Scientiae Radices, **2**(2), 118-189 (2023)

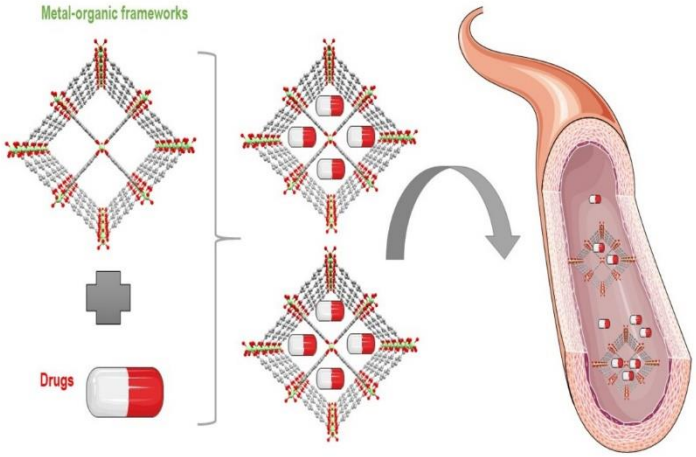
Review

Metal-organic frameworks for efficient drug adsorption and delivery

Kornelia Hyjek[(1)]✉, Przemysław Jodłowski [(1)]

[(1)] Faculty of Chemical Engineering and Technology, Cracow University of Technology, 31-155 Kraków, Poland

✉ Correspondence to: kornelia.hyjek@doktorant.pk.edu.pl



Abstract: In recent years, the number of materials used as drug delivery systems (DDS) has increased dramatically. The widespread use of DDSs has improved both the safety and efficacy of therapy. The systems currently in use pose numerous drawbacks and require proper improvements. Although many modern materials are being developed, metal-organic frameworks (MOFs) deserve special attention. Thermal and chemical stability, high specific surface area, low toxicity, high biocompatibility, and great potential for modification are the main features enabling MOFs to be used as DDS. In this review, we describe MOFs, their structure, synthesis, and characterization, as well as drug loading, drug release kinetics, and bioassays. A critical approach is to outline the disadvantages as

well as the limitations of MOFs and to identify areas that need to be studied more thoroughly. Nonetheless, the prospective nature of MOFs as DDS and potential adsorbents in overdose or poisoning is presented and highlighted.

Keywords: Drug delivery systems, Metal-Organic Frameworks, Synthesis, Characterization, Drug loading, Biocompatibility

Received: 2023.05.10
Accepted: 2023.05.28
Published: 2023.06.05
DOI: 10.58332/scirad2023v2i2a03

Introduction

The pharmaceutical industry is one of the most rapidly growing, as well as the most profitable. The search for new compounds with therapeutic potential, the modification of known drugs, the search for alternative therapies, and the optimization of industrial processes are just a few of the problems confronting the pharmaceutical world. Its basis is the efficient delivery of active therapeutic ingredients (API) [1]. The selection of the right drug delivery route, as well as the choice of carrier, are quite often the "milestones" of therapy. They have a crucial effect on the bioavailability, release rate, and thus on the effectiveness of the therapeutic compound applied [2,3]. The use of drug carriers eliminates many of the limits associated with the various routes of administration. First of all, carriers act in a protective manner on the therapeutic compound, so that it is not degraded already in the initial sections of the gastrointestinal tract [4]. In addition, release can occur after a specific time, at a specific location, or be triggered by specific factors. This approach can reduce the side effects of therapy, and the effects of drug passage. Besides, a properly matched carrier, inducing the prolonged release of API, eliminates human mistakes related to the timing of intake and dosage. This minimizes the need for prolonged therapies and thus the negative side effects of drugs [5]. The development and constant search for new API delivery systems is a response to the growing number, and variety of therapeutic substances. Today, in medicine, both small-molecule and large-molecule compounds such as proteins, peptides, nucleic acids, or monoclonal antibodies are used. The latter group is challenging for effective drug delivery [1,6]. Currently, several routes for delivering therapeutic compounds are widely known and used [7,8]. The first and most widespread is oral drug administration [8,9]. Its major benefit is the rapidity and simplicity of API administration, for both hydrophilic and lipophilic compounds. This method is particularly comfortable for most patients and the safest. The oral route enables the application of drugs in solid, powder, and liquid forms. However, the main limitation is the size of the

tablets/capsules and the possibility of their rapid degradation [10,11]. Another delivery system is the ocular one [12]. Drugs for eye diseases are mainly delivered by this method. Eye drops, implants, or intravenous injections are the usual routes of ocular delivery [13]. Another option is intranasal drug delivery. Here the advantage is the direct application of the drug to the highly vascularized mucosa. This way, the API can reach the central nervous system, bypassing the blood-brain barrier. This route is extremely preferred for topical treatment. It is also possible to use the ear as a route for the administration of therapeutic compounds [14,15]. Among the alternatives for administering drugs in females is the intravaginal route. It is used for the supply of contraceptives, bactericidal and fungicidal drugs. Compounds delivered by this route achieve high bioavailability, an exceptional rate of action, and additionally exhibit less hepatotoxicity [16,17]. Another form is a rectal route of drug delivery [18]. Taking into account that the skin is the largest tissue in our body, it also can act as a route of drug supply. The current trend focuses on the application of modern carriers, transporting a variety of therapeutic substances including macromolecular compounds. The API is transposed directly through the bloodstream, thus bypassing the initial metabolism of the drug, the adverse effects of pH, the bacterial microbiome, or enzymes present in the body. Here, however, the main contribution is to overcome the skin barrier [19–22]. Hence, as we can see, the ways of delivering drug compounds are numerous. They have different features, their pros and cons. Appropriate verification of the physicochemical properties of the drug with the route of delivery is necessary, to select the most impactful route of administration. In order to increase bioavailability, minimize the side effects of taking the drug, reduce the premature degradation of the compound, and more targeted and controlled release of the drug, the use of drug delivery systems have been initiated [10,23–25].

Drug delivery systems (DDS) are designed to supply a therapeutic agent to a specific location, more precisely the diseased tissue, with simultaneous maximum protection of the drug. Additionally, treatment efficacy and patient safety are maintained. The DDSs methods have been evaluated over the years. While traditional forms of delivery such as tablets, lozenges, capsules, ointments, creams, pastes, or injections are still the most popular, many innovative forms of drug delivery are being developed [26,27]. Optimal kinetics, delivery time, release control, and patient safety and comfort are in high demand. Despite the convenience of drug delivery, accurately known doses, low manufacturing cost and minimal invasiveness, traditional drug delivery systems impose many limitations. Above all, the lack of targeted action, poor bioavailability of the drug, low absorption, and premature decomposition of the drug are the main drawbacks and the primary reason for replacing

currently known DDSs, with other, more advanced ones [27,28]. Among the many novel DDSs, one well-known application of the drug in a transdermal therapeutic system is micro-needles (MNs). Their application has enabled the penetration of high molecular weight compounds through the stratum corneum. Such a system allows slow, reproducible drug delivery, good permeability, and efficacy, but on the other hand can cause allergy and irritation, given the very small size of the micro-needles and the possibility of breaking them under the patient's skin [22,29]. They can be used in vaccine therapy (e.g., against rabies [22]), delivery of peptides (e.g., desmopressin [30]), hormones (e.g., insulin [31]), or chemotherapy (e.g., tamoxifen [32]). Microemulsions are another means of API delivery. They are becoming more advantageous due to their ease of manufacture, better penetration, high stability, and ability to dissolve both hydrophilic and lipophilic drugs. An example is a microemulsion loaded with nifedipine used in heart disease or apomorphine in Parkinson's disease [19]. Subsequently, nano micelles, nanosuspensions, or nanoparticles are other types of innovative DDS [33–35]. Liposomes are gaining a great benefit in the transport of drugs. Their structure, similar to the cell membrane, allows maximum bioavailability [36]. Commercially available are two liposome formulations for the treatment of eye diseases - Visudyne® [37] and Tears again® [38]. Dendrimers, highly branched polymers [39], carbon nanotubes [40], mesoporous silica nanoparticles [41], and quantum dots [42] are also known to be used. Intestinal and oral patches have also been developed that provide unidirectional diffusion of the drug, protecting it from the challenging environment of the gastrointestinal tract [8]. Interferon-α or calcitonin has been studied for delivery using the patches [43].

Researchers are pursuing the ideal drug delivery system, as described above. Working on new forms of API delivery is very relevant. This may be especially important in the case of cancer therapy, the main goal of which is to maximize efficacy, minimize drug side effects and increase patient comfort. The stimulated response and release of the drug are of high significance here [44]. Another issue is the treatment of psychiatric disorders. These increasingly common diseases require special delivery systems. The main demands are regular dosing, minimizing the risk of the patient skipping a dose and the potential for overdose, and increasing treatment efficiency with a reduction in the drug's passing effects [45]. Due to the constantly growing needs, novel drug delivery systems are being designed.

Up to now, we have considered traditional and innovative drug delivery systems. However, in addition to drug delivery, it is equally important to remove drugs from the body in case of poisoning. Poisoning can be caused by intentional drug overdose, drug abuse, or unintentional poisoning with a toxic substance [46]. A practiced agent for detoxifying the

body and eliminating toxins is activated charcoal. Its mechanism of action is based on binding the toxin on its surface, thereby preventing its absorption from the gastrointestinal tract. The size of the toxin, its solubility, pH, or degree of ionization are the main factors limiting adsorption. Activated charcoal is inexpensive, readily available, safe, and its use does not require any qualification [47]. Above that, it is able to absorb many substances such as antidepressants, benzodiazepines, beta-blockers, tetracyclines, barbiturates, paracetamol and many phytotoxins as ricin, strychnine, or nicotine [47,48]. However, it is not an effective adsorbent for alcohols, organic solvents, inorganic salts, or heavy metals. When considering supervised withdrawal of psychoactive substances during their overdose or detoxification treatment, active charcoal is not recommended due to fast drug adsorption which may cause negative side effects such as tachycardia, bowel blockages and dehydration. It is particularly dangerous when you are semi-conscious, for example, as a result of an overdose, in which case it can enter the lungs and be life-threatening [47,49,50]. In addition to the widely known activated carbon, several other antidotes are known [51,52]. These have been published on the GIZ-Nord website. According to "Bremen List" atropine is recommended for organophosphate poisoning, dimethylaminophenol (4-DMAP) has been found use in cyanide detoxification, naloxone for opioids, while toluidine is recommended for poisoning with methemoglobin-forming substances. The list is constantly growing, with the recent introduction of several new antidotes, more specifically glucarpidase for methotrexate overdose, icatibant for ACE inhibitor-induced angioedema, uridine triacetate for fluorouracil overdose, and deferasirox as a new chelator for iron overload [48]. Scientists around the world are working to develop substances that act as selective antidotes for a variety of toxins. One such compound is flumazenil. Currently, flumazenil is recommended for use during an overdose of psychotropics, mainly from the diazepine group, given its antagonistic effect [53,54]. Paracetamol overdose can be treated with acetylcysteine [48]. On the one hand, drugs acting as an antidote are administered, while many other practices are used to detoxify the body. A common practice during poisoning is gastric lavage. Such an action allows the removal of toxins within 60 minutes of poisoning. The position regarding this practice is not fully established, although it is effective in reducing the absorption of toxins from the stomach [55]. Another practice is premature intestinal lavage. However, for safety reasons, it is only recommended during the imminent danger of death from drug or medication abuse [56]. There are several methods to delay the absorption of the toxin and then help remove it from the body. The method depends on the type of toxic substance. Examples are hemodialysis during alcohol poisoning and salicylates or hemoperfusion, the practice of which is restricted [48]. We can conclude that there is a considerable preference

for the use of chemical compounds as antidotes compared to methods that require more interaction like gastric lavage. In the case of toxin adsorbents, a well-known and widely used one is activated carbon. Given the constantly growing number of antidotes, we can also pay attention to the way they are dosed. The administration of the antidote itself neutralizes the toxin, thereby reducing the adverse effects of poisoning and eliminating the threat to human health and life. However, this is not a method that allows for the complete removal of the toxin from the body. The ideal solution would be to combine the adsorption of the toxin with the simultaneous administration of the antidote. However, such a system has not been developed so far.

Summarizing, there are many drug delivery vehicles currently known and widely used. Both conventional forms of API delivery and novel DDS seem to have both many benefits and drawbacks. The science of drug delivery methods and systems is still ongoing and evolving. Recently, there has been increased interest in a new generation of porous materials, called metal-organic frameworks (MOFs) [25]. These innovative materials include an inorganic metallic part and an organic acid [57,58]. Many potential applications of MOFs have been demonstrated and studied, among them their use as carriers of therapeutic agents [59,60]. It was noted that certain types of MOFs have potential for biomedical applications [61]. The use of MOFs as modern drug delivery systems could provide high reproducibility of dosage, high bioavailability, stability, efficacy and gradual and controlled release [62]. Targeted and stimulated action of MOFs as DDS is also possible [63]. Besides, MOFs have very large specific surface areas, which may be additionally modified during pre- and post-synthesis treatment. In addition, they are commonly used as adsorbents for gases, among others [64]. Therefore, it is feasible to use them as adsorbents of toxins during poisoning. The use of MOFs as drug adsorbents for water purification is well-known and described in the literature [65,66]. It seems a good idea to use them for detoxification of the body. This would provide an innovative detoxification system during poisoning or overdose. In addition, it would enrich currently available antidotes.

More precisely, the synthesis, structure, characteristics and purpose of these materials are widely discussed below.

Composition of MOFs

Metal-organic frameworks (MOFs), otherwise known as porous coordination polymers, are an innovative group of highly porous materials. Their structure includes an inorganic part containing a metal ion (node) and an organic acid, which is a ligand (linker)

[67,68]. The organic and inorganic elements are connected by coordination bonds, forming one-, two- or three-dimensional networks. Although, the first MOF was discovered as early as 1989 by Hoskin and Robson [69] and later by Yaghi in 1995 [70], new types of metal-organic frameworks are still being developed today. This is related to the ability to form various combinations of metals and organic acids. By 2022, more than 90,000 different MOFs have been recorded, and more than 500,000 metal-organic frameworks have been predicted [71]. This emphasizes the infinite potential in the design and synthesis of this group of materials. Such coordination results in grids with regally repeating geometries and high crystallinity. A part of the MOFs exhibits structural flexibility, while others are characterized by a completely rigid structure. Due to their unique structure, metal-organic frameworks have a number of advantages that distinguish them from zeolites or other materials [61,68]. They are characterized by high chemical and thermal stability, large Brunauer-Emmett-Teller (BET) specific surfaces, controllable pore sizes, open metallic sites, high porosity, and very low densities. Above that, they are relatively easy to synthesize [61,68,72]. On top of that, MOFs exhibit good biocompatibility and biodegradability, effective drug loading rates, and controlled drug release, thus favorable kinetics to avoid very rapid drug release - "Burst effect" [62,73]. Consequently, it is possible to functionalize MOF surfaces to make them targeted API carriers [74,75].

Considering the structure of metal-organic frameworks, in the case of metals, it is possible to use both multivalent, monovalent metal ions and metal oxides. As for ligands, they are usually organic acids containing a minimum of two carboxylic groups introduced in the form of an alkyl chain or ring like benzene or imidazole [61,68]. Of fundamental importance is the coordination and geometry of the metal, which gives form to the network. However, it is the combination of the metal with the appropriate ligand that finally determines the type of network achieved. Despite knowing the coordination of the metal and the type of organic ligand, predicting the specific structure of the MOF is very difficult [61,76]. That's why scientists have developed the concepts of so-called secondary building units (SBUs). These are fragments composed of metal ions and oxygen atoms. They can take a variety of shapes like triangles, tetrahedrons, hexahedrons, or octahedrons. Attaching an organic linker to the SBU makes up the frame of the metal-organic framework. The next level of MOF construction is the bonding of multiple SBUs by bridging ligands and ligands connecting two metal nodes. This leads to the so-called third level of MOFs structure. Occurring here are pores of a certain size and empty volumes, forming cages. The level expands in a certain orientation and this leads to the formation of the fourth structural level. It is entirely dependent on the internal growth of the organometallic network, and thus on the conditions

of synthesis, the functionalization or lack of surface, the loading of molecules into the MOF (e.g. drugs), the presence of coordinatively unsaturated site (CUS) [61,68,76,77]. Such levels of MOF structure and composition are shown in Figure 1 and some examples of different MOFs are shown in Figure 2.

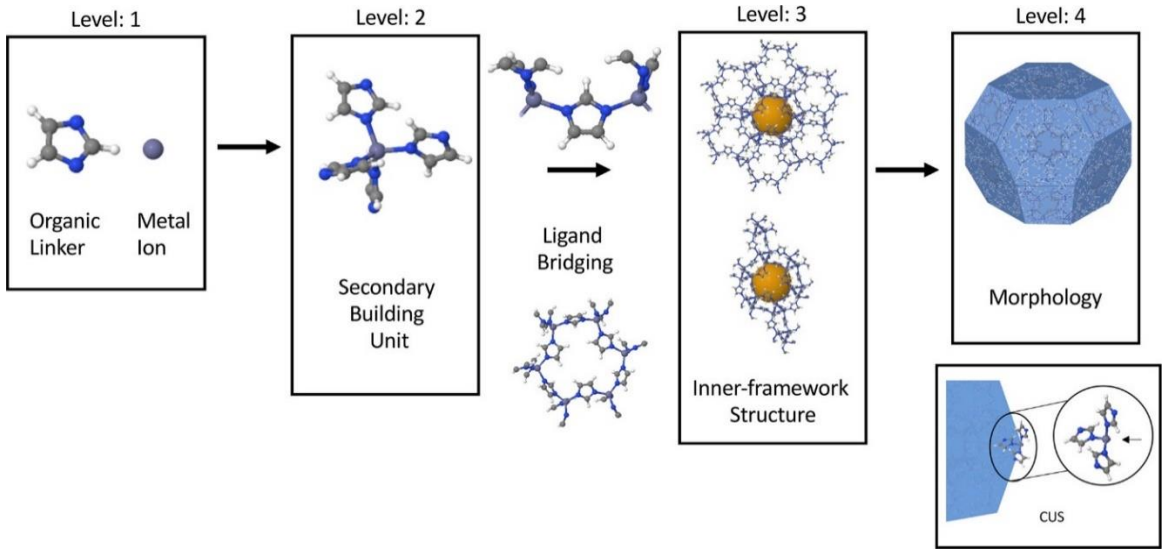


Fig. 1. Levels of structure and composition for metal-organic framework. Reprinted with permission from ref. [262]. Copyright 2021, American Chemical Society.

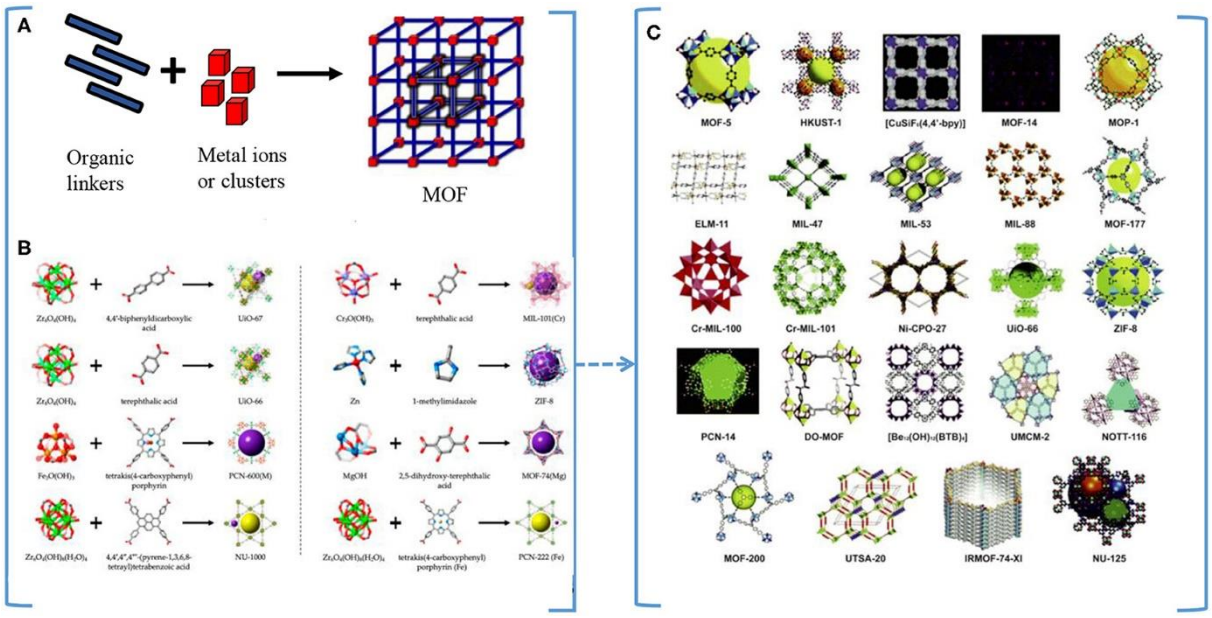


Fig. 2. Examples of metal-organic framework structures including the metallic part and the organic ligand [218].

On the other hand, we can divide MOFs according to the dimensionality of the structure. In one-dimensional (1D) MOFs, coordination bonds spread in one direction. The

voids that occur can be filled with low-mass molecules. A two-dimensional (2D) structure consists of single layers connected by edges or stacked on top of each other with weak interactions between the layers. In this case, the guest molecule can exist either between the layers or between the grids of a given layer. Three-dimensional (3D) MOFs are characterized by coordination bonds propagating in three directions. Here, the building units are connected by non-covalent hydrogen bonds and π-π type bonds, which determine the strength and direction of the network growth [68,77]. This conception is shown in Figure 3.

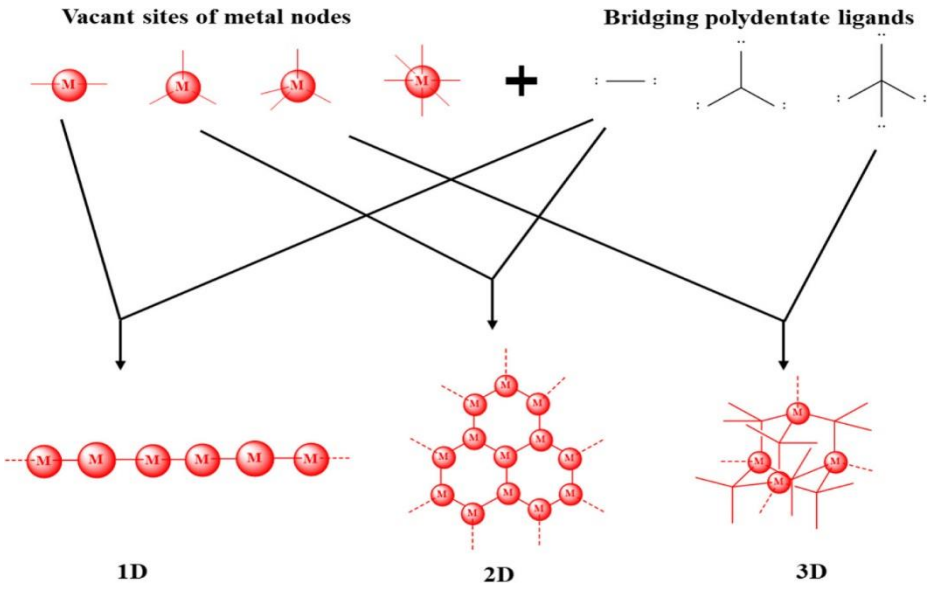


Fig. 3. Division of MOFs by the dimensionality of the structure [127].

The ability to change either metal ions or organic ligands is a unique feature of MOFs. The organic part is crucial for the physicochemical properties, including stability, of the MOF itself as well as its 3D structure. Among the numerous organic acids, carboxylates, sulfonates, phosphonates and heterocyclic compounds are the most common choices, but the first is leading the trend [60,68]. The low toxicity of ligands is of relevance when it comes to biomedical applications. One of the most commonly used linkers is benzene-1,4-dicarboxylic acid (terephthalic acid) [78]. Some examples of MOF ligands are in Figure 4.

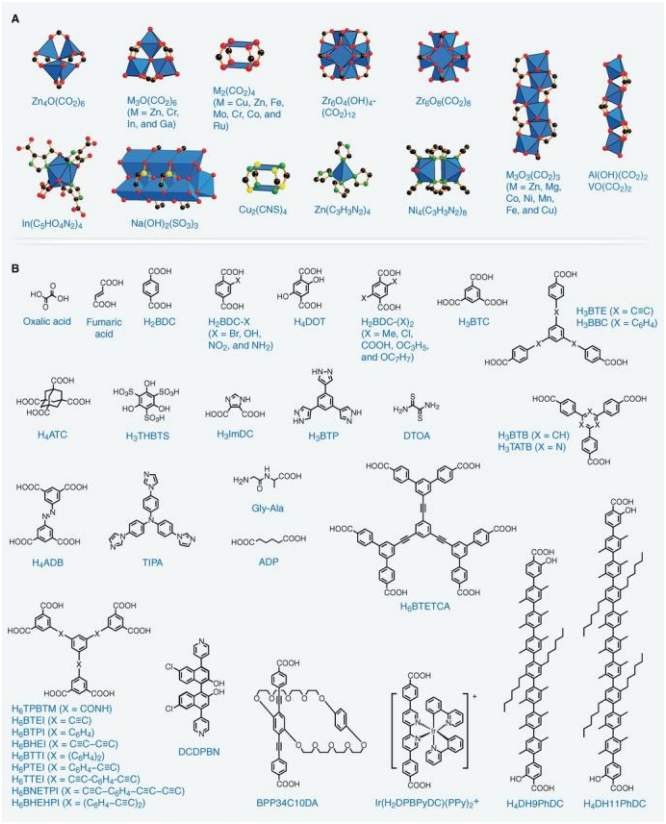


Fig. 4. Examples of inorganic SUB and organic linkers. From [288]. Reprinted with permission from AAAS.

Thus, as already highlighted, the structure of the MOF is determined by both the metallic part and the ligand used (Figure 5). When designing a metal-organic framework and selecting the components of its structure, it is necessary to pay attention to the possible application. For biomedical applications, the non-toxicity of the metal and the linker is mandatory [60]. A useful indicator of the safety of a metal is the median lethal dose (LD_{50}). The LD_{50} for the most commonly used metals in MOFs, namely zirconium, zinc, iron, magnesium, or copper, is 4.1, 0.35, 0.45, 8.1, and 0.025 g/kg, respectively [79]. Concentrating on the metallic part, we can classify MOFs into different families. The nomenclature of MOFs is dependent, as there are no strict principles. Metal-organic frameworks are usually named after their composition, application, type of backbone, or the name of the university or laboratory that developed them [79]. Referring to the last division, we distinguish the following families of MOFs [80]. Metal-organic frameworks called MIL from *Matériaux de l'Institut Lavoisier* [81], CAU, whose name derives from *Christian-Albrechts-University* [80], the UiO family first synthesized at the *Universitetet in Oslo* [82], in addition to DUT - *Dresden University of Technology* [83] or NU coming from *Northwestern University* [84]. Another approach to distinguish MOFs is the structure of their backbone. An example is the ZIF - Zeolitic Imidazolate Frameworks series. Here, the angle between the

imidazole and the metal is similar to that in the Si-O-Si bond found in molecular sieves and is 145°. The metallic part is Zn or Co, and the materials are very stable thermally and chemically [85]. Additional examples are porous coordination networks of PCNs, which have cubic octahedral nanoporous cages [86]. Isoreticular metal-organic frameworks (IRMOFs) are another type of MOF subdivision. Here, the inorganic unit is $[Zn_4O]^{6+}$, while the ligands are aromatic carboxylic acids. Figure 6 shown detailed chemical structure and crystallinity of IRMOFs. Another example is multilayer metal-organic networks (MTV MOFs), which contain a wide variety of functional groups introduced along with an organic ligand. Their number, mutual position and ratio are controlled, which can be very important in drug delivery systems [77,80,87].

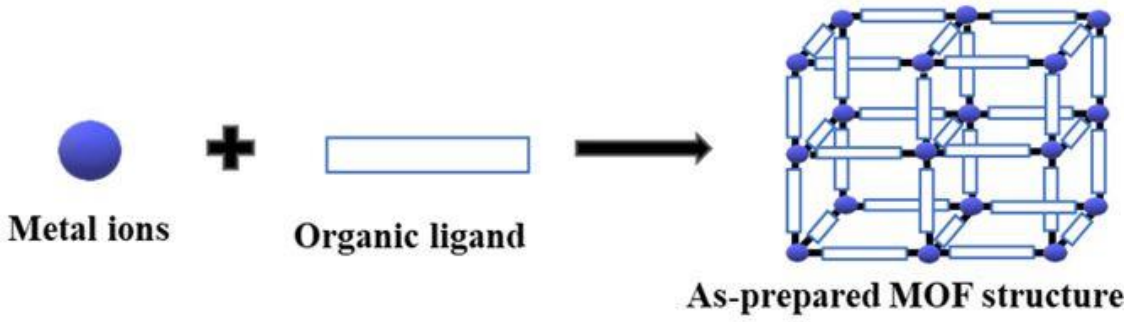


Fig. 5. Scheme for the formation of a metal-organic framework through a bond between a metal and a ligand [127].

