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DNA origami-based aptasensors

Elham Sameiyan[a], Elnaz Bagheri[a,b], Mohammad Ramezani[b], Mona Alibolandi[b], Khalil Abnous[b,c,*], Seyed Mohammad Taghdisi[d,**]

[a] Department of Pharmaceutical Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Department of Medicinal Chemistry, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[d] Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Traditional analytical techniques face many limitations such as time-consuming process, complicated sample preparation, high consumption of reagents and need for expensive equipment. So, it is important that simple, rapid and sensitive detection methods are introduced. Nucleic acids-based assays, particularly aptamers, have a great impact on modern life sciences for biological analysis and target detection. Aptamer-based biosensors with unique recognition properties including high specificity and affinity, rapid response and simple fabrication have attracted much attention. It is believed that two- and three-dimensional structures, sometimes referred to as DNA origami, using DNA aptamers can show more selective binding affinity and better stability over other nucleic acids forms. In this review, we will focus on recent advances in the development and uses of electrochemical and optical DNA origami-based aptasensors to supply readers with a comprehensive understanding of their improvements. Also, the challenges and awards of these approaches are discussed.

1. Introduction

A biosensor is generally defined as a self-contained small analytical device which includes a physiochemical transducer and a biological recognition element (Banica, 2012; Mehrotra, 2016; Turner et al., 1987). Biosensing platform creates detectable signal when a sensing element interacts precisely with its biological analyte (DNA, enzymes, proteins, antibodies, saccharides, toxins, drugs, cell receptors, tissues, whole cells and etc.) by converting recognition signal into a measurable output signal using transducer element (Eftekhari-Sis et al., 2016). In addition, more advanced techniques such as smartphone-based analytical biosensors have recently been developed and applied in biomedical diagnosis and used by patients to monitor biomarkers such as blood lipid, uric acid and blood β-Ketone outside a clinical laboratory. (Fu and Guo, 2018; Guo, 2016, 2017; Guo et al., 2018a; Huang et al., 2019). Development of such sensing systems requires a multidisciplinary research in chemistry, biology and engineering. Therefore, various biosensors including thermal biosensors, bacterial biosensors, piezoelectric biosensors, DNA-based biosensors, magnetic biosensors and etc. are used to detect numerous markers and diseases (Banica, 2012; Eftekhari-Sis et al., 2016; Mehrotra, 2016; Turner et al., 1987; Wang, 2017).

Aptasensors are a kind of biosensors that utilize aptamer as the recognition component (Hosseini et al., 2015). Aptamers are artificial synthetic single-stranded DNA or RNA sequences with size less than 25 kDa which selected *in vitro* through a method called SELEX (Systematic Evolution of Ligands by EXponential enrichment) (Abnous et al., 2017b; Charbgoo et al., 2016; Stoltenburg et al., 2007). They are able to produce unique three dimensional shapes for binding to specific ligands and show high affinity and selectivity towards their targets (Feng et al., 2014; Mokhtarzadeh et al., 2015; Nguyen et al., 2013; Stoltenburg et al., 2007; Yazdian-Robati et al., 2016). In some cases, aptamers show greater dissociation constants ranged from nanomolar to picomolar when they are compared with monoclonal antibodies (Araújo-Filho et al., 2011). Also, they exhibit significant advantages in comparison with antibodies such as high chemical stability, simple production, cost-effectiveness and ease of labeling and modification (Hosseini et al., 2015; Robati et al., 2016). Native DNA aptamers show more stability than RNA aptamers and the *in vitro* half-life of a DNA aptamer in plasma is about 30–60 min but this for an RNA aptamer is only a few seconds (Shaw et al., 1991; Takei et al., 2002; White et al., 2000).

* Corresponding author. Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
** Corresponding author.
E-mail addresses: abnouskh@mums.ac.ir (K. Abnous), taghdisihm@mums.ac.ir (S.M. Taghdisi).

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The nanoscale folding of DNA structures to generate non-arbitrary two- and three-dimensional shapes refers to the term "DNA origami" (Zadegan and Norton, 2012). DNA Molecular self-assembly is a considerable approach to create structurally versatile, highly addressable and distinct micro- and nanoscale objects (Hong et al., 2017; Nummelin et al., 2018; Seeman and Sleiman, 2018). In addition, because of the introduction of DNA origami method, custom developed DNA-based motifs can be fabricated and applied in several applications including chemical and enzymatic reactions (Gothelf, 2017; Grossi et al., 2017), drug delivery (Li et al., 2013; Linko et al., 2015), plasmonics (Kuzyk et al., 2012; Liu and Liedl, 2018; Shen et al., 2018) and aptasensors (Abnous et al. 2016b, 2017a; Danesh et al., 2016; Taghdisi et al. 2016a, 2016b, 2019) systems. In current review, we intend to investigate the use of DNA origami-based nanostructures in various aptasensors including electrochemical and optical aptasensors.

2. DNA origami-based aptasensors

2.1. DNA origami-based electrochemical aptasensors

Electrochemical aptasensors have become widespread among various analytical approaches due to their unique features, including high detection sensitivity, fast response, low cost instruments and easy miniaturization (Abnous et al., 2017b; Liu et al., 2017; Sun et al., 2017; Xia et al., 2017).

Various working electrode materials are used in electrochemical aptasensors such as platinum, gold, carbon, and mercury. Among them, gold and carbon electrodes are very popular. Glassy carbon as the most common form of carbon electrode is used for electropolymerization of probe-supporting redox hydrogels (de Lumley-Woodyear et al., 1996) or direct covalent attachment of DNA probes (Millan et al., 1992), while not suitable for direct detection of DNA oxidation peaks (Cai et al., 1996). It is also a relatively expensive material.

Gold electrodes are very useful for the preparation of modified electrodes especially self-assembled monolayers (SAMs). They are an ideal electrocatalyst for many processes, particularly oxidation of a wide range of biomolecules. However, they have limited performance in the positive potential range because of its surface oxidation. In addition, mechanical and chemical methods for producing a new surface is time consuming (Lucarelli et al., 2004).

