Trends in Analytical Chemistry

Applications of metal organic frameworks in point of care testing

--Manuscript Draft--

Manuscript Number:	TRAC-D-23-00842R1
Article Type:	Review Article
Keywords:	Metal organic frameworks; point-of-care diagnostic devices; lab-on-a-chip; cellphone-based technologies; paper-based assays
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	Marcello Locatelli
Abstract:	Diagnostic devices used in the POC today play a critical role as tools to provide essential medical surveillance data and to ensure that patients receive appropriate and timely care. These devices also allow self-analysis by the patient, increasing therapeutic adherence as well as reducing pressure on clinical structures. Recent breakthroughs in new technologies are paving the way for the next generation of POCT. Nanomaterials have been created and characterized in recent years. Due to their specific physicochemical properties, MOF nanoparticles are increasingly being used in POCT to improve analytical performance and simplify testing techniques. MOFs have been used for colorimetric or electrochemical POCT and are used as carriers for plasmonic biosensors to be resistant to environmental conditions. This review will discuss the detailed role of MOF in POCT from 2016 to 2023, in addition to the chemical synthesis and characterization methods related to the uses and applications of MOF.
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Opposed Reviewers:	
Response to Reviewers:	Response letter (POCT) Editor and Reviewer comments: Reviewer #1 This review article discusses the applications of metal organic frameworks (MOFs) in point-of-care testing (POCT). It highlights the role of MOFs in various POCT

technologies, such as colorimetric or electrochemical assays, plasmonic biosensors, and lab-on-a-chip devices. It also discusses the chemical synthesis and characterization methods related to the use of MOFs in POCT. Generally, the article emphasizes the potential of MOFs in enhancing the accuracy, efficiency, and operator-independence of diagnostic devices used at the point of care. I recommend publication after addressing the following points:
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The required spaces have been added.

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	2)The discussion section seems just a report of the results. There is not any essential critical approach. Authors should re-write this in details. Critical appraisals of the discussed methods have been added in the discussion section. 3)There are some (few) old Refs, authors should replace them with more recent ones (after 2021). We thank the reviewer for this comment. Most references have been updated, as recommended. 4)The English language has too many flaws and typos. Please drastically revise. We thank the reviewer for this comment. The manuscript has been revised for language flaws and typos. Reviewer #3 The authors are requested to clarify the following issues to strengthen this manuscript We thank the reviewer for his time and effort and for the positive evaluation. All suggestions were accepted and reported in the revised version. 1.I encourage the authors to add and mention the years covered in this review paper in the abstract We thank the reviewer for this comment. The years covered in this review paper (from 2016 to 2023) have been mentioned in the abstract. 2.At the end of the introduction, I suggest they should add few point bullets for the main objectives of this review The main objectives of this review have been added at the end of the introduction section as also suggested by Reviewer 2 (not in terms of point bullets but as sentences). 3.In the introduction section, I suggest that the authors will add and discuss information about the statistics of publications number over the years according to Scopus and/or web of science. This will show how the field of these sensors is evolving. In addition, review articles similar to this subject in the literature should be added and compared with the current work. This comment is highly appreciated. We have added and discussed information about the statistics of publications number over the years according to Scopus database. 4.I highly recommend the authors add one section by the end where they should discuss the advantages, disadvantages, and limitations of the selected sensors. They can compare each technique with each other. We thank the reviewer for this comment. The required section has been added. 5. There are some grammatical typos in the manuscript. Therefore, I suggest to check the manuscript language by a native speaker. The manuscript has been double revised, grammatical errors have been corrected.

Cover letter

Prof. Marcello Locatelli
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Dear Editor, Prof. Damia Barcelo Culleres,

Please find enclosed the revised manuscript "***Applications of metal organic frameworks in point of care testing***" submitted to the **Trends in Analytical Chemistry** as a review article. The proposal was accepted with number TRAC-20-P980 on 26 Dec 2023.

We are very grateful for the very positive evaluation of the present work (minor revisions and modification) and particularly for the Reviewers suggestions that allow improving the quality. All the suggestions were accepted and reported in the revised version using the track changes mode.

The submitted manuscript matches the journal's scopes. We hope that our manuscript will receive favorable peer reviews and subsequent publication in your esteemed journal.

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Sincerely,

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Cc: Damia Barcelo Culleres <dbcqam@cid.csic.es>
Oggetto: RE: TrAC Review Proposal

Dear Dr. Locatelli,

Please find below the accepted proposal tracking number for your reference. This number is required when you submit your Review Article via the edi

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Thanks & Regards,
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Dear Dr. Barcelo,

Please find attached a proposal for your consideration. I would be grateful if you could contact the author directly with your decision, please cc
within your area of expertise.

If accepted, please include the following in your reply to the author:

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Dear TrAC Trends in Analytical Chemistry Journal Editorial Office

I am writing this mail to bring the attached review proposal to Your attention.

Thanking you for Your kind attention and time dedicated

best regards

Marcello Locatelli

--
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Associate Professor, Analytical and Bioanalytical Chemistry University "G. d'Annunzio" of Chieti-Pescara; Department of Pharmacy Build B, level 2; '
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8LzxqriCkTlyj14zfEiQ;
Twitter: @ABL_Locatelli; Skype: marcello71079

Response letter (POCT)

Editor and Reviewer comments:

Reviewer #1

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The required spaces have been added.

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We thank the reviewer for this comment. The novelty of the work has been highlighted in the introduction section.

2) **The discussion section seems just a report of the results. There is not any essential critical approach. Authors should re-write this in details.**

Critical appraisals of the discussed methods have been added in the discussion section.

3) **There are some (few) old Refs, authors should replace them with more recent ones (after 2021).**

We thank the reviewer for this comment. Most references have been updated, as recommended.

4) **The English language has too many flaws and typos. Please drastically revise.**

We thank the reviewer for this comment. The manuscript has been revised for language flaws and typos.

Reviewer #3

The authors are requested to clarify the following issues to strengthen this manuscript

We thank the reviewer for his time and effort and for the positive evaluation. All suggestions were accepted and reported in the revised version.

1. **I encourage the authors to add and mention the years covered in this review paper in the abstract**

   We thank the reviewer for this comment. The years covered in this review paper (from 2016 to 2023) have been mentioned in the abstract.

2. **At the end of the introduction, I suggest they should add few point bullets for the main objectives of this review**

   The main objectives of this review have been added at the end of the introduction section as also suggested by Reviewer 2 (not in terms of point bullets but as sentences).

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The manuscript has been double revised, grammatical errors have been corrected.

Highlights

1. Applications of metal organic frameworks in point of care testing
2. Green evaluation of metal organic frameworks in point of care testing
3. Metal organic frameworks in colorimetry point of care testing
4. Metal organic frameworks in electrochemical point of care testing
5. Metal organic frameworks in point of care testing plasmonic biosensor

Graphical Abstract

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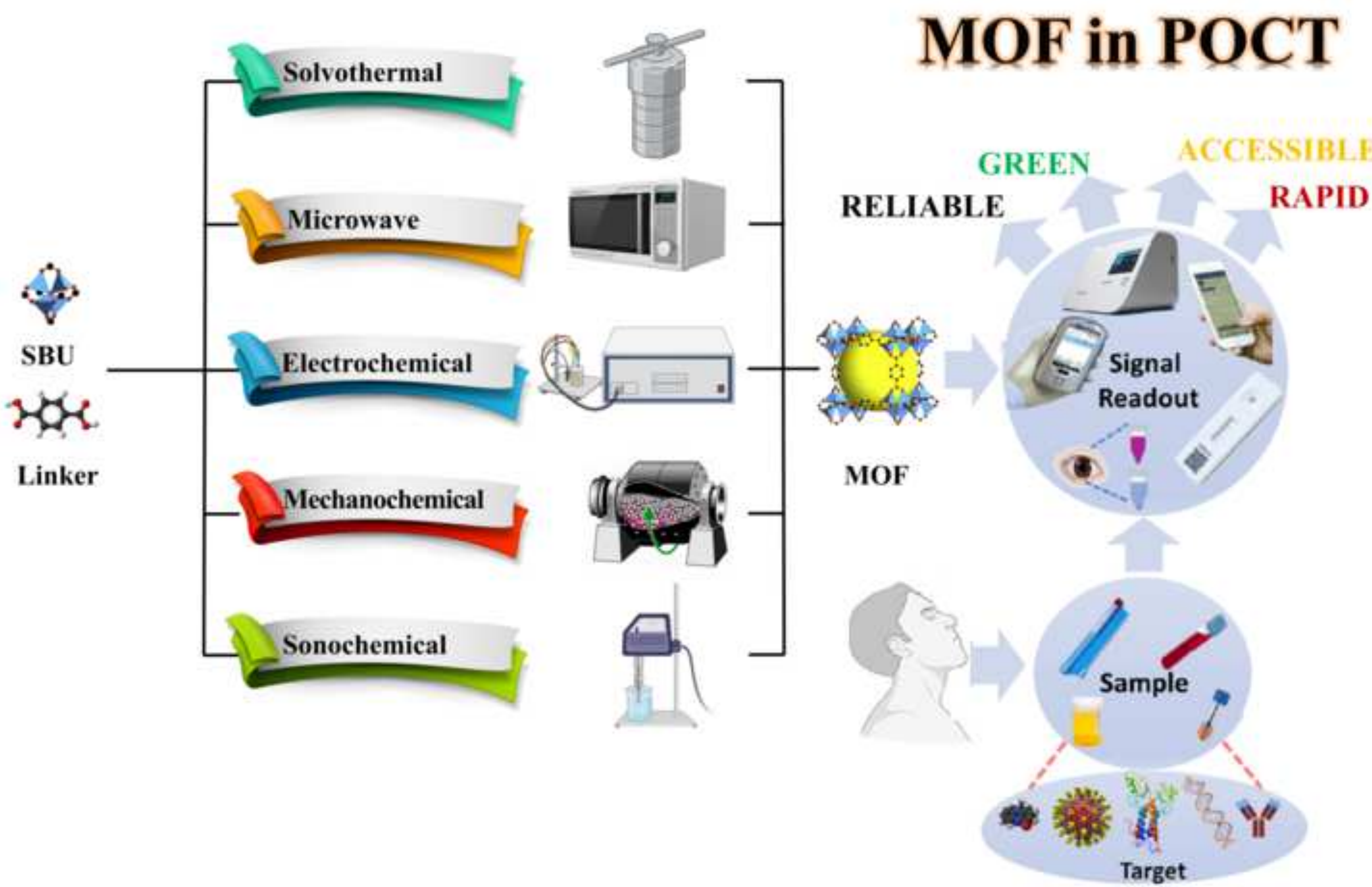

Applications of metal organic frameworks in point of care testing

Fotouh R. Mansour [1,*], Sherin F. Hammad[1], Inas A. Abdallah[2], Alaa Bedair[2], Reda M. Abdelhameed[3], Marcello Locatelli*[4]

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Abstract

Diagnostic devices used in the point-of-care (POC) today play a critical role as tools to provide essential medical surveillance data and to ensure that patients receive appropriate and timely care. These devices also allow self-analysis by the patient, increasing therapeutic adherence as well as reducing pressure on clinical structures. The development of new diagnostic tools, therefore, represents a significant challenge from a technological point of view, both in terms of overcoming current weaknesses in costs, accuracy, and performance, and from an analytical point of view in order to develop tools that are as operator-independent as possible. Recent breakthroughs in new technologies (such as cell phone-dependent technologies, paper-based procedures, and lab-on-a-chip devices) are paving the way for the next generation of point-of-care testing (POCT). Innovative assay devices, as well as efficient reagent storage techniques, are required for new POCT technologies. Nanomaterials of different forms, sizes, and compositions, such as carbon nanomaterials, quantum dots, gold and silver nanoparticles, mesoporous silica nanoparticles, and metal-organic frameworks (MOFs), have been created and characterized in recent years. Due to their specific physicochemical properties, MOF nanoparticles are increasingly being used in POCT to improve analytical performance and simplify testing techniques. MOFs have been used for colorimetric or electrochemical POCT and are used as carriers for plasmonic biosensors to be resistant to environmental conditions. This review will discuss the detailed role of MOF in POCT from 2016 to 2023, in addition to the chemical synthesis and characterization methods related to the uses and applications of MOF.

