npj | 2D materials and applications

Review

Published in partnership with FCT NOVA with the support of E-MRS

https://doi.org/10.1038/s41699-025-00603-y

2D MOF structure, electrochemical biosensing in bioelectronic applications

Check for updates

Seydanur Yücer[1,2,3], Begüm Sarac[1,2,3] & Fatih Ciftci[1,2,3] ✉

Two-dimensional (2D) metal-organic frameworks (MOFs) have emerged as a groundbreaking class of materials with wide-ranging applications across biotechnology, bioelectronics, and tissue engineering. With their unique properties such as high surface area, tunable porosity, and flexibility in incorporating various metal ions, MOFs are instrumental in advancing the capabilities of bioelectronic sensors, tissue scaffolds, and biomedical imaging technologies. In biosensing, MOFs enable highly sensitive detection of biomolecules, including glucose, DNA, and proteins, by facilitating selective molecular interactions. This is particularly crucial for wearable technologies, where early detection of physiological changes is essential for timely diagnosis of diseases such as cancer and Alzheimer's. MOFs' adjustable porosity allows for selective adsorption of biomolecules, making them highly promising in biosensor development. Additionally, MOF-based sensors exhibit outstanding biocompatibility and mechanical strength, which are critical for seamless integration into wearable substrates. MOFs have also shown great potential in tissue engineering, where they enhance the functionality of scaffolds through their ability to load and release bioactive molecules. This controlled release mechanism is pivotal for promoting tissue regeneration, angiogenesis, and even drug delivery for cancer therapies. The versatility of MOFs in modulating physical properties such as mechanical strength, coupled with their capacity for functionalization, opens new avenues for creating bioactive scaffolds tailored to specific biomedical needs. In the realm of biomedical imaging, MOFs contribute significantly as contrast agents, particularly in magnetic resonance imaging (MRI) and computed tomography (CT). Their high surface area and tunable structure improve the precision and clarity of imaging, making them indispensable for enhancing diagnostic accuracy. MOFs also enable the development of multimodal imaging systems, combining diagnostic and therapeutic functionalities into a single platform. Furthermore, MOFs are being explored for their bioelectrochemical properties, where their integration into electrodes enhances the efficiency of biosensors and energy storage devices. The synergistic effects of MOFs with nanomaterials such as MXenes and carbon-based substances boost their electrocatalytic activity, which is crucial for applications in wearable sensors and bioelectronic systems. The future of MOF-based materials is promising, particularly as researchers focus on improving their biocompatibility, scalability, and operational stability. With further development, MOFs are expected to revolutionize the fields of bioelectronics, tissue engineering, and biomedical imaging, offering innovative solutions to some of the most pressing challenges in medical science.

This study consists of the following sections: "Structure of MOFs, Impact of Key Parameters on the Synthesis and Properties of MOFs, Tissue-bioelectronic Applications, Imaging and Bioelectronic Applications, and Other Bioelectronic Applications."

MOFs have revolutionized the field of bioelectronic sensors[1–4]. The unique features of these materials, such as their large surface area, precisely tunable porosity, and exceptional adsorption properties, make them ideal for applications requiring high sensitivity and selectivity[5,6]. This is especially relevant for wearable sensors, where detecting subtle physiological changes and specific biomarkers is crucial for early disease diagnosis. MOFs offer a promising solution, with the potential to significantly improve sensor performance across

---

A full list of affiliations appears at the end of the paper. ✉e-mail: fciftci@fsm.edu.tr; faciftcii@gmail.com

various applications. This section delves into the innovative advancements and potential uses of MOF-based wearable sensors[7–9]. This paper will explore the synthesis methods of MOFs, their integration into wearable substrates, and their impact on enhancing sensor performance across various domains. MOFs play a pivotal role in advancing wearable sensors due to their unique attributes, such as a high surface area, tunable porosity, and exceptional adsorption properties.

The synthesis methods of MOFs, their integration into wearable substrates, and their impact on enhancing sensor performance across various domains will be explored. MOFs play a pivotal role in advancing wearable sensors due to their unique attributes. Wearable sensors need to detect various physiological changes and pinpoint disease-specific biomarkers early to enable accurate diagnosis of conditions like DNA damage, Alzheimer's disease, and cancer[10–12]. To achieve this, a range of nanomaterials has been developed as sensing elements, with the sensing matrix being a key component of any sensor. Notable progress has been made in improving sensor sensitivity and selectivity, with the use of common nanomaterials such as carbon-based materials and MXenes playing a significant role[13]. The use of conducting polymers, such as molecularly imprinted polymers (MIPs)[14,15], metals, metal oxides, and more recently, metal-organic frameworks, has been explored.

MOFs have generated significant interest in wearable sensors due to their unique characteristics and wide array of potential uses. These hybrid materials are formed by linking metal ions with organic molecules to create a three-dimensional porous structure. This distinctive architecture offers an exceptionally high surface area, which can be finely tuned by altering the metal ions and organic linkers during synthesis. The ability to adjust the porosity of MOFs enhances their attractiveness for wearable technology, as their large surface area and customizable features are well-suited for sensor applications. MOFs' adjustable porosity enables selective adsorption and release of various molecules, including gases, liquids, and biomolecules, making them highly promising for a range of sensing tasks. Their high sensitivity and selectivity are particularly advantageous for detecting even trace amounts of specific substances.

In wearable sensor applications, MOFs offer several key advantages. Their integration into wearable substrates is relatively simple, as they can be directly synthesized onto flexible materials or used as coatings for existing devices, resulting in lightweight and unobtrusive sensors. This feature is particularly valuable in healthcare, where non-invasive and comfortable monitoring solutions are preferred by patients. The fabrication methods for MOF-based wearable sensors vary depending on the specific application and desired properties of the device. Common synthesis techniques include solvothermal, hydrothermal, and microwave-assisted processes, which provide precise control over material growth and ensure uniformity and stability in the final sensor.

MOFs have the potential to be a key material class for developing highly sensitive wearable sensors and biosensors, thanks to their unique properties. They exhibit electrocatalytic activity in water-splitting reactions, which enhances both detection selectivity and energy efficiency. Certain metal-MOF combinations demonstrate significant electrocatalytic performance comparable to that of pure metals. Additionally, MOFs can serve as scaffolds for incorporating nanomaterials, which can positively impact sensing reactions through synergistic effects. The advancement of wearable technology has been notably enhanced by integrating MOFs as sensing materials. MOFs, consisting of metal ions or clusters linked by organic ligands, possess distinctive structural features that make them ideal for a wide range of sensing applications, including chemical, physical, and biological detection.

The use of MOF materials in bioelectronics, wearable technology, and tissue engineering marks a significant shift in the development of advanced materials (Table 1). MOFs are recognized for their unique properties, including excellent conductivity, mechanical strength, biocompatibility, and the ability to be tailored through surface functionalization. These attributes make them a versatile and innovative class of materials, with great potential to impact these critical areas. This review aims to explore the intricate relationship between MXenes and their applications, highlighting their potential to drive transformative progress in materials science, bioelectronics, tissue engineering, electrical engineering, and wearable technologies. Table 2.

Overall, MOF-based wearable sensors offer unprecedented capabilities in monitoring environmental factors and physiological parameters, contributing significantly to health monitoring and improving overall well-being. In the past decade, significant efforts have been directed towards enhancing the sensitivity of wearable pressure sensors for broader medical applications. The aim is to ensure these sensors exhibit high sensitivity, a wide sensing range, excellent reproducibility or reusability, and are minimally affected by small mechanical deformations such as finger movements. Despite the development of various skin wearable sensors, challenges like air and moisture limitations have hindered their long-term usability and adhesion to the skin.

To tackle these challenges, a wearable pressure sensor utilizing a sandwiched C-MOF/PANIF@PU design has been created. This sensor incorporates interconnected nanocomposites of C-MOF and PANIF, which are coated onto PU sponges. This results in structures that offer high specific surface areas, porous microstructures that allow for air and liquid permeability, and dependable elasticity. The sensor has shown broad sensing capabilities, with a range of up to 60 kPa, impressive sensitivity, fast response times, consistent breathability, wireless monitoring, and outstanding reproducibility over thousands of cycles. It can track various human movements, from subtle to large-scale motor actions, as well as physiological responses like blood pressure and cheek occlusion. This versatility highlights the sensor's effectiveness in monitoring a wide array of human activities[16,17].

Despite the considerable potential of MOF-based wearable sweat sensors, research in this area remains relatively limited. Sweat represents a valuable non-invasive fluid with diagnostic potential; however, several challenges must be overcome for its effective utilization. These include the management of sweat production rates, an understanding of the health implications of sweat generation, the addressing of the limitations of iontophoresis, and the mitigation of discomfort caused by wearable heaters. These challenges are particularly pertinent in the context of MOF-based sweat sensors. For example, individuals with diabetes who are required to produce sweat on multiple occasions per day for the purpose of glucose monitoring often experience considerable discomfort. This underscores the necessity for the development of more user-friendly and accurate monitoring techniques.

Moreover, factors like sweat dilution during exercise and varying glucose concentrations across different body areas pose challenges for accurate real-time glucose monitoring through sweat. This approach may not be suitable for individuals with multiple health conditions or specific demographics like the elderly, disabled, or pregnant individuals. In conclusion, while MOF-based wearable sensors show promise for various applications, including pressure sensing, addressing challenges related to sweat-based diagnostics, such as glucose monitoring, requires further research and development to ensure accuracy, comfort, and applicability across diverse user groups.

MOF-based wearable sensors provide several notable advantages, making them highly effective for various applications. Firstly, they offer a non-invasive method for monitoring vital signs, avoiding the discomfort associated with procedures like needle insertions or catheter placements. This non-invasive approach allows for continuous monitoring without causing discomfort, thereby improving user compliance. Additionally, MOFs are recognized for their exceptional sensitivity and selectivity, enabling real-time tracking of multiple biomarkers. This capability is crucial for the rapid detection of changes in vital signs, facilitating timely intervention and more effective health management. The ability to tailor MOFs to detect specific biomarkers represents a major step forward in developing personalized wearable sensors. Furthermore, MOF-based sensors can be produced at a lower cost

Table 1 | Bioelectronics application areas of metal-organic frameworks (MOFs), along with descriptions, example applications, and advantages

Application Area	Description	Example Applications	Advantages	References
Biosensors	Biosensors are devices designed to detect specific biological molecules. MOFs can be used in biosensors to create sensitive detectors for detecting various biomolecules (e.g., proteins, DNA, glucose).	Glucose sensors, DNA sensors, protein sensors	High sensitivity and selectivity enable rapid and accurate detection of biological molecules; Biocompatibility facilitates ease of use in biomedical applications.	114
Bionic Materials	Bionic materials are artificial materials designed to mimic or enhance the functions of natural biological systems. MOFs, when used in bionic implants, prosthetics, and artificial organs, can contribute to the development of bioelectronic devices (e.g., artificial eyes, hearing aids).	Artificial eye lenses, hearing devices, prosthetics	High surface area facilitates effective integration of electronic components; Biocompatibility enhances safety for in-body applications.	115,116
Biomedical Imaging	Biomedical imaging technologies are used to visualize the structures and functions of biological samples. MOFs can assist in the transportation and release of biomedical imaging agents, enhancing imaging techniques (e.g., magnetic resonance imaging, optical imaging).	Magnetic resonance imaging (MRI), optical imaging	High surface area enables high-capacity transportation of imaging agents; Controlled agent release can be achieved.	117
Bioelectrochemistry	Bioelectrochemistry involves the use of electrochemistry techniques to study chemical reactions in biological systems. MOFs, when used as electrochemical sensors and in bioelectrochemical cells, can help monitor and manipulate biological reactions.	Electrochemical sensors, bioelectrochemical cells	High surface area and porosity enable effective immobilization of electrocatalysts; Enables precise monitoring and control of electrochemical reactions.	118

compared to some traditional medical monitoring methods, potentially enhancing healthcare accessibility and improving outcomes across various socio-economic groups.

MOF-based wearable sensors offer a wide array of applications across various fields. These devices can monitor heart rate and blood pressure, providing crucial insights into cardiovascular health and aiding in the early detection of conditions like myocardial infarction or stroke. They also enable precise body temperature measurements, which are essential for identifying fever or hypothermia—potential indicators of infection or other health issues. This capability is crucial for effective fever management and delivering optimal patient care. For individuals with chronic conditions such as diabetes or hypertension, real-time monitoring of blood glucose levels or blood pressure fluctuations can greatly enhance disease management. Additionally, athletes benefit from MOF-based sensors by tracking performance and exertion during exercise, optimizing training routines, and preventing overexertion. These applications highlight the significant impact of MOF-based wearable sensors in healthcare, wellness monitoring, and performance enhancement. The future of MOF-based wearable sensors in healthcare is promising, provided they meet essential performance criteria such as sensitivity, selectivity, and long-term stability. Enhancements are expected to involve incorporating materials like carbon-based substances and metal nanoparticles to improve flexibility, stability, and conductivity. Future research is likely to focus on developing more conductive and eco-friendly MOF composites, improving mechanical properties and biocompatibility, exploring bionic structures for comfort, using 3D technologies for better stability and scalability, optimizing operational conditions, and integrating machine learning for increased accuracy. These advancements are crucial for developing high-performance MOF sensors with the potential to transform healthcare applications.

Structural of MOFs

Porous materials boasting extensive surface areas have long captivated interest within scientific and industrial spheres. Their significance is underscored by their pivotal role in chemical process technologies, where surface area directly influences performance. Researchers perpetually strive to enhance efficiency by fabricating porous materials with larger surface areas. It is a well-established fact that traditional industrial porous materials are composed mainly of inorganic structures. However, a significant change occurred in the 1990s with the advent of metal-organic frameworks (MOFs). These innovative materials represent a significant departure from earlier approaches, combining metal ions with organic ligands in a novel manner. This innovation, pioneered by Omar Yaghi, catalyzed a renaissance in research, opening new avenues for the development of high-performance porous materials.

A typical MOF embodies clusters of metals intricately linked by organic ligands, forming a distinct structure. This material architecture facilitates versatile growth patterns in one, two, or three dimensions, imparting properties such as high surface area, adjustable pore diameters, and variable geometric structures. MOFs have emerged as a prominent material category, garnering widespread attention owing to their diverse applications (Fig. 1). Gas separation and storage, catalysis, and controlled drug release and adsorption are among the myriad functionalities facilitated by MOFs. The synthesis process crucially hinges on factors like the choice of metal and ligand, alongside parameters such as temperature and solvent selection, which collectively dictate the resultant MOF's shape and properties.

MOFs synthesis methods

The synthesis of MOFs relies on various factors including reaction time and temperature, solvent selection, metal ions, organic ligands, node characteristics, counter ions, and crystallization kinetics. Typically, MOF synthesis occurs in the liquid phase, involving the mixing of solutions containing ligands and metal salts. Solvent choice depends on reactivity, solubility, and redox potential, impacting thermodynamics and activation energy. Although solid-state methods have been attempted, challenges in single crystal growth persist. MOF crystal growth often involves reaction solution underwent a gradual evaporation process over time. Solvo(hydro) thermal environments, characterized by elevated temperatures and pressures, are commonly used for MOF synthesis, considered the traditional approach. Nevertheless, alternative methodologies, including mechanochemical, electrochemical, microwave, and Sono-chemical techniques, have been devised, offering advantages of cost-effectiveness, speed, and environmental cleanliness.

Slow evaporation and diffusion methods

The slow evaporation and diffusion methods are both carried out at room temperature, eliminating the need for external energy sources. In the slow evaporation method, reagent solutions are mixed and allowed to evaporate slowly, leading to crystal formation once the concentration reaches a level that initiates nucleation and growth. This process is often expedited by using mixtures of solvents with low boiling points. Conversely, the diffusion method involves layering reagent solutions separated by a solvent layer or physical barriers, with gels sometimes used as a medium for crystallization and diffusion. Crystals form at the interface between the layers due to the gradual diffusion of the solvent containing the dissolved precipitate into the separate layers. This method is particularly effective for substances with low solubility. For example, Lim et al. present the development of a mixed matrix (MM) platform for the in-situ synthesis of MOFs using ionic polymers with ion-exchangeable sites. Alginate (ALG), a polymer with metal-ion exchangeable sites, was used for the in-situ synthesis of HKUST-1 and MOF-74 (Zn). The sequential addition of MOF components (metal ions and proton-discharged ligands) to the alginate matrix led to markedly different results, which were attributed to the difference in diffusion rates of the MOF components. This diffusion difference facilitated the transformation of BTC by Cu^{2+} ions, forming HKUST-1 layers. The alginate matrix showed high dispersion and connectivity of MOF crystals. This property was further integrated with poly(vinyl alcohol) to form a flexible mixed matrix membrane containing MOFs. Furthermore, using methylene blue and rhodamine 6 G as molecular probes, the in-situ approach was shown to be effective to produce a MOF-MM capable of size-dependent selective molecular uptake[18].

Hydrothermal and iodothermal method

Solvo(hydro)thermal reactions take place in sealed vessels under autogenous pressure, where the solvent's boiling point is surpassed. Most metal-organic frameworks (MOFs) are synthesized under these conditions (Fig. 2C)[19]. Typically, these reactions occur in polar solvents within closed vessels (autoclaves) at temperatures ranging from 50 to 260 °C, with reaction times varying from several hours to days. For reactions conducted at temperatures above 400 °C, Teflon-coated autoclaves are used. Elevated temperatures help in bond formation and ensure proper crystallization, especially when using kinetically inert ions. Temperature also affects crystal morphology, and prolonged reaction times can lead to product decomposition. To manage this, a slow cooling rate is often employed to control crystal growth. Mu et al. used a hydrothermal method and air calcination to synthesize a bimetallic MOF-derived Co_3O_4/SnO_2 nanocomposite used as a sensing material to detect ethanol. The structural, elemental composition and surface morphology of the Co_3O_4/SnO_2 nanocomposite were characterized using various analytical techniques such as X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). A comparison was made between SnO_2 nanoparticles obtained from metal-organic frameworks and bimetallic Co_3O_4/SnO_2 nanocomposite. The Co_3O_4/SnO_2 nanocomposite showed significantly improved ethanol sensing performance. The response to 100 ppm ethanol at 225 °C was 135, showing excellent reproducibility, selectivity and stability. Gas sensitivity testing revealed that the 3% (Co/Sn) Co_3O_4/SnO_2 nanocomposite is an outstanding material for gas sensing and offers strong technical potential for ethanol sensing and environmental monitoring[20].

Table 2 | MOFs production methods, application areas of methods, advantages-disadvantages comparison

Method	Application of Materials	Advantages	Disadvantages	References
Microwave Method	Applications include the production of biofuels, cellulose, oil, resins, pharmaceuticals, and metal–organic frameworks (MOFs).	Rapid crystallization, particularly high purity, and high efficiency are the defining characteristics of this product.	The process of single crystallization is a challenging task. There is no direct method for scaling up.	83
Microemulsion Method	It is used as a medium in electrochemical reactions, cosmetics and cleaning product formulations, MOF	The size and dimensions of nanoscale materials can be precisely managed and controlled.	A significant proportion of the surfactants employed are detrimental to the environment.	119
Sonochemical Method	The application areas of this technology include emulsification, solvent degassing, solid dispersion and soil formation, as well as MOF.	The product is characterized by its rapid dissolution and its environmentally friendly properties. It also modulates crystallization.	Single-criticitisation is a difficult job	120
Electrochemical Method	The field of electrochemistry encompasses a vast range of disciplines, including the study of electrode materials, batteries, electrocatalysis, electroanalysis, electrochemical sensing, and a multitude of categories related to energy and fuels, such as metal-organic frameworks (MOFs).	The substance in question exhibits a cold reaction and a fast synthesis. The process is less time-consuming.	Lower yield	121
Mechanochemical Method	The disciplines of extractive metallurgy, materials engineering MOF and medicine.	The process is environmentally friendly, as it does not require the use of high temperatures and pressures. The process is less time-consuming.	The final product is structurally amorphous, and undesirable products are formed as a result of competing reactions. Lower crystallinity.	122
Hydrothermal Method	The growth of synthetic quartz, gemstones and other single crystals of commercial value is frequently achieved through the process of hydrothermal synthesis.	The yield is high, and the process of transposition is straightforward.	The system exhibits high energy consumption and a long reaction time.	123
Diffusion Method	The field of application is the evaluation of antimicrobial activity in plants or microbial extracts, as well as the determination of the susceptibility of clinical bacterial isolates to different antibiotics.	The process does not require a high temperature, and no energy source is required.	The synthesis process is lengthy.	124

Commonly used high-boiling point solvents include dimethyl formamide (DMF), diethyl formamide (DEF), methanol (MeOH), ethanol (EtOH), and 2-ethyl-1-hexanol (H_2Eyben$_2$CO). In solvo(hydro)thermal conditions, initial reagents can undergo unexpected chemical transformations, leading to the formation of new ligands in-situ that are not possible under milder conditions. Ionothermal synthesis is a specialized variant of solvo(hydro)thermal techniques that uses ionic liquids. These liquids serve both as solvents and templates, offering a more environmentally friendly alternative to traditional organic solvents. Ionic liquids have several advantageous properties: they have low vapor pressure, high solubility for organic compounds, excellent thermal stability, and are non-flammable. These attributes make them ideal for synthesizing MOFs, as well as other materials such as zeolites and chalcogenides.

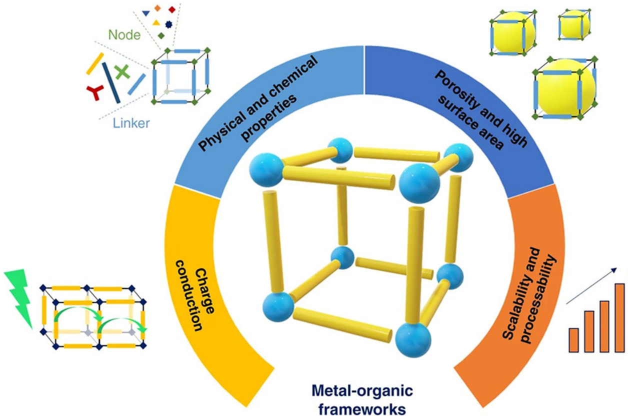


Fig. 1 | Structures and applications of MOFs.

