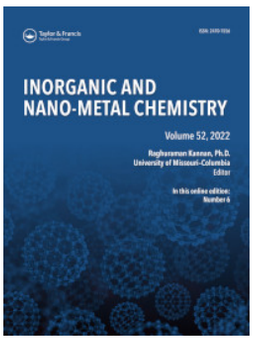

Inorganic and Nano-Metal Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsrt21

Metal organic frameworks: an effective application in drug delivery systems

Christine Jeyaseelan, Priyansh Jain, Deeya Soin & Deepshikha Gupta

To cite this article: Christine Jeyaseelan, Priyansh Jain, Deeya Soin & Deepshikha Gupta (2021): Metal organic frameworks: an effective application in drug delivery systems, Inorganic and Nano-Metal Chemistry, DOI: 10.1080/24701556.2021.1956966

To link to this article: https://doi.org/10.1080/24701556.2021.1956966

Published online: 23 Jul 2021.

INORGANIC AND NANO-METAL CHEMISTRY
https://doi.org/10.1080/24701556.2021.1956966

Taylor & Francis
Taylor & Francis Group

REVIEW

Metal organic frameworks: an effective application in drug delivery systems

Christine Jeyaseelan, Priyansh Jain, Deeya Soin, and Deepshikha Gupta

Amity Institute of Applied Sciences, Amity University, Noida, India

ABSTRACT

Metal organic frameworks (MOFs) are networks constructed from metal ions or clusters and multidentate organic linkers with coordinate bonds. They are porous and crystalline and have one, two or three directional structures. The MOFs have found varied applications in a variety of fields like catalysis, energy storage, gas purification and separation, super-capacitors to name a few. This review gives a general overview into the different methods used for the synthesis of MOFs, their structure and characteristics, also highlighting its application in drug delivery. The properties like targeted and stimulus-based delivery, nontoxic effects, multi drug loading capacity and sustained release have enhanced the use of MOFs in drug delivery. Drugs required for chronic diseases, which necessitate specific organ treatment, can be delivered to the particular site in the body by using MOFs. This paper also describes some of the ailments like pulmonary diseases, arthritis and HIV which can be treated by targeted drug delivery, using MOFs.

ARTICLE HISTORY
Received 21 February 2021
Accepted 11 July 2021

KEYWORDS
MOF; drug delivery; multi drug loading; porous; organic linkers

Introduction

There has been commendable advancement in drug delivery systems, but challenges remain, and it is these challenges that give impetus to new research. Major challenges include biocompatibility of drugs and delivery of poorly soluble drugs. An effective drug carrier, without any side effects, is another important aspect of drug delivery. Hence, to solve these challenges, researchers are directing toward "metal organic frameworks," a novel product of recent research. Metal Organic frameworks or MOFs are a kind of coordination polymer compounds having crystalline nature and long range ordered structure. They are sometimes known as inorganic-organic hybrids, but this terminology is not encouraged.[1] This is because it reflects the meaning as "a material which is made up of a mixture or combination of organic as well as inorganic components". They are porous solid materials in which there is an orderly array of metal ions adjoined to organic "linkers"[2] or "struts." They are famous for their high surface area and extremely high porosities.

The attention caught by the MOFs dates back to 1964.[3] Their study emerged from the study of zeolites. In 1995, Omar Yaghi,[4] who pioneered reticular chemistry, coined the term "metal – organic framework." Both MOFs and zeolites are synthesized using the hydrothermal or solvothermal technique in which crystals are formed out slowly from hot solution.[5] Another method of synthesis involves the use of "templates." This method is also similar that of zeolites except that here we use templates which are the secondary building units (SBUs) and organic linkers.[6]

These novel compounds have recently caught attention in the field of research due to their high surface areas and customizable properties like pore size, biodegradability chemical functionalities and electrical properties. Due to this, they have a broad range of applications like gas storage, catalysis, luminescence and ion exchange.[7] MOF's have also found to be stimulus responsive and show change in their physical and chemical properties in the presence of external stimulus like temperature, light, ions, solvents, electrons etc.[8] An effective application of MOF's containing atoms like potassium and cobalt have been found in the use of batteries.[9] Besides, many MOFs are biocompatible which makes them suitable in drug delivery systems.

Although, one of its most important property, which is still being explored by scientists all over the globe, is its capability of interacting with our biological systems based on different stimuli encountered inside our system such as pH, temperature, redox-reactions, light, glucose level etc. This bio-interaction has paved way for novel strategies in therapeutic treatments of various diseases ranging from non-lethal (asthma, osteoarthritis) to lethal (cancer) and thus making MOFs, a promising drug delivery platform. Further MOFs application in delivery of therapeutics and bio-medical drugs has widened the scope of treatment in terms of combination therapies, mode of administration of drugs, and drug release timeframe due to their tunable pore size, high surface area and pore volume with ease in modifications. The two-component system of MOFs have clearly proved its worth by mitigating the challenges faced by its organic and inorganic parts when used individualistically and creating novel allies for research and application, for the betterment of humankind.

CONTACT Deepshikha Gupta dgupta2@amity.edu Amity Institute of Applied Sciences, Amity University, Sector-125, Noida 201301, India.

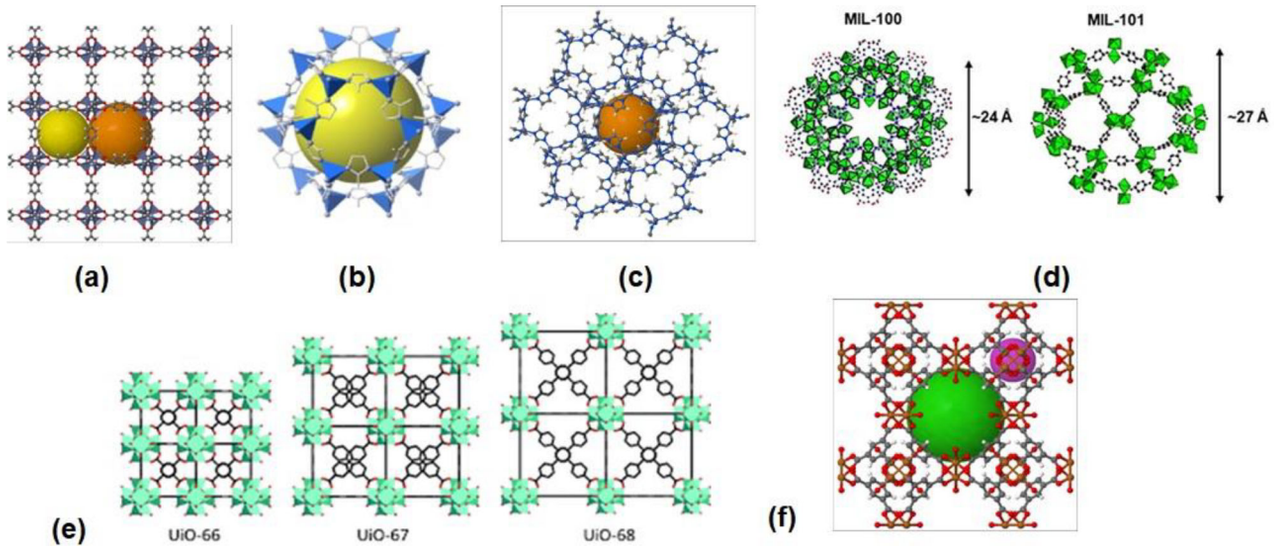

Figure 1. Structures of various MOFs (a) MOF-5 (b) ZIF-8 (c) ZIF (d) MIL-100 & MIL-101 (e) UiO-66, 67 & 68 (f) MOF199 or HKUST-1 or $Cu_3(BTC)_2$. MOF structures (a), (c) & (f) taken from Ref. [12], (b) from Ref. [13], (d) from Ref. [14] and (e) from Ref. [15].

This paper reports a discussion on the various methods of synthesis of MOFs, its structure and characteristic along with a detailed study on its applications in drug delivery systems.

Synthesis of MOFs

MOFs were initially synthesized by a technique called solvothermal synthesis which is the most popular method of synthesis so far. More than two decades after their discovery, new advancements in synthesis methods were achieved. New techniques, which involved the use of electrochemical, microwave-assisted, sonochemical and ionothermal method, came to be reported.[10] The type of route chosen for their synthesis greatly influences not only the properties of MOFs but also their applicability. For example, according to Li et al,[11] when MOF-5 or $[Zn_4O(BDC)_3]$ was synthesized using solvothermal process, it showed greater surface area and bigger volume of pores than when it was synthesized using direct mixing of triethylamine (TEA). MIL-101 with Cr metal cluster (Figure 1), a MOF which has excellent stability in presence of moisture and other chemicals, is prepared by hydrothermal synthesis under autogenous pressure conditions.[16]

Solvothermal/hydrothermal method

In this method, the reaction takes place inside a closed container or vessel, between precursors in presence a solvent/water. The reaction takes place at an autogenous pressure above the boiling point of the solvent used.[17,18] A large number of MOFs can be synthesized using this method because of its low temperature dependency.[19] It is a common synthetic route that allows comparatively fast growth of crystals which have highly crystalline nature and improved purity as well as surface area.[20] MIL-96(Cr),[21] MIL-100[22] and MIL-101 are some of the MOFs which have been prepared using this technique. The generic scheme of preparation of MOFs by this method is depicted in Figure 2. There are, however, certain modifications done in the method, over time. These modifications produced different kinds of MOFs, increased yield, and efficiency, and demonstrated methods for tuning the morphological and functional properties of MOFs. One of these advanced modifications is *Mixed Ligand MOF synthesis* which refers to creating an MOF which contains two or more iso-structural linkers in the structure. Achieving the same, can be done, either through simple mixing approach, or sometimes, via changing reaction conditions.[23] Presence of mixed linkers changes the properties and gives rise to tunable properties.[24] Yujie Ban et al.,[25] demonstrated in their study that ZIF-78, a mixed ligand MOF (contains Zn^{+2} and 2-nitroimidazolate {nIm} and 5-nitrobenzimaidazolate{nbIm}) can be tuned to a desirable size with respect to C-axis by altering the ratio of the anions in the reaction mixture. Higher ratio of nIm: nbIm yielded smaller size and lower aspect ratio in the ZIF-78 particles and vice versa. Their research demonstrated the possibilities of alteration in size and dimensions of MOFs.

