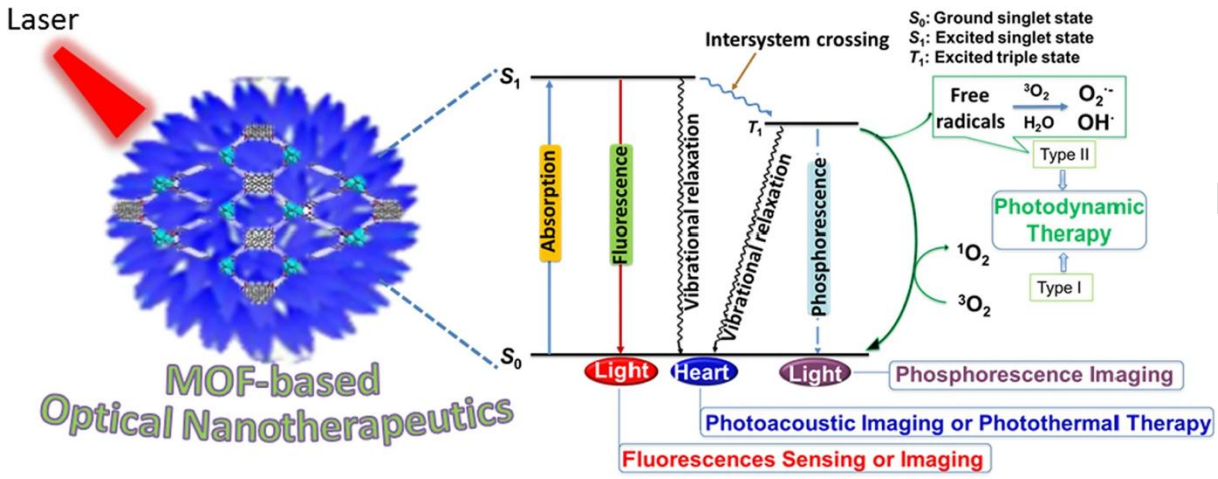

Figure 15. Schematic diagrams of the stimulated DDS based on MOF (D. Zhao et al., 2022b).

4.3. Magnetic drug carriers

Some metal-organic frameworks indicate magnetic properties. In others, nanoparticles of such properties can be introduced. Another example is MOFs demonstrating magnetic-stimulated responses. The release profile of acidic dye AO7 – Orange II sodium salt in UiO-66-type MOF containing Fe_3O_4 nanoparticles was studied by Zhan et al. (Zhan et al., 2018). Similar studies were performed for MIL-88B (Akbar et al., 2022). Based on the results from the undertaken research, it was concluded that ferromagnetic metal-organic frameworks contained lower maximal amounts of the drug; however, they revealed a lack of toxicity. The study was performed on the HEK293 T-line cells (Akbar et al., 2022).

It was also found that the magnetic properties of the metal-organic frameworks can be generated by applying cobalt, nickel, iron, or oxides as inorganic nodes occurring in the MOF structure. Another observation was the high impact of MOF magnetic properties on its adsorption capacity, which opens a wide perspective for new opportunities in therapeutics. Thus, the appropriate carrier of selected properties adjusted to the patient's needs and therapeutic requirements can be chosen. However, the applied MOF-based carrier should be biocompatible and completely safe for humans (Chowdhuri et al., 2016; Shi et al., 2021).

4.4. Multidrug therapy

Introducing the drug mixture into the MOF structure is another groundbreaking approach in the application of MOFs as drug carriers. This action is feasible due to the unique porous properties of MOF materials (particularly large specific surface areas) and their crystallinity. Scientists consider such multi-drug therapies as two approaches. According to the former model, it is possible to combine the packing of a therapeutic particle as an active substance with a second compound as a non-drug. This approach assumes a synergistic effect between two substances. A drug delivered to the bloodstream is strengthened by the second compound coupled with the drug, which enhances the final effect of the whole therapy without affecting side effects or other complications during treatment. In the case of the latter approach, there are two kinds of drugs in one MOF structure. This solution seems to be particularly useful in the treatment of serious diseases such as cancer (Abánades Lázaro et al., 2020), however, the drug doses should be limited, and the applied drugs should not cancel their effects on each other. For multidrug therapy, the MOFs of UiO-66, MIL-53 (Al), and MIL-100 (Fe) structures were investigated, whereas the studied drugs were ibuprofen and caffeine. In the case of the first two MOF structures, the release of both drugs was in the range of 80-100% (X. Li et al., 2023). Other compounds with therapeutic potential were tested as gallic acid (Sharma et al., 2019) or

hydroxycinnamic acid (L. Zhang et al., 2016). Another research referred to chemotherapeutics - floxuridine and carboplatin incorporated into MOF-808. Based on the obtained results from *in vivo* studies, an efficient and gradual drug release was found (Demir Duman et al., 2022).