Furthermore, ionic liquids provide anions and cations that can function as counter-ions or templates within MOF frameworks. Consequently, recent research has increasingly focused on utilizing these materials as a promising alternative for MOF synthesis.

Microwave method

The method is widely used for synthesizing both organic and nanoporous inorganic materials and has recently been applied to the synthesis of metal clusters and MOFs (Fig. 2A)[19]. This approach offers several benefits, including reduced reaction times, increased yields, and cost savings. For instance, the synthesis of HKUST-1 using a microwave-assisted method achieved crystals with improved yield and physical properties compared to those produced by traditional hydrothermal methods. In this process, $[Cu_3(BTC)_2(H_2O)_3]$ is formed, where BTC stands for 1,3,5-benzenetricarboxylate. Microwave irradiation, while not directly involved in crystal formation, enhances molecular movement, thus optimizing reaction concentration and temperature. This improvement promotes controlled nucleation and crystal growth, resulting in crystals with the desired shapes and sizes. Mahmoud investigated the synthesis of MOF-801 using the microwave (MW) heating method. The MW-assisted synthesis was carried out by heating the reaction mixture to 110 °C for 45 s in a MW cavity with a fixed frequency of 2.45 GHz. The obtained MOF-801 was characterized using various techniques including thermogravimetric analysis (TGA), FTIR, X-ray diffraction (XRD), scanning electron microscopy with energy dispersive X-ray (SEM-EDX), transmission electron microscopy (TEM), nitrogen gas adsorption (BET) and dynamic vapor sorption (DVS). MOF-801 particles were found to be nanosized, exhibiting a cubic crystal structure and belonging to the Pn-3 (201) space group. The crystal sizes were calculated using the Scherrer equation and values of 27 nm and 18 nm were obtained, respectively. BET analysis revealed a total specific surface area of 739.7 m^2/g. TGA results showed that the material has excellent thermal stability. SEM and TEM images confirmed the formation of octahedral

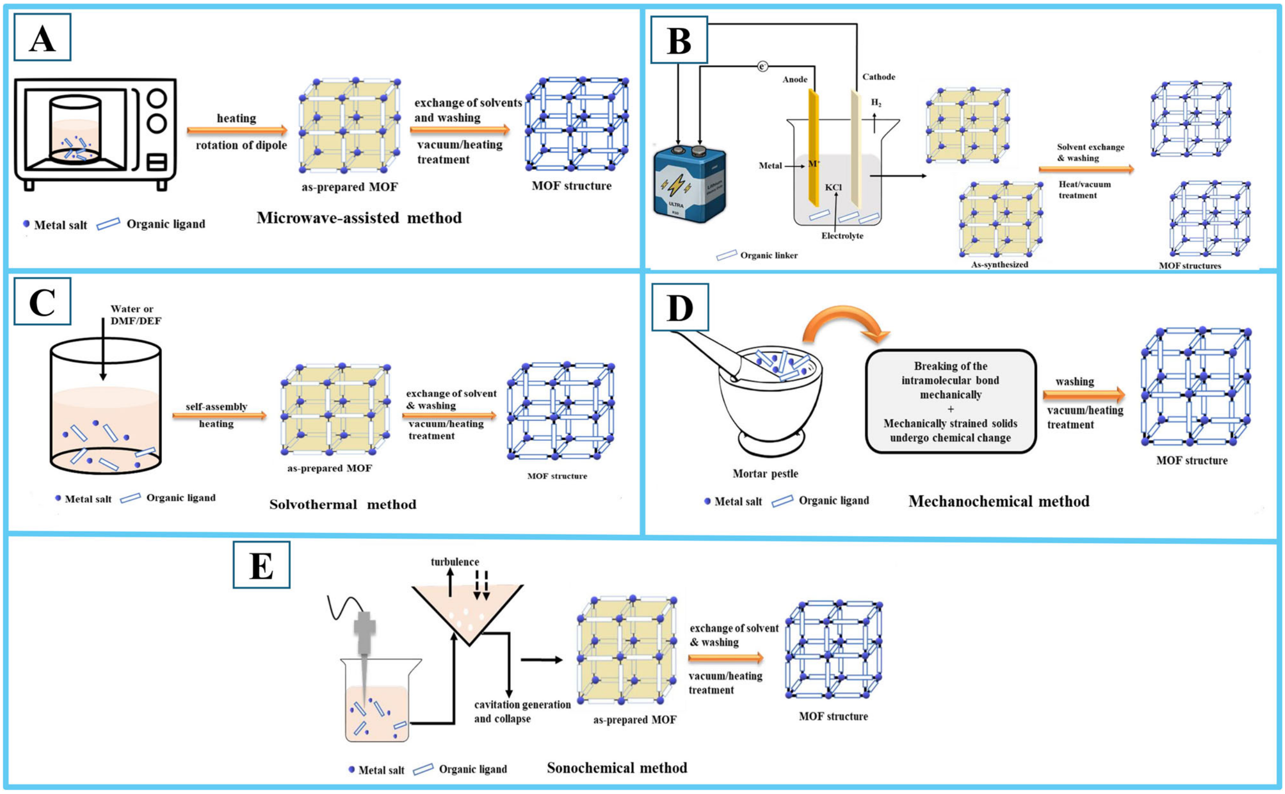


Fig. 2 | **Schematic summary of different MOF synthesis methods. A** Schematic summary, microwave-assisted MOF synthesis is shown, **B** Schematic summary shows the MOF Electrochemical Synthesis. **C** Schematic summary shows Conventional Solvothermal Synthesis. **D** Schematic summary shows the Mechanochemical Synthesis of MOF. **E** Schematic summary shows the Sonochemical Synthesis of MOF31. Copyright 2022 American Chemical Society.

fcu-MOF particles with diameters around 200 nm. The MW-assisted synthesis method demonstrated its suitability for dewatering applications by offering advantages such as high phase purity, nanocrystalline size, structural integrity, high surface area, water absorption capacity and excellent thermal stability. This study emphasizes that MW processing is a promising approach for MOF synthesis[21].

Mechanochemical method

The mechanochemical method utilizes mechanical energy instead of solvents at room temperature to form coordination bonds. This is achieved by manually grinding the required reagents or, more commonly, using automated ball mills. Sometimes, a small amount of solvent is added to the solid reaction mixture, leading to the formation of one-, two-, or three-dimensional coordination polymers. Mechanochemistry enhances mass transfer and reduces particle size while also generating localized heating and melting of reagents, which speeds up reaction kinetics (Fig. 2D)[19]. This method is environmentally friendly and aligns with green chemistry principles, producing high-purity and efficient materials with shorter reaction times. It offers a promising alternative to traditional high-temperature and pressurized solvo(hydro)thermal techniques for MOF synthesis. However, a notable drawback is the tendency to produce amorphous materials, which are unsuitable for single-crystal X-ray structural analysis. Glowniak et al. synthesized MOF-303 by a mechanochemical approach using water assisted ball milling. This method is emphasized as an environmentally friendly, safe and sustainable technique within the framework of green chemistry principles. The obtained MOF-303 exhibited a high specific surface area of 1180 m^2/g and showed an excellent CO_2 adsorption capacity of 9.5 mmol/g at 0 °C and 1 bar pressure[22].

Electrochemical method

The electrochemical method is used for the industrial-scale synthesis of MOF powders. In this process, metal ions are introduced into the reaction mixture through anodic dissolution, which also contains organic ligands and electrolytes (Fig. 2B)[19]. This method offers several advantages over solvothermal approaches, including lower reaction temperatures and faster synthesis under milder conditions. The electrochemical method has been successfully used to synthesize various MOFs, such as HKUST-1, ZIF-8, MIL-100(Al), MIL-53(Al), and NH. Researchers have explored how different reaction conditions affect the yield and structural properties of these materials. The electrochemical method stands out as one of the most efficient strategies for synthesizing MOFs designed for bioelectronic applications. This technique offers several key advantages, including low power requirements, operation under mild conditions, and excellent compatibility with biological systems. A major strength of this approach is its ability to facilitate the direct formation of MOF coatings on electrode surfaces, streamlining their incorporation into bioelectronic devices such as biosensors. MOFs synthesized via this route often demonstrate exceptional purity, well-ordered crystalline structures, and improved electrical properties, all of which enhance the overall sensitivity and performance of sensing devices. Furthermore, the electrochemical process enables precise regulation of synthesis variables like applied voltage and current, allowing customization of the MOF's structural and functional characteristics. These benefits make the electrochemical synthesis method highly practical and adaptable for the development of next-generation biosensors and other bioelectronic technologies. Cardero et al. partially converted Cu thin films and Cu_2O microstructures into MOFs, in particular $Cu_3(BTC)_2$ and Cu(TCPP), using an electrochemical process that offers more precise control and milder conditions than conventional solvothermal MOF synthesis. Initially, Cu thin films were sputter-deposited or various Cu or Cu_2O microstructures were electrochemically deposited on ITO glass substrates. These Cu thin films or Cu-based microstructures were then coated with a thin layer of $Cu_3(BTC)_2$ or Cu(TCPP) by anodic dissolution at room temperature, in the presence of organic binder molecules such as 1,3,5-benzenetricarboxylic acid (BTC) or 4,4′,4″,4‴-(Porphine-5,10,15,15,20-tetrayl)tetrakis(benzoic acid) (TCPP). The growth of Cu2O@Cu3(BTC)2 and Cu_2O@Cu(TCPP) was estimated to be 38.7% and 68.9%, respectively. The obtained core-shell Cu_2O@Cu(BTC) and Cu_2O@Cu(TCPP) microstructures were characterized using techniques such as XRD, Raman spectroscopy and UV-vis absorption spectroscopy[23].

Sonochemical method

Sonochemistry is the study of chemical transformations induced by intense ultrasonic radiation, typically ranging from 20 kHz to 10 MHz. When applied, this radiation creates bubbles within the reaction solution, leading to localized hotspots with high temperature and pressure. These extreme conditions promote chemical reactions and accelerate the formation of crystallization nuclei (Fig. 2E)[19]. Researchers have used the sonochemical method, in combination with 1-methyl-2-pyrrolidone as the solvent, to efficiently synthesize high-quality crystals of MOF-5 and MOF-177. The resulting crystals, with sizes ranging from 5 to 25 μm for MOF-5 and 5 to 20 μm for MOF-177, were produced in significantly reduced reaction times. Yu et al. synthesized porphyrin-based MOFs (MOF-525 and MOF-545) with high purity and uniform size by a sonochemical method using zirconyl chloride and tetrakis (4-carboxyphenyl) porphyrin. Benzoic acid and trifluoroacetic acid were used as modulators. The synthesis process was completed in 2.5 h and 0.5 h, which is faster compared to conventional methods. The physicochemical properties of the MOFs were analysed by X-ray diffraction (XRD), scanning electron microscopy (SEM) and N2 adsorption-desorption isotherms. UV-vis spectrometry, thermogravimetric analysis (TGA) and ICP-MS were applied to investigate defect regions. The sonochemically synthesized MOFs exhibited higher levels of defect sites and superior textural properties compared to those prepared by conventional methods. In particular, MOF-545 exhibited much smaller particle sizes (approximately 1.0 μm) than the conventionally prepared sample (~4.8 μm). Furthermore, both MOF-525 and MOF-545 showed improved chemical warfare simulation capabilities in the hydrolysis of dimethyl-4-nitrophenyl phosphate (DMNP) and exhibited higher bisphenol-A adsorption performance compared to their conventional counterparts[24].

Microemulsion method

This technique, widely used for synthesizing nanoparticles, has recently been adapted for fabricating MOFs. In water microemulsions, nanometer-sized water droplets are encapsulated by a surfactant within an organic phase. The micelles in these microemulsions function as nanoreactors, controlling nucleation and crystal growth rates. By adjusting the water-to-surfactant ratio and the type of surfactant, one can precisely control the size and number of micelles, allowing for accurate regulation of nanoscale material dimensions. However, this method has some limitations, including high costs and the environmental impact of many surfactants used in the process. Lee et al. used a microemulsion method to synthesize MOF nanocrystals in an environmentally friendly and efficient manner. The size of ZIF-8 crystals was carefully controlled using an oil-in-water microemulsion system and the process was optimized by a soft seed-mediated approach. ZIF-8 nanocrystals synthesized without the need for chemical additives showed excellent performance in catalytic activities and dye adsorption applications. This method also provides precise control over the size of ZIF-67 crystals and ZIF-derived hollow nanostructures. With high surface area, tunable morphology and energy efficiency, this approach holds significant promise for industrial-scale applications[25].

Impact of key parameters on the synthesis and properties of MOFs

MOFs have garnered significant attention in recent years due to their large surface areas, tunable pore structures, and diverse functional properties. The synthesis of MOFs is highly dependent on key parameters such as temperature, solvent selection, reaction time, and pH. These factors directly influence the morphology, porosity, and overall characteristics of the resulting crystals. This section provides an in-depth analysis of these parameters, supported by relevant studies.

Temperature

Temperature plays a crucial role in MOF synthesis, affecting nucleation rates, crystal growth, and defect formation. Lower temperatures typically yield larger, well-defined crystals due to slower nucleation and growth, while higher temperatures can produce smaller, more porous particles, albeit with a greater likelihood of structural defects. Seo et al.[26] explored the effect of temperature on Cu-BTC synthesis using microwave methods. At 140 °C, monocrystalline octahedral $Cu_3(BTC)_2(H_2O)_3$ was formed, whereas an increase to 150°C resulted in $[Cu(BTC\text{-}H_2)_2(H_2O)_2]\cdot 3H_2O$, which later transformed into $[Cu_2(OH)(BTC)(H_2O)]\cdot 2H_2O$, forming plate-like structures (~ 5 µm in size). Similarly, Chowdhury et al.[27] observed that Cu-BTC synthesized at 100°C in an ethanol-water solvent produced sharp-edged octahedral particles, while synthesis at 140 °C in an ethanol-DMF-water mixture resulted in rounded edges. Electrodeposition studies by Campagnol et al.[28] demonstrated morphological transitions based on temperature. Cu-BTC electrodeposited at room temperature formed octahedral structures, while at 200°C, cubic structures emerged. Higher temperatures also improved crystallinity, as indicated by sharper and more intense XRD peaks. Other studies have shown similar temperature effects on different MOFs. For example, Biemmi et al.[29] reported that increasing temperatures (75–180°C) led to smoother crystal edges in Cu-BTC without significantly altering particle size. Yuan et al.[30] observed a transition from undefined, urchin-like structures at room temperature to well-defined nanowires at 100 °C in Ni-MOF synthesis. Similarly, MIL-100(Fe) crystals were more polydisperse at lower temperatures (110 °C) and became more uniform at higher temperatures (190 °C)[31].

Solvent selection

Solvent choice significantly impacts MOF synthesis by affecting metal precursor solubility, nucleation rates, and final morphology. The solvent's polarity, coordination ability, and decomposition behavior all influence the resulting MOF structure. For instance, the volume of methanol in ZIF-67 synthesis dictates its morphology. As methanol volume increases, the structure transitions from a flower-like form to a multi-walled wafer, with surface area increasing from 800 to 2037 m^2/g[32]. Conversely, NH_2-MIL-125(Ti) shifts from circular platelets to octahedral particles as methanol volume increases, leading to a decrease in surface area from 1268 to 1041 m^2/g. Solvent type also determines MOF shape. Cu-BTC synthesized in a water-DMF mixture forms porous, irregular structures, whereas a water-ethanol mixture yields octahedral forms. Pure alcohol solutions result in spherical particles, while a purely aqueous medium produces low-porosity, tagliatelle-like structures. The addition of DMF enhances uniformity, particle fineness, and surface area, but excessive DMF (>14% by volume) promotes aggregation and reduces surface area. Solubility effects extend to different MOFs. For example, Cu-BDC synthesized in acetonitrile or propionitrile exhibits high aspect ratios, whereas methanol or 2-propanol favor three-dimensional structures due to stronger metal node adsorption. Similarly, ZIF-8 synthesized in DMF yields large hexagonal particles (150–200 µm), while methanol and water lead to significantly smaller particles (3–5 µm and 0.3–0.4 µm, respectively)[33].

Reaction time

The duration of synthesis directly affects crystal growth and structural stability. Short reaction times may lead to incomplete crystallization, whereas prolonged durations can cause aggregation or phase transformations. For UiO-66, solvothermal synthesis was carried out for 18, 21, and 24 h. Characterization via XRD and FTIR confirmed that all samples maintained the expected structural patterns and functional groups. SEM analysis revealed that an 18-h reaction time produced the smallest particles (~200 nm), while TGA showed stability up to 500 °C. An alternative approach using mechanical ball milling enabled the rapid synthesis of Ni-MOF within 1 min. This method eliminated the need for solvents and additives. Increasing milling duration, mechano-frequency, or introducing an assisting solvent improved reaction efficiency and yield. The synthesized Ni-MOF exhibited excellent capacitance performance[30].

pH and modulators

pH adjustment through acidic or basic modulators significantly influences metal-ligand coordination and overall framework formation. Different modulators affect nucleation rates, leading to variations in MOF morphology. Low concentrations of modulators promote well-defined, non-agglomerated particles. Increasing the concentration of alkaline modulators enhances linker deprotonation, resulting in notable morphological changes. For instance, HKUST-1 crystals transition from octahedral to spherical or rod-like forms in response to increased sodium formate concentration. Similarly, Eu-1,4-NDC-fcu-MOF crystals shift from aggregated octahedrons to uniform structures with specific shapes depending on modulator concentration[34]. Excessively high pH levels can hinder crystal formation by promoting rapid nucleation and competition between modulators and linkers for metal ion coordination. In $Dy(BTC)H_2O$ synthesis, increasing sodium acetate concentration (pH 4.4 to 5.8) transformed rod-like crystals (~60 µm) into spherical nanostructures (~71 nm). At pH >7.2, amorphous elongated structures formed[35]. Similarly, MIL-100 and MIL-110 morphologies in aluminum-based MOFs vary with pH. Highly acidic conditions (pH ~0) yield hexagonal MIL-110 rods, while slightly higher pH (0.5–0.7) favors MIL-100 octahedral structures. Dual modulation strategies provide additional control over morphology. In $[\{Cu_2(NDC)_2(DABCO)\}_n]$, acetic acid and pyridine modulation altered crystal shape from rods to nanosheets or nanocubes[36]. Post-synthetic modifications, such as pH-controlled chemical etching, also allow morphological tuning in MOFs like ZIF-8 and ZIF-67, producing cubic, tetrahedral, or hollow structures. The synthesis of MOFs is highly sensitive to key parameters, including temperature, solvent selection, reaction time, and pH. Each factor plays a critical role in determining the final morphology, porosity, and functional properties of MOFs. Understanding these influences enables precise control over MOF characteristics, facilitating their optimization for various applications. Future research should focus on fine-tuning these parameters to develop MOFs with tailored properties for advanced applications[31].

Comparison between 2D MOFs and conventional MOFs

2D MOFs have different structural and synthesis methods compared to conventional MOFs. These differences directly impact their quality and functional performance. These key details are summarized in Table 3.

Tissue-bioelectronic applications

Tissue engineering scaffolds are crucial in the reconstruction of tissues and organs, providing a foundational framework for the process. As materials science progresses and tissue engineering methodologies become more sophisticated, there's a wide array of scaffold options available. However, due to the complexity of tissue structure and function, along with the limitations of biomaterials, it is difficult for a single material to satisfy all the requirements for tissue reconstruction. This has led to growing interest in composite scaffolds with unique properties, combining base materials with active components. The core performance parameters depend on the base materials used, while active components contribute specialized service attributes, making these composite scaffolds versatile for various tissue engineering applications.

The increasing reliance on antibiotics has raised serious concerns about bacterial resistance, leading to a global need for new antimicrobial treatments. Metal-organic frameworks are a type of porous organization material made up of metal ions and organic ligands. These structures have shown promise in combining biomacromolecules like proteins and polysaccharides to create composite materials. In recent years, there has been growing interest in using MOFs and their derivatives for antibacterial purposes, demonstrating their effectiveness as powerful antibacterial agents.

Table 3 | Summarizes the comparison of 2D and conventional MOFs in terms of structure, synthesis, detection mechanism and properties

Feature / MOF Type	Atomic / Molecular Structure	Preparation Method	Characterization Method	Biosensing Mechanism	Sensitivity	Response Time	Stability	Ref.
2D MOF	Thin, layered, mostly single or few layers	Controlled exfoliation, solvothermal synthesis, layer-controlled growth	AFM, TEM, XPS for layer thickness and structural details	Surface reactions, rapid electron transfer, enhanced interaction due to high surface area	High sensitivity	Fast response	Increased flexibility and stability	125–130
Traditional (Bulk) MOF	Three-dimensional, thick and bulky structures	Conventional solvothermal or hydrothermal synthesis	PXRD, SEM, BET surface area analysis	Bulk MOFs utilize internal volume, slower response	Lower sensitivity	Relatively slower response	Moderate stability	131–134

This thorough review explores the various ways MOFs and their composites can be used to combat bacterial infections, detailing different synthesis methods and antibacterial mechanisms. Additionally, it discusses the challenges and opportunities associated with using MOF-based antibacterial materials in the rapidly evolving medical field. By providing new insights, this review aims to contribute fresh strategies for the medical application of MOF-based antibacterial materials.