Keywords

Metal organic frameworks; point-of-care diagnostic devices; lab-on-a-chip; cellphone-based technologies; paper-based assays

1. Introduction

Nowadays, conventional diagnostic procedures are frequently related to quantitative analysis of multiple biomarkers and biochemical properties in specimens within a central lab, with findings available only after many hours, if not days, of waiting. The effective miniaturization of diagnostic equipment for numerous biomarkers has resulted in the commercialization of sensitive and reliable point-of-care testing (POCT) technologies for disease diagnosis and monitoring in hospital emergency rooms and areas with limited resources [1–4]. The advantages of POCT technology over central laboratory testing include low-volume samples, minimal reagent consumption, miniature form factors, and quick turnaround times. A biological examination using POCT must be sensitive and specific, with quantitative results equivalent to existing laboratory-based procedures [5]. Medical diagnosis technology is undergoing a transformation due to the incorporation of computer technology, signal processing, biotechnology, micro- and nanotechnology, and microelectronics as its operating base progressively moves from centralized medical centers to private homes, motivated by the increasing demand for continuous real-time monitoring [6].

In recent years, the area of porous materials has witnessed substantial expansion, with the advent and fast development of metal-organic frameworks (MOFs) [7,8]. MOFs, or porous coordination polymers, are a form of complex porous material made up of inorganic clusters and organic ligands [9]. They are distinguished by great interior surface areas, with highly organized porosity, and a wide range of chemical and physical characteristics [10–12]. As a result, MOFs have demonstrated considerable potential in various applications such as ionic/molecular adsorption [13,14], gas separation [15], energy storage [16], catalysis [17,18], chemical and biosensing [19]. Chemical sensing is a procedure that employs analytical equipment with sensitive components that experience chemical changes when in contact with chemical substances, as well as a transducer that converts the chemical changes into detectable physical signals. One of the most potential applications of MOFs is chemical sensing, owing to their enormous libraries of metal centers and easily functionalized organic cages, which make them sensitive to many chemical and biological stimuli [20–22]. **Figure 1** depicts the growing number of publications on MOFs in different fields in the last two decades.

Figure 1: (a) The increasing number of publications on MOF in the last 20 years according to the Scopus database, (b) The different fields of publications in MOF research

Owing to the urgent need for POCT, extensive efforts have been made to create transducers and readout devices of different sorts to improve the sensitivity, accuracy, and application of biosensors for POC diagnosis [23].It is worth mentioning that the capacity to identify the "target" biomarker in a complex biological sample is regarded as the most crucial step in any diagnostic experiment. Antibodies are one of the most popular biorecognition components used in biodiagnostic equipment [24]. A common example is pregnancy testing using lateral flow tests based on immobilized antibodies [25,26]. Unfortunately, antibodies, like other proteins, are "fragile" in the sense that they degrade and lose bifunctionality when exposed to extreme circumstances such as elevated temperatures, elevated humidity, organic solvents, and proteolytic agents [27–30]. In resource-limited settings, certain challenges can arise when transporting, handling, and storing biosensors. These challenges may include inadequate facilities like refrigeration or electricity, limited awareness of proper handling precautions, and a lack of suitable packaging or sealing methods. As a result, the reliability of the bioanalytical results can be significantly compromised, which in turn restricts the practical applications of POC biosensors.

Therefore, MOF-based POC devices possess high potential due to their unique characteristics including great surface area, variable porosity, organic functioning, extendable shelf life, great thermal stability, and the ability to incorporate biomolecules into these hybrid materials to generate MOF biocomposites [7,31–33]. Certainly, MOFs represent an attractive basis to develop new systems for diagnostics. **Figure 2** summarizes the milestones in the development of MOF applications in POCT.

Figure 2: Timeline of the development of MOFs in POCT.

In this work, the role of MOFs in POCT is being discussed for the first time. A deep understanding of the exact roles of MOFs in POCT is crucial due to the necessity of ongoing development in POCT to address the daily challenges posed by acute and chronic diseases. The purpose of this review is to emphasize the role of MOFs in colorimetric, electrochemical, and plasmonic biosensors for POCT.

Another novel element of the present work consists in a critical evaluation of the green profile of the use of MOFs in POCT through the application of the principles of Green Sample Preparation (GSP). Although GSP is gaining ground in the analytical field in order to evaluate the environmental impact of new sample preparation procedures, is still little known and/or used. For this reason, this review has dedicated a section in which this element is discussed and how MOFs can promote better "adherence" to the principles of GSP.

2. Synthesis of MOF.

MOF synthesis has attracted a lot of interest in recent years because it allows for the creation of a broad variety of attractive structures that could also be useful in a range of applications related to porous materials. This encompasses more typical fields like catalysis, separation, and storage, which are dependent on host-guest interactions, pore size, and pore shape. Furthermore, biological applications or usages as sensor materials are actively being researched. There are different methods for synthesis of MOF as reported in **Figure 3** including conventional, microwave-assisted, sonochemical, electrochemical, and mechanochemical synthesis.

Figure 3: Overview of MOF synthesis for POCT applications.

The conventional synthesis refers to the reactions that are carried out using electric heating with no process of parallelization. The reaction temperature is an important parameter in the process of synthesis, and two approaches are often defined, solvothermal and non-solvothermal, which govern the type of reaction setups that must be utilized.

Solvothermal reactions refer to reactions occurring in closed containers at autogenous pressures above the boiling point of the solvent [34]. As a result, non-solvothermal reactions occur below or near the boiling point at ambient pressure, simplifying synthetic needs. The latter reactions are further categorized as occurring at room temperature or at higher temperatures. It is worth mentioning that chemical reactions demand some type of energy input, and reactions halt only at temperatures near to 0°K. MOF synthesis is typically performed in a solvent at temperatures ranging from room temperature to around 250°C. The energy is often delivered using traditional electric heating, in which heat is transmitted from a hot source, such as the oven, via convection. Energy can also be introduced by other sources, such as an electric potential, electromagnetic radiation, mechanical waves (ultrasound), or mechanically. The time, pressure, and energy per molecule supplied into the system are all directly tied to the energy source, and each of these factors can have a significant impact on the product created and its shape [35]. The conventional methods of MOF synthesis are well established, widely used, and can produce high-quality MOFs with good crystallinity. However, these methods require high temperatures and long reaction times, which makes these processes energy-intensive.

The interaction of electromagnetic waves with mobile electric charges explains microwave-assisted synthesis. Microwave ovens designed for materials synthesis provide monitoring of temperature and pressure during the reaction, allowing a more accurate control of reaction conditions. Microwave-assisted MOF synthesis has mostly been used to accelerate crystallization, produce nanoscale products, and increase product purity [36]. This is owing to the direct heating of the solvents and the observably increased nucleation rate. Microwave-assisted synthesis offers shorter reaction times compared to conventional methods with enhanced control over MOF properties. However, microwave-assisted synthesis has a limited capacity for large-scale synthesis and may require specialized microwave reactors.

Müller and coworkers [37] reported that electrochemical synthesis is able to exclude anions such as nitrate, perchlorate, or chloride throughout the synthesis, which is problematic for large-scale manufacturing processes. In addition to that, other advantages of the electrochemical approach for industrial processes include the ability to operate continuous operation and acquire a greater solids content than with traditional batch reactions. However, the electrochemical synthesis of MOFs is limited to specific MOF precursors that are electroactive, with potential challenges in achieving high yields and purity.

In the case of mechanochemical synthesis, mechanical force may cause a variety of physical events (mechano-physics) as well as chemical reactions [38]. The mechanical breakdown of intramolecular bonds is followed by a chemical transition in mechanochemical synthesis [38–41]. There are several reasons for the interest in mechanically activated MOF synthesis. A critical factor is linked to environmental impact. The reactions can be carried out at room temperature under solvent-free conditions. This synthetic route is certainly the best one to follow whenever the use of organic solvents can be avoided. Furthermore, the possibility of having short reaction times (between 10 and 60 minutes) often allows for quantitative reaction yields and products containing tiny particles. Furthermore, in some cases, metal salts can be replaced as the starting material by metal oxides, resulting in the creation of water as the only by-product. However, mechanochemical synthesis requires specialized milling equipment, with the potential for contamination due to milling media and equipment wear.

Sonochemistry is concerned with the chemistry that occurs when high-energy ultrasound is applied to a reaction mixture. The fundamental objective of sonochemical synthesis in MOF research was to develop a simple, rapid, energy-efficient, and ecologically acceptable room temperature approach [35]. Yet, sonochemical synthesis in MOFs has limited scale-up potential. Consequently, researchers select the synthesis method based on their specific requirements, such as scalability, reaction time, available equipment, and desired MOF properties. Figure 3 illustrates the methods of preparation of MOFs used in POCT applications.

3. Characterization and stability of MOF

After MOFs synthesis, their characterization should be done. The morphology of MOFs could be determined by one of the following techniques: scanning electron microscopy (SEM), atomic force microscopy (AFM), transmission electron microscopy (TEM), fluorescence microscopy, and Brunauer–Emmett–Teller (BET) [42]. While X-ray powder diffraction (XRPD), TEM, dynamic light scattering (DLS), and BET are used for crystal and size determination [42]. Chemical and elemental analysis could be determined by Fourier transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (NMR), thermogravimetric analysis (TGA), mass spectroscopy, and atomic absorption spectroscopy (AAS). UV/Vis spectroscopy, photoluminescence spectroscopy, and Raman spectroscopy were used for the evaluation of the optical characters [42]. Electromagnetic characteristics could be determined by magnetic force microscopy (MFM), electron paramagnetic resonance (EPR), and vibrating sample magnetometer (VSM) [42]. SEM and field emission scanning electron microscopy (FESEM) are commonly used to investigate the morphology of the surface of MOF nanoparticles. Furthermore, utilizing TEM, the fine features of the interior structure of the MOFs could be observed [43]. TEM is a very versatile technology that can answer many concerns arising from the intricacy of the nano crystalline configuration of MOFs that standard imaging methods may not be able to determine.

