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Recent advances in polyoxometalates based strategies for green synthesis of drugs

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ABSTRACT

Green synthesis of drugs is of paramount importance for current public health and a prerequisite to new drugs exploiting. Nowadays, novel strategies of disease diagnosis and therapies are in blooming development as remarkable advances have been achieved which are all highly depended on drug development. Under the current requirements to high production capacity and novel synthesis methods of drugs, green synthesis based on strategies with different ways of empowering, advanced catalysts and unique reaction equipment are attracting huge attention and of great challenging. Higher quality products and environmentally friendly synthesis conditions are becoming more and more important for manufacturing process which has new requirements for catalyst materials and synthesis processes. Polyoxometalates (POMs) are class of transition metals-oxygen clusters with precise molecular structures and superior physicochemical properties which have made longstanding and important applications upon research community of functional materials, catalysis and medicine. In this review, the recent advances of polyoxometalates based strategies for green synthesis of drugs are summarized including POMs based catalysts, alternative reaction equipment based novel synthesis protocols. The significance of POMs to pharmaceutical and industrial field is highlighted and the related perspective for future development are well discussed.

1. Introduction

Today, the healthcare and health technology industries have always been in the spotlight. With the continuous progress of medical technology, the service level of the healthcare industry is constantly being improved. It is crucial to effectively integrate technology into time sensitive and high-risk healthcare environments in order to support safe and efficient care [1]. In recent years, medical research has been in a rapidly developing stage which becomes even more diversified and precise. However, many problems arise, which are related to changes in nature, society and the environment as well as people's new pursuit for survival, longevity and health. At the same time, the development of medicine is facing challenges due to the over-division and specialization of disciplines and the dispersion of medical knowledge [2].

The process of developing new drugs is a crucial chemistry-based field that relies on chemical synthesis methods, which is an expensive and time-consuming process with a high failure rate [3]. Natural products have been the primary source of new drug entities in drug discovery, but it has now switched to high-throughput synthesis and development based on combinatorial chemistry. Using chemical synthesis methods, drug researchers can produce compounds that have specific pharmacological activity, which serves as a foundation and support for drug development. Otherwise, chemical synthesis would ideally result in a variety of structural analogues which can also be used as an alternative method to produce large quantities of desired products [4]. The development of green synthesis of drugs are a complex and lengthy process involving multiple stages and links, each of which also faces various problems. The challenges of innovation, investment in research and development, environmental pollution, and reaction stability problems are some of the key issues faced in drug synthesis. Although some constructive measures can be taken to mitigate or solve these problems, *e.g.*, environmental pollution can be reduced by strengthening inspection and testing of raw materials, stability problems can be improved or resolved in time by optimizing production processes and establishing stability testing systems. However, these solutions are far from sufficient. Consequently, we need to actively explore to find more favorable conditions for the green synthesis of drugs. Functional materials re-

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fer to materials that possess specific functions or exhibit specific properties under certain conditions and are widely used in the biomedical field. For example, gold nanoparticles are widely used throughout the medical field due to their excellent biocompatibility [5]. Graphitic polymeric carbon nitride (g-C_3N_4) has gradually attracted great interest in the field of biomedicine due to their unique element composition and photoelectric features [6]. Drug-loaded microfibers also play a crucial role in drug delivery systems (DDS) because they exhibit excellent properties and can be further developed as multifunctional textiles or biomedical materials [7]. Treating nanocellulose with ethylenediamine to obtain functionalized nanocellulose particles, which are subsequently introduced into ethylene-co-acrylic acid (EAA) matrix, studies have found that these composites retain their biocompatibility even after the introduction of functionalized nanoparticles, and composite films can be used for biomedical applications [8]. Many studies have shown that the application of new functional materials in medicine has broad prospects and potential which can improve the efficiency of medical treatment, reduce the risk of surgery, shorten the recovery time, and is conducive to the development of human health.

Polyoxometalates (POMs) have attracted considerable interest in recent years thanks to their attractiveness as transferable building blocks for the elaboration of multi-functional materials, which is in large part thanks to their unique structural and chemical properties [9,10]. POMs are negatively charged molecular metal oxides with a well-defined structure, beautiful geometry, and nanoscale dimensions [11–16]. Their size allows them to be considered as a type of oxide quantum dot with a very high surface to volume ratio [17]. POMs, as emerging inorganic metal oxides, have been proven to have significant biological activity and enormous medicinal value [18–20]. Due to their structural diversity and redox properties, POMs and their composites materials have been proven to have enormous biomedical potential and have been widely studied and applied in the medical field [21,22]. Many POMs based nanoplatforms and their unique ability to modulate reactive oxygen species (ROS) have been intensively studied and applied in the biomedical field [23]. Optimized and sensitive biomarker assays have recently been shown to have a critical impact on diagnostic quality and healthcare options. Veerappan Mani's research group studied polyoxometalate-γ-cyclodextrin metal-organic frameworks were used as electrocatalysts to fabricate highly selective sensors to detect dopamine released *in situ* [24]. Yong's team successfully developed an antibacterial platform using the smart tungsten (W)-polyoxometalate cluster paradigm [25]. It features a dual pH/GSH response, so it can quickly eliminate the biofilm and exhibit significant antibacterial activity when exposed to near-infrared laser radiation.

At present, POMs have been applied to drug synthesis, biomarker detection [24], antibacterial [26], anticancer [27], anti-Alzheimer's disease, antiviral and so on [28]. Nevertheless, the practical application of POMs is greatly limited by their instability and easy-agglomeration characteristics [29]. Some researchers have proposed that POMs can be limited to the host material to solve the above problems, but only to ensure that the constructed POM@host composite can effectively solve the problems of agglomeration, leaching and poor electrical conductivity when used alone. Therefore, improving the biocompatibility of POMs and reducing its toxicity and instability are still the focus of current researchers.

In this review, the recent research progress of POMs in green synthesis of drug *via* thermal catalysis, photocatalysis and electrocatalysis is elaborated. In addition, the relevant reports on the organic catalysis, continuous flow and biocatalysis of POMs in drug synthesis are summarized (Fig. 1). The key problems and challenges in the application of POMs in organic synthesis, the trend in future promising development is fully discussed. New milestones and insights into other functional materials applications in this research field could be gained by green synthesis of drugs using POMs-associated strategies.

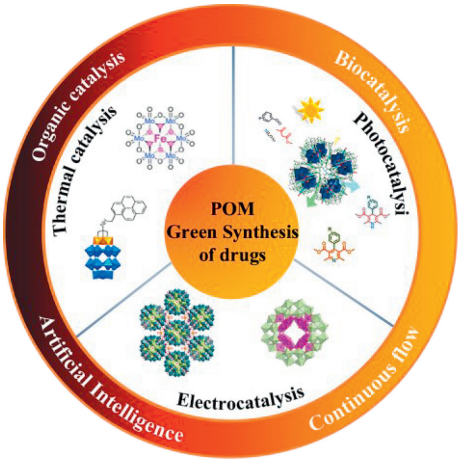

Fig. 1. POM-based nanostructures for green synthesis strategies of drugs.

2. Current drug synthesis process

The search for environmentally friendly methods of drug synthesis is guided by the principles of green chemistry, the goal is to explore ways to produce pharmaceuticals and chemicals that are environmentally friendly, with the use of green solvents, advanced catalysts, and suitable reaction conditions being considered [30]. Green synthesis processes can lead to the development of synthetic schemes and equipment that simplify chemical manufacturing processes with unique catalysts that search for optimal green solvents and achieve novel reactions with minimal by-products. Therefore, green drug synthesis methods are as effective or more effective than traditional drug synthesis methods [31].

2.1. Organic catalysis of drug synthesis

Pharmaceutical chemistry aims to design and synthesize new, highly purified biologically active molecules that meet specific criteria and have the potential to be safe and effective drugs [32]. The design of safe, sustainable and non-polluting materials and processes is an ongoing goal of chemical scientists, which drives the greening of the industry.

The use of organocatalytic systems for the synthesis of fine chemicals offers a powerful eco-friendly strategy due to the reaction conditions and ease of set-up of the organocatalytic systems, air and water [33]. However, the high loading and difficult separation of organic catalysts have generated widespread interest in their immobilization on surfaces to allow simple recycling and reuse of the catalysts. Many organic compounds such as pyridines, alkaloids, amino acids, piperidines and pyrrolidines were immobilized on solid materials to provide loaded organic catalyst [34]. In addition, the development of various heterogeneous methods for homogeneous catalysts to minimize the consumption of materials such as solvents, energy and time can bring significant economic and environmental benefits.

POMs catalysts can incorporate transition metals to tune their physical and chemical properties to create catalytically active sites in their structures. Zhao *et al.* synthesized four inorganic-organic hybrids based on 2,6-bis(2′-pyridyl)−4-hydroxypyridine (LOH) ligands and POMs using a solvothermal method [35]. They all present fascinating supramolecular structures through weak interactions of hydrogen bonds.

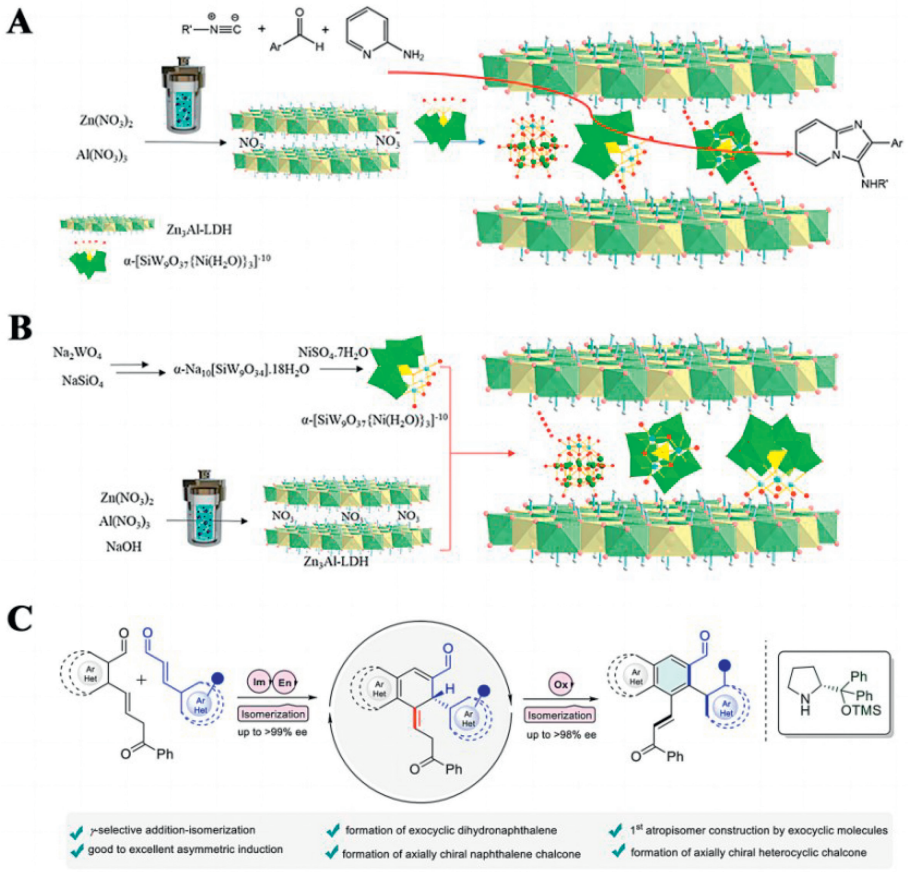

Fig. 2. (A) Illustration of the procedure for the SiW_9Ni_3@Zn_3Al nanocomposite and the synthesis route of amino imidazothiazole over the POM–LDH catalyst. (B) Illustration of the procedure for the SiW_9Ni_3@Zn_3Al nanocomposite and the synthesis route of amino imidazothiazole over the POM-LDH catalyst. Reproduced with permission [36]. Copyright 2023, Springer Nature. (C) Asymmetric synthesis of an unprecedented exocyclic dihydronaphthalene and an axially chiral naphthalene chalcone has been disclosed. Reproduced with permission [41]. Copyright 2023, American Chemical Society.