Bioactive factors play a pivotal role in fostering tissue regeneration and fostering conducive microenvironments. In the realm of texture making engineering scaffolds, incorporating privileged factors functionalities through surface coating, internal loading, direct adsorption, or grafting proves effective in enhancing cell attachment, fostering renewal, and support tissue scaffold vascularization. MOFs represent molecular architectures featuring expansive cavities and diverse pore sizes, presenting an opportunity for efficient loading and controlled release of bioactive drugs. The pore dimensions of MOFs significantly influence drug loading efficacy and release kinetics. Loading drugs into MOFs can be achieved through encapsulation or surface modification techniques. Moreover, MOFs possess the capability to respond to internal or external environmental changes within the body, thereby enabling targeted drug delivery. Their potential in breaching the blood-brain barrier makes them particularly valuable for drug encapsulation applications. Integration of MOFs with tissue engineering scaffold materials not only provides structural support but also enhances tissue repair efficiency by delivering inflammation reducers, against bacteria or tissue repair enhancer agents. Additionally, MOFs can encapsulate gene therapy drugs, thereby augmenting their transfection efficacy and stability. These frameworks have shown promises in fostering angiogenesis, osteogenic differentiation, and tissue regeneration. Leveraging MOFs for loading bioactive factors onto tissue engineering scaffolds can significantly enhance cell adhesion, regeneration, and vascularization processes. In summary, MOFs harbor substantial potential for encapsulating drugs and bioactive factors, thereby serving therapeutic objectives effectively.

In the biomedical field, iron-based Fe-MOFs, especially MIL-53 (Fe), have garnered significant interest due to their low toxicity, structural adaptability, and biodegradability. MIL-53 (Fe) is composed of Fe (III) octahedra linked by terephthalate anions, making it a promising candidate for various biomedical applications. Researchers have successfully synthesized nanoscale Fe-MOFs that are used for delivering anti-tumor and retroviral drugs. These nanoscale frameworks have demonstrated favorable properties in both laboratory and animal studies, including excellent degradability, safety, and imaging capabilities[37–39]. Ren et al.[40] multifunctional antibacterial platform has been created using a chitosan (CS) and HKUST-1 antibacterial film. This system is designed to release copper ions in a controlled manner, minimizing the risk of cytotoxicity[40]. Exploiting the flexibility of Fe-MOFs, Leng et al.[41] MIL-53 (Fe) was chosen for encapsulating the anti-cancer drug oridonin, achieving a high drug loading capacity of 56.25% (w/w) with a sustained release over seven days. Additionally, the drug-loading potential of Fe-MOFs was explored using magnetic and fluorescence imaging techniques[42]. Notably, Hollow Fe-MOFs-5-NH_2 exhibited an impressive drug loading capacity of up to 35% (w/w) with pH-responsive release properties. Additionally, the inclusion of Fe^{3+} ions in these MOFs enhanced their magnetic resonance imaging (MRI) capabilities (Fig. 3A)[43]. Further functionalization of Fe-MOFs with folic acid (FA) and fluorescent agents has been shown to improve their targeted drug delivery and fluorescence imaging capabilities. This advancement could significantly broaden the applications of Fe-MOFs in biomedicine[44].

Copper (Cu) is an essential trace element crucial for maintaining bioactivity, known for its chemical stability and low toxicity. Its significance extends to various biological functions, including the activation of cell energy production, regulation of metabolism, anti-aging properties, synthesis of elastin, and formation of human nerve tissue. Consequently, copper has emerged as a widely utilized material for long-term antibacterial applications. Recent research has shown that copper-based MOF materials can effectively eliminate *S. aureus* by releasing copper ions with strong antibacterial properties. The Cu/1,3,5-benzenetricarboxylic acid (Cu/H,

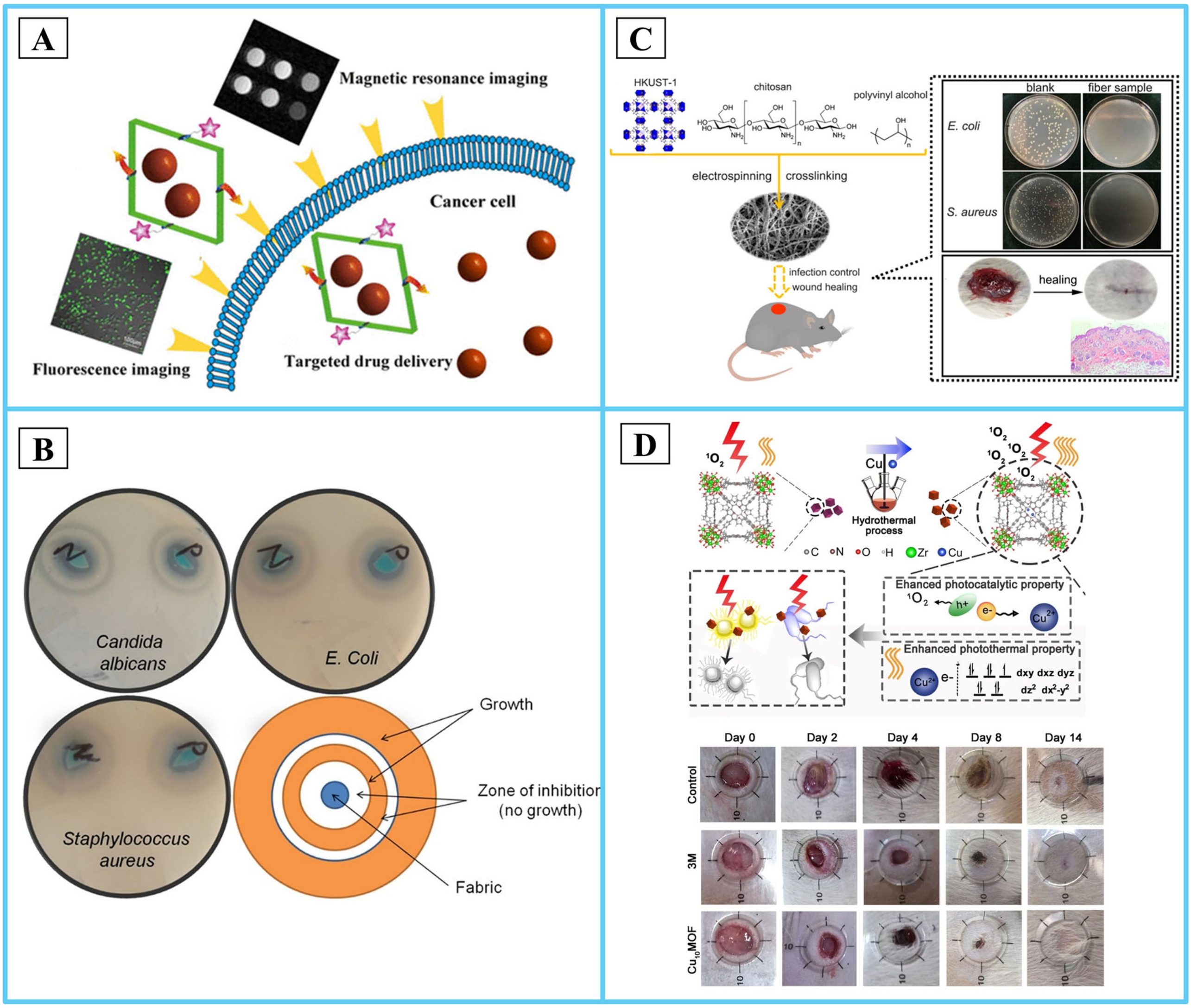


Fig. 3 | Graphical representation of different strategies for biomedical utilization of MOFs. **A** Schematic summary illustrates the formation of an advanced drug delivery system, Fe-MIL-53-NH_2-FA-5-FAM/5-FU, by conjugating the fluorescent probe 5-carboxyfluorescein (5-FAM) and the targeting molecule folic acid (FA) to Fe-MIL-53-NH_2 loaded with 5-FU 49. Copyright 2017 American Chemical Society, **B** Schematic summary illustrates the formation of Cu-BTC MOF directly within PET and Nylon fabrics, imparting antimicrobial functionality and highlighting the creation of safe, eco-friendly synthetic textiles with biocidal capabilities 50. Copyright 2018 Elsevier, **C** schematic summary illustrates that biocompatible chitosan/PVA fibers embedded with Cu-based MOF (HKUST-1), produced via blend electrospinning, enabled the development of an effective MOF-based wound dressing with strong antibacterial properties to support wound healing 51. Copyright 2020 Elsevier, **D** Schematic summary illustration below outlines the preparation methods and crystal structure of Cu-doped metal-organic frameworks (MOFs) in vivo. 52. Copyright 2020 Elsevier.

BTC) MOF, formed from Cu^{2+} and 1,3,5-H, BTC, exhibits significant antibacterial activity. This effect is attributed to the copper ions and the carboxylic groups in the organic component. Additionally, HKUST-1, also known as MOF-199 or $Cu_3(BTC)_2$, is a well-known MOF with unique square-shaped pores and is widely recognized for its diverse applications[45].

In a study, Cu-MOF nanostructures were applied to silk fibers using alternating plating solution layering techniques, resulting in a Cu-BTC MOF that showed significant antibacterial effectiveness against *Escherichia coli* (E. coli) and *Staphylococcus aureus*. Another investigation revealed that Cu-BTC, when applied to in-situ formed polyester (PET) and nylon, exhibited strong antibacterial activity against various microbial pathogens, including *E. coli*, *Staphylococcus aureus*, and *Candida albicans* (Fig. 3B)[46]. Wang et al.[47] HKUST-1/chitosan/PVA fibers were synthesized using the electrospinning method, demonstrating exceptional antibacterial effectiveness against *E. coli* and *S. aureus*, with a 99% inhibition rate. Additionally, the production of reactive oxygen species (ROS) in energy-sensitive metal-organic frameworks (MOFs) can be enhanced or initiated by external energy sources, such as light or ultrasound (Fig. 3C).

Han et al.[48] a Cu-based MOF was developed by incorporating Cu^{2+} into the porphyrin ring of PCN 224, which enhanced its photocatalytic properties and increased reactive oxygen species (ROS) production. This improvement is due to Cu^{2+}'s ability to capture electrons, reducing electron-hole recombination and speeding up carrier transfer. Adding 10% Cu^{2+} to the MOFs significantly boosted their antibacterial activity against *S. aureus*, achieving a 99.71% inhibition rate within 20 min. This effectiveness results from the combined action of ROS and heat. Overall, Cu-MOFs have proven to be highly effective in eliminating *S. aureus* and treating wound infections in vivo (Fig. 3D).

In a similar study, found that the Cu-HKUST-1@HA composite displayed enhanced nanomechanical properties, with a Young's modulus of 13.76 GPa, comparable to that of human cortical bone. It also had a negative zeta potential of -16.3 mV at pH 7.4 and showed biocompatibility with human dermal fibroblasts at concentrations up to 1000 µg/mL, without

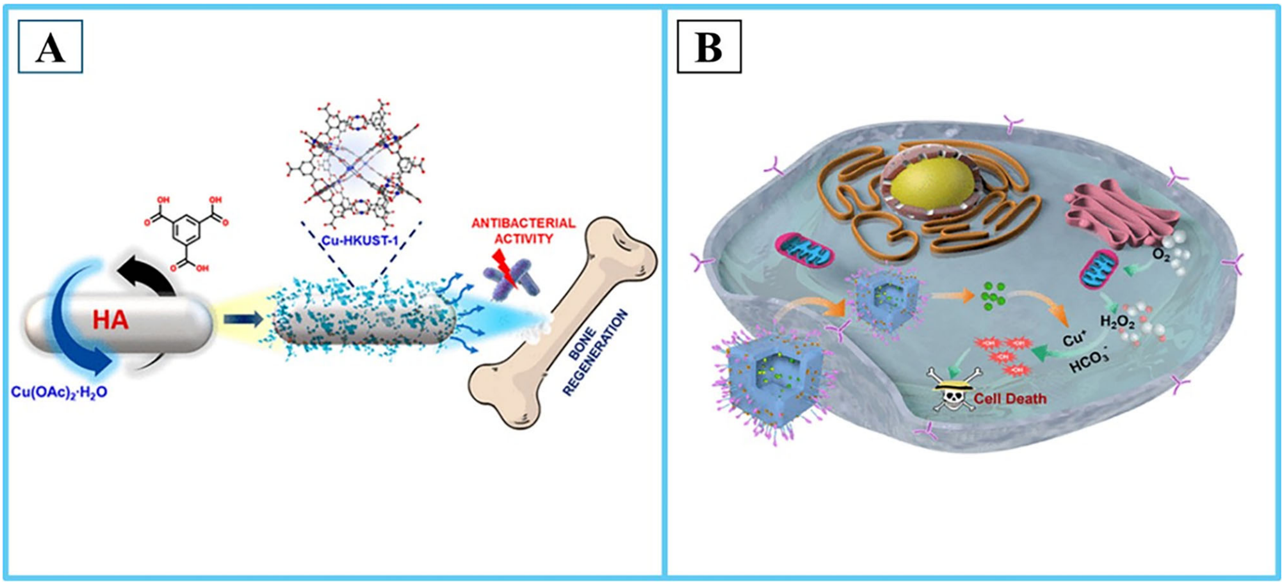


Fig. 4 | Schematic overview of MOF-based nanocomposites for biomedical applications. **A** Schematic summary, Cu-HKUST-1@HA composite formed by coating hydroxyapatite (HA) nanoparticles with Cu-HKUST-1 was shown to exhibit excellent potential for bone tissue regeneration due to its strong antibacterial properties, biocompatibility and bone-like mechanical strength 61. Copyright 2023 American Chemical Society. **B** Schematic summary shows that hollow ZIF-8/Au/CuS/FA nanocomposites serve as a promising platform for sensitive anticancer therapy and generation of reactive oxygen species 62. Copyright 2020 American Chemical Society.

causing ex vivo hemolysis. Additionally, the composite maintained chemical stability for 21 days in a buffer-simulated physiological fluid and exhibited antibacterial properties. These attributes make it a promising candidate for bone tissue regeneration (Fig. 4A)[49].

In a recent study, researchers developed a novel approach using a multifunctional system incorporated into a microneedle-like patch for treating cutaneous melanoma and promoting skin regeneration. This system utilized CuS-Zeolitic imidazolate framework-8 (ZIF-8), enhanced with CuS nanoparticles for improved photothermal conversion. Additionally, the framework was loaded with camptothecin, a hydrophobic chemotherapeutic drug, making it a versatile platform for both photothermal therapy and drug delivery (Fig. 4B)[50].

Zirconium-based MOFs (ZrMOFs), notably UiO-66 (Universitetet i Oslo), hold promise for applications in tissue engineering and biomedicine due to their advantageous properties such as low toxicity and high stability under various conditions including mechanical, thermal, acidic, and aqueous environments. UiO-66, the first Zr-nano-MOF, comprises a zirconium oxide complex linked by 1,4-benzene dicarboxylic acid ligands. By incorporating different functional groups like eNH_2 and NO_2, ZrMOFs with varying pore sizes and release kinetics can be tailored. Generally, nano ZrMOFs are regarded as safe materials suitable for diverse biomedical applications[51–54].

In a similar study, IRMOF-1, with a pore size matching the drug Oridonin (ORI), demonstrated high drug loading capacity (57.93% by weight) and effective release profile (about 90% in 24 h at pH 7.4). When modified with PEG and a cell-penetrating peptide (CPP44), it enabled targeted delivery to hepatic tumor lines, exhibited acid-responsive drug release, enhanced antitumor effects, minimal toxicity, and rapid clearance from the body. This suggests that MOF-based systems with tailored pore sizes have significant potential for personalized cancer therapy (Fig. 5A)[55].

In a similarly study, has developed a novel nano-drug delivery system aimed at tackling infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), known for their resistance to many antibiotics. The system features a nano silver metal-organic framework (Ag-MOF) using 2-methylimidazole as the ligand and silver nitrate as the ion source, with vancomycin (Vanc) incorporated as the therapeutic agent. This Ag-MOF-based delivery system demonstrated pH-responsive properties and favorable biocompatibility, crucial for effective in vivo application. Testing in a mouse model of MRSA pneumonia revealed that the PLT@Ag-MOF-Vanc system provided significantly better anti-infective performance compared to free vancomycin, without notable toxicity. These results suggest that PLT@Ag-MOF-Vanc could be a promising and targeted approach for addressing MRSA infections amidst rising antibiotic resistance (Fig. 5B)[56].

In a separate study, a scaffold made from poly(L-lactic acid) (PLLA) micro/nanofibers was used to deliver metal-organic framework (MOF) nanomaterials containing curcumin and Zn^{2+} for treating diabetic wounds. The integration of curcumin into the MOF structure improved its bioavailability at the wound site and allowed for a controlled release. This regulated release of curcumin and Zn^{2+} from the scaffold provided antioxidant and anti-inflammatory effects, helping to reduce the inflammatory response in the wound[57]. Silver-based antibacterial agents, including both traditional and nano-silver forms, have been approved by the U.S. Environmental Protection Agency due to their low toxicity and broad-spectrum sterilization capabilities. While silver nanoparticles (Ag NPs) are known for their strong antibacterial properties, they are prone to aggregation, which limits their even distribution in substrates. Conversely, silver-based metal-organic frameworks (MOFs) serve as a reservoir for the controlled release of silver ions (Ag^+), harnessing their inherent bactericidal properties for sustained antibacterial activity. Recent studies have also highlighted the antibacterial potential of MOFs incorporating other metals such as magnesium, cobalt, and zirconium. In the field of implant surgery, where residual osteosarcoma cells or infectious bacteria can hinder successful implant integration with natural bone, researchers have been exploring innovative solutions. For example, Zhang et al.[58]. The goal of this study was to assess the effectiveness of a composite material combining magnesium-based metal-organic frameworks (Mg-MOF74) with strontium-substituted hydroxyapatite (Sr-HA) for treating localized injuries. The research demonstrated that Mg-MOF74 was successful in eliminating nearby pathogens, including *S. aureus*, *E. coli*, and *Saos-2* cells, while simultaneously supporting the growth and differentiation of osteoblasts (Fig. 5C).

Similarly, Aguado et al.[59] devised a straightforward method for synthesizing Co-SIM-1, a novel analog of the zinc-based MOF SIM-1. This material exhibited notable antimicrobial properties and durability

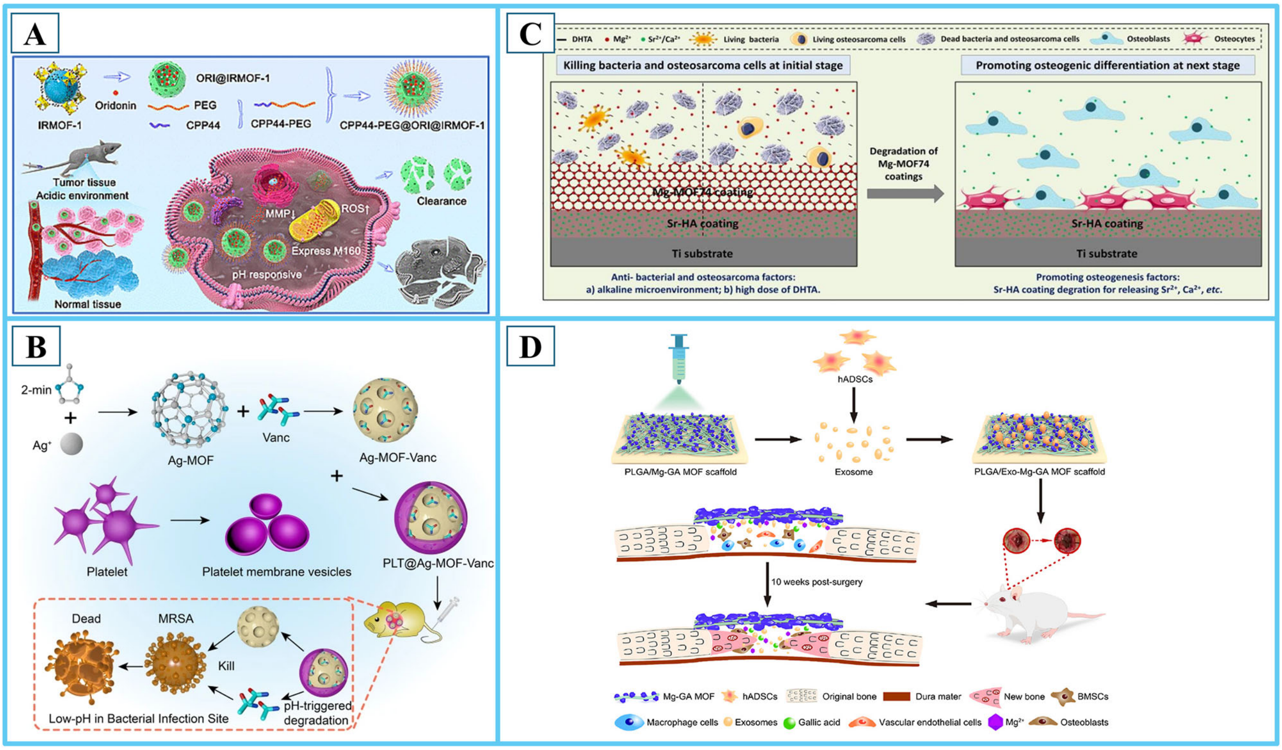


Fig. 5 | Schematic overview of MOF-based platforms for drug delivery, antibacterial therapy, and tissue regeneration. **A** Schematic summary illustrates that pore size-adjusted IRMOFs provide effective and safe nanoplatforms for Oridonin loading and tumor-specific delivery with pH-responsive drug release 67. Copyright 2022 American Chemical Society, **B** In the schematic summary, PLT@Ag-MOF-Vanc, a vancomycin-loaded nanocarrier coated with platelet membranes, was shown to provide potent antibacterial effects, pH-sensitive drug release and excellent biocompatibility for safe and targeted MRSA treatment in a mouse model 68. Copyright 2021 Springer Nature, **C** Schematic summary illustrates the possible mechanisms by which Sr-HA-MOF74 substrates exert antibacterial effects, suppress osteosarcoma and enhance bone regeneration 69. Copyright 2019 Elsevier, **D** Schematic summary shows a PLGA/Mg-GA MOF composite scaffold functionalized with human ADSC-derived exosomes that was evaluated for its ability to promote bone healing, blood vessel formation and reduce inflammation in a rat skull defect model 70. Copyright 2022 Elsevier.

attributed to its controlled release of cobalt ions in a biocide solution. Cobalt-based organic frameworks present an attractive avenue for antimicrobial applications due to their simplicity, cost-effectiveness, and accessibility of commercial ligands. Thus, future developments in this area hold promise for economically feasible antimicrobial materials. MOFs nanoparticles are frequently utilized in antimicrobial therapy either independently or in conjunction with other materials to bolster their antimicrobial properties. Beyond the incorporation of antimicrobial drugs, MOFs exhibit several mechanisms for antimicrobial action. Primarily, certain MOFs contain antimicrobial metal ions such as Zn^{2+}, Cu^{2+}, and Zr^{2+}. Through gradual MOF decomposition, these metal ions are continuously released, serving as effective antibacterial agents under specific conditions. For instance, Sandomierski et al.[60] developed a method to improve the clinical performance of titanium-based materials by applying a coating of methyl vanillate-modified ZIF-8 (MV@ZIF-8) onto titanium surfaces modified with polydopamine (PDA). This modification aimed to enhance both the anti-infection properties and the bone regeneration capabilities of the titanium substrates. Their research into the antibacterial mechanisms of MOFs revealed that ZIF-8 facilitates a controlled, sustained release of Zn^{2+} ions. These Zn^{2+} ions interact electrostatically with the negatively charged bacterial membranes, increasing their permeability. Furthermore, MV@ZIF-8 nanoparticles help form pores in the cell membranes, disrupting membrane integrity and leading to bacterial cell death[60].