The hydrodynamic size (to be considered as the diameter of a sphere that has the same translational diffusion speed as the particle) and the surface charge are determined by DLS and zeta potential analysis, respectively. The BET nitrogen adsorption/desorption technique is instead employed to evaluate the pore size distribution and surface area of nano MOFs [44].

X-rays are exploited in the case of XRD (X-ray diffraction) analysis, which provides information on the identification of the structure and phase of crystalline materials based on the diffraction pattern. In the case of crystalline compounds, it is sharp and narrow, while the diffraction pattern for amorphous compounds includes both a noise-related signal and generally broad peaks produced by non-crystalline compounds [45,46].

NMR spectroscopy is applied to monitor and confirm the existence of guest molecules inside the pores of MOFs and organic linkers. This technique is often applied also in the configuration for solid-state analysis as some MOFs are not soluble in any organic solvent and appear in the solid state [47,48].

FTIR is commonly used to confirm the appropriateness of a synthesis. In general, the FTIR signals used to detect functional groups in the structure of MOFs are mainly related to carbonyl groups (1800–1500 cm^{-1}), primary and secondary amino groups (3600–3300 cm^{-1}), and metal-oxygen bonding (600–400 cm^{-1}) [49]. X-ray photoelectron spectroscopy (XPS), compared to the previous ones, represents a quantitative spectroscopic approach that uses the photoelectric effect to examine the chemical state of the surface of the compound, its experimental formula, and the electronic state of the metal ions included in the structure of the MOF. This technique, therefore, represents a valid tool for characterizing the suitable ionic state of metal ions with a variety of electronic states used in the production of various MOFs [50,51]. Some MOFs show luminescence and fluorescent features as a result of delocalized π-electron and metal-to-ligand or ligand-to-metal charge transfer, and they are employed in a variety of biological applications such as cell investigation and sensing [52]. Furthermore, when fluorescent materials such as gold nanoparticles and quantum dots are introduced into MOFs during the production process, photoluminescence spectroscopy as a way of interrogating the electrical structure of the MOFs is beneficial [53]. UV/Vis spectroscopy might be used to study organic linkers, medicinal compounds, and biological macromolecules containing π-electrons with high conjugation [54].

During the sample preparation process, contact surface with the sample should be maximized to increase yield and enhance selectivity, mechanical, thermal, and chemical stability. In the case of MOFs, the coordination and strength of the metal ion bond, the conformation, and size of the pores are the main elements influencing the final characteristics of the MOF and, consequently, its applicability [55]. The primary challenges in enhancing the chemical stability of MOFs are typically addressed with liquid water and water vapor. Therefore, it is advisable to focus on solutions in this regard. When considering structures like MOFs, it is important to note they have weak points at the nodes, especially related to the metal-linker bonds. In these areas of the structure, the formation of a protonated linker and a knot linked with hydroxide (or water) can be observed due to hydrolysis. These reactions are typically accelerated by acidic solutions, leading to the formation of the protonated linker. On the other hand, basic solutions tend to induce the formation of hydroxide. Given these challenges, the stability of MOFs should be evaluated in such solutions (as well as in a neutral environment) by examining signals from powder X-ray diffraction (PXRD) analysis [55]. When assessing the stability of MOFs, it is also crucial to consider that thermal deterioration can occur (resulting in breakage of the node-linker bond) and thus observe how thermal stability is directly correlated to the strength of this bond. Thermal degradation processes include phenomena like amorphization, fusion, dehydration, dehydrogenation, or graphitization [54-58]. To characterize MOFs thermally, TGA and differential scanning calorimetry (DSC) methods are commonly employed. TGA is highly useful for initial screening, while DSC is preferred for more detailed measurements related to the thermal properties (heat flow, phase transitions, and specific heat capacity).

From TGA experiments, it can be observed that between 50°C and 100°C, solvent molecules within the typical porosities of MOFs are released, while between 100°C and 200°C, the coordinated solvent molecules are released. At this stage, the TGA analysis shows a plateau (indicating whether the MOF has a porous crystalline structure), ending at the temperature where partial disintegration of the MOF structure and partial volatilization begin [55].

Certain critical issues related to the thermal stability of some MOFs are the main limitations of their applications in areas such as carbon dioxide capture from exhaust gases and their use as catalysts in methanol production from synthesis gases (H_2 and CO). In recent years, hydrothermally stable MOFs have been synthesized and utilized as heat accumulators (they absorb and desorb aqueous vapors) [58]. In such cases, their stability is evaluated by exposing them to steam at various temperatures and pressures and then measuring parameters such as surface area or porosity using the PXRD technique [59,60].

MOFs are known for their high porosity, which inherently reduces their mechanical stability. Consequently, MOFs are less mechanically stable compared to zeolites, as anticipated. Under mechanical loading, this instability may manifest as phase transitions, partial collapse of pores, or even amorphization [61–64].

4. Applications of MOF in POCT

The rising danger of epidemic or chronic illnesses, as well as the high cost of operative pharmaceuticals, has resulted in greater support, discussion, and desire for the use of POC diagnostic skills [65]. Now, biosensors made of various materials and constructed using various detection techniques are being researched to overcome the present barriers to efficiently detecting these diseases. MOFs have been identified as a viable material for enhancing the detection limit and specificity of biosensors for the detection of these diseases [32,66–68]. In the following section, the role of MOFs in POCT will be discussed in detail.

4.1. Applications of MOF in colorimetric POCT

Usually, colorimetric-based POCT employs colorimetric test strips for detection and quantification, which depend on the values of chromaticity in images captured by the mobile camera to assess the level of concentration [69–71]. In addition to test strip fabrication, microfluidic paper-based analytical devices (μPADs) [72] play an important role in POCT [73]. The principle of the color change of the MOF in colorimetry POCT could depend on using direct colorimetric change based on a certain reaction. Luan and coworkers [73] used cerium-based MOF for the colorimetric assay of uric acid and glucose, as indicated in **Figure 4**. In this work, the authors built the Ce-MOF-based OPSlipChip for selective uric acid and glucose detection to provide a point-of-care testing platform. To replace the lateral flow test, this tool used an externally actuated method and a molecular threading strategy, inspired by the previously disclosed Slip Chip technology and molecular threading-dependent mass transport strategy. The functional parts of the two sheets were not aligned while the chip was in the "OFF-state," and the hydrophobic part coated with paraffin wax was under the reaction regions of the top sheet. As a result, the sample may be retained in the reaction areas through incubation, and then the conversion from the target analyte to H_2O_2 can be completed. The loaded OPSlipChip was transformed into the "ON-state" for colorimetric analysis after incubation by sliding. Due to the slide caused by external actuation, the liquid sample was able to move to the desirable locations. The molecular threading was triggered during the "ON-state". The sheet, when coupled with Ce-MOF, will cause rapid capillary pumping of water molecules and molecular threading of solute via solute-solvent interaction in the direction of gravity. Compared to linear mass transfer in lateral flow, the transit distance of molecular threading in this system was substantially shorter.

Figure 4. (A) Schematic representation of the procedures on an OPSlipChip based on CEF-MOF; (B) The Ce-MOF-based OPSlipChip's operational concept and functional change; (C) Ce-MOF mediated molecular threading strategy creates a bio-like barrier for proteins in serum.

An alternative strategy in the use of MOF in colorimetric POCT consists of preparing a fluorescent strip with the help of luminescent MOFs, the color of which is modified with the addition of the target analyte with the help of the UV lamp. This strategy was successfully applied for POCT related to several diseases including Parkinson's disease [74,75], cancer [76,77], COVID-19 [78], Alzheimer's disease [79], diabetes [80,81], liver dysfunction and bone disorders [82]. However, this approach is not very attractive in POCT due to the need for a UV lamp, which is generally not available in most clinics. This makes the application of these MOF-based fluorescent strips not that practical.

Noble metal nanomaterials, especially nanoclusters composed by Au and Ag, have attracted increased attention in recent years as preferred options for fluorescent probes, owing to several exceptional advantages such as high fluorescence (FL) intensities for fluorometric detections [83–87]. An enormous challenge in terms of conservation (i.e., optical blenching) may be used for fluorescent nanoprobes (i.e. photosensitive Ag nanoparticles), particularly those coated on test strips, which may prevent fluorometric test strips from being used in large-scale analysis applications. Cai and coworkers [76] developed a luminescent test strip for POCT using gold-silver (Au-Ag) nanospheres and ZIF-8, for investigating trace cysteine (Cys) in Hela cells. Au-Ag bimetallic nanoclusters were first synthesized using protein-based biomineralization and then harvested via a desolvation process to create Au-Ag nanospheres with high fluorescence selectively suppressed by Cys. Nanospheres were coated onto test strips before being coated with ZIF-8 via a vacuum-assisted rapid drying technique with superhydrophobic patterns. It was revealed that the test strips could not only create uniform coatings of fluorescent nanoprobes, but also increased fluorescence, environmental and storage stability due to the ZIF-8 shell, as shown in **Figure 5**.

Figure 5. (A) The primary procedure and mechanism of Au-Ag@ZIF-8 based fluorometric test strips for Cys analysis, including Au-Ag coating, ZIF-8 shelling and Cys immersion assays. (B) The reactions on which the device is based to detect Cys via BSA encapsulation of Au-Ag nanospheres, ZIF-8 shelling and release of Au-Ag@ZIF-8 triggered by PBS and the Cys-induced fluorescence quenching of Au -Ag@ZIF-8.

In addition to assessing Cys in biological samples, the fluorometric test strips aided in the determination of Cys in Hela cells with a linear range of concentrations from 0.0032 to 32.0 µM, making them promising for POCT of low-level Cys for early clinical diagnosis of diseases such as cancer. Furthermore, the proposed technique for producing stable and uniform test strips using MOF coatings and superhydrophobic templates could be adapted for creating diverse solid-state test platforms for a wide range of analytical applications.

Yu and coworkers [82] developed lanthanide MOF based paper microchip for visual dopamine assay. The authors suggested a ratiometric fluorescence dopamine assay that combines a particular dopamine-resorcinol chemical reaction with a multifunctional lanthanide metal-organic framework (Ln-MOF). First, Eu-BTC (1,3,5-benzenetricarboxylic acid) was synthesized and then modified to produce Cu@Eu-BTC, which performs many functions at the same time, including internal fluorescence standard, nanoreactor, cooperative catalytic effects and enhancement of color change. The Cu@Eu-BTC dispersion-based approach was ultrasensitive (limit of detection, LOD, was 0.01 µM) and had a broad-spectrum linear response (0.04–30 µM) to dopamine in the blood. Even more critically, it showed high selectivity for dopamine even in the presence of adrenaline and norepinephrine analogues. As shown in **Figure 6**, a portable and visible dopamine test was designed using a simple, functional paper microchip. The paper microchip was created by coating glass fiber filter paper with Cu@Eu-BTC and resorcinol. Point-of-care dopamine testing can be accomplished with the help of the visual testing machine and the MOF paper microchip. **Table 1** summarize the colorimetric applications of MOF in POCT.