Aflatoxin B1 (AFB1) is a mycotoxin produced by many species of *Aspergillus*. Recently, our group developed an electrochemical aptasensor to detect aflatoxin B1 (AFB1) using a π-shape structure of Aptamer (Apt)-Complementary strands of aptamer (CSs) complex on the surface of electrode and exonuclease I enzyme (Exo I). Exo I as a sequence independent enzyme that specifically digests ssDNA from its 3′-end, is a cost-effective enzyme and has acceptable buffer compatibility (Zhao et al., 2014; Zheng et al., 2012). In this work, the π-shape structure acts as a double-layer physical obstacle, thus preventing access of $[Fe(CN)_6]^{3-/4-}$ as redox agent to the electrode surface. Moreover, Exo I is responsible for signal amplification. In the absence of AFB1, this structure is intact and almost its sequences are protected against Exo I activity. Thus, only a weak peak response is measured. However, in the presence of target, aptamer interacts with AFB1 and disassociates from its CSs. Thus, redox probe can access to the electrode surface and consequently a strong electrochemical signal is observed following the addition of Exo I and digestion of CS1 (Fig. 1). It is notable that pre-treatment with salmon sperm DNA was used to detect AFB1 in real samples. Limit of detection (LOD) of this sensing system was 2 pg/mL with a linear range of 7–500 pg/mL (Abnous et al., 2017a).

Tetracyclines are broadly utilized antibiotics in veterinary and human medicine. In another study, a new M-shape electrochemical aptasensor was introduced for ultrasensitive determination of tetracyclines based on Apt- CSs complex, Exo I and gold electrode. In this system, the M-shape structure plays as a gate for the reaching of redox marker to the electrode surface. In the absence of tetracycline, this construction is preserved and consequently CSs are protected from digestion by Exo I, resulting in a weak current response. In the presence of tetracycline, interaction of aptamer and its target happens which leads to its separation from the CSs and disassembly of M-shape structure. Upon addition of Exo I on the surface of electrode, CS1 and CS2 are digested and so, the electrochemical signal is intensified. It is noteworthy that pre-treatment with salmon sperm DNA was applied to measure tetracycline in real samples. LOD of this aptasensor was calculated to be 450 pM with a wide linearity in the range of 1.5 nM–3.5 μM for tetracycline. In addition, the proposed electrochemical aptasensor was able to detect effectively tetracycline in serum and milk samples with LODs of 710 and 740 pM, respectively (Taghdisi et al., 2016a). Although this system is very sensitive and has a low limit of detection for the target but its fabrication and also target detection take a long time due to its multi-stage nature.

Myoglobin (Mb) has been shown to play an important role in acute myocardial infarction (AMI) (Kim et al., 2014; Wang et al. 2015b, 2015c) which is one of the leading causes of mortality worldwide (Lee et al., 2015; Wang et al., 2015a). A specific and sensitive electrochemical aptasensor based on Y-shape structure of dual-aptamer (DApt)-CS conjugate, Exo I and gold electrode was presented for detection of Mb by our team. The Y-shape structure was introduced as a barrier, thus preventing the access of redox agent to the electrode surface and Exo I also acted as a signal amplifier. Without introduction of Mb, the Y-shape structure of DApt-CS conjugate keeps its structure and the CS is protected from degradation by ExoI, leading to less access of redox marker to the surface of gold electrode and a weak redox current. On the other hand, with the addition of the Mb, DApt binds to Mb and is separated from the CS and away from the electrode surface. It has been revealed that aptamers bind to their corresponding targets with a better binding constant compared to their complementary strands (Song et al., 2016; Wu et al., 2015; Yang et al., 2014). The alone CS is affected by the enzyme and digested from its 3′-end, leading to more access of the redox marker to the electrode surface and the enhancement of signal response. The proposed aptasensor presented great specificity for Mb with a limit of detection (LOD) as low as 27 pM (Taghdisi et al., 2016b). However, the application of Exo I could enhance the cost and time of target detection.

Similarly, another electrochemical aptasensor with an arch-shape was introduced to detect streptomycin. Streptomycin is a natural aminoglycoside antibiotic applied in veterinary and human medicine. This structure was able to efficiently prevent the access of redox agent to the electrode surface both by creating a physical obstacle and its negative charge. This biosensor was developed based on Exo I, Arch-shape structure of Apt-CS conjugate and gold electrode. The Arch-shape construction of Apt-CS conjugate is preserved in the absence of streptomycin and so, the CS is sheltered from digestion by Exo I, resulting in the less access of $[Fe(CN)_6]^{3-/4-}$ to the electrode surface and a weak peak current. With the addition of target, the conjugate of Apt/target is formed and CS is released from the Apt. Thus, CS is digested under the influence of Exo I, leading to further access of the redox marker to the electrode surface and the improvement of the current signal (Fig. 2). The LOD measured for streptomycin was measured to be 11.4 nM (Danesh et al., 2016).

However, the application of Exo I in this method and other mentioned aptasensors could increase the cost and time of target detection. This enzyme need long incubation time even 1.5 h (Danesh et al., 2016; Taghdisi et al., 2016b). Nevertheless, the huge benefits of these systems including their high specificity and sensitivity have offset this challenge.

The presence of ampicillin (Ampi) as an antibiotic in various substances, like milk and water samples due to its extreme use (Yu et al., 2018) can result in adverse effects on human health including seizures and allergic reactions (Ge et al., 2019). For this purpose, an electrochemical aptasensor was constructed based on the use of a ladder-