The process of tissue repair and regeneration heavily relies on managing inflammation effectively. Prolonged inflammation typically hampers tissue regeneration, underscoring the importance of timely alleviation of inflammation. Recent research has highlighted MOFs as promising materials with anti-inflammatory properties. For instance, Kang et al.[61]. The potential of magnesium-based metal-organic frameworks (Mg-MOFs) combined with gallic acid (GA) as an organic ligand within PLGA for reducing inflammation in bone injury repair has been explored. Magnesium ions (Mg^{2+}) are known to influence inflammatory responses, while GA, a polyphenolic compound, offers antioxidant and anti-inflammatory properties by inhibiting inflammatory mediators and ROS production in macrophages. In vivo studies have confirmed the anti-inflammatory benefits of Mg-GA supplementation. Although the exact mechanisms through which GA reduces inflammation are not fully understood, it is believed that GA may work by decreasing the release of inflammatory cytokines, chemokines, and adhesion molecules, as well as by reducing the infiltration of inflammatory cells. Further research has focused on functionalizing Mg-GA with exosomes and integrating these into scaffolds to enhance their anti-inflammatory, osteogenic, and vascularization-promoting effects, thereby potentially accelerating bone regeneration. This approach opens up promising avenues for future research, particularly in understanding the specific mechanisms behind the anti-inflammatory, osteogenic, and vascularization-enhancing properties of Mg-GA and EXO-Mg-GA (Fig. 5D).

A critical factor for successful tissue regeneration in tissue engineering is ensuring an adequate blood supply, regardless of the tissue type. One of the significant challenges with biomaterials used for tissue repair is achieving sufficient vascularization, particularly in the central regions of scaffolds where blood vessel formation is often inadequate. Without proper vascularization, newly formed tissues cannot obtain the necessary nutrients and oxygen, leading to cell death and incomplete healing. Rapid formation of new capillary networks is essential, especially in larger tissues, where new blood vessels need to sprout from existing ones and connect through the extracellular matrix. To overcome this challenge, developing biocompatible materials that promote blood vessel formation is crucial. Research suggests

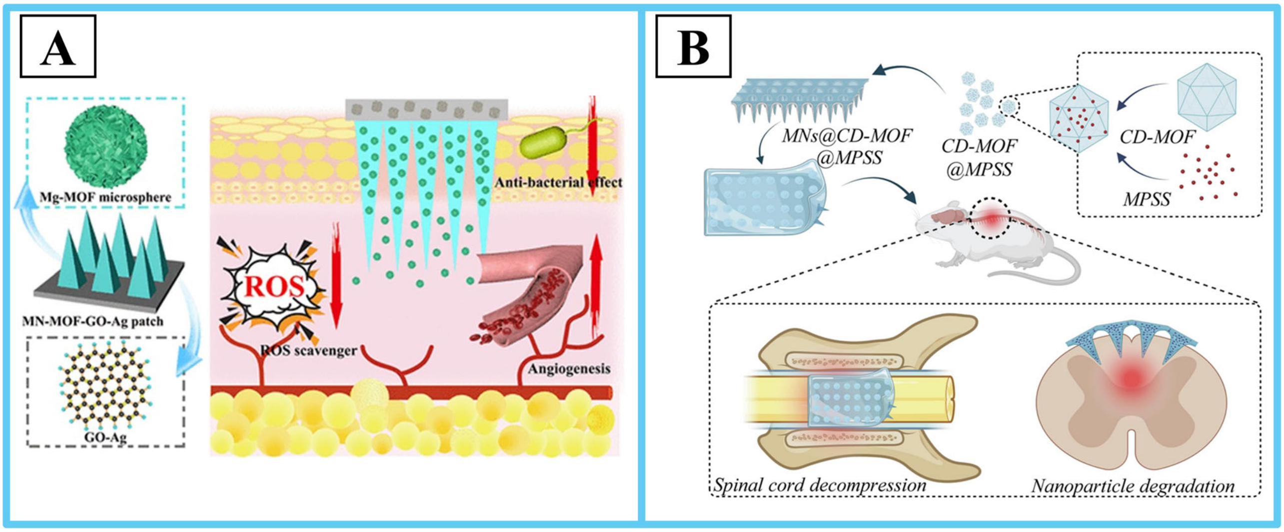


Fig. 6 | Illustrative summary of microneedle-assisted MOF platforms developed for wound healing and spinal cord injury treatment. A Schematic summary shows the creation of a magnesium-organic framework microneedle patch (MN-MOF-GO-Ag) designed for transdermal use, offering combination therapy to accelerate diabetic wound healing 74. Copyright 2021 American Chemical Society. **B** The schematic summary illustrates the creation of an innovative drug delivery system (MNs@CD-MOF@MPSS) that combines β-cyclodextrin metal-organic frameworks (CD-MOF) with microneedles (MNs) to enable precise transdural targeting of drugs for the treatment of spinal cord injury (SCI) 75. Coyright 2023 Elsevier.

that MOFs may aid in angiogenesis through the release of metal ions during their degradation. For instance, magnesium has been shown to enhance angiogenesis and wound healing by promoting cell migration and proliferation. Taking inspiration from this, Yin et al.[62] Mg-MOFs were integrated into a poly(γ-glutamic acid) (γ-PGA) hydrogel, which was subsequently incorporated into a microneedle (MN) patch. The controlled release of Mg^{2+} ions from the Mg-MOFs were found to promote angiogenesis (Fig. 6A).

Nerve injuries or defects pose significant challenges in clinical practice, often leading to poor outcomes and considerable impairment in patients' lives. In a recent study by Zhai et al.[63] a new method has been developed using a β-cyclodextrin metal-organic framework (CD-MOF) incorporated into a microneedle (MN) system for the controlled delivery of methylprednisolone sodium succinate (MPSS) directly to the site of spinal cord injury (SCI) through the dura. This innovative approach offers new potential for spinal cord injury treatment with targeted drug delivery. While research on MOFs in neural tissue engineering, especially in vivo, is still emerging, the promising results of MOF-based biomaterials in bone and wound healing, along with the potential of MOF nanoparticles for nerve repair, suggest a hopeful future for these materials in neural tissue engineering (Fig. 6B).

The mechanical characteristics of natural biomaterials utilized in tissue engineering scaffolds are often lacking. However, incorporating nanoparticles presents a viable approach to enhance these properties. Among nanoparticle options, MOF nanoparticles are particularly noteworthy due to their distinctive structure and chemical interactions. Within PLLA/ZIF-8 composites, the combination of ZIF-8 particles and PLLA matrix serves to bolster tensile strength, compressive strength, and stiffness by establishing robust interfacial bonds. Furthermore, the incorporation of ZIF-8 has shown promise in significantly augmenting the mechanical properties of HA. In bioprinted hydrogel structures, the addition of ZIF-8 nanoparticles proves effective in regulating and enhancing mechanical properties. Studies also demonstrate that MOFs contribute to enhancing hydrogel mechanical strength through synergistic interactions. Consequently, leveraging MOFs in the design and manipulation of hydrogels introduces novel avenues for developing more resilient 3D printing bioinks (Fig. 7A)[64].

Recent studies on MOFs have highlighted the antibacterial effectiveness of various metal ions such as silver, zinc, iron, magnesium, manganese, and copper. This review categorizes MOFs based on their metal components and explores their antimicrobial applications, including those using silver, zinc, copper, cobalt, and other metals. In tissue engineering, which focuses on repairing damaged tissues or organs, incorporating MOFs that release drugs with anti-inflammatory, antibacterial, or tissue-repairing properties into scaffold materials is a promising strategy. This method not only provides essential structural support but also promotes tissue regeneration through the controlled release of therapeutic agents. Beyond traditional pharmaceuticals, MOFs also offer the potential to encapsulate gene therapy agents, such as microRNAs (miRNAs), for use in tissue engineering. For example, Feng et al.[65] encapsulation of pro-angiogenic miR-21 and pro-osteogenic miR-5106 into ZIF-8 nanoparticles was accomplished using a one-pot synthesis method. In vitro studies revealed that miRNA loading in miR@ZIF-8 nanoparticles was highly efficient. The miRNAs contained within the ZIF-8 pores are shielded from RNase degradation, resulting in superior transfection efficiency and stable cellular expression compared to traditional methods like Lipo3000. Additionally, the pH-responsive nature of ZIF-8 enables controlled release of miRNAs in acidic endolysosomal environments. Experiments demonstrated that ZIF-8 nanoparticles loaded with functional miRNAs significantly promoted angiogenesis and osteogenic differentiation in bone marrow mesenchymal stem cells. These miR@ZIF-8 nanoparticles were then integrated into an alginate gel to create a composite hydrogel for cranial defect repair, leading to notable improvements in both angiogenesis and bone formation. This study highlights the potential of MOFs as advanced nucleic acid delivery systems for tissue regeneration, opening new research and application possibilities.

MOFs exhibit a diverse range of compositions, with organic ligands playing a pivotal role in their 3D supramolecular organization and physicochemical properties. Common organic linkers such as carboxylates, phosphonates, sulfonates, and heterocyclic compounds influence MOF characteristics including stability, degradability, bioavailability, and toxicity in biological settings. Selecting the appropriate organic linker is crucial, as it impacts MOF's physical and chemical nature, with some chosen for their low toxicity, biocompatibility, or ability to carry high drug loads. Biomolecules like amino acids, nucleobases, and sugars also find application in MOF structures, particularly in the emerging field of BioMOFs. For instance, Chao et al.[66] devised an antioxidant system using MOF-818 integrated with a hydrogel for wound healing. This innovative approach effectively regulates the microenvironment of chronic wounds by mitigating ROS, facilitating the transition from inflammation to tissue regeneration, particularly beneficial in diabetic wound care.

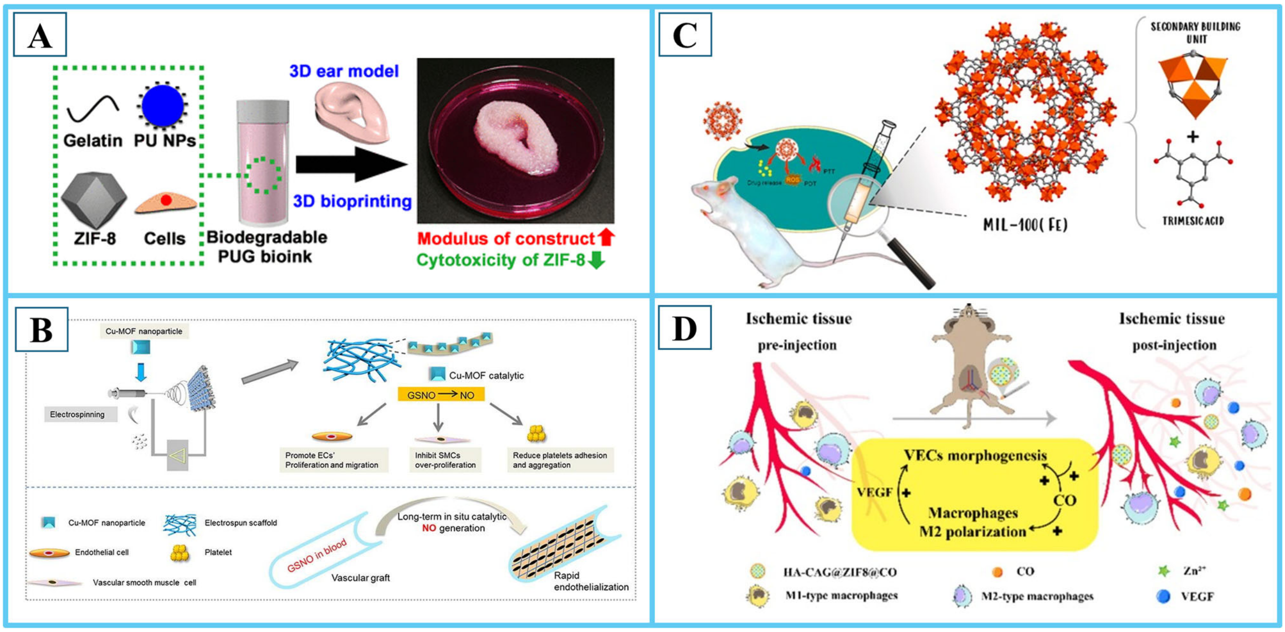


Fig. 7 | Illustrative summary of multifunctional MOFs designed for drug delivery, catalytic therapy, and bioactive molecule release. **A** Schematic summary illustrates that incorporating ZIF-8 into PUG bioink improves structural stability and modulus, although excessive amounts of ZIF-8 may reduce cell viability 76. Copyright 2021 American Chemical Society, **B** Schematic summary, it illustrates the encapsulation of Cu-MOF nanoparticles within PCL, which enhances the stability of Cu-MOF in serum and supports sustained NO catalytic activity. This is validated by in vitro assays and in-situ implantation models 79. Copyright 2021 Elsevier, **C** Schematic summary highlights advances in the synthesis of micro- and nano-sized MIL-100 (Fe), examines its physicochemical stability under varying pH, temperature and physiological environments, and illustrates interactions in its biomedical uses, including biosensing, phototherapy, encapsulation techniques and drug delivery 80. Copyright 2021 Elsevier, **D** Schematic overview illustrates carbon monoxide delivery using bioactive zinc metal-organic frameworks, inspired by organisms' self-repair processes. This method highlights cellular communication and promotes cooperative interactions for enhanced effectiveness. 81. Copyright 2023 Elsevier.

The growing significance of nanozymes in disease diagnosis and treatment is due to their many advantages. In bacterial therapy, various nanomaterials with enzyme-like properties have been explored as potential solutions for bacterial infections. Despite this, challenges such as poor dispersion, aggregation, toxicity, and non-specific catalytic activity have limited the progress of these materials in bacterial theranostics. Additionally, concerns about the environmental impact of metal oxide nanoparticles used in nanozymes highlight the need for new, stable, and efficient nanomaterials. To advance the field of nanozymes for antibacterial applications, it is crucial to explore and develop innovative materials that address these issues.

Peroxidase nanozymes primarily catalyze the breakdown of hydrogen peroxide, producing highly reactive hydroxyl (•OH) free radicals. These radicals are extremely toxic to bacterial cells. While hydrogen peroxide itself has bactericidal properties, excessive concentrations can be harmful to normal tissues and can interfere with wound healing. Recently, Hu et al.[67] a novel hybrid nanozyme was developed by integrating ultrathin two-dimensional MOFs with ultra-small gold nanoparticles (UsAuNPs) through an in-situ reduction process. Although UsAuNPs are known for their excellent enzyme-mimicking capabilities, their high surface area makes them prone to instability and aggregation. The MOFs serve as a stabilizing matrix, preventing the aggregation of UsAuNPs while enhancing their peroxidase-like activity in converting hydrogen peroxide (H_2O_2) into highly reactive hydroxyl radicals (•OH). This hybrid nanozyme demonstrated significant antibacterial activity and promoted wound healing even at low concentrations of H_2O_2.

Cardiovascular disease poses a major global health challenge, characterized by high morbidity, mortality, and treatment costs, affecting both individuals and society at large. MOFs have shown significant potential in addressing these issues, particularly in two main areas: the development of drug-eluting stents and the engineering of blood vessel tissues. Copper-based MOFs are especially noteworthy for their ability to catalyze the production of nitric oxide (NO) from endogenous S-nitrosothiols (RSNOs), a key component in creating antithrombotic coatings for cardiovascular implants. For example, M199 incorporated into polycaprolactone (PCL) electrospun fibrous scaffolds demonstrates prolonged NO catalytic activity, which supports endothelial cell migration, reduces platelet adhesion and activation, and improves the uptake of acetylated low-density lipoprotein (Ac-LDL) (Fig. 7B)[68].

Recently, non-copper-based MOFs have gained attention as promising alternatives. A notable example is the iron-based MOF MIL-101(Fe). (Fig. 7C)[69] MIL-101(Fe) has shown promise in cardiovascular applications. It serves multiple roles when incorporated into PVA/DCS vascular scaffolds, including acting as a mechanical enhancer, a sustained-release heparin (Hep)-loaded MOF, and an agent for B-ultrasound and CT imaging. These modifications have been effective in preventing blood coagulation and promoting vascular endothelialization[70]. Additionally, ZIF-8 nanoparticles, which are loaded with carbon monoxide and coated with HA-CAG peptide to boost bioactivity, show promise in targeting and modulating vascular endothelial cells and macrophages, thereby facilitating angiogenesis. While these nanoparticles are currently used in treating critical limb ischemia, they present exciting possibilities for angiogenesis therapy and may extend to the development of tissue-engineered blood vessels (Fig. 7D)[71].

Currently, the preparation methods for MOF-based functionalized biomaterials primarily involve solution blending and in-situ growth techniques. Diversifying these methods would facilitate broader applications of these materials. While existing research has mainly focused on wound healing and bone repair due to MOFs' prominent antibacterial properties and the high risk of infection in these injuries, there is potential for broader applications. Previous studies have indicated that MOFs not only exhibit antibacterial effects but also promote tissue regeneration, angiogenesis, and inflammation inhibition, suggesting their significant potential in various areas of tissue engineering. Therefore, it is crucial to explore and expand the applications of MOF-based functional materials in tissue engineering beyond traditional uses.

For a composite to be suitable for intra-articular administration, it must be injectable. While MOFs in solution can be injected, incorporating them into hydrogel formulations offers additional advantages, such as slower clearance and the ability to transition from a liquid to a solid state after injection. This combination ensures that the composite will adapt to the defect site upon injection. Injectable MOF-hydrogel composites, such as RB@MPMW[72], and MOF@HA@PCA[73], has shown effectiveness in animal models for treating osteoarthritis. Specifically, the injectability of RB@MPMW has underscored the potential of MOF microcarrier composites with coatings. The accompanying graphical representation outlines the key factors necessary for designing and fabricating an optimal composite for osteoarthritis treatment, as previously discussed.

Imaging and bioelectronic applications

Metal-organic frameworks are crucial in bioelectronic applications due to their ability to conduct ions and electrons, their hybridization with biomolecules, and their role in sensing mechanisms for biosensors. These functionalities enhance the capabilities of MOFs in biomedical and environmental fields by improving processes like biomolecule transport, controlled release, and detection.

- Ionic and Electronic Conductivity: MOFs possess the unique ability to exhibit both ionic and electronic conductivity. This dual functionality is particularly beneficial in bioelectronic devices, as it facilitates the integration of electronic signals with ion transport in biological systems. Riberio et al. explores MOFs as innovative materials offering both ionic and electronic conductivity. A proton-electron dual-conductive MOF was developed, incorporating tetrathiafulvalene (TTF)-phosphonate linkers and lanthanum ions. The formation of partially oxidized TTF stacks, along with S---S interactions, facilitates electron transport through a hopping mechanism, achieving a conductivity of 7.2 × 10^-6 S cm^-1 at room temperature. Additionally, the material demonstrates proton conductivity of 4.9 × 10^-5 S cm^-1, attributed to the presence of free -POH groups. These findings highlight the significant potential of MOF-based systems for developing advanced ionic and electronic conductivity materials[74].
- Biomolecule-MOF Hybrids: MOFs can integrate with biomolecules to create biohybrid structures, which facilitate biocatalytic reactions and biosensor applications. Biomolecules such as saccharides, nucleobases, amino acids, peptides, proteins, and porphyrins can be incorporated into bio-MOFs to improve their properties. The exceptional physicochemical characteristics, biocompatibility, and multifunctionality of bio-MOFs are highlighted in areas like drug delivery, bioimaging, biosensing, separation, catalysis, and environmental cleanup. By merging biology, medicine, and materials science, these materials represent a promising interdisciplinary field. The optimization of biocompatibility, morphology, and multifunctionality drives advancements in biomedical, therapeutic, diagnostic, and environmental technologies[75].
- Biosensors and Detection: MOFs serve as a valuable platform for biosensors due to their distinct features, including high surface area, adjustable pore sizes, and excellent adsorption properties. In the construction of electrochemical (EC) biosensors, MOFs are employed to immobilize probe molecules such as antibodies, DNA, and aptamers. They offer an efficient platform for detecting critical biomarkers for early cancer detection, including cancer markers, microRNA, and live cancer cells. Various strategies have been developed for creating EC biosensors, including the use of monometallic MOFs, bimetallic MOFs, luminophore-linked MOFs, and MOF-based nanocomposites. These advancements are poised to make significant contributions to the future development of biosensing technologies[75].
- Biomolecule delivery and transport: MOFs have garnered significant attention in anticancer therapy and the controlled release and transport of biomolecules due to their distinctive features, including high surface area, adjustable porosity, biocompatibility, and ease of fabrication. Smart MOFs are especially promising due to their capacity to be activated by specific endogenous or exogenous triggers, releasing their therapeutic payloads only under designated conditions. The tumor microenvironment (TME) offers an opportunity to leverage MOFs for targeted delivery, allowing the controlled release of therapeutic agents specifically aimed at cancer cells. This review focuses on recent advancements in the development of MOF-based nanoparticles loaded with biomolecules, emphasizing their potential for controlled release and efficient cargo transport[76].