In another approach of *Mixed Metal MOF synthesis*, transmetalation or exchange of metal cation nodes in the structure of MOF can lead to both novel and multiple functionalities.[26] There can be partial exchange or complete exchange, depending upon the metal ions and the desired outcome. There are considerable benefits using mixed metal MOFs over conventional mono-metallic MOFs. It can be either achieved by one-pot synthesis (by mixing two metal ion salts in a definite ratio) or by PSM (soaking the mono-metallic MOF in a concentrated solution containing second metal ion). It is observed that mixed metal ions are superior in terms of flexibility of release in response to stimulus.[27]

The functionality of MOFs can be diversified either in the pre-synthetic stage (which poses some limitations) or in the post-synthetic stage (which circumvents limitations and allows advantageous results).[28] *Post Synthetic Modification (PSM)* in simple terms can be understood as, subjecting the crystals of MOF to various chemical reactions, which leads to the formation of new bonds between diverse functionalities

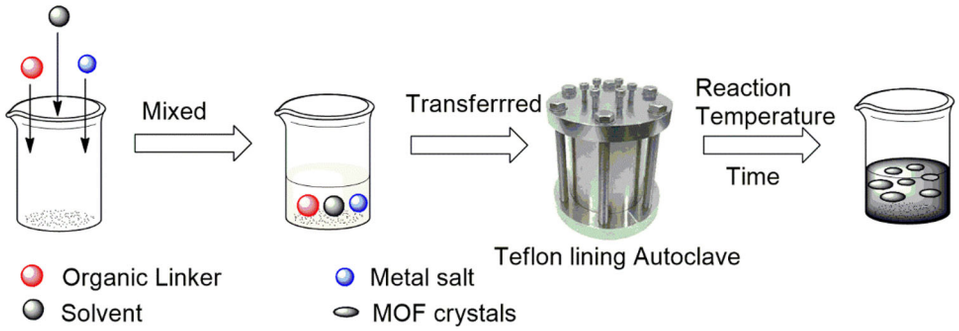

Figure 2. Schematic representation of solvothermal technique of MOF.

and the framework as a whole, without affecting the integrity of the crystal.[29] Some of the PSM strategies may include amide couplings, isocyanate condensations, "click" chemistry, and other reactions.[28] PSM can be particularly advantageous for the fact that multiple chemicals can be incorporated within the pores of a single framework, which increases its applications as a drug delivery agent and catalysis. For instance, Li Baiyan *et al,* prepared a bi-functional MOF catalyst using MIL-101.[30] All the above mentioned techniques are advancements in solvothermal synthesis, which increases the tunability of the MOFs to a large extent and therefore expands its applications in otherwise difficult arenas.

Microwave synthesis

Microwave aided synthesis was developed in order to increase the kinetics and efficiency of reaction.[31] The principle behind this technique is that the energy acquired from the microwaves is used to make electromagnetic waves that interacts with electrical charges in the sample. The interaction results in alteration of the molecules permanently.[32] Some of the MOFs synthesized with this method are UiO-67,[33] MOF-5[31] (Figure 1a) and MOF-74 (Ni).[34]

Sono-chemical synthesis

In sono-chemical synthesis, ultra-sound radiations are used. According to Suslick et al.,[35] this method arises from acoustic cavitation during which implosion of bubbles takes place. This, consequently, creates hot spots having temperature $\sim$ 5000 K and pressure about 1800 atmosphere with the rate of cooling exceeding 10^9 Ks^{-1}. Unlike solvothermal synthesis it is a solvent free method that can be carried out at room temperature. It is also considered to be a green synthetic method for synthesis of MOFs.[36] Figure 3 represents the sonochemical synthesis of Lipase-MOF. Nadar and Rathod[37] studied that when Lipase enzyme shows enhanced activity when it is treated with low intensity ultrasonic radiation. This highly activated lipase is then encapsulated with Zeolitic imidazolate framework-8 or ZIF-8 (Figure 1b) by biomineralization to form Lipase-MOF.

Iono-thermal process

Fused salts or ionic liquids have recently caught attention as green solvents due to their favorable solvating properties and potential applications like that in biocatalysis.[38] They are also used in synthesizing MOFs. An important advantage of using ionic liquids is that the solvent can be gradually altered i.e., the cations and anions can be substituted with a different set, each alteration provides a new reaction environment, thereby modifying the properties of the resulting MOF.[39] $Cu_3(BTC)_2$ as shown in (Figure 1f) is an example of MOF which was prepared using this method.[40]

Synthesis using surfactants

The use of surfactants for the synthesis of MOFs is a recent development which has proved very effective since it helps to determine the dimensions, phases and morphologies by functioning as foaming agents, wetting agents, emulsifiers, detergents, or even dispersants.[41,42] Qichun Zhang et al.[43] have reported the synthesis of mercury seledinostannates by surfactant thermal method using PEG-400 as the reactant medium which gave a product which was kinetically stable and could be transformed into thermodynamically stable phase by increasing the reaction time. The growth of crystalline materials in surfactants has helped synthesize crystals with varying structures and properties. Other surfactants having neutral, acidic, basic, anionic and cationic characteristics like octanoic acid or hexadecyltributylphosphonium bromide have been studied for the preparation of Zinc based MOF's.[44] The surfactant thermal method has been used not only for one dimensional but 3 dimensional networks also with single as well as mixed metals.[45,46] A system for mixed phase MOF's with Ni(II) ions has also found to exhibit 3 D hydrogen bonded network and 3 D 2-fold interpenetrating framework.[47] A similar study has also been reported with Co(II) using surfactants.[48]

Morphology and size control of crystals of MOFs

Nucleation and crystal growth occur in the process of synthesis of MOFs. During this, self-assembly takes place between metal-oxygen clusters and organic unit. There are several factors which decide the architecture of the MOF crystals.Nature of solvents, pH, molar ratio of reactants, pressure and temperature some of those factors.[7] The solvents define the coordination environment of the reaction. It can also participate in the reaction by coordinating with the metal ion or by acting as guest molecule in the overall lattice.[49] The pH of the medium where the reaction takes place directly influences the crystallization and growth of

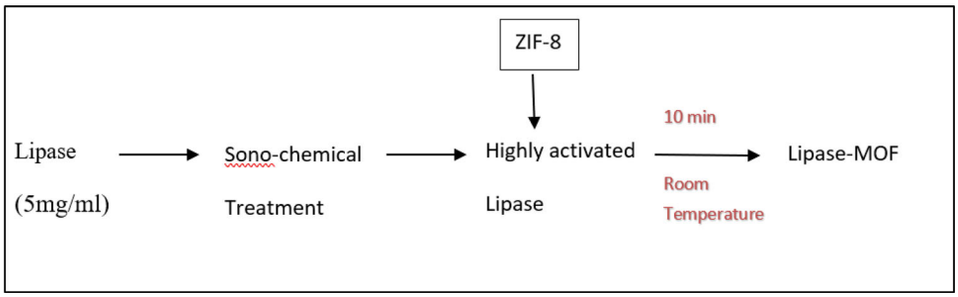

Figure 3. Representation of Sonochemical synthesis of Lipase-MOF.

Table 1. Effect of pH on crystals of MOFs.

Reactants	pH	Product composition (different molecular formula)	Structural information of unit	Color	Reference
1,3-adamantanedi-acetic acid (H_2ADA) + $[Co(NO_3)_2.6H_2O$	5	$[Co(HADA)_2(bpp)]_n$	1-D Zig-zag chains	–	[51]
	6	$\{[Co(ADA)(bpp)(CH_3OH)]H_2O\}_n$	2-D infinite layer	–	
	7	$[Co_2(ADA)_2(bpp)]_n$	1-D looped chain	–	
Co(II) + 3,3′,5,5′-tetra(1H-imidazole-1-yl)-1,1′-biphenyl(L) + 1,3,5-benzene tricarboxylate (BTC)	5	$[Co(L)(HBTC)_2(\mu_2\text{-}H_2O)(H_2O)_2]\cdot 3H_2O$	2-D network	Pink	[52]
	7	$[Co_3(L)_2(BTC)_2]\cdot 4H_2O$	2-D double layer	Purple	
	9	$[Co_2(L)(BTC)(\mu_2\text{-}OH)(H_2O)_2]\cdot 2H_2O$	3-D network	Brown	
4-sulfocalixarene + Mn	2	$\{H[(C_{28}H_{20}O_{16}S_4)Mn(H_2O)4Mn_{0.5}(H_2O)_2]\}_n \cdot 6nH_2O$	1-D structure	–	[53]
	4	$\{NH_4[(C_{28}H_{20}O_{16}S_4)Mn(H_2O)4Mn_{0.5}(H_2O)2]\}_n.5nH_2O$	2-D structure	–	
	5	$[(C_{28}H_{20}O_{16}S_4)Mn_2(H_2O)_8]_n.6nH_2O$	1-D structure	–	

the metal organic frameworks. For instance, Yuan et al.,[50] showed in their results of pH-modulated synthesis of MOF-5 sheets that at low pH, mixture of organic ligand and Zn^{+2} formed a large cubic structure, whereas on pH modulation, they formed smaller cubes which could be dissolved and re-crystallized into uniform sheets. pH acts as an external stimulus and has great influence in deciding the coordination modes of carboxylic acid ligand present during the synthesis of MOFs.[7] Changing the pH also affects the color and the dimension of complex as depicted from Table 1.

Molar ratio of the reactants also plays important role in synthesis of MOFs. This is because the topological pattern of crystals depends upon reactant's stoichiometry. Yin et al.[54] studied the effect of molar ratio. They synthesized different 1,2,4 triazole ligand (TAZ) based Cd compounds varying in topology based on the molar ratio of reactants. Among these, $[Cd_3Cl_3(TAZ)_3(DMF)_2]_n$ was formed exhibiting 3 D network when molar ratio of reactants was 1:1.2 . On the other hand, $[CdCl_2(TAZ)]_{n.}$ $n(H_2O)$ was formed when metal/ligand ratio was 1:1.7. It was also found that coordination number of (TAZ) changed from 3 in former to 2 in later compound.

It is vital to comprehend the factors which influence the nucleation and crystal growth of MOFs which, in turn, will help to control and tailor the morphology and size of crystals in delivering the targeted properties of MOF crystals. This demands a more specific synthesis approach considering the mechanism of crystallization.[55] Some of those methods are discussed below:

Deprotonation regulation synthesis

The alteration in deprotonation rate of organic units or linkers has been found to be affected by change in concentration of reactant. This was found during the synthesis of NH_2-MIL-125 (Ti) crystals. Modifying the crystal morphology by altering the deprotonation rate is known as deprotonation regulation synthesis.[56]

Coordination modulation synthesis

Introducing additives in the crystallization process can contribute in modifying the morphology and size. According to Kitagawa et al.,[57] morphology of crystals of $[(Cu_2(ndc)_2(dabco))_n]$ was altered with coordination modulation of carboxylic acid additive. In this case, it was acetic acid which obstructs the coordination present between metal clusters and linkers. This affects the lattice structure and growth of these crystals. Further, effect of coordination modulation on morphology of an MOF called HKUST-1 was studied by Diring S et al.[58] The effect was observed by using additives, lauric acid, acetic acid and dodecanoic acid. HKUST-1 is a copper-based metal-organic framework also known as MOF-199 or $Cu_3(BTC)_2$.