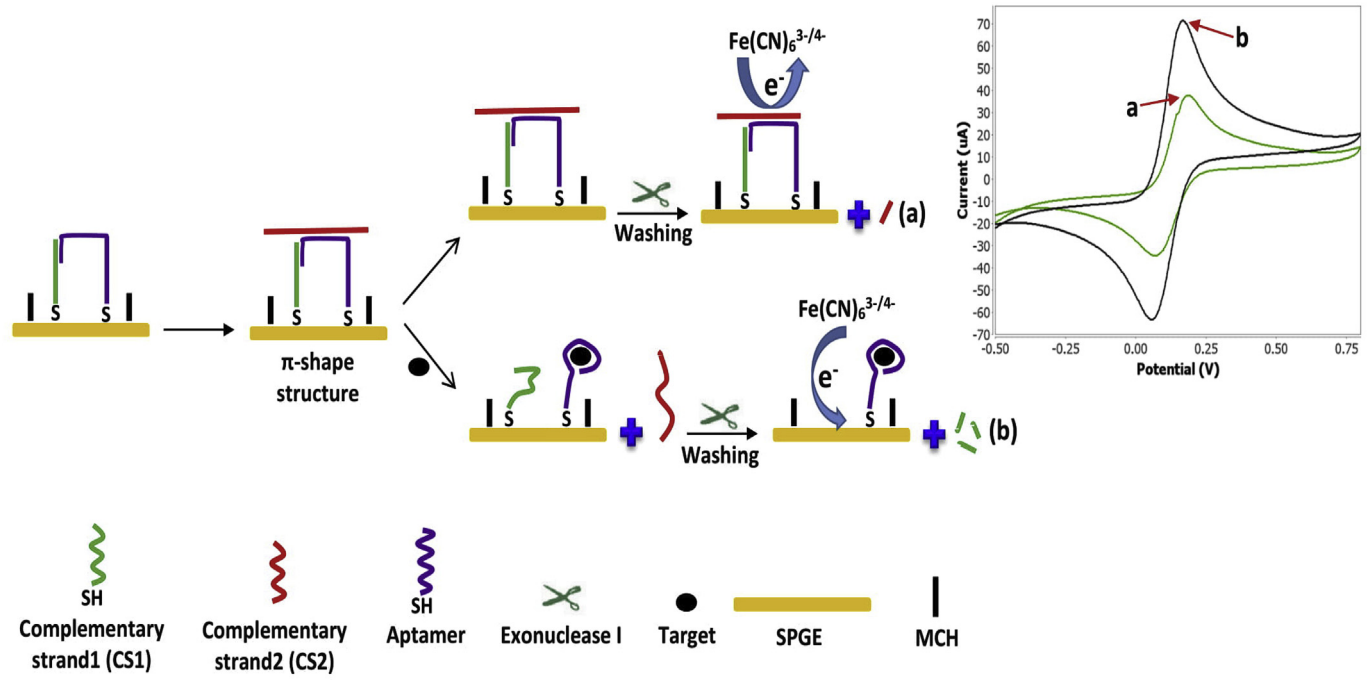

Fig. 1. Schematic diagram of the sensing platform for detection of AFB1 based on the π-shaped structure of Apt-CSs. Reprinted with permission from Ref (Abnous et al., 2017a).

shaped DNA structure as a multi-layer physical barrier on the electrode surface. This structure which is composed of several ssDNAs can prevent the access of the [Fe (CN) 6]$^{3-/4-}$ to the surface of electrode through physical prohibition and electrostatic repulsion between the negatively charged redox agent and the negatively charged phosphate groups of the immobilized ssDNAs and aptamer (Chen et al., 2014; Zhao et al., 2015). The Ampi aptamer is required for the formation of the ladder-shaped DNA construction on the electrode surface. So, in the presence of Ampi, aptamer is paired with its target and the ladder-shaped DNA construction is disassembled and released from the surface of electrode. This resulting to the high access of redox marker to the surface of electrode with a robust redox current. While in the absence of Ampi, the entire structure remains unbroken and prevents the entry of redox agent to the electrode surface, resulting in a weak electrochemical signal (Fig. 3). However, fabrication of the ladder-shaped DNA construction on the electrode surface requires several steps and multiple ssDNAs. As a result, the overall process time and detection costincrease. Although, this analytical system has covered these defects by its high sensitivity and specificity. The LOD of this sensor was reported as low as 1 pM with the linear range of 7 pM–100 nM (Taghdisi et al., 2019).

Terminal deoxynucleotidyl transferase (TdT) is a DNA polymerase that catalyzes repetitive addition of nucleotides to the 3′-end of a DNA molecule without any template to build a long ssDNA (Guo et al., 2018b; Luo et al., 2017). In this regard, the ability of this enzyme was applied to design an electrochemical aptasensor for detection of bisphenol A (BPA), an important organic monomer that is broadly used in

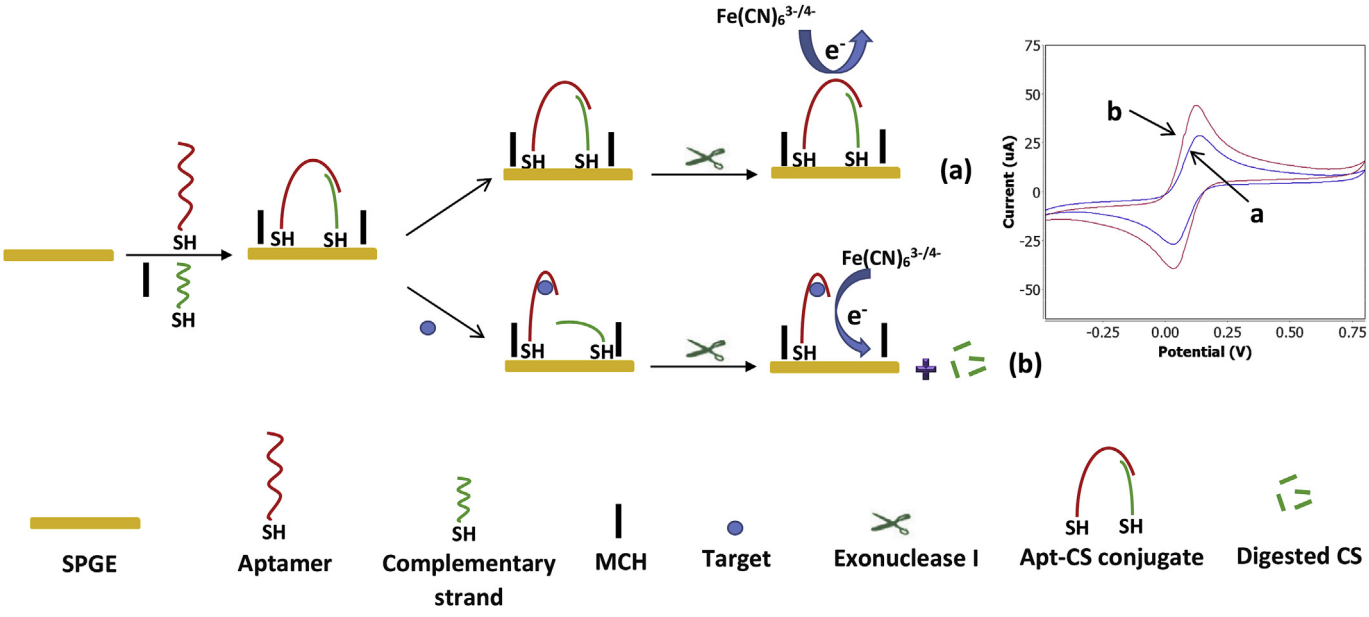

Fig. 2. Schematic illustration of the arch-shaped aptasensor for detection of streptomycin. Reprinted with permission from Ref (Danesh et al., 2016).