5. TOXICITY, BIOSAFETY AND BIOCOMPATIBILITY OF MOF

The aforementioned wide medical applications of metal-organic frameworks refer to cancer therapies, bioimaging, contrast agents, and novel drug delivery systems that can trigger a stimulated response or targeted DDS. Their popularity in biomedical applications is still growing, as are innovative ideas for further use. The growing potential for medical applications of MOFs prompted scientists to study their toxicity and possible effects on the human body. The research highlighted the possibility of MOFs interacting with cells or tissues and the influence of MOF structure on their toxicity, however, an overwhelming amount of research indicated the lack of toxic effects of the metal-organic framework and their high biocompatibility. To prove the absence of toxic effects, several in vitro and in vivo tests were conducted (Wiśniewska et al., 2023). For example, MOF-74 (Mg) with nanometric and micrometric particle size was investigated. The obtained results showed a lack of cytotoxicity on the HeLa cell line below concentrations of 1000 μg/ml and 500 μg/ml (for nano- and micro-sized particles, respectively) with the absence of cardiotoxicity, the nano-sized particles, however, revealed higher biosafety in in vivo studies (Z. Zhu et al., 2020). In other research, the influence of MOFs' molecular size on their toxicity was determined (D. Wang et al., 2022). It was evidenced that ZIF-67 particle size below 400 nm caused notable growth in this MOF toxicity (D. Wang et al., 2022). In turn, Daun et al. (Duan et al., 2018) developed composite materials by loading doxorubicin (known as a chemotherapeutic agent) into the structure of amorphous ZIF-8 (AZIF-8). The composite was incubated in a 4T1 line for 48 h, and the release of the drug from the structure was observed for this system with a simultaneous drop in toxicity compared to pure MOF. On the other hand, the highly aggressive character in contact with cancer cells, rapid drug release, and high drug accumulation in the tumor were evidenced (Duan et al., 2018). The proposed therapy revealed high efficacy, which is depicted in Figure 16.

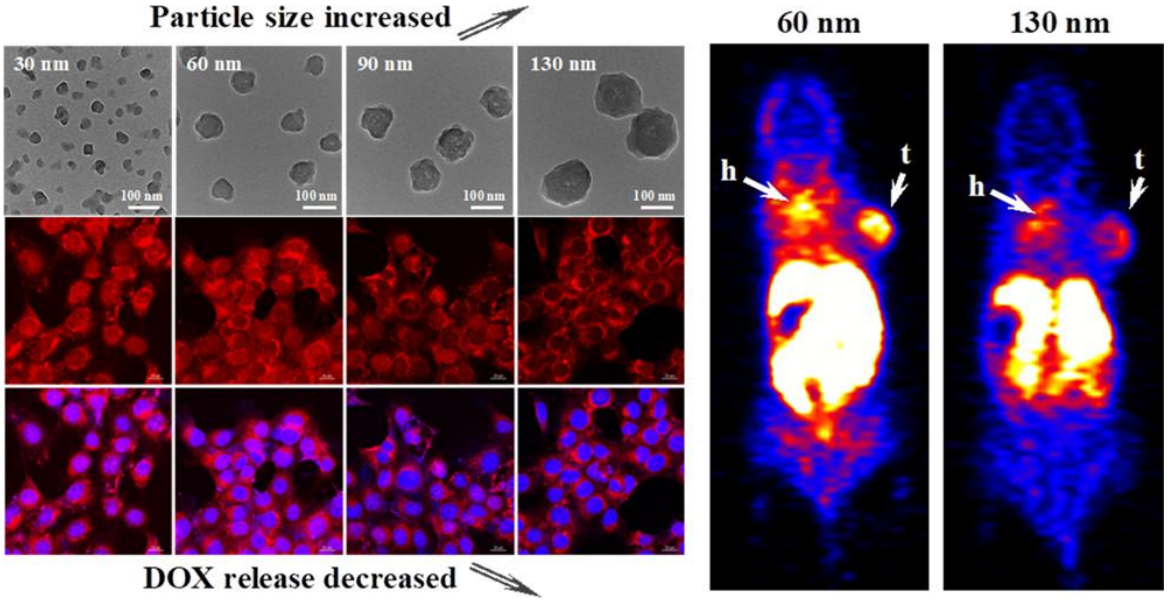

Figure 16. DOX@AZIF-8 of different sizes exhibited significant differences in tumor accumulation and anticancer efficacy. Reprinted with permission from (Duan et al., 2018). Copyright 2018 American Chemical Society.