Surfactant modulation synthesis

Adding surfactants is another way for the modulated synthesis of MOFs. Cetyl trimethyl ammonium bromide (CTAB) is an example of surfactant.[59] They can modify the morphology and size because they can get absorbed on specific facet(s) of MOF during the crystallization process.

Structure of MOFs

There are mainly two components in the MOFs -the cluster of metal ions and the organic units. The metal ion clusters are also known as Secondary building units or the SBUs. The organic units called the linkers. They are present between the SBUs and give rise to their crystalline and porous characteristics[60] (Figure 4). The linkers can have mono, di, tri or tetra valency.[61] They act as bridging

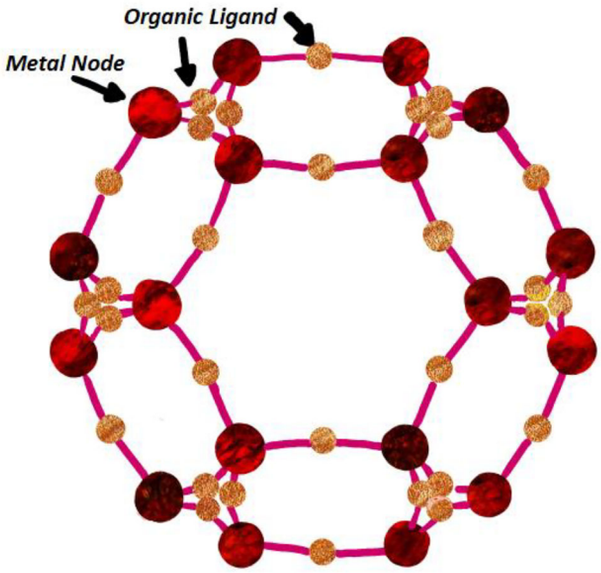

Figure 4. Basic component of a MOF, metal node and organic linker.

Table 2. MOFs having different characteristics produced using same SBU and different linkers.

Metal	Linker	MOF	Reference
Zn	Benzimidazole	ZIF-7	[65]
	2-methylimidazole	ZIF-8	[65]
	Imidazolate-2-carboxyaldehyde (ICA)	ZIF-90	[65]
Cu	Benzene-1,3,5-Tricarboxylic acid(BTC)	MOF-199/HKUST-1	[66]
Fe	Trimesic acid	MIL-100	[63]
	1,4-dibenzoic acid (1,4 BDC)	MIL-88	[67]

ligands and the most common ones are di or tri-carboxylic acids as their backbones are rigid. Terephthalic acid, 2-aminoterephthalic acid,[62] trimesic acid[63] or BTC[64] (benzene tricarboxylic acid) are some of the examples of linkers.

The structure and other characteristics of the MOF rely upon the type of metal ion and linker is present. This is illustrated from Table 2.

The volume of the pores can be adjusted by modifying the linkers[68] whereas depending upon the coordination number of the metal ions, one, two- or three-dimensional extended networks can be created. The first row D-block elements are known for their coordination property and therefore, their MOFs are more popular. Dense and rigid structures formed by highly connected metal–oxo clusters and rigid organic linkers are usually more stable. Also higher coordination numbers and thus more rigid framework structures. On the contrary, this is not in the case of those MOFs which have a s-block metal ion. The s-block center results in ionic interactions with carboxylate oxygen which can be attributed to the large difference in the electronegativity. So, the coordination environment is directed toward coordination saturation and many factors play role in achieving that environment. Also, the s-orbital is spherical in nature and makes the metal-ligand bond non directional.[69] This makes it arduous for coordination geometry to be predicted and have control over.[70] Therefore, MOFs which have a s-block metal ion are less known. The linearly oriented ligands form square planar as well as cubic structured MOFs. Some MOFs like $[Cu_3(btc)_2(H_2O)_3]$[66] are known to have open metal sites. These open sites are formed due to partial coordination in metal atoms by solvent molecules during synthesis. The MOF is activated and the solvent is removed thereby creating a void for the required guest molecule.[71] This void so formed is called the *open metal site.*

Applications of metal-organic-frameworks in drug delivery systems

MOF based drug delivery systems are gaining popularity in recent times due to various reasons like fine structural properties like high porosity, tunable size,[72] chemical tunability, flexibility in network topology, biocompatibility,[73,74] biodegradability.[75] MOFs show outstanding advantages such as high surface area, high porosity, easy modification in the physical and chemical properties of MOFs, moderate coordination bonds making MOFs stable yet biodegradable, well defined structural features for host-guest interaction studies. These unique properties make MOFs an excellent candidate for DDS and cancer therapy.[76] In order to prepare good biocompatible MOF for biomedical applications it is important that the organic linkers should be of low toxicity with biocompatible nature. For this purpose, Bio-MOFs have been prepared using endogenous ligands like amino acids, proteins, porphyrins, nucleotides, saccharides etc. These diverse Bio-MOFs can be designed for special purpose biomedical applications including bio-sensing, bio-imaging, and disease treatment.[77] The focus of this paper is to dwell into applications of MOF in drug delivery systems. Hence it would be worthwhile to discuss some of the tunable properties of MOF in the backdrop of DDS. While considering any particle for the potential drug carrier, it must be evaluated on its size, bio-compatibility, bio-degradability, toxicity and water stability. When the size of MOF particles was scaled down to nanoscale, these nano-MOFs (NMOFs) can act as efficient nanocarriers to deliver agents for imaging, chemotherapy, photothermal therapy, or photodynamic therapy. NMOFs have a great potential, especially as DDSs. It is because internalization of nano-drug carriers is easier and favored because of the small size, as discussed by Isabel et al.[78] in their study on Zr-MOF for dual drug delivery. MOFs of the series MIL, UiO are generally stable in aqueous phase. However, NMOFs show low water dispersity, hence in order to increase their bioavailability, there are generally silica encapsulated or polymer coated. NMOFs' bio-pathway is invariably analyzed in-vivo to ensure it is degraded naturally in the body after it has successfully completed the task of delivery. ^{89}Zr-UiO-66/Py–PGA-PEG-F3 can serve as an image-guidable, tumor-selective cargo delivery nanoplatform.[79] The analysis performed on MIL-88, MIL-101, HKUST-1 etc by Zhou et al.[80] adds to the evidence that NMOFs are generally bio-degradable. Even the drug release capacity of NMOFs is slower, and thus more effective as demonstrated in their experiment by Witri et al.[36] in which they used Zn -based NMOF to find that release rate dropped from 85% to 25% when the drug was loaded on NMOF. Having discussed few important properties of MOFs

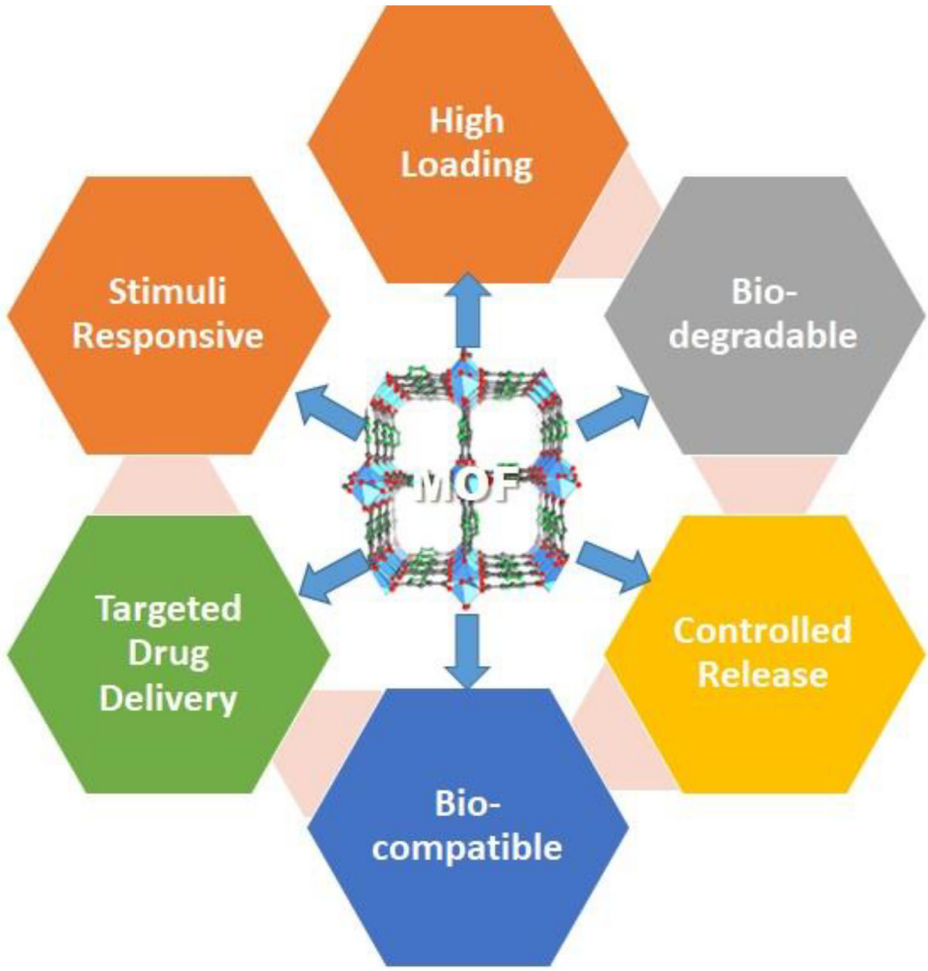

Figure 5. Advantage of MOFs as drug delivery system.

and NMOFs in the light of DDS parameters, the next section brings in detail the application of MOFs in and as DDS. Some of them are as shown in Figure 5 and are discussed in brief below:

Controlled and prolonged drug release capacity

Further, the potential use of MOFs and its composites with other materials as drug delivery agents are justified, based on its ability to stretch the drug release period considerably which invariably mean a greater controlled delivery of drugs. For instance, Liangyu Lu et al.,[81] synthesized a composite of nano -sized amine-functionalized MOF – UiO-66-NH_2 and epoxy-functionalized polysilsesquioxane (encapsulation layer). They used it to deliver ibuprofen drug and demonstrated a controlled release, establishing it as an eligible platform for controlled delivery of the drug. It is also seen that drug release capability of MOFs can be modified positively by converting the crystalline structure of the MOF into the amorphous. Claudia Orellana-Tavra et al.,[82] achieved an increase up to 30 days from 2 days in the release of model drug calcein (because of its similarity to anti-cancer drug doxorubicinin) through the Zr-based MOF UiO-66 which had undergone amorphization via ball-milling. They successfully concluded that this method of structural collapse can be used to increase the time of the delivery of drug significantly.

