

Review

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Frameworks-Enhanced Electrochemiluminescence in Biosensing

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Review

Frameworks-Enhanced Electrochemiluminescence in Biosensing

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Abstract: Electrochemiluminescence (ECL) has attracted increasing concerns owing to its intrinsic advantages of high sensitivity, good stability, and low background. Considering the fact that framework nanocrystals such as metal-organic frameworks and covalent organic frameworks have the accurate molecular structures, a series of frameworks-based ECL platforms are developed for decoding the emission fundamentals. The integration of fluorescent ligands into frameworks significantly improves the ECL properties due to the arrangement of molecules and intramolecular electron transfer. Moreover, the frameworks various topology can be easily functionalized with the recognition elements to trace the targets for signal readout. These ECL enhancement strategies lead to a series of sensitive analytical methods for protein biomarkers, DNA, small biomolecules, and cells. In this review, we have summarized recent advances in various functions of frameworks during ECL process, and constructions of frameworks-based ECL platforms for biosensing. The frameworks-based ECL nanoemitters and the enhancement mechanisms show both theoretical innovation and potential applications in designing ECL biosensing systems.

Keywords: electrochemiluminescence; frameworks; biosensing; nanoemitters

1. Introduction

Electrochemiluminescence (ECL) is a classic and powerful analytical technique involving a redox process at electrodes where excited states are electrochemically generated and emit light [1,2]. Benefitting from its unique light-free luminescence mechanism, ECL has many advantages for analysis, such as high sensitivity, good stability, and low background [3]. Nowadays, ECL has been widely applied in the areas of environmental monitoring [4], cell sensing [5], imaging [6], food [7], and water safety [8]. Over several decades of research, the variety of ECL emitters has substantially increased, and they can be broadly classified into inorganic system (such as Ir or Ru complexes), organic system (such as luminols), and semiconductor nanomaterials [9]. Recently, several novel nanomaterials have been used as luminophores in ECL, such as Au nanomaterials [10], quantum dots [11], and frameworks [12]. The combinations of ECL techniques and these new materials broaden the scope of ECL applications.

Frameworks containing metal-organic frameworks (MOFs), covalent-organic frameworks (COFs), and hydrogen-bonded organic frameworks (HOFs), have been developed rapidly since the 21st century [13,14]. Owing to their flexible, synthetically controllable and adjustable structure, frameworks have been utilized in the various areas such as energy storage, sewage treatment, gas separation, catalysis and biosensing [15]. Also, frameworks are gradually regarded as one of the most promising nanomaterials in ECL assays. Different from other ECL luminophores like metal complexes and quantum dots, predesigned structures of frameworks make them more suitable and efficient in ECL processes. For example, Yin's group designed an ECL-active MOF by using ruthenium complex as ligand and more intense ECL emission was observed with the aid of graphene oxide [16]. By combining predesigned structure with post-modification, frameworks provide various strategies to regulate their ECL signals for adapting the requirement. Furthermore, the structures of frameworks are utilized dexterously to create novel ECL enhancement mechanisms for developing sensitive and stable analytical methods. Overall, the variation of ECL signal highly depends on the

optoelectronic properties of frameworks, which are adjustable by designation or post-modification [17].

Therefore, integrating the frameworks and ECL methods is of great significance to construct high-performance biosensing platforms. In recent years, the roles of frameworks in ECL processes develop rapidly with multifunctions in biosensing. Initially, frameworks were used as carriers of classic luminophores or catalysts to accelerate the ECL reactions, but they later became ECL emitters for biosensing platform establishment, achieving successful analysis of proteins, nucleic acids, small molecules and cells. In this review, the various functions of frameworks in ECL emission are first analyzed to show the rapid development in this area (Figure 1). Then, the frameworks-enhanced ECL biosensing applications in recent years are introduced and analyzed. Finally, the perspectives and potential issues are proposed, which may guide the great development of framework-based ECL biosensing systems.

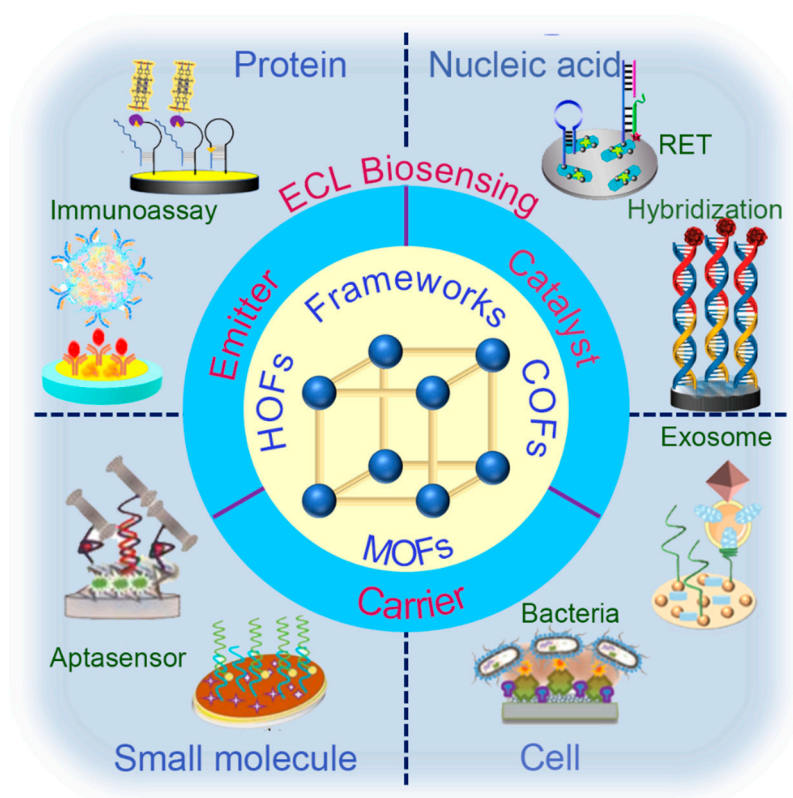


Figure 1. Schematic illustration of roles of frameworks in ECL processes and their ECL applications in biosensing.

2. The Roles of Frameworks in ECL Processes

Although the combination of frameworks with ECL demonstrates the great potentials in signal readout, low conductivities and inert electrochemical properties of frameworks may result in poor sensing performance. Therefore, frameworks were often used as carrier of efficient ECL emitters like quantum dots (QDs) or Ru complexes, or catalyst to strengthen ECL emission during the initial period. After the report of the electroactive MOF [12], frameworks gradually began to be used as the emitters in ECL processes and various ECL-active frameworks were extensively applied in biosensing with several emerging signal amplification strategies.

2.1. The Carriers of ECL Luminophores

The outstanding features of frameworks, such as adjustable reticular structure, large surface area, tunable pore sizes and functionalized sites make them competent to be used as carrier. In early

report, classic ECL luminophores (Ru complexes, luminol and QDs et al.) were integrated with frameworks by encapsulation or post-modifications.