A separate group of research was to evaluate the biodistribution of ZrO_2, which can form the inorganic ingredient of the metal-organic framework. A single dose of zirconia in the range of 100-350 mg/kg was selected as safe for humans, and it was observed that the injection of this dose into the human body did not change weight, blood biochemistry, histomorphology, and hematology. However, further and more detailed study of the metabolism of zirconium-based carriers is needed (Y. Yang et al., 2019). Another study indicated the toxicity of Fe carriers such as nanoMIL-53, nanoMIL-88, nanoMIL-100, and nanoMIL-101 on mouse macrophage J774.A1, human leukemia (CCRF-CEM), human multiple myeloma (RPMI-8226), and human cervical adenocarcinoma (HeLa) cell lines; no overall cytotoxicity, however, was evidenced. The toxicity of ZIF-8 and UiO-66 was also compared, and higher toxicity was found for the latter MOF on the HeLa cell line (Ruyra et al., 2015). The conducted tests indicated the lowest toxicity for MOF-74 (Mg) among all studied materials, considering experiments on HepG2 and MCF7 cell lines and zebrafish embryos. An interesting situation was observed for nano-MIL-101, which showed significantly higher toxicity in in vivo tests than on cell lines (Ruyra et al., 2015). It was evidenced that the degradation of MOFs and the release of metal ions building their structure can lead to the growth of the MOF's toxic nature similar to other parameters such as the size and shape of MOF grains, as well as framework charge (Ruyra et al., 2015). In other

studies, the route of the drug administration on mechanisms of action and overall safety for patients were investigated. In the case of inhaled MOFs, it was shown that hydrophilic molecules can overcome the epithelial cell barrier and migrate into the circulatory system safely and effectively (F. Hao et al., 2022). Rojas et al. (Rojas et al., 2018) indicated that oral administration of MOFs can lead to the penetration of the circulatory system by overcoming the gastrointestinal barrier without its disruption. The oral absorption of the drug released from MOFs is highly effective, indicating the extremely large bioavailability of metal-organic frameworks (Rojas et al., 2018). Furthermore, it was evidenced that the functionalization of MOFs' surfaces improved their framework stability in the digestive system and the efficiency of their penetration, as shown in Figure 17.

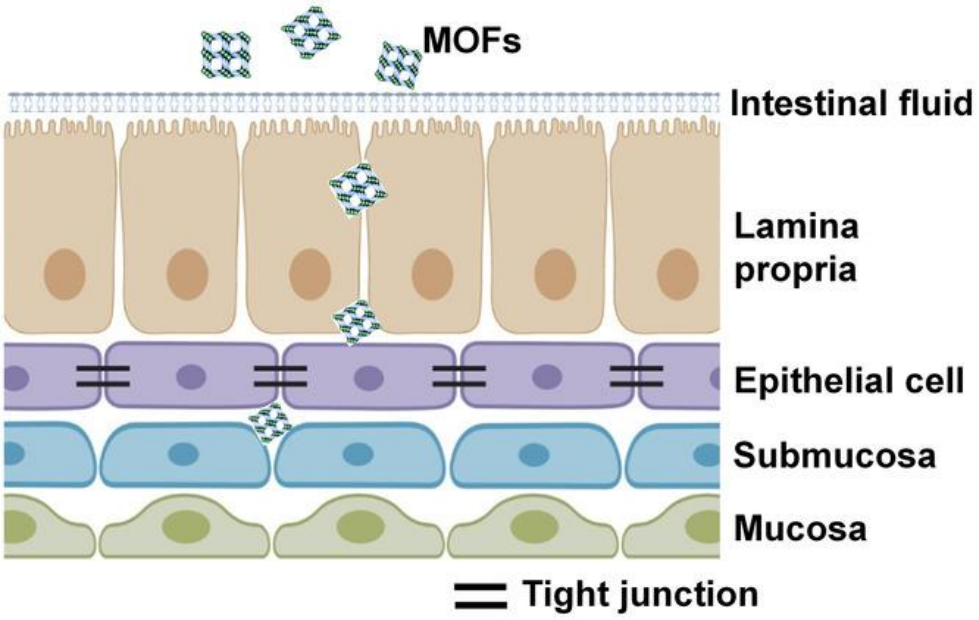

Figure 17. Schematic of the gastrointestinal tract and its uptake route of MOFs (F. Hao et al., 2022).

The dermal administration of drug-containing MOFs can also be realized due to the positive electric charge of the metal-organic frameworks or deposited nanoparticles (Rojas et al., 2018). He et al. (Y. He et al., 2021) reported the high bioavailability of doxorubicin-loaded MOFs and their high efficacy in this way of administration, evidenced by a significant reduction in tumor size associated with lung cancer (Y. He et al., 2021). In turn, Jodłowski et al. (Jodłowski et al., 2022) studied the effectiveness of COVID-19 treatment with Zr-MOF doped with acriflavine. They reported a very high treatment efficacy and an inhibitory effect of the MOF-released drug on viral activity. Even at low concentrations of the released drug, activity was detected,

highlighting the high bioavailability of the metal-organic framework-based carrier (Jodłowski et al., 2022). Additionally, it was shown that MOFs can have a protective effect on the loaded drug molecule and exhibit cardioprotective character due to the gradual and targeted release of the drug (Jodłowski et al., 2021). Other studies showed the antibacterial properties of MOF-based silk bandages loaded with levofloxacin (Dymek et al., 2024). The bandages released the drug for 72 hours with continuous activity and efficacy. The antibacterial activity applies to both Gram-positive and Gram-negative bacteria, emphasizing the wide potential application and high efficiency of the studied system (Dymek et al., 2024).