Enhanced solubility of amorphous and poorly soluble drugs

MOFs have been proved to successfully pacify the conventional weakness of insolubility or low solubility of amorphous drugs. The drug and MOF-5 composite has shown a quality dissolution and super saturation in simulated environments (gastric).[83] γ-Cyclodextrin based MOF notified generally as CD-MOF has been explored to improve the solubility and thus bioavailability poorly soluble AZL[84] (azilsartan – a poorly soluble drug-340-fold increase), solubilized sulfadiazin[85] with superfine nano-Ag (50-fold increase). Activated CD-MOF using supercritical CO_2 was found to assist an increased solubility of another insoluble drug HKN (honokiol).[86] Further CD-MOF cages were also identified to mega-load valsartan and thereby increase its solubility.[84]

Delivery of drugs containing otherwise toxic metal ions

It has been observed that MOFs can also be used to deliver otherwise toxic drugs such as Arsenic trioxide (anti-tumor drug). Zn-MOF-74 had been successfully employed in-vitro to deliver Arsenic drugs. It loads high amount of drug and shows pH stimulated release of the drug in the acidic pH range present around cancer cells and not around the pH range of normal tissue micro-environment.[87]

Table 3. Different modes of drug delivery using MOFs.

Sl. no.	Disease type	Mode of administration with MOF	MOF used	Advantages	Reference
1.	Cancer and bacterial diseases	Topical-subcutaneous	$Zn_4O(dmcapz)_3$	High-loading and controlled release	[93]
2.	Diabetes	Transdermal	Insulin and glucose-oxidase loaded cobalt doped ZIF-8	Painless microneedles, glucose responsive	[90]
3.	Laryngeal diseases	Inhalation (laryngeal)	Scutellarin (SCU) encapsulated CD-MOF	Increased laryngeal deposition	[94]
4.	Diabetes mellitus/insulin	Oral	Fe-based MIL-100	Sidestep potential problems with delivery through injection	[95]
5	Pain/inflammation (ibuprofen-Na)	Oral	Zr-based UiO-66-PDC	pH-responsive release delivering more in intestinal environment	[96]

Multi-drug loading

Multi-drug loading in a single delivery agent has been challenging and therefore rare and developing. Despite the odds, the approach has been proved beneficial for anti-cancer therapy. A novel strategy of multivariate modulation has allowed Abanades Lazaro et al.,[88] to load three drugs successfully in a Zr-MOF UiO-66 via defect loading and fourth drug is incorporated in the pores during the post-synthetic modulation. Thus, a combination of drugs was loaded in significant amounts in a single nano-carrier. They confirmed their technique to be versatile and reproducible for other MOF systems and applications. Other example includes UiO-66-NH_2 based modified MOF (redox-responsive) which is examined to deliver combination of 5-fluorouracil and dichloroacetic acid which works synergistically against cancer by Liu et al.[89] In another experiment, Jie Shen et al.,[90] coated ZIF-90 with spermine-modified acetylated dextran (SAD). The nanocomposite thus prepared served as a cargo for carrying two compounds-doxorubicin (DOX) attached to ZIF-90 network and IR780 (a photosensitiser) attached onto SAD shell, for combined chemo and photodynamic therapy.

Stimulus based-targeted drug delivery

MOF-based stimuli-responsive systems have been developed including pH-, magnetic-, ion-, temperature-, pressure-, light-, humidity-, redox-, and multiple stimuli-responsive systems for the designing controllable delivery of anticancer drugs.[91] Alijani et al.,[92] developed a new nano composite with UiO-66-NH_2 MOF modified with aptamer AS1411 (Fe_3O_4@MOF-DOX-CDs-Apt). The new nano-carrier showed death of 77% of breast cancer cells in 24 hours due to higher targeting of human breast cancer cells along with pH stimulated release. The MOF based agent was harmless to normal cells. In addition, carbon dots helped in bio-imaging of cancer cells. Other examples are discussed in anti-cancer drug delivery.

Different modes of delivery

MOFs have been found useful to administer certain drugs in ways, which were conventionally not possible. It has also improved certain drug administration systems, therefore, avoiding the possible side effects. Some of the examples are given in Table 3.

Personalized care

The emerging need for personalized medicine and its recent applications in preventive and targeted treatment of diseases like cancer, rheumatoid arthritis, asthma etc. have revealed the gap between existing and next generation medicine.[97–99] According to National Cancer Institute[100] (NCI) USA, personalized medicine can be understood as a spectrum of methodologies applied to study the person's specific genetic or protein or physiological information and use the same to prevent, diagnose and treat the disease and also track the effectiveness of the treatment. MOFs and its composites have been identified to help in developing methodologies for personalized medicinal care.[101] For instance, use of platelet membrane coated Zn based MOF for delivering siRNA for gene silencing purposes[102] for cancer treatment development, use of ZIF-8 in gene delivery purposes,[100] and Sr-HCOOH MOFs role in gene expression regulation,[103] all lay foundation for further development of precision medicine.

Applications in different arenas of diseases

Occular drug delivery

Mitigating the conventional drawbacks of traditional drop methodology for occular drug delivery, Gandara-Loe et al.,[104] have designed a novel nano-MOF based Drug delivery platform (UiO-67@polyurethane film) customizable as constituent element of contact lens, lacrimal stoppers and/or sub-tenon inserts. It has shown excellent absorption to release ratio with the popular glaucoma therapy drug, brimonidine tartrate, thereby subsiding need of excess drug concentration (to compensate loss during drop application) and its related side effects.

Neurodegenerative diseases drug delivery

MOFs have found a place in the diagnosis and therapy of neuro-degenerative disorders. For example- Zhao et al.,[105] have fabricated an advanced drug delivery platform notified as Fe-MIL-88B-NH_2-NOTA-DMK-6240/MB, which successfully helped in the diagnosis of Alzheimer's disease and in pacifying the symptoms. Further neural stem cells transplantation therapy for treatment of Alzheimer's and other neuro-degenerative disorders are under scrutiny of research and use of MOF (H_2O_2-responsive) has been explored with successful and promising results in mice model.[106]

Diabetes-insulin oral delivery

The alternative to popular sub-cutaneous injection of insulin is the oral delivery, but it doesn't find space due to very low bioavailability of insulin in this approach. However, this approach can help sidestep the potential risks and complications of the former. In pursuit to make oral delivery of insulin feasible Zhou et al.,[95] have used Fe-based MIL-100 nanoparticles with surface modifications to form an insulin delivery agent which could be administered orally due to pH responsive mechanism of unloading. The principle of personalized medicine is further accomplished via development of glucose level responsive MOF based insulin delivery platforms, example ZIF-8 based system prepared by Duan et al.[107]

Pulmonary drug delivery

MOFs have also found use in delivery of drugs for treating pulmonary diseases because of its property of deep lung penetration in addition to other advantageous properties like high porosity, better drug loading etc. UiO-66 based nanoparticles form good candidates for this purpose.[108] CD-MOF is also found to be a promising material for drugs of respiratory diseases.[106] Budesonide, a pulmonary disease relief drug, especially for asthma symptoms, was loaded on γ-cyclodextrin MOF (CD-MOF) to improve its delivery.[109] Another composite using Fe-MIL-100 (MOF) for carrying theophylline (a drug for asthma and chronic obstructive pulmonary disease) is also tested to be useful, nontoxic carrier.[110]

Osteoarthritis therapeutic treatment

Sr-HCOOH MOF is shown to deliver ketoprofen in the system to alleviate symptoms of osteoarthritis. However, its effect of inhibiting gene expression IL-1β, iNOS, and RANKL has opened the discussion of it being a drug rather than just a drug carrier.[103] Further Mg-HCOOH- MOF is also suggested for the treatment of osteoarthritis.[111]

Anti-HIV drug delivery

MOF- MIL-100 nanoparticles have been found to be a potential platform for loading of a preventive drug AZT-TP and its intracellular delivery thereby preventing the chances of HIV infection largely in HIV target cells, thus MOFs have given rise to new possibilities in treatment of HIV and AIDS.[112]

Anti-microbial drug delivery

MOFs have been widely used as an anti-bacterial drug delivery agent.[113] Some instances are: Cu/H_3_BTC MOF is used as an antibacterial therapeutic agent against *Staphylococcus aureus* and *Escherichia coli*.[114] Liu et al.,[115] fabricated an ZIF-8 encapsulated with Humic acid which showed excellent light-responsive antibacterial activity with zinc ion assisted photothermal therapy. When solubilized sulfadiazin (an anti-bacterial drug) was co-delivered with superfine nano silver using CD-MOF, it presented enhanced efficacy of the drug and its effect in treatment.[85]

Anti-cancer drug delivery

This is the most widely explored field for applications of MOFs as drug delivery system (DDS). This is due to the availability of targeted delivery possibilities based on modifications and different stimulus.

Owing to use of aerobic glycolysis as a metabolism pathway by tumor cells, a low pH micro-environment is created around them.[116] Various MOFs are found to be pH-responsive with higher unloading at low pH (2-5) and slower at normal tissue pH of 7.4. This paves way for targeted anti-cancer therapy based on MOFs. For example, pH responsive Cu-based MOF DDS against A549 and HeLa cells was developed by Liu et al.[109]

Further, the integrated approach of diagnosis and treatment has led the way toward better targeted therapies such as dual-responsive MOFs. In this pursuit, Lin et al.,[117] developed a Zr-based MOF functionalized with acetaldehyde-modified cysteine which worked as a dual responsive DDS (responsive to both pH and GSH) for the release of anti-cancer drug methotrexate. Similarly, a Zn-based MOF (referred as Zn-TBDA) is a pH and temperature responsive smart drug carrier developed by Wenxin et al.,[118] A pH and redox sensitive dual release drug delivery platform using ZIF-8 with organosilica shell has also been developed for anticancer drug doxorubicin.[119]

MOFs have further opened possibilities of easier modes of drug administration which is truly revolutionary, especially in a disease like cancer, for instance, to design more efficient oral delivery DDS for colon cancer, Javanbakht et al.,[120] forged a nanocomposite of the Zn-based MOF loaded with 5-fluorouracil and carboxymethylcellulose-a biopolymer. The resultant was performed well in simulated gastro-intestinal environment, emerging as a novel potential oral delivery vehicle for colon cancer drug 5-FU. Javanbakht et al.,[121] made a composite by adding Zn-based MOF (MOF-5) along with carboxymethylcellulose to graphene oxide, which they used to deliver anticancer drug effective against K562 cells. More examples of MOFs used as stimulus sensitive anticancer drug delivery agents are listed in Table 4.

Table 4. Examples of MOFs used in anti-cancer drug delivery and their properties.