$[Co_{2.5}(LOH)(LO)_2(H_2O)_2(PW_{12}O_{39})]\cdot 3CH_3CN\cdot 2OH$ can be used as an effective multiphase catalyst to promote the cycloaddition reaction of carbon dioxide, and $[Mn(LOH)_2]\cdot(PW_{12}O_{40})\cdot 2CH_3CN\cdot H_3O$ has high catalytic activity for the ODS reaction, both of which are promising multiphase catalysts with the advantages of easy recovery and good recovery stability. Moaser *et al.* used a selective ion exchange technique to insert three nickel-substituted Keggin-type polyoxometalates α-$[SiW_9O_{37}\{Ni(H_2O)\}_3]^{-10}$ (SiW_9Ni_3) into Zn_3Al based layer-double hydroxide (Zn_3Al-LDH) to synthesize the nano-composite SiW_9Ni_3@Zn_3Al (Fig. 2A) [36]. The synergistic catalytic effect of SiW_9Ni_3 polyoxometalate with Zn_3Al-LDH precursor suggests that SiW_9Ni_3@Zn_3Al composites have higher catalytic performance. The complex can facilitate the synthesis of the small molecule backbone of the drug-like aminoimidazole pyridine under mild solvent-free conditions by the well-known Groebke-Blackburn-Bienaymé reaction (Fig. 2B). For the synthesis of aminoimidazole pyridine in a three-group classified Ugi reaction (isocyanide), SiW_9Ni_3@Zn_3Al showed better catalytic performance (yield of ~98%) than SiW_9Ni_3 and Zn_3Al-NO_3. In particular, Zn_3Al-NO_3 not only displays excellent ability to support highly dispersed and directly immobilized SiW_9Ni_3 guests, but also improves the catalytic activity of the composites through the synergistic effect of the Zn^{2+} of the double hydroxide of the Zn_3Al-NO_3 layer and the Lewis acid sites of the POM anion.

Organic catalysis is one of the three pillars of asymmetric catalysis, and the rapid development of organometallic chemistry and catalysis has contributed to many breakthroughs in organic synthesis, however the widespread use of metal compounds highlights the importance of environmental and toxicity issues [37]. A recent trend in the pharmaceutical industry is the replacement of catalytic metal complexes with organic catalysts. The efficacy and synthetic versatility of asymmetric organic catalysis and the use of a large number of efficient small-molecule organic catalysts have enriched the field of organic synthesis, including chiral proline derivatives, heterocyclic carbenes, chiral thioureas, and phase transfer catalysts (PTCs) [38].

Since the beginning of the 21st century, the effectiveness of asymmetric organic catalytic technology and the multifunctionality of synthesis have made significant contributions to the field of organic synthesis [39]. A new three-component catalytic coupling reaction of alkynyl borate, diazomethane and aliphatic/aromatic ketones has been developed by Deliaval *et al.* The reaction has very high enantioselectivity and diastereoselectivity (up to three consecutive stereocenters) and allows for the synthesize tertiary chiral enolates with axially chiral CF_3 groups in a single operative step [40]. In addition, the reaction is carried out under mild, neutral, metal-free conditions and allows the application of aliphatic ketones and a wide range of substituents such as bromine, nitro and methyl sulfonyl group with a high level of functional group tolerance. Yadav *et al.* revealed an unprecedented asymmetric synthesis of an exocyclic dihydronaphthalene and an axially chiral naphthalene chalcone achieving good to excellent asymmetric induction [41]. This is the first report of an exocyclic molecule capable of synthesizing an axially chiral chalcone *via* a diamine-catalyzed stepwise asymmetric vinyl domino double-isomerization catalyzed by diamine (Fig. 2C). For the first time, it is shown that exocyclic

molecules are superior in axial induction. The present methodology allows the formation of different types of chalcone derivatives (axially chiral or achiral) and it is expected that the obtained products will find a large number of applications in different disciplines.

2.2. Continuous flow of drugs synthesis

Continuous flow chemistry, as a widely applicable technology in various fields such as pharmaceuticals, agricultural chemicals, petrochemicals, and fine chemical production, has received widespread attention [42]. In the pharmaceutical field, continuous flow chemistry is one of the most innovative methods, which can significantly improve chemical synthesis and accelerate the process from early drug discovery to manufacturing [43]. In addition, flow chemistry provides a fast and simple amplification strategy, which has become a research hotspot in both academia and industry [44].

Traditional batch processing typically involves lengthy reactions, formation of by-products, and complex purification procedures [45]. Compared with traditional batch synthesis, continuous flow chemistry can improve the selectivity of target molecules, achieve faster amplification and higher synthesis efficiency by more accurately controlling reaction parameters such as temperature, pressure, reagent dosage, and residence time [46]. It also has fast heat and mass transfer rates, which can significantly improve the overall safety of organic synthesis processes even under harsh reaction conditions. This model is more reliable and repeatable, and can be quickly scaled up continuous flow processes by changing the reactor volume and reducing process optimization.

To date, many new continuous flow drug synthesis processes have been developed over the decades [47]. Jin *et al.* developed a new five-step pathway for the synthesis of erlotinib for the treatment of non-small cell lung cancer and pancreatic cancer using a continuous flow synthesis process, including etherification, nitrification, reduction, addition, and cyclization [48]. Each step was successfully optimized for a continuous flow process, which increased the safety of the process and also greatly reduced the reaction time, with a total residence time of 25.1 min. Cao *et al.* established a continuous flow synthesis method combined with a multistage cascade purification process for the synthesis of cardiovascular drugs dibutyl adenosine cyclic calcium phosphate [49]. The limitations of long production cycle, large amount of highly toxic reagent and unstable yield in traditional batch process are eliminated. Replacing the highly toxic solvent pyridine with acetonitrile, a continuous flow acylation reaction can achieve quantitative conversion within 20 min. The separation yield of continuous processing is as high as 92%, with a purity of 99%.

Microfluidic reactions based on polyoxometalate (POMs) have also been developed. Tao *et al.* developed a microfluidic reactor based on polyoxometalate (POMs) [50]. In this reactor, glycerol peroxidation can be prepared by layer by layer on the capillary tube. The yield selectivity of lactic acid (LA) is high, with a TOF of up to 20,000 h^{-1}, compared to 200 h^{-1} in batch mode. The POM microfluidic reactor is easy to prepare, scalable, highly stable and reusable. They present a simple scheme for making these POM microfluidic reactor (POM-MR) catalysts (Fig. 3A). The use of this reactor eliminates the problem of catalyst product separation, minimizes mass transfer difficulties, and promotes very short residence times. Under optimized reaction conditions, HPMo MR (2) was used to produce 95% LA at a glycerol conversion rate of 98%, with a TOF 100 times higher than the batch mode.

Multistep flow synthesis methods have been used to obtain complex organic molecules with a variety of biologically active natural products [51]. Although the continuous flow strategy has advantages, most of its reported synthesis does not exceed two steps, while multi-step synthetic reactions often require off-line intermediate purification [52]. Russell and Jamison designed a method for the synthesis of the antimicrobial agent linezolid through a continuous flow sequence involving seven chemical transformations (Fig. 3B) [53]. The method achieves the highest amount of chemical conversions in a completely continuous manner, without the need for solvent exchange, or interruption of intermediate work or purification. Linezolid was synthesized in seven steps with a total residence time of 27 min, a separation yield of 73% and a flux of 816 mg/h.

Drug development is a lengthy process. Compared to traditional drug development programs, microfluidic technology has become a revolutionary technology, providing a miniaturized and highly controllable environment for the occurrence of biological (chemical) reactions.

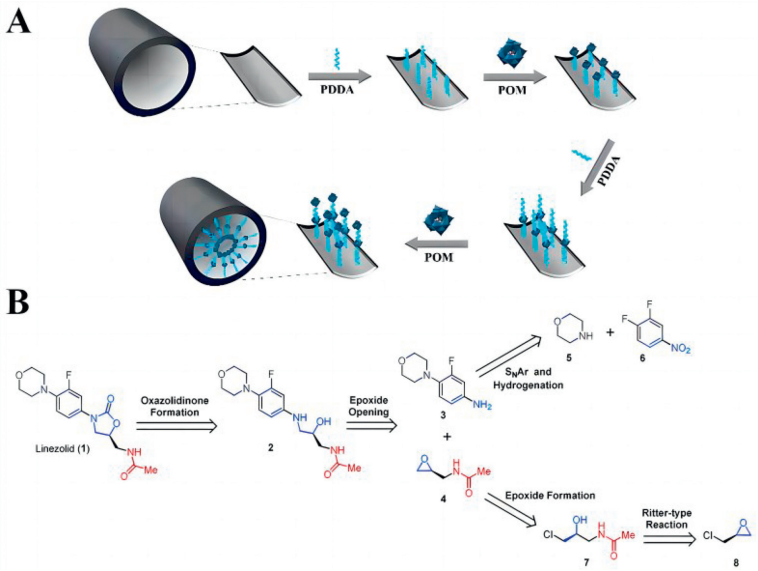

Fig. 3. (A) Schematic for preparation of HPMo-MR (2) based on electrostatic assembly. Reproduced with permission [50]. Copyright 2019, Wiley. (B) Synthesis planning for linezolid (**1**). In the synthetic strategy proposed for **1**, epoxide **4** was to be accessed through a Ritter-type reaction of (+)-epichlorohydrin (**8**) followed by ring closure of amide **7**. Synthesis and coupling of aniline **3** with **4** followed by oxazolidinone formation would generate the target API. Reproduced with permission [53]. Copyright 2019, Wiley.