Encapsulation of ECL luminophores into frameworks is a widely applied strategy to make frameworks better ECL performance. Through introducing guest materials, the host frameworks get the improved ECL efficiency while largely maintain their own original properties. Therefore, encapsulation gives a flexible way to prepare frameworks with promising ECL activity. In view of porous structure of frameworks, Qin et al. prepared Ru(bpy)₃²⁺-functionalized MOF thin films using the self-assembly approach (Figure 2a). The plenty of Ru(bpy)₃²⁺ molecules in Ru-MOF films showed intense ECL emission and excellent behavior in detection of the human heart-type fatty-acid-binding protein [18]. Also, classic luminol-based frameworks are conducted through this method. Tang et al. synthesized porous Zn-based MOF, which loaded a large amount of luminol by encapsulating into its pores. The resulting Zn-MOF@luminol as the signal probe achieved a strong ECL signal for detecting concanavalin A [19]. Furthermore, luminophores with large sizes, such as QDs or g-C₃N₄, can be encapsulated in frameworks with high surface areas. As shown in Figure 2b, Fe(III)-MIL-88B-NH₂@ZnSe was successfully prepared via one pot method. By using Fe(III)-MIL-88B-NH₂ as efficient coreaction accelerator, the biosensor realized the sensitive detection of squamous cell carcinoma antigen in human serum [20]. Qin et al. designed a triethanolamine-functionalized MOF on graphene oxide nanosheets to accomplish a rapid label-free ECL immunosensor for detection of human copeptin [21].

On the basis of porosity and large surface area, frameworks are considered to be suitable for post-modification with functional materials to obtain specific properties [22], which can be conducted through covalent or noncovalent bonding. For example, Wang et al. combined zeolitic imidazolate frameworks and luminol-capped Ag nanoparticles to form a luminol-AgNPs@ZIF-67 system via electrostatic interaction, which had ~115-fold enhanced ECL comparing to the luminol system [23]. Besides, QDs were merged onto MIL-53 through noncovalent adsorption and the resulting MIL-53@QDs platform demonstrated the large ECL intensity enhanced by surface plasmon resonance process between AuNPs and CdS QDs for kanamycin and neomycin biosensing [24]. Furthermore, Liu's group developed a nanoreactor based on Ru(bpy)₃²⁺-doped nanoporous zeolite nanoparticles (Ru@zeolite) [25], in which frameworks not only served as carrier of Ru complexes through post-modification, but also confined spatially for the efficient collision reactions *in situ* ECL reactions.

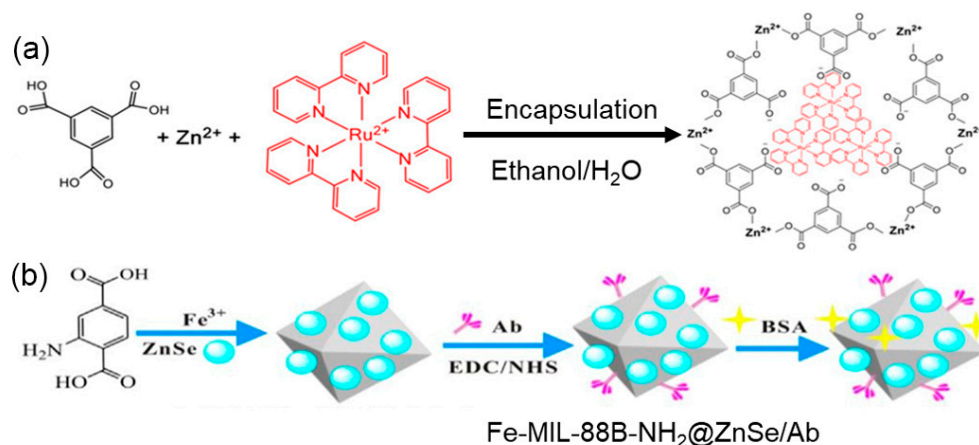


Figure 2. (a) Schematic diagram of synthesis of (Ru(bpy)₃²⁺)-functionalized MOF (Ru-MOF). Reproduced from [18] with permission from American Chemical Society. (b) Illustration for the construction of Fe(III)-MIL-88B-NH₂@ZnSe/Ab. Reproduced from [20] with permission from Elsevier.

2.2. The Catalyst in ECL Processes

By integrating catalytically active components, frameworks have been utilized as electrocatalysts, such as oxygen reduction reaction and CO₂ reduction for a long time [26,27]. More intense ECL emission will be observed when decisive elementary reactions are accelerated during

ECL process. For instance, Zn tetrakis(carboxyphenyl)-porphyrin (TCPP) linkers in MOF-525 acted as ECL active centers to facilitate the conversion from dissolved oxygen to singlet oxygen for enhanced ECL (Figure 3a). Based on MOF-525-Zn as signal amplifying probes, an ultrasensitive ECL sensor was proposed for detection of protein kinase A activity with a linear range from 0.01 to 20 U mL⁻¹ and detection limit of 0.005 U mL⁻¹ [28]. Furthermore, the inorganic Zr–O clusters of MOF-525 were simultaneously served as the recognition sites of phosphate groups for specific bioanalysis.

On the other hand, MOFs was utilized as a coreactant accelerator to enhance the ECL of CdTe QDs through accelerating the generation of sulfate radical anion (SO₄^{•-}) which was critical in producing excited states of QDs, further realizing ultrasensitive bioanalysis of cardiac troponin-I antigen [29]. Similarly, the 2D Fe-Zr metal-organic layers were applied for the construction of ECL immunosensor by utilizing its peroxidase-like activity, which could effectively enhance the ECL signal of luminol through H₂O₂ catalysis [30]. Additionally, Song et al. designed a signal-amplified ECL sensor chip via by synergistic catalysis of Au–Pd bimetallic nanocrystals and mixed-valence Ce-based MOFs for fast reduction of dissolved O₂ (Figure 3b). By integrating the three-electrode detection system into the self-assembled microfluidic chip, the developed sensor showed high sensitivity for procalcitonin detection with the automation and portability of the detection process [31]. In a word, by introducing active catalytic sites or utilizing intrinsic properties, frameworks have nanozyme-like functions for ECL catalytic enhancement.

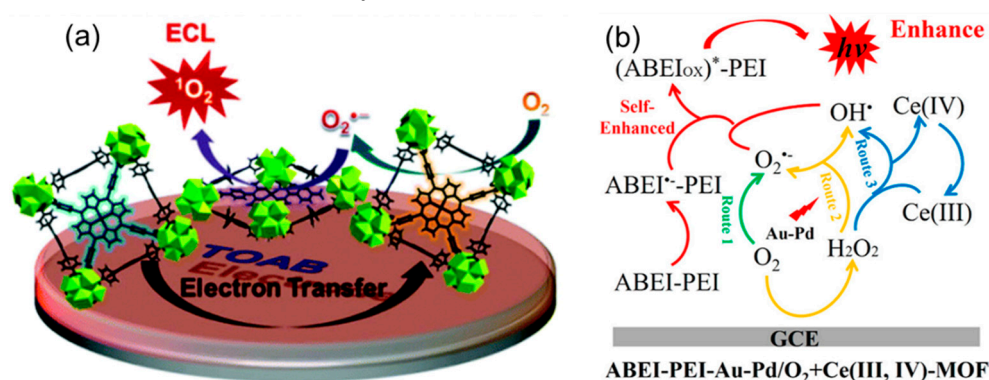


Figure 3. (a) Schematic illustration for the ECL catalysis mechanism of singlet oxygen based on MOF-525. Reproduced from [28] with permission from Royal Society of Chemistry. (b) Supposed ECL catalysis mechanism for Au–Pd/O₂ + Ce(III, IV)-MOF system. Reproduced from [31] with permission from American Chemical Society.