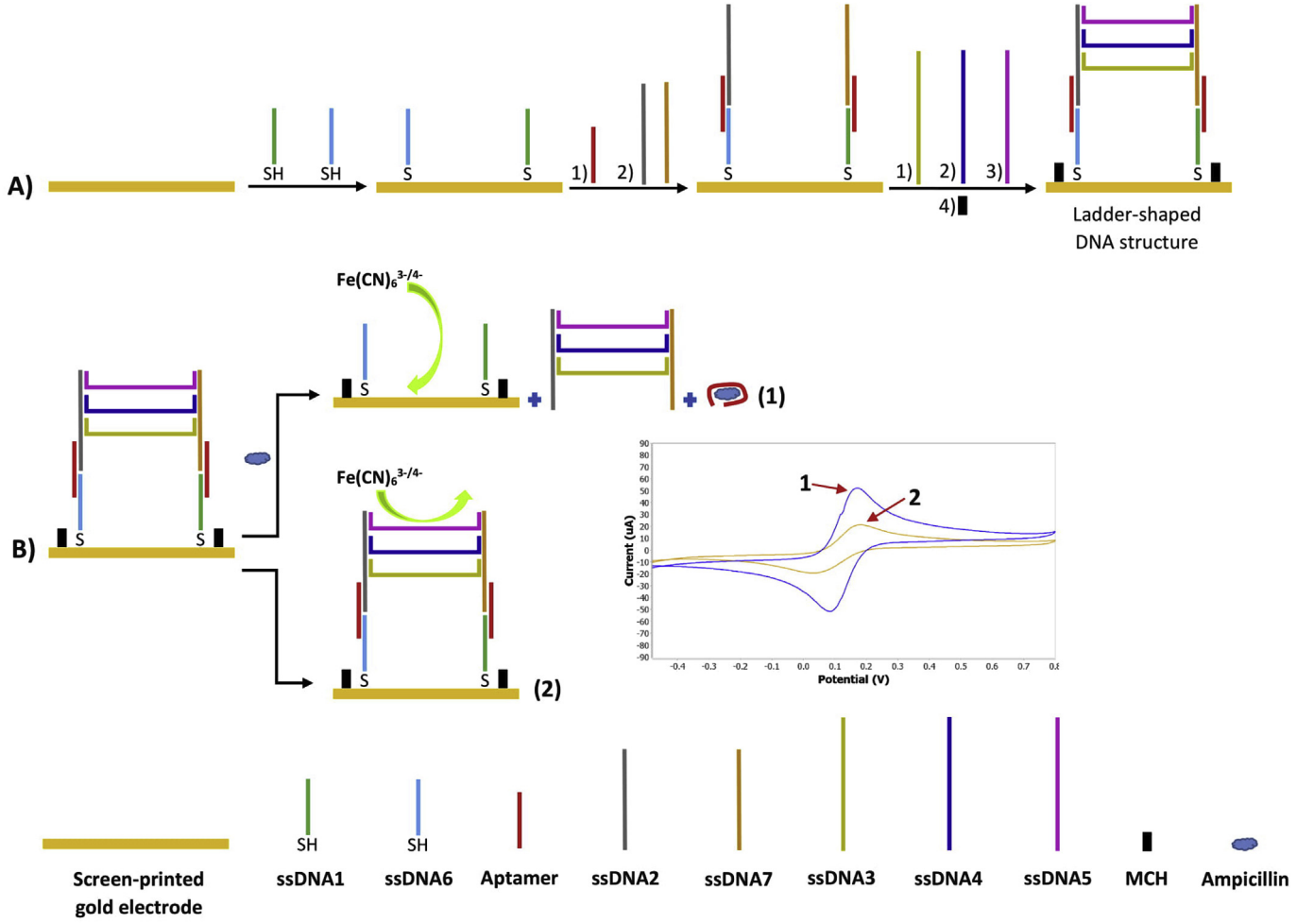

Fig. 3. Schematic diagram of the fabrication procedure and function of the ladder-shaped DNA structure for detection of Ampi. Reprinted with permission from Ref (Taghdisi et al., 2019).

water containers and considered as a big issue for human health (Kanagavalli and Senthil Kumar 2018; Mirzajani et al., 2017). This sensing system was designed using nontarget-induced bridge assembly and aptamer length extension caused by TdT. In the lack of BPA, TdT enzyme adds a poly T sequence to the 3′ terminus of Apt and prolongs Apt length. Then, this poly T is hybridized with poly A of CS fixed on the electrode surface, leading to formation of a bridge as a negatively charged physical barrier on the surface of electrode. So, the access of $[Fe(CN)6]^{3-/4}$ is limited to the electrode surface and resulting in a week electrochemical response. On the contrary, when BPA is present in the environment, the access of TdT to the 3′-end of Apt is significantly reduced because of the formation of Apt-BPA complex, resulting in the lack of bridge assembly and high access of redox probe to the electrode surface. Consequently, a strong electrochemical signal is detected (Fig. 4). The linear range for this aptasensor was reported to be 0.08–15 nM and its detection limit was 15 pM (Abnous et al., 2018a). However, in this system, the application of TdT enzyme can increase the cost of aptasensor and its target detection time due to its long incubation time (90 min).