2.3. Biocatalysis of drug synthesis

Biocatalysis is the conversion of substrates into products using isolated enzymes or enzymes within cells [54]. It has now become an important aspect of modern organic synthesis and is increasingly used in drug synthesis to make the production process green and more sustainable [55]. As one of the best solutions for "green chemistry", biocatalysis has many benefits compared to chemical catalysis in the synthesis of drugs and drug intermediates [56]. For example, biocatalysis can significantly shorten the multi-step reaction synthesis route in classical chemical methods [57]. Biocatalytic reactions are usually carried out under mild reaction conditions and avoid the use of toxic reagents, which can produce fewer by-products and waste [58,59]. Biocatalysts typically exhibit excellent chemical selectivity, regional selectivity, and stereoselectivity, which are crucial for drug production [60]. In addition to drug development and synthesis, biocatalysis also plays a role in drug discovery and can support the synthesis of many active ingredients at an early stage to build the entire scaffold in a targeted and preparative manner. The search for new enzymes, such as through protein engineering or genome mining, screening or tweaking of substrates and product ranges, makes biocatalysts competitive tools for academic and pharmaceutical applications [61].

POMs are a combination of oxygen and early transition metals in high oxidation states, and most of their applications are concentrated in catalysis [27,62]. Various catalytically active metal ions can be introduced into the blank POM structure and function like the catalytic center of a natural enzyme [63]. Therefore, POM and its derivatives are promising alternatives for mimicking enzyme activity. The use of POM based materials as artificial enzymes has impressive catalytic activity and special adjustability, not only ensuring high enzyme activity, but also improving specificity and even simulating the catalytic functions of multiple natural enzymes by introducing the required active sites [64]. POMs with different structural forms can combine with different metal atoms to obtain new inorganic compositions with enzyme mimicry properties. For example, Li *et al*. synthesized tetranuclear Zr^{iv} substituted POMs, which exhibit peroxidase like activity [65]. POM can be assembled with functional materials to improve its performance and potential practical applications. For example, the dipeptide POMs oxidized graphene ternary hybrid prepared by precipitation method has higher peroxidase activity compared to individual POMs [66]. Inorganic-organic hybrids based on POMs and transition metal complexes are another similar strategy for building new enzyme mimics. For example, Gao *et al*. synthesized two new hybrids from sandwich tungstite or stibnite modified with copper(II) -imidazole complex, which showed higher peroxidase-like activity than Keggin-type POM near physiological pH [67].

Enzyme-catalyzed reactions have many attractive properties for the synthesis of chiral intermediates because the reactions can be carried out at room temperature and atmospheric pressure, thus limiting or avoiding isomerization, racemization, isomerization, and rearrangement [68]. Due to these advantages, interest in developing biocatalytic processes to obtain drug intermediates has increased dramatically. Since about 57% of active pharmaceutical ingredients are chiral molecules, most chiral drugs are marketed in their homochiral form [69]. Over the past 30 years, both academia and pharmaceutical companies have been working to develop efficient procedures to obtain homochiral compounds with high yields and excellent enantiomeric excess [70]. Biocatalysis is now being added to other tools mature in green chemistry, such as organic catalysis, multicomponent reactions and solvent-free synthesis, which have successfully achieved API synthesis [71]. Green synthesis of pregabalin for the treatment of various central nervous system diseases using biocatalysis is a successful example of reducing the environmental impact of chiral production [72]. The lipid-catalyzed decomposition of cyano diesters yields the desired enantiomers of (S)mono acids and increases the process yield to 40% in only one cycle step, providing excellent performance in terms of yield and enantioselectivity, which helps to make the biocatalytic process environmentally friendly compared to first-generation syntheses. The synthesis of rositine, a drug widely used to treat depression, can also be highly improved by biocatalysis [71].

Biocatalysts exhibit high selectivity and activity under mild reaction conditions, and have the advantages of biodegradability and nontoxicity in the preparation of chiral intermediates [73]. In the past few decades, many enzyme catalytic processes have been successfully established and expanded, and corresponding biocatalytic systems are becoming a universal method for the synthesis of enantiomeric pure compounds on both laboratory and industrial scales [74].

2.4. Progress of artificial intelligence in drug synthesis

Traditional drug design requires a significant amount of research time and development costs. Computational methods, including computer-aided drug design and artificial intelligence (AI), may accelerate the efficiency of drug discovery by minimizing time and financial costs [75]. Artificial intelligence has great potential in the predictive chemistry and synthesis planning of small molecules, which has the advantages of improving efficiency, reducing costs, shortening time, reducing the number of field workers, achieving precise operation, *etc*., and has made remarkable research progress in the field of drug discovery and development [76]. At present, artificial intelligence is being promoted in different scientific fields, including chemistry.

In the process of drug development, drug molecular design is an important step. With the continuous development of artificial intelligence technology, drug molecular design is also given more possibilities and feasibility. At present, artificial intelligence technology is mainly applied to the simulation and prediction of drug molecules in drug molecular design. Through the simulation of drug molecules, scientists can predict the effects of drug molecules and other aspects of information. The prediction of this information often relies on complex algorithms and mathematical models.

In pharmaceutical chemistry, computational methods supported by computer-aided drug design and chemical informatics have long been used to help identify and optimize active compounds [77]. So far, a large number of publications related to artificial intelligence have emerged in the literature related to pharmaceutical chemistry, and it is expected to further increase. In addition, in recent years, computational methods have been widely applied in the field of improving the effectiveness of drug discovery and synthesis, resulting in a large number of new drugs being approved for market [75]. In the pharmaceutical field, computer algorithms can be used to perform tasks that would otherwise rely on human intelligence. It can help scientists and biotechnologists streamline the process of drug discovery and development, assist in diagnosis, and automate repetitive work tasks that waste time and human resources.

Generative chemical language models (CLMs) can be used to generate molecular structures from scratch by learning from textual representations of molecules [78]. Here, Moret *et al*. shows that mixing CLM can further leverage the bioactivity information available for training compounds. To calculate the ligands designed for phosphoinositol 3-kinase (PI3K-γ), they created a collection of virtual molecules with the resulting CLM. The virtual compound library uses a CLM-based classifier for bioactivity prediction. This second hybrid CLM was pre-trained on the patented molecular structure and fine-tuned using a known PI3K gamma ligand. A novel PI3K-γ ligand with submicromolar activity was identified, highlighting the scaffold jumping potential of this method.

With the increasing complexity of manufacturing processes and the increasing demand for efficiency and better product quality, modern manufacturing systems are attempting to endow machines with human knowledge and constantly change manufacturing practices [79]. The application of artificial intelligence in the manufacturing industry can be proven to be a method to promote the development of the pharmaceutical industry [80]. The new chemical computer platform helps with digital automation of molecular synthesis and manufacturing, combining various chemical codes and operating using a scripting language called chemical assembly. It has been successfully used in the synthesis and manufacturing of sildenafil, diphenhydramine hydrochloride, and lufenamide, with yield and purity significantly similar to those synthesized manually [76].

3. Green drug synthesis under thermocatalysis with polyoxometalates based materials as catalysts

The scientific study of POMs has come a long way since molybdenum blue was first described in 1778 [81]. The structure of POMs is rich and complex, the chemical composition is mainly Mo, W, V, Nb, heteroatoms can be P, As, B, Al, Si, Ge, S and other atoms. Polyoxometalate structure can be divided into saturated and unsaturated structure. It is well known that there is a general correlation between the complexity of a compound's structure and the function it exhibits. The wide variability of the chemical composition and the large number of unusual structural types allow polyformaldehyde to exhibit a wide variety of different properties, which has attracted many researchers to continuously explore the synthetic strategies, structural regulation, properties and applications of polyformaldehyde materials and related catalytic application [82–85]. Thermal catalysis is the use of catalysts to reduce the activation energy of the reaction, thereby accelerating the efficiency of the reaction. Thermal catalysis has fast reaction rate and high selectivity, which can greatly improve the reaction efficiency and reaction quality. As a traditional and most widely used catalytic method, it has been widely used in chemical, petrochemical, energy and other fields. For example, it plays an important role in the selective oxidation of alcohols. However, traditional thermal catalysis methods to achieve high selectivity and conversion often require high temperature and pressure conditions and, in some cases, precious metals [86]. And the traditional practice of synthesizing, manufacturing, and processing drugs has led to serious adverse consequences for humans and the environment. Therefore, the green synthesis of drugs is also an essential condition.

Imines are a key component of various agricultural, pharmaceutical, and bioactive *N*-heterocyclic compounds because they have different reactivity [87]. Imines are an important organic compound with a wide range of applications. It can be used as an important raw material in drugs, catalysts, dyes and other fields. In medicine: Many imine compounds are biologically active and can be used to treat a variety of diseases. For example, heparin, commonly used by people with liver cirrhosis, is an imine compound that can be used to prevent blood clots from forming. In agriculture: imines are also used in the synthesis of pesticides to kill pests and weeds. There is also imipenem, which belongs to the class of beta-lactam antibiotics, which has a broad spectrum of antibacterial effects and can be used to treat serious gram-negative bacterial infections, such as pneumonia, peritonitis, and septicemia. Usually, imines are formed by condensation of aldehydes or carbonyl compounds with amines in the presence of an acid catalyst, and of the several alternative methods of imine synthesis in recent years, direct oxidative coupling of alcohols and amines is the most promising because alcohols are readily available and inexpensive, and more importantly the only by-product of hydrogen and water. However, the reported catalysts are based on precious metals (ruthenium [4], gold [5], platinum [6], and palladium [7]), which we do not want.

Thus, it has recently been shown that efficient synthesis of imines from oxidative coupling of aromatic amines and fatty amines with primary alcohols has been achieved in the presence of base $(t\text{-BuOK})_2$ and oxygen by using the easily synthesized and scalable POM catalyst $Na_{12}[WZn_3(H_2O)_2(ZnW_9O_{34})_2](ZnWZn_3)$ (Fig. 4A). In the presence of bases, POM catalysts have high catalytic activity against primary alcohols and amines, with good substrate range and functional group tolerance. Therefore, polyoxometalate plays an important role in the reaction of synthetic compounds and in increasing the yield.