Numerous metal-organic frameworks are considered as biosafe and biocompatible compounds, however, non-toxic metals and ligands should be used to obtain this type of material. The metallic part is responsible for the toxicity of the whole structure. The median lethal dose (LD_{50}) is used to verify this parameter. Metals such as potassium, zinc, iron, and zirconium have oral LD_{50} of 0.215 g/kg, 0.35 g/kg, 0.45 g/kg, and 4.1 g/kg, respectively (S. He et al., 2021). In addition, copper and magnesium are biocompatible and suitable for drug delivery systems (S. He et al., 2021). Moreover, zirconium and titanium exhibit poor adsorption in the human body, making these blocks useful for cosmetic applications. The selection of linkers implicates unique properties and also affects the toxicity of MOFs. For example, biphenylenedicarboxylic acid, which is the building block of UiO-67, has a biosafety profile. On the other hand, fumaric acid or benzenedicarboxylic acid derivatives increase toxicity (Tamames-Tabar et al., 2014). For organic linkers, the hydrophobic and hydrophilic balance plays a major role. It was indicated that hydrophobic and polar ligands were more biologically safe because the compound could be easily excreted and did not accumulate in human tissues (Baati et al., 2013). Hence, both linkers and metal can affect human health and life, but the toxicity of the organic part is more complicated and not as clear as the metal part. One of the solutions to this problem is to develop MOFs with biocomponents, such as carbohydrates, peptides, or amino acids, which are non-toxic and only partially stable (Singh et al., 2021). Another parameter affecting MOFs' toxicity is their particle size. For biomedical applications, particles smaller than 200 nm should be most suitable. Nanosized MOFs allow controlling the rate of drug delivery and efficacy (P. Chen et al., 2020). Small and nano-sized particles can permeate through biological membranes and the blood stream during inhalation (Wiśniewska et al., 2023). On the other hand, larger nanoMOF sizes (>200 nm) increase toxicity and inflammation affect (F. Hao et al., 2022). Comparing the size of micro and nanoparticles, the latter are characterized by a higher IC_{50} (inhibitory concentration), so high doses of this MOF are recommended. Last but not least is the MOF's biodistribution. It was also evidenced that MOF-based materials tended to accumulate in the

liver (Xie et al., 2020), kidneys (Zhuang et al., 2020), lungs (Maeda et al., 2000) and cancer cells (Xiao et al., 2020). However, these materials were safe and harmless to the human heart. Furthermore, metal-organic structures did not indicate toxicity in both in vitro and in vivo studies, with simultaneous biosafety and feasibility.

6. METAL-ORGANIC FRAMEWORKS IN DEPENDENCY TREATMENT – A POTENTIAL MEDICAL MILESTONE

Metal-organic frameworks seem to be desirable materials for medical applications. They demonstrate high adsorption ability in the context of drug removal or release, biocompatibility, and lack of toxicity. Although research on medical applications of MOFs is already advanced, further knowledge development in this area is needed (Lawson et al., 2021b). Given the fast-growing pharmaceutical industry and the ever-increasing needs of the market, there are currently several shortcomings and elements for improvement, e.g., drug addictions. This problem is still growing, and the average age of addicted people is still decreasing (Mercurio et al., 2022). Furthermore, the accessibility of drugs such as amphetamine, methamphetamine, cocaine, mephedrone, LSD, or MDMA is becoming increasingly easier with simultaneous drops in price (Mead and Parrott, 2020). The remedy for these problems is the administration of an antidote neutralizing the effects of the drug, including its overdosing (Müller and Desel, 2013), according to the currently known Bremen list (Schaper et al., 2013). For instance, in the case of the poisoning with compounds from the synthetic cathinone group, e.g., mephedrone (4-methylmethcathinone, 4-MMC), the well-known β-blocker propranolol (PRO) is used as an antidote. Another example is poisoning with opioids, including heroin, morphine, or fentanyl, for which naloxone is recommended. The next known compound is flumazenil, which is used against the abuse of benzodiazepines (Müller and Desel, 2013). Apart from applying antidotes in the form of compounds, physical procedures can also be used, such as gastric lavage, premature bowel lavage, or hemodialysis. However, these activities already require specialized medical equipment and/or skilled staff (Madhuri et al., 2020). The only fully accepted adsorbent that complies with the requirements of a medical product is activated carbon (Hassen and Abdulkadir, 2022). Nevertheless, the application of activated charcoal as a medical adsorbent of psychoactive substances is dangerous due to the risk of tachycardia, bowel blockages, and dehydration as a result of the rapid removal of the drug from the body. Thus, it may be concluded that in the pharmaceutical market, suitable adsorbents of high effectiveness and safety during overcoming an overdose are needed. MOFs seem to be good candidates for the

adsorption of hazardous materials due to their features, such as large specific areas, and ultrahigh overall porosity, and optimal adsorption kinetics.