2.3. ECL nanoemitters

Considering the structures of framework units, introducing ECL luminophores as linkers is thought to be a proper approach to establish framework-based ECL emitters. Due to the intrinsic structural features, framework-based emitters are considered to be promising material for ECL biosensing based on the combining advantages of framework emitters and ECL techniques [32]. Because of efficient energy migration [33], Ru complexes-based linkers were applied for designing ECL-active frameworks since 2010. Ru(II) bipyridine (Ru(bpy)₃²⁺) derivatives as ligands can be synthesized into the frameworks by coordination with metal ions or clusters [34]. For example, the functionalized Ru-based MOF nanosheets compositing of carboxyl-rich tris(4,4'-dicarboxylic acid-2,2'-bipyridyl) Ru(II) and Zn²⁺ nodes, exhibited good water solubility and excellent ECL performance (Figure 4a). By employing Ru-MOF as ECL probe, a “signal-on” ECL immunosensor was designed for selective detection of cardiac troponin I in the range from 1 fg/mL to 10 ng/mL [35]. However, Ru complexes are costly in adjusting their structures and large in steric size, which inevitably restrict its application in direct framework synthesis. In fact, Ru complexes are more often modified onto frameworks through a post-synthesized route which make frameworks work like carrier rather than nanoemitter [36,37]. Meanwhile, other ECL-active organic ligands, such as porphyrin derivative, perylene-3,4,9,10-tetracarboxylate and 9,10-anthracene dibenzoate (DPA), were utilized in

constructing MOF emitters for the proprotein convertase subtilisin/kexin type 9, microRNAs and MCU1 detection, respectively [38–40].

Inspired by aggregation-induced emission (AIE) luminophores which show stronger photoluminescence in aggregated state than that of the isolated one [41,42], frameworks constructed by AIE molecules become attractive in ECL sensing. Typically, tetraphenylethylene (TPE)-based AIEgens are most reported in recent researches thanks to designable molecular structures. For instance, a fiber-like MOF, synthesizing by coordination of Zn^{2+} and 1,1,2,2-tetrakis(4-(pyridin-4-yl)phenyl)ethane (TPPE), showed more intense ECL emission than its ligand TPPE in presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) (Figure 4b and 4c). More significantly, different from the constant ECL intensity using tri-*n*-propylamine (TPrA) coreactant, DABCO exhibited time-dependent ECL intensity due to the intrareticular electron transfer through coordination interaction between DABCO and Zn^{2+} [43]. In another work, Wei's group synthesized a dumbbell plate-shaped MOF consisted of 1,1,2,2-tetra(4-carboxylbiphenyl)ethylene and Zr(IV) cations, which was utilized as ECL tag for neuron-specific enolase detection by sandwich-type immunoreaction [44]. Besides, two-dimensional AIEgen-based MOF was also fabricated into efficient ECL biosensing platform [45], which restricted the intramolecular free rotation and vibration of these ligands and then reduced the non-radiative transition. The combination of AIE ligands and frameworks paved a potential way for better ECL sensors, that is, the large surface area and porous properties of MOFs made ECL reactions more effective while the AIE molecular motion would be restricted by the rigid MOF structure, which was theoretically beneficial to AIE emission [46].

Identically, the luminophores can be introduced into frameworks by serving as the ion nodes. Due to good photoluminescent emission and successful applications in biosensing [47], self-luminescent lanthanide MOFs (Ln-MOFs) are considered promising luminophores in ECL reactions. Dai's group synthesized La^{3+} -BTC MOFs as ECL emitter and highly active reactor simultaneously to construct a gene sensor. With the assistance of crystal violet, good performance toward p53 gene analysis was gotten through co-quenching effect mechanism [48]. Furthermore, Eu-based Ln-MOFs were prepared with 5-boronoisophthalic acid and Eu (III) ions. ECL emission mechanism was identified to be that 5-bop was excited with ultraviolet photons to generate a triplet-state, which then triggered Eu (III) ions for red emission. The Eu-MOFs showed great sensitivity in ECL immunoassay for Cytokeratins21-1 detection [49].

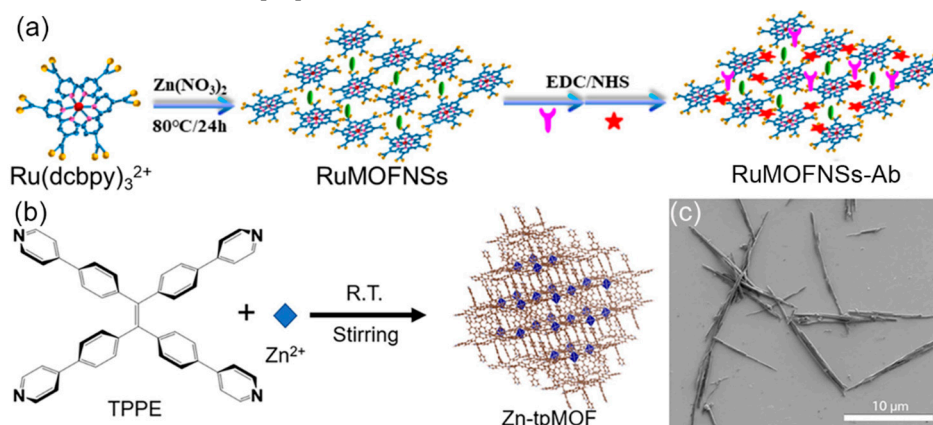


Figure 4. (a) Schematic illustration for the fabrication process of Ru-MOF nanosheet. Reproduced from [35] with permission from American Chemical Society. (b) The synthesis of and (c) SEM image of Zn-tpMOF. Reproduced from [43] with permission from Elsevier.

In order to obtain better biosensing performance, higher ECL efficiency is urgently needed. Conventional coreactant ECL is convenient in operation but inefficient in electron transfer due to intermolecular route. Thanks to a shortened pathway of mass transport and electron transfer, intramolecular electron transfer process is recognized as a promising solution [50]. Inspired by this theory, a mixed-ligand MOF (m-MOF) was designed for proof of concept by integrating with two ligands, one as a luminophore and the other as a coreactant, on one metal node for self-enhanced ECL

[51]. As shown in Figure 5a and 5b, the resulting m-MOF had highly ordered crystalline unit proved by comparing of experimental PXRD pattern and theoretical simulation. Then, m-MOF exhibited greatly enhanced ECL compared to its ligand and Zn-DPA MOF, indicating high efficiency of intrareticular charge transfer process (Figure 5c). Finally, the proposed stepwise ECL mechanism of m-MOF was given as a result of local excitation in the DPA unit, which was identified through density functional theory calculation (Figure 5d). Overall, the mixed-ligand approach successfully shortens the pathway of charge transfer, providing a new idea in ECL platform design.