Amide groups are prevalent in a variety of natural products, pharmaceuticals, polymers, fine chemicals, and commonly used synthetic scaffolds. Especially in medicine, there are more amide drugs, which can be divided into four categories: non-steroidal anti-inflammatory drugs, anti-cancer drugs, analgesic drugs, and antidepressants. Amides are an important class of drug molecules, whose molecular structure is based on the formation of amide

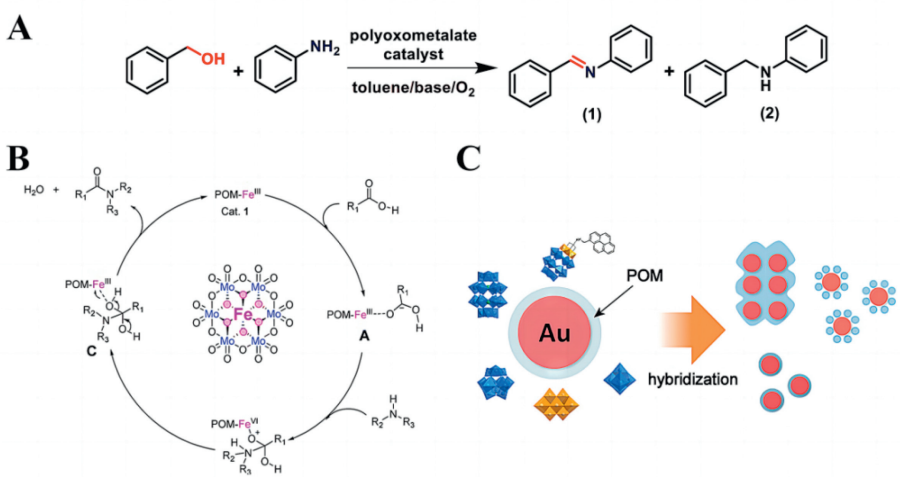

Fig. 4. (A) Polyoxometalate catalyzed transformation of *N*-phenyl-1-phenylmethanimine. Reproduced with permission [87]. Copyright 2020, Elsevier. (B) A reasonable mechanism for the direct N-acylation reaction of amines and carboxylic acids catalyzed by iron. Reproduced with permission [88]. Copyright 2021, Royal Society of Chemistry. (C) Illustration of the procedure forming gold nanoparticle-POM hybrids (AuNP-POMs) without involving reduction of the POM species. Reproduced with permission [93]. Copyright 2019, American Chemical Society.

bonds, and have a wide range of pharmacological activities and clinical applications. These drugs are widely used in analgesia, anti-cancer, anti-depression, hypoglycemia and so on. For example, common NSAIDs such as aspirin, indomethacin, and ibuprofen are a class of drugs used to relieve pain, fever, and inflammation. Their molecular structure consists of an aromatic ring and an amide bond. Also, common analgesics such as aminoketone and fentanyl, which usually work by interfering with neurotransmission to relieve pain, are also amides. Also, Paxil, fluoxetine, venlafaxine and other common amides used to treat depression, these drugs usually improve mood by affecting the metabolism and reuptake of neurotransmitters. In conclusion, amides are a very important class of drug molecules, and their molecular structure has a wide range of application and research value. So far, many methods of synthesizing amides have been reported. Most amide bond synthesis involves the use of stoichiometric coupling reagents, resulting in expensive and wasteful procedures. Currently, most amide synthesis is done by coupling carboxylic acids and amines with highly reactive acyl chlorides, anhydrides, or coupling agents [88]. However, this method produces large amounts of toxic chemical waste and can introduce complex synthetic steps, which has led the ACS Green Chemistry Institute to select "avoiding amide-forming reagents with poor atomic economy" as one of the most important tasks facing organic chemists. Catalytic amidation is an attractive alternative to cost-effective synthesis of amides from carboxylic acids and amines.

POMs are a class of discrete metal oxides that are considered inorganic ligands that coordinate with metal centers. They are not only reversible redox and strongly acidic at the atomic or molecular level, but also show a high tolerance to oxidative degradation and hydrolysis, which is quite different from traditional transition metal catalyst compounds and complexes [89–92]. In recent years, Wang's group has developed an efficient and environmentally friendly Fe-POM catalyst, which has multi-functional and synthetic practicability and can be used for cross-coupling carboxylic acids and amines to form amide products with a wide range of substrates (Fig. 4B). This method provides a range of complex secondary and tertiary amides under optimized reaction conditions without radical stoichiometric reagents. In addition, Fe-POM catalysts exhibit high efficiency and stability after multiple uses. In addition, the system can be used to convert readily available amines and carboxylic acids into diamides, which are important compounds in medicinal chemistry. For example, diamides can serve as the backbone of drug molecules, such as the diamide structure found in many antibiotics and pain medications. In addition, diamides have important biological significance, and many biological macromolecules, such as proteins and nucleic acids, contain diamide structures. Diamides are important organic compounds and have a wide range of applications.

POMs have applications in a variety of research fields, from catalysis to medicine and biology, because POM clusters represent a large class of compounds that exhibit a wide range of shapes, sizes, and topologies. Due to its polyanionic properties, structural diversity, and redox properties, POMs have also been used as an end-sealing ligand for nanoparticle synthesis (Fig. 4C) [93].

Nanotechnology is a revolutionary field, modernizing many techniques, scientific instruments, and medical applications [94,95]. The development of nanoscale materials has opened up many avenues for interdisciplinary collaborative science. Nanoparticles exhibit unique and significantly varied chemical, physical and biological properties compared to bulk materials that have the same chemical composition. Nanoparticles exhibit size- and shape-related properties that are of interest in applications ranging from biosensing and catalysts to optics, antibacterial activity, chemical sensors, and wireless electronic logic and storage schemes. The nanoparticle is synthesized from precious metals such as silver, gold and palladium, of which gold is a fascinating metal with long-term medicinal properties. Gold exhibits high chemical stability, dispersity, biocompatibility and inertness under physiological conditions, making it a compelling target for all areas of research in life sciences, biomedicine and materials science. Gold nanoparticles have been used as antimicrobial agents, cancer therapies and diagnostic tools for fluorescence tomography, among others [96]. And a new, simple synthesis method has been described for preparing gold nanoparticle POM hybrids, which is to heat $AuNO_3(PMe_3)$ solution in acetonitrile and use tetrabutylammonium (TBA) as the antioxygen ion in the microwave at 120 °C in the presence of appropriate polyformaldehyde substances. This method can produce POM-terminated gold nanoparticles without excessive reduction of the solution leading to the decomposition and recombination of POM.

Artificial enzymes, which can be used as substitutes for natural enzymes, have attracted great attention in the fields of catalysis, biosensing, diagnosis and therapy due to their high stability and low cost [97]. POMs, as a class of inorganic metal oxides, have shown great potential in simulating enzyme activity due to their clear structure, adjustable composition, high catalytic efficiency and easy storage. Ce^{IV}-POMs have been shown to act as artificial proteases that promote the selective hydrolysis of peptide bonds (Fig. 5A) [98]. In recent years, several artificial enzymes based on POM have been developed to varying degrees, covering different types of POMs and their derivation-based imitative enzyme functions. Moreover, recent studies have further noted that the POMs could function as artificial nucleases (Fig. 5B) [99].

Neurodegenerative diseases involve the progressive loss of neuronal structure or function due to abnormal protein aggregation. Despite their important impact on human health and the economy, effective treatments have rarely been reported. Alzheimer's disease is a typical neurodegenerative disease that involves a variety of molecular signaling pathways, and β-amyloid toxicity is the leading theory of its pathogenesis. A review of the literature shows that POMs have been found to hydrolyze proteins, making it an ideal candidate for the treatment of neurodegenerative diseases. Guan and colleagues created the CeONP@POMs com-

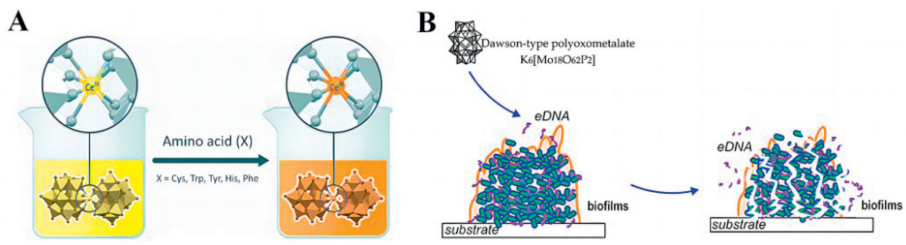

Fig. 5. (A) Using amino acid building blocks as a simple model to study the origin of simultaneous reduction of CeIV to CeIII ions. Reproduced with permission [98]. Copyright 2020, American Chemical Society. (B) Dawson-type polyoxometalate $K_6[P_2Mo_{18}O_{62}]$ exhibits high cleavage ability towards eDNA secreted by Escherichia coli, thereby eradicating bacterial biofilm. Reproduced with permission [99]. Copyright 2023, American Chemical Society.

posite by coating cerium oxide nanoparticles (CeONP) with three types of POMs, including Wells-Dawson, Keggin and Anderson-type POM, as an artificial protease to prevent the neurotoxicity of beta-amyloid. Of the three types of POM, Wells-Dawson POM ($K_6[P_2W_{18}O_{62}]$) was particularly effective at removing beta-amyloid aggregates, presumably due to the relatively low surface potential and high electronegativity of the constituent atoms [100]. At present, chemotherapy remains the primary method of treatment for highly metastatic malignancies, however, most reported multifunctional nanoprobes and therapeutics have hydrodynamic diameters that exceed the filtering threshold of the kidney. As a result, these agents are metabolized by the kidneys and absorbed by the reticuloendothelial system of the liver and spleen. It is worth noting that POMs based materials have made many new research advances for cancer treatment. For example, Yong *et al*. reported the use of GdW_{10} as a radiosensitizer for radiation therapy, and Wu *et al*. set up a large ring polymolybdate cluster as a photothermal for synergistic photothermal therapy and chemotherapy.

Zhu's group used activated carbon supported POM as a catalyst to oxidize toluene to benzaldehyde in acetic acid through air, which improved the disadvantages of the original method which polluted the environment and was difficult to be applied in food and medicine fields [101]. Wei's group proposed an anderson POM for the oxidation of carboxylic acids to aldehydes in water. This method uses oxygen as the only oxidant under mild conditions and is also suitable for various aldehyde derivatives with different functional groups [102]. The team of Parac-Vogt used readily available Zr(IV) and Hf(IV) substituted POM to catalyze the formation of simple, safe and inexpensive amide bonds between unactivated carboxylic acids and free amines under mild conditions [103]. This method has low catalyst load and does not use dehydrating agent or desiccant.

In summary, POMs play an important role in the direction of thermocatalytic drug synthesis, and has many advantages in the synthesis of some important intermediates such as imines and amides. However, the conditions of some synthetic reactions are too harsh for POMs to be stable, so great efforts are still needed to overcome these shortcomings. In the future, by regulating the structure and composition of polyacid catalysts, the catalytic activity and selectivity can be further improved. In addition, the carrier materials of polyacid catalysts are also a research hotspot. The stability and recyclability of catalysts can be improved by selecting suitable carrier materials.