Sr. no.	MOF	Stimulus	Advantages	Reference
1.	UiO-66-$(SH)_2$	Redox-sensitive	Glutathione -triggered	[73]
2.	Fe3O4@MIL-100@CMD@Mab@Dau	Antibody-responsive	Targets HER2 cancer cells	[122]
3.	MIL-53	pH and temperature sensitive	Targets Glioblastoma cells	[123]
4.	UiO-AZB@5-FU	Light responsive	Excellent control due to external stimuli-based approach	[124]
5.	ZIF-8	pH-responsive	Targets breast cancer (3hb5 oxidoreductase receptor) and liver cancer (2h80 lipid binding protein)	[125]

Conclusion

MOFs have been found to be one of the most versatile materials for carrying out research and applying it in various fields as per the current day requirements. They have gained rightful popularity since their recognition in 1964, owing to its far end nature of properties like high porosity with uniform pore structure with tunability, flexibility, high surface area, high loading capacity. Moreover, these properties can be attuned via different synthesis (solvothermal, microwave, sonothermal, ionothermal etc) and post synthesis modification processes (co-ordination modulation, surfactant modulation etc). The combination of complexity of structure/composition and flexibility of properties have given access to range of its emerging applications, for instance, gas exchange, supercapacitors, bio-sensing, photocatalysis etc.

Based on this review it can be concluded that, there are various methods by which MOFs can be synthesized and depending on the combination of metal ion and linker, many types of MOFs can be prepared. The method used for synthesis would depends on the properties which are required for a particular application. There is an overview of the size and morphology of the MOFs and their structure also. The emphasis in the paper is on the application of MOFs in drug delivery. Some of the characteristics which make the application of MOFs in drug delivery effective are their controlled and prolonged delivery, enhanced solubility for poorly soluble drugs, usage for drugs containing toxic ions, a number of drugs which can be loaded together, and it can also be made as a stimulus-based application. The specificity can be seen in the treatment of various diseases like ocular, anti-cancer, anti-diabetic, neurogenerative etc.

The current research in MOFs focuses on discovering new framework topologies and engineering better responsive MOFs with modifying its surface, pore size, load capacity and solubility. However, the future is predicted to contain different green synthetic approaches for MOFs along with applied changes in crystal structure to observe and achieve desirable consequences. The future research should focus on first, exploiting the bio-interacting capabilities of MOFs to the maximum, in order to engineer and deliver economic, effective and precision medicine therapies to the public and second, to maximize the use of MOFs into the eco-friendly technologies along with its use in reducing pollution. With the ever-changing world, and the growing pollution and the newly emerging threats to our health, we need to be armed to counter and reverse the apocalyptic changes for which the wheels are in motion already. MOFs with their promising results in various technological and bio-medical fields can prove to be revolutionary if correctly exploited.

Acknowledgment

The authors are grateful to Amity University for providing the required resources for reviewing the research work and presenting it in the form of an article.

Disclosure statement

The authors declare no competing financial interest.

ORCID

Deepshikha Gupta http://orcid.org/0000-0001-7199-3618

References

1. Batten, S. R.; Champness, N. R.; Chen, X.-M.; Garcia-Martinez, J.; Kitagawa, S.; Öhrström, L.; O'Keeffe, M.; Paik Suh, M.; Reedijk, J. Terminology of Metal–Organic Frameworks and Coordination Polymers (IUPAC Recommendations 2013). *Pure Appl. Chem.* **2013**, *85*, 1715–1724. DOI: 10.1351/PAC-REC-12-11-20.
2. Soni, S.; Bajpai, P.; Arora, C. A Review on Metal-Organic Framework: Synthesis, Properties and Application. *Character. Appl. Nanomater.* **2020**, *3*, 551. DOI: 10.24294/can.v2i2.551.
3. Bailar, J. C. Jr. Coordination Chemistry. *Prep. Inorg. React.* **1964**, 1, 1–27.
4. Yaghi, O. M.; Li, G.; Li, H. Selective Binding and Removal of Guests in a Microporous Metal–Organic Framework. *Nature* **1995**, *378*, 703–706. DOI: 10.1038/378703a0.
5. Cheetham, A. K.; Férey, G.; Loiseau, T. Open-Framework Inorganic Materials. *Angew. Chem. Int. Ed.* **1999**, *38*, 3268–3292. DOI: 10.1002/(SICI)1521-3773(19991115)38:22<3268::AID-ANIE3268>3.0.CO;2-U.
6. Bučar, D.-K.; Papaefstathiou, G. S.; Hamilton, T. D.; Chu, Q. L.; Georgiev, I. G.; MacGillivray, L. R. Template-Controlled Reactivity in the Organic Solid State by Principles of Coordination-Driven Self-Assembly. *Eur. J. Inorg. Chem.* **2007**, *2007*, 4559–4568. DOI: 10.1002/ejic.200700442.
7. Seetharaj, R.; Vandana, P. V.; Arya, P.; Mathew, S. Dependence of Solvents, pH, Molar Ratio and Temperature in Tuning Metal Organic Framework Architecture. *Arabian J. Chem.* **2019**, *12*, 295–315. DOI: 10.1016/j.arabjc.2016.01.003.
8. Li, C.; Wang, K.; Li, J.; Zhang, Q. Recent Progress in Stimulus-Responsive Two-Dimensional Metal–Organic Frameworks. *ACS Mater. Lett.* **2020**, *2*, 779–797. DOI: 10.1021/acsmaterialslett.0c00148.
9. Wang, K.; Bi, R.; Huang, M.; Lv, B.; Wang, H.; Li, C.; Wu, H.; Zhang, Q. Porous Cobalt Metal-Organic Frameworks as Active Elements in Battery-Supercapacitor Hybrid Devices. *Inorg. Chem.* **2020**, *59*, 6808–6814. DOI: 10.1021/acs.inorgchem.0c00060.
10. Rubio-Martinez, M.; Avci-Camur, C.; Thornton, A. W.; Imaz, I.; Maspoch, D.; Hill, M. R. New Synthetic Routes towards MOF Production at Scale. *Chem. Soc. Rev.* **2017**, *46*, 3453–3480. DOI: 10.1039/c7cs00109f.
11. 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.
12. Chemtube3d.com. *Inorganic Chemistry-Metal Organic Frameworks*. https://www.chemtube3d.com/category/inorganic-chemistry/metal-organic-frameworks/accessed on 10'th February 2021.
13. Lee, Y.-R.; Jang, M.-S.; Cho, H.-Y.; Kwon, H.-J.; Kim, S.; Ahn, W.-S. ZIF-8: A Comparison of Synthesis Methods. *Chem. Eng. J.* **2015**, *271*, 276–280. DOI: 10.1016/j.cej.2015.02.094.
14. Trung, T. K.; Ramsahye, N. A.; Trens, P.; Tanchoux, N.; Serre, C.; Fajula, F.; Férey, G. Adsorption of C5–C9 Hydrocarbons in Microporous MOFs MIL-100 (Cr) and MIL-101 (Cr): a Manometric Study. *Microporous Mesoporous Mater.* **2010**, *134*, 134–140. DOI: 10.1016/j.micromeso.2010.05.018.
15. Yin, R.; Li, T.; Tian, J. X.; Xi, P.; Liu, R. H. Ursolic Acid, a Potential Anticancer Compound for Breast Cancer Therapy.