Because of the very high flexibility during the design of metal-organic frameworks, it is feasible to obtain materials with very different physicochemical properties such as pore size, BET surface area, toxicity, bioavailability and many others. Thus, we are able to select appropriate characteristics depending on the potential application of the network. Consequently, MOFs have a wide range of applications, which have been widely documented [62,71,88–90]. One of the primary applications of MOFs is their use in low-pressure gas adsorption processes, for example, during gas separation or purification [68,91,92]. Methane storage [93], carbon dioxide purification [94], or hydrogen sulfide capture [95] have been described. In addition, work is underway on hydrogen storage in MOF structures, which is particularly important energetically, assuming high hydrogen energies that exceed those of fuels, as well as safety considerations associated with storing the gas in cylinders [96]. The lack of dead volume or high specific surface areas are among the many features of MOFs that underscore the validity of such an application [68]. Another is the utilization of MOFs in catalytic processes. Active sites in the form of metallic nodes, the possibility of introducing metallic nanoparticles as additional active sites, or porosity, provide opportunities to use

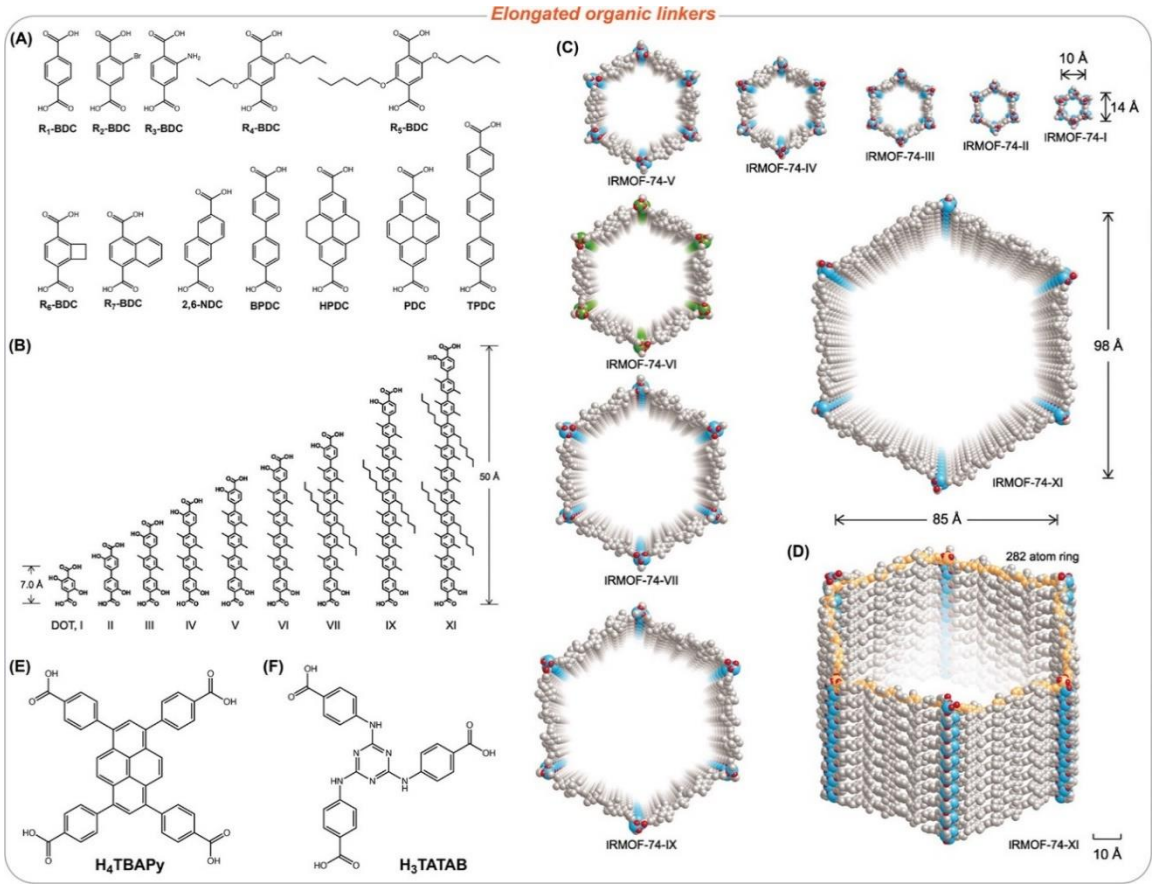


Fig. 6. Chemical structure and perspective views of IRMOFs. Adapted with permission from ref. [87]. Copyright 2022, American Chemical Society.

MOFs as heterogeneous catalysts. Their catalytic application in hydrogenation, oxidation, Friedel-Craft's alkalization reactions, and many others have been described [71,91,97,98]. These materials can also find some electrochemical applications. This applies mainly to MOF composites, which can be used as batteries, sensors, or condensers. The introduction of guest species increases the sensing or luminescence capabilities of MOFs. Among the most sensitive sensors are lanthanide-based networks, which are related, to their large coordination sphere [90,99,100]. One of the most promising applications of metal-organic frameworks is biomedical applications. According as highlighted earlier, it is very significant to properly deliver the therapeutic substances. Controlled pore size, structure, low cytotoxicity, high loading capacity, and controlled release or stability of MOF materials are the main features that confirm the validity of applying MOFs as API carriers [57,58,73]. Besides, their surface can be functionalized, making them targeted DDS. An example is the use of folic acid on the MOF surface [101–104]. It allows the material to reach the cancer cell, binding to folate receptors on its surface and initiating drug release in the tumor environment. Lactobionic acid or glycyrrhetinic acid are also used as targeting agents for

hepatic cancer [105]. Hyaluronic acid is widely used as well, to support the effectiveness of cancer therapy [86,106]. Another idea is to functionalize the surface with chitosan [107,108]. Its function is to protect the structure of the MOF and thus the drug molecule itself. This protects against earlier metabolism of the API and enhances the therapeutic effect. A similar function is performed by PEG, biotin, or polysaccharides [104,109,110]. An additional major advantage is the ability to release the drug from the MOF at a well-defined pH. This is extremely important in cancer therapy, where the release of the therapeutic substance should occur in the pH range of 4 to 6. This ability of MOFs reduces the side effects of chemotherapeutics and increases their selective action in a specific region [108,111,112]. The literature describes the pH-stimulated release of doxorubicin [44,108,112] or 5-FU [102,113–115] commonly used in cancer treatment. The magnetic properties of MOFs can also contribute to guiding drug release [74,116–118]. Such delivery systems are finding use as contrast agents in NMR [62,118]. Among others, the release of ibuprofen from MIL-53, whose surfaces were functionalized with Fe_3O_4, was studied in this way [119]. MOFs have been used as delivery systems for anti-cancer drugs, anti-bacterial drugs, eye diseases, lung diseases and many others. Worth highlighting seems to be the use of metal-organic frameworks in cosmetics. More specifically, it is possible to use MOFs to carry substances used in cosmetics today, such as caffeine, as well as their use in cutaneous treatments, including local, dermal preparations or skin therapies. MOFs show the potential for detecting parabens – preservatives used in cosmetics. In this case, cosmetic utility is provided by such MOFs' characteristics as skin permeability, sebum adsorption capability and antimicrobial potential [120,121]. This underscores the considerable biomedical importance of MOFs. A summary of chemotherapeutics carried by MOFs is shown in Table S1. The perspective applications of metal-organic frameworks are also emphasized by the existence of nano MOFs, or nanoscale MOFs (NMOFs) [122,123]. These are used in nanotechnology and nanomedicine. Generally speaking, nanotechnology is one of the forward-looking branches of science and applies to various types of industries from computer systems, communications, and space industries to nanomedicine. The use of nanoparticles is becoming increasingly common. A breakthrough in nanotechnology turned out to be fullerene C_{20}, which shows exceptionally high susceptibility to functionalization. By the example of C_{20}, the validity of the [3+2] cycloaddition reaction and the Diels-Alder reaction was demonstrated in the functionalization of carbon-based nano compounds in future nanomedicine, such as drug delivery, was demonstrated [124]. NMOFs are a group of hybrid materials, but in nano sizes, which gives them unique characteristics combining those of nanomaterials and metal-organic frameworks, for example, some of them are inherently

biodegradable due to weaker metal-ligand bonds in the network. They are highly porous and have large channels, low cytotoxicity, or regulated stability for stimulated drug release. For the aforementioned reasons, NMOFs can serve as nanocarriers in nanomedicine, among others [125,126].

Synthesis and Characterization

Several methods have been developed so far for the synthesizing of MOFs. It is worth mentioning that the specific MOF synthesis method affects the physicochemical properties of MOF such as morphology, structural and acidic properties. Metal-organic frameworks are very sensitive to changes in synthesis conditions such as temperature, time, solvent, or modulator used during the synthesis. Therefore, it is very important to maintain analogous conditions when synthesizing MOF materials. MOFs can be synthesized in a classical way using solvothermal or hydrothermal methods [68,127]. Those methods are widely used due to their simplicity and low equipment costs. Taking into account years of research on MOFs, methods have been developed that are in line with the principles of Green Chemistry, more ecological and economical. Alternative ways of synthesis utilize microwave or ultrasound (sonochemistry) irradiation. Additionally, MOFs can be synthesized electrochemically, in an ionothermal manner. In addition, numerous methods describing the use of mechanochemistry have been reported [60,128]. This underscores the very great possibilities for the synthesis of metal-organic frameworks, as well as the potential for research on the effects of synthesis conditions on the character and properties of the material. A brief description of the synthesis methods, along with their possible modifications, are described below. Moreover, commonly used syntheses are shown in Figure 7.

Solvothermal (hydrothermal) synthesis

This method is relatively simple and undemanding. It involves dissolving a metal and a linker in a solvent or mixture of solvents. Both aprotic and protonated solvents can be used. The former group includes DMF, DEF, DMSO, DMA, toluene, or acetonitrile, among others. Of the second group, methanol and ethanol are mainly applied. The method becomes known as hydrothermal if water is used as the solvent [127,129]. Synthesis can be carried out in two ways: above the boiling point of the solvent used and under increased pressure, or in or below its boiling point at ambient pressure, in which case the method is called nonsolvothermal. The prevalent reaction temperature affects the vessel used. If high temperatures are used (above 400 K), the reaction should be carried out in Teflon cups and

sealed stainless steel autoclaves. For lower temperatures, glass vessels are acceptable [128]. The solvothermal method is characterized by good yields with well-crystallized MOF particles and high specific surface areas. It is also an easily reproducible and one-step method. The main disadvantages of this method are the long reaction time, the use of large amounts of solvents, often toxic, and the formation of by-products [60,130]. Examples of metal-organic frameworks synthesized by the solvothermal method include MOF-5 [131], MOF-74 [132], and UiO-66 [133].

Mechanochemical synthesis

This type of synthesis involves mixing metal salts and organic ligands using a mortar or ball mill. Due to high mechanical energy, intramolecular bonds are broken, and thus a chemical conversion takes place. After the grinding process, the resulting mixture is heated, resulting in the evaporation of water and volatile compounds. Characteristic features of this method are its high rapidity and simplicity, use of room conditions (i.e. temperature), and lack of solvents, which makes it environmentally friendly and inexpensive. The absence of solvents makes it very good for synthesizing MOFs for biomedical applications [60]. The mechanochemical method was first used in 2006, where a metal-organic network was obtained by grinding $Cu(OAc)_2H_2O$ with isonicotinic acid [134]. In addition, the mechanochemical synthesis of ZIF-8 [135] was documented, and the method had very high yields.

Microwave synthesis.

Recently, the use of microwave radiation has become very widespread. This is related to its environmental friendliness. Here there is an interaction between the electromagnetic field and the moving charge of the solvent. More precisely, electromagnetic energy is converted into thermal energy, and the constant dipole moment of the molecule is associated with the applied electric field, which rapidly heats the liquid mixture. The molecules, arranging themselves in the electromagnetic and oscillatory field, constantly change their position. By applying the proper frequency, the particles effectively collide with each other, increasing both the temperature and kinetic energy of the system. The fraction of microwave radiation absorbed is 300 to 300 000 MHz. Additionally, a solvent with the ability to transmit the radiation is necessary. This form of synthesis is energy-efficient since the radiation itself causes direct heating of the mixture. Furthermore, it is quick, reproducible, and the product is characterized by high purity [136,137]. On the other hand, replacing the process for industrial use could be demanding. Using microwave synthesis, it

was successfully prepared MIL-100 (Al) [138] and UiO-66 from Zr and Hf [139]. This method has been used in the synthesis of MOFs since 2005.

Sonochemical synthesis (ultrasound).

Here the method is based on the use of mechanical vibrations in the range of 20 kHz to 10 MHz. A metal salt and an organic linker are dissolved in a suitable solvent and then subjected to ultrasound. Given the phenomenon of cavitation that occurs (the formation of bubbles in the solution, and their subsequent collapse, when ultrasound is applied), and the consequent increase in temperature to about 5000 K and pressure up to 1000 bar, additional cooling of the mixture is often necessary. The use of this alternative method of synthesis significantly accelerates the reaction time, in addition, the method is environmentally friendly, inexpensive, and ensures homogeneous nucleation [127]. Since 2008, sonochemistry has had known practical applications in MOF synthesis. Several MOF syntheses utilizing ultrasound irradiation were reported so far including MOF-5 [140], HKUST-1 [141], ZIF-8 [141,142], or Hf-MIL-140A and Zr-MIL-140A [143].

Electrochemical synthesis.

The electrochemical method consists of using a metallic electrode (anode) immersed in a solution. This avoids the use of metal salts, which eliminates the formation of by-products. A suitable electrode is placed in an electrolyte solution with a dissolved linker, and then a certain voltage is applied. The metal dissolves and its ions are located on the outer surface of the electrode, allowing them to combine with the linker and synthesize the network. The reaction produces hydrogen gas. This type of synthesis is characterized by mild conditions and speed [60,127]. On the other hand, MOF electrochemical synthesis is inefficient. HKUST-1 or MIL-53 (Al) [144], among others, have been synthesized this way.

Ionothermal synthesis.

It involves the use of ionic liquids (ILs) or eutectic mixtures. They act as solvents with low volatiles, as well as good thermal stability, high solubility, and good ionic conductivity. The use of ILs distinguishes this method from solvothermal synthesis. It has found application in the synthesis of chiral MOFs. However, the main limitation is the lack of controlled and reproducible MOF network formation, due to the lack of effective hydrogen bond donor and acceptor atoms [60].

Other, less typical, methods for synthesizing organometallic networks have also been described in the literature. These include synthesis by spray drying or chemical vapor deposition [60,127,128].

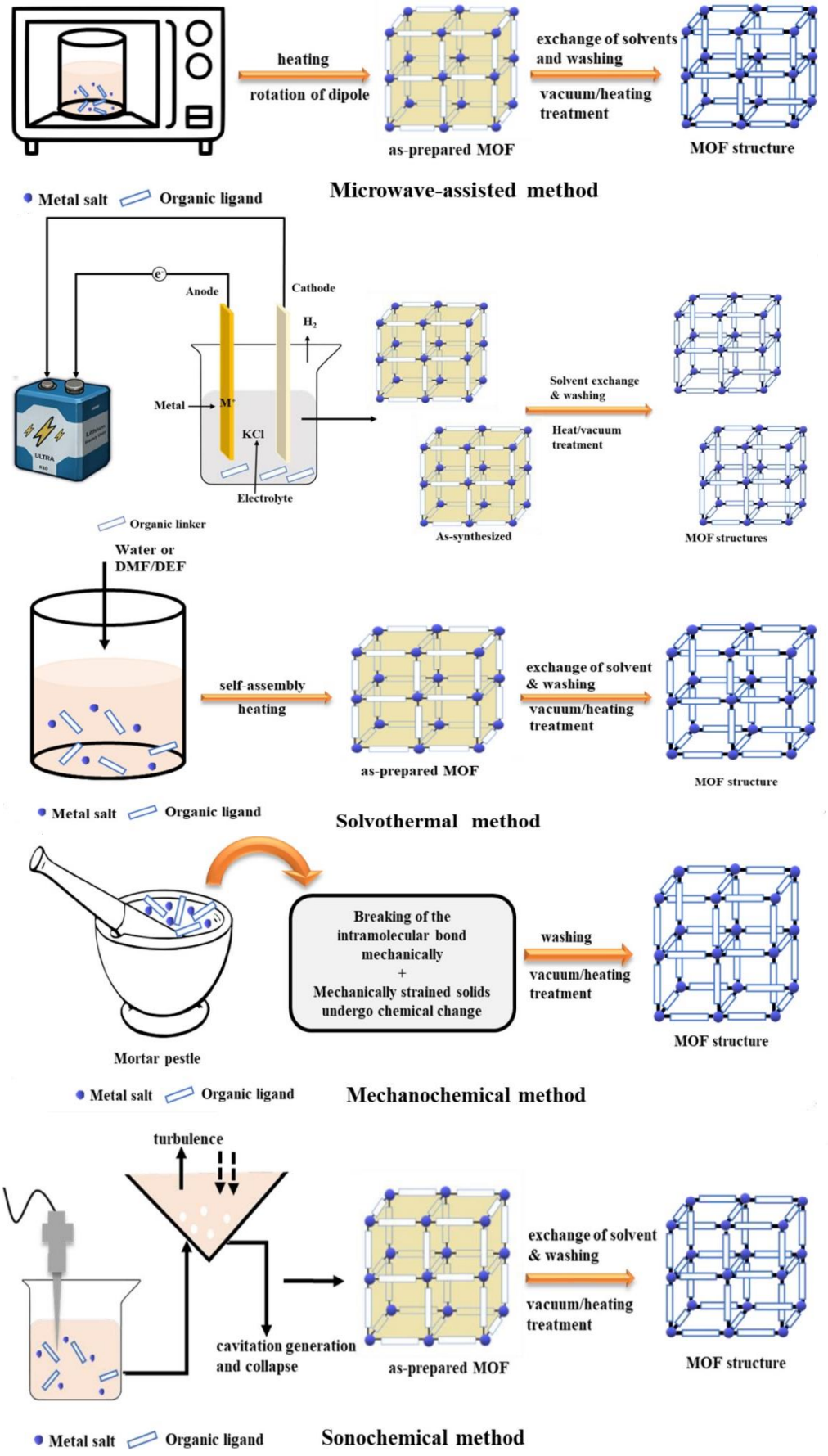


Fig. 7. Methods of metal-organic framework synthesis [127].

Once the metal-organic framework has been synthesized, it is imperative to characterize it. Bearing in mind the porosity and high crystallinity of MOFs, the most suitable techniques to characterize them have been described. The basic test is single-crystal XRD or powder X-ray diffractometry (PXRD) analysis. Single-crystal XRD is relatively difficult to perform because MOFs are characterized by large crystal sizes. In this analysis, it is necessary to select a crystal with a size of 5 - 10 μm and very good resolving power. Data collection at low measurement temperatures is preferred [128]. On the other hand, a more important test than single-crystal XRD is PXRD. It allows us to evaluate the crystallinity of the sample. Thanks to this, we can simply evaluate the correctness and effectiveness of the synthesis made and understand the differences between different syntheses. The experimental diffractogram should be compared with literature data or computer modeling [145]. It is also possible to use neutron X-ray diffractometry. However, it requires the use of deuterium, which is relatively expensive [61]. Another method to learn about the nature of MOFs is an analysis using infrared radiation. Fourier Transform Infrared Spectroscopy (FTIR), Attenuated Total Reflectance (ATR-FTIR) and Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFTS) are commonly used. Particularly noticeable on the spectra of the studied MOFs are the bands at 1597 and 1406 cm^{-1}, which correspond successively to asymmetric and symmetric stretching vibrations of O-C-O bonds. In addition, there is a band at 1504 cm^{-1} associated with the benzene ring, more precisely caused by the C=C vibration. The C=O stretching vibration occurs at 1626 cm^{-1}. The DRIFTS technique is suitable for determining the presence of functional groups and anything attached to the MOF surface. It is also helpful in the analysis of composites, for example, after the adsorption of gases or toxins, or also after the introduction of drugs into the MOF structure [83,139]. A complementary method to the aforementioned technique is Raman spectroscopy [146–149]. Also used to identify specific functional groups in the MOFs structure. It allows us to observe groups invisible in infrared. Moreover, it is possible to quickly verify the purity of the MOF. NMR analysis is useful here. It determines the proportion of linkers and even the presence of solvent in the structure of the metal-organic framework. The main problem can be the difficulty of dissolving MOFs in solvents used in the NMR technique [150–152]. It is also very important to determine the thermal stability of MOFs. This is especially important if we are studying a newly synthesized material. For this purpose, we can use thermogravimetric analysis (TGA). It is possible to determine the mass loss of the metal-organic framework with increasing temperature. Combining TGA with mass spectrometry (MS) makes it possible to determine which particles are responsible for the change in the mass of the MOF. It is

necessary to select a suitable gas for analysis and determine the influence of the environment on the MOF decomposition process [82,127]. One of the most important methods for characterizing MOFs is to determine the Brunauer-Emmett-Teller (BET) specific surface area. This parameter further informs us about the size of the pores in the MOF and the distribution of the pore volume. In practice, this is the determination of nitrogen sorption and desorption isotherms at low temperatures. The size of the BET surface area allows us to assess the potential adsorption capacity of the metal-organic framework [59,100]. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are used to evaluate the surface morphology of the MOF. It is possible to visualize the structure and determine the size of pores in the MOF [67,153–156]. In order to fully analyze the metal-organic framework and combine experimental and computer chemistry, it is possible to apply theoretical methods like density functional theory (DFT) [82,157,158].

Originally, metal-organic framework synthesis was simply based on mixing the proper amounts of the reaction components in the right solvent to obtain a specific MOF structure. However, over the years, numerous methods of modified syntheses allowing for the preparation of MOF with specific and tuned structure parameters have been developed. In practice, modification of metal-organic frameworks is mainly based on increasing the number and size of crystals and thus affecting the crystallinity of the material. This is done by using suitable modulators. Usually, monocarboxylic acids, organic and inorganic bases, or/and acids are used, with a pKa smaller than the pKa of the ligand [104,159,160]. The modulator competes with the ligand for a site at the metal, coordinates with the metal, and is then involved in the generation of structural defects. The defects are associated with bond disruption and deformation of the metal-organic framework. Another mechanism for the addition of the modulator involves the deprotonation of linker molecules. This results in accelerated attachment of the linker to the MOF's building units. In the literature, studies are available on the use of modulators such as formic acid, acetic acid, hydrochloric acid (HCl), benzoic acid, hydrofluoric acids (HF), or trifluoroacetic acid (TFA). The use of TFA has been proven to create more active sites, while HF used during MOF synthesis increases the crystallinity and porosity of the material [161–163]. Formic acid, acetic acid, or hydrochloric acid affect the increase in the number of crystals and the number of defects and crystallinity, while benzoic acid, can control both the number and size of crystals and defects [83,164–166]. There are two main types of defects called missing linker and missing cluster. The defect nature and their impact on MOF structure are shown in Figure 8. Moreover, the use of benzoic acid provides high reproducibility of the synthesis. Furthermore, it is feasible to introduce a functional group on the surface of the MOF. This is usually done at the synthesis

stage, using a mixture of linkers. Linkers are selected so that one of them has an additional group in the form of a side chain, which will not be part of the backbone of the MOF. One type of linker containing three side chains can be used. The most commonly introduced groups are: - NH_2 [105,149,167,168], -COOH [169], -OH [170], -SO_3H [171]. The addition of a functional group can reduce the thermal stability of MOFs, and decrease the specific surface area or pore size, but its effect on the physicochemical properties of the structure is not significant. When MOFs are used as DDS, higher degrees of drug loading in the structure with functional groups are often reported. A correlation of higher degrees of drug loading in MOFs in which the added functional group had a low hydrogen bond acceptor capacity was noted. The addition of a functional group also affects release kinetics. It can contribute to a slower and more gradual release of the drug [77,104,172,173]. The synthesis of UiO-66 with side groups -Br, -H, -NO_2, -Cl, -CH_3, and -2CF_3 has also been reported in the literature [174,175].

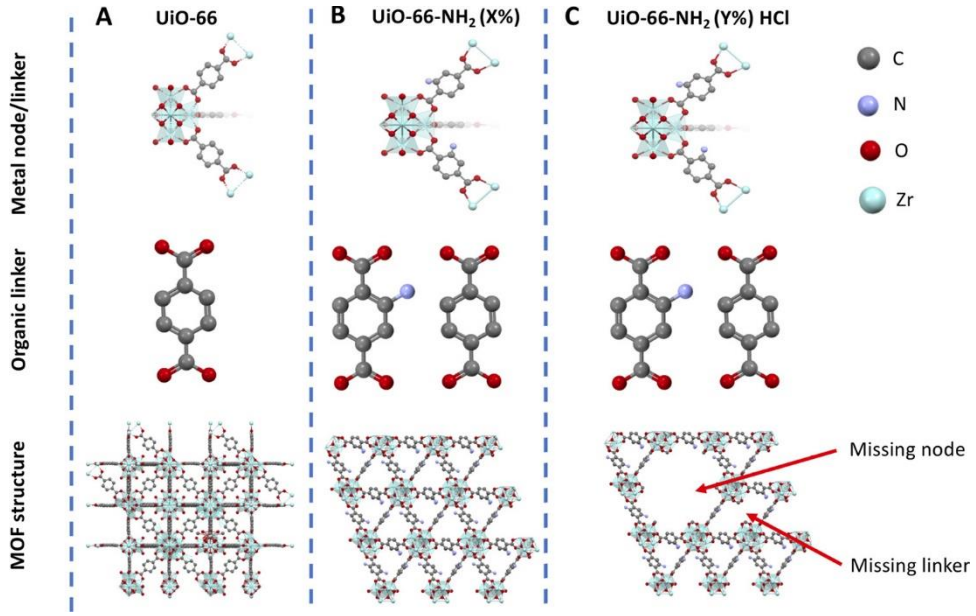


Fig. 8. Difference in the structure of UiO-66-NH_2 without defects and with defects. Influence of HCl on the metal-organic framework [149].

MOFs as drug delivery systems

Looking at many features [59,72,87], metal-organic frameworks, show high biomedical potential. The main topic of interest and research of scientists is the use of MOFs as carriers of therapeutic substances [58–60,73,176,177]. For these materials to serve the indicated application, it is necessary to load the drug in the MOF structure. Currently, the following methods of loading the drug are distinguished: encapsulation, direct assembly, and

post-synthetic strategy [61,178]. Although the former two are among the classic and well-known methods, the third is relatively new (Figure 9).

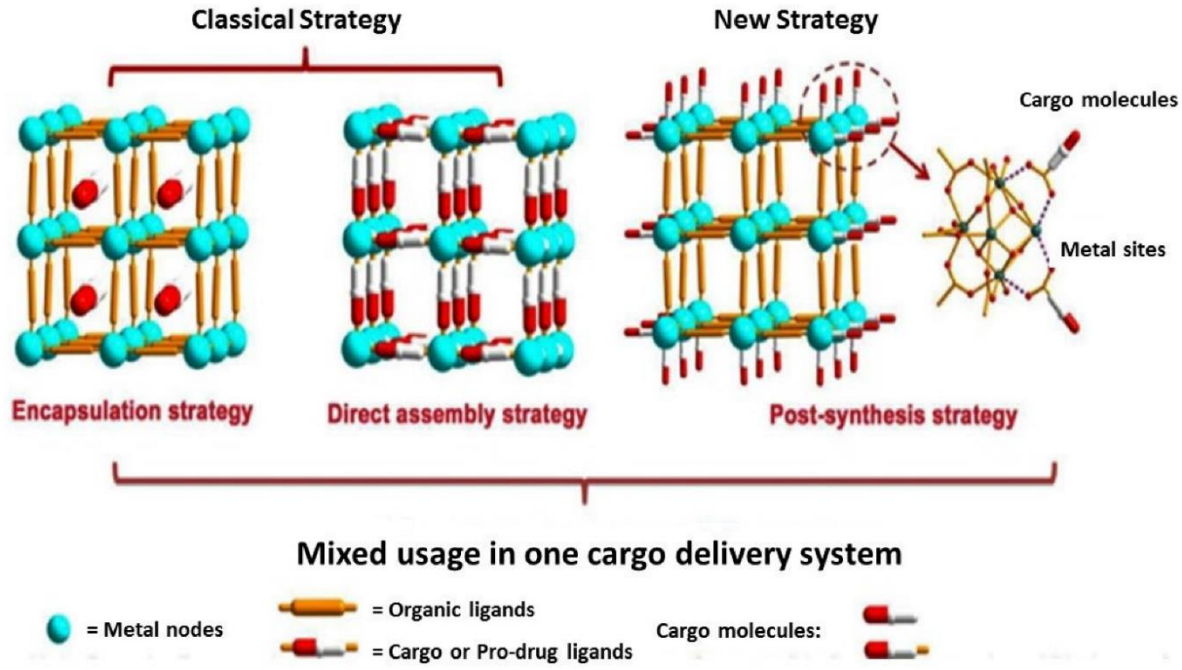


Fig. No.9. Cargo-loading strategies for MOFs [289].