4. Green drug synthesis under photocatalysis with polyoxometalates based materials as catalysts

Photocatalysis is the change in the rate of a chemical reaction or its initiation in the presence of a substance, a photocatalyst, which absorbs light and participates in the chemical transformation of a reaction partner in the presence of ultraviolet, visible or infrared radiation. There are various photocatalysts for photocatalytic reactions, and polyoxometalates (polyoxometalates) are one of them. Compared to other photocatalysts. Polyoxometalates are anionic inorganic metal–oxygen clusters in which the coordinated metallic elements in an octahedralenvironment of oxygen atoms are in a high oxidation state (often d_0 configuration). It compared with silica, perovskites and oxides has good thermal stability, improve the activity of the catalyst, thus further promote the photocatalytic reaction. Polyoxometalates as photocatalysts are not only used to solve environmental problems, but also play a great role in catalytic synthesis to promote the efficient and green production of more chemical products.

As an efficient catalyst, POMs have high photoconductivity and photocatalysis. The previous part has introduced the related research progress of thermal catalysis in detail, and the following will introduce the research results of POMs in the field of photocatalysis.

Adhikary's team proposed methoxy poly oxygen catalytic synthesis of imine [87]. Among various kinds of POMs just, a Sandwich POM $Na_{12}[WZn_3(H_2O)_2(ZnW_9O_{34})_2]$ ($ZneWZn_3$) is a promising catalyst for the oxidation of primary alcohols. First, benzyl alcohol and aniline react in the presence of Zn-WZn_3 to synthesize imines (Fig. 6A). The development of this catalyst greatly reduces the production cost of the reaction, which is in line with the original intention of green chemistry and has made its own contribution to the development of green chemistry. The synthesis of imines can be also achieved through various methods. Shi's team published an article on the direct generation of imine from alkenes and amines through photocatalysis in 19 years [104]. They developed ZnW-PYI, which they used as a photocatalyst for the reaction. The design of the catalyst allows the reaction to proceed under milder conditions, which makes the electron transfer during the reaction easier and more efficient, speeding up the forward progress of the reaction. The catalyst itself can be easily separated from the reaction product, which greatly improves the reuse rate and provides a new way for green synthesis of imine. Two schemes were used to achieve imine synthesis (Fig. 6B). The first is a series reaction to directly synthesize imines from alkenes, designed with the idea of using imine activation to directly synthesize imines from enamines. ZnW-PYI promotes solar energy conversion and oxygen activation of amide synthesis during the reaction process, controls the reaction rate, and realizes multi-step reactions. However, the second reaction scheme is: self-aerobic oxidative coupling of alkenes and amines through an aldehyde intermediate.

Furthermore, Jiao's team employed POMs as a catalyst for the nitration of aniline [105]. Anilines are commonly used in industrial chemicals as raw materials for many products such as dyes, pigments, rubber and pharmaceuticals. But most of the precious metal catalyst and its derivatives of aniline production needed to drive reaction, thus produce cheap catalysts is of crucial importance. The structure of POMs remains intact during the process of multi-electron transfer, enabling it to accommodate multiple electrons and protons. As a result, it facilitates the redox process of multi-electron nitrobenzene. A new precious metal-free photocatalyst, {ZnW-TPT}, was prepared by incorporating a Zn-substituted monovacant Keggin polyanion $[SiZnW_{11}O_{39}]^{6-}$ and a photoactive organic bridging link 2,4,6-tri(4-pyridyl)−1,3,5-triazine (TPT) into a framework, in this structure, $[SiZnW_{11}O_{39}]^{6-}$ and TPT direct match between ligand and $\pi-\pi$ interactions help light generated charge carrier separation and migration, thus enhancing the photocatalytic activity of {ZnW-TPT}. {ZnW-TPT} can efficiently catalyze the photocatalytic reduction of nitrobenzene to aniline using hydrogen hydrate as the donor. {ZnW-TPT} the UV–vis spectra shows a center with an optical absorption band of about 350 nm, with high absorbability, with this feature it can use solar energy. Through the above, it is not difficult to find that the rational application of solar energy will add a strong color to the development of green chemistry. The good photochromic property of {ZnW-TPT} is beneficial for photocatalysis. In the reduction reaction of nitrobenzene, current generally accepted step hydrogenation and condensation reaction. Therefore, the reduction of nitrobenzene is carried out by a condensation reaction using {ZnW-TPT} as a catalyst and a dihydrate as a proton donor. This is part of the catalytic reaction mechanism. As a new type of efficient green catalyst, ZnW-TPT application will provide a good solution for the green synthesis of aniline (Fig. 6C), and provide new ideas for the synthesis of other photocatalytic catalysts.

In April 2022, Gu and his team developed crystalline porous ionic salts assembled from polymetallic oxides and cation capsules as green catalysts for selective photocatalytic aerobic oxidation of aromatic alcohols to aldehydes [106]. Metal-organic cages (MOCs)

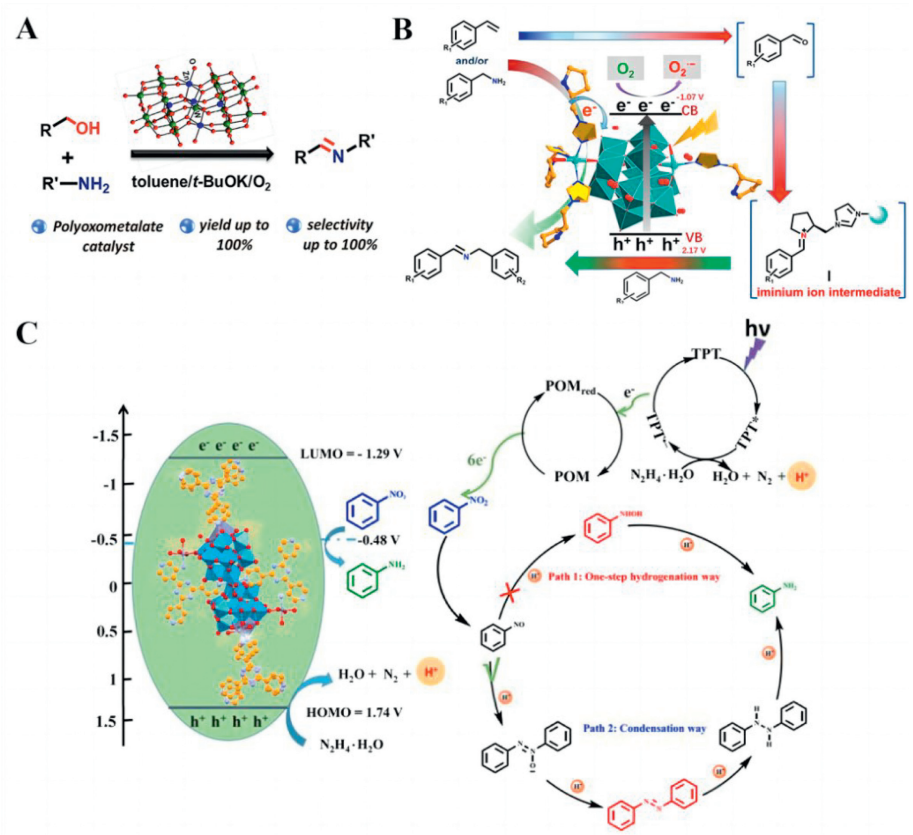

Fig. 6. (A) Two ideas for ZnW-PYI catalyzed imine synthesis. The left side shows the direct synthesis of imines, and the right side shows the synthesis of aldehyde intermediates followed by the synthesis of imines. Reproduced with permission [104]. Copyright 2019, Royal Society of Chemistry. (B) $ZnWZn_3$ as a catalyst for light catalytic synthesis of imine. Reproduced with permission [87]. Copyright 2020, Elsevier. (C) Proposed photocatalytic mechanism of nitrobenzene reduction. Reproduced with permission [105]. Copyright 2022, Royal Society of Chemistry.

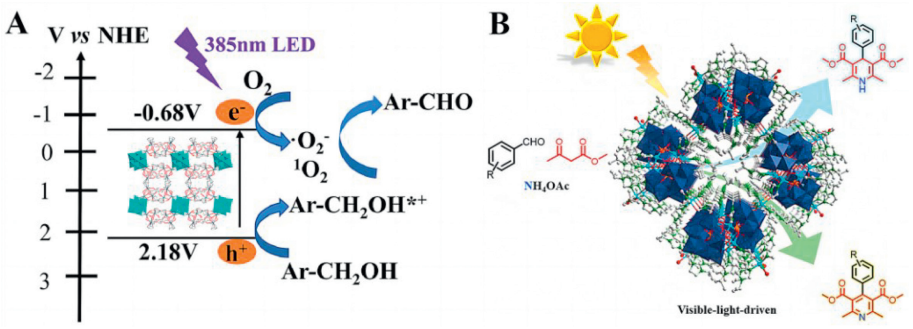

Fig. 7. (A) The flkajd possible photocatalytic oxidation mechanism of aromatic alcohols with CPISs (crystalline porous ionic salts) $[W_{10}O_{32}]\{[Cp_3Zr_3(\mu_3\text{-}O)(\mu_2\text{-}OH)_3]_2(BPDC)_3\}_2{\cdot}12DMA{\cdot}2CCl_4$ as photocatalyst. Reproduced with permission [106]. Copyright 2023, Elsevier. (B) Photocatalytic pyridine synthesis. Reproduced with permission [110]. Copyright 2023, Elsevier.

are considered as discrete metal-organic components with intrinsic porosity, tunable structure and function. This suggests that the combination of MOC and POM may be a very effective strategy for fabricating porous solids with customized functionality and better performance than individual components (Fig. 7A). The photocatalytic activity of the aerobic oxidation of formaldehyde by aromatic alcohols and the conversion rate of the products were improved due to the selection of such catalysts. The application of this catalyst also provides a new direction for the selection of catalysts for other photo driven reactions in the future. Polyethylene oxide same tower acid ester other photocatalytic reaction can take place under mild conditions, such as paraffin functionality to form olefins or ketone, polymerization of olefins, as well as to the water-borne organic pollutants to the interpretation of the advanced oxidation process. The design of MOC further enriches the selection of catalysts for photocatalytic reactions.

Of course, POMs also have a good effect on nanostructures as green catalysts, such as the use of porphyrin-polyoxometalate electrostatic hybrid film photocatalytic synthesis of silver dendrites, the mechanism of the reaction is that the porphyrin can be excited by visible light, electrons are transferred to the good catalyst of POM [107]. Therefore, the Ag nanoparticles will take on the appearance of giant Ag dendrites. The contact area of silver nanoparticles was further increased to improve the utilization rate of silver nanoparticles.