Figure 6. The visual dopamine analysis procedure and quantification of dopamine in serum samples fortified with different concentration levels (0.3–20 M) using the MOF paper microchip and a smartphone-based visual analysis device. (B/R) represents the difference in the Δ(B/R) value between the experimental group (with a definite level of dopamine) and the control group (without the analyte).

Table 1. Colorimetric applications of MOF in POCT

4.2. Applications of MOF in electrochemical POCT

As reported in the previous sections, accessible POCTs become increasingly important to promote individual health self-assessment and reduce drastically the infection in chronic patients, whose mortality from infection is worrying. For example, POCTs for heart rate, blood pressure, and glucose can proficiently monitor key chronic diseases and reduce serious or unintended harm through rapid diagnosis [33].

Electrochemical signal sampling plays a key role in POCT. In this field, the use of miniaturized electrochemical sensors (MEC) to detect traces of analyte, such as small organic molecules, metal ions, and biomolecules should be highlighted [92-95]. Such measurements are made by considering changes in current, voltage, potential or impedance, which are mainly caused by the redox process of molecules [89]. The electrodes used in this type of measurement are modified in order to increase their selectivity by conjugation with specific recognition elements (aptamers, antibodies and receptors of interest), while maintaining simplicity, ease of use, reduced preparation of the sample, fast analysis times, portability and low cost [90]. Due to the superior benefits of electrochemical (EC) technologies, significant research efforts are currently being prepared to create new POCT sensors for trace quantities analysis in numerous fields directly related to environmental monitoring, food safety, and health care [91–93].

The improvement of electrical designs and interconnected circuits for readout systems allows for a low-cost biosensor production method. The combination of bioelectronics with the knowledge can result in the development of nanoscale equipment capable of competing with traditional systems [94,95]. As indicated previously, MOFs are a distinct family of materials that are porous, crystalline, and self-assembled by single or multi metal ions or metallic clusters, as well as organic linkers via coordination bonds [96–99]. Some research highlights the use of MOFs in integrated analytical equipment. However, due of their weak electron transport capability, MOFs alone are regarded electrically insulating, preventing their direct usage in electrochemical sensing [100–102]. To solve this shortcoming, MOF-composites platforms were developed, in which MOFs were combined with conducting materials to improve electron transmission and operate as electrochemical sensors [103,104]. Palanisamy and coworkers [9] developed MOF-nanohybrids for integrated POCT of SARS-CoV-2 viral antigen/pseudo virus utilizing electrochemical biosensor chip. As reported in **Figure 7**, the creation of a biosensor test strip for the detection of SARS-CoV-2 viral antigens utilizing a handheld portable POC equipment and comparing it to a regularly used electrochemical instrument was developed.

Figure 7. Time-dependent one-step-one-pot hydrothermal synthesis scheme of $CoFeBDCNH_2$-$CoFe_2O_4$ MOF nanohybrids and other products with increasing reaction times to produce and detect SARS-CoV-2 viral antigen using portable device.

When the performances are evaluated in buffer and serum medium, the LOD was determined to be 6.68 fg/mL and 6.20 fg/mL, respectively, with good precision and specificity. In this configuration, the $CoFeBDCNH_2$-MOF and $CoFe_2O_4$ nanomaterials as MOF nanohybrids allowed synergistic effects to be achieved, further improving performances. From studies evaluating the electrochemical activity of the various materials, it was possible to investigate the conductive impact of each material in order to finally select the best material to use for the detection of the SARS-CoV-2 viral antigen. Accordingly, the sensing ability of the newly fabricated electrodes was investigated using electrochemical impedance spectroscopic (EIS) experiments. Finally, MOF nanohybrids generated after a 120-minute reaction period were used as a substrate for SARS-CoV-2 viral antigen detection as they had the highest conductivity among all tested materials.

Wei and coworkers [33] developed Cobalt-MOF modified carbon cloth (CC)/paper hybrid electrochemical button-sensor for nonenzymatic glucose diagnostics. In this work, a compact, resilient, and easy-to-use electrochemical analytical chip was created for non-enzymatic quantitative glucose detection using a Cobalt-MOF (Co-MOF/CC/Paper). A highly integrated electrochemical analytical chip with a flexible Co-MOF/CC sensing interface has been successfully developed, substantially improving the specific area and catalytic sites compared to the standard flat electrode (**Figure 8**).

Figure 8. Pictures of the button sensor and 3D diagram of the analysis procedure.

The button-sensor enabled quick quantitative detection of glucose in a variety of complex biological matrices, including serum, urine, and saliva, with the necessary selectivity, stability, and durability. The developed nanozyme-based electrochemical analytical chip accomplished reliable non-enzymatic electrocatalysis with the benefits of low cost, high environmental tolerance, and simplicity of manufacture and showed significant promise for the use of quick on-site analysis in personalized diagnosis and disease prevention.

4.3. Applications of MOF in POCT plasmonic biosensor

Surface plasmonic resonances (SPRs), which consist of the resonant coupling of electromagnetic waves to the collective oscillations of free electrons in metals, are widely used due to the possibility of controlling the properties of light at the nanoscale [105,106]. The ability to amplify and confine light to dimensions significantly smaller than the incident wavelength has opened up new paths in integrated nanophotonic and miniaturized optoelectronic systems. Light is intensified and confined at the interface of two media with dielectric constants of opposite signs, often a dielectric and a metal, and decays rapidly as it is dragged away from contact. Due to their integration into microfluidic systems and great sensitivity to changes in dielectric characteristics at the interface, plasmonic platforms are suitable for low-cost POCT devices. (mainly caused by adsorption processes) [107,108].

Owing to their greater binding affinity and selectivity, antibody-antigen interactions serve as the basis for a variety of standard bioassays such as enzyme-linked immunosorbent assay [109], immunoblotting [110], and immune precipitation [111]. In this context, and thanks to the rapid development and widespread application of diagnostic procedures in the biomedical field, the development of biosensors in the lab-on-a-chip configuration has been observed, in which antibodies are widely used as an extremely selective towards the analytical target through multiple signal transduction platforms (electrochemical [112], magnetic [113], and optical [114]). The main problem related to the use of antibodies is their low stability at room temperature and high temperatures, as well as limitations regarding their stability in non-aqueous liquids (as occurs in the case of transducer surfaces after the immobilization process). To maintain their bio-functionality (recognition capability), antibody-based diagnostic reagents and biosensor chips must be kept at a closely controlled temperature (refrigerated). This important requirement involves the use of a supply chain of individual points of sale and use at a controlled temperature (the so-called "cold chain"), in which the temperature at which the handling and movement procedures are promptly verified and maintained. The cold chain, therefore, requires an increase in costs and a greater environmental impact compared to conventional procedures. Furthermore, it is not always feasible in pre-hospital settings and/or with limited resources such as those possibly present in urban and rural clinics, developing countries, disaster-stricken areas, and battlefields, where maintaining specific conditions may not always be feasible [115]. From this perspective, the development of innovative and alternative methods to preserve the biorecognition capacity of antibodies is of fundamental importance, thus reducing or eliminating the need for the cold chain while simultaneously increasing the shelf life, the reproducibility of the measurements, and the ease of use.

To provide a possible solution to this problem, the possibility of encapsulating a wide variety of biomolecules in MOFs by growing in the presence of the biomolecules in mild biocompatible circumstances (aqueous solution and through reactions at room temperature) is currently being studied [116]. This aspect also allows the activity of the encapsulated biomolecules (for example, enzymes) to be protected and maintained even in unfavorable environmental conditions (high temperatures and organic solvents) [117]. Wang and coworkers [118] developed MOF coatings to be applied in particular to maintain the biological recognition of antibodies immobilized on sensor surfaces subjected to high temperatures. Unlike other methods, which involved mixing protein (enzyme) with MOF precursors in solution, ZIF-8 was produced on bio-nanoconjugates immobilized on gold nanorods. A simple water rinse process just before utilizing the biochip totally dissolved the MOF protective layer, restoring the sensor surface's bio-functionality (**Figure 9**).

Figure 9: Diagram relating to the process of using MOFs to increase the thermal stability of antibody-based plasmonic biochips, which would eliminate the cold chain and allow their use in environments with limited resources.

Due to its high sensitivity, cost efficiency and great potential for use in diagnostics, a plasmonic nanobiosensor based on localized surface plasmon resonance refractive index sensitivity has been used as a platform to monitor various phases of fabrication, including conjugation of antibodies onto the surface of plasmonic nanostructures, MOF formation and removal [119]. It is worth mentioning that the detection of bioanalytes was also possible. The results demonstrated using IgG/anti-IgG as a test system, indicating that the MOF layer significantly enhanced the stability of the model antibody at room temperature, 40, and 60°C.

Wang and coworkers [120] developed biochips with MOF coating for POCT. In this work, a localized surface plasmon resonance (LSPR) refractive index sensitivity-dependent plasmonic nanobiosensor was employed as a POC biosensor model, with gold nanorods (AuNRs) as nano transducers. The manufacturing steps of the plasmonic biosensor (including antibody attachment to the surface of AuNRs, growth and removal of the MOF layer, and bioanalyte detection) were evaluated by monitoring the LSPR wavelength shift of AuNRs. In addition to this, the ability of the MOF-based approach to resist several adverse environmental conditions (including increased temperature, organic solvent and proteolytic degradation) which would result in the denaturation of antibodies and loss of bifunctionality of the biochips was evaluated, as indicated in **Figure 10**.

Figure 10. Scheme of how a ZIF-8 encapsulated antibody manages to maintain its biofunctionality even when subjected to extreme environmental conditions, significantly increasing the reliability and usefulness of biochips in resource-limited settings.

The findings indicated that the ZIF-8 protective layer significantly increased the stability and usability of biochips for use in resource-limited situations, as well as in poor and middle-income nations. After a day of incubation at temperatures up to 80°C, the ZIF-8-coated biochips retained more than 80% of their identification capacity, serving as a proxy for long-term storage at room temperature. High-temperature storage efficacy can be increased by extending the growth time and thickness of the ZIF-8 film, underlining the need for complete encapsulation of the antibody.

5. Evaluation of the green profile

A very important element to take into consideration also concerns the impact of the procedure on the environment. If green chemistry (GC) was born in the 90s and green analytical chemistry (GAC) in the early 2000s, given the current state of knowledge it is essential to also consider green sample preparation (GSP) [121–123]. The GSP considers 10 fundamental principles linked to the critical step of sample preparation:

Principle 1. Favor in situ sample preparation

Principle 2. Use safer solvents and reagents

Principle 3. Target sustainable, reusable and renewable materials

Principle 4. Minimize waste

Principle 5. Minimize sample, chemical and material amounts

Principle 6. Maximize sample throughput

Principle 7. Integrate steps and promote automation

Principle 8. Minimize energy consumption
Principle 9. Select the most environmentally friendly post-sample preparation setup for analysis
Principle 10. Ensure safe procedures for the operator.