Crit. Rev. Food Sci. Nutr. **2018**, *58*, 568–574. DOI: 10.1080/10408398.2016.1203755.
16. Lee, Y.-R.; Kim, J.; Ahn, W.-S. Synthesis of Metal-Organic Frameworks: A Mini Review. *Korean J. Chem. Eng.* **2013**, *30*, 1667–1680. DOI: 10.1007/s11814-013-0140-6.
17. Stock, N.; Biswas, S. Synthesis of Metal-Organic Frameworks (MOFs): Routes to Various MOF Topologies, Morphologies, and Composites. *Chem. Rev.* **2012**, *112*, 933–969. DOI: 10.1021/cr200304e.
18. Cohen, S. M. Postsynthetic Methods for the Functionalization of Metal-Organic Frameworks. *Chem. Rev.* **2012**, *112*, 970–1000. DOI: 10.1021/cr200179u.
19. Hoskins, B. F.; Robson, R. Design and Construction of a New Class of Scaffolding-Like Materials Comprising Infinite Polymeric Frameworks of 3D-Linked Molecular Rods. A Reappraisal of the Zinc Cyanide and Cadmium Cyanide Structures and the Synthesis and Structure of the Diamond-Related Frameworks [N (CH3) 4][CuIZnII (CN) 4] and CuI [4, 4', 4", 4"'-Tetracyanotetraphenylmethane] BF4. xC6H5NO2. *J. Am. Chem. Soc.* **1990**, *112*, 1546–1554. DOI: 10.1021/ja00160a038.
20. McKinstry, C.; Cathcart, R. J.; Cussen, E. J.; Fletcher, A. J.; Patwardhan, S. V.; Sefcik, J. Scalable Continuous Solvothermal Synthesis of Metal Organic Framework (MOF-5) Crystals. *Chem. Eng. J.* **2016**, *285*, 718–725. DOI: 10.1016/j.cej.2015.10.023.
21. Long, P.; Wu, H.; Zhao, Q.; Wang, Y.; Dong, J.; Li, J. Solvent Effect on the Synthesis of MIL-96 (Cr) and MIL-100 (Cr). *Microporous Mesoporous Mater.* **2011**, *142*, 489–493. DOI: 10.1016/j.micromeso.2010.12.036.
22. Otun, K. O. Temperature-Controlled Activation and Characterization of Iron-Based Metal-Organic Frameworks. *Inorg. Chim. Acta* **2020**, *507*, 119563. DOI: 10.1016/j.ica.2020.119563.
23. Chavan, S. M.; Shearer, G. C.; Svelle, S.; Olsbye, U.; Bonino, F.; Ethiraj, J.; Lillerud, K. P.; Bordiga, S. Synthesis and Characterization of Amine-Functionalized Mixed-Ligand Metal–Organic Frameworks of UiO-66 Topology. *Inorg. Chem.* **2014**, *53*, 9509–9515. DOI: 10.1021/ic500607a.
24. Zhang, X.; Gao, Y.; Liu, H.; Liu, Z. Fabrication of Porous Metal–Organic Frameworks via a Mixed-Ligand Strategy for Highly Selective and Efficient Dye Adsorption in Aqueous Solution. *CrystEngComm* **2015**, *17*, 6037–6043. DOI: 10.1039/C5CE00862J.
25. Ban, Y.; Li, Y.; Liu, X.; Peng, Y.; Yang, W. Solvothermal Synthesis of Mixed-Ligand Metal–Organic Framework ZIF-78 with Controllable Size and Morphology. *Microporous Mesoporous Mater.* **2013**, *173*, 29–36. DOI: 10.1016/j.micromeso.2013.01.031.
26. Lalonde, M.; Bury, W.; Karagiaridi, O.; Brown, Z.; Hupp, J. T.; Farha, O. K. Transmetalation: Routes to Metal Exchange within Metal–Organic Frameworks. *J. Mater. Chem. A* **2013**, *1*, 5453–5468. DOI: 10.1039/c3ta10784a.
27. Abednatanzi, S.; Gohari Derakhshandeh, P.; Depauw, H.; Coudert, F.-X.; Vrielinck, H.; Van Der Voort, P.; Leus, K. Mixed-Metal Metal-Organic Frameworks. *Chem. Soc. Rev.* **2019**, *48*, 2535–2565. DOI: 10.1039/c8cs00337h.
28. Wang, Z.; Cohen, S. M. Postsynthetic Modification of Metal-Organic Frameworks. *Chem. Soc. Rev.* **2009**, *38*, 1315–1329. DOI: 10.1039/b802258p.
29. Song, Y.-F.; Cronin, L. Postsynthetic Covalent Modification of Metal-Organic Framework (MOF) Materials. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 4635–4637. DOI: 10.1002/anie.200801631.
30. Li, B.; Zhang, Y.; Ma, D.; Li, L.; Li, G.; Li, G.; Shi, Z.; Feng, S. A Strategy toward Constructing a Bifunctionalized MOF Catalyst: post-Synthetic Modification of MOFs on Organic Ligands and Coordinatively Unsaturated Metal Sites. *Chem. Commun. (Camb.)* **2012**, *48*, 6151–6153. DOI: 10.1039/c2cc32384b.
31. Blăniță, G. *Microwave Assisted Synthesis of MOF-5 at Atmospheric Pressure. Rev. Roum. Chim.* **2011**, *56*, 583–588.
32. Anumah, A. Metal-Organic Frameworks (MOFs): Recent Advances in Synthetic Methodologies and Some Applications. *Chem. Methodol.* **2019**, *3*, 283–305.
33. Vakili, R.; Xu, S.; Al-Janabi, N.; Gorgojo, P.; Holmes, S. M.; Fan, X. Microwave-Assisted Synthesis of Zirconium-Based Metal Organic Frameworks (MOFs): Optimization and Gas Adsorption. *Microporous Mesoporous Mater.* **2018**, *260*, 45–53. DOI: 10.1016/j.micromeso.2017.10.028.
34. Chen, C.; Feng, X.; Zhu, Q.; Dong, R.; Yang, R.; Cheng, Y.; He, C. Microwave-Assisted Rapid Synthesis of Well-Shaped MOF-74 (Ni) for CO2 Efficient Capture. *Inorg. Chem.* **2019**, *58*, 2717–2728. DOI: 10.1021/acs.inorgchem.8b03271.
35. Suslick, K. S.; Hyeon, T.; Fang, M.; Cichowlas, A. A. Sonochemical Synthesis of Nanostructured Catalysts. *Mater. Sci. Eng. A* **1995**, *204*, 186–192. DOI: 10.1016/0921-5093(95)09958-1.
36. Lestari, W. W.; Arvinawati, M.; Martien, R.; Kusumaningsih, T. Green and Facile Synthesis of MOF and Nano MOF Containing Zinc (II) and Benzen 1, 3, 5-Tri Carboxylate and Its Study in Ibuprofen Slow-Release. *Mater. Chem. Phys.* **2018**, *204*, 141–146. DOI: 10.1016/j.matchemphys.2017.10.034.
37. Nadar, S. S.; Rathod, V. K. Encapsulation of Lipase within Metal-Organic Framework (MOF) with Enhanced Activity Intensified under Ultrasound. *Enzyme Microb. Technol.* **2018**, *108*, 11–20. DOI: 10.1016/j.enzmictec.2017.08.008.
38. Yang, Z.; Pan, W. Ionic Liquids: Green Solvents for Nonaqueous Biocatalysis. *Enzyme Microb. Technol.* **2005**, *37*, 19–28. DOI: 10.1016/j.enzmictec.2005.02.014.
39. Oh, H.-C.; Jung, S.; Ko, I.-J.; Choi, E.-Y. Ionothermal Synthesis of Metal-Organic Framework. In *Recent Advancements in the Metallurgical Engineering and Electrodeposition*; IntechOpen, November 5th, **2018**.
40. Liu, L.; Wei, H.; Zhang, L.; Li, J.; Dong, J. Ionothermal Synthesis of the Metal-Organic Framework Compound Cu3 (BTC) 2. In *Studies in Surface Science and Catalysis*; Elsevier, **2008**; 174, part A, 459–462.
41. Li, P.; Cheng, F.-F.; Xiong, W.-W.; Zhang, Q. New Synthetic Strategies to Prepare Metal–Organic Frameworks. *Inorg. Chem. Front.* **2018**, *5*, 2693–2708. DOI: 10.1039/C8QI00543E.
42. Zhao, J.; Liu, X.; Wu, Y.; Li, D.-S.; Zhang, Q. Surfactants as Promising Media in the Field of Metal-Organic Frameworks. *Coord. Chem. Rev.* **2019**, *391*, 30–43. DOI: 10.1016/j.ccr.2019.04.002.
43. Xiong, W.-W.; Li, P.-Z.; Zhou, T.-H.; Tok, A. I. Y.; Xu, R.; Zhao, Y.; Zhang, Q. Kinetically Controlling Phase Transformations of Crystalline Mercury Selenidostannates through Surfactant Media. *Inorg. Chem.* **2013**, *52*, 4148–4150. DOI: 10.1021/ic4002169.
44. Gao, J.; Ye, K.; Yang, L.; Xiong, W.-W.; Ye, L.; Wang, Y.; Zhang, Q. Growing Crystalline Zinc-1,3,5-Benzenetricarboxylate Metal–Organic Frameworks in Different Surfactants. *Inorg. Chem.* **2014**, *53*, 691–693. DOI: 10.1021/ic402692p.
45. Gao, J.; Ye, K.; He, M.; Xiong, W.-W.; Cao, W.; Lee, Z. Y.; Wang, Y.; Wu, T.; Huo, F.; Liu, X.; et al. Tuning Metal–Carboxylate Coordination in Crystalline Metal–Organic Frameworks through Surfactant Media. *J. Solid State Chem.* **2013**, *206*, 27–31. DOI: 10.1016/j.jssc.2013.07.031.
46. Gao, J.; He, M.; Lee, Z. Y.; Cao, W.; Xiong, W.-W.; Li, Y.; Ganguly, R.; Wu, T.; Zhang, Q. A Surfactant-Thermal Method to Prepare Four New Three-Dimensional Heterometal–Organic Frameworks. *Dalton Trans.* **2013**, *42*, 11367–11370. DOI: 10.1039/c3dt51103k.
47. Zhao, J.; Wang, Y.; Dong, W.; Wu, Y.; Li, D.; Liu, B.; Zhang, Q. A New surfactant-introduction strategy for separating the pure single-phase of metal-organic frameworks. *Chem. Commun. (Camb.)* **2015**, *51*, 9479–9482. DOI: 10.1039/c5cc02043c.
48. Yu, X.; Toh, Y. S.; Zhao, J.; Nie, L.; Ye, K.; Wang, Y.; Li, D.; Zhang, Q. Surfactant-Thermal Method to Prepare Two New