Another study described a sensitive electrochemical aptasensor for determination of carcinoembryonic antigen (CEA) as an important tumor biomarker (Canizares et al., 2001; Gold and Freedman, 1965; Sener et al., 1989; Tiernan et al., 2013). The proposed system is based on hairpin structure of CEA aptamers (Apt1 and Apt2) and their CS. Upon addition of CEA, the hairpin structures of aptamers change and the CS can be hybridized to Apt1 and Apt2 applying its 5′-end and 3′-end, respectively. As a result, a bridge is formed on the surface of electrode which reduces the electrochemical signal owing to its hindering effects as a negative charge substance and physical barrier. However, in the lack of target, the hairpin structures of aptamers are well-maintained on the electrode surface and CS could not bind to them, leading to no bridge assembly and a strong current response is detected. This sensing system indicated a low detection limit (0.9 pg/mL) with a broad linear range (3 pg/mL to 40 ng/mL) (Taghdisi et al., 2018).

In another work, our group introduced a highly sensitive electrochemical aptasensor that was based on H-Shape structure of Apt-CSs conjugate and target-triggered detachment of Apt from CSs for detection of cocaine. H-shape structure of Apt-CSs conjugate plays a role as a barrier on the surface of electrode for the access of redox probe. This structure remains intact without the presence of cocaine. Therefore, the redox marker does not have access to the electrode surface, resulting in a week current response. In the presence of cocaine, aptamer is separated from its CSs and attaches to its target. Thus, gate is opened and $[Fe(CN)6]^{3-/4-}$, could have access to the surface of electrode, resulting in improvement of the electrochemical signal. LOD of the introduced electrochemical aptasensor was reported as low as 0.228 nM with a well linear range of 0.3–15 nM (Abnous et al., 2016b).

Interferon-gamma (IFN-γ) which increases at the early levels of tuberculosis infection can be a good marker to diagnose latent tuberculosis (Diel et al., 2008; Hussain et al., 2010; Kabeer et al., 2012). Therefore, an electrochemical aptasensor was developed for IFN-γ determination based on a triple-helix molecular switch (THMS). In this system, without introduction of IFN-γ, the structure of THMS is

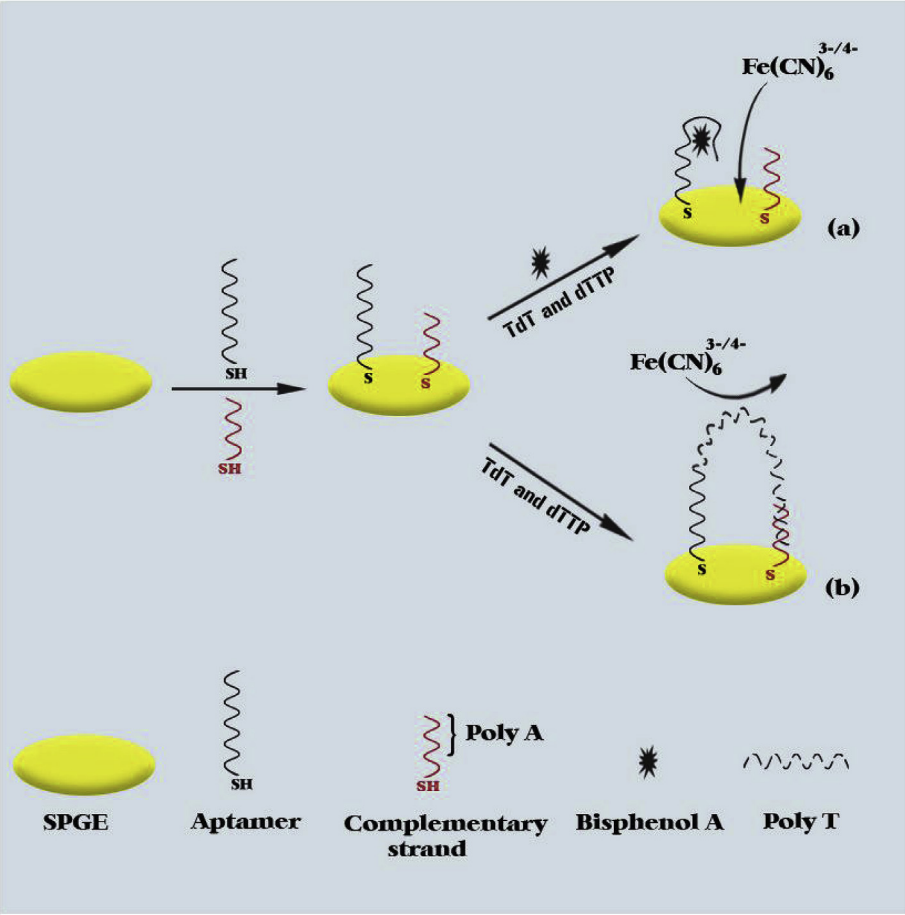

Fig. 4. Schematic illustration of the electrochemical aptasensor for BPA detection based on nontarget-induced bridge assembly. Reprinted with permission from Ref (Abnous et al., 2018a).

protected on the surface of electrode. Thus, high amounts of redox agent, methylene blue (MB), can be attached to THMS, leading to a strong electrochemical signal. The MB contains a positive charge that can be coupled to THMS via intercalative binding and electrostatic force (Huang et al., 2015; Lee et al., 2013; Zhang et al., 2010). In the presence of IFN-γ, Apt–IFN–γ complex quits the surface of electrode and the construction of THMS is disassembled. Consequently, less amount of MB is attached to the signal transduction probe (STP) and a weak peak current is detected. To use the aptasensor in real samples, the IFN-γ spiked serum samples were treated with 30 μg/mL salmon sperm DNA. This selective and sensitive biosensor had a 3 pg/mL detection limit and a dynamic range from 10 to 1500 pg/L (Abnous et al., 2017c). Although the use of the THMS-modified electrode remarkably enhances the sensitivity of the aptasensor, the THMS design is difficult and time-consuming in a way that the aptamer can detect its target well.