MOFs are hybrid materials comprising metal ions or clusters connected by organic ligands. The flexibility of their structure, their porous nature and their capacity to precisely adjust pore size and surface features make MOFs highly suitable for applications in biological sensing and imaging. In contrast to inorganic nanomaterials such as graphene, graphene oxide, and gold nanoparticles, MOFs offer distinctive benefits for biological applications due to their biodegradability and the utilization of biocompatible components. MOFs have recently been employed in the detection of DNA, RNA, enzyme activity, and small molecules, as well as in magnetic resonance imaging (MRI) and computed tomography (CT), which are essential for clinical diagnostics. MRI is an advanced medical imaging technique that generates detailed images of the human body. It allows for the observation and analysis of various physiological processes and anatomical structures through the use of electromagnetic radiation, magnetic field gradients, and magnetic fields.

MRI is particularly useful for distinguishing between tumors and other tissues, including healthy ones. Unlike PET or CT scans, MRI does not involve ionizing radiation or X-rays, making it a safer option. It provides superior spatial resolution and can penetrate tissues without limitation. However, MRI's lower sensitivity is a notable drawback, which is addressed by using contrast agents.Contrast agents in MRI fall into two main categories: T1 (positive contrast) agents augment the longitudinal relaxation time, thereby rendering tissues to appear brighter on MRI scans. Conversely, T_2 (negative contrast) agents abbreviate the transverse relaxation time, which results in darker images. In clinical practice and diagnostic imaging, contrast agents containing iron, manganese, and gadolinium are frequently employed.These agents, particularly those containing transition metals like Mn^{2+} or Gd^{3+} with significant magnetic moments and multiple unpaired electrons, are effective in enhancing the relaxation of water protons, thus improving MRI contrast. They also help to reduce the toxicity associated with traditional contrast agents.Conversely, gold, with its high atomic number and increased X-ray attenuation, is a promising candidate for CT imaging using X-rays. The multifunctional properties of MOFs) make them highly effective as MRI contrast agents at targeted locations, thanks to their exceptional tumor-targeting and loading capabilities. The use of contrast agents in computed tomography (CT) and magnetic resonance imaging (MRI) has gained significant attention, leading to the development of various methods for early cancer diagnosis.New MOFs (NMOFs) incorporating gadolinium (Gd), which offer adjustable sizes and high multi-valence for Gd (III), hold promise for addressing the limitations of current Gd-chelate contrast agents used in clinical settings. Research by Tian et al.[77] explored the potential of combining Gd-NMOFs with gold nanoparticles (AuNPs) to create a bimodal imaging agent suitable for both CT and MRI. They developed AuNPs/Gd-MOF composites with enhanced stability by coating Gd-NMOFs with poly (acrylic acid) (PAA) and then reducing and depositing Au ions. These hybrid nanocomposites were subsequently assessed for their performance in both CT and MRI imaging.

Recent research has concentrated on the development of sophisticated imaging contrast agents for the accurate, non-invasive in vivo evaluation of pathological conditions. Notwithstanding the aforementioned advancements, challenges such as false positives, ambiguous imaging outcomes, and the dearth of efficacious dual-mode imaging methodologies persist. One promising approach is the creation of MRI contrast agents (CAs) with intrinsic dual-mode T1/T2 imaging capabilities. This study examines the development and characterization of nanostructured coordination polymers (NCPs) synthesized in a single step, which exhibit dual-mode T1/T2

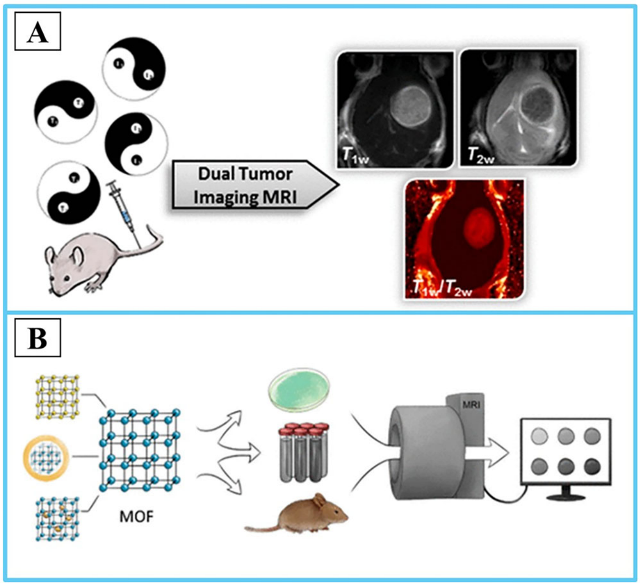


Fig. 8 | Schematic overview of MOF-based nanomaterials developed as MRI contrast agents. A Schematic summary demonstrates the dual T1/T2 MRI contrast potential of Fe-based NCPs with high colloidal stability. The study includes in vitro models, ex vivo tests and in vivo MRI and focuses on a preclinical murine glioblastoma model 90. Copyright 2018 American Chemical Society. **B** Schematic overview explores the role of metal-organic frameworks (MOFs) and composite materials as MRI contrast agents, highlighting their structural features, design approaches, and potential for heteronuclear MRI applications 91. Copyright 2022 American Chemical Society.

MRI contrast. The synthesis of these NCPs integrates various paramagnetic ions (Fe^{3+}, Gd^{3+}, Mn^{2+}) with organic ligands, facilitating polymerization and stabilizing the nanostructure. Among the materials tested, iron-based NCPs demonstrated superior colloidal stability, low toxicity, and effective dual T1/T2 MRI contrast, addressing limitations observed in previous contrast agents. The dual-mode functionality was evaluated through in vitro phantoms, ex vivo and in vivo MRI studies, and a preclinical murine glioblastoma model. The Fe-NCPs demonstrated high-contrast performance, offering simultaneous positive and negative contrast rapidly and safely. Biodistribution studies revealed that the nanoparticles remained within the tumor and were gradually cleared from the system, indicating their biodegradability. Compared to commercially available contrast agents, these nanoplatforms offer significant advantages, highlighting their potential as advanced dual-mode MRI contrast agents (Fig. 8A)[78].

In a related study examined the potential of metal-organic frameworks (MOFs) and their composite materials as contrast agents for magnetic resonance imaging (MRI). Metal-organic frameworks (MOFs) are regarded as a highly promising avenue of research for potential applications in magnetic resonance imaging (MRI) due to their adaptable designs and high metal ion content. This review examined significant advancements in the field over the past five years and classified the materials into three main categories. The subject of this study is the classification of materials into three main categories: MRI-active MOFs, MOF-based composite materials, and MRI-active compounds incorporated into MOFs. Furthermore, the study presented an overview of MOF-based materials employed in heteronuclear MRI, including imaging techniques utilizing 129Xe and 19 F (Fig. 8B)[79].

Theragnostic nanoagents, which combine diagnostic and therapeutic capabilities into a single platform, have gained significant interest in cancer treatment. However, there remains a need for more effective and safer agents for both detection and treatment. To meet this need, a core-shell PB@MIL-100(Fe) dual metal-organic framework (MOF) nanoparticle (d-NMOF) has been developed for multimodal imaging applications (Fig. 9A)[80]. Wang et al.[81] effectiveness of combining chemotherapy with theragnostic functions was assessed through both in vitro and in vivo studies. The core-shell PB@MIL-100(Fe) dual metal-organic framework (d-NMOF) nanoparticles demonstrated significant advancements in the field by integrating the benefits of each MOF component. The MIL-100(Fe) provides a high surface area for pH-responsive release of artemisinin, while the inner PB layer contributes a photothermal effect. Additionally, the nanoparticles serve as potent contrast agents for dual-modal T1-T2 MRI imaging. The d-NMOFs combine multimodal imaging capabilities with synergistic chemo-photothermal treatment, and the reduced toxicity of both artemisinin and the d-NMOFs highlight their potential as a promising, safe, and effective approach for cancer therapy (Fig. 9B). The analysis of pores and the characterization of exceptionally large surfaces in MOF particles underscore the significance of designing multifunctional MOFs for drug delivery. In a separate notable study, Liu et al.[82] reported the development of a Mn-bisphosphonate nanocarrier (NCP) that self-assembled with high loadings of zoledronate (63 ± 5 wt%) and Mn^{2+} ions (13.3 ± 4 wt%). This NCP shows considerable promise for applications in cancer therapy and magnetic resonance imaging (MRI). To optimize drug release kinetics and improve targeting specificity for cancer cells, the Mn-bisphosphonate NCP was coated with a lipid, pegylated, and functionalized with anisamide. These modifications significantly enhanced the cytotoxicity of the agent against human breast and pancreatic cancer cells. In vitro MRI studies confirmed the effectiveness of the Mn-bisphosphonate NCP as a T1 contrast agent and validated the targeting capability of the anisamide-functionalized NCP. This multifunctional NCP offers a promising platform for developing theragnostic nanomaterials with a wide range of biomedical applications.

A significant challenge in the field of healthcare is the effective and safe delivery of drugs using non-toxic nanocarriers. A significant limitation of the majority of current carrier materials is their low drug-loading capacity, frequently below 5 wt% of the drug relative to the carrier. Additionally, these materials often exhibit a rapid release of the drug from their external surfaces. The use of porous hybrid solids, which can be manufactured with bespoke structures and pore sizes, represents a promising avenue for enhancing drug delivery and imaging applications. This is due to the fact that such solids can facilitate more effective drug interactions and achieve higher loadings. This study underscores the potential of non-toxic porous iron(III)-based metal-organic frameworks (MOFs) with engineered cores, surfaces, and imaging capabilities as effective nanocarriers. These MOFs have demonstrated significant promise for the controlled delivery of challenging drugs, including busulfan, azidothymidine triphosphate, doxorubicin, and cidofovir, which are used in cancer and AIDS treatments. Furthermore, the incorporation of diagnostic capabilities could facilitate the development of personalized theragnostic therapies.

In another study, Manganese-doped titanium metal-organic framework (Mn–Ti MOF) nanosheets were synthesized and employed in microwave therapy for the treatment of liver cancer. The Mn–Ti MOFs displayed a rapid temperature increase in normal saline solutions, which was enhanced by their porous structure and facilitated ion collisions induced by microwaves. Furthermore, the Mn-doped Ti MOFs exhibited an enhanced generation of singlet oxygen (^{1}1;O^{2}) under low-power microwave irradiation in comparison to the undoped Ti MOFs. This is likely due to the narrower band gap resulting from manganese doping. Furthermore, the introduction of manganese doping resulted in an enhancement of T1 contrast in magnetic resonance imaging, with a r2/r1 ratio of 2.315. In mouse models with HepG2 tumors, the administration of microwave-triggered Mn–Ti MOFs resulted in a considerable reduction in tumor size after 14 days of treatment. These findings indicate that Mn–Ti MOFs have the potential to serve as effective sensitizers for integrated microwave thermal and dynamic therapies in liver cancer treatment (Fig. 9C)[83]. In a related study, a novel core-shell nanoparticle, CuS@Fe-based metal-organic framework (Fe-MOF), was developed for the purpose of cancer therapy. The nanoparticles in question feature a hexagonal CuS nanoplate core encased in an amorphous Fe-MOF shell. This design enhances near-infrared (NIR) photo absorption and photothermal conversion efficiency

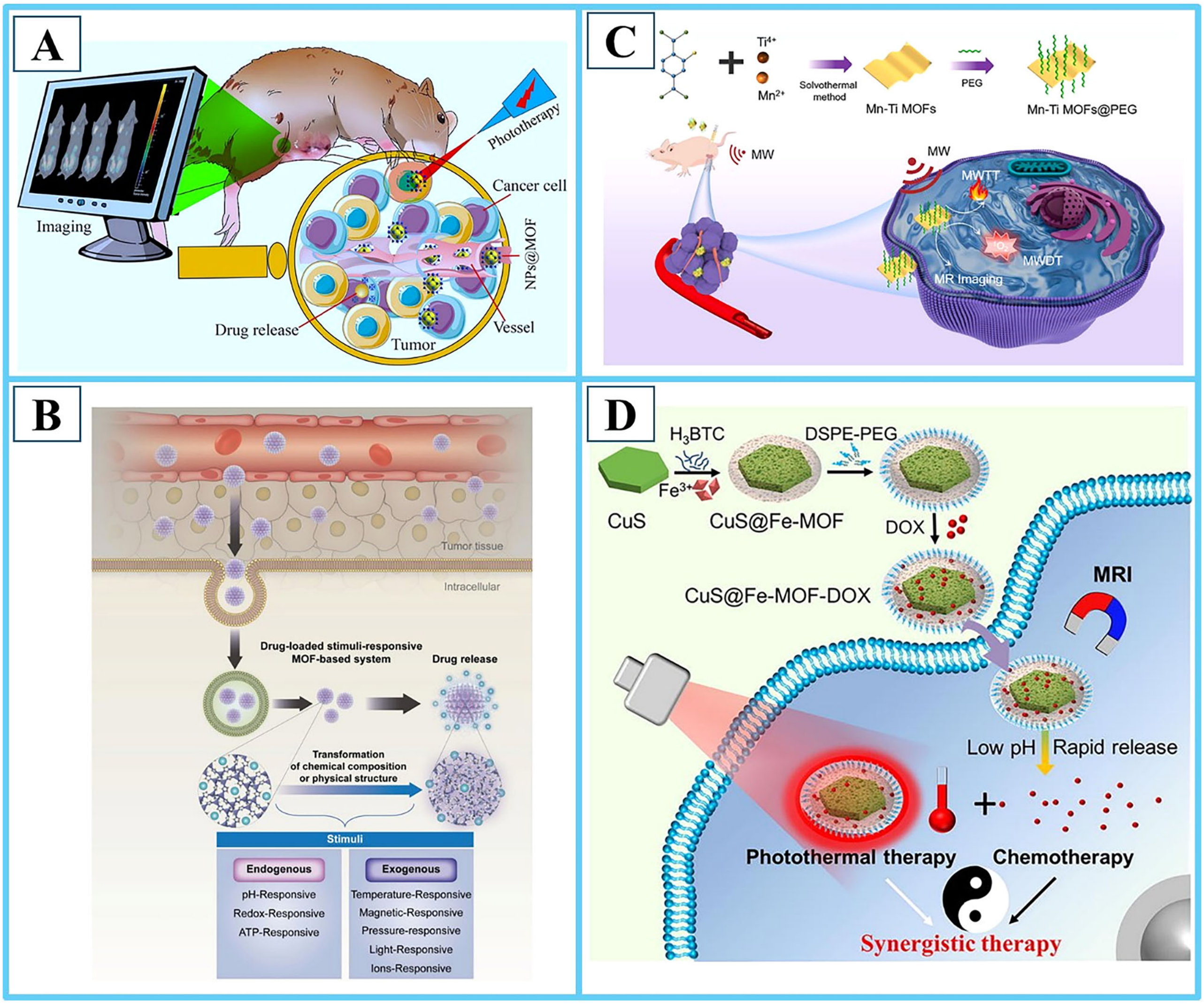


Fig. 9 | Illustrative summary highlighting MOF-derived nanosystems designed for drug delivery, imaging, and synergistic therapeutic strategies. **A** Schematic summary illustrates its application towards core-shell MOF (NP@MOF) nanostructures, focusing on the potential of magnetic, quantum dot (QD), gold (Au) and gadolinium (Gd) cores for applications in drug delivery, multimodal imaging and combined cancer therapies. 90. Copyright 2023 Elsevier, **B** Schematic summary illustration depicts a stimuli-responsive drug delivery system based on metal-organic frameworks (MOFs) 91. Copyright 2018 Wıley, **C** Schematic summary presents the application of Mn-doped Ti MOF nanosheets in microwave therapy and highlights their ability to achieve targeted tumor ablation, enhanced $^1O^2$ production, improved T1 MRI contrast and successful treatment outcomes in HepG2 tumor models. 23. Copyright 2023 Elsevier, **D** Schematic summary shows the multifunctional design of CuS@Fe-MOF nanoplatforms including photothermal therapy, chemotherapy, MRI, LSPR enhancement and pH-sensitive DOX release. This integrated system provides effective tumor ablation through synergistic therapy while maintaining high biocompatibility, resulting in minimal side effects. 94. Copyright 2020 Elsevier.

(39.7%) due to the localization of surface plasmon resonance (LSPR) in CuS. The Fe-MOF shell enables the efficient loading of doxorubicin (DOX) at 27.5%, facilitates pH-responsive drug release, and provides strong magnetic resonance imaging (MRI) capabilities. The combination of photothermal effects from CuS and controlled DOX release resulted in the effective targeting and destruction of cancer cells in vitro. In vivo, the CuS@Fe-MOF-DOX nanoparticles enabled tumor monitoring through MRI and thermal imaging, resulting in a significant reduction in tumor size and destruction via a combined photothermal and chemotherapy approach. This approach proved more efficacious than either treatment alone, with minimal adverse effects observed in mice (Fig. 9D)[84]. Overall, the incorporation of MOFs in bioelectronic applications offers promising advancements in medical imaging and diagnostics, providing more precise, efficient, and targeted approaches to healthcare.

MOFs exhibit great potential in various applications such as gas storage, separation, catalysis, and sensors due to their high surface area, tunable pore sizes, and functional properties. However, several challenges must be addressed for their practical implementation. One significant issue is the limited pore size, often below 2 nm, which can hinder mass transfer; introducing hierarchical porosity by selectively removing unstable organic linkers can overcome this problem[85]. Additionally, MOFs generally have poor electrochemical stability and low electrical conductivity, limiting their use in electrocatalysis; incorporating nanostructured materials like metal oxides or porous carbons can enhance their performance. Another crucial challenge is water stability, especially for wastewater treatment applications; designing MOFs with strong acidic metal ions (e.g., Cr^{3+}, Al^{3+}, Fe^{3+}, Zr^{4+}) and weak basic azolate ligands (e.g., imidazolates) can improve durability in aqueous environments. Furthermore, the efficiency of MOFs in photocatalytic applications, such as CO_2 reduction, water splitting, and pollutant degradation, depends on optimizing their structural and electronic properties, which can be achieved by precisely tuning metal nodes and organic linkers. Ultimately, maximizing the practical potential of MOFs requires optimizing their structural properties, enhancing stability, and modifying them with suitable functional groups, enabling more effective and efficient solutions in energy storage, environmental remediation, and catalysis[86].

MOFs have emerged as promising materials in biomedical imaging due to their inherent properties such as high porosity, customizable structures, and multifunctionality. However, their practical application is often hindered by concerns related to toxicity and degradability. Addressing these challenges is crucial to enhance their safety and efficacy in imaging applications. One of the primary concerns is the potential toxicity arising from the metal ions used in MOF structures. Certain metals, such as cadmium (Cd^{2+}), though commonly utilized, pose significant toxicity risks. In contrast, metals like iron (Fe^{2+}) and zinc (Zn^{2+}) are less toxic and more compatible with biological systems, offering safer alternatives for biomedical use. To mitigate toxicity, current research emphasizes the use of biocompatible metals such as magnesium (Mg) and calcium (Ca)[87]. Additionally, surface modifications, including polymer coatings and functionalization, are being explored to reduce cytotoxic effects, thereby enhancing the safety profile of MOFs in imaging contexts. Degradability presents another challenge, as many MOFs are prone to decomposition under physiological conditions, leading to the release of potentially harmful metal ions or organic linkers. Stability during imaging procedures is critical. Strategies to enhance MOF stability include the use of hydrophobic coatings, cross-linking agents, and biodegradable linkers. These approaches help ensure that MOFs maintain structural integrity during imaging and degrade safely post-application, facilitating efficient biological clearance. Furthermore, controlling degradation rates by adjusting metal-ligand bond strength or employing specific linkers can prevent premature breakdown and aggregation in vivo. For instance, zirconium-based MOFs like UiO-66 exhibit high stability in acidic environments, making them suitable candidates for biological applications[88]. In addition to structural optimization, rigorous biocompatibility assessments are essential. Comprehensive in vitro and in vivo studies focusing on biodistribution, metabolism, and clearance are vital for understanding how MOFs interact with biological systems. Such investigations provide critical insights for optimizing MOF design, ensuring safety, and paving the way for their clinical application. By implementing these strategies—thoughtful metal selection, surface modifications, and controlled degradation—MOFs can be designed to overcome current limitations, advancing their potential as effective and safe imaging agents[89].

Regarding sensing applications, MOF-based sensors are primarily categorized into four types: fluorescence, colorimetric, electrochemical, and surface-enhanced Raman scattering (SERS). Each type offers distinct advantages and faces specific limitations, as summarized in Table 3.

Other bioelectronic applications

In the field of contemporary biomedical research, significant progress has been achieved in various domains, including disease diagnosis and treatment. A key driver of these advancements is the development of innovative materials facilitated by materials science and nanotechnology. Among these materials, metal-organic frameworks (MOFs) stand out due to their promising structural properties. MOFs have attracted substantial interest in biomedical research for several compelling reasons. Their unique structural characteristics, formed through the coordination of metal ions with organic ligands, lead to the creation of highly porous frameworks with large surface areas. This distinctive structure is a primary factor behind their growing use in biomedical applications. These frameworks exhibit ideal properties for numerous biomedical applications, including use as drug carriers, imaging agents, and biosensors. For example, the nanoporous nature of MOFs enables them to encapsulate large amounts of drugs or biological molecules, rendering them effective carriers for drug delivery systems. Another significant benefit of MOFs in the biomedical field is their tunable chemical and physical properties. The synthesis of MOFs can be achieved through the combination of different metal ions and organic ligands, thus allowing for the design of MOFs with desired properties. For instance, if a specific drug is to be targeted to a particular tissue, the surface chemistry and size of MOFs can be customized to facilitate this goal. Moreover, the biocompatibility of MOFs represents another crucial feature that renders them an attractive option for biomedical applications. When the appropriate metal ions and ligands are selected, MOFs present minimal toxicity risks and are unlikely to cause harm to the body. This ensures the safe utilization of MOFs in biomedical applications. In conclusion, the reasons and benefits of utilizing MOFs in the biomedical field are numerous and diverse. Due to their distinctive nanoporous structures, adaptable chemical and physical properties, and high biocompatibility, MOFs are regarded as optimal materials for a multitude of biomedical applications.