Encapsulation strategy

The main idea behind it is to pack the drug in the pores or channels of the metal-organic framework using non-covalent bonds. The MOF structure is maintained. The procedure applies to drugs of both hydrophilic, lipophilic, and amphiphilic charity [61,73,178,179].

Direct assembly

Consists of building the drug into a MOF structure already at the synthesis stage, where the drug serves as a ligand. The interaction between the incorporated drug and the MOF is a coordination bond. This method ensures homogeneous distribution of the drug in the network but is often appropriate for small molecular weight compounds. Sufficient pore size contributes to delaying the release (diffusion of the drug), and the MOF backbone has a protective effect on the molecule. Mechanochemical methods are the preferred form of synthesis, to eliminate the destructive effects of solvents on the API [178]. This method is often referred to as one-pot synthesis [61]. In this approach, it is necessary to pay attention to the selection of a non-toxic metal ion and a drug with a possible organic linker function [177,179,180]. For example, such an approach can be loaded with anti-osteoporotic

bisphosphonate drugs such as pamidronate [59,181] or alendronate [182]. The one-pot method can also be considered as direct introduction of the drug into the crystal or coating on the surface [62,183,184]. There are advantages to this method, such as reduced reaction time. On the other hand, the incorporation of larger molecules such as proteins, enzymes, or macromolecular drugs may be challenging and requires a different approach. Recently, the co-crystallization method utilizing direct drug encapsulation during the crystallization process is under vigorous investigation [61]. The main advantage of this method is that the properties of the drug are preserved and its stability is increased. This is often the case on both laboratory and industrial scales. It has been possible to precipitate ibuprofen (IBU) [185] or methotrexate (MTX) [186] in this manner.

Post synthetic strategy

Here it is based on loading the drug onto the surface of the MOF. Coordination or covalent bonds can be formed between the metal, linker and drug. Another possibility is to adsorb the drug on the surface. Then hydrogen bonds or Van der Waals interactions are the main forces. Nowadays, most research is focused on this way of loading the drug, especially when it comes to anticancer therapies, targeted drug delivery, or the loading of several therapeutic molecules. Another name for this method is surface loading. Due to weak interactions, rapid drug release may occur. A possible and used approach is the impregnation of the drug. More precisely, the drug from the solution passes into the interior of the network, thanks to the presence of pores [84,174,187]. Using impregnation, it has been possible to load caffeine [188,189], among others.

The therapeutic compound may be also loaded into the pores of the MOF by post-synthetic encapsulation. This involves mixing the metal-organic framework along with the drug in a single solution, then evaporating the solution and washing the surface to remove the unbound drug. A future approach for loading the drug is so-called biomimetic mineralization [61]. It mainly applies to macromolecules like proteins or nucleic acids. In short, it involves building a biomolecule into a MOF, with the molecule becoming the nucleation site for its crystallization [190,191]. On the one hand, the molecule is protected from degradation in the human body, and its release is much slower and more gradual. On the other hand, it determines the size of pores or surface morphology, taking part in the structure of the skeleton [180,190–192]. Biomimetic mineralization for the encapsulation of

some substances is shown in Figure 10.

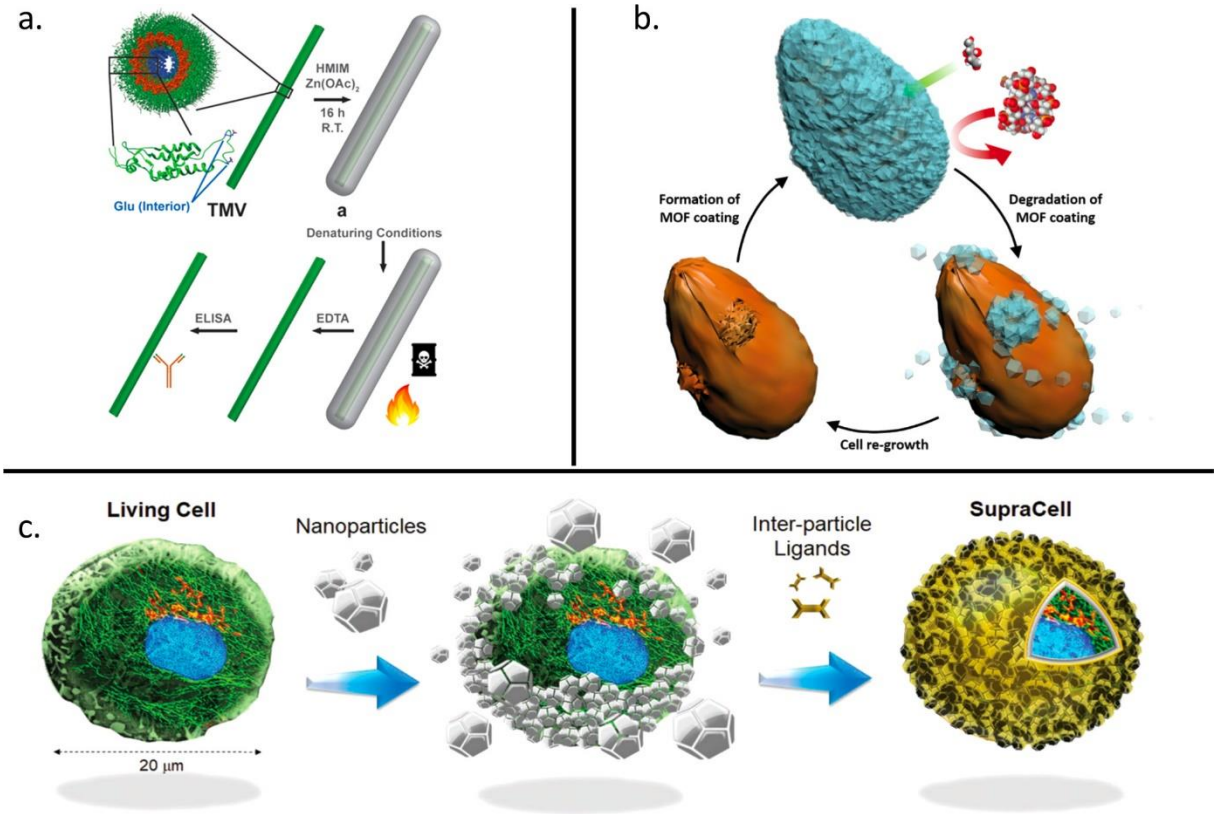


Fig. No.10. Encapsulation by biomimetic mineralization and delivery of a) TMV and b) cytoprotective exoskeletons. C) SupraCell constructions for encapsulating living cells. Reprinted with permission from ref. [61]. Copyright 2021, American Chemical Society.

The efficiency of drug loading in a metal-organic framework depends on many factors. Unquestionably, the specific surface area, the number of structural defects, and the size or volume of the pores are critical to the success of the process [83,180,193]. The structure of MOFs is relatively flexible, but largely changes depending on host-guest interactions. Phenomena such as breathing of the structure or its swelling depend on the degree of drug loading and the interactions mentioned above. Chemical properties such as the construction of the ligand or metallic center are also of great importance. They significantly influence the strength of drug-structure interactions, often resulting in the desired π–π bond [60,61,73,80]. Numerous groups of MOFs have been described in the literature considering their properties and their ability to achieve high degrees of drug loading [57,68,113,114,176,194,195]. For example, networks from the Zr-MOF group are characterized by the presence of a large metal center, with a non-toxic and biocompatible nature [104,196–198]. The controlled release of many drugs from MOFs belonging to the mentioned group has been presented. Among them, drugs such as 5-fluorouracil (5-FU) [102,199], camptothecin (CPT) [73], acriflavine (ACF) [152], tramadol (Tr) [154]. Another

widely described group of MOFs is those based on the Fe center. Given the occurrence and utility of iron for humans, these types of networks represent a useful and highly biocompatible drug carrier [193,200–202]. An example of Fe-mediated delivery of oridonin (Ori) [203], a chemotherapeutic agent, or the osteoporosis treatment drug alendronate (Alen) [204,205] has been described. Above that, the presence of some metal ions such as Ni^{2+} or Cu^{2+} limits the possibility of their use in drug delivery systems. This is related to their high toxicity [206]. Besides, some MOF structures degrade faster when exposed to water. One such network is MOF-5 [207,208]. Very often this can be an advantage, especially when tuning hydrophobic and poorly water-soluble APIs. Then, the use of a water-sensitive metal-organic framework can enable drug delivery, as well as accelerate the achievement of a minimum therapeutic dose. An example of such a drug is curcumin (CUR) [209,210]. Structures that degrade more rapidly under acidic conditions like ZIF-8 are also known and described, and they are sensitive to decreasing environmental pH. Assuming an acidic pH prevailing in the vicinity of tumor tissues, the use of this type of carrier may contribute to the effectiveness of chemotherapy [85,112,135,194,211]. The release of doxorubicin (DOX) [116] or 5-FU [115] from ZIF-8 has been studied, with a gradual and targeted release of the drug and reduced side effects of therapy observed.

As outlined above, there are several ways to load the drug into the MOF structure. The second aspect is to confirm its existence. There are several techniques, serving such a purpose. The primary test to determine both the correctness of the synthesis and the crystallinity of the MOFa sample and the drug@MOF composite is powder X-ray diffractometry (PXRD). Comparison of the diffractogram of the synthesized MOF with literature data demonstrates the conformity of the materials and the correctness of the synthesis [65,67,100,202]. Identification of functional groups and bonds in the structure is possible by Fourier transform infrared spectroscopy (FTIR) [102,152,162,167,187,209,212] and μRaman spectroscopy [146,152,212]. A comparison of the bands present on the spectrum of pristine MOF with the spectral bands of the drug@MOF composite is necessary to determine the loading efficiency of the drug. It is very often observable that the dependence of the increase in the intensity of specific bands with the increase in the degree of drug loading into MOF. Nuclear magnetic resonance (NMR) analysis provides additional confirmation of the presence of the drug in the metal-organic framework [101,150,151,185]. Also, the presence of the drug is indicated by thermogravimetric analysis (TGA) [82,168,185]. This analysis is also used to assess the protection of the drug from temperature degradation. It is also possible to compare the specific surface area, for example, as measured by the Brunauer–Emmett–Teller (BET) isotherm of the MOF before

and after drug loading. As a result of successful loading, the surface area should decrease, which can be explained, among other things, by the occupation of pores in the structure [59,100,152,205,212,213]. If we want to find out about the change in MOF morphology, as well as pore size, scanning electron microscopy (SEM) [83,139,154,155] and transmission electron microscopy (TEM) [65,214] analysis is useful. In the case of surface adsorption of a drug onto a MOF, measuring the zeta potential can help evaluate the drug loading of the MOF. For example, in the case of using a metal-organic framework as a carrier for chloroquine (CQ), a potential drug against the SARS-CoV-2 virus, a number of studies have been conducted to confirm the effective incorporation of the drug into the MOF. The presence of CQ was confirmed using PXRD, ATR-FTIR, or Raman maps. An area of the so-called CQ marker verifying the presence of the drug was clearly shown on the spectra [212]. Conformation for effective CQ loading is shown in Figure 11.

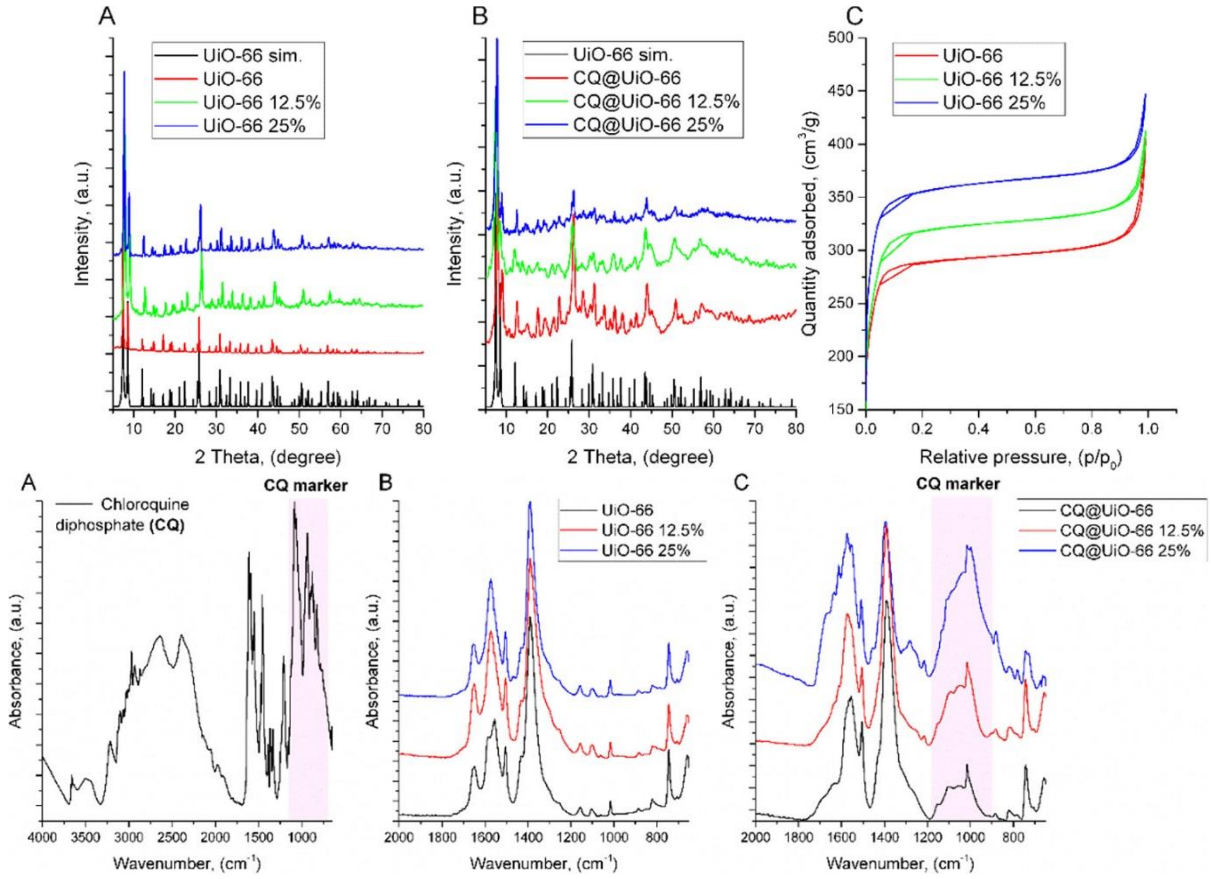


Fig. No.11. Methods for characterizing MOFs and evaluating the effectiveness of loading CQ into the MOF structure. Reprinted with permission from ref. [212]. Copyright 2021, American Chemical Society.

Consecutively, after demonstrating the drug loading of the structure, we can study the release of the drug from the structure. The target is to define the release kinetics of a therapeutic substance [81,112,113,193,215]. In doing so, it is essential to take into account

factors such as temperature, the pH of the solution into which we are releasing the drug and the presence of ions in the solution. They have a critical effect on the process of leaving the drug and its rapidity [152,216]. Significant differences have been shown when studying the kinetics of drug release into different environments, such as during the release of acriflavine (ACF). The study showed an inhibitory effect of the presence of ions in the medium. Smaller amounts of ACF were released into a solution simulating human body fluid (SBF) and into PBS acidified buffer, compared to the amount released into deionized water [152]. The presence of ions in the medium can promote ion exchange between the drug and the anions in the solution, and this can be a limiting factor in the release of the drug from the structure. They may hinder the exit of the drug from the MOF structure, and thus be the reason why less drug is released into the medium [60,111,115,217] For the stability of MOFs in ion-rich solutions, including for the mentioned SBF, gastric fluid simulant solution (SGF) and buffers such as PBS, TRIS, HEPES, destructive effects of the environment on the metal-organic framework have been observed (Figure 12). Ions in the solutions, particularly phosphate ions, pretend to replace organic linkers, causing ligand-ion competition. As a result, the linker leaches out and the stability of MOFs decreases. The ions then take on the character of Lewis bases. This effect is particularly pronounced for MOFs made of multivalent metals. Another factor that can affect the use of MOFs is their environmental reaction-dependent behavior. Although most materials are classified as chemically stable, they show sensitivity to degradation under strongly alkaline conditions. Under such conditions, substitution of the linker by hydroxide ions can occur. Particularly unstable in the presence of alkali are MOFs whose backbone is composed of a multivalent metal and a ligand containing carboxylates. An acidic environment can also accelerate MOF degradation. Under such conditions, MOFs with divalent metal centers and azoles in the form of ligands are more unstable. we can regard this as a disadvantage and a broad limitation of metal-organic framework applications. On the other hand, MOF matrices exhibiting pH variability have been used as drug carriers with simulated responses. It is promising to use such materials as drug carriers for anticancer therapy [146,211,218,219]. These include the ZIF [211] or MIL [123] series, among others. As for the effect of temperature, it is not so much important. In biomedical applications, what is relevant is the stability and functionality of the materials at human body temperature (36.6 ^{O}C), or raised temperature during fever (up to 43 ^{O}C).

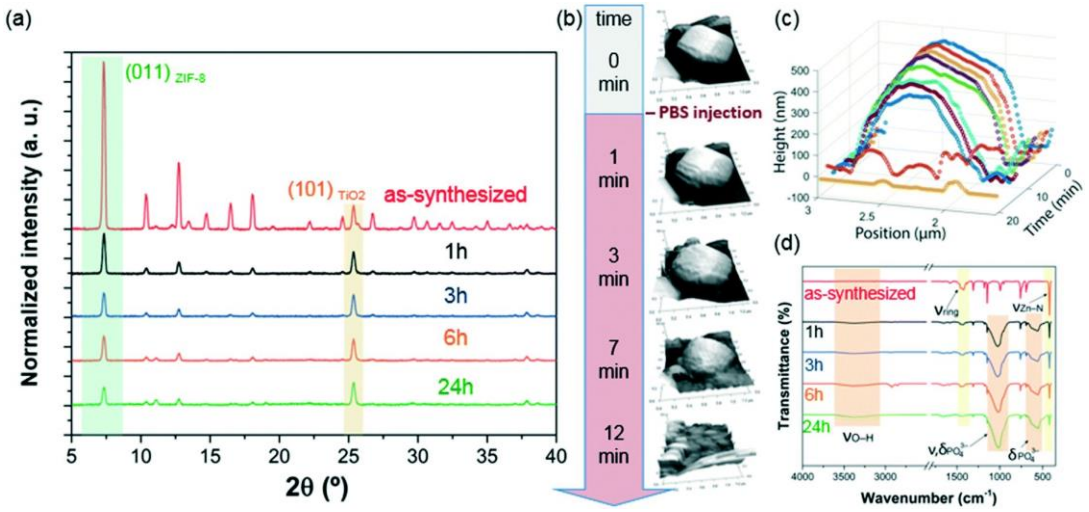
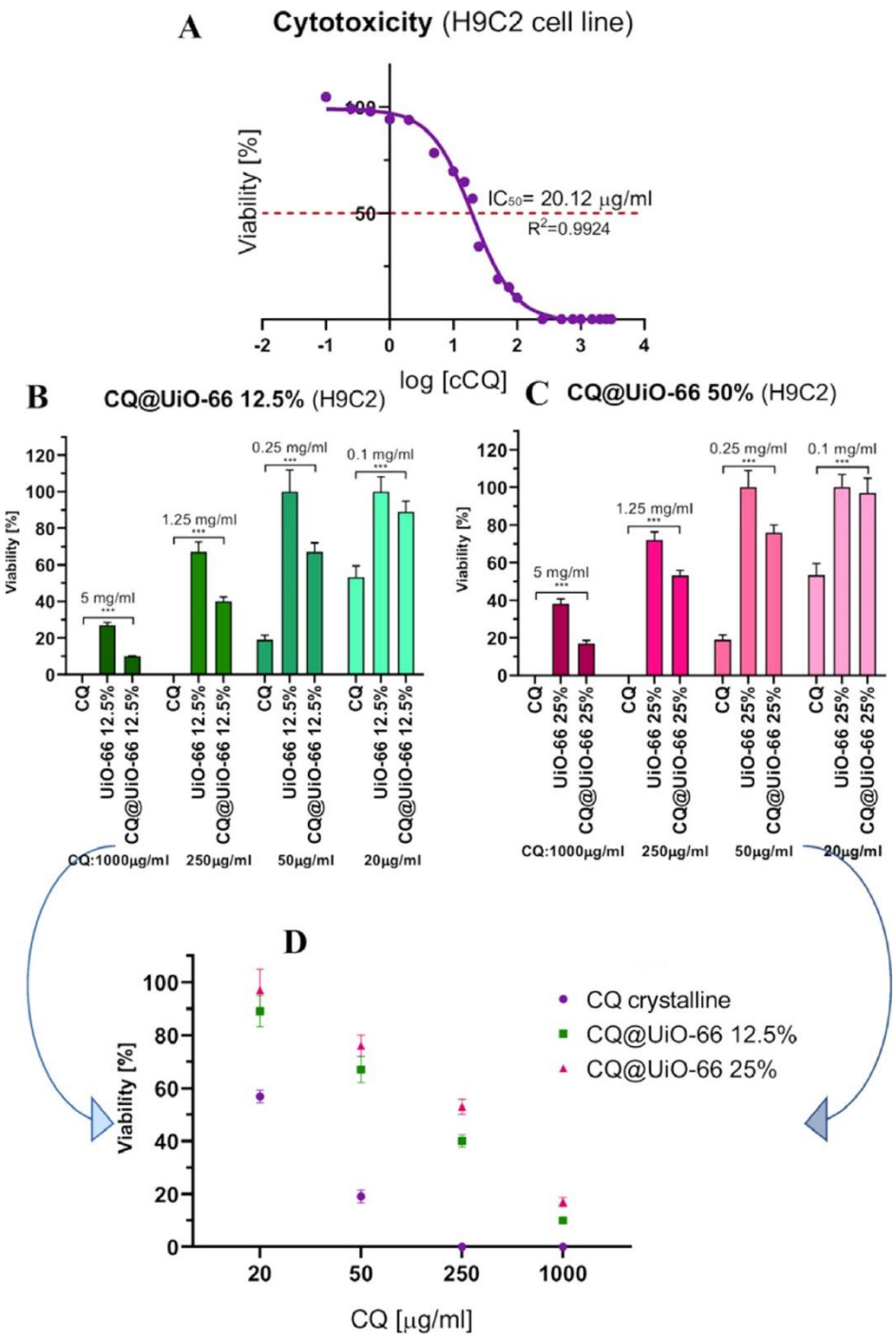


Fig. No.12. Stability of ZIF-8 in PBS solution [211].

Biocompatibility and uptake

Metal-organic frameworks are characterized by a high possibility of design and change. It can affect both the chosen metallic center and the organic linker. What form the spatial structure ultimately takes determines its physicochemical properties and thus its possible applications. Focusing on biomedical applications, the most significant criteria are the absence of cytotoxicity and high biocompatibility [61,220,221]. In this case, the metallic center plays a key role. The most popular in medical applications is the use of metal ions Zn^{2+}, Mg^{2+}, Fe^{3+}, Ca^{2+}, Co^{2+} and Zr^{4+} [206,221]. We can also meet centers in the form of Gd^{3+} [73,80] and even Eu^{3+} [102,140,222,223]. The ligands are usually characterized by low cytotoxicity. The high importance of medical applications is also evidenced by the existence of a structure called Bio-MOF, especially Bio-MOF-1, Bio-MOF-100 and Bio-MOF-13 [62,178,224]. The framework is built by one of the four nitrogenous bases that build DNA, specifically adenine. Bio-MOFs are a class of materials in which the ligands used are amino acids, aminosacharides and even proteins. In the aforementioned applications, Bio-MOFs bring many advantages, e.g. greater stability under physiological conditions, very high biocompatibility and molecular recognition, resembling biological processes [225,226]. One study performed was based on determining the change in cell viability of MCF7 and SkBr3 cells using the MTT assay. A 100% cell survival rate was observed after 72 h of incubation [227]. Such results give a very positive prognosis for using Bio-MOFs as DDS, even for chiral drugs. This represents a wide field of research. In addition to cytotoxicity, biodistribution, and pharmacokinetics are very important parameters for biomedical utilization of MOFs. The former determines the tendency of MOFs to accumulate in the human body. Numerous studies confirm the accumulation of MOFs in the liver and kidneys. This is related to how and

by what route nanoparticles are removed from the body. When MOFs are used in chemotherapy, they can accumulate in tumor tissues. Pharmacokinetics, on the other hand, follows the fate of the metal-organic framework until it is excreted from the body. The toxicity of MOFs is assessed by changes in body weight, organ status, histological observations, and evaluation of biochemical parameters [221]. No abnormalities were observed for MIL-88 [228], MIL-100 [153], or MOF-74 (Mg) [229]. Another test was the treatment of HepG2 cells with MIL-53 (Fe) for 24 h. No cellular changes were noticed, and in added, the network showed very good biocompatibility. In the same experiment, the cytotoxicity of the pure Ori compound and the Ori@MIL-53 (Fe) composite was tested. A significant time- and dose-dependent decrease in cell death was observed. This underlines the controlled and slow release of Ori from the MOF structure, demonstrating high therapeutic potential while maintaining treatment safety [203]. In one study, cardiotoxicity tests were also performed for pure CQ, pure UiO-66 and CQ@Ui-66 composites. Results are shown on Figure 13. In the case of CQ, heartbeats are reduced and the heartbeat rhythm becomes irregular. In the case of MOF, no such relationship was observed, as for CQ-loaded UiO-66. Such a result demonstrates not only the lack of toxicity of MOFs, but also its protective effect on the structure of the drug - the network not only protects the molecule from degradation, but also eliminates the side effects of the drug, reducing its negative impact on the body. This can prove to be extremely important when using heavy drugs, such as chemotherapeutics [212]. One article managed to study the kinetics of ACF release and demonstrate its inhibitory effect on the SARS-CoV-2 virus. A toxicity study showed that the use of MOFs as carriers improved the safety profile, as well as reduced the mortality of D.rerio tested. Loading the drug into MOFs contributed to slower drug release and provided a cardioprotective effect (Figure 13) [152].


A
Cytotoxicity (H9C2 cell line)
Viability [%]
IC50= 20.12 µg/ml
R2=0.9924
log [cCQ]
B
CQ@UiO-66 12.5% (H9C2)
C
CQ@UiO-66 50% (H9C2)
5 mg/ml
1.25 mg/ml
0.25 mg/ml
0.1 mg/ml
CQ
UiO-66 12.5%
CQ@UiO-66 12.5%
UiO-66 25%
CQ@UiO-66 25%
CQ:1000µg/ml
250µg/ml
50µg/ml
20µg/ml
D
CQ crystalline
CQ@UiO-66 12.5%
CQ@UiO-66 25%
CQ [µg/ml]

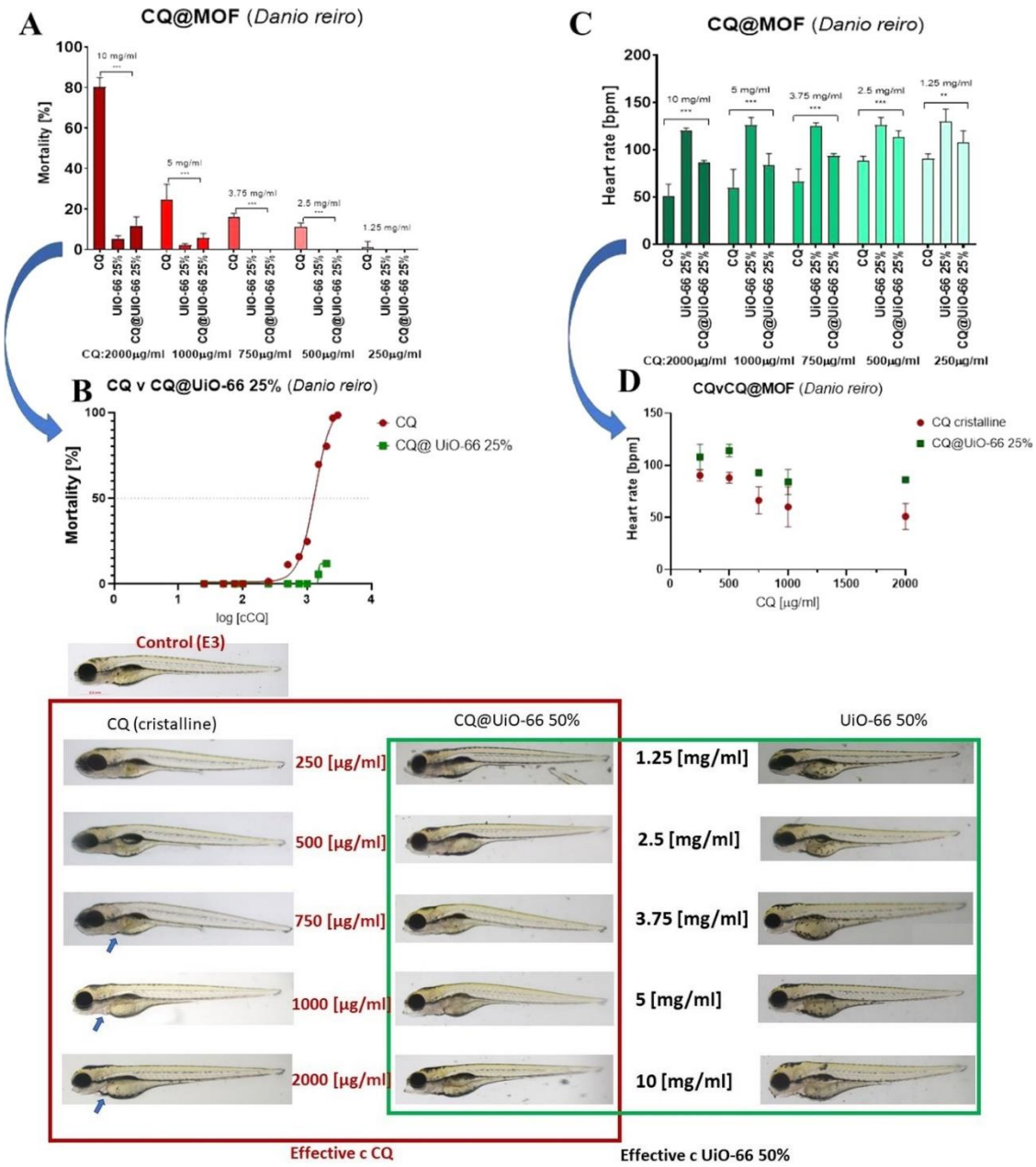


Fig. 13. *In vitro* and *in vivo* cytotoxicity studies, as well as CQ release efficiency studies with CQ@UiO-66. Reprinted with permission from ref. [212]. Copyright 2021, American Chemical Society.