While most previous catalysts for POMs have been on homogeneous systems, Guo's group has focused on heterogeneous photocatalysis, preferably developing photocatalytic materials in more

recyclable forms for applications [108]. So, they by silica, with the uniform POMs mesoporous molecular sieve MCM-41 or MCM-48, NaY zeolite, layered double hydroxide, amorphous phase of TiO_2 and polymer membranes or alkylation enzyme and other light active support materials to do this, to prepare water-resistant solid POMs. Their advantage lies in their ability to expand the contact area of POMs, increase their catalytic activity, improve their catalytic efficiency, and speed up the reaction process. As a kind of photocatalytic materials, the light absorption ability of POMs is one of great factors that affect the photocatalytic activity. Porous materials also play an enormous role. In this review, we further demonstrate the design, fabrication, optical absorption properties, morphology, surface physicochemical properties and heterogeneous photocatalytic behavior of other novel solid-state POMs (*e.g.*, amino-functionalized mesoporous silica/Ti kinase, dual-mode multi-mode multi-tungstic acid-anatase TiO_2 nanocomposite, Fe-polytungstate fabric, single vacuum Keggin unit Si/Ti composite film and three-dimensional ordered macroporous single vacuum Keggin unit Ti composite film). Emphasized the precast solid POMs in the ultraviolet and visible region of the high photocatalytic activity, and the catalyst recycling more easily from the reaction system.

Without toxic or dangerous oxidant or solvent, looking for new catalyst for industrial application of green synthesis of adipic acid is of great significance. Here, Anderson type POMs $[Ni(OH)_6W_6O_{18}]^{4-}$ was used for the first time as an efficient oxidation catalyst for the green synthesis of adipic acid using aqueous H_2O_2 as oxygen donor [109]. In the absence of organic solvent and phase transfer catalyst, the yield of adipic acid reached 95.6% and 90.9% with cyclohexanediol and cyclohexene as substrates, respectively. Based on spectral characterization and density functional theory calculations, the detailed catalytic mechanism of this green catalytic synthesis method at the atomic level is presented.

In terms of light catalytic synthesis, except for small molecular organic compounds utilizing the catalytic properties of polyacids, as in some organic macromolecular material has been widely used, in the synthesis of pyridine class of drugs, such as nifedipine or nimodipine in the treatment of cardiovascular diseases, polymetallic oxygen sour salt has played a huge role, Huang team in April this year published about an unprecedented 2-fold interpenetrated **lvt** open framework built from Zn6 ring seamed trivacant polyoxotungstates used for photocatalytic synthesis of pyridine derivatives [110]. Previously, pyridine was obtained by oxidation of dihydropyridine, but this involves the need for a high oxidant catalyst and the cost of a two-step reaction. Therefore, their team has developed new type polymetallic oxygen sour salt for light catalytic synthesis of pyridine (Fig. 7B). Visible light gathering ability to induce the LCU-22 ($Zn(1\text{-ipIM})_3]_2[Zn_6(AsW_9O_{33})_2(1\text{-ipIM})_6]\cdot 2(1\text{-HipIM})$, 1-ipIM = 1-isopropyl imidazole) more under visible light illumination photoelectric charge carrier, so as to improve the photocatalytic performance. As an environmentally friendly and renewable catalyst, the zinc and POM active centers in LCU-22 function as Lewis acid and oxidation site, respectively, in the photocatalytic reaction, but their combination namely LCU-22 can significantly improve the catalytic activity of each component. It can be used repeatedly in the catalytic process, greatly saving the reaction cost, in line with the concept of green chemistry. It can be used as a green and efficient catalyst in the photo driven synthesis of pyridine derivatives, promoting the development of green chemistry.

The development of green photocatalytic polyoxometalate synthesis is slow and time-consuming. Nowadays, a variety of small molecular organic compounds have been synthesized by POMs catalysis, which are subsequently applied to the synthesis of drug molecules. We now need to develop more polymetallic oxygen sour salt into drug synthesis application, so we can use light greatly for green synthesis. What is insufficient is that we lack the application of POMs in the synthesis of drug macromolecules. We hope that more POMs can be developed and applied to photocatalytic drug synthesis in the future, so as to further develop green chemistry.

5. Green drug synthesis under electrocatalysis with polyoxometalates based materials as catalysts

Electrochemical methods are often described as inherently sustainable, and their development stems from the opportunities of green chemistry, improved atomic economics, and the control of the reaction environment [111]. In the field of electrocatalysis, including C–C coupling, C–H activation and stereoselective heterocyclic reactions have been explored [112]. Compared with traditional approaches for reduction and oxidation, electrocatalysis has several fascinating features: (1) The electrochemical reaction is usually carried out at atmospheric pressure and room temperature, which is considered to be mild reaction conditions [113]. (2) Replacing redox reagents with current helps to reduce costs and improve environmental compatibility [114]. (3) The working potential of the electrode can be precisely adjusted to match the redox potential of the compound in the electrolyte [115]. (4) The selectivity of the reaction can be realized by the adjustment of electrode materials and the control of current and voltage [116]. At present, as a green and simple synthesis method, electrocatalysis has become an effective tool for sustainable synthesis of target molecules from simple materials under environmentally friendly conditions and has attracted much attention in the field of medicine and pharmacology [117]. However, many catalytic processes depend on the availability of catalysts and the stable immobilization of highly active catalysts on high surface area electrodes. While the abundance of transition metal-based catalysts on Earth has been explored, the complexity of many catalytic composites and the lack of suitable structural models to explore structure-function-activity-stability relationships is an obvious challenge [118].

POMs have been widely used in the field of catalysis due to its negative charge and special structural stability, ability to achieve strong and powerful electronic interactions and exhibit multifunctional redox properties [119]. The metal sites in nanoscale POMs can be easily replaced by other redox-active transition metals or combined with other inorganic ligands to design catalysts [120]. At the same time, POMs can also be modified by functional organic molecules to construct organic-inorganic hybrid materials [121]. This allows the designed catalyst to combine the properties of POMs and ligand, which has greater application potential in catalysis. In addition, benefiting from nanoscale reaction sites, the structure, composition, and reactivity can be regulated at the molecular level, POMs are dispersed to the maximum extent at accessible reaction sites on the electrode surface and can exhibit significant reactivity under chemical conditions [122]. In the pharmaceutical industry, achieving the goal of green drug synthesis has long been an important research direction. In view of the excellent performance of POMs in the catalysis field and the advantages of electrosynthesis over other synthesis methods, polyoxometalate based materials as catalysts to synthesize drugs by electrochemical means have become a growing interest for researchers [123].

5.1. Catalysts of polyoxometalates based inorganic materials

POMs can be finely tuned at the molecular level through different elements, changing its chemical properties and developing new materials with good catalytic activity [124]. Sato *et al.* controlled the growth of manganese oxide in the reaction cavity inside the ring of POM ($[P_8W_{48}O_{184}]^{40-}$) and successfully synthesized manganese oxide with discrete nanostructures with

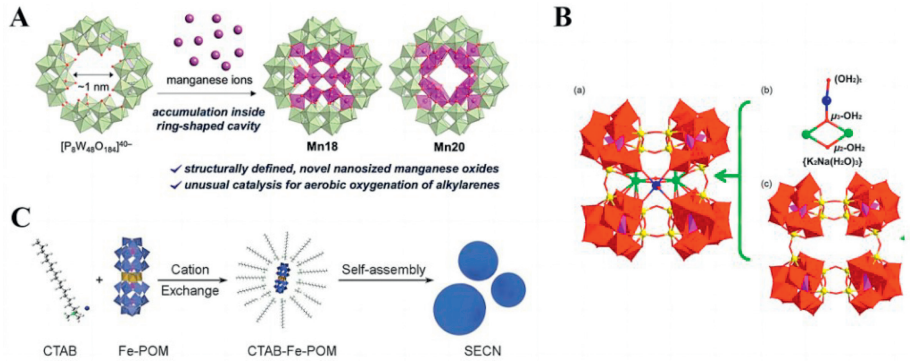

Fig. 8. (A) Synthesis of structurally defined novel nanosized manganese oxides inside a ring-shaped POM cavity. Reproduced, with permission [125]. Copyright 2022, Wiley. (B) (a) The structure of $[\{K_2Na(H_2O)_3\}@\{(Ti_2O)_2\text{-}(Ti_4O_4)_2(GeW_9O_{36})_4\}]^{25-}$; (b) The central $\{K_2Na(H_2O)_3\}$ core; (c) The ring-shaped structure of $[(Ti_2O)_2(Ti_4O_4)_2(GeW_9O_{36})_4]^{28-}$. Reproduced with permission [126]. Copyright 2022, Springer. (C) Schematic illustration of the formation of SECN. Reproduced with permission [127]. Copyright 2023, American Chemical Society.

18 core structure, which has high catalytic activity for the oxidation of various alkyl arene (Fig. 8A) [125]. Li *et al.* added high-valence Ti^{4+} ions to the lacunar POM, a novel 12-tris POM $K_{10}H_{15}[\{K_2Na(H_2O)_3\}@\{(Ti_2O)_2\text{-}(Ti_4O_4)_2$ (a-α−1,3,5-$GeW_9O_{36})_2$ (a-α−2,3,4-$GeW_9O_{36})_2\}]\cdot 45H_2O$ was prepared (Fig. 8B) [126]. It can effectively catalyze the oxidation of various thioethers and 2-chloroethyl ethyl sulfides. And Huang *et al.* synthesized Fe-substituted POM $(C_{19}H_{42}N)_{15}[(P_2W_{15}O_{56})_2Fe_3]$(CTAB-Fe-POM) and self-assembled in mixed solvent to form surfactant-encapsulated composite nanospheres (SECN) for alkene epoxidation (Fig. 8C) [127].

Sulfonamides are the majority of sulfur-containing drugs approved by the U.S. Food and Drug Administration (FDA). Sulfonamides and disulfides have important applications in drug production and are a topic worthy of further investigation [128] Sulfonamides, especially cyclic sulfonamides, combine with other components to produce a variety of pharmacological effects such as hypoglycemic, diuretic, anti-tumor and anti-hypertensive, and are important pharmacophores. For the synthesis of medium-sized cyclosulfonamides, there are some limitations such as complex substrate structure and harsh reaction conditions through transition metal-catalyzed intramolecular coupling reaction. However, the synthesis of 7-membered and 9-membered cyclosulfonamides can be avoided by selective oxidation-radical cascade addition. Zhang *et al*. reported for the first time an example of the formation of a medium-sized ring by a cascade of radical reactions composed of 1,*N*-alkenyl groups: 7- and 9-membered sulfonamides were successfully synthesized by electrochemical cyclization of 1,6-enyne in water-resistant radical reaction conditions [129].

The synthesis of sulfonamide by traditional thermodynamic method has high pressure, complicated steps, and requires strong oxidants [130]. Although direct electrocatalytic coupling is a mild catalytic system, it is still in its early stage, and there are still some problems that have not been addressed, such as the need to use precious metal electrodes and the complexity of electrode manufacturing [131]. Therefore, in terms of sulfonamides and disulfides, the electrocatalytic coupling of thiols and amines/thiols is not well developed at present. In the case of anodization, the electric current drives the electron transfer by shuttling electrons between the electrode surface and the organic substrate, which results in a high overpotential on the electrode surface, as compared to the direct electrolytic process [132]. During indirect electrolysis, overpotential of electron transfer can be avoided, and electrode passivation can also be mitigated by preventing the formation of polymer films on the electrode surface. In addition, the interfacial interaction between the electrode and the electrocatalyst is negligible, and the chemical, regional, or stereoselectivity of the reaction can be more effectively modulated by catalyst design [133]. In order to overcome the obstacle of poor adhesion of pom on the electrode surface during the electrocatalytic reaction, Liu *et al.* processed POMs into the form of porous foam, and successfully synthesized di-copper substituted phosphotungstate based foam material ($PW_{10}Cu_2$@CMC). This material can be successfully applied to the indirect electrocatalytic synthesis of sulfonamides and disulfides, and the yield of S-N/S-S bond construction is up to 99% (Fig. 9A) [134].