6.1. MOFs – perspective medical adsorbent

As mentioned above, activated charcoal is used as a medical adsorbent against overdoses of toxins such as ricin, strychnine, antidepressants, tetracyclines, or barbiturates. In this relatively cheap material, the adsorption of toxic substances is based on the binding of the hazardous compounds on its surface, preventing body poisoning. However, the adsorption can be limited by the size of the absorbed toxin particle, pH, solubility, or surface charge. Despite its availability, the use of activated carbon as an adsorbent during poisoning is not always possible. It can take place in the case of the removal of psychoactive substances from a patient's body when too sharp an adsorption kinetics is observed. It means that the drug removal is too fast and can cause deoxygenation, tachycardia, or intestinal obstruction. It must be emphasized that the administration of activated carbon in an unconscious state is life-threatening [132](Zellner et al., 2019). In turn, other sorbent materials have not been approved for medical use. Interestingly, for metal-organic frameworks, a very high potential was noticed (Gangu et al., 2016).

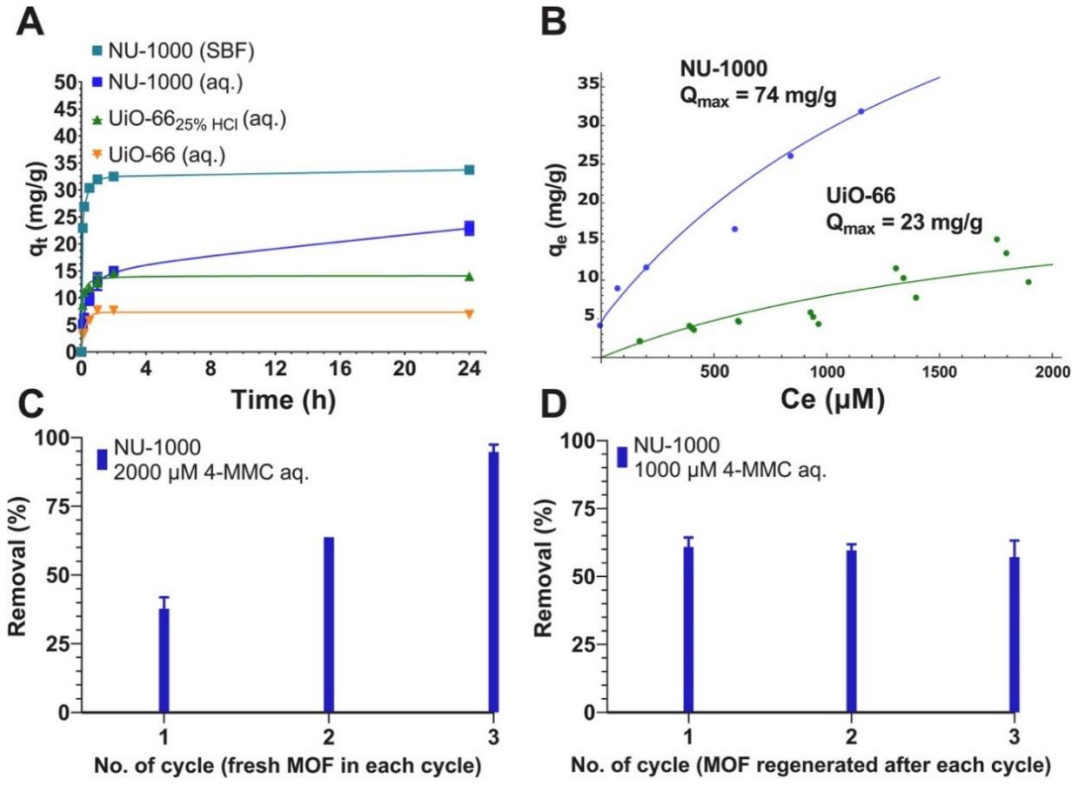

Figure 18. 4-MMC removal efficiency on prepared Zr-MOFs (A), equilibrium loading in prepared Zr-MOFs (B), 4-MMC cascade removal efficiency on NU-1000 (C) (Jodłowski, Dymek, et al., 2023).