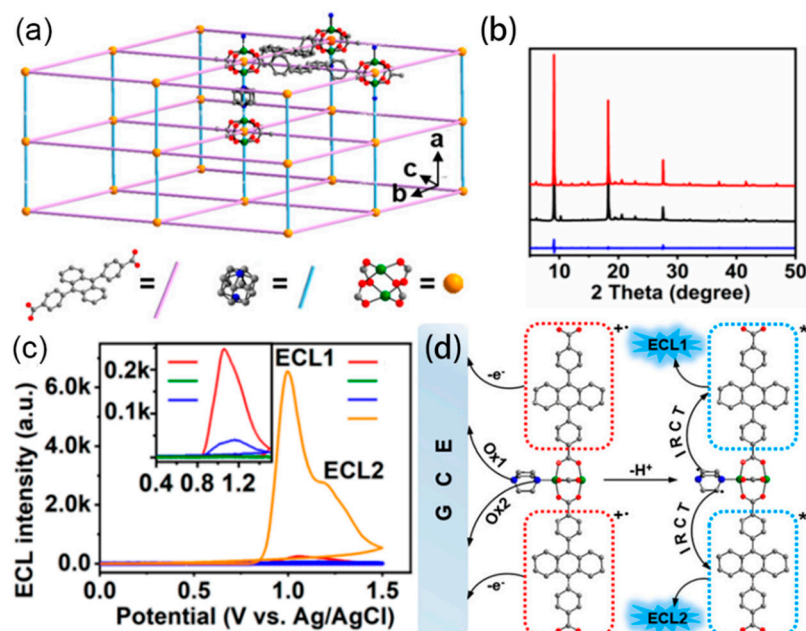


Figure 5. (a) 3D structure of m-MOF. (b) PXRD pattern of m-MOF (black), simulated result (red), and their difference (blue). (c) ECL curves of DPA-modified GCEs (red) in presence of DABCO, and of DPA- (green), s-MOF- (blue) and m-MOF (orange)-modified GCEs in 0.1 M PBS. (d) Stepwise ECL mechanism of m-MOF. Reproduced from [51] with permission from American Chemical Society.

As a novel member of frameworks, COFs gradually became fascinating in ECL applications. Firstly, Li et al gave a general advice on how to design COFs with highly efficient ECL [52]. Meanwhile, Lei's group provided detailed mechanism on enhanced ECL of COFs [53]. Based on donor-acceptor (D-A) units, a luminescent *t*-COF was synthesized as ECL emitter by integrating triazine and triphenylamine as donor and acceptor units in the reticular skeleton, respectively (Figure 6a). Revealed by PXRD analysis, the *t*-COF showed crystalline structure with diffraction peaks at $2\theta = 4.4, 7.7, 8.9, 11.8$ and 22.5° , which were assigned to the 100, 110, 200, 210, and 001 facets, respectively (Figure 6b). Compared to other two COFs, *t*-COF had magnificent ECL performance in TPrA/PBS (Figure 6c), indicating the importance of D-A structure in *t*-COF during ECL reaction. The simulated charge density difference between 1st excited state and ground state of COF demonstrated electron density loss on the triazine units and electron density gain on the triphenylamine units, confirming the charge transfer between triphenylamine and triazine units (Figure 6d). Furthermore, the efficient charge transfer could be identified by the movement of HOS/LUS to the Fermi level when holes/electrons were doped (Figure 6e). Finally, the competitive oxidation mechanism was given out that triazine unit gained electrons from the TPrA[•] while triphenylamine unit was oxidized by oxidative TPrA^{•+} (Figure 6f, left) or electrode (Figure 6f, right), leading to dual ECL emissions.

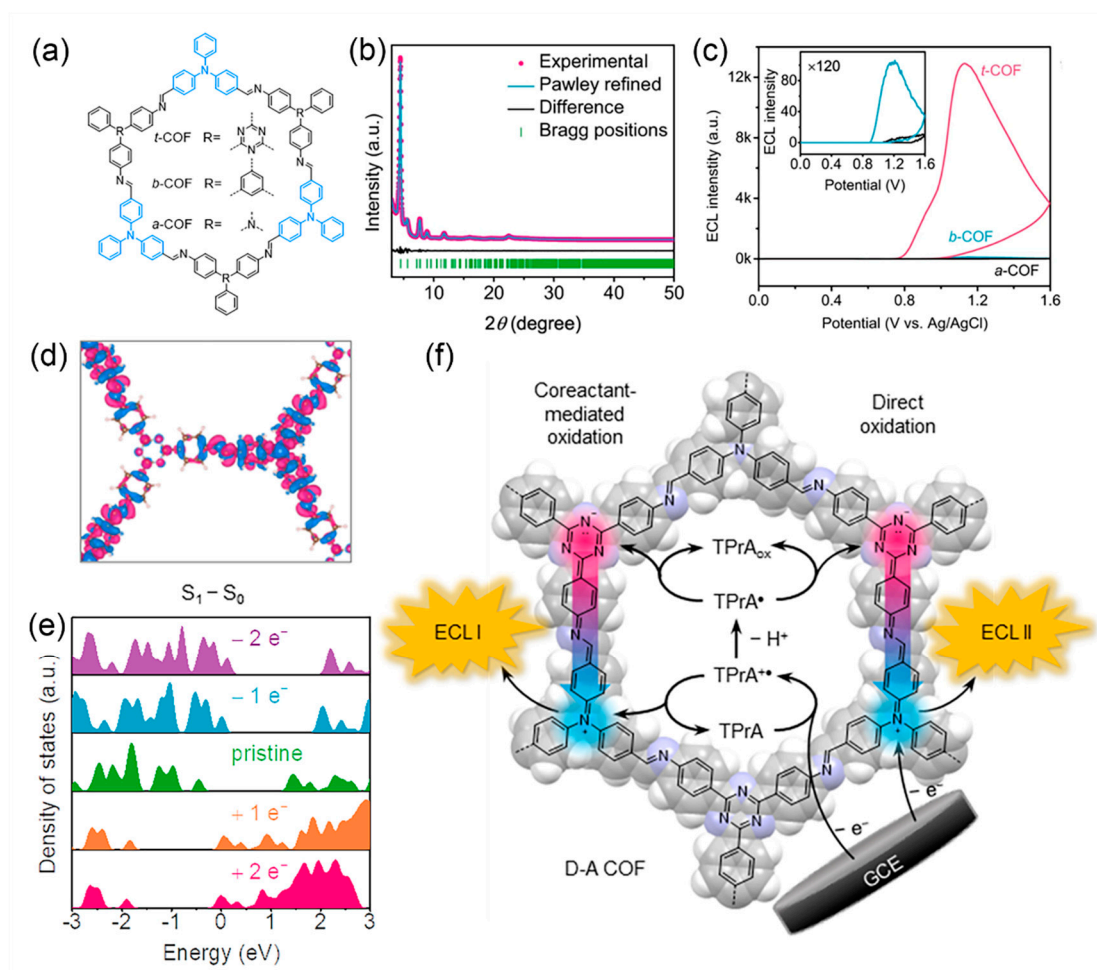


Figure 6. (a) Structure of TFPA-based COFs. (b) PXRD patterns of *t*-COF and their difference. (c) ECL curves of three COFs modified GCEs in presence of 20 mM TPrA. (d) The difference charge density between 1st excited state and ground state of *t*-COF. (e) Density of states of *t*-COF doped with different electron/hole numbers. (f) Competitive oxidation mechanism via intrareticular charge transfer. Reproduced from [53] with permission from Nature Publishing Group.