In particular, considering these principles and applying them to metal organic frameworks in point of care testing, in all the various declinations and configurations covered in this review, it is immediately clear how they respond perfectly to several points. Specifically:

- ✓ Principle 1. Favor *in situ* sample preparation - these are metal organic frameworks in point of care testing systems that do not require particular sample treatment procedures and therefore can be considered as "*in situ*" or, in some cases "*on line*" procedures;
- ✓ Principle 2. Use safer solvents and reagents - solvents are often not necessary, the biological sample is used directly to obtain the instrumental response for the analysis;
- ✓ Principle 4. Minimize waste and Principle 5. Minimize sample, chemical and material amounts - metal organic frameworks in point of care testing devices generally require a minimum amount of sample and/or solvents, as they are portable (or wearable) devices, resulting in reduced waste;
- ✓ Principle 7. Integrate steps and promote automation - the use of these metal organic frameworks in point of care testing devices allows the reduction of sample manipulation with consequent reduction of waste, reduction of possible errors in the measurement with consequent improvement in the precision and trueness of the procedure. In particular, this point is widely respected by wearable devices;
- ✓ Principle 8. Minimize energy consumption - compared to "classic" (HPLC-UV/Vis, GC-FID) or hyphenated (HPLC and GC-MS) configurations, a portable/wearable device based on metal organic frameworks powered by a small battery certainly shows a much better green profile;
- ✓ Principle 9. Choose the greenest possible post-sample preparation configuration for analysis - simple, readily available detection such as the use of smartphones, desktop scanners, paper strips are the basis for a green profile in general terms
- ✓ Principle 10. Ensure safe procedures for the operator - speaking of POCT and portable and/or wearable devices, it is clear how these ensure the safety of the operator/patient.

6. Perspectives and conclusion

MOFs are materials with extremely high surface areas and organized porous cages that have been studied over the past decades. Due to their design flexibility and tendency towards functionalization, they have shown promise in a variety of applications, including chemical sensing. As a result, they have been recognized as sophisticated materials with the potential for use in analytical instruments for chemical and biochemical sensing applications where high sensitivity is required, such as in environmental monitoring and personal diagnostics. It is worth indicating that MOFs have a high surface area for adsorption, a coherent pore structure to govern mass transport, and a wide variety of physical characteristics, including chemoresistant, electrical, and optical capabilities, which make them excellent for chemical detection. Each type of MOF in POCT offers unique advantages and disadvantages, which should be considered based on the specific requirements of the application. Colorimetric MOF-based sensors have high selectivity, producing relatively stable colors that can be detected by naked eye, but these sensors have limited dynamic range compared to the other detection methods. Electrochemical MOF-based sensors offer Improved sensitivity, and less vulnerability to interference, but the long term stability of electrodes should be taken into account besides the probable matrix effect [124]. Plasmonic MOF-based biosensor offer real-time monitoring capabilities, with a high potential for label-free detection, but the experimental design and optimization could be challenging, in addition to the overall high cost.

POCT could be performed using smartphones, μPADs, and simpler devices. Nowadays, the concern of POCTs tends towards wearable sensor. Traditional public health systems are plagued by limited, delayed and sometimes inefficient medical services, particularly in the face of the pandemic and an aging population. Wearable and portable sensors provide immediate access to health monitoring without the need for sophisticated systems. Wearable and portable sensors are becoming increasingly popular due to their ability to provide frequent and continuous monitoring of physiological data through dynamic, non-invasive assessments of biomarkers present in biological fluids such as tears, sweat, interstitial fluid, and saliva. Current improvements have focused on creating optical and electrochemical wearable sensors, as well as non-invasive monitoring of biomarkers such as metabolites, hormones, and microorganisms. Microfluidic sampling, multimodal sensing and portable systems have been combined with flexible materials to improve wearability and ease of operation. Although wearable sensors show promising results and increased reliability, a better understanding of the relationship between target sample concentrations in blood and non-invasive biological fluids is needed.

By combining traditional textiles with diagnostic, therapeutic and protective medical devices, e-textiles can be used on the human body as POC platform technologies, keeping an eye on the patient's vital signs and putting treatment plans in place around to the clock. Therefore, our prospects of integrating MOFs into wearable sensors and electronic fabrics will increase significantly in the coming years.

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The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

All Authors contributed equally to Conceptualization; Investigation; Project administration; Resources; Supervision; Roles/Writing - original draft; and Writing - review & editing.

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Figure 1

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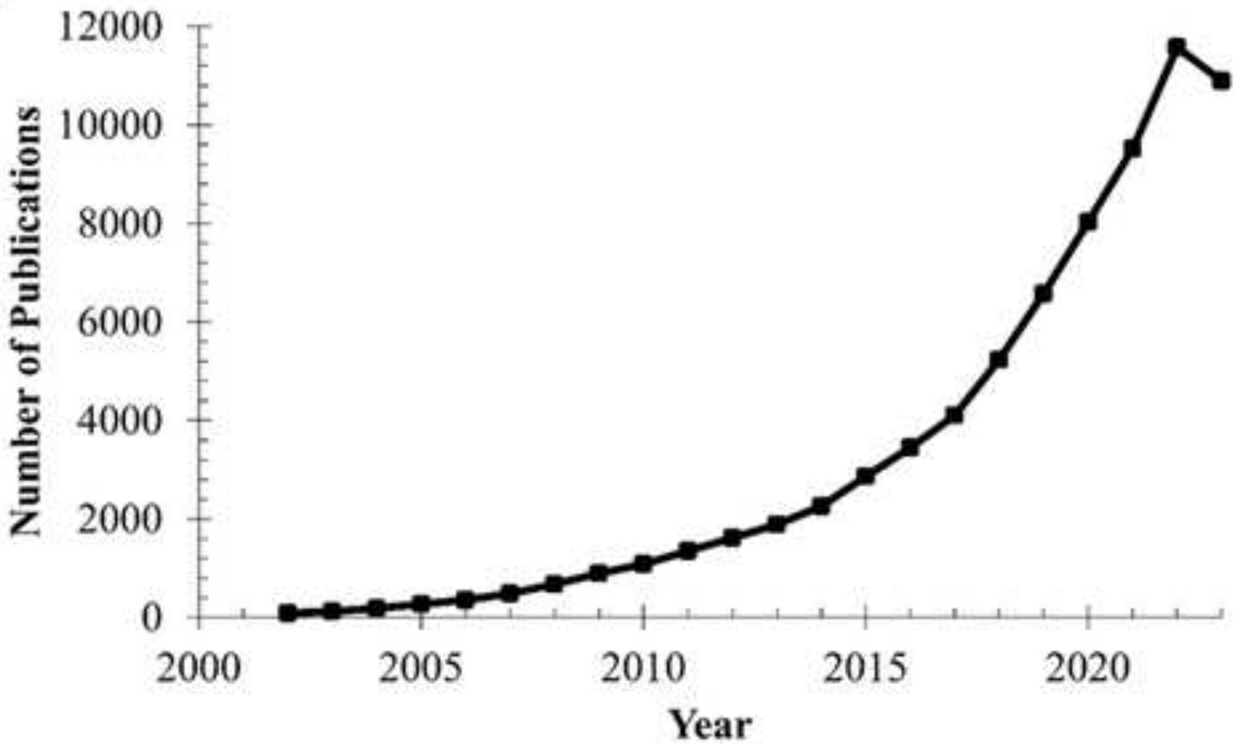
(a)



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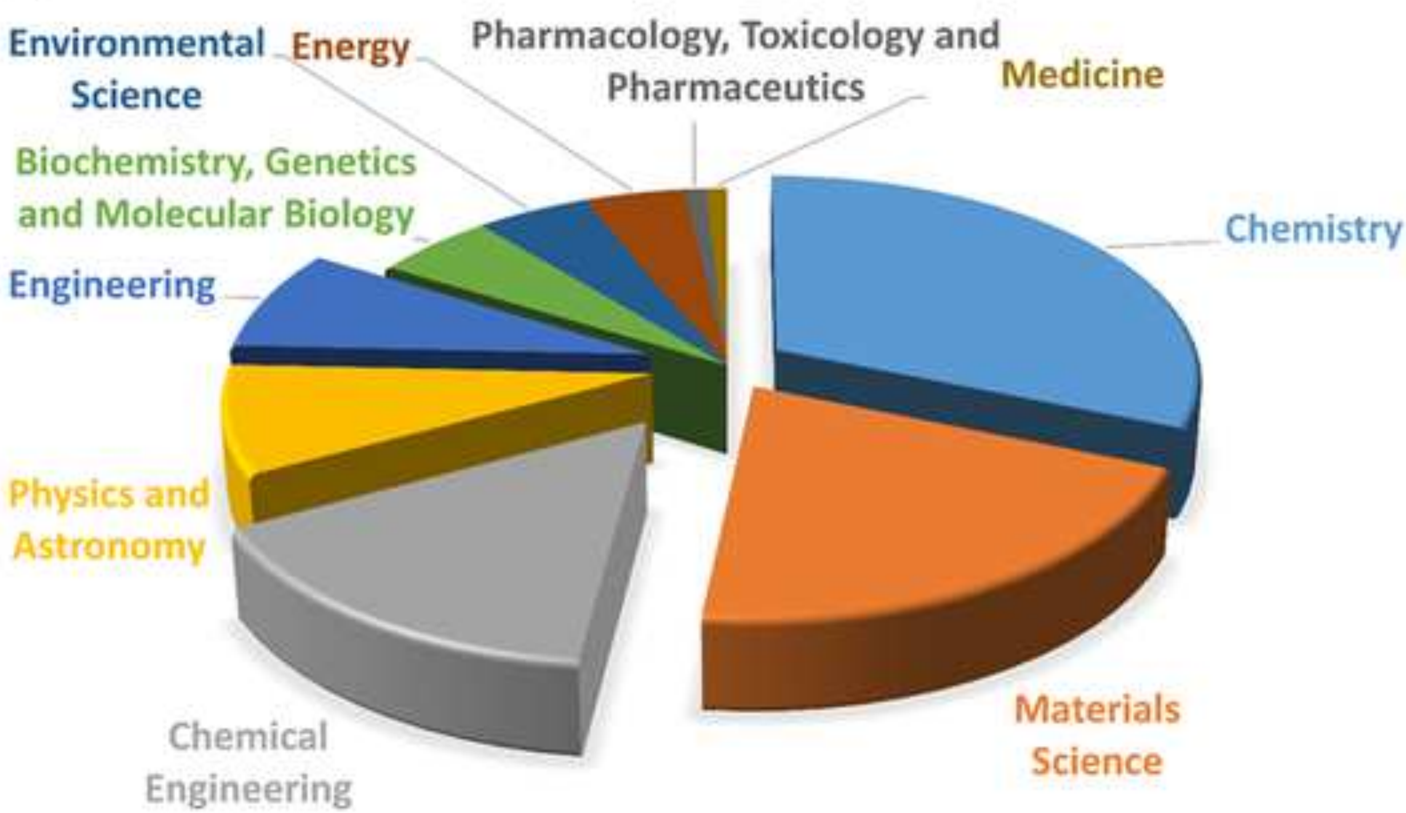