According to preliminary results, MOFs are completely safe for humans, biocompatible, and they can be administered by various routes, such as oral, intravenous, subcutaneous, intramuscular, and inhalation (Wiśniewska et al., 2023; Z. Zhu et al., 2020). Furthermore, their use was reported in the process of wastewater treatment from pharmaceuticals (Prasetya and Li, 2021; Wu et al., 2018; H. Yang et al., 2020). Therefore, a medical application of this mode of operation is possible. Zirconium-based MOFs were investigated as adsorbents of 4-MMC (Jodłowski, Dymek, et al., 2023). Among others, the kinetics of adsorption was studied, and an efficient and fast adsorption of drugs over the MOF surface was found. Further comparison between two media, i.e., distilled water and a solution of simulated body fluid (SBF), led to the conclusion that the contact of MOF with the SBF solution resulted in the production of a hydroxyapatite layer on MOF's surface. For distilled water, this effect was not observed. The obtained results reflect higher efficiency of the adsorption process in SBF solution with a simultaneous maintaining a safe kinetics of the removal of toxins from the body. Figure 18 illustrates the results from kinetic calculations referring to sorption plots, equilibrium loading, and cascade removal efficiency on chosen structures of metal-organic frameworks (Jodłowski, Dymek, et al., 2023).

The research on the adsorption of hazardous substances over MOF materials was extended to include a biological aspect. In paper (Jodłowski, Dymek, et al., 2023), the cardioprotective nature of the Zr-MOFs was reported, as well as the positive effect of mephedrone on cardiac defects and dysfunction. Furthermore, it was evidenced that in the presence of MOFs in mephedrone solution, parameters such as locomotory and heart rate decreased, returning from the ultrahigh (dangerous) values specific to the state in which mephedrone directly influenced the work of internal organs. On the one hand, it was the lack of toxicity of MOFs (when the studies involve MOFs deprived of 4-MMC solution) and the efficiency as medical adsorbents during in vivo studies (for the studies conducted in the coexistence of MOFs and 4-MMC solution). Based on a series of experiments on zebrafish (Danio Rerio), it was possible to determine the IC50 (50% of mortality) for mephedrone. At concentrations above 1000 μM, the fertilized Danio Rerio eggs were destroyed, and the embryos did not develop. However, after the addition of MOFs, the fishes remained alive (Figure 19).

As a final experiment, for the determination of adsorption efficiency and its influence on living organisms, a color preference test was performed. In the beginning, the default fish color preference was determined. After 5 minutes of testing, it was observed that Danio Rerio preferred a blue environment and spent more time in a blue area. In the second step, an

association between administering a given substance and being in a specific environment was created. Therefore, mephedrone was added to a less preferred environment. In the last step to determine the efficiency of MOFs for Danio Rerio, MOF was also added to the environment. It was observed that fish, after the addition of MOF, did not stay preferably longer in either of the areas, and their movement was stochastic. The observed phenomena can be explained by the absorption of mephedrone by MOF, leading to the situation in which the larvae do not become addicted to the adsorbed drug, thus, they return to the color preference before their addiction (Jodłowski, Dymek, et al., 2023).

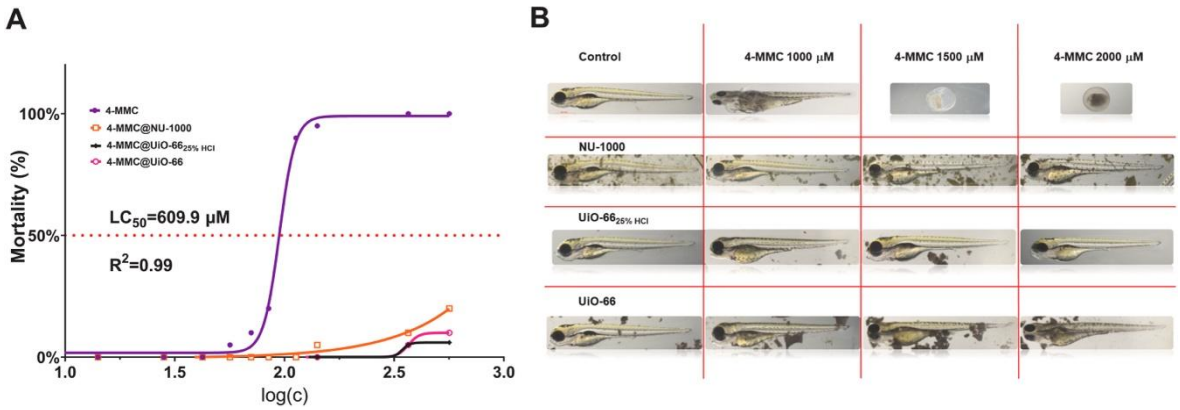

Figure 19. Toxicity of 4-MMC alone and with MOFs. The value of LC50 for 4-MMC at 96 hpf (A), Effectiveness of MOFs (B) (Jodłowski, Dymek, et al., 2023).

Similar studies were performed for other psychoactive substances, such as amphetamine, methamphetamine, cocaine, and MDMA (Jodłowski et al., 2024). The obtained results were similar to those received for mephedrone, which confirmed the MOFs as effective and promising adsorbents for further medical purposes (Jodłowski et al., 2024).