Additional confirmation of the low cytotoxicity of metal-organic frameworks is provided by an experiment conducted on HEK-232, Vero and HaCaT cell lines. The study involved determining the toxicity of MOFs used to remove uremic toxins in kidney disease. The network was to act as an effective adsorbent and function as an artificial kidney. Both sorption profiles and bioassays were successful [149]. The complete safety and validity of MOF materials in this type of application was confirmed and shown on Figure 14.

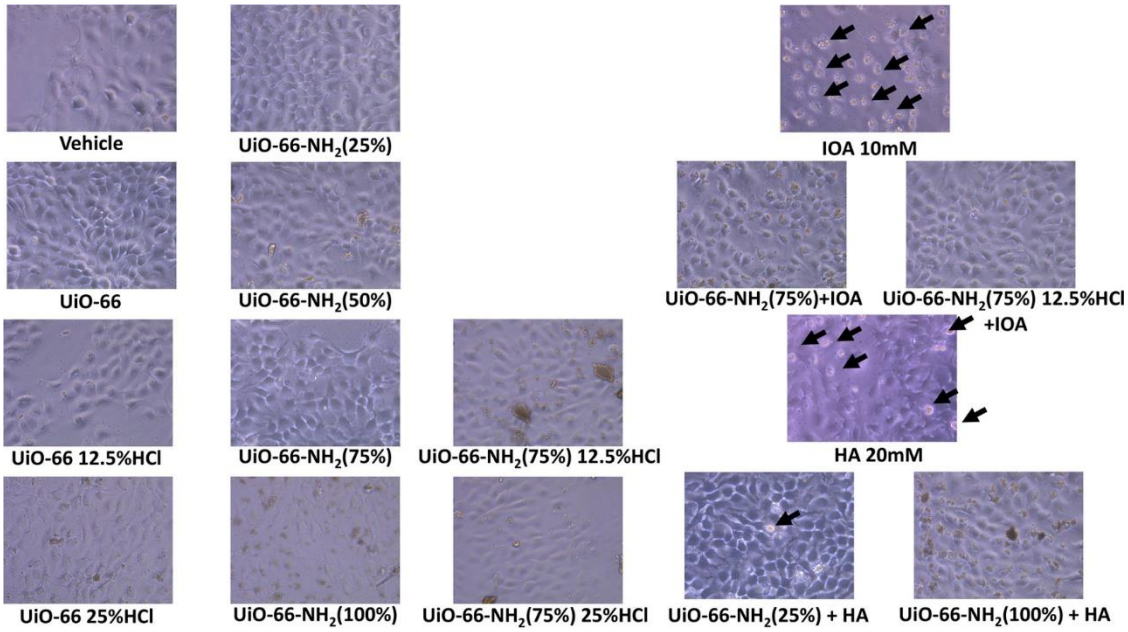


Fig. No.14. Compare the toxicity of UiO-66 and hippuric acid on a cell line HaCaT [149].

As discussed above, some of the structures are water-sensitive, so they can contribute to the transfer of hydrophobic drugs, thereby increasing their bioavailability and enhancing absorption [221]. Metal-organic frameworks show degradability in the presence of ions, or more precisely, buffer solutions [227,230,231]. This is also useful, more precisely as controlled and targeted drug delivery systems, e.g. pH-stimulated DDS for chemotherapeutics [80,115,116,193,227]. If we are interested in increasing structural stability, the MOF can be modified by coating its surface, which was also discussed earlier. Such a solution protects both the network and the therapeutic substance, which will reduce side effects associated with earlier drug degradation and API transition effects. This approach has also been documented in the literature [86,104,111,112,199,232,233].

Perspective and case study

Photodynamic and photothermal anti-cancer therapy

Despite numerous studies, work is still underway on the most optimal and effective approach to treating cancer. Both photodynamic therapy (PDT) and photothermal therapy (PTT) are attracting much attention from researchers. These therapies use the action of photosensitizers, which absorb light in a specific wavelength range, to produce reactive oxygen species (ROS). ROS induces apoptosis of tumor cells [213]. Porphyrins have so far not shown much effectiveness in cancer treatment, which is related to their poor solubility in aqueous media. One study has demonstrated the effect of metal-organic frameworks containing porphyrin-like monatomic Fe^{3+} centers. It is based on the mechanism of action of

single-atom catalysts. The main idea is to disperse the metal ion in the porphyrin-like sites through nitrogen coordination bonding. A MOF was constructed, containing the ligand Fe-TCPP (TCPP = tetrakis(4-methoxycarboxyphenyl)porphyrin)) and Zr_6 clusters. The material absorbed light from the near-infrared (NIR) range. The high efficiency of the synthesized material was demonstrated. This justified the need for additional research on the application of MOFs containing single iron atomic centers [234]. Another research group worked on using ZIF-8 and ZIF-67 as a combined platform to deliver chemotherapeutics and produce oxygen. The first MOF was loaded with DOX, released in response to low environmental pH. The second was modified to degrade H_2O_2 and produce oxygen, and consequently ROS. This two-step approach minimized cell hypoxia while inducing tumor death. This underscores the great potential of MOFs in innovative ways to fight cancer [235]. UiO-66 or IRMOFs have also been tested in such an application. Future research offers many possibilities, for example, combining PDT and PTT with other forms of treatment such as immunotherapy or radiation therapy [236]. Examples of using MOFs in PDT and PTT are shown in Figure 15 and Figure 16.

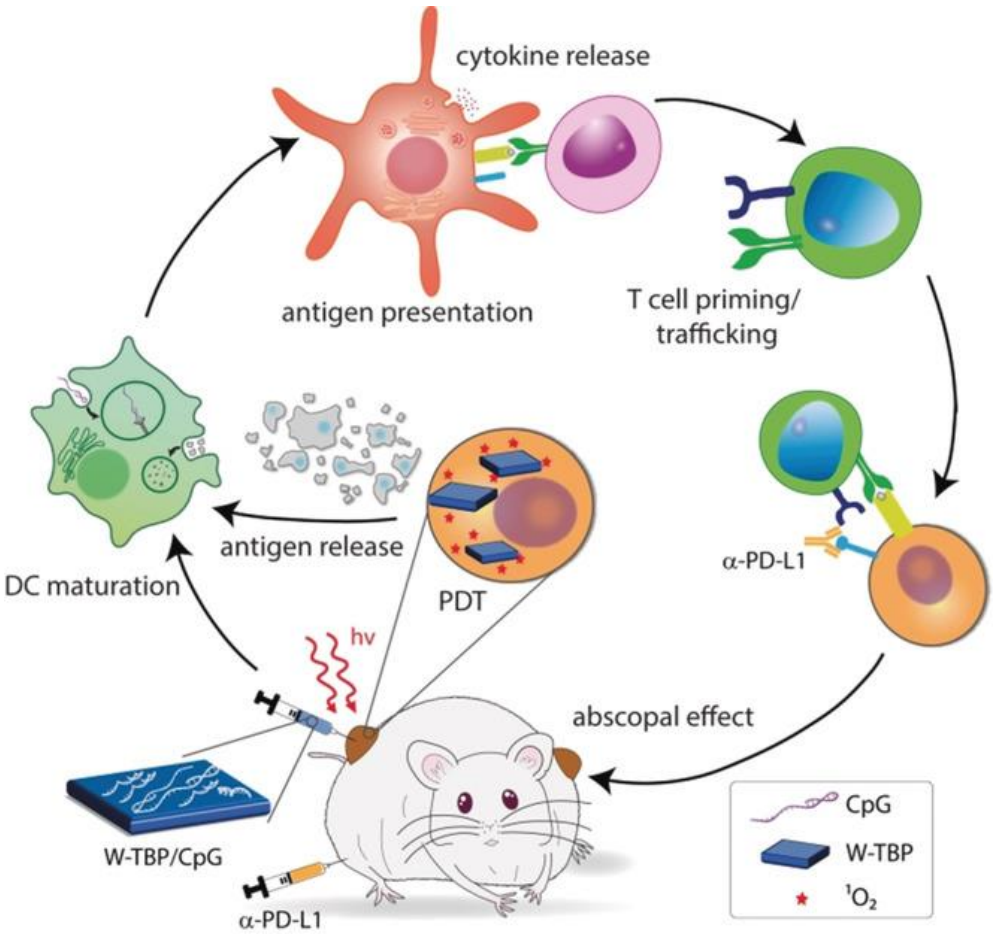


Fig. No.15. The use of MOFs in PDT therapy as an upgrade in cancer treatment effectiveness. Reprinted with permission ref. [290].Copyright, 2019 Wiley.

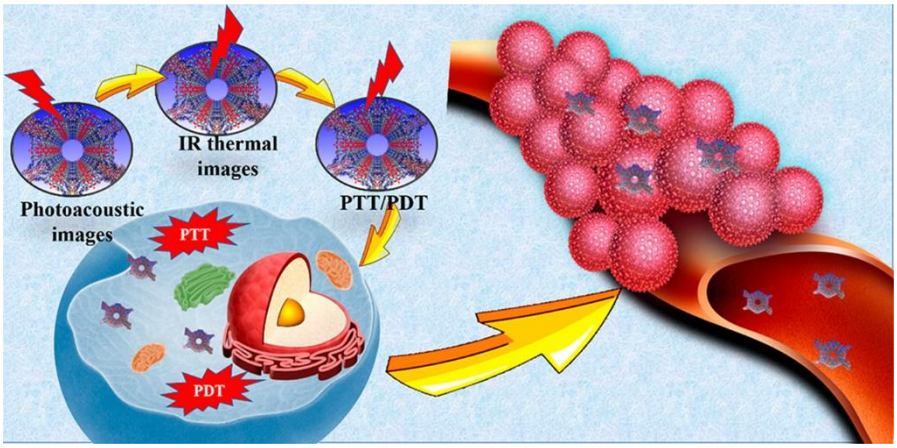


Fig. No.16. NIR-Stimulation of Single Atom Iron Centers in P-MOF as effecient PDT and PTT cancer therapy. Adapted with permission from ref. [234].Copyright 2019, American Chemical Society

Magnetic Drug Delivery System

The effectiveness of treatment highly depends on the drug carriers. To make metal-organic frameworks more programs it is possible to make them magnetic. One study involved introducing Fe and Mn into the structure of MIL-88B loaded with 5-FU. Giving a magnetic character makes it feasible to target control drug tuning externally, outside the patient's body. Ferromagnetic materials are characterized by a lower viscosity and thus a lower degree of encapsulation. Nevertheless, studies have shown their low cytotoxicity against HEK293T cells [237]. Commonly used in magnetic MOFs are iron oxides exhibiting ferromagnetism or superparamagnetism, mainly Fe_3O_4 and γ-Fe_2O_3. The use of nanoparticles of cobalt, nickel and their oxides is also known [238]. Other studies demonstrate the possibility of using magnetic MOFs, more specifically MIL-101 (Fe) and MIL-53 (Fe) as carriers of nimesulide (Nim) [239]. This approach offers new possibilities, and more targeted drug delivery, dependent on controlled external conditions, which is an advantage [240].

Simulated response

Metal-organic frameworks are distinguished by their ability to induce a so-called simulated story. This has found wide application in the release of therapeutic substances. The metal-organic framework can be sensitive to: the pH of the environment, to the presence of glucose, glutathione (GSH) or enzymes (such a mechanism is called redox responsive), adenosine triphosphate (ATP), the presence of metal ions, to H_2S, light, temperature and pressure. Therefore, depending on the structure, it shows different sensitivity [241]. Susceptibility to environmental pH is a desirable feature of DDS. The surrounding environment for tumors, endosomes, or lysosomes is lower than for blood or healthy tissue. Several MOFs, including the best-known UiO-66, MIL, and ZIF are

characterized by instability under acidic conditions, which can lead to drug release in a specific environment, thereby improving treatment efficacy. The effectiveness of delivering an autophagy inhibitor, more precisely 3-methyladenine (3-MA) from ZIF-8 in anti-cancer therapy was demonstrated. The metal-organic framework released larger amounts of 3-MA in the acidic tumor environment, which was due to the aforementioned instability of ZIF-8 under the given conditions. The ability of the pH-stimulated response to reduce the side effects of therapy was confirmed by *in vivo* studies [242]. Of course, several acid-fast MOFs are known. The pH-dependent drug release process can be related to coordination bond protonation, bond cleavage, or guest-host interaction [44,224]. More interesting research demonstrated the utility of metal-organic frameworks, specifically Zn-MOF-74 as delivery systems for arsenic trioxide. Despite its toxicity, this compound shows therapeutic potential in the treatment of cancer, for example, white blood cells, brain or breast cancer. The main limitation of its use is the lack of suitable carriers, providing high therapeutic efficacy while minimizing toxicity. The use of Zn-MOF-74 made it possible to achieve the desired effect. In addition, more efficient and faster release of As(III)-drugs was demonstrated in a pH-reduced environment, which is typical of the tumor microenvironment. This underscores the potential usefulness of the aforementioned metal-organic framework in cancer therapies due to more efficient drug delivery under acidic conditions and lower sensitivity of the network, which favors release kinetics [243]. In the case of GSH-sensitive materials, this relationship is used to deliver chemotherapeutics. After all, GSH levels are about 100 higher in tumor tissue than in blood, and it is a very strong reducer. Currently, the design of MOFs with ligands containing disulfide bonds, which in the presence of GSH breaks (redox reaction) and releases the drug, is in practice. Drug release in response to glucose concentration is associated with MOF modification and the introduction of glucose oxidase (GOx). In a glucose-rich environment, it acts as a catalyst for the reduction of glucose to gluconic acid and H_2O_2. This causes acidification of the environment and thus degradation of the metal-organic framework. Enzyme sensitivity involves modification of the MOF surface with specific compounds that undergo redox reactions in the presence of the enzymes involved. The MOF structure is violated and the drug is released [80,196,244]. Stimulated drug response has been shown in Figure 17. Due to the specificity of enzymes, API release occurs at a specific site in the human body. ATP, which is very common in cells, has coordination abilities. As an unstable compound, it can initiate the formation of ATP-ion complexes in the metal backbone [245,246]. Cu-containing ions can, in the presence of sulfur, more specifically H_2S, degrade the MOF structure to produce CuS precipitates. This happens because the coordination of copper and sulfur is stronger than that of copper with a structural ligand [80,115,237]. For

the light-simulated response, the researchers focus on projecting ligands containing light-sensitive elements. Parameters such as temperature and pressure also affect the structural stability of the material [80]. Increasing the first parameter promotes faster drug release, but we focus on human body temperatures (36.6 ^{O}C) and elevated temperatures around tumor tissues or during disease [180,219,247–249]. In the case of pressure, the elevated value promotes prolonged drug release for up to 2 to 8 days [250]. However, taking into account the human body, the use of this parameter is not significant in the simulated response.

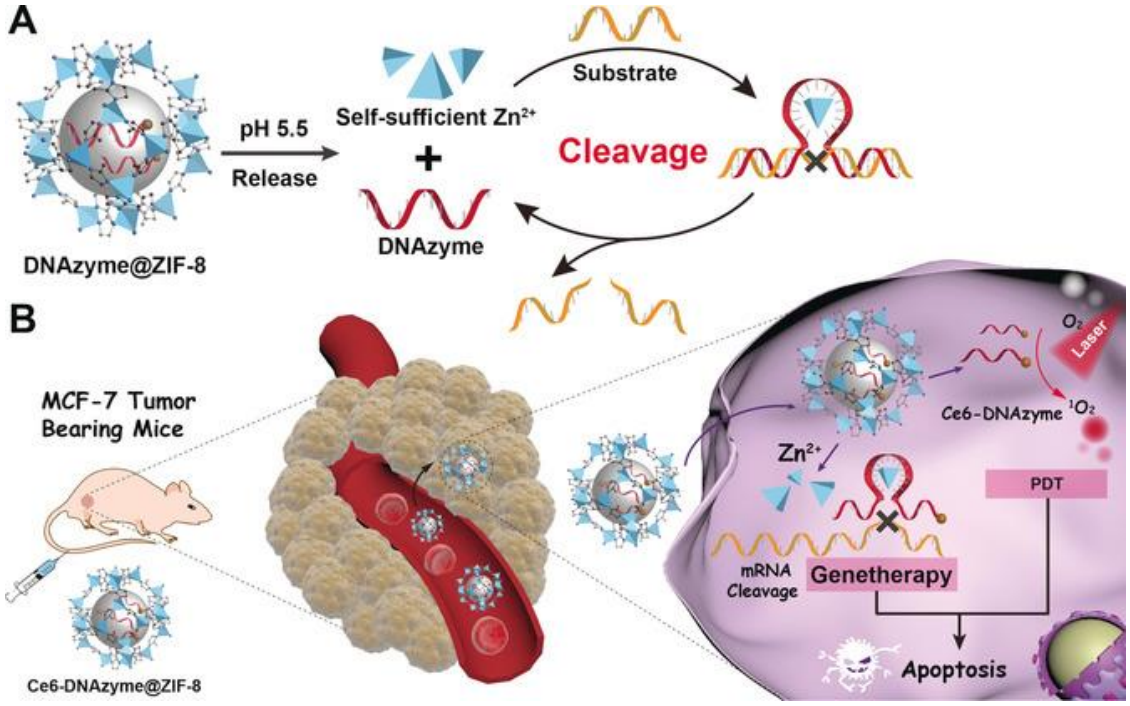


Fig. No.17. MOFs as drug delivery systems a) with stimulated response sensitive to pH enviroment and b) in PTD therapy . Reprinted with permission ref. [291]. Copyright, 2019 Wiley.

Targeting drug delivery

The stimulatory response of MOFs described above is a type of physicochemical targeting. Targeted drug delivery, triggered by modification of the surface of a MOF or its ligand, is also available. This type of delivery is called active targeting. Metal-organic frameworks as targeting DDS are shown in Figure 18. The mechanism involves overexpression of the target cell's receptor to the compound with which the MOF surfaces have been modified. Compounds such as folic acid, glycyrrhetinic acid and lactobionic acid can serve as targeting agents for drug release into tumor cells, as previously described [101]. The effect of folic acid in this regard has already been well studied [74,101–105,108,251–253]The release of 5-FU, DOX, or curcumin (CCM) from MOFs modified with

folic acid has been tested. Another compound that can serve as a targeting agent is anizamide, to which tumor cell receptors are sensitive [253]. A group of researchers has proved the effect of dioleoyl L-α-phosphatidyl-ethanolamine (DOPE) as a directional factor on leukemia cancer cells. They study the functionalization of MOFs with DOPE [254]. Proved analogous effect of coating the surface of a metal-organic framework with HA hyaluronic acid in cancer treatment [86,106,255]. Nanoparticles based on albumin BSA have a similar effect on directional therapy [111]. Qi et al. focused on the use of anti-EpCAM antibodies, which they placed on the surface of MOFa. They, too, succeeded in increasing the efficiency of the therapy by this means [254,256]. Targeted delivery of APIs allows increasing selectivity by delivering the drug to the site of the diseased tissue while limiting its accumulation in healthy cells. The surface of the MOF can also be functionalized to increase its stability under physiological conditions. This has been described previously [40].

MOF's cocktail of drugs

The number of publications on the biomedical application of MOFs is increasing every year. This is indirectly related to the enormous opportunities these materials give us when it comes to drug delivery. Some of the scientific papers refer to packing two drugs in an edible MOF carrier. This approach is possible if the chosen material has the right pore size. Another factor is to pay attention to the physicochemical nature of the drugs and the safety aspect. In such a situation, it is necessary to reduce the doses of drugs and to select them in such a way that their simultaneous application does not pose a danger to the patient and that their effects are not opposed to each other [44,116,257,258]. Simultaneous administration of 5-FU and DOX using a metal-organic framework has been studied [259]. Another team worked on the simultaneous delivery of a mixture of folforinox with 5-FU or leucovorin or irinotecan or oxaliplatin. Such trials have been successful [260]. Duman et al. developed a dual-drug delivery system of floxuridine (FUDR) and carboplatin (CARB) for liver cancer therapy. In his study, he used MOF-808, the surface of which was functionalized with poly(acrylic acid-mannose acrylamide) (PAAMAM) glycopolymer, which provided greater selectivity and high efficiency of therapy, confirmed by *in vivo* studies [258]. On the other hand, we can consider packing into the structure a drug and a compound with therapeutic potential, which would increase the effectiveness of the therapy. For example, gallic acid (GA), hydroxycinnamic acids (CHC) and other natural or plant antioxidants can increase the effectiveness of cancer therapy, as highlighted by numerous studies [177,261,262].

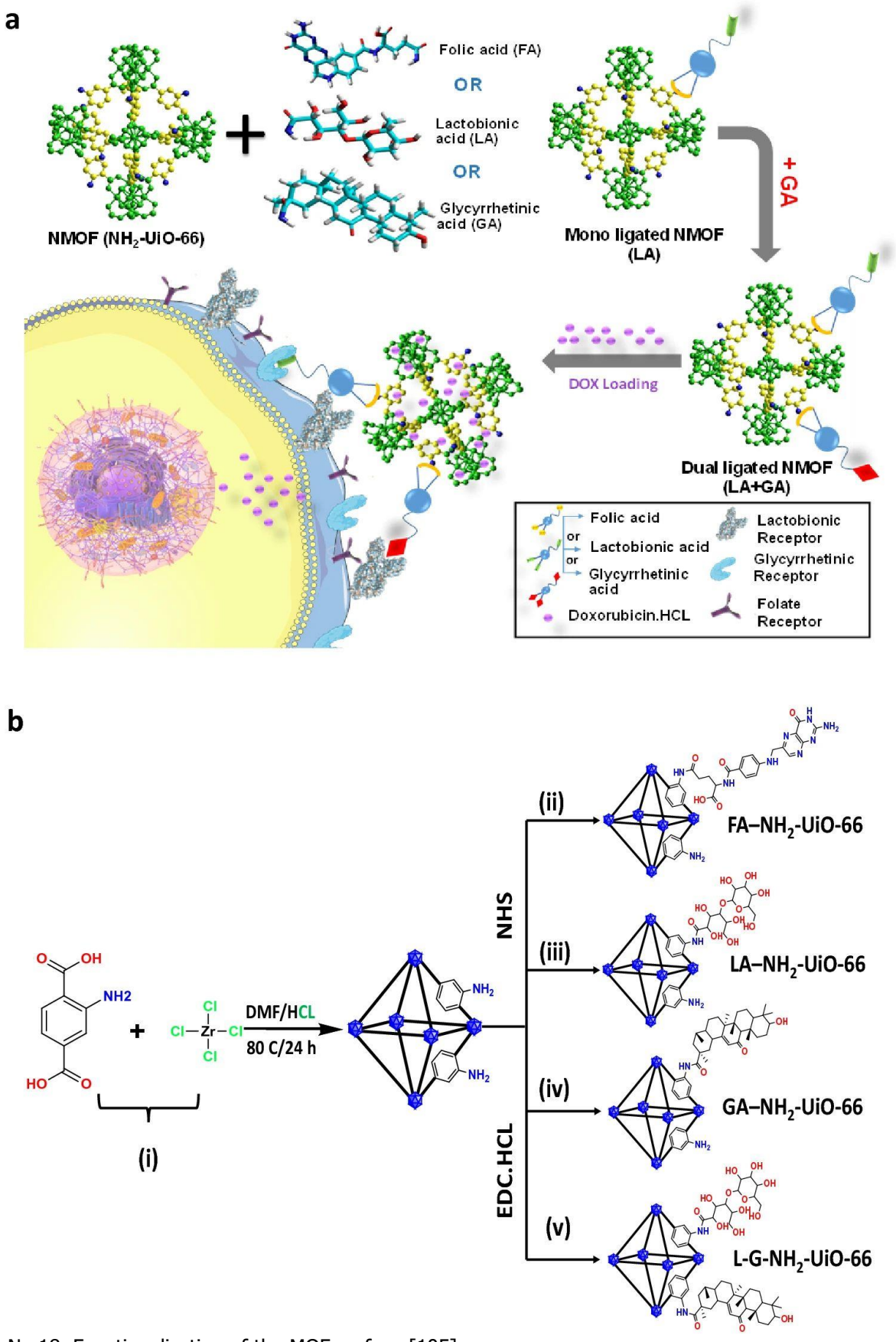


Fig. No.18. Functionalization of the MOF surface [105].

From pro-drug to drug inside MOFs

An innovative approach is the packing of pro-drugs in the structure of MOFs. Pro-drugs are compounds from which the synthesis of the drug proper occurs via a simple reaction, but very often they do not exhibit as high cytotoxicity as the drug. The packing of pro-drugs in the MOF can lead to the synthesis of the drug at a designated site in the body, e.g. the diseased tissue, which increases the targeting and effectiveness of the therapy [263]. In the literature, we can find studies on this approach in the application of MOFs. One experiment involved packing a cis-platinum pro-drug, cis,cis,trans-[PtIV(NH_3)2(Cl)$_2$($O_2CCH_2CH_2CO_2H$)-(OH)] in UiO-66. The indicated pro-drug requires only reduction to Pt(II), which occurs in a highly reducing environment. Such an environment exists in the proximity of cancerous tissue [167,264]. Subsequent studies show the possibility of producing nitric oxide NO (Figure 19). This endogenous compound is a regulator of the cardiovascular system, often used in treatment. Compounds from the dinitrosyl iron complexes (DNICs) group are used to synthesize NO. In the experiment, [Fe_2(μ-SCH_2CH_2COOH)$_2$(NO)$_4$] (DNIC-2) was used as an NO prodrug. It was loaded in MIL-88B. It was shown that the acid-sensitive MOF in gastric and stomach environments, under the influence of ligand protonation, releases both DNIC-2 and NO. In this case, both the prodrug and the drug serve to treat chronic cardiovascular disorders. The bioavailability of NO after oral administration was increased, resulting in a decrease in systolic blood pressure (SBP) [265]. Pro-drugs are known to be used as ligands of the metal-organic framework. It has also been successful in loading a new indocyanine green (IR820), combined with cytarabine (Ara). This results in the removal of the bond with Ara and the formation of the Ara-IR820 pro-drug. Pure Ara drug show very low loading rates in MOFs, which is a big problem. In contrast, the IR820 dye has been approved by the United States Food and Drug Administration (FDA) for clinical use in PTT. This approach offers the possibility of loading the drug efficiently while maintaining the effectiveness of PTT therapy [255].

MOF-based hydrogels

In recent years, hydrogel materials have seen the forefront in medicine, for example, in wound treatment and delivery of active ingredients. Given the increasing popularity of MOFs and hydrogels, researchers have developed hydrogel materials based on metal-organic frameworks. Again, this highlights the wide range of biomedical applications of MOFs. The processes for synthesizing the materials are numerous; from the simplest format, it involves

adding a MOF to a precursor polymer solution. What happens is that the metal-organic framework is surrounded by the polymer by slow radical polymerization and a hydrogel with the characteristics of both components is formed. The matrices used are usually gelatin and alginate. The use of the mentioned materials in water purification has been studied [266].