HOFs comprised solely of pure organic or metal–organic units connected by intermolecular H-bonds, were also found to have ECL enhancement properties comparing to their monomers. Zhang et al. synthesized a triazinyl-based HOF through N...H hydrogen bond self-assembly aggregation. The resulting HOF showed highly enhanced ECL efficiency (21.3%) relative to the Ru(bpy)₃²⁺ standard, and was applied for ultrasensitive kanamycin biosensing [54]. Benefiting from the densely stacked structure, Lei's group proposed HOFs-based ECL enhancement mechanism via the intrareticular electron coupling (IREC) pathway [55]. Utilizing multiple H-bonds and π -interactions, HOF-101 with 1,3,6,8-tetra(4-carboxylphenyl)pyrene as ligand was synthesized (Figure 7a). Compared with 1,3,6,8-tetracarboxypyrene-based HOF-100 and bare electrode, HOF-101 modified GCE showed significantly enhanced ECL in presence of TPrA due to the IREC effect (Figure 7b). Through model simulation, the charge density difference between S₁ and S₀ of HOF-101 was illustrated (Figure 7c), showing mutual electron density depletion and accumulation of vertical stacking units. This IREC pathway in HOF-101 achieves ECL enhancement by accelerating electron transfer between anion radicals and cation radicals (Figure 7d).

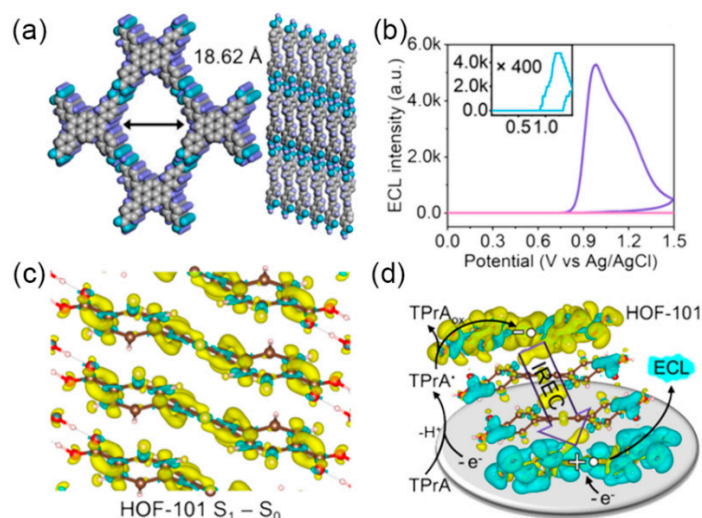


Figure 7. (a) Pore structure and stacking of HOF-101. (b) ECL curves of HOF-101 (purple), HOF-100 (blue) and bare electrode (pink) in presence of 20 mM TPrA. (c) The difference of charge density distribution between S_1 and S_0 of HOF-101. (d) IREC-driven ECL mechanism of HOF-101 with neutral charge density difference. Reproduced from [55] with permission from Royal Society of Chemistry.

3. Framework-Enhanced ECL for Biosensing

Sensitive, specific, and reliable detection of tumor markers is vital for early diagnosis of cancer, which brings hope to human patients for cancer prevention. Based on the unique physical properties, chemical compositions, and functional methods, frameworks-enhanced ECL may provide the ultrasensitive and comprehensive assay for monitoring these markers. By combining with biological tools, the framework-based biosensors can distinguish various biomarkers such as proteins, nucleic acid, cell, and small molecules in clinical analysis.

3.1. Proteins

Proteins are typical biomacromolecules which are generally analyzed through immunoassays. Once a protein is clinically certified as disease-related biomarker for diagnosis, it will get much attention in ultrasensitive detection. For example, to improve survival of patients, the cancer markers are of great significance in guidance of early tumor diagnosis and introducing appropriate targeted therapies [56]. Integrating with highly specific immunoreactions, ECL immunoassays are powerful tools for protein detections. Alpha-fetoprotein (AFP) is a well-known biomarker for diagnosis of liver malignant tumor [57]. Zhao et al. synthesized a bimetallic NiZn MOF nanosheets to amplify cathodic luminol ECL through synergistic effect of the bimetallic catalyst in AFP immunodetection [58]. Li et al. designed a signal-off ECL biosensor for AFP detection by utilizing MnO_2 nanosheet/polydopamine dual-quenching effect towards $\text{Ru}(\text{bpy})_3^{2+}$ -functionalized MOF [59].

Cytokeratin 19 fragment 21–1 is recognized as an essential biomarker of non-small cell lung cancer with high specificity. Wei's group constructed a "signal-on" ECL immunosensor for this biomarker detection by using a copper doped terbium MOF as a luminescent tag, which exhibited strong ECL emission with $\text{K}_2\text{S}_2\text{O}_8$ as a coreactant through electrocatalyzing the reduction of $\text{S}_2\text{O}_8^{2-}$ [60]. In the same group, a biocompatible tris(4,4'-dicarboxylic acid-2,2'-bipyridyl)ruthenium(II) [$\text{Ru}(\text{dcbpy})_3^{2+}$] functionalized γ -cyclodextrin MOF not only served as a carrier to immobilize the detection antibody via a Pd-N bond but also facilitated the electron-transfer rate to amplify the ECL signal [61], providing the ultrasensitive method for early diagnosis of lung cancer.

According to the different roles of frameworks in ECL processes, various signal transductions can be realized in analysis of same targets. For example, a hollow hierarchical MOF was employed as a carrier to graft Ru complexes as a signal amplification with catalytic hairpin assembly strategy [62], showing excellent selectivity and high sensitivity for thrombin determination. By tuning the

reaction time, a series of porphyrin Zr-MOFs (PCN-222) with different specific surface areas, pore sizes, structures, and surface charge states, were synthesized (Figure 8a), which served both as the ECL emitter, coreactant promoter, and a connection in the ECL immunoassay [63]. Furthermore, Xiao's group designed a COF-based ECL biosensor with conductivity- and pre-reduction-enhanced ECL, which overcame the intrinsic poor conductivity of COF [64]. With the aid of signal amplification of the aptamer/protein proximity binding-induced 3D bipedal DNA walker, the constructed ECL sensor realized the supersensitive detection of thrombin (Figure 8b).

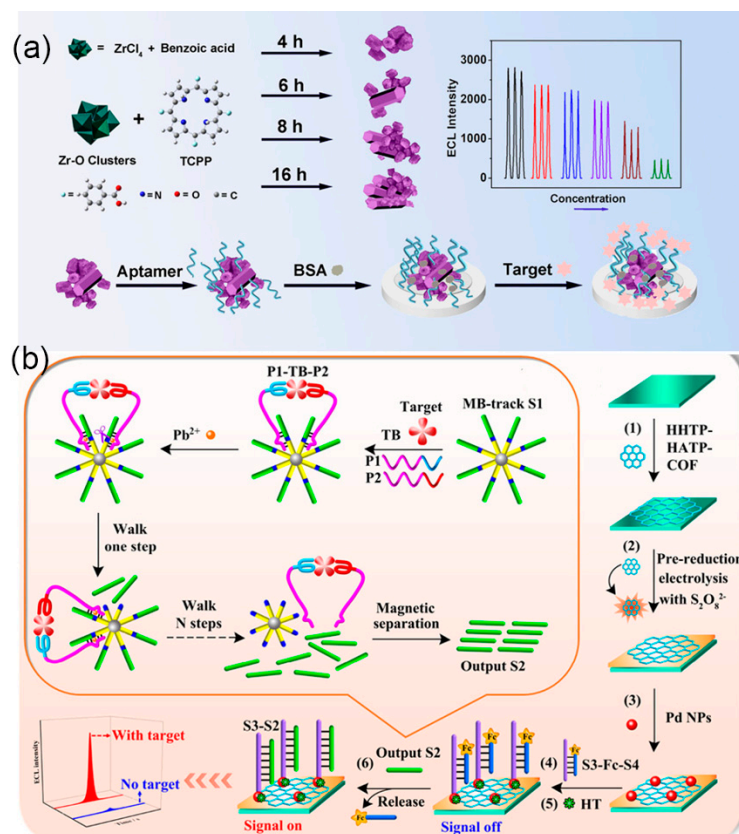


Figure 8. (a) Stepwise construction PCN-222-based thrombin biosensor. Reproduced from [63] with permission from American Chemical Society. (b) Preparation procedure and DNA walker amplification principle of COF-based ECL sensor. Reproduced from [64] with permission from American Chemical Society.