Among other analytical studies using DNA origami can be referred to an electrochemical aptasensor that was introduced for zeatin determination. Zeatin is a type of phytohormone which can regulate plat growth. The matrix electrode used in this system consists of a gold nanoparticles (AuNPs) and MoS_2 nanosheet-modified glassy carbon electrode (AuNPs/MoS2/GCE). In this system, the DNA probe is initially fixed on the surface of matrix electrode and then, the DNA aptamer and assistance DNA are hybridized with the DNA probe, leading to the formation of Y-type DNA. DNA aptamer was modified with two biotins at its both terminals. Subsequently, avidin modified alkaline phosphatase (Avidin-ALP) can be trapped on the electrode surface via the interaction between avidin and biotin. Under the catalytic effect of ALP, hydrolysis reaction of p-nitrophenyl phosphate disodium salt hexahydrate (PNPP) occurs to make p-nitrophenol (PNP) that can be electrochemically oxidized to show an electrochemical oxidation signal. Upon addition of zeatin, the aptamer-target complex is formed and aptamer is detached from the electrode surface, followed by depletion of the amount of ALP on the electrode surface and decrease of its catalytic activity, leading to observation of a week electrochemical oxidation signal. The detection limit of this system was calculated to be 16.6 pM while the logarithm value of zeatin concentration was in the range of 50 pM–50 nM (Zhou et al., 2018).

Sun et al. designed a competitive and label-free electrochemical aptasensor for determination of HepG2 tumor cells by using DNA origami technology. In the first step, the DNA nanotetrahedron (NTH) containing the TLS11a aptamer probe with a high affinity for liver cancer HepG2 cells, is fixed on the surface of a screen-printed gold electrode (SPGE). Then, nanoprobes (nanoprobe1 and nanoprobe2) are constructed by Pd–Pt nanocages labeled with horseradish peroxidase (HRP), hemin/G-quadruplex DNAzyme, and two complementary DNA (cDNA1 and cDNA2). Nanoprobes are immobilized on the SPGE substrate via DNA hybridization and form dendritic structure (DS) nanoprobes with self-assembly approaches. The high amount of HRP, G-quadruplex/hemin DNAzyme and nanocages of the created DS nanoprobes can considerably strengthen the electrochemical response and increase the sensitivity of the sensor. When target cells are introduced into the designed system, they bind to NTH-based aptamer probe, thus DS nanoprobes are released from the SPGE, resulting in a weak peak current (Fig. 5). This method revealed high sensitivity and selectivity toward HepG2 with LOD of 5 cells per mL (Sun et al., 2018).

Lipopolysaccharides (LPS) can be named endotoxins are the main ingredient of the outer membrane of Gram-negative bacteria (Gutsmann et al., 2007; Li et al., 2004; Therisod et al., 2001). They are

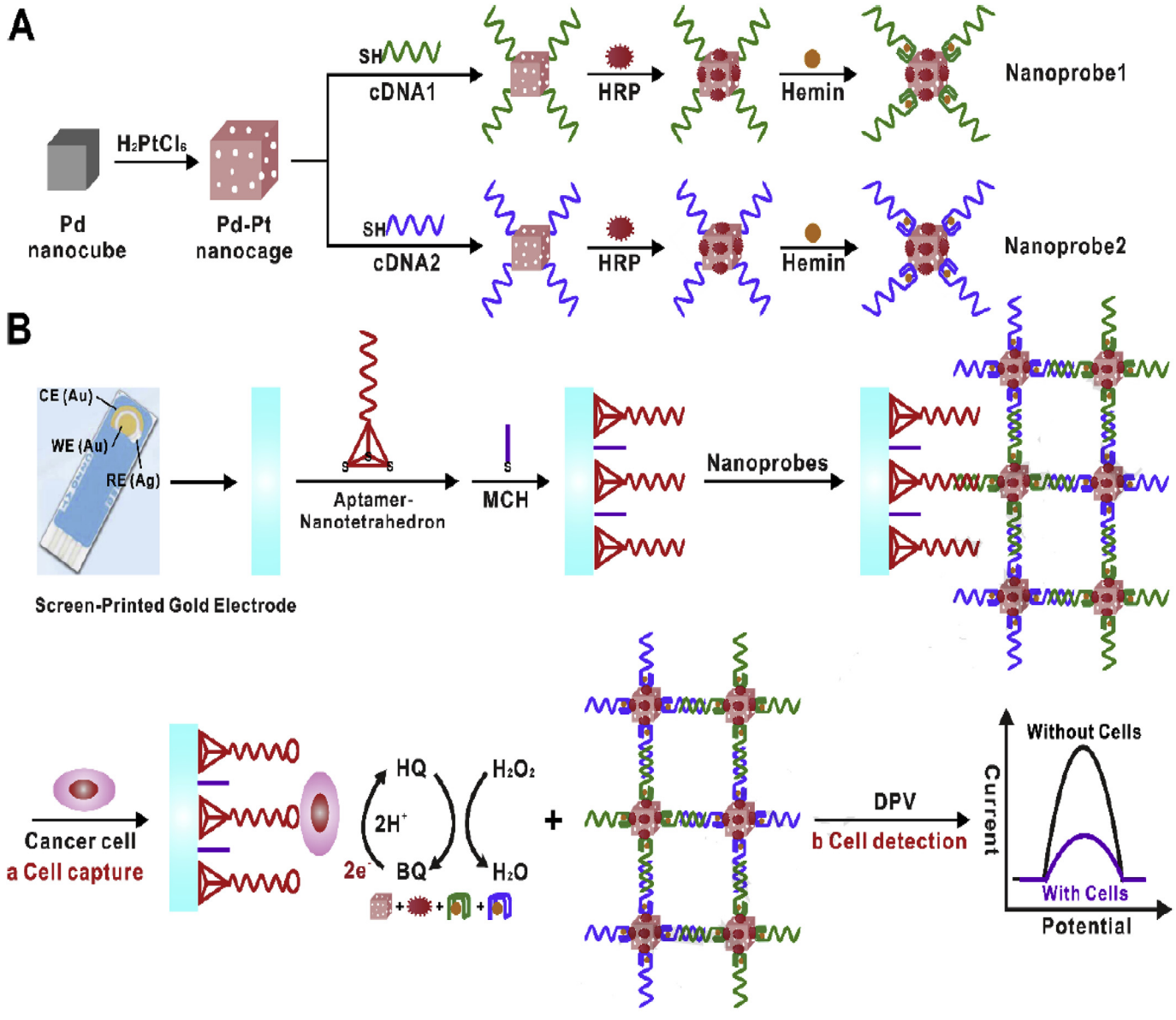

Fig. 5. Fabrication process of the electrochemical aptasensor for HepG2 tumor cells detection using the DNA nanotetrahedron, HRP, hemin/G-quadruplex DNAzyme. Reprinted with permission from Ref (Sun et al., 2018).

considered as the primary cause of septic shock (Dellinger et al., 2013; Martin, 2012), blood clotting (Kotani et al., 1985) and pyrogenic reaction (Murai et al., 1987). Since LPS indicates high biological activity and toxicity even at low concentration (Beutler and Rietschel, 2003; Warren et al., 2010), the sensitive and specific determination of LPS is of great importance for food and medical security.