To prepare $PW_{10}Cu_2$@CMC, they synthesized $(TBA)_4H_3[PW_{10}Cu_2O_{38}(H_2O)]$ ($PW_{10}Cu_2$) by adding two Cu atoms instead of two W atoms to a Keggin type $[PW_{12}O_{40}]$ 3-polyanion, then a certain amount was added to CMC aqueous solution for high-speed stirring and freeze drying to obtain the heterometallic polyoxometalate. Interestingly, the synthesized $PW_{10}Cu_2$@CMC not only had good dispersions, but also had an ultra-low density ($<$0.07 cm^3/g) and could be successfully spread on the surface of flowers. Under the optimized conditions, the yield of CMC, copper chloride, $PW_{10}Cu_2$ and other comparison samples was much lower than that of $PW_{10}Cu_2$@CMC, which proved that the synergistic effect of foam morphology and $PW_{10}Cu_2$ can promote mass transfer and expose the active site to enhance the activity, which can improve the indirect electrocatalytic performance. Then, also under optimized conditions, the range and versatility of electrochemical cross-dehydrogenation coupling reactions of aromatic and aliphatic amine derivatives are explored. Under optimized conditions, the range and versatility of electrochemical cross-dehydrogenation of aromatic and aliphatic amine derivatives were investigated and the S-H bond self-coupling was extended by using MBT and a variety of substituted thiophenes to construct symmetric disulfide compounds. The transformation mechanism is illustrated: In the presence of $PW_{10}Cu_2$@CMC, the thiol and amine undergo single-electron transfer on the anode surface to produce thiol and amino radicals, respectively, which combine to produce the desired S-N bond products; meanwhile, the thiol radicals undergo dimerization to form disulfide compounds.

CO, NH_3, nitrate, iodate, *etc*. are all important small molecules in the pharmaceutical industry and play a crucial role in drugs and medicinal chemistry [135]. For example, biological ammonia synthesis addresses only a small fraction of the global ammonia demand, and nitrogen reduction under mild conditions is extremely challenging [136]. Therefore, novel catalysts are needed to synthesize these small molecules. To date, high-performance NRR catalysts have mainly relied on noble metals (Pt, Pd, Au, Ru, *etc*.) and lanthanide ions [137]. Since molybdenum (Mo) in nitrogenase is the active center for N_2 fixation under mild conditions, in addition atomic tungsten (W) catalyst shows the best performance

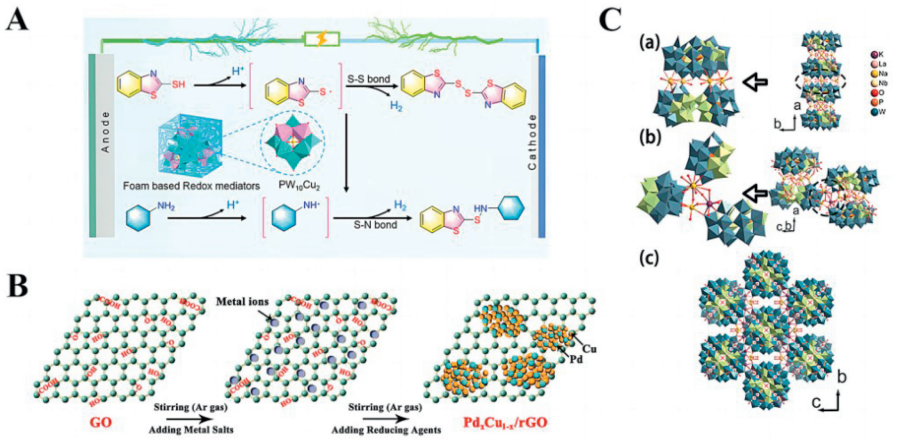

Fig. 9. (A) The plausible mechanism for the formation of *N*-cyclohexyl-2-benzothiazolesulfenamide (**1c**) electrocatalyzed by $PW_{10}Cu_2$@CMC (44 wt%). Reproduced with permission [134]. Copyright 2023, Wiley. (B) Schematic illustration of the preparation of Pd_xCu_{1-x}/rGO. Reproduced with permission [139]. Copyright 2021, Elsevier. (C) (a) The connection mode of polyanions along a axis. (b) The connection of polyanions in bc plane. (c) 3D structures of 1-La viewed from a axis. Reproduced with permission [141]. Copyright 2018, Wiley.

for NRR with a starting potential of 0.25 V [138]. Yin *et al.* used $H_3PW_6Mo_6O_{40}$ (PW_6Mo_6) POM, a polyoxometalate with heteronuclear W/Mo structure and attractive electron/proton reservoir properties, as an excellent matrix and fixed it on reduced graphene oxide (rGO) through the calcination process to form W/Mo@rGO (Fig. 9B) [139]. Then, Pt was transplanted onto the surface of W/Mo@rGO by *in situ* plating treatment to obtain PT-W/Mo@rGO-6 to further improve the performance of NRR under ambient conditions. The synergistic effect of Mo and W plays an important role in the activation and dissociation of N_2. As a doping agent, Mo has a d-electronic structure different from W, which can adjust the electronic structure of the W basis matrix and reduce the energy barrier of N≡N bond dissociation, thus achieving efficient NRR. At the same time, the performance of electrocatalytic NRR can be further improved by a trace amount of electroplated Pt. The resulting Pt-W/Mo@rGO-6 catalyst yields 79.2 μg h^{-1} mg_{cat}^{-1} ammonia at low voltage −0.3 V *vs.* RHE, which is superior to most of the state-of-the-art W/ Mo-based catalysts.

The ability of POMs anions to accept different numbers of electrons resulting in mixed valence makes these compounds attractive for electrode modification and electrocatalysis studies [15]. Immobilization of them on electrodes not only simplifies their electrochemical study but also facilitates their application. Zhou *et al.* proposed a method to construct P_2MO_{18}-functionalized OMC (P_2Mo_{18}/OMC) by immobilizing the polyoxometalate $H_6P_2Mo_{18}O_{62}{\cdot}xH_2O$ on the surface of an ordered mesoporous carbon (OMC) channel [140]. By this method, glassy carbon (GC) electrodes modified with P_2Mo_{18} were prepared and their electrochemical properties and electrochemical catalysis were investigated for the first time and it was demonstrated that the P_2Mo_{18}/OMC/GC electrodes have high stability, fast response and good electrocatalytic activity for the reduction of nitrite, bromate, iodate and hydrogen peroxide. Due to the large specific surface area, uniform pore size, and controllable structure of the immobilized P_2Mo_{18}, the added nitrite is rapidly transferred through the surface and thus reduced by the immobilized P_2Mo_{18}, and the response time of the P_2Mo_{18}/OMC/GC electrode to nitrite is less than 25 s. This indicates that the P_2Mo_{18}/OMC/GC electrode not only has a high sensitivity in 1 mol/L sulfuric acid solution at an operating potential of 0.00 V, but also has a fast response to nitrite. Weng *et al.* synthesized tetrameric polyanions containing a mixture of Dawson type units $\{P_2W_{12}Nb_6\}$ and lanthanide ions in acidic solution, $K_4Na_8H_4\{[Nb_4O_6(H_2O)_4Na_4(H_2O)_8][LaP_2W_{12}Nb_6O_{61}(H_2O)_7]_4\}_{60}H_2O$, $K_4N_{48}H_4\{[Nb_4O_6(H_2O)_4Na_4(H_2O)_8][CeP_2W_{12}Nb_6O_{61}(H_2O)_7]_4\}_{58}H_2O$, $K_4Na_8H_4\{[Nb_4O_6(H_2O)_4Na_4(H_2O)_8][PrP_2W_{12}Nb_6O_{61}(H_2O)_7]_4\}_{78}H_2O$ and $K_4Na_8H_4\{[Nb_4O_6(H_2O)_4Na_4(H_2O)_8][NdP_2W_{12}Nb_6O_{61}(H_2O)_7)_4\}_{66}H_2O$ [141]. These polyanions are composed of two dimer Dawson subunits and an Adamantan-like $\{Nb_4O_6\}$ cluster, and are the first pom constructed of Dawson subunits $\{P_2W_{12}Nb_6O_{62}\}$ and lanthanide ions, where the lanthanide ions are coordinated by two $\{P_2W_{12}Nb_6\}$ units and water molecules (Fig. 9C). It has good activity for the reduction of bromate in solution.

5.2. Catalysts of polyoxometalates based inorganic-organic hybrid materials

In addition to the catalysts composed of POM and inorganic ligands, the catalysts composed of POM and organic ligands can promote molecular stability, enhance redox capacity, fully express their respective catalytic advantages or produce synergistic effects [142]. POMs can catalyze the oxidation of alcohols to aldehydes in a green and efficient manner, and L-proline can be used as a green catalyst to synthesize pharmacologically active heterocyclic compounds. Dai *et al.* designed a POM-L-proline bifunctional organic catalyst [143]. The POMs component of the catalyst catalyzes the oxidation of alcohol to aldehydes, and then the pyrrolidine group of the L-proline component is continuously used as the catalytic site to synthesize ideal heterocyclic compounds in series reaction, with a yield of up to 97% (Fig. 10A). Using 4-meaniline, 4-Cl-benzaldehyde and barbiturate as substrates, it was proved that POMs could only promote the first oxidation step and pyrrolidine was the key catalytic site for the subsequent three-component condensation reaction. The catalytic mechanism of the one-pot alcohol oxidation/three-component condensation reaction was proposed by studying the synergistic catalysis of L-proline covalently linked by Mn-Anderson POM. First, the Mn-Anderson skeleton of the L-Pro-modified compound $H_2\{MnMo_6O_{18}[(OCH_2)_3CNHC_5H_8NO]_2\}^-$ catalyzes the oxidation of alcohol to an aldehyde, which is activated by pyrrolidine grafted on POM to obtain intermediate (**I**), and then enolization of barbiturate reacts with intermediate **I** enolate to form intermediate **II**. After removal of L-Pro-Mn-Anderson from intermediate **II**, 5-aryl barbiturate **7** was generated. Subsequently, L-Pro-Mn-Anderson can activate intermediate **7** to facilitate the reaction with aniline to form intermediates **III** and **IV**, followed by an intramolecular reaction to obtain the target product (Fig. 10B). This catalytic reaction can also be used for a range of electron-rich and electron-deficient aromatic alcohols.