Besides, some proteins can be detected by utilizing their bioactive properties. For example, telomerase can extend the length of specific DNA, indicating the possibility as a signal switch. By monitoring bioactivity, telomerase was already analyzed by several well-designed ECL methods [65,66]. In Lei's group, an ECL telomerase biosensor was proposed with BODIPY-based MOF nanoemitter composed of pyridine-substituted BODIPY, terephthalic acid ligand and Zn nodes (Figure 9a) [67]. The BODIPY-based MOF showed the P6/m trigonal crystal system, reducing over-aggregation of BODIPY for enhanced optical signals (Figure 9b). After elaborative design, the BODIPY-based MOF ECL sensors reached good sensitivity under different telomerase concentration (Figure 9c). The mechanism of this sensor was that the DNA hairpin opened when telomerase appeared, allowing MOF to approach the electrode surface for ECL signal generation (Figure 9d). Integrating with unique immunoreactions, framework-based ECL biosensors become powerful for protein detection (Table 1).

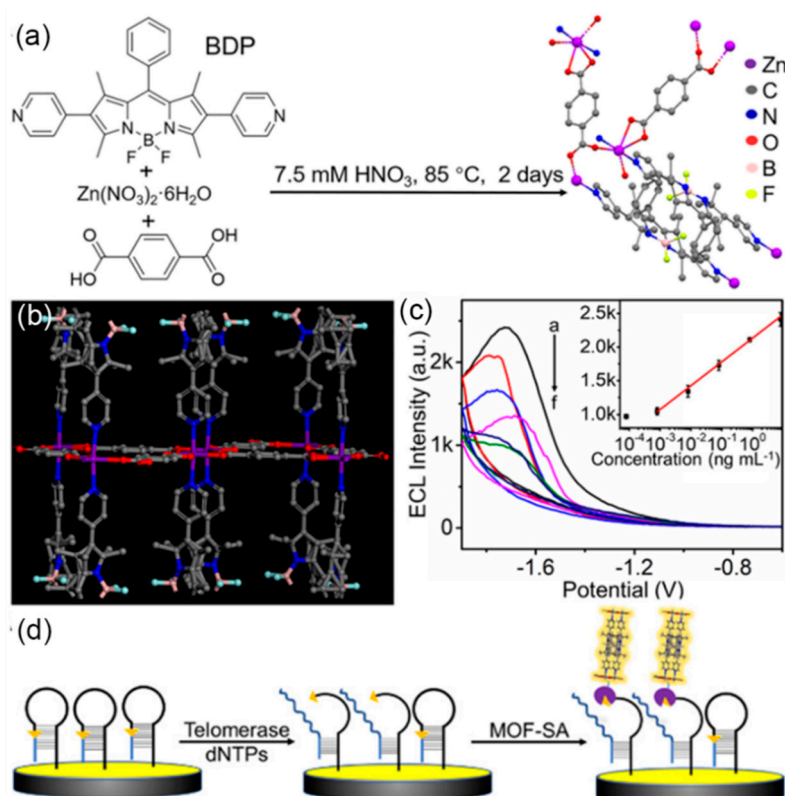


Figure 9. (a) Synthesis of BODIPY-based MOF. (b) The spatial structure of MOFs. (c) ECL response under different telomerase concentrations. (d) Schematic diagram of the stepwise telomerase recognition. Reproduced from [67] with permission from Royal Society of Chemistry.

Table 1. A summary of framework-enhanced ECL for detection of proteins.

Targets	Frameworks	Linear range	LOD	Ref.
AFP	NiZn MOF	0.00005 to 100 ng/mL	0.98 fg/mL	[58]
AFP	$\text{Ru}(\text{bpy})_3^{3+}$ @TMU-3	0.01 pg/mL to 5 ng/mL	10.7 fg/mL	[59]
AFP	Magnetic MOF@CdSnS	1 fg/mL to 100 ng/mL	0.2 fg/mL	[68]
CYFRA21-1	Pd-ZIF-67	0.01 to 100 ng/mL	2.6 pg/mL	[60]
CYFRA21-1	$\text{Ru}@ \gamma\text{-CD-MOF}$	0.1 pg/mL to 50 ng/mL	0.048 pg/mL	[61]
Thrombin	Ru-UiO-66-NH_2	100 fM-100 nM	31.6 fM	[62]
Thrombin	PCN-222	50 fg/mL to 100 pg/mL	2.48 fg/mL	[63]
Thrombin	Conductive COF	100 aM to 1 nM	62.1 aM	[64]
Telomerase	BODIPY MOF	8.0×10^{-4} to 8.0 ng/mL	0.43 pg/mL	[67]
PSA	Ru-MOF	5 pg/mL to 5 $\mu\text{g/mL}$	1.78 pg/mL	[69]
PSA	MOF/Au/DNAzyme	0.5 to 500 ng/mL	0.058 ng/mL	[70]
CEA	N,B-doped Eu MOF	0.1 pg/mL to 1 $\mu\text{g/mL}$	0.06 pg/mL	[71]
NSE	J-aggregated MOF	10 pg/mL to 50 ng/mL	7.4 pg/mL	[72]
Peptide	Cu:Tb-MOF	1.0 pg/mL to 50 ng/mL	0.68 pg/mL	[73]
ALP	π -conjugated COF	0.01 to 100 U/L	7.6×10^{-3} U/L	[74]
D-dimer	RuZn MOFs	0.001~200 ng/mL	0.20 pg/mL	[75]

3.2. Nucleic Acids

In the analysis of nucleic acids, signal amplification techniques such as catalytic hairpin assembly (CHA) [76], rolling circle amplification [77] and hybridization chain reaction [78], have been widely used for a long time. Combined with these powerful tools, a series of framework-based ECL genosensors are being developed rapidly for ultrasensitive nucleic acid detection.