In a study by Liu et al., gold nanoparticles (AuNPs) were used with metal-organic framework (MOF) composites as signal probes to create an ultra-sensitive electrochemical immunoassay for detecting C-reactive protein (Fig. 10A)[90]. This immunoassay employs an electron transfer mechanism. Gold nanoparticles (AuNPs) are particularly advantageous in electrochemical biosensors due to a number of factors, including their exceptional biocompatibility, ease of functionalization with -SH and -NH2 groups, extensive surface area, stability, and distinctive optical characteristics (Fig. 10B)[91]. It is established that gold nanoparticles (AuNPs) facilitate electron transfer and support the immobilization of biomolecules. In this study, gold nanoparticles (AuNPs) are attached to metal-organic frameworks (MOFs) using a silicon dioxide layer, thereby facilitating the integration of multiple sensor probes. A highly sensitive and selective electrochemical sensor for lead ions (Pb^{2+}) has been developed using a DNA-functionalized iron-porphyritic metal-organic framework (MOF) (Fe-P) n. The stable (Fe-P) n-MOF generates a number of signaling species, thereby enhancing the sensitivity of the sensor. The incorporation of graphene (GR) linked to the (Fe-P) n-MOF through AuNPs enhances the selectivity of the detection process. The research introduces an advanced electrochemical biosensor, comprising a three-dimensional origami device designed for the detection of Pb^{2+}. The sensor employs an AuNP-modified paper working electrode (Au-PWE) and DNA-functionalized (Fe-P) n-MOF-Au-GR hybrids as signal probes. Upon encountering Pb^{2+}, GR is cleaved at the ribonucleotide (rA) site, generating short oligonucleotide fragments that are associated with the (Fe-P) n-MOF. Subsequently, these fragments hybridize with the hairpin DNA that is immobilized on the surface of the Au-PWE[92]. This study presents a sensitive electrochemical (EC) bioanalytical method for detecting Pb^{2+}, using signal probes composed of Au-modified paper working electrodes (Au-PWE) and (Fe-P)n-MOF-Au-GR hybrids[93]. The Au-PWE demonstrated a large active surface area and excellent conductivity, essential for efficient hairpin DNA binding and electron transfer. As a result, the µ-PAD EC biosensor emerges as a straightforward, affordable, and highly sensitive tool with strong stability, making it an ideal choice for detecting Pb^{2+}. Additionally, it shows potential as an effective device for measuring Pb^{2+} levels in biological systems (Fig. 11A)[94].

The proposed microfluidic origami electrochemical biosensor shows significant promise for local market applications. Further research suggests that MOF-based logic platforms could be an effective method for diagnosing asthma in clinical environments. Asthma, a common chronic condition, is associated with reduced hydrogen sulfide (H2S) production in the lungs, which can serve as an early biomarker. However, detecting H2S in biological systems poses challenges, requiring sensors that are nanoscale, highly biocompatible, capable of real-time detection, and exhibiting excellent selectivity, sensitivity, and water stability.

In order to address these challenges, the INHIBIT logic gate, which utilizes a Europium complex (EUC), incorporates Ag^{+} and H_2S as input signals, with the fluorescence intensity of EUC serving as the output. The MOF-based probe exhibits a rapid response, high selectivity, and excellent sensitivity for the detection of H_2S in physiological conditions, effectively distinguishing it from other substances. EAUC has been demonstrated to possess low cytotoxicity and good biocompatibility, as evidenced by MTT assays and cell viability tests on PC12 cells, thereby establishing its suitability for in vivo H_2S detection. Furthermore, the EAUC system demonstrated the capacity to detect H_2S in diluted serum samples. These findings suggest that MOF-based logic platforms have considerable potential for the detection of H_2S in biological systems, making them valuable tools for the preliminary diagnosis of asthma (Fig. 11B)[95].

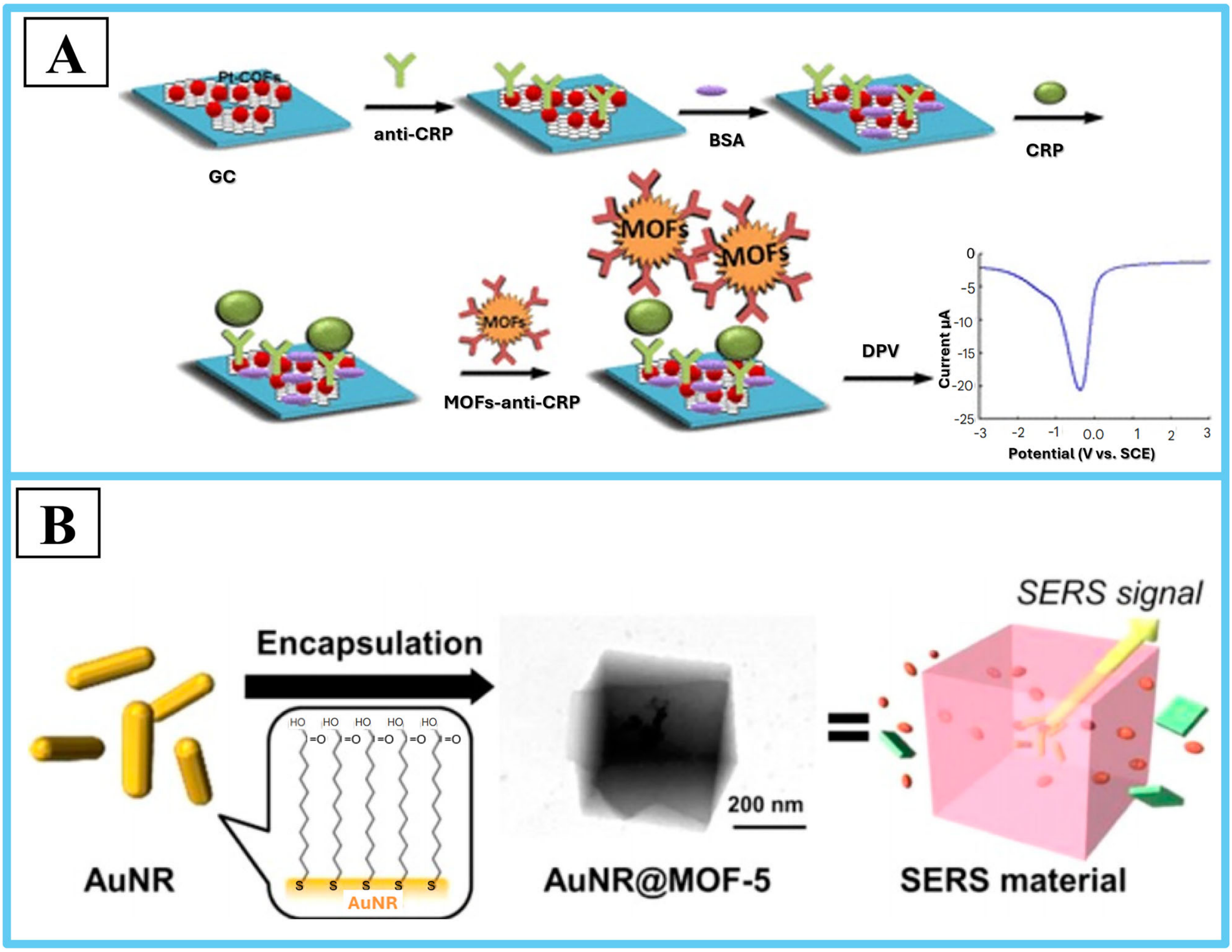
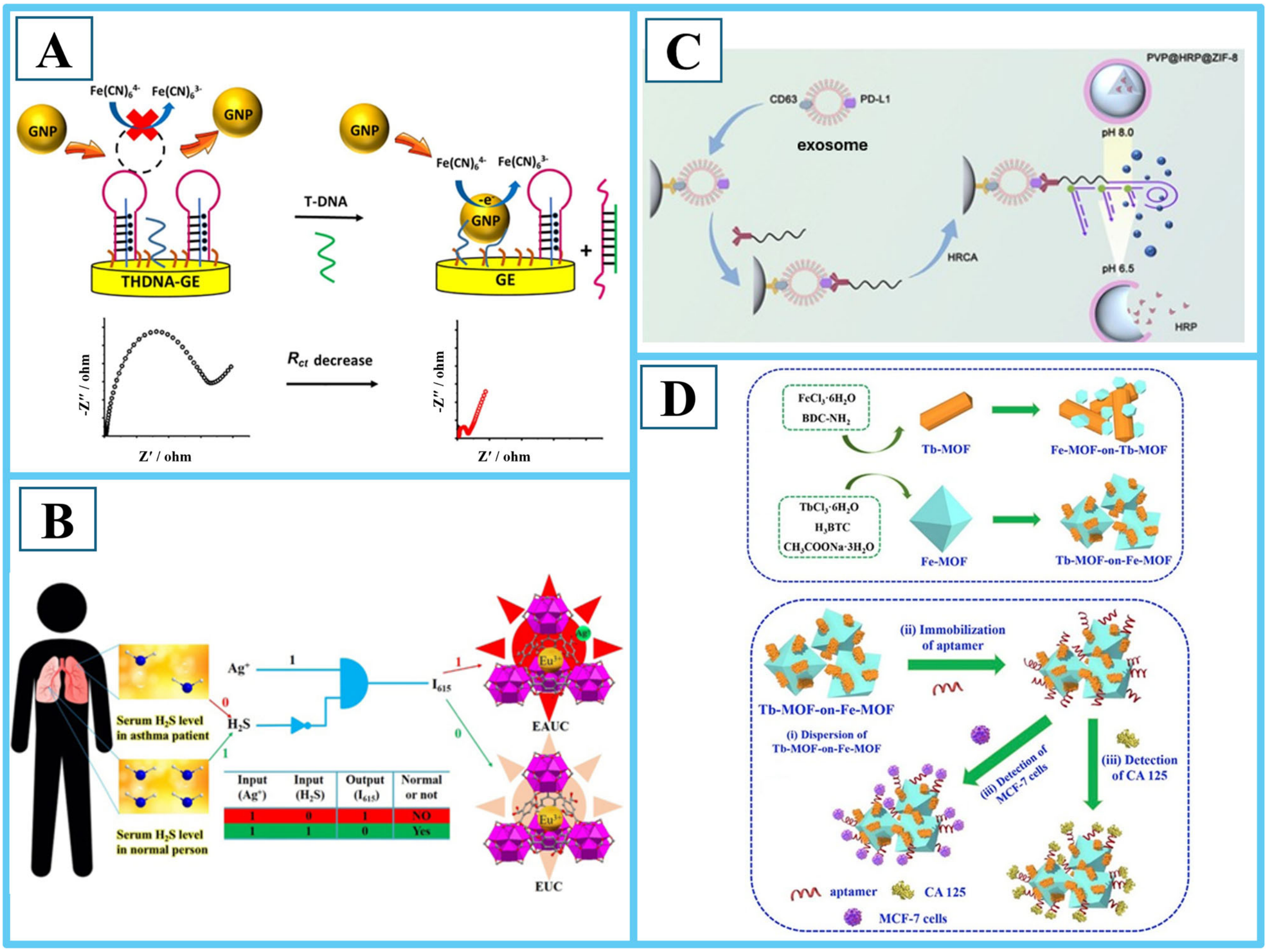


Fig. 10 | Schematic overview of MOF-based sensing platforms for electrochemical and optical detection. A Schematic summary shows a simple and sensitive electrochemical immunoassay designed for CRP detection, offering improved sensitivity, selectivity and affordability, using Au-MOFs as novel signaling probes allowing direct detection of Cu^{2+} ions 105. Copyright 2016 American Chemical Society. **B** Schematic summary illustrates the development of solution-based SERS sensors by coating gold nanorods with a metal-organic framework (MOF). This design enables consistent and accurate detection of target or guest molecules in suspension by increasing stability and reproducibility 106. Copyright 2013 American Chemical Society.

The design of EAUC is driven by two key advantages over the previously reported Eu^{3+}/Cu^{2+}@UiO-66-(COOH)$_2$. Firstly, EAUC exhibits a notable increase in lanthanide luminescence compared to Eu^{3+}/Cu^{2+}@UiO-66-(COOH)$_2$, a benefit attributed to the sensitizing effect of Cu^{2+} ions[96]. Secondly, respiratory virus infections are known to play a significant role in triggering asthma attacks. In this regard, the antibacterial properties of Ag$^+$ ions are especially valuable. The presence of Ag$^+$ ions enhance the signal-to-noise ratio significantly, improving the accuracy of detection. Thus, Ag$^+$ ions not only help in addressing the bacterial component but also contribute to more precise detection capabilities[97,98]. In a separate study, Mohan et al.[99] objective is to introduce a novel approach that employs luminescent and electrochemical MOF sensors for the detection of cancer biomarkers. In the field of healthcare, there is a pressing need for the development of rapid and cost-effective diagnostic techniques that can be relied upon to provide accurate results. The current methods used for the detection of cancer often exhibit low sensitivity and selectivity, in addition to being time-consuming and expensive. To address these challenges, Mohan et al. investigated the potential of porous metal-organic frameworks (MOFs), which offer advanced structural and porous properties that could facilitate the detection of biomarkers. In a similar study, investigated the potential application of analogous approaches to ovarian cancer, which is the most lethal gynecological malignancy and a principal cause of cancer-related mortalities globally. The high mortality rate associated with ovarian cancer is largely attributable to late-stage diagnoses, which are often the result of a lack of early and specific biomarkers for the disease. Recent research has indicated the potential of ovarian cancer-associated microRNAs (miRNAs) as key biomarkers, given their role in regulating cellular processes. These miRNAs offer considerable promise for the enhancement of diagnostic, prognostic, and therapeutic strategies. Despite the excellent analytical performance of traditional miRNA assays, such as RT-qPCR, microarrays, and RNA sequencing, their high cost and impracticality in low-resource settings have prompted interest in simpler, faster, and more affordable miRNA biosensor technologies. Electrochemical sensors have demonstrated considerable potential for point-of-care diagnostics, offering a combination of simplicity, sensitivity, multiplexing capabilities and low cost. This study reviews the role of microRNAs (miRNAs) in ovarian cancer and examines recent advancements in biosensing technologies, including nanotechnology-based, optical and electrochemical methods, for the detection of miRNAs[100]. In this study, Wang et al.[101] electrochemical biosensor method has been developed for the precise detection of exosomes positive for programmed death ligand-1 (PD-L1) using DNA amplification-sensitive metal-organic frameworks, specifically PVP@HRP@ZIF-8. Exosomes,



Input (Ag^+)	Input (H_2S)	Output (I_{615})	Normal or not
1	0	1	NO
1	1	0	Yes

Fig. 11 | Schematic overview of MOF-based biosensing platforms for nucleic acid, exosome, and gas detection. A Schematic summary illustrates the development of a label-free electro-chemical DNA biosensor based on gold nanoparticles (GNP) mediated electron transfer, providing sensitive, rapid nucleic acid detection that simplifies complex preparation processes. 109. Copyright 2021 Elsevier, **B** Schematic summary highlights the use of nanoscale $Eu^{3+}/Ag@UiO\text{-}66\text{-}(COOH)_2$ (EAUC) composites to form a MOF-based logic gate for sensitive and selective H_2S detection and presents a promising approach for early asthma diagnosis with minimal toxicity. 110. Copyright 2019 Elsevier, **C** Schematic summary shows the sensitive electro-chemical detection of PD-L1 positive exosomes captured using magnetic beads via the HRCA-sensitive PVP@HRP@ZIF-8 biosensor platform 111. Copyright 2020 Elsevier, **D** Schematic diagram shows the preparation of Fe-MOF-on-Tb-MOF and Tb-MOF-on-Fe-MOF nanostructures, along with the fabrication process for an aptasensor utilizing these two types of TbFe-MOFs. For illustrative purposes, the aptasensor based on Tb-MOF-on-Fe-MOF will be discussed as an example 112. Copyright 2019 Elsevier.

which are small vesicles released by cancer cells, have gained considerable attention in liquid biopsy applications due to their higher abundance compared to circulating tumor cells, which are often present in very low numbers, even in advanced cancer stages. Moreover, exosomes offer a more comprehensive profile than cell-free nucleic acids. The surface proteins of these exosomes are indicative of the originating tumors, providing valuable information for targeted cancer management, including the detection of PD-L1, A critical immune checkpoint molecule has been identified on exosomes originating from breast cancer cells, which represent the most common cancer among women worldwide. The detection of PD-L1-positive (PD-L1 +) exosomes can act as a prognostic indicator for anti-PD-1 immunotherapy, offering valuable insights for the development of targeted cancer treatment strategies[101]. Cao et al.[102] a new electrochemical biosensing method has been developed for the accurate detection of PD-L1+ exosomes using DNA amplification-responsive metal-organic frameworks, specifically PVP@HRP@ZIF-8. This technique targets PD-L1+ exosomes, which are associated with breast cancer progression and responses to immunotherapy. The method involves capturing exosomes with anti-CD63-functionalized magnetic beads, which are then paired with an anti-PD-L1 capture probe. Following this, hyperbranched rolling circle amplification occurs in-situ, leading to the disassembly of PVP@HRP@ZIF-8 and the release of enzymes that boost electrochemical signals for detecting exosomes. The technique demonstrated a linear detection range for PD-L1+ exosomes from 1×10^3 to 1×10^{10} particles/mL, with a detection limit of 334 particles/mL. Elevated levels of circulating PD-L1+ exosomes were observed in undiluted serum samples from breast cancer patients, especially those with metastatic disease, and these levels were found to correlate with tumor stage and disease progression. This biosensing approach shows promise for enhancing the diagnosis and monitoring of breast cancer through the detection of exosomes (Fig. 11C).

Aptamers are distinguished by their ability to bind specifically and strongly to target molecules through complementary shape interactions and intricate three-dimensional structures[103]. Aptamers have become an attractive alternative to antibodies in biosensing applications. Various methods have been utilized to develop aptamer-based sensors (apt sensors) for detecting target analytes, including fluorescence spectroscopy and surface plasmon resonance (SPR)[104], colorimetric methods[105] and electrochemical techniques[106]. Electrochemical apt sensors are highly esteemed for a number of advantages, including their compact design,

Table 4 | Comparison of different detection techniques.

Technique	Advantages	Disadvantages	References
Fluorescent	Simple design, high sensitivity and selectivity, good reproducibility	Poor stability and reusability, expensive equipment, interference from background fluorescence, quenching effect	135
Colorimetric	Cost-effective, easy fabrication and operation, rapid visual detection, good reproducibility	Lower sensitivity and selectivity, limited stability	136
Electrochemical	Fast analysis, potential for miniaturization, extremely low detection limits, high selectivity	Complex interface design, low repeatability and stability, limited reusability	137
SERS	Ultra-high sensitivity and selectivity, rapid detection, minimal sample volume, applicability to complex samples, non-destructive	Poor reproducibility, requires large and expensive equipment, need for labeling	138

Addressing these challenges through design improvements and functional modifications will be essential to fully leverage the potential of MOF-based sensors and imaging agents in biomedical applications.

Table 5 | Electrochemical biosensor performances based on 2D MOFs.

2D MOF Modified Electrode	Method	Analyte	Linear Range	LOD	References
2D MOFs as Non-enzymatic Electrochemical Sensors					
NiCo-MOFNs	Amperometric	Glucose	1 μM–8 mM	0.29 μM	139
Co-MOF/GCE	Amperometric	H_2O_2	0.5–832.5 μM	0.69 μM	140
Cu-TCPP/Au/p(PX)/GCE	DPV	Dopamine	5–125 μM	1.0 μM	141
Ni-MOF/Hemin/GCE	DPV	H_2O_2	1 μM–0.4 mM	0.2 μM	142
Co-MOF/NF	Amperometric	Glucose	0.001 mM–3 mM	1.3 mM	143
Ni@Cu-MOF/GCE	CV	Glucose	5 μM–2500 μM	1.67 μM	144
2D MOFs as Electrochemical Nucleic Acid Based Biosensors					
Apt/521-MOF/AE	EIS	Mucin 1	0.001–0.5 ng/mL	0.12 pg/mL	145
SGC8/Zn-MOF-on-Zr-MOF/AE	EIS	PTK 7	0.001–1.0 ng/mL	0.84 pg/mL	146
aptamer-BPNSs/TH/Cu-MOF/GCE	SWV	miR3123	2 pM–2 μM	0.3 fM	147
Apt/Co-MOF@TPN-COF/AE	EIS	AMP	1.0 fg/mL–1.2 ng/mL	0.217 fg/mL	148
Ru-MOF/Fe_3O_4@SiO_2@Au	ECL	miRNA-141	1 fM–10 pM	0.3 fM	110
2D MOFs as Electrochemical Immunosensors					
PtNi@Cu-TCPP(Fe)-Ab_2/BSA/Ab_1/Au@MWCNTs/GCE	Amperometric	CALP	200 fg/mL–50 ng/mL	137.7 fg/mL	149
PEI-GO@Ab_2/Ab_1/BSA/Ag/Cu-TCPP(Fe)/MWCNTs/GCE	Amperometric	SMM	1.186–28.051 ng/mL	0.395 pg/mL	150
AntiSNE/Er-TAPPI/AE	EIS	NSE	10.0 fg/mL–1.2 ng/mL	7.1 fg/mL	151
Co/Ni MOF/luminol-AgNps	ECL	AFP	1 pg/mL–100 ng/mL	0.417 pg/mL	152

cost-effectiveness, high efficiency, ease of use, and exceptional selectivity and sensitivity[107]. In a related study, an ultra-sensitive electrochemical immunosensor was developed for detecting RACK1, utilizing 11-cyanoundecyltrimethoxysilane (11-CUTMS) as the immobilization matrix for the biorecognition element. This approach proved effective for loading anti-RACK1 antibodies. The electrochemical properties of the sensor were evaluated using electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV). The interaction between anti-RACK1 antibodies and RACK1 antigens was monitored using the single frequency technique (SFI). The sensor demonstrated a notable response to the RACK1 antigen, with a detection limit of 10.8 fg/mL and a linear detection range of 0.036–2.278 pg/mL ($R^2 = 0.999$). It is distinguished by its high sensitivity, selectivity, and specificity, as well as its excellent reproducibility, stability, and reusability. The sensor's effectiveness was validated in human serum samples, highlighting its potential for clinical use[108]. Wang et al.[109] two novel bimetallic core-shell nanostructures, Tb-MOF-on-Fe-MOF and Fe-MOF-on-Tb-MOF, were designed and synthesized for the first time using a MOF-on-MOF approach. These advanced nanostructures serve as transducer materials in apt sensors. For demonstration, an apt sensor was developed to detect carbohydrate antigen (CA) 125 with high sensitivity by immobilizing it on these bimetallic nanomaterials (Fig. 11D)[109].