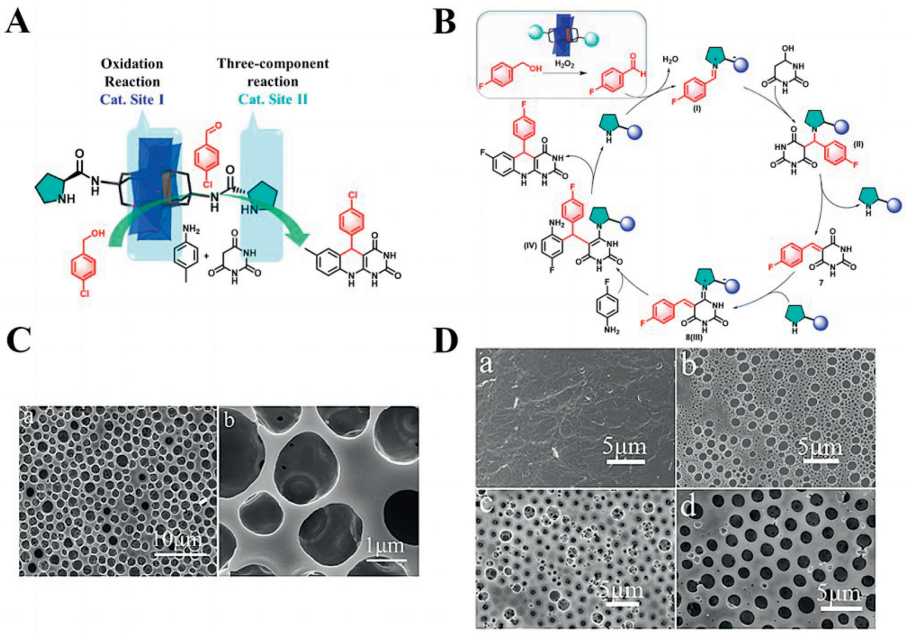

Fig. 10. (A) Schematic presentation of the L-Pro-Mn-Anderson bifunctional molecular catalyst for the one-pot alcohol oxidation/three-component reaction. (B) The proposed mechanism for the one-pot alcohol oxidation/three-component condensation reaction. L-Pro-Mn-Anderson has been simplified for clarity. Reproduced with permission [143]. Copyright 2023, Royal Society of Chemistry. (C) (a) SEM images of the honeycomb structure prepared from 3 mg/mL SEP chloroform solution at low magnification and (b) higher magnification. (D) SEM images of the honeycomb structure prepared at different relative humidities (a) 20%, (b) 40%, (c) 70% and (d) 90%. Other conditions: temperature 25 °C, concentration 3 mg/mL, and with the same spreading volume. Reproduced with permission [147]. Copyright 2018, Royal Society of Chemistry.

As a class of nano-inorganic clusters, POMs have a wide range of application potential [144]. However, many practical applications of POMs rely on the fabrication of POM-based device architectures [145]. Among them, POM-based film preparation has become a favorable method. So far, many fabrication techniques for POM-based composite films have been developed [146]. However, the fabrication of thin films is relatively complex and cumbersome. Therefore, it is necessary to find a simple method to prepare functionalized POMs-based thin film materials. Zhang *et al.* selected $K_7Na_3[Cu_4(H_2O)_2(PW_9O_{34})_2]\cdot 20H_2O$ ($Cu_4(PW_9)_2$), a polyoxophosphotungstate, as the active unit and successfully fabricated $(DODA)_{10}(Cu_4(PW_9)_2)$ honeycomb films in a one-step process (DODA: dimethyldioctadecylammonium) [147]. Firstly, surfactant-encapsulated Polyoxometalates (SEP) complexes with an ordered honeycomb structure were successfully obtained using the well-known respiration pattern method. The magnetically ordered honeycomb-like material was then successfully deposited directly on indium tin oxide (ITO) substrates *via* a SEP chloroform solution (Figs. 10C and D). The cyclic voltammetry response shows the redox coupling of $Cu_4(PW_9)_2$. The high electrocatalytic activity of the modified electrode for the reduction of BrO^{3-} provides a new POM based film material for the field of electrochemistry.

The most important property of POMs is their ability to undergo a variety of reversible redox processes without significant degradation, which makes them an ideal candidate class for a variety of multi-electron catalytic reactions [148]. Importantly, POMs can also be deposited on different surfaces without significantly altering their redox properties [149]. Due to the simple process, mild conditions, and controllable thickness of the immobilized film, the addition of conductive polymer matrix has become the most promising one for the preparation of POM based film materials [150]. Time-coulomb method was used to control the amount of electrodeposited POM and X-ray photoelectron spectroscopy (XPS) was used to verify the elemental composition, which confirmed the integrity of POM in polypyrrole film. The organic-inorganic composite films were electrochemically characterized by cyclic voltammetry and AC impedance, and the electrocatalytic function showed comparable stability at pH 4.5, comparable to the LOD and linearity ranges of other electrocatalytic devices. The limit of detection (LOD) of the prepared films was up to 0.5 μmol/L.

Metal-organic framework (MOFs) thin films are considered attractive candidates for various electrocatalytic applications to achieve high current densities [151]. However, the electrical insulating nature of most MOFs and their poor chemical stability in water hinder their application in electrocatalysis [152]. Ho *et al.* assumed that zirconium based MOFs with good stability in water and appropriate pore size were selected as porous carriers to fix the water-soluble and catalytically active POMs to form a water-stable multiphase electrocatalyst [153]. In electrochemical processes, a POM-based catalyst with redox activity should enable redox jumps to transport charge in Zr-MOFs. Therefore, they chose to incorporate a redox-active vanadium-based POM, sodium decvanadate ($Na_6V_{10}O_{28}$), into the porphyrin Zr-MOF, NU-902, by impregnation, continuous washing and solvent exchange. Due to the electrostatic interaction between the hex zirconium node and POM, and the fact that the size of the decvanadate conforms to the one-dimensional channel of NU-902, the $[V_{10}O_{28}]^{6-}$ anion can be synthetically immobilized in Zr-MOF. The resulting material, $V_{10}O_{28}$@NU-902, retains the crystallinities of NU-902 and has Brunauer-Emmett -Teller (BET) surface areas of 1190 m^2/g. It exhibits redox hopping behavior in aqueous electrolytes and displays electrocatalytic activity for the oxidation of dopamine (DA).

Electrocatalysis utilizes electricity as a clean redox agent to achieve electrically driven chemical reactions, providing new reaction modes and many advantages for sustainable green preparation of pharmaceutical compounds [154]. Although electrochemical methods are often used to control the selectivity of the reaction, they often require the use of environmentally harmful solvents and require large amounts of supporting electrolytes that may be difficult to remove after the completion of the electrolysis, so electrocatalytic methods cannot be easily generalized. The combination

of these two topics, POMs and electrochemistry, is an exciting and interesting area of research that holds great promise for future directions in drug synthesis [113].

6. Conclusion and perspectives

Chemical synthesis plays a key role in research and development in the pharmaceutical field. Green chemistry aims to guide the development of more sustainable synthetic methods and chemical processes and to adapt traditionally existing procedures by making them both economically and environmentally acceptable. Unfortunately, the synthesis of drugs often involves the use of many toxic and expensive chemicals and solvents that consume energy and are accompanied by the generation of large amounts of waste, exposing the pharmaceutical industry to serious environmental problems. Properties such as POMs' structural stability, ease of modification, and versatile redox properties make POMs-based nanoplatforms have unlimited potential in the field of drug synthesis.

(1) POMs have great potential for thermocatalysis synthesis of green drugs, such as the application of POMs to catalyze the synthesis of imine and amide groups, in many important drugs and drug intermediates. Compared with other common acid-base and metal catalysts, POMs exhibit excellent selectivity and high catalytic efficiency in catalysis, with fewer and environmentally friendly by-products in the synthesis of drugs. POMs can be rationally designed on molecular and atomic scales to regulate acidity, redox potential, and enhanced stability, among others. However, some POMs catalysts synthesize reactions under more demanding conditions in which POMs are difficult to stabilize, which hinders their further application, so great efforts are still needed to overcome these problems. Future research directions for POMs catalysts in organic synthesis include, but are not limited to, structural design and optimization of catalytic performance. The catalytic activity and selectivity of POMs catalysts can be further improved by modulating their structures and components. In addition, the carrier material of polyacid catalysts is also a research hotspot which can improve the stability and recyclability of the catalysts by choosing suitable carrier materials.

(2) The use of POMs as catalysts for the electrocatalytic synthesis of drugs overcomes the harsh conditions required by traditional redox methods such as high temperature and high pressure, and can be carried out under mild conditions. Importantly, the redox potentials of the compounds can be precisely matched by adjusting the conditions of electrode materials, current, and working potential, and even selective reactions can be realized to obtain the target products. Novel POMs catalysts composed of POMs with inorganic ligands and organic ligands are often stable and capable of producing synergistic catalytic effects. However, the structure, function, and stability models of complex catalytic materials still need to be further explored.

(3) POMs catalysts have been used to synthesize a variety of small molecule organic compounds by photocatalytic means and are now being applied to the synthesis of drug molecules. Although the progress of POMs photocatalysis for the synthesis of drug molecules has been slow, POMs have been successfully used to replace noble metal catalysts in the photocatalytic synthesis of imines, anilines, and pyridines, among others. Compared with the traditional way of synthesizing drug molecules using precious metal catalysts, POM, as an inexpensive catalyst, can solve the problem of expensive catalysts, as well as improve catalyst utilization and realize one-step reactions. Of course, the use of POMs catalysts faces many challenges and requires researchers to further explore different applications of POMs-based catalysts for photocatalytic green drug synthesis in order to synthesize drug molecules more efficiently and greener. Currently, POMs are not widely used in drug macromolecule synthesis, and in the future, it is expected to develop more POMs catalysts for photocatalytic drug synthesis applications.

(4) Nowadays, the innovation of green and friendly modern drug synthesis methods, POMs catalysts are also developed continuously. Whether in traditional organocatalytic drug synthesis or flow chemical synthesis, POMs catalysts play a great role in drug synthesis by virtue of their adjustable physicochemical properties and excellent catalytic performance synergizing with the synthesis method's own advantages. In the field of biocatalysis, POMs catalysts can act as natural enzymes and are promising alternatives for mimicking enzyme activity. In the future, POMs catalysts are expected to be added to other more mature green synthesis processes to play a greater role.

Declaration of competing interest

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

CRediT authorship contribution statement

Yiming Ju: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Yao Cheng:** Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Data curation. **Haiyang Wang:** Conceptualization, Formal analysis, Supervision, Writing – review & editing. **Dejin Zang:** Conceptualization, Project administration, Supervision, Validation, Writing – review & editing.

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