6.2. The incorporation of antidote into MOFs structure to create Antidote@MOFs

Promising results on the medical application of metal-organic frameworks in the context of drug delivery and adsorption of hazardous substances for living organisms prompted us to reply to the question of whether it is possible to use MOFs as carriers of well-known antidotes. It was found that MOFs can be used as Drug Delivery Systems (DDS), and numerous biological studies confirmed their non-toxic nature, which makes these materials future-oriented with a high implementation potential. For instance, metal-organic frameworks as carriers for propranolol (PRO) can be considered. Propranolol is known as a compound used against mephedrone poisoning and belongs to the group of β-adrenergic receptor antagonists which,

apart from treating hypertension or heart problems, can minimize the effects of 4-MMC abuse (Caplan et al., 2020; Sakagami et al., 2023). PRO reduces blood pressure and heartbeat rate, preventing tachycardia and thus eliminating the potential side effects of mephedrone use (Mercurio et al., 2022).

The possibility of using MOFs as PRO carriers was evidenced by the efficient and gradual release of the drug from the metal-organic framework to the studied zebrafish (Hyjek et al., 2024). The slow release of the therapeutic substance allowed for the maintenance of an adequate dose in the bloodstream and a prolonged effect without the need for reapplication. Furthermore, a slow drug release into the SBF solution allowed us to avoid side effects and confirmed the high safety of MOF use. One research referred to biological studies, in which a propranolol-containing composite (PRO@MOF) was immersed in the 4-MMC solution to use MOFs as antidote carriers during an overdose. The studied systems were applied to zebrafish. The lack of toxic effects of MOFs, their biocompatibility, and the high efficacy of the proposed therapy was evidenced by, among others, a reduction of heartbeat, locomotion, and mortality for the investigated living organisms (Hyjek et al., 2024).

6.3. Dual MOF-based detoxification system

A further step, being a continuation of the previous research, could be a dual-organism detoxification system based on two kinds of metal-organic frameworks. The former MOF material plays the role of adsorbent, which reduces the poison concentration in the studied environment (e.g., in blood), whereas the action of the latter MOF is based on the release of substances that could react with the poison (in this case drugs) leading to the formation of products safe for the studied organisms followed by the reverse of the effects of an overdose. The proposed assumption seems to be feasible based on the physicochemical properties of the studied MOFs, including the results on the drug adsorption and release kinetics, as well as their stability and cytotoxicity. Assuming small therapeutic doses, the synthesis of such systems should be relatively cheap, and their administration would be easy, without the necessity of professional staff employment. This approach could reduce overdose-related mortality. The proposed dual detoxification system for living organisms seems to be an effective and forward-looking step for the medical and pharmaceutical industries. Moreover, the proposed solution would fill the currently existing gap of medical absorbents and could constitute a huge milestone in addiction treatment.

Table 1. Biomedical applications of MOFs.

Application	Examples
Biosensing	Detection of protein and enzymes (G. Zhang et al., 2016) Detector of HIV-1 and HBV virus (X. Zhu et al., 2013)
Bioimaging	Contrast of tissue imaging (Saeb, Rabiee, Mozafari, and Mostafavi, 2021) MRI, PET and CT technique (S. He et al., 2021)
Cancer therapy	
• **PTT**	PTT against HepG2 cancer by sorafenib@ZIF-8 (Q. Hu et al., 2023)
• **PTD**	Photosensitizers incorporate in MOF against cancer (Sharma et al., 2019)
Bone regeneration	Restoring the function of mesenchymal stem cell by Ca^{2+}, Sr^{2+} MOFs (Y. Zhao et al., 2024) Promoting osteoblast activity, enhancing bone formation, and supporting structural integrity by Ca^{2+}, Sr^{2+} MOFs (Y. Zhao et al., 2024)
Drug delivery system	
• **Targeted**	Folic acid (Abazari et al., 2019), peptide (Mugaka et al., 2021) and polymer (Demir Duman et al., 2022) as an enhancement factor in therapy
• **Stimulated**	Dependent on pH (MOF-74) (Schnabel et al., 2020), H_2S (ZIF-8) (H. Zhao et al., 2021), H_2O_2 (MIL-100) (L. Zhang et al., 2018), light and temperature (PCN-224) (D. Feng et al., 2012)
• **Magnetic**	Functionalized MIL-88A by Fe_3O_4 (Zhan et al., 2018)
• **Multidrug**	Combine floxouridne and carboplatine loaded into MOF-808 in anticancer therapy (Demir Duman et al., 2022)
Medical adsorbent and detoxification system	Removal psychoactive substances such as 4- MMC (Jodłowski, Dymek, et al., 2023), cocaine, amphetamine, methamphetamine, MDMA (Jodłowski et al., 2024) in human body Deliver antidote during 4-MMC overdose (Hyjek et al., 2024)