MOFs stand out in electrochemical biosensor applications due to their high surface area, tunable porosity, and chemical flexibility. The presented data in Table 4 confirms the high sensitivity and low detection limits (LOD) of MOF-based sensors, particularly for critical analytes like glucose (LOD as low as 0.29 μM) and miRNA (LOD as low as 0.3 fM). These results clearly demonstrate the potential of MOFs in achieving high-performance biosensing. However, to provide a comprehensive understanding of MOF performance, it is crucial to compare these findings with other established material systems such as carbon nanotubes (CNTs), graphene derivatives, and metal nanoparticles. Table 5.

- Carbon Nanotubes (CNTs): CNTs are known for their exceptional electrical conductivity and large surface area, allowing rapid electron transfer. While they offer ultra-low detection limits similar to MOFs, their surface often requires chemical modification to ensure effective biomolecule immobilization, which can complicate fabrication processes.
- Graphene and Derivatives: These materials provide high electrical conductivity and mechanical flexibility. Nevertheless, the production processes can be complex, and ensuring reproducibility at large scales remains challenging.
- Metal Nanoparticles: Although they offer high catalytic activity and sensitivity, challenges such as particle aggregation and limited biocompatibility can affect long-term stability and performance.

In comparison, MOFs offer distinctive advantages, such as tunable porosity and versatile chemical structures, allowing for the fine-tuning of selectivity towards target analytes. Moreover, MOFs enable the design of hybrid materials (e.g., MOF-carbon composites) to overcome intrinsic limitations like low electrical conductivity, thereby achieving detection limits comparable or superior to other material systems.

The detection limits presented in Table 4 highlight that MOF-based sensors can reach femtomolar levels, which is on par with or even superior to other advanced materials. For instance, miRNA detection achieved with Ru-MOF/Fe_3O_4@SiO_2@Au (LOD: 0.3 fM) is among the most sensitive results reported. Similarly, glucose detection with NiCo-MOFNs shows a competitive LOD of 0.29 μM. These benchmarks underscore MOFs' capacity to meet the stringent sensitivity requirements in bioelectronic sensing, particularly for applications demanding ultra-low analyte concentrations[110]. While MOFs demonstrate exceptional performance metrics, integrating comparative insights with other material systems enriches the discussion. The adaptability of MOFs for hybrid systems (e.g., MOF-carbon nanotube composites) positions them as versatile materials that can be optimized for specific bioelectronic applications. Future research should focus on expanding these comparisons, particularly under standardized conditions, to further clarify the unique advantages and potential limitations of MOFs relative to alternative materials[111].

Future opportunities and conclusion

The future of metal-organic frameworks (MOFs) in biotechnology and biomedical engineering holds vast potential. In biosensors, further advancements could lead to the development of more compact, portable, and cost-effective devices, enabling point-of-care diagnostics and real-time monitoring of health conditions. Enhancing the selectivity and sensitivity of MOF-based biosensors for a wider range of biomolecules could revolutionize early disease detection and personalized medicine. Stimuli-responsive metal-organic framework nanoparticles (NMOFs) offer a versatile platform for controlled drug release and biomedical applications due to their porous structure, biocompatibility, low toxicity, and efficient permeability. Drug release can be triggered through external stimuli like chemical factors, physical triggers, or biological markers. Another approach involves incorporating structural information within NMOFs to induce degradation and release the drug. These systems are used in cancer therapy, anti-coagulation treatments, and artificial pancreas development. The potential of multifunctional drug delivery systems and future applications of these stimuli-responsive nanoparticles continue to expand in various biomedical fields[112]. MOFs exhibit remarkable advantages in the realms of biotechnology and biomedical engineering, particularly when compared to other nanomaterials. Their highly customizable pore structures, extensive surface area, and flexible architecture make them ideal for delivering drugs in a controlled and sustained manner. These attributes are especially beneficial for long-term treatment strategies, such as managing chronic illnesses and facilitating targeted drug delivery. Beyond drug delivery, MOFs possess the capability to integrate imaging agents within their porous networks. This characteristic allows them to be utilized in both diagnostic and theranostic platforms, where they can act as effective contrast materials in imaging methods like magnetic resonance imaging (MRI), computed tomography (CT), and fluorescence imaging. MOFs have also proven to be highly effective in biosensing technologies. The presence of metal ions within their frameworks serves as active catalytic sites, significantly improving the sensitivity and specificity of biosensors. As a result, MOFs are well-suited for detecting and transporting a broad spectrum of biological molecules, including small compounds, peptides, proteins, nucleic acids, and tools used in gene editing. Additionally, MOF-based biosensors can be engineered to selectively interact with specific cell types or anatomical regions, increasing their potential for use in clinical diagnostics and biomedical imaging. In conclusion, the structural adaptability and multifunctional nature of MOFs distinguish them from traditional nanomaterials, offering promising opportunities across various biomedical and biotechnological applications[113]. For bionic materials, exploring new MOF compositions and structures can improve the integration and functionality of artificial organs and tissues. Advances in MOF synthesis and processing techniques could lead to materials with superior mechanical properties and biocompatibility, opening up possibilities for more complex tissue engineering applications. In biomedical imaging, future research could focus on optimizing MOFs for multimodal imaging, combining MRI with other imaging techniques such as PET or CT, to provide comprehensive diagnostic information. Developing MOFs with targeted delivery capabilities could further enhance the precision of imaging and therapy. Bio electrochemical applications of MOFs can be expanded to include more efficient energy storage and conversion devices, such as biofuel cells and supercapacitors. Investigating the electrochemical properties of MOFs at the nanoscale could lead to breakthroughs in sustainable energy technologies. However, MOFs encounter significant challenges in large-scale manufacturing and cost management, such as expensive raw materials, low efficiency, waste production, and stability concerns. To address these issues, it is important to focus on developing affordable and sustainable materials, optimizing manufacturing processes, utilizing environmentally friendly solvents, and adopting innovative synthesis techniques. Additionally, enhancing the durability of MOF structures and advancing production technologies are key factors in overcoming these challenges. MOFs have already shown immense promise across various applications in biotechnology and biomedical engineering. Their versatility, combined with ongoing advancements in materials science, points to a future where MOF-based technologies become integral to medical diagnostics, therapeutic interventions, and bioelectronic devices. Continued interdisciplinary research and collaboration will be key to unlocking the full potential of these innovative materials, ultimately improving healthcare outcomes and advancing the field of bioengineering.

Data availability

No datasets were generated or analysed during the current study.

Received: 22 January 2025; Accepted: 21 August 2025;
Published online: 29 September 2025

References

1. Campbell, M. G. & Dincă, M. Metal–organic frameworks as active materials in electronic sensor devices. *Sensors (Switzerland)* **17**. https://doi.org/10.3390/s17051108 (2017).
2. Chidambaram, A. & Stylianou, K. C. Electronic metal-organic framework sensors. *Inorg. Chem. Front.* **5**, 979–998 (2018). vol.
3. Mancuso, J. L., Mroz, A. M., Le, K. N. & Hendon, C. H. Electronic structure modeling of metal-organic frameworks. *Chem. Rev.* **120**, 8641–8715 (2020).
4. Zhang, L. T., Zhou, Y. & Han, S. T. The role of metal–organic frameworks in electronic sensors. *Angew. Chem.* **133**, 15320–15340 (2021).
5. Dolgopolova, E. A. et al. Electronic properties of bimetallic metal-organic frameworks (MOFs): tailoring the density of electronic states through MOF modularity. *J. Am. Chem. Soc.* **139**, 5201–5209 (2017).
6. Lu, C., Clayville, B., Choi, J. Y. & Park, J. 2D metal-organic frameworks as an emerging platform with tunable electronic structures. *Chem* **9**, 2757–2770 (2023). volat.
7. Sharma, A., Singh, A., Gupta, V., Sundramoorthy, A. K. & Arya, S. Involvement of metal organic frameworks in wearable electrochemical sensor for efficient performance. *Trends Environ. Anal. Chem.* **38** https://doi.org/10.1016/j.teac.2023.e00200 (2023).
8. Meskher, H., Belhaouari, S. B. & Sharifianjazi, F. Mini review about metal organic framework (MOF)-based wearable sensors: challenges and prospects. *Heliyon* https://doi.org/10.1016/j.heliyon.2023.e21621 (2023).
9. Cherusseri, J., Pandey, D., Sambath Kumar, K., Thomas, J. & Zhai, L. Flexible supercapacitor electrodes using metal-organic frameworks. *Nanoscale* https://doi.org/10.1039/d0nr03549a (2020).

10. Zhao, H. et al. Wearable sensors and features for diagnosis of neurodegenerative diseases: a systematic review. *Digital Health* **9** https://doi.org/10.1177/20552076231173569 (2023).
11. Sigcha, L. et al. Deep learning and wearable sensors for the diagnosis and monitoring of Parkinson's disease: a systematic review. *Expert Syst. Appl.* **229** https://doi.org/10.1016/j.eswa.2023.120541 (2023).
12. Rovini, E., Maremmani, C. & Cavallo, F. How wearable sensors can support parkinson's disease diagnosis and treatment: a systematic review. *Front. Neurosci.* **11** https://doi.org/10.3389/fnins.2017.00555 (2017).
13. Gürbüz, B. & Ciftci, F. Bio-electric-electronics and tissue engineering applications of MXenes wearable materials: a review. *Chem. Eng. J.* **489**, 151230 (2024).
14. Leibl, N., Haupt, K., Gonzato, C. & Duma, L. Molecularly imprinted polymers for chemical sensing: a tutorial review. *Chemosensors* **9** https://doi.org/10.3390/chemosensors9060123 (2021).
15. Fresco-Cala, B., Batista, A. D. & Cárdenas, S. Molecularly imprinted polymer micro- and nano-particles: a review. *Molecules* **25** https://doi.org/10.3390/molecules25204740 (2020).
16. Wang, Y., Chao, M., Wan, P. & Zhang, L. A wearable breathable pressure sensor from metal-organic framework derived nanocomposites for highly sensitive broad-range healthcare monitoring. *Nano Energy* **70**, 104560 (2020).
17. Baumann, A. E., Burns, D. A., Liu, B. & Thoi, V. S. Metal-organic framework functionalization and design strategies for advanced electrochemical energy storage devices. *Commun. Chem.* https://doi.org/10.1038/s42004-019-0184-6 (2019).
18. Lim, J., Lee, E. J., Choi, J. S. & Jeong, N. C. Diffusion control in the in situ synthesis of iconic metal-organic frameworks within an ionic polymer matrix. *ACS Appl. Mater. Interfaces* https://doi.org/10.1021/acsami.7b17662 (2018).
19. 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* https://doi.org/10.1021/acsomega.2c05310 (2022).
20. Mu, Y. et al. Hydrothermal synthesis of a bimetallic metal-organic framework (MOF)-derived Co3O4/SnO2 composite as an effective material for ethanol detection. *Dalt. Trans*. https://doi.org/10.1039/d3dt03322h. (2023).
21. Mahmoud, M. M. Microwave-assisted fast synthesis of MOF-801. *Mater* **6**, 100316 (2025).
22. Glowniak, S., Szczesniak, B., Choma, J. & Jaroniec, M. Mechanochemical synthesis of MOF-303 and its CO2 adsorption at ambient conditions. *Molecules* **29**, 2 (2024).
23. Araújo-Cordero, A. M., Caddeo, F., Mahmoudi, B., Bron, M. & Wouter Maijenburg, A. Direct electrochemical synthesis of metal-organic frameworks: Cu3(BTC)2 and Cu(TCPP) on copper thin films and copper-based microstructures. *Chempluschem* https://doi.org/10.1002/cplu.202300378 (2024).
24. Yu, K. et al. Sonochemical synthesis of Zr-based porphyrinic MOF-525 and MOF-545: enhancement in catalytic and adsorption properties. *Microporous Mesoporous Mater*. https://doi.org/10.1016/j.micromeso.2021.110985 (2021).
25. Lee, J. et al. Soft seed-mediated dimensional control of metal-organic framework nanocrystals through oil-in-water microemulsions. *Inorg. Chem. Front*. https://doi.org/10.1039/d3qi01567j (2023).
26. Seo, Y. K. et al. Microwave synthesis of hybrid inorganic-organic materials including porous Cu3(BTC)2 from Cu(II)-trimesate mixture. *Microporous Mesoporous Mater*. https://doi.org/10.1016/j.micromeso.2008.10.035 (2009).
27. Chowdhury, P., Bikkina, C., Meister, D., Dreisbach, F. & Gumma, S. Comparison of adsorption isotherms on Cu-BTC metal organic frameworks synthesized from different routes. *Microporous Mesoporous Mater*. https://doi.org/10.1016/j.micromeso.2008.07.029 (2009).
28. Campagnol, N. et al. High pressure, high temperature electrochemical synthesis of metal-organic frameworks: films of MIL-100 (Fe) and HKUST-1 in different morphologies. *J. Mater. Chem. A* https://doi.org/10.1039/c3ta10419b (2013).
29. Biemmi, E., Christian, S., Stock, N. & Bein, T. High-throughput screening of synthesis parameters in the formation of the metal-organic frameworks MOF-5 and HKUST-1. *Microporous Mesoporous Mater*. https://doi.org/10.1016/j.micromeso.2008.06.040 (2009).
30. Yuan, M. et al. Morphology-controlled synthesis of Ni-MOFs with highly enhanced electrocatalytic performance for urea oxidation. *Inorg. Chem*. https://doi.org/10.1021/acs.inorgchem.9b01124 (2019).
31. Łuczak, J. et al. Morphology control through the synthesis of metal-organic frameworks. *Adv. Colloid Interface Sci.* https://doi.org/10.1016/j.cis.2023.102864 (2023).
32. Xiao, Y., Song, B., Chen, Y., Cheng, L. & Ren, Q. ZIF-67 with precursor concentration-dependence morphology for aerobic oxidation of toluene. *J. Organomet. Chem*. https://doi.org/10.1016/j.jorganchem.2020.121597 (2020).
33. Hu, S. et al. Solvothermal synthesis of NH2-MIL-125(Ti) from circular plate to octahedron. *CrystEngComm* **16**, 9645–9650 (2014).
34. Zhao, X. Y., Shi, Y. S., Pang, M. L., Zhang, W. N. & Li, Y. H. Facile fabrication of Eu-1,4-NDC-fcu-MOF particles for sensing of benzidine. *Main. Gr. Chem.* **19**, 117–124 (2020).
35. Guo, H. et al. Combining coordination modulation with acid-base adjustment for the control over size of metal-organic frameworks. *Chem. Mater*. https://doi.org/10.1021/cm202593h (2012).
36. Tsuruoka, T. et al. Nanoporous nanorods fabricated by coordination modulation and oriented attachment growth. *Angew. Chemie - Int. Ed*. https://doi.org/10.1002/anie.200901177 (2009).
37. Zhu, R. et al. Fe-based metal organic frameworks (Fe-MOFs) for bio-related applications. *Pharmaceutics* https://doi.org/10.3390/pharmaceutics15061599 (2023).
38. Du, C. et al. Fe-based metal organic frameworks (Fe-MOFs) for organic pollutants removal via photo-Fenton: a review. *Chem. Eng. J.* **431** https://doi.org/10.1016/j.cej.2021.133932 (2022).
39. Quintero-Alvarez, F. G., Rojas-Mayorga, C. K., Mendoza-Castillo, D. I., Aguayo-Villarreal, I. A. & Bonilla-Petriciolet, A. Physicochemical modeling of the adsorption of pharmaceuticals on MIL-100-Fe and MIL-101-Fe MOFs. *Adsorpt. Sci. Technol.* **2022**, 14 (2022).
40. Ren, X. et al. Copper metal-organic frameworks loaded on chitosan film for the efficient inhibition of bacteria and local infection therapy. *Nanoscale* **11**, 11830–11838 (2019).
41. Leng, X. et al. Biocompatible Fe-based micropore metal-organic frameworks as sustained-release anticancer drug carriers. *Molecules* **23**, 2490 (2018).
42. He, S. et al. Metal-organic frameworks for advanced drug delivery. *Acta Pharm. Sin. B* **11**, 2362–2395 (2021).
43. Gao, X. et al. Controllable synthesis of a smart multifunctional nanoscale metal-organic framework for magnetic resonance/optical imaging and targeted drug delivery. *ACS Appl. Mater. Interfaces* **9**, 3455–3462 (2017).
44. 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.* **48**, 17291–17297 (2019).
45. Shams, S. et al. Cu/H3BTC MOF as a potential antibacterial therapeutic agent against: Staphylococcus aureus and Escherichia coli. *N. J. Chem.* **44**, 17671–17678 (2020).
46. Emam, H. E., Darwesh, O. M. & Abdelhameed, R. M. In-growth metal organic framework/synthetic hybrids as antimicrobial fabrics and its toxicity. *Colloids Surf. B Biointerfaces* **165**, 219–228 (2018).