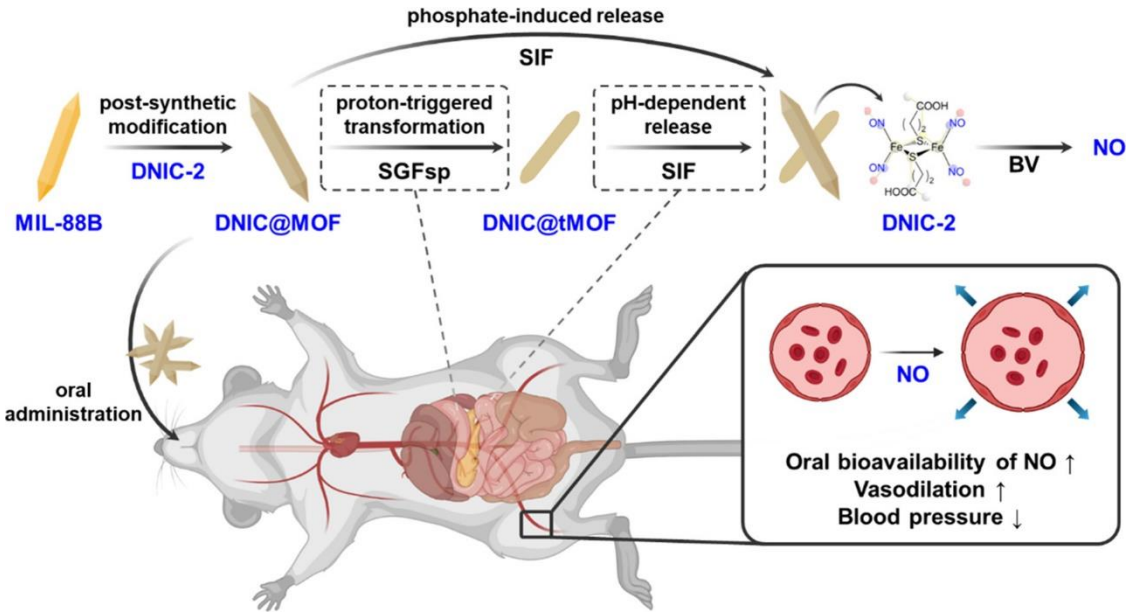


Fig. No.19. Utilization of a metal-organic framework loaded with a prodrug for drug delivery. Adopted with permission from ref. [265]. Copyright 2022, American Chemical Society.

And for medical applications in wound treatment - copper and zinc MOFs loaded with vitamins and drug release, for example, with UiO-68. MOF-based hydrogels show greater stability than powder metal-organic frameworks, which broadens the application possibilities. In addition, they retain high porosity and gain greater structural flexibility [267].

MOFs vs. MNs

Another example of the adaptability and utilization of MOFs in modern medical and pharmaceutical trends involves the possibility of creating microneedles (MNs) containing MOFs. The characteristics and advantages of MNs were described above in the article. A research group proposed the use of ZIF-8 in micro-needles containing methacrylate hyaluronic acid (MeHA-MN). The idea of the study was to apply a microneedle that would destroy bacterial capsules and, under oxidative stress, release Zn^{2+} ions, which interfere with bacterial metabolism, destroy the membrane and thereby induce bacterial death. In addition, low-molecular-weight HA, formed from the hydrolysis of MeHA, promotes angiogenesis and collagen accumulation. The whole process results in faster wound healing in a painless and highly effective manner [268]. Another team developed glucose-stimulated insulin secretion. Insulin (Ins) and glucose oxide (GOx) were loaded into ZIF-8 having an additional cobalt

center, and the material was then encapsulated in MNs. The whole mechanism of action is relatively compiled. It involves the separation of GOx and conversion to gluconic acid with the generation of H_2O_2. The resulting acid reduces the pH of the environment, resulting in the degradation of ZIF-8 and the release of insulin and Co^{2+}. The cobalt ion degrades hydrogen peroxide and can then be chelated before the EDTA-SiO_2 contained in the MN and then removed. This is a modern and painless approach to treating diabetes [269]. MNs adapted to treat once-diabetic patients were also developed. These consisted of a poly(γ-glutamic acid) (γ-PGA) hydrogel and loaded with an Mg-MOF containing Ag and gallic acid (GA). The ions accelerate cell migration and regeneration, while gallic acid destroys ROS and promotes anti-oxidation. Such dressings accelerate wound healing, as shown in *in vitro* and *in vivo* studies [270]. The innovative application of MOFs in MNs is shown in Figure 20.

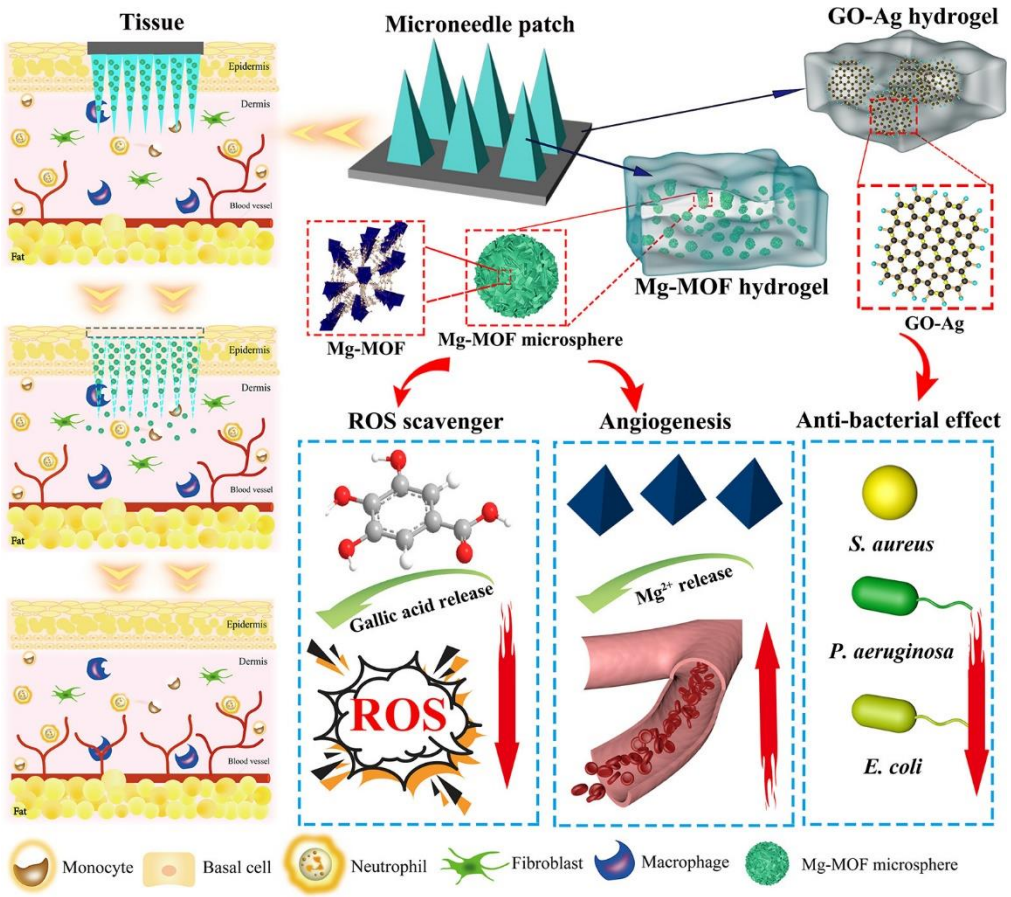


Fig. No.20. MOF-based microneedles and their utility in wound healing. Reprinted with permission from ref. [270].Copyright 2021 American Chemical Society.

3D MOFs printing

The last decade has seen the development of techniques and applications of 3D printing. This area in catalysis and medicine is being intensively developed. Metal-organic frameworks have also found their application here. One study involved the development of a

new ink for 3D printers. This ink was water-soluble Zr-MOF, more precisely MOF-525, which will significantly affect the strength of the ionogels produced. In addition, it was capable of changing color when in contact with acidic compounds [271]. Another case described the use of a mixture of ethanol and HKUST-1 as printing ink. The resulting mixture was used to print monoliths. They were characterized by very good rheology, which made it possible to print other MOFs using this method [272]. In addition, the monoliths had a BET of 1134 m^2/g and high-volume mesopores. These studies are the basis for the development of knowledge on printed MOFs and leave a large field of research [273].

Disease diagnostics

The use of MOFs in disease diagnosis, especially cancer, is widely described in the literature. It focuses on active or passive drug delivery to tumor cells, however with some modifications. This is because suitably modified MOFs are used, which reach the tissue in question but contain a suitable contrast compound used in magnetic resonance imaging (MRI), X-ray computed tomography (CT), positron emission tomography (PET), optical imaging, and photoacoustic imaging (PA). For example, Gd^{3+}, $Mn^{2+,}$ or Mn^{3+} ions, as well as both Fe^{3+} and Fe_3O_4, serve as contrast in MRI [274]. An example of using MIL-88A, MIL-100 and MIL-101 as natural enhancers in MRI is described [229]. For CT, the presence of Zr and Hf is useful [275]. When MOF is adopted, laser irradiation of the tissue and identification of the tumor site occurs. Metal-organic frameworks have been developed for breast, prostate and lung cancer diagnosis [276,277]. They are highly sensitive, painless, safe and effective for use.

Adsorption and detection of psychoactive compounds

A very interesting and little-studied approach is the adsorption of psychoactive compounds. Although the adsorptive properties of MOFs have been known for a very long time and extensively studied, the adsorption of such compounds has not been focused on until now. Metal-organic frameworks are used to adsorb gases [64,278,279] and even drugs, which have applications in water purification processes [280,281]. An interesting approach is the use of MOFs as materials that absorb cannabinoids and simultaneously serve their detection. The study involved selecting MOFs with high affinity for water and Δ^9-Tetrahydrocannabinol (THC). This was to serve the selective adsorption of THC from exhaled air. The goal was to develop a detection system for cannabinoids during routine police checks, something along the lines of how a breathalyzer works [282]. Another very interesting study in this area was the adsorption of amphetamine on ZIF-8. It was possible to demonstrate the high sorption capacity of the material [194]. Similar attempts were made

to adsorb amphetamine-like compounds, which were also successful [222]. The number of articles emphasizes that this area is little studied and leaves great opportunities for future research. This gives us another application potential for MOF networks.

Drug adsorbents – novel detoxification system

Drug adsorption is also a very important biomedical application. According to the review of currently used adsorbents made at the beginning of the article, the number of adsorbents approved for use is severely limited. This gives us the opportunity to use metal-organic frameworks as drug adsorbents in situations of intentional drug overdose or poisoning. Zhang et al. tested the utility of MIL-101 as an adsorbent for antipsychotic drugs. The study was conducted on serum samples collected from the hospital, highlighting the feasibility of such an application. MIL-101 adsorbed isperidone, quetiapine, aripiprazole and their metabolites [283]. Most of the studies describe the efficient and selective adsorption of drugs from water, which is expected to highlight the potential for MOFs to be used in the environmental department, and more specifically for the treatment of pharmaceutical wastewater, which is currently a challenge [218,284,285]. The adsorption of 5-FU, caffeine (CAF) on ZIF-8 [286], brimonidine tartrate commonly used in eye diseases adsorbed on UiO-66, sulfacetamide [287] or sulfonamide antibiotics on MIL-101 (Cr) has been studied [281]. This research status provides an opportunity to study MOFs as detoxification systems for the body, which is currently poorly studied.

Conclusions

To conclude, the use of metal-organic frameworks in biomedical applications is a completely justifiable and promising area of research. MOFs tend to exhibit high thermal and chemical stability and, above all, very high variability during design. It is possible to use a variety of metal ions and organic linkers so that the network exhibits very low toxicity and high bioavailability. Another opportunity is to modify the surface of the MOF, which allows us to create a targeted drug delivery system, thereby increasing the efficiency and effectiveness of the therapy. The surface of the MOF can be coated to protect both the network and the loaded drug from early degradation. This minimizes the drug's transition effects and side effects. Scientists have succeeded in developing magnetic drug delivery systems and others in which drug release, occurs under the influence of external, or internal factors such as pH, GSH, etc. This is called a simulated response. Besides, metal-organic frameworks can be used for bioimaging or disease diagnosis. A considerable amount of research about MOFs in biomedical applications focuses on their utility in PDT and PTT for cancer treatment. Up to

now, networks have also been designed in which two drugs have been encapsulated, forming a mixture, allowing the doses of both drugs to be reduced, thus minimizing side effects. Pro-drugs have also been capped in MOFs, allowing the synthesis of a given drug to occur at a specific location in the human body. MOFs are currently being used in 3D printing techniques, and hydrogels or micro-needles based on MOFs are being formulated, themes that are currently being explored in the scientific world. This review also demonstrates the potential use of MOFs as drug adsorbents during overdose or poisoning. Although we can find examples of the use of metal-organic frameworks as drug adsorbents in the literature, the research focuses on their adsorption from water for wastewater treatment. The idea of designing and using metal-organic frameworks as modern detoxification systems seems to be an innovative solution. The need is also supported by the lack of a sufficient number of specific drug adsorbents used for medical purposes, as described in the review.

Naturally, metal-organic frameworks have many disadvantages. First of all, some of them are not stable in water, in acidified environments, or ion-rich solutions. Drug release kinetics then become more complicated and less desirable. The degradation of MOFs is also associated with the accumulation of their ligands and metals in human tissues. Here, appropriate toxicity and safety studies are needed. There is also a lack of viable clinical studies that could certify the forward-looking nature of metal-organic frameworks, not only on an academic scale but also on an industrial. The different behavior of MOFs in vivo, and in vitro also needs to be studied and explained in more detailed and thorough medical studies. Subliminally, more research and trials are required to gain more knowledge about MOFs in biomedical applications. So far, scientists have studied only part of the issues in this area, but further, there is a wide field of research.

Acknowledgments

The work was supported by the National Science Centre, Poland, under the research project "MOF-antidote: Novel detoxification materials based on metal-organic frameworks for drugs of abuse removal – synthesis, chemical characterization, toxicity and efficacy in vivo and in vitro studies", no. UMO-2021/43/B/NZ7/00827.

References

[1] Trucillo, P.; Drug Carriers: Classification, Administration, Release Profiles, and Industrial Approach. *Processes* **2021**, 9, 1–18. DOI: 10.3390/pr9030470

[2] Tiwari, G.; Tiwari, R.; Sriwastawa, B.; Bhati, L.; Pandey, S.; Pandey, P.; Bannerjee, S.K.; Drug Delivery Systems: An Updated Review. *Int. J. Pharm. Investig.* **2012**, 2, 2–11.

DOI: 10.4103/2230-973X.96920

[3] Rahman, H.S.; Othman, H.H.; Hammadi, N.I.; Yeap, S.K.; Amin, K.M.; Samad, N.A.; Alitheen, N.B.; Novel Drug Delivery Systems for Loading of Natural Plant Extracts and Their Biomedical Applications. *International Journal of Nanomedicine* **2020**, 15, 2439–2483. DOI: 10.2147/IJN.S227805

[4] Lou, L.; Novel Drug Delivery Systems. *Curr. Rev. Pain.* **1999**, 3, 411-416. DOI: 10.1007/s11916-999-0084-z

[5] Gao, H.; Jiang, X.; [The progress of novel drug delivery systems]. *Yao Xue Xue Bao* **2017**, *52*, 181–188.

[6] Loftsson, T.; Brewster, M.E.; Drug Solubilization and Stabilization by Cyclodextrin Drug Carriers, in.: *Drug Delivery Strategies for Poorly Water-Soluble Drugs*, (Ed.: Douroumis D.; Fahr, A.) **2013**, 67–101, Wiley. DOI: 10.1002/9781118444726.ch3

[7] Bhosale, M.; Borkar, P.; Routes of Drug Administration, in.: *Textbook of pharmacology*, (Ed.: Bhandari P.R.) **2020**, 6–9, Thieme. ISBN: 9789390553150

[8] Homayun, B.; Lin, X.; Choi, H.J.; Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. *Pharmaceutics* **2019**, 11, 129. DOI: 10.3390/pharmaceutics11030129

[9] Talevi, A.; Quiroga, P.A.M.; ADME Processes in Pharmaceutical Sciences: Dosage, Design, and Pharmacotherapy Success. **2018**, Springer. ISBN: 9783319995939.

[10] Anantrao, J.H.; Nath, P.A.; Nivrutti, P.R.; Drug Penetration Enhancement Techniques in Transdermal Drug Delivery System: A Review. *J. Pharm. Res. Int.* **2021**, 33*,* 46–61. DOI: 10.9734/jpri/2021/v33i19b31337

[11] Kaur, G.; Arora, M.; Ravi Kumar, M.N.; V Oral Drug Delivery Technologies-A Decade of Developments. *J. Pharmacol. Exp. Ther.* **2019**, 370, 529–543. DOI: 10.1124/jpet.118.255828

[12] Bourganis, V.; Kammona, O.; Alexopoulos, A.; Kiparissides, C. Recent Advances in Carrier Mediated Nose-to-Brain Delivery of Pharmaceutics. *Eur. J. Pharm. Biopharm.* **2018**, *128*, 337–362. DOI: 10.1016/j.ejpb.2018.05.009

[13] Yang, W.; Veroniaina, H.; Qi, X.; Chen, P.; Li, F.; Ke, P.C.; Soft and Condensed Nanoparticles and Nanoformulations for Cancer Drug Delivery and Repurpose. *Adv. Ther.* **2020**, 3, 1900102. DOI: 10.1002/adtp.201900102

[14] Erdő, F.; Bors, L.A.; Farkas, D.; Bajza, Á.; Gizurarson, S.; Evaluation of Intranasal Delivery Route of Drug Administration for Brain Targeting. *Brain Res. Bull.* **2018**, 143*,* 155–170. DOI: 10.1016/j.brainresbull.2018.10.009

[15] Ulusoy, S.; Bayar Muluk, N.; Karpischenko, S.; Passali, G.C.; Negm, H.; Passali, D.;

Milkov, M.; Kopacheva-Barsova, G.; Konstantinidis, I.; Dilber, M.; et al. Mechanisms and Solutions for Nasal Drug Delivery - a Narrative Review. *Eur. Rev. Med. Pharmacol. Sci.* **2022**, 26, 72–81. DOI: 10.26355/eurrev_202212_30487

[16] Osmałek, T.; Froelich, A.; Jadach, B.; Tatarek, A.; Gadziński, P.; Falana, A.; Gralińska, K.; Ekert, M.; Puri, V.; Wrotyńska-Barczyńska, J.; et al. Recent Advances in Polymer-Based Vaginal Drug Delivery Systems. *Pharmaceutics* **2021**, 13. DOI: 10.3390/pharmaceutics13060884

[17] Major, I.; McConville, C.; Vaginal Drug Delivery for the Localised Treatment of Cervical Cancer. *Drug Deliv. Transl. Res.* **2017**, 7, 817–828. DOI: 10.1007/s13346-017-0395-2

[18] Rathi, R.; Sanshita; Kumar, A.; Vishvakarma, V.; Huanbutta, K.; Singh, I.; Sangnim, T.; Advancements in Rectal Drug Delivery Systems: Clinical Trials, and Patents Perspective. *Pharmaceutics* **2022**, 14, 2210. DOI: 10.3390/pharmaceutics14102210

[19] Shukla, T.; Upmanyu, N.; Agrawal, M.; Saraf, S.; Saraf, S.; Alexander, A.; Biomedical Applications of Microemulsion through Dermal and Transdermal Route. *Biomed. Pharmacother.* **2018**, 108, 1477–1494. DOI: 10.1016/j.biopha.2018.10.021

[20] Ching, L.; Gupta, M.; Transdermal Drug Delivery Systems in Diabetes Management : A Review. *Asian J. Pharm. Sci.* **2020**, 15, 13–25. DOI: 10.1016/j.ajps.2019.04.006

[21] Qindeel, M.; Hameed, M.; Ahmed, N.; Recent Trends, Challenges and Future Outlook of Transdermal Drug Delivery Systems for Rheumatoid Arthritis Therapy. *J. Control. Release* **2020**, 327, 595–615. DOI: 10.1016/j.jconrel.2020.09.016

[22] Waghule, T.; Singhvi, G.; Kumar, S.; Monohar, M.; Microneedles : A Smart Approach and Increasing Potential for Transdermal Drug Delivery System. *Biomed. Pharmacother.* **2019**, 109, 1249–1258. DOI: 10.1016/j.biopha.2018.10.078

[23] Nayak, K.; Misra, M.; A Review on Recent Drug Delivery Systems for Posterior Segment of Eye. *Biomed. Pharmacother.* **2018**, 107, 1564–1582. DOI: 10.1016/j.biopha.2018.08.138

[24] Patra, J.K.; Das, G.; Fraceto, L.F.; Vangelie, E.; Campos, R.; Rodriguez, P.; Susana, L.; Torres, A.; Armando, L.; Torres, D.; et al. Nano Based Drug Delivery Systems : Recent Developments and Future Prospects. *J. Nanobiotechnology* **2018**, 16, 71. DOI: 10.1186/s12951-018-0392-8

[25] Li, C.; Wang, J.; Wang, Y.; Gao, H.; Wei, G.; Huang, Y.; Yu, H.; Gan, Y.; Recent Progress in Drug Delivery. *Acta Pharm. Sin. B* **2019**, 9, 1145–1162. DOI: 10.1016/j.apsb.2019.08.003

[26] Del Valle, E.M.M.; Galán, M.A.; Carbonell, R.G.; Drug Delivery Technologies: The Way Forward in the New Decade. *Ind. Eng. Chem. Res.* **2009**, 48, 2475–2486,

DOI: 10.1021/ie800886m

[27] Yasmin, F.; Najeeb, H.; Shaikh, S.; Hasanain, M.; Naeem, U.; Moeed, A.; Koritala, T.; Hasan, S.; Surani, S.; Novel Drug Delivery Systems for Inflammatory Bowel Disease. *World J. Gastroenterol.* **2022**, 28, 1922–1933. DOI: 10.3748/wjg.v28.i18.1922

[28] Adepu, S.; Ramakrishna, S.; Controlled Drug Delivery Systems: Current Status and Future Directions. *Molecules* **2021**, 26, 5905. DOI: 10.3390/molecules26195905.

[29] Hutton, A.R.J.; Quinn, H.L.; McCague, P.J.; Jarrahian, C.; Rein-weston, A.; Co, P.S.; Gerth-guyette, E.; Zehrung, D.; Larrañeta, E.; Donnelly, R.F.; Transdermal Delivery of Vitamin K Using Dissolving Microneedles for the Prevention of Vitamin K Deficiency Bleeding. **2018**, 541, 56–63. DOI: 10.1016/j.ijpharm.2018.02.031

[30] Bora, P.; Kumar, L.; Bansal, A.K.; Microneedle Technology for Advanced Drug Delivery : Evolving Vistas. *Crips* **2008**, 9, 7–10.

[31] Zhu, M.; Liu, Y.; Jiang, F.; Cao, J.; Kundu, S.C.; Lu, S.; Combined Silk Fibroin Microneedles for Insulin Delivery. *ACS Biomater. Sci. Eng.* **2020**, 6, 3422–3429. DOI: 10.1021/acsbiomaterials.0c00273

[32] Bhatnagar, S.; Kumari, P.; Pattarabhiran, S.P.; Venuganti, V.V.K.; Zein Microneedles for Localized Delivery of Chemotherapeutic Agents to Treat Breast Cancer: Drug Loading, Release Behavior, and Skin Permeation Studies. *AAPS PharmSciTech* **2018**, 19, 1818–1826. DOI: 10.1208/s12249-018-1004-5

[33]Amreddy, N.; Babu, A.; Muralidharan, R.; Panneerselvam, J.; Srivastava, A.; Ahmed, R.; Mehta, M.; Munshi, A.; Ramesh, R.; Recent Advances in Nanoparticle-Based Cancer Drug and Gene Delivery. *Adv. Cancer Res.* **2018**, 137, 115–170. DOI: 10.1016/bs.acr.2017.11.003

[34] Jacob, S.; Nair, A.B.; Shah, J.; Emerging Role of Nanosuspensions in Drug Delivery Systems. *Biomater. Res.* **2020**, 24, 3. DOI: 10.1186/s40824-020-0184-8

[35] Bose, A.; Roy Burman, D.; Sikdar, B.; Patra, P.; Nanomicelles: Types, Properties and Applications in Drug Delivery. *IET nanobiotechnology* **2021**, 15, 19–27. DOI: 10.1049/nbt2.12018

[36] Wang, X.; Wang, S.; Zhang, Y.; Advance of the Application of Nano-Controlled Release System in Ophthalmic Drug Delivery. *Drug Deliv.* **2016**, 23, 2897–2901. DOI: 10.3109/10717544.2015.1116025

[37] Akhter, M.H.; Ahmad, I.; Alshahrani, M.Y.; Al-Harbi, A.I.; Khalilullah, H.; Afzal, O.; Altamimi, A.S.A.; Najib Ullah, S.N.M.; Ojha, A.; Karim, S.; Drug Delivery Challenges and Current Progress in Nanocarrier-Based Ocular Therapeutic System. *Gels* **2022**, 8, DOI: 10.3390/gels8020082

[38] Tawfik, M.; Chen, F.; Goldberg, J.L.; Sabel, B.A.; Nanomedicine and Drug Delivery to the Retina: Current Status and Implications for Gene Therapy. *Naunyn-Schmiedeberg's Arch Pharmacol* **2022**, 395, 1477-1507. DOI: 10.1007/s00210-022-02287-3

[39] Qamar, Z.; Qizilbash, F.F.; Iqubal, M.K.; Ali, A.; Narang, J.K.; Ali, J.; Baboota, S.; Nano-Based Drug Delivery System: Recent Strategies for the Treatment of Ocular Disease and Future Perspective. *Recent Pat. Drug Deliv. Formul.* **2019**, 13, 246–254. DOI: 10.2174/1872211314666191224115211

[40] Pérez-Herrero, E.; Fernández-Medarde, A.; Advanced Targeted Therapies in Cancer: Drug Nanocarriers, the Future of Chemotherapy. *Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft fur Pharm. Verfahrenstechnik e.V* **2015**, 93, 52–79. DOI: 10.1016/j.ejpb.2015.03.018

[41] Gisbert-Garzarán, M.; Lozano, D.; Vallet-Regí, M.; Mesoporous Silica Nanoparticles for Targeting Subcellular Organelles. *Int. J. Mol. Sci.* **2020**, 21, 9696. DOI: 10.3390/ijms21249696.

[42] Matea, C.T.; Mocan, T.; Tabaran, F.; Pop, T.; Mosteanu, O.; Puia, C.; Iancu, C.; Mocan, L.; Quantum Dots in Imaging, Drug Delivery and Sensor Applications. *Int. J. Nanomedicine* **2017**, 12, 5421–5431. DOI: 10.2147/IJN.S138624

[43] Banerjee, A.; Mitragotri, S.; Intestinal Patch Systems for Oral Drug Delivery. *Curr. Opin. Pharmacol.* **2017**, 36, 58–65. DOI: 10.1016/j.coph.2017.08.005

[44] Chen, Z.; Wan, L.; Yuan, Y.; Kuang, Y.; Xu, X.; Liao, T.; Liu, J.; Xu, Z.Q.; Jiang, B.; Li, C.; PH/GSH-Dual-Sensitive Hollow Mesoporous Silica Nanoparticle-Based Drug Delivery System for Targeted Cancer Therapy. *ACS Biomater. Sci. Eng.* **2020**, 6, 3375–3387. DOI: 10.1021/acsbiomaterials.0c00073

[45] Courtenay, A.J.; Mcalister, E.; Mccrudden, M.T.C.; Vora, L.; Steiner, L.; Levin, G.; Levy-nissenbaum, E.; Shterman, N.; Kearney, M.; Mccarthy, H.O.; et al. Hydrogel-Forming Microneedle Arrays as a Therapeutic Option for Transdermal Esketamine Delivery. *J. Control. Release* **2020**, 322, 177–186. DOI: 10.1016/j.jconrel.2020.03.026

[46]Morgan, J.R.; Wang, J.; Barocas, J.A.; Jaeger, J.L.; Durham, N.N.; Babakhanlou-Chase, H.; Bharel, M.; Walley, A.Y.; Linas, B.P.; Opioid Overdose and Inpatient Care for Substance Use Disorder Care in Massachusetts. *J. Subst. Abuse Treat.* **2020**, 112, 42-48. DOI: 10.1016/j.jsat.2020.01.017

[47] Zellner, T.; Prasa, D.; Färber, E.; Hoffmann-Walbeck, P.; Genser, D.; Eyer, F.; The Use of Activated Charcoal to Treat Intoxications. *Dtsch. Arztebl. Int.* **2019**, 116, 311–317. DOI: 10.3238/arztebl.2019.0311

[48] Müller, D.; Desel, H.; Common Causes of Poisoning: Etiology, Diagnosis and Treatment.