7. OUTLOOK

Metal-organic frameworks are a group of materials developing very rapidly and in many directions. On the one hand, methods of synthesizing MOF structures are still being improved. Scientists are focusing on the use of ecological and economical ways, which would fit in with the trends of Green Chemistry and take into account the growing environmental restrictions while maintaining the efficiency and, most importantly, reproducibility of the synthesis (Souza et al., 2020). Hence, the constant development of microwave radiation (Couzon et al., 2022), ultrasound (Abazari et al., 2018) or electrochemical methods (Butova et al., 2016), or other environmentally friendly methods is highly desirable. Above that, the phenomenon of "defect engineering" is constantly being studied (Shearer et al., 2016). The influence on the type, amount, or concentration of modulators used and the structure of MOFs, mainly their porosity or specific surface area (X. Zhang et al., 2022) are still under vigorous investigation. On the other hand, more and more potential applications of metal-organic frameworks are found every year (D. Li et al., 2024). Their structure and closely related physicochemical characteristics of the material allow for a variety of practically unlimited applications.

The use of metal-organic frameworks in catalytic processes is well known, mainly as heterogeneous catalysts (Gharib et al., 2021), in gas separation processes (H. Li et al., 2019), purification of gases from gas mixtures (Lee et al., 2021), or gas storage (Peng et al., 2013). This application, especially gas purification and gas storage, seems to be a very promising topic. Given the growing problem with CO_2 and the need to reduce its emissions, capturing the said gas from the air and then accumulating it in MOF structures seems to be a promising solution (D. M. Chen et al., 2015; Y. Zhang, Zhang, et al., 2019). Metal-organic frameworks could also revolutionize the future of energy, more precisely, the application of hydrogen. Due to their excellent adsorption and storage capabilities, it is possible to use MOFs as H_2 storage (Wong-Foy et al., 2006). Again, this underscores their wide-ranging capabilities and, most importantly, the possibility of practical application and usefulness in the problems of the modern world.

There are numerous examples, such as the use of MOFs in new types of batteries (Xue et al., 2019) or as detection probes (Tran et al., 2023). Unsurprisingly, the greatest progress is in the medical and pharmaceutical fields. This is because metal-organic frameworks are finding more and more influential applications there (Awasthi et al., 2022). In fact, MOFs are used not only as traditional drug delivery system (Maranescu and Visa, 2022) but also as stimulated (W. Cai et al., 2019), targeted (Alves et al., 2021), or specially protected systems against adverse conditions in the human organism (Liang et al., 2015). This approach significantly increases

the effectiveness of the therapy while minimizing its side effects. In addition, MOFs are used in the fight against the most common and fatal disease, *i.e.*, cancer. In this case, they can not only be employed as carriers of chemotherapeutics (Saeb, Rabiee, Mozafari, Verpoort, et al., 2021a) but can also be combined with other, less toxic compounds, increasing the effectiveness of treatment (Ho et al., 2020). Above that, it is possible to utilize them in highly effective and forward-looking photothermal (PTT) (Zheng et al., 2021) and photodynamic (PTD) therapies (Ni et al., 2020), as well as in the diagnosis of diseases as biomedical sensors (Zhou et al., 2018).

A breakthrough in the field of MOFs has been the development of structures based on fragments of biological compounds that can reduce the toxicity of the framework and significantly affect the bioavailability of administered drugs (J. Liu et al., 2022). Following modern trends, metal-organic frameworks can also be used as micro-needles – new transdermal therapy systems with high efficacy and minimized pain sensation compared to traditional injections (M. Yin et al., 2021). In the field of hydrogel materials, MOF structures are also finding their place. Studies have been conducted on MOF-hydrogel systems that accelerate the wound healing process (L. Wang et al., 2019).

In this review, the wide range of applications of metal-organic frameworks was reviewed, showing their unprecedented characteristics that can be successfully utilized, especially in pharmacology and future medicine. Nevertheless, for biomedical applications, both low performance and higher cost are not limiting due to the specificity of the mentioned therapies. In addition, it is necessary to comprehend the physicochemical properties of MOFs to be able to choose the appropriate application for a given framework. It is very helpful, and sometimes necessary, to use computational chemistry methods. Besides the structure verification and the IR/Raman spectroscopy interpretation, as was mentioned in the section 2.2, the computational methods, in the case of MOFs at the DFT level of theory, are indispensable for the interpretation of other experimental techniques like thermogravimetry, X-ray diffractometry, and all other spectroscopies, *e.g.*, XPS, NMR, EPR, or XAS.

Metal-organic frameworks, like any type of material, have many advantages and disadvantages. However, the feature that distinguishes MOFs from other spatial structures is their unlimited application potential. Therefore, it is necessary to conduct additional research on their physicochemical properties, toxicity, and effects on the human body, as well as work on more effective, efficient, and environmentally friendly methods of their synthesis. In addition, it is necessary to develop new structures, for example, based on biological compounds or other organic ligands, depending on the purpose. Undoubtedly, although these materials are

constantly being researched and new structures are being developed, their potential is enormous, and the knowledge needs to be explored.

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