As noncoding RNAs, microRNAs (miRNA) regulate the expression of messenger RNA by binding to complementary sequences. Once alterations in miRNA expression happened, messenger RNA expression would be disrupted, which led to potential oncogenic changes [79]. Therefore, it is crucial to construct reliable and sensitive biosensors for miRNA detection. With the structural development of frameworks, framework-based ECL genosensors for miRNA analysis were extensively investigated. For instance, Wang et al. synthesized Zn MOF as the self-enhanced ECL emitter with dual ligands of DPA and *N,N*-diethylethylenediamine for miRNA-21 detection [80]. DPA was a typical luminophore in ECL while DEAEA could be used as both coreactant and a morphologic regulator, which led to strong and stable ECL emission by efficient intramolecular electron transfer process. Based on CHA and ECL resonance energy transfer, this sensor realized 'signal-off' mode signal amplification in presence of miRNA-21. Similarly, Xue et al. developed the microRNA-141 ECL bioassay by using the dual-ligand MOF which simultaneously contained the luminophore TPE derivative and the coreactant ligand (1,4-diazabicyclo[2.2.2]octane) in the structural unit [81]. Using DNA triangular prism as signal switch to detect microRNA-141, this ECL biosensor achieved the low detection limit at the level of 22.9 aM. Furthermore, a dual-wavelength multifunctional ECL biosensor was established for rapid simultaneous detection of dual targets miRNA-141 and miRNA-155 [82]. As shown in Figure 10a, the Zr MOFs@PEI@AuAg nanocomposite exhibited the intense and stable dual-wavelength ECL emissions. Since ECL emissions of the nanocomposite at two wavelengths of 535 nm and 644 nm were both quenched by resonance energy transfer, this sensor achieved good linear relation for miRNA analysis at two different wavelengths (Figure 10b). The experiment of ECL stability showed low signal change, indicating well accuracy and convincing stability in simultaneous detection of miRNAs (Figure 10c). Besides, classic DNA walker-based signal amplification strategy is also used for MOF sheet-based ECL sensor in the detection of oral cancer overexpressed 1 gene [83].

To overcome intrinsic low conductivity in MOFs, a conductive NiCo bimetal-organic framework nanorod was successfully applied in miRNA-141 detection, broadening the horizon of conductive MOFs in ECL sensing application [84]. Furthermore, with the long-range orderly arrangement and effective intramolecular charge transfer, a pyrene-based sp² COF was synthesized as an efficient ECL emitter via polycondensation of tetrakis(4-formylphenyl)pyrene and 2,2'-(1,4-phenylene)-diacetonitrile. Because of topologically linking of pyrene luminophores and aggregation-induced emissive luminogens, the luminescent COF showed strong and stable ECL emission [85], leading to a highly sensitive microRNA-21 biosensor.

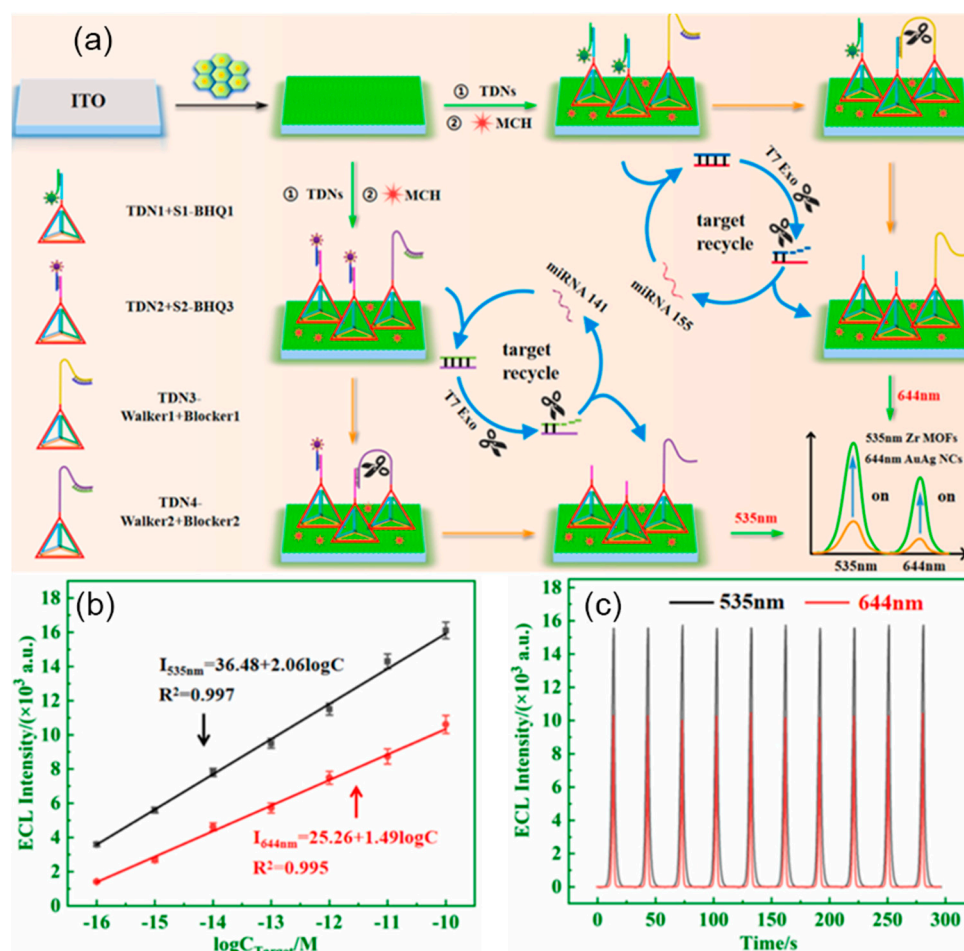


Figure 10. (a) Schematic illustration of ECL biosensing platform based on Zr MOFs@PEI@AuAg nanocomposite for simultaneous detection of dual microRNAs. (b) Plot of the ECL intensity as a function of the logarithm of target miRNAs concentration at 535 nm and 644 nm. (c) ECL signal stability. Reproduced from [82] with permission from Elsevier.

As great threat to health, virus also get much attention in ultrasensitive detection. For instance, Zika virus, a member of the Flaviviridae family virus, are suspected to be associated with severe congenital malformations [86]. Mao's group quantified Zika virus based on Zr-based metal-organic gel and Fe-MIL-88 MOFs as electrode matrix and nanotag, respectively [87]. The double quenching effect originated from Fe-MIL-88 MOFs as both an ECL acceptor and metal active centers to consume co-reactant, resulted in distinct turn-off signal in presence of virus. On the other hand, Shan's group designed 2D MOF with an excellent ECL performance by combining the photosensitizer ZnTCPP and the electroactive $[\text{Co}_2(-\text{CO}_2)_4]$ secondary building units for Sars-Cov-2 gene analysis [88]. The ECL sensor achieved rapid nonamplified detection of the RdRp gene of SARS-CoV-2 with an extremely low limit of detection (30 aM). Overall, by integrating appropriate frameworks with well-designed DNA sequences, these above methods show great performance in nucleic acids analysis, which expand the application of frameworks in biosensing.

3.3. Small molecules

Comparing to traditional analytical methods like chromatography and enzyme catalysis, frameworks-based ECL methods are more sensitive and convenient for small molecule detection. For the determination of small molecules, utilizing specific recognition between aptamer and target is the most common strategy. For instance, the transduction of aptamer configurations alters the distance between signal promoter and ECL luminophores, resulting in signal change by introducing target molecules (Figure 11a). The Plasmon-enhanced ECL aptasensor displayed highly sensitive detection

for lincomycin [89]. Based on suitable aptasensor, a wide range of molecules can be efficiently detected, such as kanamycin [90], sulfadimethoxine [91] and isocarboxiphos [92].

Based on the quenching effect between MOF radicals and oxidized dopamine (Figure 11b), dopamine can be analyzed without the aid of aptamer [43]. This hindrance to ECL was highly relevant to dopamine concentration, and then was applied to construct an ECL method for highly sensitive detection dopamine in serum samples (Figure 11c). Similarly, uric acid [93], rutin [94] and deoxynivalenol [95] can also be directly measured by frameworks-based ECL sensors. Besides, metal ions with potential harm for human health are generally analyzed by inductively coupled plasma-mass spectrometry, ion chromatography and atomic absorption spectroscopy, requiring expensive instruments and staff costs. The inhibition effect of metal ions towards ECL makes them detectable through well-designed frameworks-based ECL sensors [96].