Figure 2

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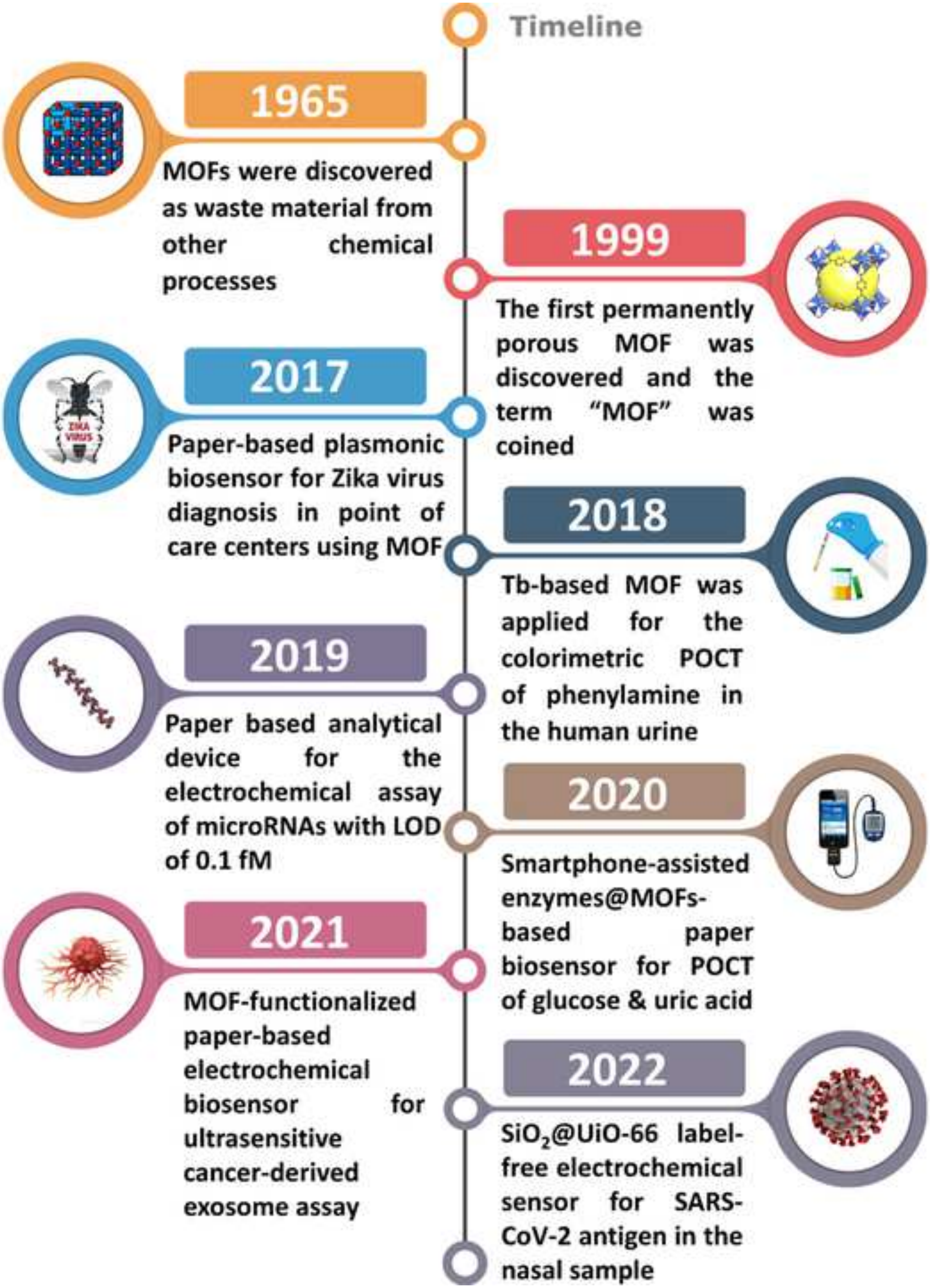

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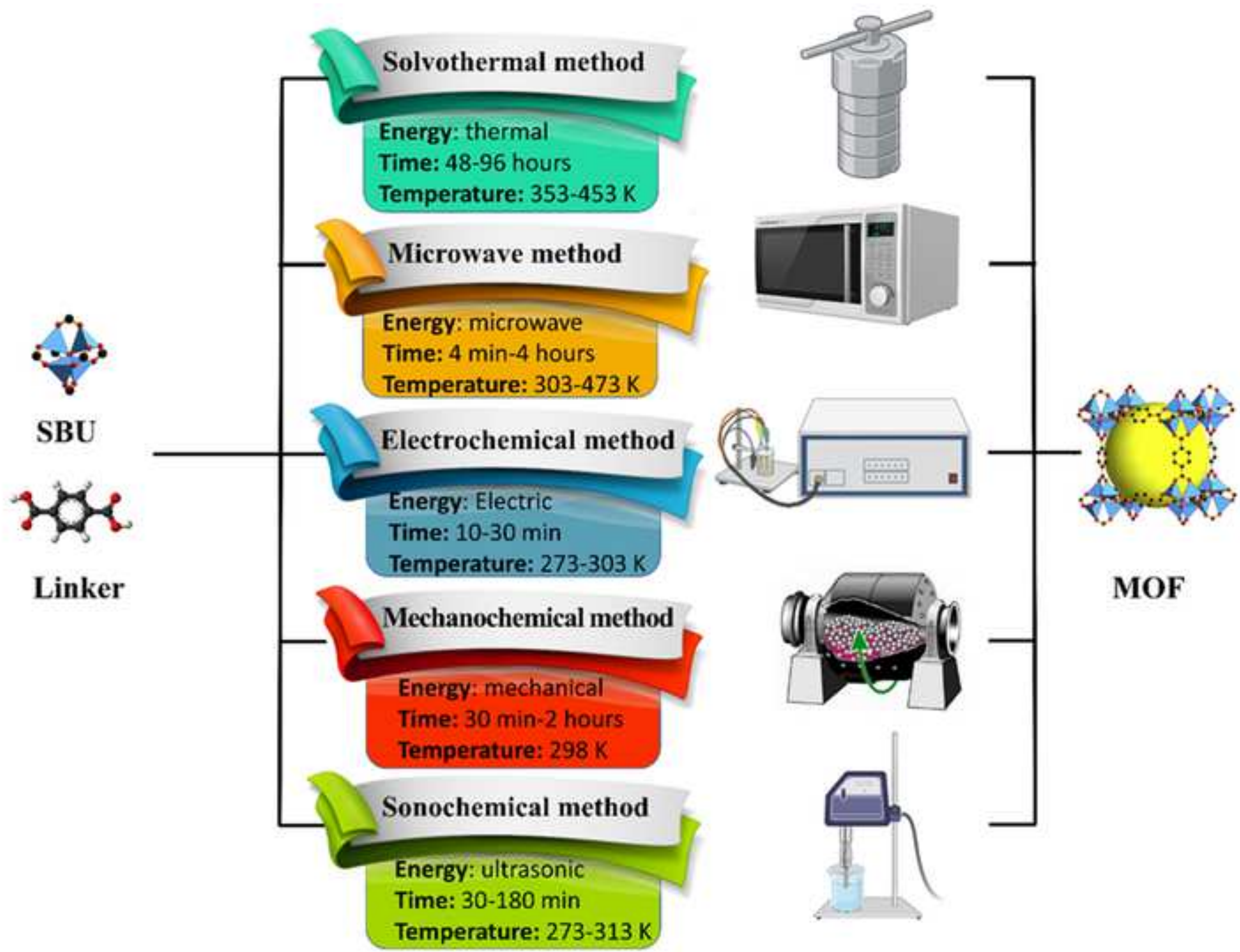

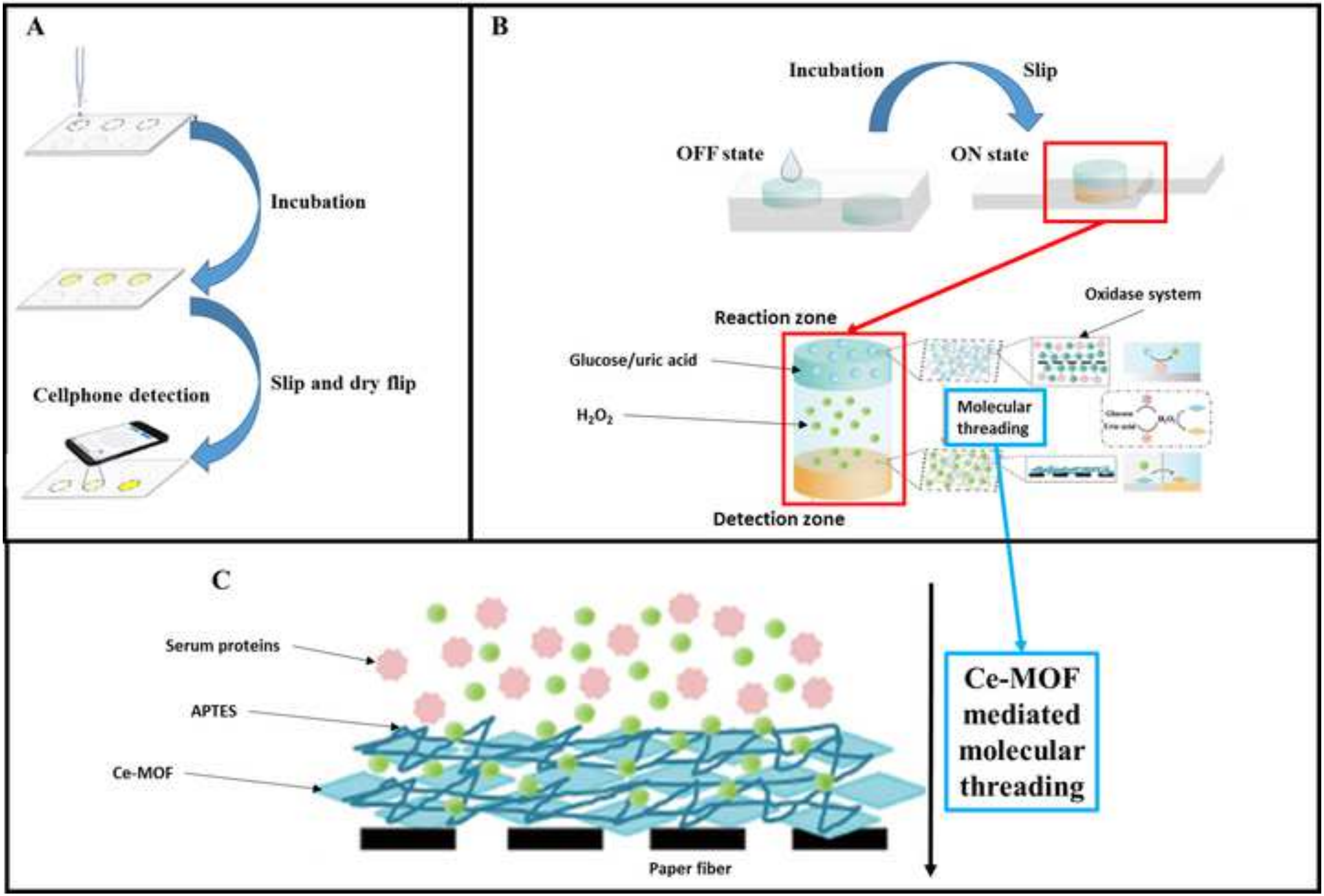
A
Incubation
Slip and dry flip
Cellphone detection
B
Incubation
Slip
OFF state
ON state
Reaction zone
Oxidase system
Glucose/uric acid
H_2O_2
Molecular threading
Detection zone
C
Serum proteins
APTES
Ce-MOF
Paper fiber
Ce-MOF mediated molecular threading