In this regard, Xie et al. developed an electrochemiluminescence (ECL) aptasensor for detecting LPS based on self-assembled tetrahedron DNA dendrimers. The ECL method in this system consists of the combination of doxorubicin (Dox), a well-known double stranded DNA (dsDNA) intercalator (Jiang et al., 2012) with the ECL luminophore of N-(aminobutyl)-N-(ethylisoluminol) (ABEI) which could noncovalently be attached to dsDNA through intercalation and with the help of Dox. Self-assembled tetrahedron DNA dendrimers play the role of an effective nanocarriers to reach a great loading efficiency for Dox-ABEI conjugate which can considerably amplify ECL signal output. The process for the detection of LPS in this system is as follows: At first the hybrid of LPS binding aptamer (LBA) and its partial CS are assembled onto the surface of Au@Fe3O4 magnetic nanocomposites. In the presence of LPS, cDNA is detached from the hybrid and released into the sample. This cDNA by hybridizing with the hairpin probe H1 on the electrode surface, makes it open and next, the cDNA could be more released from the H1-cDNA duplex in the presence of another biotin-labeled hairpin DNA Biotin-H2. The recycling of cDNA is comprehended to strengthen the response signal and greatly H1-Biotin-H2 duplex could be observed after the cyclic procedure. Next, the H1-Biotin-H2 duplex is further employed to interact with streptavidin (SA), followed by biotinylated tetrahedron DNA dendrimers (G2) binding that is intercalated through numerous Dox-ABEI (G2-Dox-ABEI) to reach quantitative determination of LPS. The designed strategy displayed a detection limit of 0.18 fg/mL for LPS (Xie et al., 2016).

In the two last mentioned aptasensors, the fabrication of sensing platforms are time-consuming because several steps are needed to form them which can also increase the cost of detection. But on the other hand, there is a strong point for all of the aptasensors mentioned here that it is possible to extend these sensing methods for different targets by using their suitable aptamers and CSs.

The LODs and linear ranges of the aforementioned electrochemical

Table 1
LODs and linear ranges of the electrochemical aptasensors.

Method	LOD	Linear range	Analyte	Reference
Based on the formation of π-shape structure	2 pg/mL	7–500 pg/mL	Aflatoxin B1	Abnous et al. (2017a)
Based on the formation of M-shape structure	450 pM	1.5 nM to 3.5 μM	Tetracyclines	Taghdisi et al. (2016a)
Based on the formation of Y-shape structure	27 pM	100 pM to 40 nM	Myoglobin	Taghdisi et al. (2016b)
Based on the formation of Arch-shape structure	11.4 nM	30–1500 nM	Streptomycin	Danesh et al. (2016)
Based on the formation of Ladder-shaped structure	1 pM	7 pM to 100 nM	Ampicillin	Taghdisi et al. (2019)
Based on the nontarget-induced extension of aptamer length and formation of a physical barrier	15 pM	0.08–15 nM	Bisphenol A	Abnous et al. (2018a)
Based on the target-induced bridge assembly	0.9 pg/mL	3 pg/mL to 40 ng/mL	Carcinoembryonic antigen	Taghdisi et al. (2018)
Based on the formation of H-shape structure	0.228 nM	0.3–15 nM	Cocaine	Abnous et al. (2016b)
Based on the formation of a triple-helix molecular switch structure	3 pg/mL	10–1500 pg/L	Interferon-gamma	Abnous et al. (2017c)
Based on the MoS_2 nanosheets and enzymatic signal amplification	16.6 pM	50 pM–50 nM	Zeatin	Zhou et al. (2018)
Based on the formation of a self-assembled DNA nanostructure	5 cells per mL	–	HepG2 tumor cells	Sun et al. (2018)
Based on the formation of self-assembled tetrahedron DNA dendrimers	0.18 fg/mL	–	Lipopolysaccharides	Xie et al. (2016)

aptasensors are summarized in Table 1.

2.2. DNA origami-based optical aptasensors

Quick response, high sensitivity, and simple operation are the features that have made the optical sensing methods popular. Applying aptamers as the recognition elements and several optical techniques as the signal transductions provides opportunities for assessment of targets (Robati et al., 2016). In the following sections, DNA origami-based optical aptasensors are categorized into two main groups of fluorescent and colorimetric techniques.

2.2.1. DNA origami-based fluorescent aptasensors

Some features of the aptamer-based fluorescent methods make them particularly valuable for design of sensing approaches, including their rapid detection speed, simplicity and high specificity (Joo et al., 2017; Musumeci et al., 2017; Song et al., 2017; Taghdisi et al., 2017). Two main classes for the fluorescent aptasensors can be considered: labeled and label-free fluorescence aptasensors. Generally, the use of labeled aptasensors is preferable to their non-labeled counterparts. However, the major disadvantages of the labeled aptasensors are their high price and sometimes time-consuming multistage procedures (Ng et al., 2016).

Recently, our group proposed a fluorescent aptasensor based on a DNA pyramid nanostructure (DPN) and PicoGreen (PG) dye for determination of ochratoxin A (OTA), a common mycotoxin can be found in different food products. The constructed DPN is a DNA nanostructure made of short dsDNA building blocks and the OTA aptamer (Apt). In this system, PG was employed as a fluorescent agent due to its high selectivity and sensitivity for binding to dsDNA. So that, its fluorescence increases more than 1000-fold upon its attachment to dsDNA, while the free PG displays no or very low fluorescence (Chen et al., 2015a; Song et al., 2016). Without the presence of OTA in the designed approach, the pyramid structure of DPN is completely preserved and following the addition of PG, it can be intercalated into dsDNA blocks of DPN, leading to a very strong fluorescence emission. But upon addition of target, Apt is separated from the DPN structure and forms the Apt-OTA conjugate. This will disrupt DPN structure and weaken the fluorescence emission. It should be mentioned that pre-treatment with salmon sperm DNA was utilized to recognize OTA in serum and grape juice samples. The designed aptasensor presented great specificity to its target with a LOD as low as 0.135 nM with a linear range of 0.3–10 nM (Nameghi et al., 2016). The main drawback of this analytical system is the use of long sequences in the building of DPN that increases the cost of biosensor. In addition, PG further enhances the overall cost of the method as an expensive dye.