Dtsch. Arztebl. Int. **2013**, 110, 690–700. DOI: 10.3238/arztebl.2013.0690

[49] Hassen, J.H.; Abdulkadir, H.K.; Recent Developments in the Use of Activated Charcoal in Medicine. *J. Med. Sci.* **2022**, 91, e647. DOI: 10.20883/medical.e647

[50] Song, Y.; Manian, M.; Fowler, W.; Korey, A.; Kumar Banga, A.; Activated Carbon-Based System for the Disposal of Psychoactive Medications. *Pharmaceutics* **2016**, 8, 31. DOI: 10.3390/pharmaceutics8040031

[51] Graudins, A.; Lee, H.M.; Druda, D.; Calcium Channel Antagonist and Beta-Blocker Overdose: Antidotes and Adjunct Therapies. *Br. J. Clin. Pharmacol.* **2016**, 81, 453–461. DOI: 10.1111/bcp.12763

[52] Chiew, A.L.; Gluud, C.; Brok, J.; Buckley, N.A.; Interventions for Paracetamol (Acetaminophen) Overdose. *Cochrane database Syst. Rev.* **2018**, 2, CD003328. DOI: 10.1002/14651858.CD003328.pub3

[53] An, H.; Godwin, J.; Flumazenil in Benzodiazepine Overdose. *C. Can. Med. Assoc. J. = J. l'Association medicale Can.* **2016**, 188, E537. DOI: 10.1503/cmaj.160357

[54] Hood, S.D.; Norman, A.; Hince, D.A.; Melichar, J.K.; Hulse, G.K.; Benzodiazepine Dependence and Its Treatment with Low Dose Flumazenil. *Br. J. Clin. Pharmacol.* **2014**, 77, 285–294 DOI: 10.1111/bcp.12023.

[55] Madhuri, P.; Mukherjee, A.; Manna, S.; Dhar, M.; Amitraz Poisoning: Early Gastric Lavage Can Prevent Life-Threatening Complications. *J. Fam. Med. Prim. care* **2020**, 9, 2129–2131. DOI: 10.4103/jfmpc.jfmpc_1268_19

[56] Zavaliy, L.B.; Petrikov, S.S.; Simonova, A.Y.; Potskhveriya, M.M.; Zaker, F.; Ostapenko, Y.N.; Ilyashenko, K.K.; Dikaya, T.I.; Shakhova, O.B.; Evseev, A.K.; et al. Diagnosis and Treatment of Persons with Acute Thallium Poisoning. *Toxicol. reports* **2021**, 8, 277–281. DOI: 10.1016/j.toxrep.2021.01.013

[57] Orellana-tavra, C.; Ko, M.; Li, A.; Stock, N.; Fairen-jimenez, D.; Biocompatible, Crystalline, and Amorphous Bismuth-Based Metal – Organic Frameworks for Drug Delivery. *ACS Appl. Mater. Interfaces* **2020**, 12, 5633-5641. DOI: 10.1021/acsami.9b21692

[58] Chedid, G.; Yassin, A.; Recent Trends in Covalent and Metal Organic Frameworks for Biomedical Applications. *Nanomaterials* **2018**, 8, 1–27. DOI: 10.3390/nano8110916

[59] Saeb, M.R.; Rabiee, N.; Mozafari, M.; Mostafavi, E.; Metal-Organic Frameworks (MOFs)-Based Nanomaterials for Drug Delivery. *Materials* **2021**, 14, 3652. DOI: 10.3390/ma14133652

[60] He, S.; Wu, L.; Li, X.; Sun, H.; Xiong, T.; Liu, J.; Metal-Organic Frameworks for Advanced Drug Delivery. *Acta Pharmaceutica Sinica B* **2021**, 11, 2362-2395.

DOI: 10.1016/j.apsb.2021.03.019

[61] Lawson, H.D.; Walton, S.P.; Chan, C.; Metal-Organic Frameworks for Drug Delivery: A Design Perspective. *ACS Appl. Mater. Interfaces* **2021**, 13, 7004–7020. DOI: 10.1021/acsami.1c01089

[62] Osterrieth, J.W.M.; Fairen-Jimenez, D.; Metal–Organic Framework Composites for Theragnostics and Drug Delivery Applications. *Biotechnol. J.* **2021**, 16, 2000005. DOI: 10.1002/biot.202000005

[63] Cai, W.; Wang, J.; Chu, C.; Chen, W.; Wu, C.; Liu, G.; Metal – Organic Framework-Based Stimuli-Responsive Systems for Drug Delivery. *Advanced Science* **2019**, 6, *1801526*, DOI: 10.1002/advs.201801526

[64] Strauss, I.; Chakarova, K.; Mundstock, A.; Mihaylov, M.; Hadjiivanov, K.; Guschanski, N.; Caro, J.; UiO-66 and UiO-66-NH 2 Based Sensors : Dielectric and FTIR Investigations on the Effect of CO_2 Adsorption. *Microporous Mesoporous Mater.* **2020**, 302, 110227. DOI: 10.1016/j.micromeso.2020.110227

[65] Imanipoor, J.; Mohammadi, M.; Dinari, M.; Ehsani, M.R.; Adsorption and Desorption of Amoxicillin Antibiotic from Water Matrices Using an Effective and Recyclable MIL-53(Al) Metal-Organic Framework Adsorbent. *J. Chem. Eng. Data* **2021**, 66, 389–403. DOI: 10.1021/acs.jced.0c00736

[66] Jonckheere, D.; Steele, J.A.; Claes, B.; Bueken, B.; Claes, L.; Lagrain, B.; Roeffaers, M.B.J.; De Vos, D.E.; Adsorption and Separation of Aromatic Amino Acids from Aqueous Solutions Using Metal-Organic Frameworks. *ACS Appl. Mater. Interfaces* **2017**, 9, 30064–30073. DOI: 10.1021/acsami.7b09175

[67] Taghvimi, A.; Tabrizi, A.B.; Dastmalchi, S.; Javadzadeh, Y.; Metal Organic Framework Based Carbon Porous as an Efficient Dispersive Solid Phase Extraction Adsorbent for Analysis of Methamphetamine from Urine Matrix. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2019**, 1109, 149–154. DOI: 10.1016/j.jchromb.2019.02.005

[68] Gangu, K.K.; Maddila, S.; Mukkamala, S.B.; Jonnalagadda, S.B.; A Review on Contemporary Metal-Organic Framework Materials. *Inorganica Chim. Acta* **2016**, 446, 61–74. DOI: 10.1016/j.ica.2016.02.062

[69] Hoskins, B.F.; Robson, R.; Infinite Polymeric Frameworks Consisting of Three Dimensionally Linked Rod-like Segments. *J. Am. Chem. Soc.* **1989**, 111, 5962–5964. DOI: 10.1021/ja00197a079

[70] Hoskins, B.F.; Robson, R.; Infinite Polymeric Frameworks Consisting of Three Dimensionally Linked Rod-like Segments. *J. Am. Chem. Soc.* **1989**, 111, 5962–5964. DOI: 10.1021/ja00197a079

[71] Jones, C.W. Metal-Organic Frameworks and Covalent Organic Frameworks: Emerging Advances and Applications. *J. Am. Chem. Soc.* **2022**, 2, 1504–1505. DOI: 10.1021/jacsau.2c00376

[72] Gao, H.; Shen, H.; Wu, H.; Jing, H.; Sun, Y.; Liu, B.; Chen, Z.; Song, J.; Lu, L.; Wu, Z.; et al. Review of Pristine Metal-Organic Frameworks for Supercapacitors: Recent Progress and Perspectives. *Energy and Fuels* **2021**, 35, 12884–12901. DOI: 10.1021/acs.energyfuels.1c01722

[73] Rojas, S.; Arenas-Vivo, A.; Horcajada, P.; Metal-Organic Frameworks: A Novel Platform for Combined Advanced Therapies. *Coord. Chem. Rev.* **2019**, 388, 202–226. DOI: 10.1016/j.ccr.2019.02.032.

[74] Gao, X.; Zhai, M.; Guan, W.; Liu, J.; Liu, Z.; Damirin, A.; Controllable Synthesis of a Smart Multifunctional Nanoscale Metal-Organic Framework for Magnetic Resonance/Optical Imaging and Targeted Drug Delivery. *ACS Appl. Mater. Interfaces* **2017**, 9, 3455–3462, DOI: 10.1021/acsami.6b14795

[75]Zhao, J.; Yin, F.; Ji, L.; Wang, C.; Shi, C.; Liu, X.; Yang, H.; Wang, X.; Kong, L.; Development of a Tau-Targeted Drug Delivery System Using a Multifunctional Nanoscale Metal-Organic Framework for Alzheimer's Disease Therapy. *ACS Appl. Mater. Interfaces* **2020**, 12, 44447–44458. DOI: 10.1021/acsami.0c11064

[76] Yaghi, O.M.; O'Keeffe, M.; Ockwig, N.W.; Chae, H.K.; Eddaoudi, M.; Kim, J.; Reticular Synthesis and the Design of New Materials. *Nature* **2003**, 423, 705–714. DOI: 10.1038/nature01650

[77] Haldar, R.; Maji, T.K.; Metal-Organic Frameworks (MOFs) Based on Mixed Linker Systems: Structural Diversities towards Functional Materials. *CrystEngComm* **2013**, 15, 9276–9295. DOI: 10.1039/c3ce41438h

[78] Perera, I.R.; Hettiarachchi, C. V; Ranatunga, U.; 7. Metal – Organic Frameworks in Dye-Sensitized Solar Cells, in.: Advances in Solar Energy Research, (Ed.:Tyagi, H; Agarwal, A.K.; Chakraborty, P.R.; Powar, S.) **2019**, Springer Singapore. ISBN 9789811333026

[79] Horcajada, P.; Gref, R.; Baati, T.; Allan, P.K.; Maurin, G.; Couvreur, P.; Férey, G.; Morris, R.E.; Serre, C.; Metal–Organic Frameworks in Biomedicine. *Chem. Rev.* **2012**, 112, 1232–1268. DOI: 10.1021/cr200256v

[80] Wang, Y.; Yan, J.; Wen, N.; Xiong, H.; Cai, S.; He, Q.; Hu, Y.; Peng, D.; Liu, Z.; Liu, Y.; Metal-Organic Frameworks for Stimuli-Responsive Drug Delivery. *Biomaterials* **2020**, 230, 119619. DOI: 10.1016/j.biomaterials.2019.119619

[81] Gorban, I.E.; Soldatov, M.A.; Butova, V. V; Medvedev, P. V; Burachevskaya, O.A.; Belanova, A.; Zolotukhin, P.; Soldatov, A. V.; L -Leucine Loading and Release in

MIL-100 Nanoparticles. *Int. J. Mol. Sci.* **2020**, 21, 9758. DOI: 10.3390/ijms21249758

[82] Valenzano, L.; Civalleri, B.; Chavan, S.; Bordiga, S.; Nilsen, M.H.; Jakobsen, S.; Lillerud, K.P.; Lamberti, C.; Disclosing the Complex Structure of UiO-66 Metal Organic Framework: A Synergic Combination of Experiment and Theory. *Chem. Mater.* **2011**, 23, 1700–1718. DOI: 10.1021/cm1022882

[83] Abazari, R.; Reza Mahjoub, A.; Slawin, A.M.Z.; Carpenter-Warren, C.L.; Morphology- and Size-Controlled Synthesis of a Metal-Organic Framework under Ultrasound Irradiation: An Efficient Carrier for PH Responsive Release of Anti-Cancer Drugs and Their Applicability for Adsorption of Amoxicillin from Aqueous Solution. *Ultrason. Sonochem.* **2018**, 42, 594–608. DOI: 10.1016/j.ultsonch.2017.12.032

[84] Wang, T.C.; Vermeulen, N.A.; Kim, I.S.; Martinson, A.B.F.; Stoddart, J.F.; Hupp, J.T.; Farha, O.K.; Scalable Synthesis and Post-Modification of a Mesoporous Metal-Organic Framework Called NU-1000. *Nat. Protoc.* **2015**, 11, 149–162, DOI :10.1038/nprot.2016.001

[85] Proenza, Y.G.; Longo, R.L.; Simulation of the Adsorption and Release of Large Drugs by ZIF-8. *J. Chem. Inf. Model.* **2020**, 60, 644–652. DOI: 10.1021/acs.jcim.9b00893

[86] Kim, K.; Lee, S.; Jin, E.; Palanikumar, L.; Lee, J.H.; Kim, J.C.; Nam, J.S.; Jana, B.; Kwon, T.H.; Kwak, S.K.; et al. MOF × Biopolymer: Collaborative Combination of Metal-Organic Framework and Biopolymer for Advanced Anticancer Therapy. *ACS Appl. Mater. Interfaces* **2019**, 11, 27512–27520. DOI: 10.1021/acsami.9b05736

[87] Liu, M.; Zu, L.; Hudson, Z.M.; Mechanistic Principles for Engineering Hierarchical Porous Metal-Organic Frameworks. *ACS Nano* **2022**, 16, 13573–13594. DOI: 10.1021/acsnano.2c06587.

[88] Sun, Y.; Zheng, L.; Yang, Y.; Qian, X.; Fu, T.; Li, X.; Yang, Z.; Yan, H.; Cui, C.; Tan, W.; Metal–Organic Framework Nanocarriers for Drug Delivery in Biomedical Applications. *Nano-Micro Lett.* **2020**, 12, 1–29. DOI: 10.1007/s40820-020-00423-3

[89] Nalaparaju, A.; Jiang, J. Metal−Organic Frameworks for Liquid Phase Applications. *Adv. Sci.* **2021**, 8, 2003143. DOI: 10.1002/advs.202003143

[90] Chattopadhyay, K.; Mandal, M.; Maiti, D.K.; Smart Metal-Organic Frameworks for Biotechnological Applications: A Mini-Review. *ACS Appl. Bio Mater.* **2021**, 4, 8159–8171. DOI: 10.1021/acsabm.1c00982

[91] Baheri, T.; Yamini, Y.; Shamsayei, M.; Tabibpour, M.; Application of HKUST-1 Metal-Organic Framework as Coating for Headspace Solid-Phase Microextraction of Some Addictive Drugs. *J. Sep. Sci.* **2021**, 44, 2814–2823. DOI: 10.1002/jssc.202100070

[92]Wang, Z.; Liu, L.; Li, Z.; Goyal, N.; Du, T.; He, J.; Li, G.K.; Shaping of Metal-Organic

Frameworks: A Review. *Energy and Fuels* **2022**, 36, 2927–2944. DOI: 10.1021/acs.energyfuels.1c03426

[93] Peng, Y.; Krungleviciute, V.; Eryazici, I.; Hupp, J.T.; Farha, O.K.; Yildirim, T.; Methane Storage in Metal–Organic Frameworks: Current Records, Surprise Findings, and Challenges. *J. Am. Chem. Soc.* **2013**, 135, 11887–11894. DOI: 10.1021/ja4045289

[94]Pirzadeh, K.; Esfandiari, K.; Ghoreyshi, A.A.; Rahimnejad, M.; CO_2 and N_2 Adsorption and Separation Using Aminated UiO-66 and $Cu_3(BTC)_2$: A Comparative Study. *Korean Journal of Chemical Engineering* **2020**, 37, 513-524. DOI: 10.1007/s11814-019-0433-5

[95] Islamoglu, T.; Chen, Z.; Wasson, M.C.; Buru, C.T.; Kirlikovali, K.O.; Afrin, U.; Mian, M.R.; Farha, O.K.; Metal-Organic Frameworks against Toxic Chemicals. *Chem. Rev.* **2020**, 120, 8130–8160. DOI: 10.1021/acs.chemrev.9b00828

[96] Liu, X.; Liang, T.; Zhang, R.; Ding, Q.; Wu, S.; Li, C.; Lin, Y.; Ye, Y.; Zhong, Z.; Zhou, M.; Iron-Based Metal-Organic Frameworks in Drug Delivery and Biomedicine. *ACS Appl. Mater. Interfaces* **2021**, 13, 9643–9655. DOI: 10.1021/acsami.0c21486

[97] Cavka, J.H.; Jakobsen, S.; Olsbye, U.; Guillou, N.; Lamberti, C.; Bordiga, S.; Lillerud, K.P.; A New Zirconium Inorganic Building Brick Forming Metal Organic Frameworks with Exceptional Stability. *J. Am. Chem. Soc.* **2008**, 130, 13850–13851. DOI: 10.1021/ja8057953

[98] Wu, G.; Ma, J.; Li, S.; Guan, J.; Jiang, B.; Wang, L.; Li, J.; Wang, X.; Chen, L.; Magnetic Copper-Based Metal Organic Framework as an Effective and Recyclable Adsorbent for Removal of Two Fluoroquinolone Antibiotics from Aqueous Solutions. *J. Colloid Interface Sci.* **2018**, 528, 360–371. DOI: 10.1016/j.jcis.2018.05.105

[99] Zhou, J.; Tian, G.; Zeng, L.; Song, X.; Bian, X.W.; Nanoscaled Metal-Organic Frameworks for Biosensing, Imaging, and Cancer Therapy. *Adv. Healthc. Mater.* **2018**, 7, 1800022. DOI: 10.1002/adhm.201800022

[100] Akhter, S.; Mohd Zain, N.K.; Shalauddin, M.; Singh, V.K.; Misnon, I.I.; Sharma, R.K.; Das, S.; Basirun, W.J.; Johan, M.R.; Jose, R.; Tri-Metallic Co-Ni-Cu Based Metal Organic Framework Nanostructures for the Detection of an Anticancer Drug Nilutamide. *Sensors Actuators, A Phys.* **2021**, 325, 112711. DOI: 10.1016/j.sna.2021.112711.

[101] Dong, H.; Yang, G.X.; Zhang, X.; Meng, X. Bin; Sheng, J.L.; Sun, X.J.; Feng, Y.J.; Zhang, F.M.; Folic Acid Functionalized Zirconium-Based Metal–Organic Frameworks as Drug Carriers for Active Tumor-Targeted Drug Delivery. *Chem. - A Eur. J.* **2018**, 24, 17148–17154. DOI: 10.1002/chem.201804153

[102] Abazari, R.; Ataei, F.; Morsali, A.; Slawin, A.M.Z.; Carpenter-Warren, C.L.;

A Luminescent Amine-Functionalized Metal-Organic Framework Conjugated with Folic Acid as a Targeted Biocompatible PH-Responsive Nanocarrier for Apoptosis Induction in Breast Cancer Cells. *ACS Appl. Mater. Interfaces* **2019**, 11, 45442–45454. DOI: 10.1021/acsami.9b16473

[103] Hashemzadeh, A.; Amerizadeh, F.; Asgharzadeh, F.; Darroudi, M.; Avan, A.; Hassanian, S.M.; Landarani, M.; Khazaei, M.; Delivery of Oxaliplatin to Colorectal Cancer Cells by Folate-Targeted UiO-66-NH2. *Toxicol. Appl. Pharmacol.* **2021**, 423, 115573. DOI: 10.1016/j.taap.2021.115573

[104]Abánades Lázaro, I.; Haddad, S.; Rodrigo-Muñoz, J.M.; Orellana-Tavra, C.; Del Pozo, V.; Fairen-Jimenez, D.; Forgan, R.S.; Mechanistic Investigation into the Selective Anticancer Cytotoxicity and Immune System Response of Surface-Functionalized, Dichloroacetate-Loaded, UiO-66 Nanoparticles. *ACS Appl. Mater. Interfaces* **2018**, 10, 5255–5268. DOI: 10.1021/acsami.7b17756

[105] Fytory, M.; Arafa, K.K.; El Rouby, W.M.A.; Farghali, A.A.; Abdel-Hafiez, M.; El-Sherbiny, I.M.; Dual-Ligated Metal Organic Framework as Novel Multifunctional Nanovehicle for Targeted Drug Delivery for Hepatic Cancer Treatment. *Sci. Rep.* **2021**, 11, 19808. DOI: 10.1038/s41598-021-99407-5

[106] Ji, P.; Wang, L.; Wang, S.; Zhang, Y.; Qi, X.; Tao, J.; Wu, Z.; Hyaluronic Acid-Coated Metal-Organic Frameworks Benefit the ROS-Mediated Apoptosis and Amplified Anticancer Activity of Artesunate. *J. Drug Target.* **2020**, 28, 1096–1109. DOI: 10.1080/1061186X.2020.1781136

[107] Rojas, S.; Horcajada, P.; Metal – Organic Frameworks for the Removal of Emerging Organic Contaminants in Water. *Chem. Rev.* **2020**, 120, 8378-8415. DOI: 10.1021/acs.chemrev.9b00797

[108] Chowdhuri, A.R.; Singh, T.; Ghosh, S.K.; Sahu, S.K. Carbon Dots Embedded Magnetic Nanoparticles @Chitosan @Metal Organic Framework as a Nanoprobe for PH Sensitive Targeted Anticancer Drug Delivery. *ACS Appl. Mater. Interfaces* **2016**, 8, 16573–16583. DOI: 10.1021/acsami.6b03988

[109] Abánades Lázaro, I.; Haddad, S.; Rodrigo-Muñoz, J.M.; Marshall, R.J.; Sastre, B.; Del Pozo, V.; Fairen-Jimenez, D.; Forgan, R.S.; Surface-Functionalization of Zr-Fumarate MOF for Selective Cytotoxicity and Immune System Compatibility in Nanoscale Drug Delivery. *ACS Appl. Mater. Interfaces* **2018**, 10, 31146–31157. DOI: 10.1021/acsami.8b11652.

[110] Chen, D.; Yang, D.; Dougherty, C.A.; Lu, W.; Wu, H.; He, X.; Cai, T.; Van Dort, M.E.; Ross, B.D.; Hong, H.; In Vivo Targeting and Positron Emission Tomography Imaging

of Tumor with Intrinsically Radioactive Metal-Organic Frameworks Nanomaterials. *ACS Nano* **2017**, 11, 4315–4327. DOI: 10.1021/acsnano.7b01530

[111] Liang, Z.; Yang, Z.; Yuan, H.; Wang, C.; Qi, J.; Liu, K.; Cao, R.; Zheng, H.; A Protein@metal-Organic Framework Nanocomposite for PH-Triggered Anticancer Drug Delivery. *Dalt. Trans.* **2018**, 47, 10223–10228. DOI: 10.1039/c8dt01789a

[112] Ren, S.Z.; Zhu, D.; Zhu, X.H.; Wang, B.; Yang, Y.S.; Sun, W.X.; Wang, X.M.; Lv, P.C.; Wang, Z.C.; Zhu, H.L.; Nanoscale Metal-Organic-Frameworks Coated by Biodegradable Organosilica for PH and Redox Dual Responsive Drug Release and High-Performance Anticancer Therapy. *ACS Appl. Mater. Interfaces* **2019**, 11, 20678–20688. DOI: 10.1021/acsami.9b04236.

[113] Hu, Z.; Qiao, C.; Xia, Z.; Li, F.; Han, J.; Wei, Q.; Yang, Q.; Xie, G.; Chen, S.; Gao, S.; A Luminescent Mg-Metal-Organic Framework for Sustained Release of 5-Fluorouracil: Appropriate Host-Guest Interaction and Satisfied Acid-Base Resistance. *ACS Appl. Mater. Interfaces* **2020**, 12, 14914–14923. DOI: 10.1021/acsami.0c01198

[114] Liu, W.; Zhong, Y.; Wang, X.; Zhuang, C.; Chen, J.; Liu, D.; Xiao, W.; Pan, Y.; Huang, J.; Liu, J.; A Porous Cu(II)-Based Metal-Organic Framework Carrier for PH-Controlled Anticancer Drug Delivery. *Inorg. Chem. Commun.* **2020**, 111, 107675. DOI: 10.1016/j.inoche.2019.107675

[115] Zhao, H.; Zhao, Y.; Liu, D.; pH and H_2S Dual-Responsive Magnetic Metal-Organic Frameworks for Controlling the Release of 5-Fluorouracil. *ACS Appl. Bio Mater.* **2021**, 4, 7103–7110. DOI: 10.1021/acsabm.1c00710

[116] Yang, J.C.; Chen, Y.; Li, Y.H.; Yin, X.B.; Magnetic Resonance Imaging-Guided Multi-Drug Chemotherapy and Photothermal Synergistic Therapy with PH and NIR-Stimulation Release. *ACS Appl. Mater. Interfaces* **2017**, 9, 22278–22288. DOI: 10.1021/acsami.7b06105

[117]Gao, X.; Zhai, M.; Guan, W.; Liu, J.; Liu, Z.; Controllable Synthesis of a Smart Multifunctional Nanoscale Metal – Organic Framework for Magnetic Resonance / Optical Imaging and Targeted Drug Delivery. *ACS Appl. Mater. Interfaces* **2017**, 9, 3455-3462. DOI: 10.1021/acsami.6b14795

[118] Cui, R.; Zhao, P.; Yan, Y.; Bao, G.; Damirin, A.; Liu, Z.; Outstanding Drug-Loading/Release Capacity of Hollow Fe-Metal-Organic Framework-Based Microcapsules: A Potential Multifunctional Drug-Delivery Platform. *Inorg. Chem.* **2021**, 60, 1664–1671. DOI: 10.1021/acs.inorgchem.0c03156

[119] Xue, Y.; Zheng, S.; Xue, H.; Pang, H.; Metal-Organic Framework Composites and Their Electrochemical Applications. *J. Mater. Chem. A* **2019**, 7, 7301–7327. DOI:

10.1039/C8TA12178H

[120] Mallakpour, S.; Nikkhoo, E.; Hussain, C.M.; Application of MOF Materials as Drug Delivery Systems for Cancer Therapy and Dermal Treatment. *Coord. Chem. Rev.* **2022**, 451, 214262. DOI: 10.1016/j.ccr.2021.214262

[121] Duan, W.; Qiao, S.; Zhuo, M.; Sun, J.; Guo, M.; Xu, F.; Liu, J.; Wang, T.; Guo, X.; Zhang, Y.; et al. Multifunctional Platforms: Metal-Organic Frameworks for Cutaneous and Cosmetic Treatment. *Chem* **2021**, 7, 450–462. DOI: 10.1016/j.chempr.2020.11.018

[122] Sohrabi, H.; Javanbakht, S.; Oroojalian, F.; Rouhani, F.; Shaabani, A.; Majidi, M.R.; Hashemzaei, M.; Hanifehpour, Y.; Mokhtarzadeh, A.; Morsali, A.; Nanoscale Metal-Organic Frameworks: Recent Developments in Synthesis, Modifications and Bioimaging Applications. *Chemosphere* **2021**, 281, 130717. DOI: 10.1016/j.chemosphere.2021.130717.

[123] Bellido, E.; Guillevic, M.; Hidalgo, T.; Santander-Ortega, M.J.; Serre, C.; Horcajada, P.; Understanding the Colloidal Stability of the Mesoporous MIL-100(Fe) Nanoparticles in Physiological Media. *Langmuir* **2014**, 30, 5911–5920. DOI: 10.1021/la5012555

[124] Siadati, S.A.; Rezazadeh, S. The Extraordinary Gravity of Three Atom 4π-Components and 1,3-Dienes to C20-NXn Fullerenes; a New Gate to the Future of Nano Technology. *Sci. Radices* **2022**, 01, 46–68. DOI: 10.58332/v22i1a04

[125] Zhao, D.; Zhang, W.; Wu, Z.H.; Xu, H.; Nanoscale Metal−Organic Frameworks and Their Nanomedicine Applications. *Front. Chem.* **2022**, 9, 834171. DOI: 10.3389/fchem.2021.834171.