Figure 5

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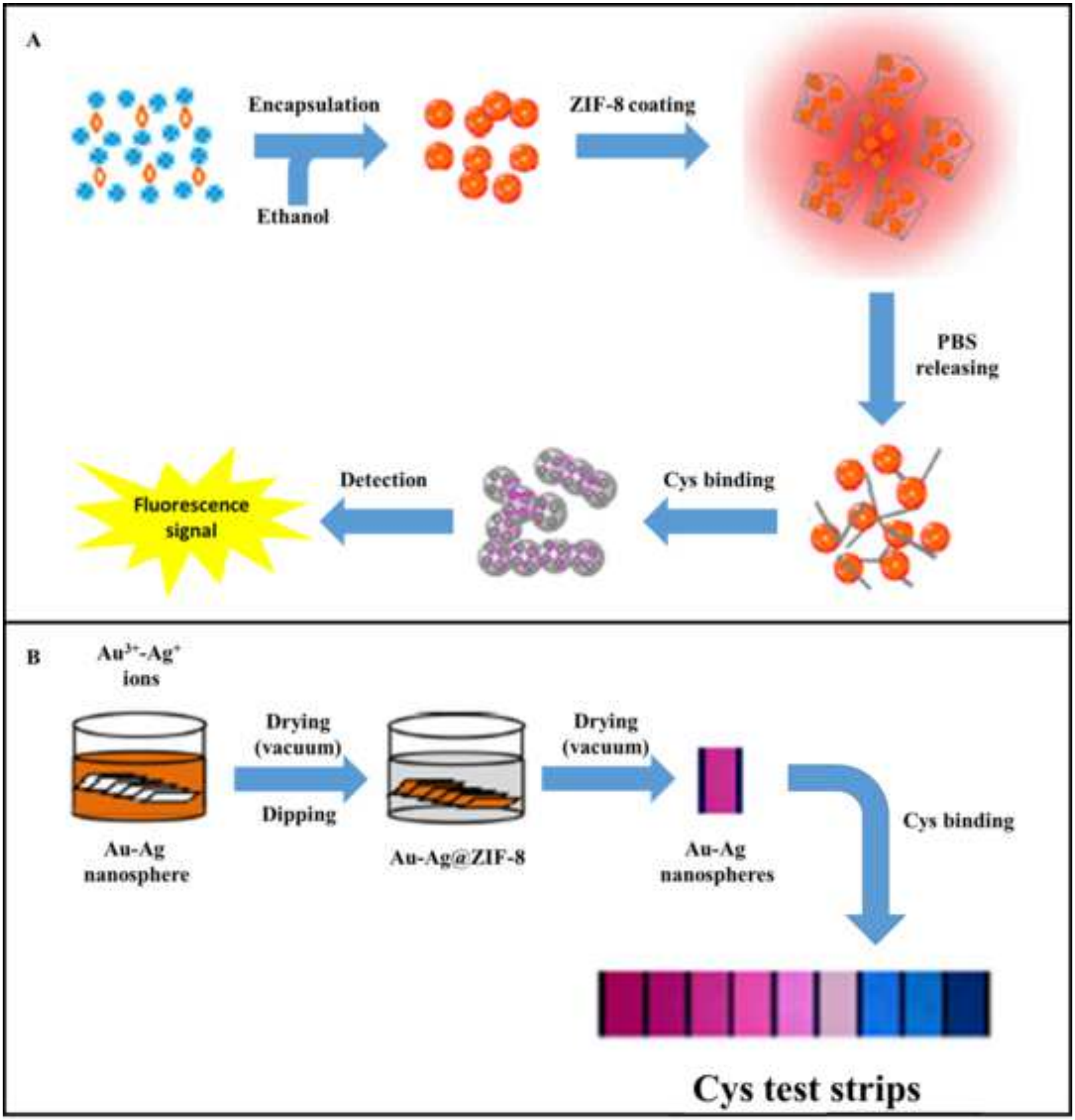
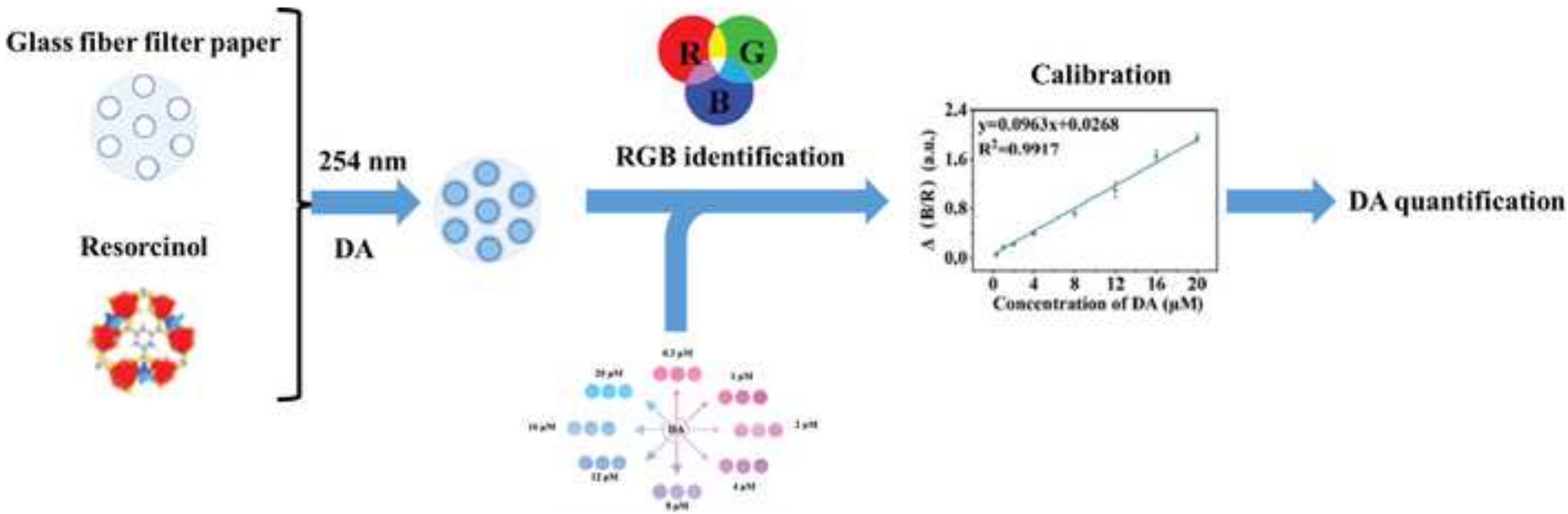


Figure 6 Click here to access/download;Figure;MOF in POCT - figure 6 R1.tif



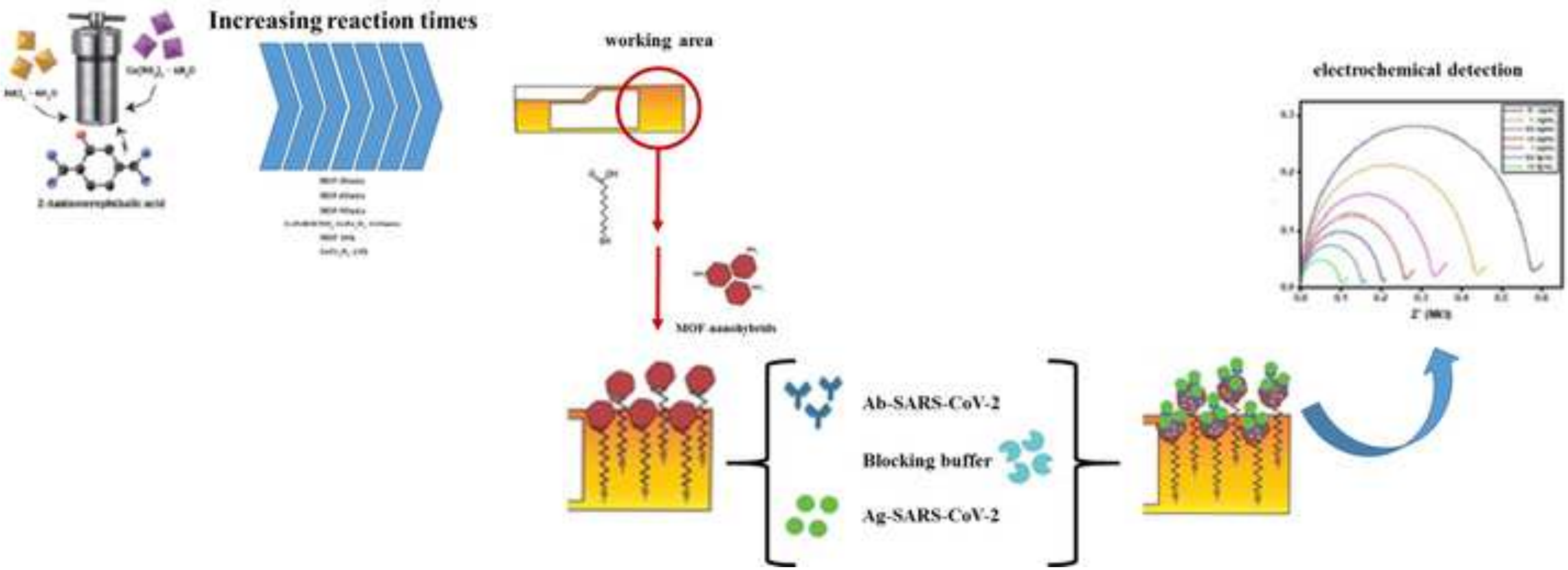

Increasing reaction times
working area
electrochemical detection
MOF nanohybrids
Ab-SARS-CoV-2
Blocking buffer
Ag-SARS-CoV-2