47. Wang, S. et al. Incorporation of metal-organic frameworks into electrospun chitosan/poly (vinyl alcohol) nanofibrous membrane with enhanced antibacterial activity for wound dressing application. *Int. J. Biol. Macromol.* **158**, 9–17 (2020).
48. Han, D. et al. Enhanced photocatalytic activity and photothermal effects of Cu-doped metal-organic frameworks for rapid treatment of bacteria-infected wounds. *Appl. Catal. B Environ.* **261**, 118248 (2020).
49. Fandzloch, M. et al. Cu-HKUST-1 and Hydroxyapatite-the interface of two worlds toward the design of functional materials dedicated to bone tissue regeneration. *ACS Biomater. Sci. Eng.* **9**, 4646–4653 (2023).
50. Gao, L., Wu, Z., Ibrahim, A. R., Zhou, S. F. & Zhan, G. Fabrication of folic acid-decorated hollow ZIF-8/Au/CuS nanocomposites for enhanced and selective anticancer therapy. *ACS Biomater. Sci. Eng.* **6**, 6095–6107 (2020).
51. Mahmoud, L. A. M. et al. Zirconium-based MOFs and their biodegradable polymer composites for controlled and sustainable delivery of herbicides. *ACS Appl. Bio Mater.* **5**, 3972–3981 (2022).
52. Rezaee, R., Montazer, M., Mianehro, A. & Mahmoudirad, M. Biomedical applicable cellulose fabric modified with zirconium-based metal-organic frameworks (Zr-MOFs). *Starch/Staerke* **73**, 2100120 (2021).
53. Aden, S. F. et al. Controlled delivery of ciprofloxacin using zirconium-based MOFs and poly-caprolactone composites. *J. Drug Deliv. Sci. Technol.* **88**, 104894 (2023).
54. Li, Z. et al. Functional groups influence and mechanism research of UiO-66-type metal-organic frameworks for ketoprofen delivery. *Colloids Surf. B Biointerfaces* **178**, 1–7 (2019).
55. Cai, M. et al. Aperture modulation of isoreticular metal organic frameworks for targeted antitumor drug delivery. *ACS Appl. Mater. Interfaces* **14**, 36366–36378 (2022).
56. Huang, R. et al. Platelet membrane-camouflaged silver metal-organic framework drug system against infections caused by methicillin-resistant Staphylococcus aureus. *J. Nanobiotechnol.* **19**, 229 (2021).
57. Wang, Y. et al. Hierarchical micro/nanofibrous scaffolds incorporated with curcumin and zinc ion eutectic metal organic frameworks for enhanced diabetic wound healing via anti-oxidant and anti-inflammatory activities. *Chem. Eng. J.* **402**, 126273 (2020).
58. Zhang, Y., Shen, X., Ma, P., Peng, Z. & Cai, K. Composite coatings of Mg-MOF74 and Sr-substituted hydroxyapatite on titanium substrates for local antibacterial, anti-osteosarcoma and pro-osteogenesis applications. *Mater. Lett.* **241**, 18–22 (2019).
59. Aguado, S. et al. Antimicrobial activity of cobalt imidazolate metal-organic frameworks. *Chemosphere* **113**, 188–192 (2014).
60. Sandomierski, M., Jakubowski, M., Ratajczak, M. & Voelkel, A. Zeolitic Imidazolate Framework-8 (ZIF-8) modified titanium alloy for controlled release of drugs for osteoporosis. *Sci. Rep.* **12**, 9103 (2022).
61. Kang, Y. et al. Exosome-functionalized magnesium-organic framework-based scaffolds with osteogenic, angiogenic and anti-inflammatory properties for accelerated bone regeneration. *Bioact. Mater.* **18**, 26–41 (2022).
62. Yin, M. et al. Multifunctional magnesium organic framework-based microneedle patch for accelerating diabetic wound healing. *ACS Nano* **15**, 17842–17853 (2021).
63. Zhai, X. et al. Microneedle/CD-MOF-mediated transdural controlled release of methylprednisolone sodium succinate after spinal cord injury. *J. Control. Release* **360**, 236–248 (2023).
64. Hsieh, C. T., Ariga, K., Shrestha, L. K. & Hsu, S. Development of MOF reinforcement for structural stability and toughness enhancement of biodegradable bioinks. *Biomacromolecules* **22**, 1053–1064 (2021).
65. Feng, H. et al. Delivery of therapeutic miRNAs using nanoscale zeolitic imidazolate framework for accelerating vascularized bone regeneration. *Chem. Eng. J.* **430**, 132867 (2022).
66. Chao, D. et al. Specific nanodrug for diabetic chronic wounds based on antioxidase-mimicking MOF-818 nanozymes. *J. Am. Chem. Soc.* **144**, 23438–23447 (2022).
67. Hu, W. C., Younis, M. R., Zhou, Y., Wang, C. & Xia, X. H. In situ fabrication of ultrasmall gold nanoparticles/2D MOFs hybrid as nanozyme for antibacterial therapy. *Small* **16**, 2000553 (2020).
68. Zhang, X. et al. A metal-organic-framework incorporated vascular graft for sustained nitric oxide generation and long-term vascular patency. *Chem. Eng. J.* **421**, 129577 (2021).
69. Quijia, C. R. et al. Application of MIL-100(Fe) in drug delivery and biomedicine. *J. Drug Delivery Sci. Technol.* **61** https://doi.org/10.1016/j.jddst.2020.102217 (2021).
70. Liu, C. et al. Decellularized scaffold-based artificial vascular patch for porcine vascular repair. *ACS Appl. Bio Mater.* **6**, 1071–1080 (2023).
71. Wang, X. et al. CO delivery nanosystem based on regenerative bioactive zinc MOFs highlights intercellular crosstalk for enhanced vascular remodeling in CLI therapy. *Chem. Eng. J.* **452**, 139670 (2023).
72. Xue, S. et al. Cartilage-targeting peptide-modified dual-drug delivery nanoplatform with NIR laser response for osteoarthritis therapy. *Bioact. Mater.* **6**, 2372–2389 (2021).
73. Xiong, F. et al. PH-responsive and hyaluronic acid-functionalized metal-organic frameworks for therapy of osteoarthritis. *J. Nanobiotechnol.* **18**, 139 (2020).
74. Ribeiro, C. et al. Mixed ionic and electronic conductivity in a tetrathiafulvalene-phosphonate metal–organic framework. *J. Am. Chem. Soc.* **147**, 63–68 (2025).
75. Shahzaib, A., Shaily, Kamran, L. A. & Nishat, N. The biomolecule-MOF nexus: recent advancements in biometal-organic frameworks (Bio-MOFs) and their multifaceted applications. *Mater. Today Chem.* **34**, 101781 (2023).
76. Coluccia, M., Parisse, V., Guglielmi, P., Giannini, G. & Secci, D. Metal-organic frameworks (MOFs) as biomolecules drug delivery systems for anticancer purposes. *Eur. J. Med. Chem.* **244**, 114801 (2022).
77. Tian, C., Zhu, L., Lin, F. & Boyes, S. G. Poly(acrylic acid) bridged gadolinium metal-organic framework-gold nanoparticle composites as contrast agents for computed tomography and magnetic resonance bimodal imaging. *ACS Appl. Mater. Interfaces* **7**, 17765–17775 (2015).
78. Suárez-García, S. et al. Dual T1/ T2 nanoscale coordination polymers as novel contrast agents for MRI: a preclinical study for brain tumor. *ACS Appl. Mater. Interfaces* **10**, 38819–38832 (2018).
79. Bunzen, H. & Jirák, D. Recent advances in metal-organic frameworks for applications in magnetic resonance imaging. *ACS Appl. Mater. Interfaces* **14**, 50445–50462 (2022).
80. Khan, S. et al. Core–shell inorganic NP@MOF nanostructures for targeted drug delivery and multimodal imaging-guided combination tumor treatment. *Adv. Colloid Interface Sci.* **321** https://doi.org/10.1016/j.cis.2023.103007 (2023).
81. Cai, W. et al. Metal–organic framework-based stimuli-responsive systems for drug delivery. *Adv. Sci.* **6** https://doi.org/10.1002/advs.201801526 (2019).
82. Liu, D., He, C., Poon, C. & Lin, W. Theranostic nanoscale coordination polymers for magnetic resonance imaging and bisphosphonate delivery. *J. Mater. Chem. B* **2**, 8249–8255 (2014).
83. Qin, Q. et al. Mn-doped Ti-based MOFs for magnetic resonance imaging-guided synergistic microwave thermal and microwave dynamic therapy of liver cancer. *Bioact. Mater.* **27**, 72–81 (2023).

84. Wang, Z. et al. Construction of CuS@Fe-MOF nanoplatforms for MRI-guided synergistic photothermal-chemo therapy of tumors. *Chem. Eng. J.* **400**, 125877 (2020).
85. Wang, K. Y. et al. Creating hierarchical pores in metal–organic frameworks via postsynthetic reactions. *Nat. Protoc*. https://doi.org/10.1038/s41596-022-00759-7 (2023).
86. He, T., Kong, X. J. & Li, J. R. Chemically stable metal-organic frameworks: rational construction and application expansion. *Acc. Chem. Res.* **54**, 3083–3094 (2021).
87. Kumar, P. et al. Regeneration, degradation, and toxicity effect of MOFs: opportunities and challenges. *Environ. Res.* **176**, 108488 (2019).
88. Chattopadhyay, K., Mandal, M. & Maiti, D. K. A review on zirconium-based metal-organic frameworks: synthetic approaches and biomedical applications. *Materials Advances* https://doi.org/10.1039/d3ma00735a (2023).
89. Feng, L., Wang, K. Y., Day, G. S., Ryder, M. R. & Zhou, H. C. Destruction of metal-organic frameworks: positive and negative aspects of stability and lability. *Chem. Rev.* **120**, 13087–13133 (2020).
90. Liu, T. Z. et al. Metal-organic framework nanomaterials as novel signal probes for electron transfer mediated ultrasensitive electrochemical immunoassay. *Anal. Chem.* **88**, 12516–12523 (2016).
91. Sugikawa, K., Nagata, S., Furukawa, Y., Kokado, K. & Sada, K. Stable and functional gold nanorod composites with a metal-organic framework crystalline shell. *Chem. Mater.* **25**, 2565–2570 (2013).
92. Wang, X. et al. 3D origami electrochemical device for sensitive Pb2+ testing based on DNA functionalized iron-porphyrinic metal-organic framework. *Biosens. Bioelectron.* **87**, 108–115 (2017).
93. Lawal, A. T. Recent developments in electrochemical sensors based on graphene for bioanalytical applications. *Sens. Bio-Sens. Res.* **41**, 100571 (2023).
94. Wang, J. et al. Electrochemical detection of DNA by formation of efficient electron transfer pathways through adsorbing gold nanoparticles to DNA modified electrodes. *Microchem. J.* **169**, 106581 (2021).
95. Zhang, X. et al. Nanoscale fluorescent metal–organic framework composites as a logic platform for potential diagnosis of asthma. *Biosens. Bioelectron.* **130**, 65–72 (2019).
96. Zhang, X. et al. Turn-on and ratiometric luminescent sensing of hydrogen sulfide based on metal-organic frameworks. *ACS Appl. Mater. Interfaces* **8**, 32259–32265 (2016).
97. Marambio-Jones, C. & Hoek, E. M. V. A review of the antibacterial effects of silver nanomaterials and potential implications for human health and the environment. *J. Nanopart. Res.* **12**, 1531–1551 (2010).
98. Rai, M., Yadav, A. & Gade, A. Silver nanoparticles as a new generation of antimicrobials. *Biotechnol. Adv.* **27**, 76–83 (2009).
99. Mohan, B. et al. Fabricated metal-organic frameworks (MOFs) as luminescent and electrochemical biosensors for cancer biomarkers detection. *Biosens. Bioelectron.* **197** https://doi.org/10.1016/j.bios.2021.113738 (2022).
100. Aziz, N. B. et al. MicroRNAs in ovarian cancer and recent advances in the development of microRNA-based biosensors. *Analyst* **145**, 2038–2057 (2020).
101. Wang, D. R., Wu, X. L. & Sun, Y. L. Therapeutic targets and biomarkers of tumor immunotherapy: response versus non-response. *Signal Transduct. Targeted Ther.* **7** https://doi.org/10.1038/s41392-022-01136-2 (2022).
102. Cao, Y. et al. Identification of programmed death ligand-1 positive exosomes in breast cancer based on DNA amplification-responsive metal-organic frameworks. *Biosens. Bioelectron.* **166**, 112452 (2020).
103. Meng, H. M. et al. Aptamer-integrated DNA nanostructures for biosensing, bioimaging and cancer therapy. *Chem. Soc. Rev.* **45**, 2583–2602 (2016).
104. Gedi, V. et al. Sensitive on-chip detection of cancer antigen 125 using a DNA aptamer/carbon nanotube network platform. *Sens. Actuators, B Chem.* **256**, 89–97 (2018).
105. Wei, H., Li, B., Li, J., Wang, E. & Dong, S. Simple and sensitive aptamer-based colorimetric sensing of protein using unmodified gold nanoparticle probes. *Chem. Commun.* **36**, 3735–3737 (2007).
106. Jalalian, S. H., Karimabadi, N., Ramezani, M., Abnous, K. & Taghdisi, S. M. Electrochemical and optical aptamer-based sensors for detection of tetracyclines. *Trends Food Sci. Technol.* **73**, 45–57 (2018).
107. Taghdisi, S. M., Danesh, N. M., Ramezani, M., Emrani, A. S. & Abnous, K. A novel electrochemical aptasensor based on Y-shape structure of dual-aptamer-complementary strand conjugate for ultrasensitive detection of myoglobin. *Biosens. Bioelectron.* **80**, 532–537 (2016).
108. Törer, H., Aydın, E. B. & Sezgintürk, M. K. A label-free electrochemical biosensor for direct detection of RACK 1 by using disposable, low-cost and reproducible ITO based electrode. *Anal. Chim. Acta* **1024**, 65–72 (2018).
109. Wang, M. et al. Construction of Tb-MOF-on-Fe-MOF conjugate as a novel platform for ultrasensitive detection of carbohydrate antigen 125 and living cancer cells. *Biosens. Bioelectron.* **142**, 111536 (2019).
110. Shao, H. et al. Ruthenium-based metal organic framework (Ru-MOF)-derived novel Faraday-cage electrochemiluminescence biosensor for ultrasensitive detection of miRNA-141. *Sens. Actuators, B Chem.* **268**, 39–46 (2018).
111. Ulhakim, M. T. et al. Review—recent trend on two-dimensional metal-organic frameworks for electrochemical biosensor application. *J. Electrochem. Soc.* **167**, 136509 (2020).
112. Zhou, Z., Vázquez-González, M. & Willner, I. Stimuli-responsive metal-organic framework nanoparticles for controlled drug delivery and medical applications. *Chem. Soc. Rev.* https://doi.org/10.1039/d0cs01030h (2021).
113. Teixeira de Alencar Filho, J. M. et al. Metal organic frameworks (MOFs) with therapeutic and biomedical applications: a patent review. *Expert Opin. Ther. Patents* **31**, 937–949 https://doi.org/10.1080/13543776.2021.1924149 (2021).
114. Elfadil, D., El-Sayyad, G. S. & Ali, G. A. M. Metal-organic framework composite-based biosensors: biomedical applications. in *Handbook of Nanosensors* https://doi.org/10.1007/978-3-031-16338-8_40-1 (2024).
115. Qiu, Y. et al. Biomedical applications of metal-organic framework (MOF)-based nano-enzymes. *New J. Chem.* https://doi.org/10.1039/d1nj04045f. (2021).
116. Shyngys, M. et al. Metal-organic framework (MOF)-based biomaterials for tissue engineering and regenerative medicine. *Front. Bioeng. Biotechnol.* https://doi.org/10.3389/fbioe.2021.603608 (2021).
117. Chai, W. et al. Recent progress in functional metal–organic frameworks for bio-medical application. *Regener. Biomater.* https://doi.org/10.1093/rb/rbad115 (2024).
118. Wang, C., Liu, S. & Ju, H. Electrochemiluminescence nanoemitters for immunoassay of protein biomarkers. *Bioelectrochemistry* https://doi.org/10.1016/j.bioelechem.2022.108281 (2023).
119. Zheng, W., Hao, X., Zhao, L. & Sun, W. Controllable preparation of nanoscale metal-organic frameworks by ionic liquid microemulsions. *Ind. Eng. Chem. Res*. https://doi.org/10.1021/acs.iecr.7b00694 (2017).
120. Vaitsis, C., Sourkouni, G. & Argirusis, C. Sonochemical synthesis of MOFs. in *Metal-Organic Frameworks for Biomedical Applications* https://doi.org/10.1016/B978-0-12-816984-1.00013-5 (2020).
121. Gupta, S., Murthy, C. N. & Prabha, C. R. Recent advances in carbon nanotube based electrochemical biosensors. *Int. J. Biol. Macromol.* https://doi.org/10.1016/j.ijbiomac.2017.12.038 (2018).
122. Chen, D., Zhao, J., Zhang, P. & Dai, S. Mechanochemical synthesis of metal–organic frameworks. *Polyhedron* https://doi.org/10.1016/j.poly.2019.01.024 (2019).
123. Maliha, Z. et al. Investigation of copper/cobalt MOFs nanocomposite as an electrode material in supercapacitors. *Int. J. Energy Res*. https://doi.org/10.1002/er.8406 (2022).

124. Zhou, Y., Zhang, X. F., Yao, J. & Wang, H. Contra-diffusion synthesis of metal-organic framework separation membranes: a review. *Sep. Purif. Technol*. https://doi.org/10.1016/j.seppur.2022.121837 (2022).
125. Liu, Q. et al. Twofold interpenetrated 2D MOF nanosheets generated by an instant in situ exfoliation method: morphology control and fluorescent sensing. *Adv. Mater. Interfaces* https://doi.org/10.1002/admi.202000813 (2020).
126. Liu, L. L. et al. Fabrication of ultrathin single-layer 2D metal-organic framework nanosheets with excellent adsorption performance: via a facile exfoliation approach. *J. Mater. Chem. A* https://doi.org/10.1039/d0ta07959f (2021).
127. Li, J. et al. Rapid electron transfer via hetero-interface engineering of 2D MOF anchored Ti3C2 MXene nanosheet for enhanced photocatalytic disinfection. *Appl. Catal. B Environ.* **339**, 123163 (2023).
128. Hu, W. C. et al. Ultrasensitive detection of bacteria using a 2D MOF nanozyme-amplified electrochemical detector. *Anal. Chem.* **93**, 8544–8552 (2021).
129. Song, J. et al. 2D metal-organic frameworks for ultraflexible electrochemical transistors with high transconductance and fast response speeds. *Sci. Adv.* **9**, 9627 (2023).
130. Wu, Y., Luo, Y., Chu, P. K. & Menon, C. Revealing the conductivity stability of 2D Cu-MOFs as flexible electrodes: demonstration of triboelectric nanogenerators. *Nano Energy* **111**, 108427 (2023).
131. Xu, G. R. et al. Metal organic framework (MOF)-based micro/nanoscaled materials for heavy metal ions removal: the cutting-edge study on designs, synthesis, and applications. *Coord. Chem. Rev.* **427**, 213554 (2021).
132. Paul, A., Karmakar, A. & Pombeiro, A. J. L. Aspects of hydrothermal and solvothermal methods in MOF chemistry. https://doi.org/10.1142/9789811283208_0009 (2024).
133. Klimakow, M., Klobes, P., Thünemann, A. F., Rademann, K. & Emmerling, F. Mechanochemical synthesis of metal-organic frameworks: a fast and facile approach toward quantitative yields and high specific surface areas. *Chem. Mater.* **22**, 5216–5221 (2010).
134. An, Y. et al. The stability of MOFs in aqueous solutions—research progress and prospects. *Green. Chem. Eng.* **5**, 187–204 (2024).
135. Natarajan, S. & Jana, A. Fluorescent MOFs for selective sensing of toxic cations (Tl3+, Hg2+), ánd highly oxidizing anions [(CrO4)2-, (Cr2O7)2-, (MnO4)-]. *Chempluschem* **82**, 1153–1163 (2017).
136. Mohamed, R. M., El-Sheikh, S. M., Kadi, M. W., Labib, A. A. & Sheta, S. M. A novel test device and quantitative colorimetric method for the detection of human chorionic gonadotropin (hCG) based on Au@Zn-salen MOF for POCT applications. *RSC Adv.* **13**, 11751–11761 (2023).
137. He, B. et al. Freestanding metal-organic frameworks and their derivatives: an emerging platform for electrochemical energy storage and conversion. *Chem. Rev.* **122**, 10087–10125 (2022).
138. Qin, H. et al. Recent progress in the application of metal organic frameworks in surface-enhanced raman scattering detection. *Biosensors* **13**, 479 (2023).
139. Li, W., Lv, S., Wang, Y., Zhang, L. & Cui, X. Nanoporous gold induced vertically standing 2D NiCo bimetal-organic framework nanosheets for non-enzymatic glucose biosensing. *Sens. Actuators B Chem*. https://doi.org/10.1016/j.snb.2018.10.150 (2019).
140. Liu, B. et al. Facile preparation of well conductive 2D MOF for nonenzymatic detection of hydrogen peroxide: relationship between electrocatalysis and metal center. *J. Electroanal. Chem.* https://doi.org/10.1016/j.jelechem.2019.113804 (2020).
141. Qiu, Z., Yang, T., Gao, R., Jie, G. & Hou, W. An electrochemical ratiometric sensor based on 2D MOF nanosheet/Au/polyxanthurenic acid composite for detection of dopamine. *J. Electroanal. Chem.* **835**, 123–129 (2019).
142. Shu, Y. et al. Nickel metal-organic framework nanosheet/hemin composite as biomimetic peroxidase for electrocatalytic reduction of H2O2. *J. Electroanal. Chem.* **845**, 137–143 (2019).
143. Li, Y. et al. Co-MOF nanosheet array: a high-performance electrochemical sensor for non-enzymatic glucose detection. *Sens. Actuators B Chem*. https://doi.org/10.1016/j.snb.2018.09.076 (2019).
144. Xue, Z., Jia, L., Zhu, R. R., Du, L. & Zhao, Q. H. High-performance non-enzymatic glucose electrochemical sensor constructed by transition nickel modified Ni@Cu-MOF. *J. Electroanal. Chem*. https://doi.org/10.1016/j.jelechem.2019.113783 (2020).
145. He, L. et al. 2D zirconium-based metal-organic framework nanosheets for highly sensitive detection of mucin 1: Consistency between electrochemical and surface plasmon resonance methods. *2D Mater.* **4**, 025098 (2017).
146. Zhou, N. et al. Two-dimensional oriented growth of Zn-MOF-on-Zr-MOF architecture: A highly sensitive and selective platform for detecting cancer markers. *Biosens. Bioelectron.* **123**, 51–58 (2019).
147. Sun, Y., Jin, H., Jiang, X. & Gui, R. Black phosphorus nanosheets adhering to thionine-doped 2D MOF as a smart aptasensor enabling accurate capture and ratiometric electrochemical detection of target microRNA. *Sens. Actuators, B Chem.* **309**, 127777 (2020).
148. Liu, X. et al. Novel nanoarchitecture of Co-MOF-on-TPN-COF hybrid: Ultralowly sensitive bioplatform of electrochemical aptasensor toward ampicillin. *Biosens. Bioelectron*. https://doi.org/10.1016/j.bios.2018.09.089 (2019).
149. Dong, L. et al. An enzyme-free ultrasensitive electrochemical immunosensor for calprotectin detection based on PtNi nanoparticles functionalized 2D Cu-metal organic framework nanosheets. *Sens. Actuators B Chem.* **308**, 127687 (2020).
150. Xiao, J. et al. A novel signal amplification strategy based on the competitive reaction between 2D Cu-TCPP(Fe) and polyethyleneimine (PEI) in the application of an enzyme-free and ultrasensitive electrochemical immunosensor for sulfonamide detection. *Biosens. Bioelectron.* **150**, 111883 (2020).
151. Li, Y. et al. Zirconium-porphyrin complex as novel nanocarrier for label-free impedimetric biosensing neuron-specific enolase. *Sens. Actuators B Chem*. https://doi.org/10.1016/j.snb.2020.128090 (2020).
152. Wang, S. et al. A highly sensitive and stable electrochemiluminescence immunosensor for alpha-fetoprotein detection based on luminol-AgNPs@Co/Ni-MOF nanosheet microflowers. *Sens. Actuators B Chem*. https://doi.org/10.1016/j.snb.2020.127919 (2020).

Acknowledgements

All authors would like to acknowledge the support provided by Fatih Sultan Mehmet Vakif University Technology Transfer Office.

Author contributions

S.Y., B.S. and F.C. contributed equally to this manuscript. S.Y., B.S. and F.C. wrote the manuscript equally. S.Y. and B.S. designed the structure of the manuscript. S.Y., B.S. and F.C. reviewed and edited the manuscript. All authors have read and approved the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Fatih Ciftci.

Reprints and permissions information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2025

---

[1]Faculty of Engineering, Department of Biomedical Engineering, Fatih Sultan Mehmet Vakıf University, Istanbul, Turkey. [2]BioriginAI Research Group, Department of Biomedical Engineering, Fatih Sultan Mehmet Vakıf University, Istanbul, Turkey. [3]Biomedical Electronic Design Application and Research Center (BETAM), Fatih Sultan Mehmet Vakıf University, Istanbul, Turkey. ✉e-mail: fciftci@fsm.edu.tr; faciftcii@gmail.com