[126] Zhong, X. fang; Sun, X.; Nanomedicines Based on Nanoscale Metal-Organic Frameworks for Cancer Immunotherapy. *Acta Pharmacol. Sin.* **2020**, 41, 928–935. DOI: 10.1038/s41401-020-0414-6

[127] Yusuf, V.F.; Malek, N.I.; Kailasa, S.K.; Review on Metal-Organic Framework Classification, Synthetic Approaches, and Influencing Factors: Applications in Energy, Drug Delivery, and Wastewater Treatment. *ACS Omega* **2022**, 7, 44507–44531. DOI: 10.1021/acsomega.2c05310

[128] Butova, V. V; Soldatov, M.A.; Guda, A.A.; Lomachenko, K.A.; Lamberti, C.; Metal-Organic Frameworks: Structure, Properties, Methods of Synthesis and Characterization. *Russ. Chem. Rev.* **2016**, 85, 280–307. DOI: 10.1070/rcr4554

[129] Yuan, G.; Tan, L.; Wang, P.; Wang, Y.; Wang, C.; Yan, H.; Wang, Y.Y.; MOF-COF Composite Photocatalysts: Design, Synthesis, and Mechanism. *Cryst. Growth Des.* **2022**, 22, 893–908. DOI: 10.1021/acs.cgd.1c01071

[130] Akeremale, O.K.; Ore, O.T.; Bayode, A.A.; Badamasi, H.; Adedeji, J.; Durodola, S.S.;

Results in Chemistry Synthesis , Characterization , and Activation of Metal Organic Frameworks (MOFs) for the Removal of Emerging Organic Contaminants through the Adsorption-Oriented Process : A Review. *Results Chem.* **2023**, 5, 100866. DOI: 10.1016/j.rechem.2023.100866

[131] Hausdorf, S.; Baitalow, F.; Seidel, J.; Mertens, F.O.R.L.; Gaseous Species as Reaction Tracers in the Solvothermal Synthesis of the Zinc Oxide Terephthalate MOF-5. *J. Phys. Chem. A* **2007**, 111, 4259–4266. DOI: 10.1021/jp0708291

[132] Scheurle, P.I.; Mähringer, A.; Haug, T.; Biewald, A.; Axthammer, D.; Hartschuh, A.; Harms, L.; Wittstock, G.; Medina, D.D.; Bein, T.; Helical Anthracene-Ethyne-Based MOF-74 Analogue. *Cryst. Growth Des.* **2022**, 22, 2849–2853. DOI: 10.1021/acs.cgd.1c01145

[133] Ma, D.; Han, G.; Gao, Z.F.; Chen, S.B.; Continuous UiO-66-Type Metal-Organic Framework Thin Film on Polymeric Support for Organic Solvent Nanofiltration. *ACS Appl. Mater. Interfaces* **2019**, 11, 45290-45300. DOI: 10.1021/acsami.9b16332

[134] Pichon, A.; Lazuen-Garay, A.; James, S.L.; Solvent-Free Synthesis of a Microporous Metal-Organic Framework. *CrystEngComm* **2006**, 8, 211–214. DOI: 10.1039/b513750k

[135] Taheri, M.; Bernardo, I. Di; Lowe, A.; Nisbet, D.R.; Tsuzuki, T.; Green Full Conversion of ZnO Nanopowders to Well-Dispersed Zeolitic Imidazolate Framework-8 (ZIF-8) Nanopowders via a Stoichiometric Mechanochemical Reaction for Fast Dye Adsorption. *Cryst. Growth Des.* **2020**, 20, 2761–2773. DOI: 10.1021/acs.cgd.0c00129

[136] Couzon, N.; Ferreira, M.; Duval, S.; El-Achari, A.; Campagne, C.; Loiseau, T.; Volkringer, C.; Microwave-Assisted Synthesis of Porous Composites MOF-Textile for the Protection against Chemical and Nuclear Hazards. *ACS Appl. Mater. Interfaces* **2022**, 14, 21497-21508. DOI: 10.1021/acsami.2c03247

[137] Babu, R.; Roshan, R.; Kathalikkattil, A.C.; Kim, D.W.; Park, D.W.; Rapid, Microwave-Assisted Synthesis of Cubic, Three-Dimensional, Highly Porous MOF-205 for Room Temperature CO_2 Fixation via Cyclic Carbonate Synthesis. *ACS Appl. Mater. Interfaces* **2016**, 8, 33723–33731. DOI: 10.1021/acsami.6b12458

[138] Qiu, M.; Guan, Q.; Li, W.; Controllable Assembly of Al-MIL-100 via an Inducing Occupied Effect and Its Selective Adsorption Activity. *Cryst. Growth Des.* **2016**, 16, 3639–3646. DOI: 10.1021/acs.cgd.6b00103

[139] Andrade, P.H.M.; Henry, N.; Volkringer, C.; Loiseau, T.; Vezin, H.; Hureau, M.; Moissette, A.; Iodine Uptake by Zr-/Hf-Based UiO-66 Materials: The Influence of Metal Substitution on Iodine Evolution. *ACS Appl. Mater. Interfaces* **2022**, 14, 29916–29933. DOI: 10.1021/acsami.2c07288

[140] Tao, C.A.; Hu, Z.; Meng, L.; Wang, F.; Wang, J.; Sonochemical Synthesis of Photoluminescent Nanoscale Eu(III)-Containing Metal-Organic Frameworks. *Medziagotyra* **2015**, 21, 554–558. DOI: 10.5755/j01.ms.21.4.9695

[141] Li, Z.-Q.; Qiu, L.-G.; Xu, T.; Wu, Y.; Wang, W.; Wu, Z.-Y.; Jiang, X.; Ultrasonic Synthesis of the Microporous Metal–Organic Framework $Cu_3(BTC)_2$ at Ambient Temperature and Pressure: An Efficient and Environmentally Friendly Method. *Mater. Lett.* **2009**, 63, 78–80. DOI: 10.1016/j.matlet.2008.09.010

[142] Ho, P.H.; Salles, F.; Renzo, F. Di; Trens, P.; Nationale, E.; Chimie, S. De; Charles, I.; One-Pot Synthesis of 5-FU @ ZIF-8 and Ibuprofen @ ZIF-8 Nanoparticles. DOI: 10.1016/j.ica.2019.119229

[143] Jodłowski, P.J.; Kurowski, G.; Dymek, K.; Oszajca, M.; Piskorz, W.; Hyjek, K.; Wach, A.; Pajdak, A.; Mazur, M.; Rainer, D.N.; et al. From Crystal Phase Mixture to Pure Metal-Organic Frameworks – Tuning Pore and Structure Properties. *Ultrason. Sonochem.* **2023**, 95, 106377. DOI: 10.1016/j.ultsonch.2023.106377

[144] Martinez Joaristi, A.; Juan-Alcañiz, J.; Serra-Crespo, P.; Kapteijn, F.; Gascon, J.; Electrochemical Synthesis of Some Archetypical Zn^{2+}, Cu^{2+}, and Al^{3+} Metal Organic Frameworks. *Cryst. Growth Des.* **2012**, 12, 3489–3498. DOI: 10.1021/cg300552w

[145] Gao, Z.; Lai, Y.; Zhang, L.; Lin, Y.; Xiao, L.; Luo, Y.; Luo, F.; Synthesis, Characterization, and Electrocatalytic Activity Exploration of MOF-74: A Research-Style Laboratory Experiment. *J. Chem. Educ.* **2021**, 98, 3341–3347. DOI: 10.1021/acs.jchemed.1c00583

[146] Li, X.; Lachmanski, L.; Safi, S.; Sene, S.; Serre, C.; Grenèche, J.M.; Zhang, J.; Gref, R.; New Insights into the Degradation Mechanism of Metal-Organic Frameworks Drug Carriers. *Sci. Rep.* **2017**, 7, 13142. DOI: 10.1038/s41598-017-13323-1

[147] Bishwas, M. Sen; Poddar, P.; Raman Spectroscopy-Based Sensitive, Fast and Reversible Vapour Phase Detection of Explosives Adsorbed on Metal–Organic Frameworks UiO-67. *New J. Chem.* **2021**, 45, 7145–7153. DOI: 10.1039/d0nj04915h

[148] Socrates, G.; Infrared and Raman Characteristic Group Frequencies: Tables and Charts. 2001, Wiley. ISBN 0471852988

[149] Roman, J.; Szumera, M.; Dymek, K.; Kurowski, G.; Kuterasin, Ł.; Sitarz, M.; Pajdak, A.; Kurach, Ł.; Boguszewska-czubara, A.; Jodłowaki, P.J.; In Search of Effective UiO-66 Metal – Organic Frameworks for Artificial Kidney Application. *ACS Appl. Mater. Interfaces* **2021**, 13, 45149-54160. DOI: 10.1021/acsami.1c05972

[150] Li, X.; Porcino, M.; Qiu, J.; Constantin, D.; Martineau-Corcos, C.; Gref, R.; Doxorubicin-Loaded Metal-Organic Frameworks Nanoparticles with Engineered Cyclodextrin

Coatings: Insights on Drug Location by Solid State Nmr Spectroscopy. *Nanomaterials* **2021**, 11, 945. DOI: 10.3390/nano11040945

[151] Du, X.; Fan, R.; Qiang, L.; Xing, K.; Ye, H.; Ran, X.; Song, Y.; Wang, P.; Yang, Y. Controlled Zn2+-Triggered Drug Release by Preferred Coordination of Open Active Sites within Functionalization Indium Metal Organic Frameworks. *ACS Appl. Mater. Interfaces* **2017,** 9, 28939–28948. DOI:10.1021/acsami.7b09227

[152] Jodłowski, P.J.; Dymek, K.; Kurowski, G.; Jaśkowska, J.; Bury, W.; Pander, M.; Wnorowska, S.; Targowska-Duda, K.; Piskorz, W.; Wnorowski, A.; et al. Zirconium-Based Metal–Organic Frameworks as Acriflavine Cargos in the Battle against Coronaviruses—A Theoretical and Experimental Approach. *ACS Appl. Mater. Interfaces* **2022**, 14, 25, 28615-28627. DOI:10.1021/acsami.2c06420

[153] Rezaei, M.; Abbasi, A.; Varshochian, R.; Dinarvand, R.; Jeddi-Tehrani, M. NanoMIL-100(Fe) Containing Docetaxel for Breast Cancer Therapy. *Artif. Cells, Nanomedicine Biotechnol.* **2018**, 46, 1390–1401. DOI:10.1080/21691401.2017.1369425

[154] Javanbakht, S.; Shadi, M.; Mohammadian, R.; Shaabani, A.; Amini, M.M.; Pooresmaeil, M.; Salehi, R. Facile Preparation of PH-Responsive k-Carrageenan/Tramadol Loaded UiO-66 Bio-Nanocomposite Hydrogel Beads as a Nontoxic Oral Delivery Vehicle. *J. Drug Deliv. Sci. Technol.* **2019**, 54, 101311. DOI:10.1016/j.jddst.2019.101311

[155] Shi, K.; Aviles-Espinosa, R.; Rendon-Morales, E.; Woodbine, L.; Salvage, J.P.; Maniruzzaman, M.; Nokhodchi, A. Magnetic Field Triggerable Macroporous PDMS Sponge Loaded with an Anticancer Drug, 5-Fluorouracil. *ACS Biomater. Sci. Eng.* **2021**, 7, 180–195. DOI:10.1021/acsbiomaterials.0c01608

[156] Ni, W.; Xiao, X.; Li, Y.; Li, L.; Xue, J.; Gao, Y.; Ling, F. DETA Impregnated Attapulgite Hybrid ZIF-8 Composite as an Adsorbent for the Adsorption of Aspirin and Ibuprofen in Aqueous Solution. *New J. Chem.* **2021**, 45, 5637–5644. DOI:10.1039/d0nj05743f

[157] Yang, B.; Wheeler, J..; Sorensen, B.; Steagall, R.; Nielson, T.; Yao, J.; Mendez-Arroyo, J.; Ess, D.H. Computational Determination of Coordination Structure Impact on Adsorption and Acidity of Pristine and Sulfated MOF-808. *Mater. Adv.* **2021**, 2, 4246–4254. DOI:10.1039/d1ma00330e

[158] Addicoat, M.A.; Vankova, N.; Akter, I.F.; Heine, T. Extension of the Universal Force Field to Metal–Organic Frameworks. *J. Chem. Theory Comput.* **2014**, 10, 880–891, DOI:10.1021/ct400952t

[159] Zhang, X.; Shi, X.; Zhao, Q.; Li, Y.; Wang, J.; Yang, Y.; Bi, F.; Xu, J.; Liu, N. Defects Controlled by Acid-Modulators and Water Molecules Enabled UiO-67 for Exceptional Toluene Uptakes : An Experimental and Theoretical Study. *Chem. Eng. J.* **2022**, 427,

131573. DOI:10.1016/j.cej.2021.131573.

[160] Shearer, G.C.; Chavan, S.; Bordiga, S.; Svelle, S.; Olsbye, U.; Lillerud, K.P. Defect Engineering: Tuning the Porosity and Composition of the Metal-Organic Framework UiO-66 via Modulated Synthesis. *Chem. Mater.* **2016**, 28, 3749–3761. DOI:10.1021/acs.chemmater.6b00602

[161] Feng, Y.; Chen, Q.; Jiang, M.; Yao, J. Tailoring the Properties of UiO-66 through Defect Engineering: A Review. *Ind. Eng. Chem. Res.* **2019**, 58, 17646–17659. DOI:10.1021/acs.iecr.9b03188

[162] Vermoortele, F.; Bueken, B.; Voorde, B. Van De; Vandichel, M.; Houthoofd, K.; Vimont, A.; Daturi, M.; Waroquier, M.; Speybroeck, V. Van; Kirschhock, C.; et al. Synthesis Modulation as a Tool To Increase the Catalytic Activity of Metal – Organic Frameworks: The Unique Case of UiO-66(Zr). *J. Am. Chem. Soc*. **2013**, 135, 31, 11465-11468. DOI: 10.1021/ja405078u

[163] Zhang, L.; Li, Y.; Yuan, S.; Zhang, S.; Zheng, H.; Liu, J. Bioactivity Focus of α -Cyano-4- Hydroxycinnamic Acid (CHCA) Leads to Effective Multifunctional Aldose Reductase Inhibitors. *Scientific Reports* , **2016**, 6, 1–13. DOI:10.1038/pj.2016.37

[164] Atzori, C.; Shearer, G.C.; Maschio, L.; Civalleri, B.; Bonino, F.; Lamberti, C.; Svelle, S.; Lillerud, K.P.; Bordiga, S. Effect of Benzoic Acid as a Modulator in the Structure of UiO-66: An Experimental and Computational Study. *J. Phys. Chem. C* **2017**, 121, 9312–9324. DOI:10.1021/acs.jpcc.7b00483

[165] Zahn, G.; Zerner, P.; Lippke, J.; Kempf, F.L.; Lilienthal, S.; Schröder, C.A.; Schneider, A.M.; Behrens, P. Insight into the Mechanism of Modulated Syntheses: In Situ Synchrotron Diffraction Studies on the Formation of Zr-Fumarate MOF. *CrystEngComm* **2014**, 16, 9198–9207. DOI:10.1039/c4ce01095g

[166] Mao, W.; Huang, R.; Xu, H.; Wang, H.; Huang, Y.; Huang, S.; Zhou, J. Effects of Acid Modulators on the Microwave-Assisted Synthesis of Cr/Sn Metal-Organic Frameworks. *Polymers (Basel).* **2022**, 14, 3826. DOI:10.3390/polym14183826

[167] Mocniak, K.A.; Kubajewska, I.; Spillane, D.E.M.; Williams, G.R.; Morris, R.E. Incorporation of Cisplatin into the Metal-Organic Frameworks UiO66-NH2 and UiO66-Encapsulation vs. Conjugation. *RSC Adv.* **2015**, 5, 83648–83656. DOI:10.1039/c5ra14011k

[168] Molavi, H.; Zamani, M.; Aghajanzadeh, M.; Kheiri Manjili, H.; Danafar, H.; Shojaei, A. Evaluation of UiO-66 Metal Organic Framework as an Effective Sorbent for Curcumin's Overdose. *Appl. Organomet. Chem.* **2018**, 32, 1–10. DOI:10.1002/aoc.4221

[169] Custelcean, R.; Gorbunova, M.G. A Metal−Organic Framework Functionalized with

Free Carboxylic Acid Sites and Its Selective Binding of a Cl(H2O)4- Cluster. *J. Am. Chem. Soc.* **2005**, 127, 16362–16363. DOI:10.1021/ja055528o

[170] Yin, X.B.; Sun, Y.Q.; Yu, H.; Cheng, Y.; Wen, C. Design and Multiple Applications of Mixed-Ligand Metal-Organic Frameworks with Dual Emission. *Anal. Chem.* **2022**, 94, 4938–4947. DOI:10.1021/acs.analchem.1c02949

[171] Mortazavi, S.-S.; Abbasi, A.; Masteri-Farahani, M. Influence of SO3H Groups Incorporated as Brønsted Acidic Parts by Tandem Post-Synthetic Functionalization on the Catalytic Behavior of MIL-101(Cr) MOF for Methanolysis of Styrene Oxide. *Colloids Surfaces A Physicochem. Eng. Asp.* **2020**, 599, 124703. DOI:10.1016/j.colsurfa.2020.124703

[172] Fan, G.; Dundas, C.M.; Zhang, C.; Lynd, N.A.; Keitz, B.K. Sequence-Dependent Peptide Surface Functionalization of Metal-Organic Frameworks. *ACS Appl. Mater. Interfaces* **2018**, 10, 18601–18609. DOI:10.1021/acsami.8b05148

[173] Ge, J.; Liu, L.; Shen, Y. Facile Synthesis of Amine-Functionalized UiO-66 by Microwave Method and Application for Methylene Blue Adsorption. *J. Porous Mater.* **2016**, 24, 647-655. DOI:10.1007/s10934-016-0301-1

[174] Molavi, H.; Moghimi, H.; Taheri, R.A. Zr-Based MOFs with High Drug Loading for Adsorption Removal of Anti-Cancer Drugs: A Potential Drug Storage. *Appl. Organomet. Chem.* **2020**, 34, 4–9. DOI:10.1002/aoc.5549

[175] Cunha, D.; Gaudin, C.; Colinet, I.; Horcajada, P.; Maurin, G.; Serre, C. Rationalization of the Entrapping of Bioactive Molecules into a Series of Functionalized Porous Zirconium Terephthalate MOFs. *J. Mater. Chem. B* . **2013**, 1, 1101–1108. DOI:10.1039/c2tb00366j

[176] Fantham, M.; Mishra, A.; Silvestre-albero, J.; Haddad, S.; Aba, I.; Osterrieth, J.W.M.; Schierle, G.S.K.; Kaminski, C.F.; Forgan, R.S.; Fairen-jimenez, D. Design of a Functionalized Metal – Organic Framework System for Enhanced Targeted Delivery to Mitochondria´. *J. Am. Chem. Soc.*, **2020**, 142, 6661-6674. DOI:10.1021/jacs.0c00188

[177] Abánades Lázaro, I.; Wells, C.J.R.; Forgan, R.S. Multivariate Modulation of the Zr MOF UiO-66 for Defect-Controlled Combination Anticancer Drug Delivery. *Angew. Chemie - Int. Ed.* **2020**, 59, 5211–5217. DOI:10.1002/anie.201915848

[178] Maranescu, B.; Visa, A. Applications of Metal-Organic Frameworks as Drug Delivery Systems. *Int. J. Mol. Sci.* **2022**, 23, 4458. DOI:10.3390/ijms23084458

[179] Zheng, H.; Zhang, Y.; Liu, L.; Wan, W.; Guo, P.; Nyström, A.M.; Zou, X. One-Pot Synthesis of Metal-Organic Frameworks with Encapsulated Target Molecules and Their Applications for Controlled Drug Delivery. *J. Am. Chem. Soc.* **2016**, 138, 962–968.

DOI:10.1021/jacs.5b11720

[180] Sun, X.; He, G.; Xiong, C.; Wang, C.; Lian, X.; Hu, L.; Li, Z.; Dalgarno, S.J.; Yang, Y.W.; Tian, J. One-Pot Fabrication of Hollow Porphyrinic MOF Nanoparticles with Ultrahigh Drug Loading toward Controlled Delivery and Synergistic Cancer Therapy. *ACS Appl. Mater. Interfaces* **2021**, 13, 3679–3693. DOI:10.1021/acsami.0c20617

[181] Vassaki, M.; Papathanasiou, K.E.; Hadjicharalambous, C.; Chandrinou, D.; Turhanen, P.; Choquesillo-Lazarte, D.; Demadis, K.D. Self-Sacrificial MOFs for Ultra-Long Controlled Release of Bisphosphonate Anti-Osteoporotic Drugs. *Chem. Commun.* **2020**, 56, 5166–5169. DOI:10.1039/d0cc00439a

[182] He, C.; Liu, D.; Lin, W. Nanomedicine Applications of Hybrid Nanomaterials Built from Metal-Ligand Coordination Bonds: Nanoscale Metal-Organic Frameworks and Nanoscale Coordination Polymers. *Chem. Rev.* **2015**, 115, 11079–11108. DOI:10.1021/acs.chemrev.5b00125

[183] Wang, X.; Wang, X.; Han, Y.; Li, H.; Kang, Q.; Wang, P.; Zhou, F. Immunoassay for Cardiac Troponin i with Fluorescent Signal Amplification by Hydrolyzed Coumarin Released from a Metal-Organic Framework. *ACS Appl. Nano Mater.* **2019**, 2, 7170–7177. DOI:10.1021/acsanm.9b01685

[184] Li, L.; Han, S.; Zhao, S.; Li, X.; Liu, B.; Liu, Y. Chitosan Modified Metal-Organic Frameworks as a Promising Carrier for Oral Drug Delivery. *RSC Adv.* **2020**, 10, 45130–45138. DOI:10.1039/d0ra08459j

[185] Winterlich, M.; Efthymiou, C.G.; Papawassiliou, W.; Carvalho, J.P.; Pell, A.J.; Mayans, J.; Escuer, A.; Carty, M.P.; McArdle, P.; Tylianakis, E.; et al. A Biocompatible ZnNa2-Based Metal-Organic Framework with High Ibuprofen, Nitric Oxide and Metal Uptake Capacity. *Mater. Adv.* **2020**, 1, 2248–2260. DOI:10.1039/d0ma00450b

[186] Pooresmaeil, M.; Namazi, H. D-Mannose Functionalized MgAl-LDH/Fe-MOF Nanocomposite as a New Intelligent Nanoplatform for MTX and DOX Co-Drug Delivery. *Int. J. Pharm.* **2022**, 625, 122112. DOI:10.1016/j.ijpharm.2022.122112

[187] Zhang, F.M.; Dong, H.; Zhang, X.; Sun, X.J.; Liu, M.; Yang, D.D.; Liu, X.; Wei, J.Z. Postsynthetic Modification of ZIF-90 for Potential Targeted Codelivery of Two Anticancer Drugs. *ACS Appl. Mater. Interfaces* **2017**, 9, 27332–27337. DOI:10.1021/acsami.7b08451

[188] Devautour-Vinot, S.; Martineau, C.; Diaby, S.; Ben-Yahia, M.; Miller, S.; Serre, C.; Horcajada, P.; Cunha, D.; Taulelle, F.; Maurin, G. Caffeine Confinement into a Series of Functionalized Porous Zirconium MOFs: A Joint Experimental/Modeling Exploration. *J. Phys. Chem. C* **2013**, 117, 11694–11704. DOI:10.1021/jp402916y

[189] Cunha, D.; Ben Yahia, M.; Hall, S.; Miller, S.R.; Chevreau, H.; Elkaïm, E.; Maurin, G.; Horcajada, P.; Serre, C. Rationale of Drug Encapsulation and Release from Biocompatible Porous Metal-Organic Frameworks. *Chem. Mater.* **2013**, 25, 2767–2776. DOI:10.1021/cm400798p

[190] Liang, K.; Ricco, R.; Doherty, C.M.; Styles, M.J.; Bell, S.; Kirby, N.; Mudie, S.; Haylock, D.; Hill, A.J.; Doonan, C.J.; et al. Biomimetic Mineralization of Metal-Organic Frameworks as Protective Coatings for Biomacromolecules. *Nat. Commun.* **2015**, 6, 4–11. DOI:10.1038/ncomms8240

[191] Li, S.; Dharmarwardana, M.; Welch, R.P.; Benjamin, C.E.; Shamir, A.M.; Nielsen, S.O.; Gassensmith, J.J. Investigation of Controlled Growth of Metal–Organic Frameworks on Anisotropic Virus Particles. *ACS Appl. Mater. Interfaces* **2018**, 10, 18161–18169. DOI:10.1021/acsami.8b01369

[192] Alsaiari, S.K.; Qutub, S.S.; Sun, S.; Baslyman, W.; Aldehaiman, M.; Alyami, M.; Almalik, A.; Halwani, R.; Merzaban, J.; Mao, Z.; et al. Sustained and Targeted Delivery of Checkpoint Inhibitors by Metal-Organic Frameworks for Cancer Immunotherapy. *Sci. Adv.* **2021**, 7, 1–11. DOI:10.1126/sciadv.abe7174

[193] Karimi Alavijeh, R.; Akhbari, K. Biocompatible MIL-101(Fe) as a Smart Carrier with High Loading Potential and Sustained Release of Curcumin. *Inorg. Chem.* **2020**, 59, 3570–3578. DOI:10.1021/acs.inorgchem.9b02756

[194] Cao, S.; Tang, T.; Xi, C.; Chen, Z. Fabricating Magnetic GO/ZIF-8 Nanocomposite for Amphetamine Adsorption from Water: Capability and Mechanism. *Chem. Eng. J.* **2021**, 422, 130096. DOI:10.1016/j.cej.2021.130096

[195] Usman, K.A.S.; Maina, J.W.; Seyedin, S.; Conato, M.T.; Payawan, L.M.; Dumée, L.F.; Razal, J.M. Downsizing Metal–Organic Frameworks by Bottom-up and Top-down Methods. *NPG Asia Mater.* **2020**, 12, 58. DOI:10.1038/s41427-020-00240-5

[196] Lei, B.; Wang, M.; Jiang, Z.; Qi, W.; Su, R.; He, Z. Constructing Redox-Responsive Metal-Organic Framework Nanocarriers for Anticancer Drug Delivery. *ACS Appl. Mater. Interfaces* **2018**, 10, 16698–16706. DOI:10.1021/acsami.7b19693

[197] Winarta, J.; Shan, B.; Mcintyre, S.M.; Ye, L.; Wang, C.; Liu, J.; Mu, B. A Decade of UiO-66 Research: A Historic Review of Dynamic Structure, Synthesis Mechanisms, and Characterization Techniques of an Archetypal Metal–Organic Framework. *Cryst. Growth Des.* **2020**, 20, 1347–1362. DOI:10.1021/acs.cgd.9b00955

[198] Dai, S.; Simms, C.; Dovgaliuk, I.; Patriarche, G.; Tissot, A.; Parac-vogt, T.N.; Serre, C. Monodispersed MOF-808 Nanocrystals Synthesized via a Scalable Room-Temperature Approach for E Ffi Cient Heterogeneous Peptide Bond Hydrolysis. *Chem. Mater.* **2021**,

33, 7057-7066. DOI:10.1021/acs.chemmater.1c02174

[199] Javanbakht, S.; Hemmati, A.; Namazi, H.; Heydari, A. Carboxymethylcellulose-Coated 5-Fluorouracil@MOF-5 Nano-Hybrid as a Bio-Nanocomposite Carrier for the Anticancer Oral Delivery. *Int. J. Biol. Macromol.* **2020**, 155, 876–882. DOI:10.1016/j.ijbiomac.2019.12.007

[200] Souza, B.E.; Möslein, A.F.; Titov, K.; Taylor, J.D.; Rudić, S.; Tan, J.C. Green Reconstruction of MIL-100 (Fe) in Water for High Crystallinity and Enhanced Guest Encapsulation. *ACS Sustain. Chem. Eng.* **2020**, 8, 8247–8255. DOI:10.1021/acssuschemeng.0c01471

[201] Li, A.; Yang, X.; Chen, J. A Novel Route to Size-Controlled MIL-53(Fe) Metal-Organic Frameworks for Combined Chemodynamic Therapy and Chemotherapy for Cancer. *RSC Adv.* **2021**, 11, 10540–10547. DOI:10.1039/d0ra09915e

[202] Bikiaris, N.D.; Ainali, N.M.; Christodoulou, E.; Kostoglou, M.; Kehagias, T.; Papasouli, E.; Koukaras, E.N.; Nanaki, S.G. Dissolution Enhancement and Controlled Release of Paclitaxel Drug via a Hybrid Nanocarrier Based on Mpeg-Pcl Amphiphilic Copolymer and Fe-Btc Porous Metal-Organic Framework. *Nanomaterials* **2020**, 10, 1–30. DOI:10.3390/nano10122490

[203] Leng, X.; Dong, X.; Wang, W.; Sai, N.; Yang, C.; You, L.; Huang, H.; Yin, X.; Ni, J. Biocompatible Fe-Based Micropore Metal-Organic Frameworks as Sustained-Release Anticancer Drug Carriers. *Molecules* **2018**, *23*, 1–13. DOI:10.3390/molecules23102490

[204] Chu, B.; Lan, C.; Yin, J.-H.; Liu, M.; Meng, L.; Xu, N. NH2-MIL-101(Fe) Nanozyme-Based Dual-Modality Sensor for Determination of Alendronate Sodium and Study of Two-Dimensional Correlation Spectroscopy. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **2022**, 283, 121752. DOI:10.1016/j.saa.2022.121752

[205] Golmohamadpour, A.; Bahramian, B.; Shafiee, A.; Ma'mani, L. Slow Released Delivery of Alendronate Using β-Cyclodextrine Modified Fe–MOF Encapsulated Porous Hydroxyapatite. *J. Inorg. Organomet. Polym. Mater.* **2018**, 28, 1991–2000. DOI:10.1007/s10904-018-0871-2

[206] Ruyra, A.; Yazdi, A.; Espín, J.; Carné-Sánchez, A.; Roher, N.; Lorenzo, J.; Imaz, I.; Maspoch, D. Synthesis, Culture Medium Stability, and in Vitro and in Vivo Zebrafish Embryo Toxicity of Metal-Organic Framework Nanoparticles. *Chem. - A Eur. J.* **2015**, 21, 2508–2518. DOI:10.1002/chem.201405380

[207] Denisov, G.L.; Primakov, P. V; Korlyukov, A.A. Solvothermal Synthesis of the Metal-Organic Framework MOF-5 in Autoclaves Prepared by 3D Printing. **2019**, 45, 836–

842. DOI:10.1134/S1070328419120030

[208] Li, J.; Cheng, S.; Zhao, Q.; Long, P.; Dong, J. Synthesis and Hydrogen-Storage Behavior of Metal – Organic Framework MOF-5. *Int. J. Hydrogen Energy* **2009**, 34, 1377–1382. DOI:10.1016/j.ijhydene.2008.11.048

[209] Yin, D.; Hu, X.; Cai, M.; Wang, K.; Peng, H.; Bai, J.; Xv, Y.; Fu, T.; Dong, X.; Ni, J.; et al. Preparation, Characterization, and In Vitro Release of Curcumin-Loaded IRMOF-10 Nanoparticles and Investigation of Their Pro-Apoptotic Effects on Human Hepatoma HepG2 Cells. *Molecules* **2022**, 27, 3940. DOI:10.3390/molecules27123940