Figure 8

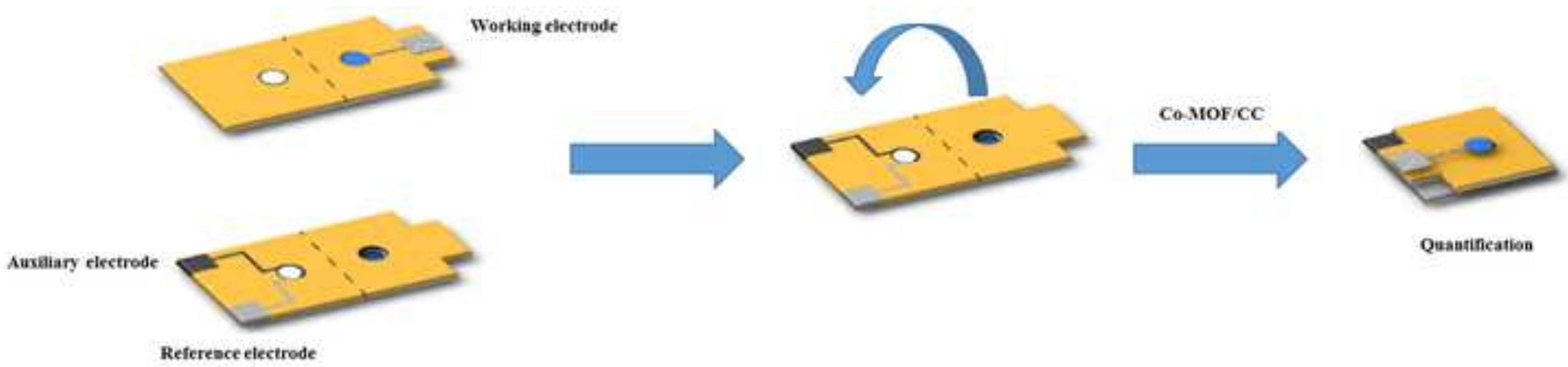
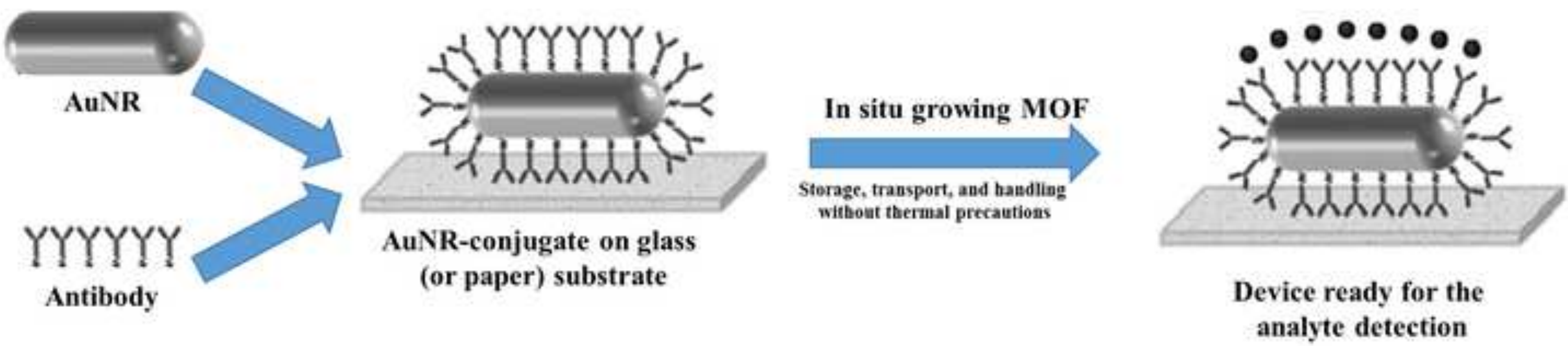

Working electrode
Auxiliary electrode
Reference electrode
Co-MOF/CC
Quantification

Figure 9


AuNR
Antibody
AuNR-conjugate on glass (or paper) substrate
In situ growing MOF
Storage, transport, and handling without thermal precautions
Device ready for the analyte detection

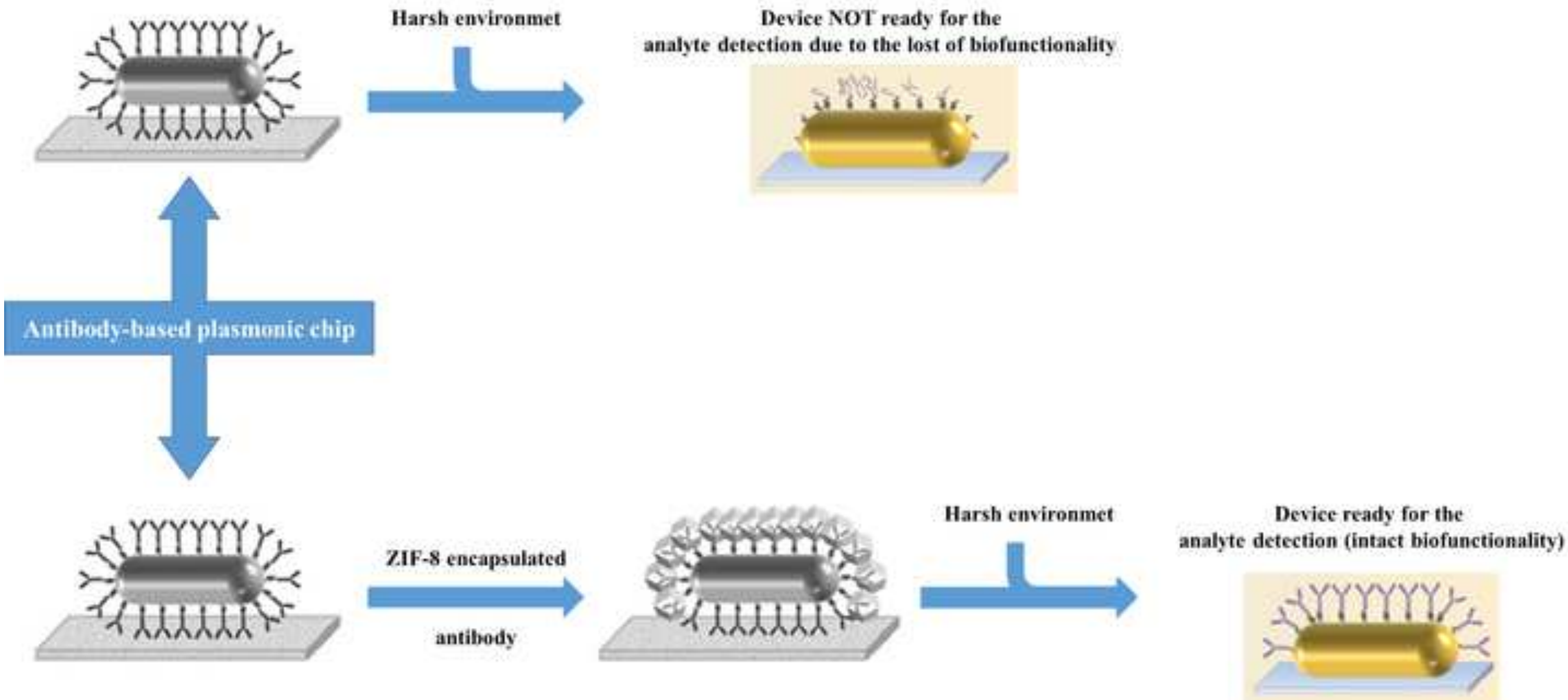

Harsh environmet
Device NOT ready for the
analyte detection due to the lost of biofunctionality
Antibody-based plasmonic chip
ZIF-8 encapsulated
antibody
Harsh environmet
Device ready for the
analyte detection (intact biofunctionality)

Table 1. Colorimetric applications of MOF in POCT

Sample	Sample volume	Analyte	MOF component	MOF synthesis	Colorimetric principle	Visual sensing tool	Linearity range	LOD	%RSD	REF
Serum Urine	N/A	Glucose	EU^{+3}-Zr- 2,2′-bipyridine-5,5′-dicarboxylic acid	Conventional synthesis (solvothermal)	FLD based colorimetric assay	POC Diagnostics logic detector	0.1 µM–10 µM, 10 µM–10 mM,>10 mM)	0.23 µM and 0.25 µM in urine and serum	N/A	[69]
Serum	150 µL	Uric acid and glucose	Cerium terephthalic acid	Conventional synthesis (non-solvothermal)	Direct colorimetric assay	The origami paper Slip Chip (OPSlipChip)	(0-25 mM) for glucose and (0-1000µM)for uric acid	0.069 mM and 39.6 µM for glucose and uric acid respectively.	N/A	[74]
Serum	N/A	Dopamine	Terbium ZrCl4 and H4btec	Conventional synthesis (solvothermal)	FLD based colorimetric assay	Portable test paper	0-350 µM	0.06 µM	2.05 and 5.86.	[75]
Serum sample	30 µL	Dopamine	Eu–BTC (1,3,5-benzenetricarboxylic acid)	Conventional synthesis (non-solvothermal)	FLD based colorimetric assay	Paper microchip	0.3–20 µM	0.08 µM	≤6.83%	[76]
Serum samples	100 µL	Glutathione and cysteine	Ag/Eu@Ni-MOF	Conventional method (hydrothermal)	FLD based colorimetric assay	N/A	5-250 µM	0.20 µM and 0.17µM for cysteine and glutathione respectively	N/A	[80]
Human blood	2 µL	Glucose and peroxide	Cobalt -terephthalic acid	Conventional synthesis (solvothermal)	FLD based colorimetric assay	Paper-based devices	50 µM - 15 mM	16.3 and 3.2 µM	3.47	[81]
Human serum	N/A	Alkaline phosphatase activity	Cu@Eu-BTC	Conventional synthesis (solvothermal)	FLD based colorimetric assay	Portable assay tube	1-12 U/ L	0.24 U/L	≤9.5	[82]
Human urine	N/A	phenylamine	Terbium -2,2-bipyridine-5,5-dicarboxylic acid	Conventional synthesis (solvothermal)	FLD based colorimetric assay	Paper strip	0.005 to 5mg/mL	5 µg/mL	3-7%	[88]
Gastric juice	5 µL	Acidity sensor	1-hydroxypyrene@ Co/Tb- dipicolinic acid	Conventional synthesis	FLD based colorimetric assay	Paper-based pH microsensor	0.3–7.8	N/A	<5.4	[89]
Solid pharmaceuticals	N/A	Water	Eu-dipicolinic acid/2-aminophthalic acid	Conventional (non-solvothermal)	FLD based colorimetric assay	Paper-Based Water Microsensor	0−100% v/v	0.01% v/v	≤5.8	[90]

Declaration of interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Main text R1 track changes

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