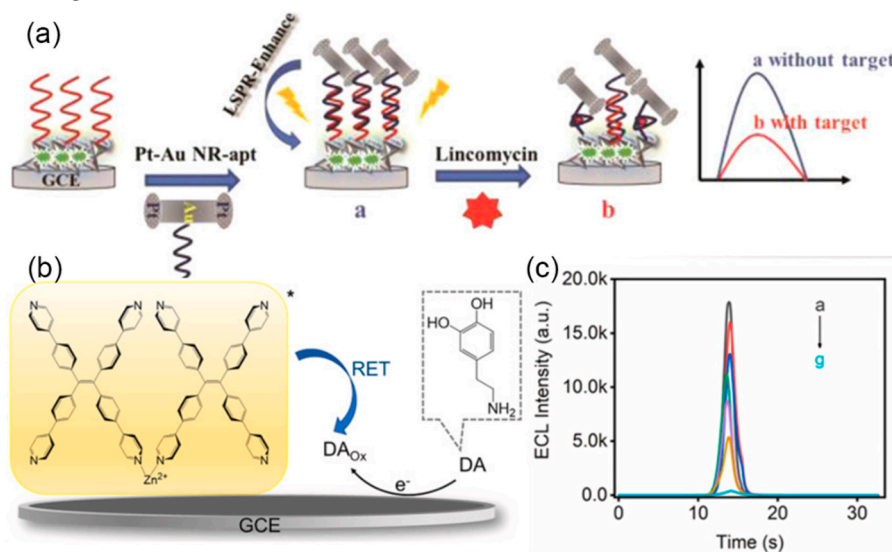


Figure 11. (a) Stepwise illustration of Eu MOF-based aptasensor for lincomycin detection. Reproduced from [89] with permission from American Chemical Society. (b) Quenching mechanism of dopamine ECL detection. (c) Variation of ECL intensity at different concentrations of dopamine: 0, 0.01, 0.1, 1, 10, 100, and 1000 μM from a to g. Reproduced from [43] with permission from Elsevier.

3.4. Cellular analysis

With the combination of ECL-biotechnology, framework-based ECL sensors for cell-related analysis gradually emerge. Typically, Liu's group realized single molecule movement visualization at the cellular membrane through capturing photoluminescence signals of the designed Ru(bpy)₃²⁺ embedded MOF complex (RuMOFs) [97]. With the aid of the nanoconfinement effect within frameworks, RuMOFs had splendid ECL intensity at single molecule level, which was conducive to visualize the distribution of RuMOFs-labeled membrane PTK7 proteins at low-expressing cells, demonstrating great potential of frameworks-based ECL systems in cellular monitoring.

Bacteria may cause great harm for health while existing in human circulatory system, indicating importance of sensitive detection. Utilizing steric hindrance on electron transfer, *Vibrio parahaemolyticus* [98] and *Escherichia coli* [99] can be successfully analyzed by ECL sensors based on Ru-MOF and NH₂-MIL-53(Al) signal reporters, respectively. Besides, exosome as subcellular structure is also accurately detected by well-designed ECL sensors with different signal transduction. For example, Cui's group constructed a label-free HepG2-derived exosome ECL sensor based on the selectivity of CD63 peptide in recognizing CD63 proteins on exosome surface and strong coordination interactions between Zr⁴⁺ of Zn-TCPP/UiO-66-NH₂ and the phosphate head of exosomes (Figure 12). The ECL biosensor exhibited good sensitivity with a detection range from 1.00×10^4 to 3.16×10^6 particles/μL, which is better than most of the existing label-free methods for detecting exosomes [100], showing the great prospects of framework-based ECL in sensitive bioassays.

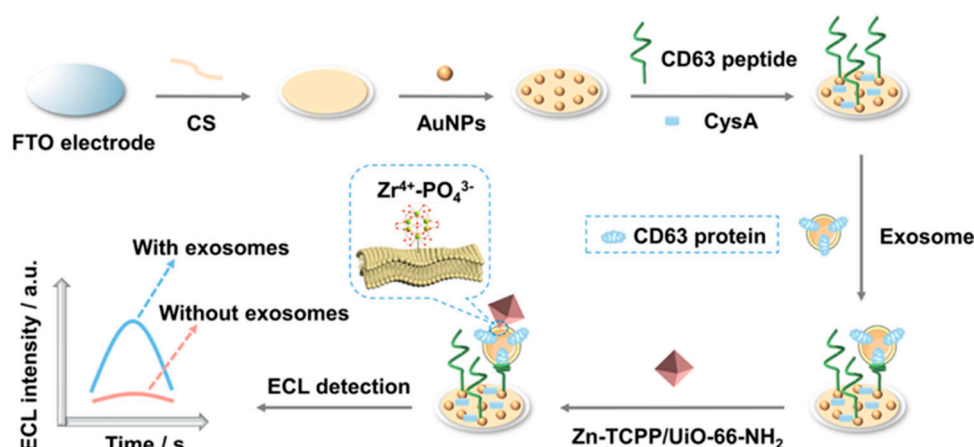


Figure 12. ECL biosensor construction and detecting HepG2-derived exosomes. Reproduced from [100] with permission from American Chemical Society.

4. Conclusion and Perspectives

Frameworks are a kind of widely used materials in ECL analysis owing to the flexible structure, long-range ordered units and controllable modification with some recognition elements. According to the functions in the ECL process, frameworks have been exploited as carrier of luminophores, catalyst of ECL reactions and crystalline emitters. Based on innovation of ECL mechanisms, the reticular biosensors gain more efficient ECL for signal amplification, which improves the sensitivity of biosensing. Different from MOFs, the metal-free COFs and HOFs have been rapidly developed and constructed a lots of biocompatible analytical methods. To date, framework-based ECL biosensors have been successfully utilized in the detection of proteins, nucleic acids, small molecules and cells by integrating specific functional materials, facilitating the further development of ECL techniques.

Actually, the researches on frameworks-based ECL systems are much more mature than several years ago but challenges still exist. To further expand its application and improve its biosensing performance, some aspects should be deliberated in future works: (1) It's crucial to explore near-infrared ECL-active frameworks for developing *in vivo* biosensing and bioimaging because of good penetrability and low scattering in NIR [101]. (2) The 3D sp^2 carbon-conjugated COFs may accelerate charge transfer through the largely conjugated electron structure, resulting in high ECL efficiency. (3) In order to develop single molecule ECL imaging technique [102], frameworks at nanoscale with intense ECL emission are promising crystalline nanoemitters. (4) The framework characteristics of self-luminescence such as orthogonal luminescence lifetime [103], can be endowed through the introduction of lanthanide elements, which may be used for designing ECL sensors. (5) Multivariate MOFs containing multiple metals have greater selectivity in catalysis for acceleration of charge transfer, which improves the efficiency of ECL reactions, leading to strong ECL emission [104]. In a word, the key of ECL techniques relies heavily on the improvement of emitters, suggesting that ECL-active frameworks with good stability, easy accessibility and high ECL efficiency are urgently required in future researches.

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