[210] Zhong, T.; Li, D.; Li, C.; Zhang, Z.; Wang, G. Turn-on Fluorescent Sensor Based on Curcumin@MOF-5 for the Sensitive Detection of Al(3). *Anal. Methods* **2022**, 14, 2714–2722. DOI:10.1039/d2ay00849a

[211] Velásquez-Hernández, M.D.J.; Ricco, R.; Carraro, F.; Limpoco, F.T.; Linares-Moreau, M.; Leitner, E.; Wiltsche, H.; Rattenberger, J.; Schröttner, H.; Frühwirt, P.; et al. Degradation of ZIF-8 in Phosphate Buffered Saline Media. *CrystEngComm* **2019**, 21, 4538–4544. DOI:10.1039/c9ce00757a

[212] Jodłowski, P.J.; Kurowski, G.; Kuterasiński, Ł.; Sitarz, M.; Jeleń, P.; Jaśkowska, J.; Kołodziej, A.; Pajdak, A.; Majka, Z.; Boguszewska-Czubara, A. Cracking the Chloroquine Conundrum: The Application of Defective UiO-66 Metal-Organic Framework Materials to Prevent the Onset of Heart Defects : The Vivo and in Vitro. *ACS Appl. Mater. Interfaces* **2021**, 13, 312–323. DOI:10.1021/acsami.0c21508

[213] Saeb, M.R.; Rabiee, N.; Mozafari, M.; Verpoort, F.; Voskressensky, L.G.; Luque, R. Metal – Organic Frameworks (MOFs) for Cancer Therapy. *Materials* **2021**, 14, 7277. DOI: 10.3390/ma14237277

[214] Wang, Z.; Fu, Y.; Kang, Z.; Liu, X.; Chen, N.; Wang, Q.; Tu, Y.; Wang, L.; Song, S.; Ling, D.; et al. Organelle-Specific Triggered Release of Immunostimulatory Oligonucleotides from Intrinsically Coordinated DNA–Metal–Organic Frameworks with Soluble Exoskeleton. *J. Am. Chem. Soc.* **2017**, 139, 15784–15791. DOI:10.1021/jacs.7b07895

[215] He, L.; Liu, Y.; Lau, J.; Fan, W.; Li, Q.; Zhang, C. Recent Progress in Nanoscale Metal-Organic Frameworks for Drug Release and Cancer Therapy. *Nanomedicine* **2019**, 14, 1343–1365. DOI:10.2217/nnm-2018-0347

[216] Nurhayati, S.; Nisa, K.; Indrianingsih, A.W.; Darsih, C.; Kismurtono, M. Formulation and in Vitro Study of Propranolol Hydrochloride Controlled Release from Carboxymethyl Chitosan-Based Matrix Tablets. *Indones. J. Chem*. **2013**, 13, 242-247. DOI:10.22146/ijc.21283

[217] Lawson, S.; Rownaghi, A.A.; Rezaei, F. Combined Ibuprofen and Curcumin Delivery Using Mg-MOF-74 as a Single Nanocarrier. *ACS Appl. Bio Mater.* **2022**, 5, 265–271. DOI:10.1021/acsabm.1c01067

[218] Russo, V.; Hmoudah, M.; Broccoli, F.; Iesce, M.R.; Jung, O.-S.; Di Serio, M. Applications of Metal Organic Frameworks in Wastewater Treatment: A Review on Adsorption and Photodegradation. *Front. Chem. Eng.* **2020**, 2, 1–13. DOI:10.3389/fceng.2020.581487

[219] Bůžek, D.; Adamec, S.; Lang, K.; Demel, J. Metal-Organic Frameworks: Vs. Buffers: Case Study of UiO-66 Stability. *Inorg. Chem. Front.* **2021**, 8, 720–734. DOI:10.1039/d0qi00973c

[220] Awasthi, G.; Shivgotra, S.; Nikhar, S.; Sundarrajan, S.; Ramakrishna, S.; Kumar, P. Progressive Trends on the Biomedical Applications of Metal Organic Frameworks. *Polymers (Basel).* **2022**, 14, 1–29. DOI:10.3390/polym14214710

[221] Singh, N.; Qutub, S.; Khashab, N.M. Biocompatibility and Biodegradability of Metal Organic Frameworks for Biomedical Applications. *J. Mater. Chem. B* **2021**, 9, 5925–5934. DOI:10.1039/d1tb01044a

[222] Zhang, Y.; Yan, B. A Novel Cucurbit[7]Uril Anchored Bis-Functionalized Metal-Organic Framework Hybrid and Its Potential Use in Fluorescent Analysis of Illegal Stimulants in Saliva. *Sensors Actuators, B Chem.* **2020**, 324, 128656. DOI:10.1016/j.snb.2020.128656

[223] Sun, R.W.Y.; Zhang, M.; Li, D.; Li, M.; Wong, A.S.T. Enhanced Anti-Cancer Activities of a Gold(III) Pyrrolidinedithiocarbamato Complex Incorporated in a Biodegradable Metal-Organic Framework. *J. Inorg. Biochem.* **2016**, 163, 1–7. DOI:10.1016/j.jinorgbio.2016.06.020

[224] Pooresmaeil, M.; Asl, E.A.; Namazi, H. A New PH-Sensitive CS/Zn-MOF@GO Ternary Hybrid Compound as a Biofriendly and Implantable Platform for Prolonged 5-Fluorouracil Delivery to Human Breast Cancer Cells. *J. Alloys Compd.* **2021**, 885, 160992. DOI:10.1016/j.jallcom.2021.160992

[225] Liu, J.; Li, Y.; Lou, Z. Recent Advancements in MOF/Biomass and Bio-MOF Multifunctional Materials: A Review. *Sustain.* **2022**, 14, 1–17. DOI:10.3390/su14105768

[226] Anderson, S.L.; Stylianou, K.C. Biologically Derived Metal Organic Frameworks. *Coord. Chem. Rev.* **2017**, 349, 102–128. DOI:10.1016/j.ccr.2017.07.012

[227] Mon, M.; Bruno, R.; Lappano, R.; Maggiolini, M.; Di Donna, L.; Ferrando Soria, J.; Armentano, D.; Pardo, E. A Biocompatible Aspartic-Decorated Metal-Organic

Framework with Tubular Motif Degradable under Physiological Conditions. *Inorg. Chem.* **2021**, 60, 14221–14229. DOI:10.1021/acs.inorgchem.1c01701

[228] Khandelwal, G.; Maria Joseph Raj, N.P.; Vivekananthan, V.; Kim, S.-J. Biodegradable Metal-Organic Framework MIL-88A for Triboelectric Nanogenerator. *iScience* **2021**, 24, 102064. DOI:10.1016/j.isci.2021.102064

[229] Horcajada, P.; Chalati, T.; Serre, C.; Gillet, B.; Sebrie, C.; Baati, T.; Eubank, J.F.; Heurtaux, D.; Clayette, P.; Kreuz, C.; et al. Porous Metal-Organic-Framework Nanoscale Carriers as a Potential Platform for Drug Delivery and Imaging. *Nat. Mater.* **2010**, 9, 172–178. DOI:10.1038/nmat2608

[230] Colwell, K.A.; Jackson, M.N.; Torres-Gavosto, R.M.; Jawahery, S.; Vlaisavljevich, B.; Falkowski, J.M.; Smit, B.; Weston, S.C.; Long, J.R. Buffered Coordination Modulation as a Means of Controlling Crystal Morphology and Molecular Diffusion in an Anisotropic Metal-Organic Framework. *J. Am. Chem. Soc.* **2021**, 143, 5044–5052. DOI:10.1021/jacs.1c00136

[231] Bunzen, H. Chemical Stability of Metal-Organic Frameworks for Applications in Drug Delivery. *ChemNanoMat* **2021**, 7, 998–1007. DOI:10.1002/cnma.202100226

[232] Filippousi, M.; Turner, S.; Leus, K.; Siafaka, P.I.; Tseligka, E.D.; Vandichel, M.; Nanaki, S.G.; Vizirianakis, I.S.; Bikiaris, D.N.; Van Der Voort, P.; et al. Biocompatible Zr-Based Nanoscale MOFs Coated with Modified Poly(ε-Caprolactone) as Anticancer Drug Carriers. *Int. J. Pharm.* **2016**, 509, 208–218. DOI:10.1016/j.ijpharm.2016.05.048

[233] Nazari, M.; Rubio-Martinez, M.; Tobias, G.; Barrio, J.P.; Babarao, R.; Nazari, F.; Konstas, K.; Muir, B.W.; Collins, S.F.; Hill, A.J.; et al. Metal-Organic-Framework-Coated Optical Fibers as Light-Triggered Drug Delivery Vehicles. *Adv. Funct. Mater.* **2016**, 26, 3244–3249. DOI:10.1002/adfm.201505260

[234] Wang, L.; Qu, X.; Zhao, Y.; Weng, Y.; Waterhouse, G.I.N.; Yan, H.; Guan, S.; Zhou, S. Exploiting Single Atom Iron Centers in a Porphyrin-like MOF for Efficient Cancer Phototherapy. *ACS Appl. Mater. Interfaces* **2019**, 11, 35228–35237. DOI:10.1021/acsami.9b11238

[235] Ren, S.Z.; Wang, B.; Zhu, X.H.; Zhu, D.; Liu, M.; Li, S.K.; Yang, Y.S.; Wang, Z.C.; Zhu, H.L. Oxygen Self-Sufficient Core-Shell Metal-Organic Framework-Based Smart Nanoplatform for Enhanced Synergistic Chemotherapy and Photodynamic Therapy. *ACS Appl. Mater. Interfaces* **2020**, 12, 24662–24674. DOI:10.1021/acsami.0c08534

[236] Zheng, Q.; Liu, X.; Zheng, Y.; Yeung, K.W.K.; Cui, Z.; Liang, Y.; Li, Z.; Zhu, S.; Wang, X.; Wu, S. The Recent Progress on Metal-Organic Frameworks for Phototherapy. *Chem. Soc. Rev.* **2021**, 50, 5086–5125. DOI:10.1039/d1cs00056j

[237] Akbar, M.U.; Badar, M.; Zaheer, M. Programmable Drug Release from a Dual-Stimuli Responsive Magnetic Metal-Organic Framework. *ACS Omega* **2022**, 7, 32588–32598. DOI:10.1021/acsomega.2c04144

[238] Zhan, X.Q.; Yu, X.Y.; Tsai, F.C.; Ma, N.; Liu, H.L.; Han, Y.; Xie, L.; Jiang, T.; Shi, D.; Xiong, Y. Magnetic MOF for AO7 Removal and Targeted Delivery. *Crystals* **2018**, 8, 1–9. DOI:10.3390/cryst8060250

[239] Ke, F.; Yuan, Y.P.; Qiu, L.G.; Shen, Y.H.; Xie, A.J.; Zhu, J.F.; Tian, X.Y.; Zhang, L. De Facile Fabrication of Magnetic Metal-Organic Framework Nanocomposites for Potential Targeted Drug Delivery. *J. Mater. Chem.* **2011**, 21, 3843–3848. DOI:10.1039/c0jm01770a

[240] Chen, J.; Liu, J.; Hu, Y.; Tian, Z.; Zhu, Y. Metal-Organic Framework-Coated Magnetite Nanoparticles for Synergistic Magnetic Hyperthermia and Chemotherapy with PH-Triggered Drug Release. *Sci. Technol. Adv. Mater.* **2019**, 20, 1043–1054. DOI:10.1080/14686996.2019.1682467

[241] Cai, M.; Chen, G.; Qin, L.; Qu, C.; Dong, X.; Ni, J.; Yin, X. Metal Organic Frameworks as Drug Targeting Delivery Vehicles in the Treatment of Cancer. *Pharmaceutics* **2020**, 12, 232. DOI:10.3390/pharmaceutics12030232

[242] Chen, X.; Tong, R.; Shi, Z.; Yang, B.; Liu, H.; Ding, S.; Wang, X.; Lei, Q.; Wu, J.; Fang, W. MOF Nanoparticles with Encapsulated Autophagy Inhibitor in Controlled Drug Delivery System for Antitumor. *ACS Appl. Mater. Interfaces* **2018**, 10, 2328–2337. DOI:10.1021/acsami.7b16522

[243] Schnabel, J.; Ettlinger, R.; Bunzen, H. Zn-MOF-74 as PH-Responsive Drug-Delivery System of Arsenic Trioxide. *ChemNanoMat* **2020**, 6, 1229–1236. DOI:10.1002/cnma.202000221

[244] Zhang, Y.; Lin, L.; Liu, L.; Liu, F.; Sheng, S.; Tian, H.; Chen, X. Positive Feedback Nanoamplifier Responded to Tumor Microenvironments for Self-Enhanced Tumor Imaging and Therapy. *Biomaterials* **2019**, 216, 119255. DOI:10.1016/j.biomaterials.2019.119255

[245] Huizenga, D.E.; Szostak, J.W. A DNA Aptamer That Binds Adenosine and ATP. *Biochemistry* **1995**, 34, 656–665. DOI:10.1021/bi00002a033

[246] Yang, X.; Tang, Q.; Jiang, Y.; Zhang, M.; Wang, M.; Mao, L. Nanoscale ATP-Responsive Zeolitic Imidazole Framework-90 as a General Platform for Cytosolic Protein Delivery and Genome Editing. *J. Am. Chem. Soc.* **2019**, 141, 3782–3786. DOI:10.1021/jacs.8b11996

[247] Ruffley, J.P.; Goodenough, I.; Luo, T.Y.; Richard, M.; Borguet, E.; Rosi, N.L.; Johnson,

J.K. Design, Synthesis, and Characterization of Metal-Organic Frameworks for Enhanced Sorption of Chemical Warfare Agent Simulants. *J. Phys. Chem. C* **2019**, 123, 19748–19758. DOI:10.1021/acs.jpcc.9b05574

[248] Cai, W.; Wang, J.; Chu, C.; Chen, W.; Wu, C.; Liu, G. Metal–Organic Framework-Based Stimuli-Responsive Systems for Drug Delivery. *Adv. Sci.* **2019**, 6, 1801526. DOI:10.1002/advs.201801526

[249] Xing, K.; Fan, R.; Wang, F.; Nie, H.; Du, X.; Gai, S.; Wang, P.; Yang, Y. Dual-Stimulus-Triggered Programmable Drug Release and Luminescent Ratiometric PH Sensing from Chemically Stable Biocompatible Zinc Metal-Organic Framework. *ACS Appl. Mater. Interfaces* **2018**, 10, 22746–22756. DOI:10.1021/acsami.8b06270

[250] Jiang, K.; Zhang, L.; Hu, Q.; Zhao, D.; Xia, T.; Lin, W.; Yang, Y.; Cui, Y.; Yang, Y.; Qian, G. Pressure Controlled Drug Release in a Zr-Cluster-Based MOF. *J. Mater. Chem. B* **2016**, 4, 6398–6401. DOI:10.1039/c6tb01756h

[251] Liu, J.; Tang, M.; Zhou, Y.; Long, Y.; Cheng, Y.; Zheng, H. A Siramesine-Loaded Metal Organic Framework Nanoplatform for Overcoming Multidrug Resistance with Efficient Cancer Cell Targeting. *RSC Adv.* **2020**, 10, 6919–6926. DOI:10.1039/c9ra09923a

[252] Gao, X.; Cui, R.; Song, L.; Liu, Z. Hollow Structural Metal-Organic Frameworks Exhibit High Drug Loading Capacity, Targeted Delivery and Magnetic Resonance/Optical Multimodal Imaging. *Dalt. Trans.* **2019**, 48, 17291–17297. DOI:10.1039/c9dt03287h

[253] Alves, R.C.; Schulte, Z.M.; Luiz, M.T.; Bento Da Silva, P.; Frem, R.C.G.; Rosi, N.L.; Chorilli, M. Breast Cancer Targeting of a Drug Delivery System through Postsynthetic Modification of Curcumin@N3-Bio-MOF-100 via Click Chemistry. *Inorg. Chem.* **2021**, 60, 11739–11744. DOI:10.1021/acs.inorgchem.1c00538

[254] Cai, M.; Chen, G.; Qin, L.; Qu, C.; Dong, X.; Ni, J.; Yin, X. Metal Organic Frameworks as Drug Targeting Delivery Vehicles in the Treatment of Cancer. *Pharmaceutics* **2020**, 12, 232. DOI:10.3390/pharmaceutics12030232

[255] Zhang, H.; Li, Q.; Liu, R.; Zhang, X.; Li, Z.; Luan, Y. A Versatile Prodrug Strategy to In Situ Encapsulate Drugs in MOF Nanocarriers: A Case of Cytarabine-IR820 Prodrug Encapsulated ZIF-8 toward Chemo-Photothermal Therapy. *Adv. Funct. Mater.* **2018**, 28, 1–10. DOI:10.1002/adfm.201802830

[256] Iranpour, S.; Bahrami, A.R.; Sh. Saljooghi, A.; Matin, M.M. Application of Smart Nanoparticles as a Potential Platform for Effective Colorectal Cancer Therapy. *Coord. Chem. Rev.* **2021**, 442, 213949. DOI:10.1016/j.ccr.2021.213949

[257] Nirosha Yalamandala, B.; Shen, W.; Min, S.; Chiang, W.; Chang, S.; Hu, S. Advances in Functional Metal-Organic Frameworks Based On-Demand Drug Delivery Systems for

Tumor Therapeutics. *Adv. NanoBiomed Res.* **2021**, 1, 2100014. DOI:10.1002/anbr.202100014

[258] Demir Duman, F.; Monaco, A.; Foulkes, R.; Becer, C.R.; Forgan, R.S. Glycopolymer-Functionalized MOF-808 Nanoparticles as a Cancer-Targeted Dual Drug Delivery System for Carboplatin and Floxuridine. *ACS Appl. Nano Mater.* **2022**, 5, 13862–13873. DOI:10.1021/acsanm.2c01632

[259] Abánades Lázaro, I.; Wells, C.J.R.; Forgan, R.S. Multivariate Modulation of the Zr MOF UiO-66 for Defect-Controlled Combination Anticancer Drug Delivery. *Angew. Chemie* **2020**, 132, 5249–5255. DOI:10.1002/ange.201915848

[260] Conroy, T.; Desseigne, F.; Ychou, M.; Bouché, O.; Guimbaud, R.; Bécouarn, Y.; Adenis, A.; Raoul, J.-L.; Gourgou-Bourgade, S.; de la Fouchardière, C.; et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *N. Engl. J. Med.* **2011**, 364, 1817–1825. DOI:10.1056/NEJMoa1011923

[261] Wu, J.; Ouyang, D.; He, Y.; Su, H.; Yang, B.; Li, J.; Sun, Q.; Lin, Z.; Cai, Z. Synergistic E Ff Ect of Metal – Organic Framework / Gallic Acid in Enhanced Laser Desorption / Ionization Mass Spectrometry. *ACS Appl. Mater. Interfaces* **2019**, 11, 38255-38264. DOI:10.1021/acsami.9b11100

[262] Lawson, H.D.; Walton, S.P.; Chan, C. Metal – Organic Frameworks for Drug Delivery: A Design Perspective. *ACS Appl. Mater. Interfaces* **2021**, 13, 7004-7020. DOI:10.1021/acsami.1c01089

[263] Abu-jaish, A.; Jumaa, S.; Karaman, R. Prodrug Overview. In Prodrugs Design: A New Era; Karaman, R., Ed.; **2014**, 77–102, Nova Publisher: Hauppauge, NY, USA. DOI:10.13140/2.1.3247.1361

[264] Larasati, L.; Lestari, W.W.; Firdaus, M. Dual-Action Pt(IV) Prodrugs and Targeted Delivery in Metal-Organic Frameworks: Overcoming Cisplatin Resistance and Improving Anticancer Activity. *Bull. Chem. Soc. Jpn.* **2022**, 95, 1561–1577. DOI:10.1246/bcsj.20220218

[265] Hong, Y.H.; Narwane, M.; Liu, L.Y.M.; Huang, Y. Da; Chung, C.W.; Chen, Y.H.; Liao, B.W.; Chang, Y.H.; Wu, C.R.; Huang, H.C.; et al. Enhanced Oral NO Delivery through Bioinorganic Engineering of Acid-Sensitive Prodrug into a Transformer-like DNIC@MOF Microrod. *ACS Appl. Mater. Interfaces* **2022**, 14, 3849–3863. DOI:10.1021/acsami.1c21409

[266] Wang, L.; Xu, H.; Gao, J.; Yao, J.; Zhang, Q. Recent Progress in Metal-Organic Frameworks-Based Hydrogels and Aerogels and Their Applications. *Coord. Chem. Rev.* **2019**, 398, 213016. DOI:10.1016/j.ccr.2019.213016

[267] Hou, X.; Sun, J.; Lian, M.; Peng, Y.; Jiang, D.; Xu, M.; Li, B.; Xu, Q. Emerging Synthetic Methods and Applications of MOF-Based Gels in Supercapacitors, Water Treatment, Catalysis, Adsorption, and Energy Storage. *Macromol. Mater. Eng.* **2022**, 2200469, 1–23. DOI:10.1002/mame.202200469

[268] Yao, S.; Chi, J.; Wang, Y.; Zhao, Y.; Luo, Y.; Wang, Y. Zn-MOF Encapsulated Antibacterial and Degradable Microneedles Array for Promoting Wound Healing. *Adv. Healthc. Mater.* **2021**, 10, 1–10. DOI:10.1002/adhm.202100056

[269] Yang, X.X.; Feng, P.; Cao, J.; Liu, W.; Tang, Y. Composition-Engineered Metal-Organic Framework-Based Microneedles for Glucose-Mediated Transdermal Insulin Delivery. *ACS Appl. Mater. Interfaces* **2020**, 12, 13613–13621. DOI:10.1021/acsami.9b20774

[270] Yin, M.; Wu, J.; Deng, M.; Wang, P.; Ji, G.; Wang, M.; Zhou, C.; Blum, N.T.; Zhang, W.; Shi, H.; et al. Multifunctional Magnesium Organic Framework-Based Microneedle Patch for Accelerating Diabetic Wound Healing. *ACS Nano* **2021**, 15, 17842–17853. DOI:10.1021/acsnano.1c06036

[271] Pal, S.; Su, Y.Z.; Chen, Y.W.; Yu, C.H.; Kung, C.W.; Yu, S.S. 3D Printing of Metal-Organic Framework-Based Ionogels: Wearable Sensors with Colorimetric and Mechanical Responses. *ACS Appl. Mater. Interfaces* **2022**, 14, 28247–2825. DOI:10.1021/acsami.2c02690

[272] Lim, G.J.H.; Wu, Y.; Shah, B.B.; Koh, J.J.; Liu, C.K.; Zhao, D.; Cheetham, A.K.; Wang, J.; Ding, J. 3D-Printing of Pure Metal-Organic Framework Monoliths. *ACS Mater. Lett.* **2019**, 1, 147–153. DOI:10.1021/acsmaterialslett.9b00069

[273] Lawson, S.; Alwakwak, A.A.; Rownaghi, A.A.; Rezaei, F. Gel-Print-Grow: A New Way of 3D Printing Metal-Organic Frameworks. *ACS Appl. Mater. Interfaces* **2020**, 12, 56108–56117. DOI:10.1021/acsami.0c18720

[274] Zhao, D.; Zhang, W.; Yu, S.; Xia, S.L.; Liu, Y.N.; Yang, G.J. Application of MOF-Based Nanotherapeutics in Light-Mediated Cancer Diagnosis and Therapy. *J. Nanobiotechnology* **2022**, 20, 1–28. DOI:10.1186/s12951-022-01631-2

[275] Dekrafft, K.E.; Boyle, W.S.; Burk, L.M.; Zhou, O.Z.; Lin, W. Zr- and Hf-Based Nanoscale Metal-Organic Frameworks as Contrast Agents for Computed Tomography. *J. Mater. Chem.* **2012**, 22, 18139–18144. DOI:10.1039/C2JM32299D

[276] Osterrieth, J.W.M.; Fairen-jimenez, D. Metal – Organic Framework Composites for Theragnostics and Drug Delivery Applications. **2020**, 2000005, 1–14. DOI:10.1002/biot.202000005

[277] Quijia, C.R.; Alves, R.C.; Hanck-Silva, G.; Galvão Frem, R.C.; Arroyos, G.; Chorilli, M. Metal-Organic Frameworks for Diagnosis and Therapy of Infectious Diseases. *Crit.*

Rev. Microbiol. **2022**, 48, 161–196. DOI:10.1080/1040841X.2021.1950120

[278] Gangu, K.K.; Maddila, S.; Mukkamala, S.B.; Jonnalagadda, S.B. A Review on Contemporary Metal-Organic Framework Materials. *Inorganica Chim. Acta* **2016**, 446, 61–74. DOI:10.1016/j.ica.2016.02.062

[279] Wu, H.; Chua, Y.S.; Krungleviciute, V.; Tyagi, M.; Chen, P.; Yildirim, T.; Zhou, W. Unusual and Highly Tunable Missing-Linker Defects in Zirconium Metal – Organic Framework UiO-66 and Their Important E Ff Ects on Gas Adsorption. *J. Am. Chem. Soc.* **2013,** 135, 10525-10532. DOI:10.1021/ja404514r

[280] De Andrade, J.R.; Oliveira, M.F.; Da Silva, M.G.C.; Vieira, M.G.A. Adsorption of Pharmaceuticals from Water and Wastewater Using Nonconventional Low-Cost Materials: A Review. *Ind. Eng. Chem. Res.* **2018**, 57, 3103–3127. DOI:10.1021/acs.iecr.7b05137

[281] Zhou, Q.; Liu, G. Urea-Functionalized MIL-101(Cr)@AC as a New Adsorbent to Remove Sulfacetamide in Wastewater Treatment. *Ind. Eng. Chem. Res.* **2020**, 59, 12056–12064 DOI:10.1021/acs.iecr.0c01037

[282] Ongari, D.; Liu, Y.M.; Smit, B. Can Metal-Organic Frameworks Be Used for Cannabis Breathalyzers? *ACS Appl. Mater. Interfaces* **2019**, 11, 34777–34786. DOI:10.1021/acsami.9b13357

[283] Zhang, Z.; Han, W.; Lou, T.; Ma, L.; Zhou, W.; Xu, Z.; Chen, M.; Wen, L.; Cheng, Y.; Ding, L. Nanoporous Ethylenediamine-Functionalized Metal-Organic Framework MIL-101 for the Removal of Proteins and Antipsychotic Drugs from Serum Samples. *ACS Appl. Nano Mater.* **2022**, 5, 17325–17334. DOI:10.1021/acsanm.2c04560

[284] Hu, Z.; Wang, Y.; Zhao, D. The Chemistry and Applications of Hafnium and Cerium(Iv) Metal–Organic Frameworks. *Chem. Soc. Rev.* **2021**, 50, 4629–4683. DOI:10.1039/D0CS00920B

[285] Rasheed, T.; Bilal, M.; Hassan, A.A.; Nabeel, F.; Bharagava, R.N.; Romanholo Ferreira, L.F.; Tran, H.N.; Iqbal, H.M.N. Environmental Threatening Concern and Efficient Removal of Pharmaceutically Active Compounds Using Metal-Organic Frameworks as Adsorbents. *Environ. Res.* **2020**, 185, 109436. DOI:10.1016/j.envres.2020.109436

[286] Proenza, Y.G.; Longo, R.L. Simulation of the Adsorption and Release of Large Drugs by ZIF-8. *J. Chem. Inf. Model.* **2020**, 60, 644–652. DOI:10.1021/acs.jcim.9b00893

[287] Farrando-Pérez, J.; Martinez-Navarrete, G.; Gandara-Loe, J.; Reljic, S.; Garcia-Ripoll, A.; Fernandez, E.; Silvestre-Albero, J. Controlling the Adsorption and Release of Ocular Drugs in Metal-Organic Frameworks: Effect of Polar Functional Groups. *Inorg. Chem.* **2022**, 61, 18861–18872. DOI:10.1021/acs.inorgchem.2c02539

[288] Furukawa, H.; Cordova, K.E.; O'Keeffe, M.; Yaghi, O.M. The Chemistry and Applications of Metal-Organic Frameworks. *Science* **2013**, 341, 1230444. DOI:10.1126/science.1230444

[289] Maranescu, B.; Visa, A. Applications of Metal-Organic Frameworks as Drug Delivery Systems. *Int. J. Mol. Sci.* **2022**, 23, 4458. DOI:10.3390/ijms23084458

[290] Ni, K.; Luo, T.; Lan, G.; Culbert, A.; Song, Y.; Wu, T.; Jiang, X.; Lin, W. A Nanoscale Metal–Organic Framework to Mediate Photodynamic Therapy and Deliver CpG Oligodeoxynucleotides to Enhance Antigen Presentation and Cancer Immunotherapy. *Angew. Chemie - Int. Ed.* **2020**, 59, 1108–1112. DOI:10.1002/anie.201911429

[291] Wang, H.; Chen, Y.; Wang, H.; Liu, X.; Zhou, X.; Wang, F. DNAzyme-Loaded Metal–Organic Frameworks (MOFs) for Self-Sufficient Gene Therapy. *Angew. Chemie Int. Ed.* **2019**, 58, 7380–7384. DOI:10.1002/anie.201902714