Cobalt Metal-Organic Frameworks. *J. Solid State Chem.* **2015**, *232*, 14–18. DOI: 10.1016/j.jssc.2015.08.048.
49. Yakovenko, A. A.; Wei, Z.; Wriedt, M.; Li, J.-R.; Halder, G. J.; Zhou, H.-C. Study of Guest Molecules in Metal–Organic Frameworks by Powder X-Ray Diffraction: Analysis of Difference Envelope Density. *Cryst. Growth Des.* **2014**, ***14***, 5397–5407. DOI: 10.1021/cg500525g.
50. Lv, Y.; Wang, S.; Zhang, R.; Zhang, D.; Yu, H.; Lu, G. pH-Modulated Formation of Uniform MOF-5 Sheets. *Inorg. Chem. Commun.* **2018**, *97*, 30–33. DOI: 10.1016/j.inoche.2018.09.003.
51. Zhang, W.-H.; Wang, Y.-Y.; Lermontova, E. K.; Yang, G.-P.; Liu, B.; Jin, J.-C.; Dong, Z.; Shi, Q.-Z. Interaction of 1,3-Adamantanediacetic Acid (H2ADA) and Ditopic Pyridyl Subunits with Cobalt Nitrate under Hydrothermal Conditions: pH Influence, Crystal Structures, and Their Properties. *Cryst. Growth Des.* **2010**, *10*, 76–84. DOI: 10.1021/cg900285b.
52. Luo, L.; Lv, G.-C.; Wang, P.; Liu, Q.; Chen, K.; Sun, W.-Y. pH-Dependent Cobalt(ii) Frameworks with Mixed 3,3′,5,5′-Tetra(1H-Imidazol-1-yl)-1,1′-Biphenyl and 1,3,5-Benzenetricarboxylate Ligands: Synthesis, Structure and Sorption Property. *CrystEngComm* **2013**, *15*, 9537–9543. DOI: 10.1039/c3ce41056k.
53. Lin, R.-G.; Long, L.-S.; Huang, R.-B.; Zheng, L.-S. pH-Controlled the Formation of 4-Sulfocalix[4]Arene-Based 1D and 2D Coordination Polymers. *Inorg. Chem. Commun.* **2007**, *10*, 1257–1261. DOI: 10.1016/j.inoche.2007.08.003.
54. Yin, P.-X.; Zhang, J.; Qin, Y.-Y.; Cheng, J.-K.; Li, Z.-J.; Yao, Y.-G. Role of Molar-Ratio, Temperature and Solvent on the Zn/Cd 1,2,4-Triazolate System with Novel Topological Architectures. *CrystEngComm* **2011**, *13*, 3536–3544. DOI: 10.1039/c0ce00762e.
55. Han, Y.; Yang, H.; Guo, X. Synthesis Methods and Crystallization of MOFs. In *Synthesis Methods and Crystallization*; IntechOpen Ltd. London,Edited by Riadh Marzouki **2020**.
56. 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.
57. Tsuruoka, T.; Furukawa, S.; Takashima, Y.; Yoshida, K.; Isoda, S.; Kitagawa, S. Nanoporous Nanorods Fabricated by Coordination Modulation and Oriented Attachment Growth. *Angew. Chem.* **2009**, *121*, 4833–4837. DOI: 10.1002/ange.200901177.
58. Diring, S.; Furukawa, S.; Takashima, Y.; Tsuruoka, T.; Kitagawa, S. Controlled Multiscale Synthesis of Porous Coordination Polymer in Nano/Micro Regimes. *Chem. Mater.* **2010**, *22*, 4531–4538. DOI: 10.1021/cm101778g.
59. Cai, X.; Lin, J.; Pang, M. Facile Synthesis of Highly Uniform Fe-MIL-88B Particles. *Cryst. Growth Des.* **2016**, ***16***, 3565–3568. DOI: 10.1021/acs.cgd.6b00313.
60. 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.
61. Czaja, A. U.; Trukhan, N.; Müller, U. Industrial Applications of Metal-Organic Frameworks. *Chem. Soc. Rev.* **2009**, *38*, 1284–1293. DOI: 10.1039/b804680h.
62. Zhang, Y.-Z.; Song, X.-S.; Yang, J.-M. Modulation of Driving Forces of UiO-66 Analog Adsorbents by Decoration with Amino Functional Groups: Superior Adsorption of Hazardous Dyes. *J. Mol. Struct.* **2020**, *1220*, 128716. DOI: 10.1016/j.molstruc.2020.128716.
63. Zhang, F.; Shi, J.; Jin, Y.; Fu, Y.; Zhong, Y.; Zhu, W. Facile Synthesis of MIL-100 (Fe) under HF-Free Conditions and Its Application in the Acetalization of Aldehydes with Diols. *Chem. Eng. J.* **2015**, *259*, 183–190. DOI: 10.1016/j.cej.2014.07.119.
64. Lee, J.; Li, J.; Jagiello, J. Gas Sorption Properties of Microporous Metal Organic Frameworks. *J. Solid State Chem.* **2005**, *178*, 2527–2532. DOI: 10.1016/j.jssc.2005.07.002.
65. Perez, E.; Karunaweera, C.; Musselman, I.; Balkus, K.; Ferraris, J. Origins and Evolution of Inorganic-Based and MOF-Based Mixed-Matrix Membranes for Gas Separations. *Processes* **2016**, *4*, 32. DOI: 10.3390/pr4030032.
66. Alaerts, L.; Séguin, E.; Poelman, H.; Thibault-Starzyk, F.; Jacobs, P. A.; De Vos, D. E. Probing the Lewis Acidity and Catalytic Activity of the Metal-Organic Framework [Cu3(btc)2] (BTC = Benzene-1,3,5-Tricarboxylate). *Chemistry* **2006**, *12*, 7353–7363. DOI: 10.1002/chem.200600220.
67. Serre, C.; Mellot-Draznieks, C.; Surblé, S.; Audebrand, N.; Filinchuk, Y.; Férey, G. Role of Solvent-Host Interactions that Lead to Very Large Swelling of Hybrid Frameworks. *Science* **2007**, *315*, 1828–1831. DOI: 10.1126/science.1137975.
68. García-Pérez, E.; Gascón, J.; Morales-Flórez, V.; Castillo, J. M.; Kapteijn, F.; Calero, S. Identification of Adsorption Sites in Cu-BTC by Experimentation and Molecular Simulation. *Langmuir* **2009**, *25*, 1725–1731. DOI: 10.1021/la803085h.
69. Flores, P. J. R.; Josue, P. *Coordination Polymers of the Alkaline Earth Metals for Applications in Synthesis and Gas Storage*; Syracuse University, New York, **2014**.
70. Banerjee, D.; Zhang, Z.; Plonka, A. M.; Li, J.; Parise, J. B. A Calcium Coordination Framework Having Permanent Porosity and High CO2/N2 Selectivity. *Cryst. Growth Des.* **2012**, *12*, 2162–2165. DOI: 10.1021/cg300274n.
71. Prestipino, C.; Regli, L.; Vitillo, J. G.; Bonino, F.; Damin, A.; Lamberti, C.; Zecchina, A.; Solari, P. L.; Kongshaug, K. O.; Bordiga, S.; et al. Local Structure of Framework Cu (II) in HKUST-1 Metallorganic Framework: spectroscopic Characterization upon Activation and Interaction with Adsorbates. *Chem. Mater.* **2006**, *18*, 1337–1346. DOI: 10.1021/cm052191g.
72. Webber, T. E.; Desai, S. P.; Combs, R. L.; Bingham, S.; Lu, C. C.; Penn, R. L. Size Control of the MOF NU-1000 through Manipulation of the Modulator/Linker Competition. *Cryst. Growth Des.* **2020**, *20*, 2965–2972. DOI: 10.1021/acs.cgd.9b01590.
73. Gong, M.; Yang, J.; Li, Y.; Gu, J. Glutathione-Responsive Nanoscale MOFs for Effective Intracellular Delivery of the Anticancer Drug 6-Mercaptopurine. *Chem. Commun. (Camb.)* **2020**, *56*, 6448–6451. DOI: 10.1039/d0cc02872j.
74. 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.
75. Christodoulou, I.; Serre, C.; Gref, R. Chapter 21 - Metal-Organic Frameworks for Drug Delivery: Degradation Mechanism and in Vivo Fate. In *Metal-Organic Frameworks for Biomedical Applications*; Mozafari, M., Ed.; Woodhead Publishing, **2020**; pp 467–489.
76. Sun, Y.; Zheng, L.; Yang, Y.; Qian, X.; Fu, T.; Li, X.; Yang, Z.; Yan, H.; Cui, C.; Tan, W.; et al. Metal-Organic Framework Nanocarriers for Drug Delivery in Biomedical Applications. *Nanomicro. Lett.* **2020**, *12*, 103. DOI: 10.1007/s40820-020-00423-3.
77. Wang, H.-S.; Wang, Y.-H.; Ding, Y. Development of Biological Metal–Organic Frameworks Designed for Biomedical Applications: From Bio-Sensing/Bio-Imaging to Disease Treatment. *Nanoscale Adv.* **2020**, *2*, 3788–3797. DOI: 10.1039/D0NA00557F.
78. Abánades Lázaro, I.; Abánades Lázaro, S.; Forgan, R. S. Enhancing Anticancer Cytotoxicity through Bimodal Drug Delivery from Ultrasmall Zr MOF Nanoparticles. *Chem. Commun. (Camb.)* **2018**, *54*, 2792–2795. DOI: 10.1039/c7cc09739e.
79. Chen, D.; Yang, D.; Dougherty, C. A.; Lu, W.; Wu, H.; He, X.; Cai, T.; Van Dort, M. E.; Ross, B. D.; Hong, H.; et al. 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.

80. Zhou, J.; Tian, G.; Zeng, L.; Song, X.; Bian, X-w. Nanoscaled Metal-Organic Frameworks for Biosensing, Imaging, and Cancer Therapy. *Adv. Healthcare Mater.* **2018**, *7*, 1800022. DOI: 10.1002/adhm.201800022.
81. Lu, L.; Ma, M.; Gao, C.; Li, H.; Li, L.; Dong, F.; Xiong, Y. Metal Organic Framework@Polysilsesequioxane Core/Shell-Structured Nanoplatform for Drug Delivery. *Pharmaceutics* **2020**, *12*, 98. DOI: 10.3390/pharmaceutics12020098.
82. Orellana-Tavra, C.; Baxter, E. F.; Tian, T.; Bennett, T. D.; Slater, N. K. H.; Cheetham, A. K.; Fairen-Jimenez, D. Amorphous Metal-Organic Frameworks for Drug Delivery. *Chem. Commun. (Camb.)* **2015**, *51*, 13878–13881. DOI: 10.1039/c5cc05237h.
83. Suresh, K.; Matzger, A. J. Enhanced Drug Delivery by Dissolution of Amorphous Drug Encapsulated in a Water Unstable Metal-Organic Framework (MOF). *Angew. Chem. Int. Ed. Engl.* **2019**, *58*, 16790–16794. DOI: 10.1002/anie.201907652.
84. Zhang, W.; Guo, T.; Wang, C.; He, Y.; Zhang, X.; Li, G.; Chen, Y.; Li, J.; Lin, Y.; Xu, X.; et al. MOF Capacitates Cyclodextrin to Mega-Load Mode for High-Efficient Delivery of Valsartan. *Pharm. Res.* **2019**, *36*, 117. DOI: 10.1007/s11095-019-2650-3.
85. Luo, T.; Shakya, S.; Mittal, P.; Ren, X.; Guo, T.; Bello, M. G.; Wu, L.; Li, H.; Zhu, W.; Regmi, B.; et al. Co-Delivery of Superfine Nano-Silver and Solubilized Sulfadiazine for Enhanced Antibacterial Functions. *Int. J. Pharm.* **2020**, *584*, 119407. DOI: 10.1016/j.ijpharm.2020.119407.
86. He, Y.; Hou, X.; Guo, J.; He, Z.; Guo, T.; Liu, Y.; Zhang, Y.; Zhang, J.; Feng, N. Activation of a Gamma-Cyclodextrin-Based Metal-Organic Framework using Supercritical Carbon Dioxide for High-Efficient Delivery of Honokiol. *Carbohydr. Polym.* **2020**, *235*, 115935. DOI: 10.1016/j.carbpol.2020.115935.
87. 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.
88. 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. Chem. Int. Ed. Engl.* **2020**, *59*, 5211–5217. DOI: 10.1002/anie.201915848.
89. Liu, C.; Xu, X.; Zhou, J.; Yan, J.; Wang, D.; Zhang, H. Redox-Responsive Tumor Targeted Dual-Drug Loaded Biocompatible Metal–Organic Frameworks Nanoparticles for Enhancing Anticancer Effects. *BMC Mater.* **2020**, *2*, 7. DOI: 10.1186/s42833-020-00013-y.
90. 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.
91. Cai, W.; Wang, J.; Chu, C.; Chen, W.; Wu, C.; Liu, G. Metal-Organic Framework-Based Stimuli-Responsive Systems for Drug Delivery. *Adv. Sci. (Weinh.)* **2019**, *6*, 1801526. DOI: 10.1002/advs.201801526.
92. Alijani, H.; Noori, A.; Faridi, N.; Bathaie, S. Z.; Mousavi, M. F. Aptamer-Functionalized Fe3O4@MOF Nanocarrier for Targeted Drug Delivery and Fluorescence Imaging of the Triple-Negative MDA-MB-231 Breast Cancer Cells. *J. Solid State Chem.* **2020**, *292*, 121680. DOI: 10.1016/j.jssc.2020.121680.
93. Noorian, S. A.; Hemmatinejad, N.; Navarro, J. A. R. Bioactive Molecule Encapsulation on Metal-Organic Framework via Simple Mechanochemical Method for Controlled Topical Drug Delivery Systems. *Microporous Mesoporous Mater.* **2020**, *302*, 110199. DOI: 10.1016/j.micromeso.2020.110199.
94. Zhao, K.; Guo, T.; Wang, C.; Zhou, Y.; Xiong, T.; Wu, L.; Li, X.; Mittal, P.; Shi, S.; Gref, R.; et al. Glycoside Scutellarin Enhanced CD-MOF Anchoring for Laryngeal Delivery. *Acta Pharm. Sin. B* **2020**, *10*, 1709–1718. DOI: 10.1016/j.apsb.2020.04.015.
95. Zhou, Y.; Liu, L.; Cao, Y.; Yu, S.; He, C.; Chen, X. A Nanocomposite Vehicle Based on Metal-Organic Framework Nanoparticle Incorporated Biodegradable Microspheres for Enhanced Oral Insulin Delivery. *ACS Appl. Mater. Interfaces* **2020**, *12*, 22581–22592. DOI: 10.1021/acsami.0c04303.
96. Wang, Y.; Lin, W.; Yu, S.; Huang, X.; Lang, X.; He, Q.; Gao, L.; Zhu, H.; Chen, J. A Biocompatible Zr-Based Metal-Organic Framework UiO-66-PDC as an Oral Drug Carrier for pH-Response Release. *J. Solid State Chem.* **2021**, *293*, 121805. DOI: 10.1016/j.jssc.2020.121805.
97. Jackson, S. E.; Chester, J. D. Personalised Cancer Medicine. *Int. J. Cancer.* **2015**, *137*, 262–266. DOI: 10.1002/ijc.28940.
98. Isaacs, J. D.; Ferraccioli, G. The Need for Personalised Medicine for Rheumatoid Arthritis. *Ann. Rheum. Dis.* **2011**, *70*, 4–7. DOI: 10.1136/ard.2010.135376.
99. Guilleminault, L.; Ouksel, H.; Belleguic, C.; Le Guen, Y.; Germaud, P.; Desfleurs, E.; Leroyer, C.; Magnan, A. Personalised Medicine in Asthma: From Curative to Preventive Medicine. *Eur. Respir. Rev.* **2017**, *26*, 160010. DOI: 10.1183/16000617.0010-2016.
100. Abdelhamid, H. N.; Dowaidar, M.; Hällbrink, M.; Langel, Ü. Gene Delivery Using Cell Penetrating Peptides-Zeolitic Imidazolate Frameworks. *Microporous Mesoporous Mater.* **2020**, *300*, 110173. DOI: 10.1016/j.micromeso.2020.110173.
101. Osterrieth, J. W.; Fairen-Jimenez, D. Metal–Organic Framework Composites for Theragnostics and Drug Delivery Applications. *Biotechnol. J.* **2021**, *16*, 2000005. DOI: 10.1002/biot.202000005.
102. Zhuang, J.; Gong, H.; Zhou, J.; Zhang, Q.; Gao, W.; Fang, R. H.; Zhang, L. Targeted Gene Silencing In Vivo by Platelet Membrane-Coated Metal-Organic Framework Nanoparticles. *Sci. Adv.* **2020**, *6*, eaaz6108. DOI: 10.1126/sciadv.aaz6108.
103. Yu, D.; Ma, M.; Liu, Z.; Pi, Z.; Du, X.; Ren, J.; Qu, X. MOF-Encapsulated Nanozyme Enhanced siRNA Combo: Control Neural Stem Cell Differentiation and Ameliorate Cognitive Impairments in Alzheimer's Disease Model. *Biomaterials* **2020**, *255*, 120160. DOI: 10.1016/j.biomaterials.2020.120160.
104. Gandara-Loe, J.; Souza, B. E.; Missyul, A.; Giraldo, G.; Tan, J.-C.; Silvestre-Albero, J. MOF-Based Polymeric Nanocomposite Films as Potential Materials for Drug Delivery Devices in Ocular Therapeutics. *ACS Appl. Mater. Interfaces* **2020**, *12*, 30189–30197. DOI: 10.1021/acsami.0c07517.
105. 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.
106. Zhou, Y.; Niu, B.; Wu, B.; Luo, S.; Fu, J.; Zhao, Y.; Quan, G.; Pan, X.; Wu, C. A Homogenous Nanoporous Pulmonary Drug Delivery System Based on Metal-Organic Frameworks with Fine Aerosolization Performance and Good Compatibility. *Acta Pharm. Sin. B* **2020**, *10*, 2404–2416. DOI: 10.1016/j.apsb.2020.07.018.
107. Duan, Y.; Ye, F.; Huang, Y.; Qin, Y.; He, C.; Zhao, S. One-Pot Synthesis of a Metal-Organic Framework-Based Drug Carrier for Intelligent Glucose-Responsive Insulin Delivery. *Chem. Commun. (Camb.)* **2018**, *54*, 5377–5380. DOI: 10.1039/c8cc02708k.
108. Jarai, B. M.; Stillman, Z.; Attia, L.; Decker, G. E.; Bloch, E. D.; Fromen, C. A. Evaluating UiO-66 Metal-Organic Framework Nanoparticles as Acid-Sensitive Carriers for Pulmonary Drug Delivery Applications. *ACS Appl. Mater. Interfaces* **2020**, *12*, 38989–39004. DOI: 10.1021/acsami.0c10900.
109. Liu, W.; Zhong, Y.; Wang, X.; Zhuang, C.; Chen, J.; Liu, D.; Xiao, W.; Pan, Y.; Huang, J.; Liu, J.; et al. 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.

110. Strzempek, W.; Menaszek, E.; Gil, B. Fe-MIL-100 as Drug Delivery System for Asthma and Chronic Obstructive Pulmonary Disease Treatment and Diagnosis. *Microporous Mesoporous Mater.* **2019**, *280*, 264–270. DOI: 10.1016/j.micromeso.2019.02.018.
111. Li, Z.; Peng, Y.; Pang, X.; Tang, B. Potential Therapeutic Effects of Mg/HCOOH Metal Organic Framework on Relieving Osteoarthritis. *ChemMedChem* **2020**, *15*, 13–16. DOI: 10.1002/cmdc.201900546.
112. Agostoni, V.; Chalati, T.; Horcajada, P.; Willaime, H.; Anand, R.; Semiramoth, N.; Baati, T.; Hall, S.; Maurin, G.; Chacun, H.; et al. Towards an Improved Anti-HIV Activity of NRTI via Metal–Organic Frameworks Nanoparticles. *Adv. Healthc. Mater.* **2013**, *2*, 1630–1637. DOI: 10.1002/adhm.201200454.
113. Kaur, N.; Tiwari, P.; Kapoor, K. S.; Saini, A. K.; Sharma, V.; Mobin, S. M. Metal–Organic Framework Based Antibiotic Release and Antimicrobial Response: An Overview. *CrystEngComm* **2020**, *22*, 7513–7527. DOI: 10.1039/D0CE01215G.
114. Shams, S.; Ahmad, W.; Memon, A. H.; Shams, S.; Wei, Y.; Yuan, Q.; Liang, H. Cu/H3BTC MOF as a Potential Antibacterial Therapeutic Agent against *Staphylococcus aureus and Escherichia coli*. *New J. Chem.* **2020**, *44*, 17671–17678. DOI: 10.1039/D0NJ04120C.
115. Liu, Z.; Tan, L.; Liu, X.; Liang, Y.; Zheng, Y.; Yeung, K. W. K.; Cui, Z.; Zhu, S.; Li, Z.; Wu, S.; et al. Zn2+-Assisted Photothermal Therapy for Rapid Bacteria-Killing Using Biodegradable Humic Acid Encapsulated MOFs. *Colloids Surf. B Biointerfaces* **2020**, *188*, 110781. DOI: 10.1016/j.colsurfb.2020.110781.
116. Annibaldi, A.; Widmann, C. Glucose Metabolism in Cancer Cells. *Curr. Opin. Clin. Nutr. Metab. Care* **2010**, ***13***, 466–470. DOI: 10.1097/MCO.0b013e32833a5577.
117. Lin, C.; He, H.; Zhang, Y.; Xu, M.; Tian, F.; Li, L.; Wang, Y. Acetaldehyde-Modified-Cystine Functionalized Zr-MOFs for pH/GSH Dual-Responsive Drug Delivery and Selective Visualization of GSH in Living Cells. *RSC Adv.* **2020**, *10*, 3084–3091. DOI: 10.1039/C9RA05741B.
118. Lin, W.; Hu, Q.; Jiang, K.; Cui, Y.; Yang, Y.; Qian, G. A Porous Zn-Based Metal-Organic Framework for pH and Temperature Dual-Responsive Controlled Drug Release. *Microporous Mesoporous Mater.* **2017**, *249*, 55–60. DOI: 10.1016/j.micromeso.2017.04.042.
119. 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.; et al. 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.
120. 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.
121. Javanbakht, S.; Pooresmaeil, M.; Namazi, H. Green One-Pot Synthesis of Carboxymethylcellulose/Zn-Based Metal-Organic Framework/Graphene Oxide Bio-Nanocomposite as a Nanocarrier for Drug Delivery System. *Carbohydr. Polym.* **2019**, *208*, 294–301. DOI: 10.1016/j.carbpol.2018.12.066.
122. Cherkasov, V. R.; Mochalova, E. N.; Babenyshev, A. V.; Rozenberg, J. M.; Sokolov, I. L.; Nikitin, M. P. Antibody-Directed Metal-Organic Framework Nanoparticles for Targeted Drug Delivery. *Acta Biomater.* **2020**, *103*, 223–236. DOI: 10.1016/j.actbio.2019.12.012.
123. Bazzazzadeh, A.; Dizaji, B. F.; Kianinejad, N.; Nouri, A.; Irani, M. Fabrication of Poly(Acrylic Acid) Grafted-Chitosan/Polyurethane/Magnetic MIL-53 Metal Organic Framework Composite Core-Shell Nanofibers for Co-Delivery of Temozolomide and Paclitaxel against Glioblastoma Cancer Cells. *Int. J. Pharm.* **2020**, *587*, 119674. DOI: 10.1016/j.ijpharm.2020.119674.
124. Roth, S. K.; Epley, C. C., Novak, J. J.; McAndrew, M. L.; Cornell, H. D.; Zhu, J.; McDaniel, D. K.; Davis, J. L.; Allen, I. C.; Morris, A. J. Grove, T. Z.; Photo-Triggered Release of 5-Fluorouracil from a MOF Drug Delivery Vehicle. *Chem. Commun.* **2018**, *54*, 7617–7620.
125. El-Bindary, A. A.; Toson, E. A.; Shoueir, K. R.; Aljohani, H. A.; Abo-Ser, M. M. Metal–Organic Frameworks as Efficient Materials for Drug Delivery: Synthesis, Characterization, Antioxidant, Anticancer, Antibacterial and Molecular Docking Investigation. *Appl. Organomet. Chem.* **2020**, *34*, e5905. DOI: 10.1002/aoc.5905.