Carcinoembryonic antigen (CEA) as a tumor marker is associated with breast (Bao et al., 2008; Thriveni et al., 2007), gastric (Lai et al., 2014), colorectal (Cierpinski et al., 2011; Wang et al., 2014) and lung (Braik et al., 2012; Yu et al., 2011) cancers and colon adenocarcinoma (Szajda et al., 2008) which increases significantly in serum of cancer patients compared to healthy people (Hasanzadeh and Shadjou, 2017). Thus, the sensitive detection of CEA in serum is very important for early diagnostic applications and clinical cancer screening. In this regard, a fluorescent aptasensor was presented for determination of CEA, using three-way junction pocket and 5,6,7-trimethyl-1,8-naphthyridin- 2-amine (ATMND) as a fluorescent probe. It has been proved that upon trapping of ATMND within the three-way junction structures particularly those with GC nucleotides repeats, ATMND fluorescence will be quenched (Roncancio et al., 2014; Sato et al., 2011).

In the lack of CEA, three-way junction structure consisting of Apt, CS1 and CS2 is formed and ATMND is trapped in this structure. So, a weak fluorescence response is detected. With the introduction of the target, the Apt-CEA complex is formed, leading to the absence of three-way junction construction. So, following the addition of ATMND, a powerful fluorescence signal can be recorded (Fig. 6). The fabricated fluorescent aptasensor indicated a detection limit of 1.5 pg/mL with a broad linearity range from 4.5 pg/mL to 30 ng/mL of CEA (Danesh et al., 2018).

2.2.2. DNA-origami based colorimetric aptasensors

Colorimetric assays especially aptamer-based colorimetric sensors have obtained a lot of attention because of their convenience and simplicity. Furthermore, the results can be monitored by the naked eye (Abnous et al., 2016a; Gao et al., 2017; Wang et al., 2017). Compared to other analytical techniques, colorimetric measurement is directly detectible. Though, its sensitivity is typically lower than other analytical methods (Liu et al., 2011; Liu and Lu, 2006; Wang et al., 2011; Xia et al., 2010).

Including sensors in this field, it can be referred to a sensitive colorimetric aptasensor used to detect cocaine based on target-triggered assembly of three-way junction pockets on the surfaces of gold nanoparticles (AuNPs) and the catalytic activity of the surfaces of AuNPs. In this study, catalytic function of AuNPs was used in place of using an artificial enzyme because it has been shown that the bioactivity of the enzymes can be easily undermined. Additionally, the preparations of enzymes are time-consuming and their purification and storage cost a lot (Chen et al., 2015b; Tang et al., 2011). In this system, without introduction of cocaine, the cocaine triple-fragment aptamer (TFA) is not formed on the surfaces of AuNPs. Consequently, 4-nitrophenol has easy access to the surfaces of AuNPs and is reduced to 4-aminophenol, resulting in a color change of sample from yellow to colorless. Due to the high affinity of TFA for cocaine, by introducing of cocaine into the system, three-way junction pockets can be formed on the surfaces of AuNPs and masked the surfaces of AuNPs. Therefore, 4-nitrophenol has less access to the surfaces of AuNPs, leading to no color change of sample (Fig. 7). The pre-treatment with acetone was used to detect

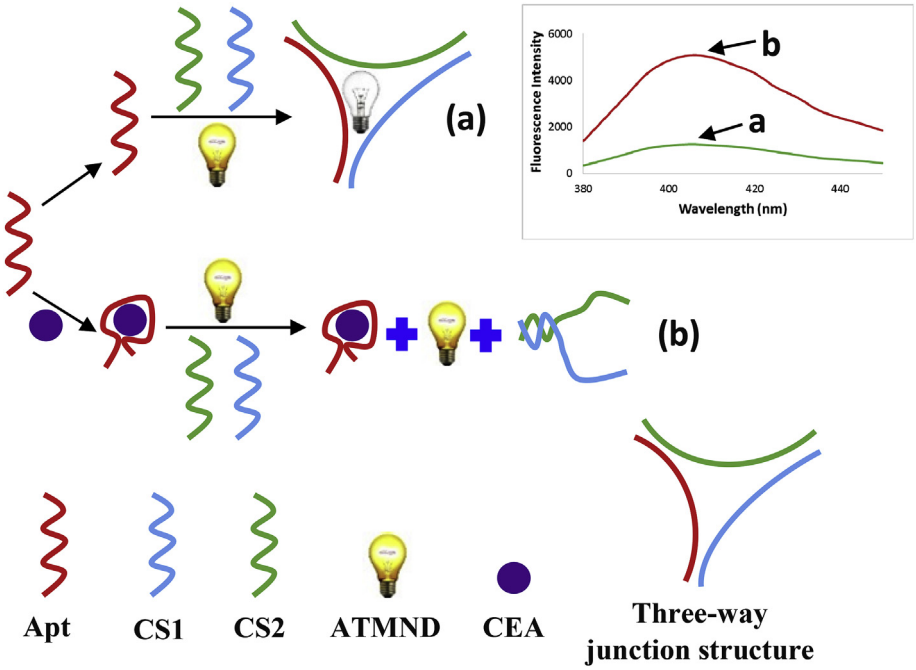

Fig. 6. Schematic representation of CEA detection by the fluorescent aptasensor using the three–way junction structure. Reprinted with permission from (Danesh et al., 2018).

cocaine in serum samples. The limit of detection of the sensing strategy was 440 pM which displayed good specificity with a dynamic range over 2–100 nM (Abnous et al., 2018b).

Despite the simplicity of such systems, the main disadvantage of these kinds of sensors is the phenomenon of the corona shield for AuNPs that can be very problematic when these sensors are exposed to complicated samples such as serum or milk (Lundqvist et al., 2011). In addition, 4-nitrophenol is toxic which may cause adverse effects for the

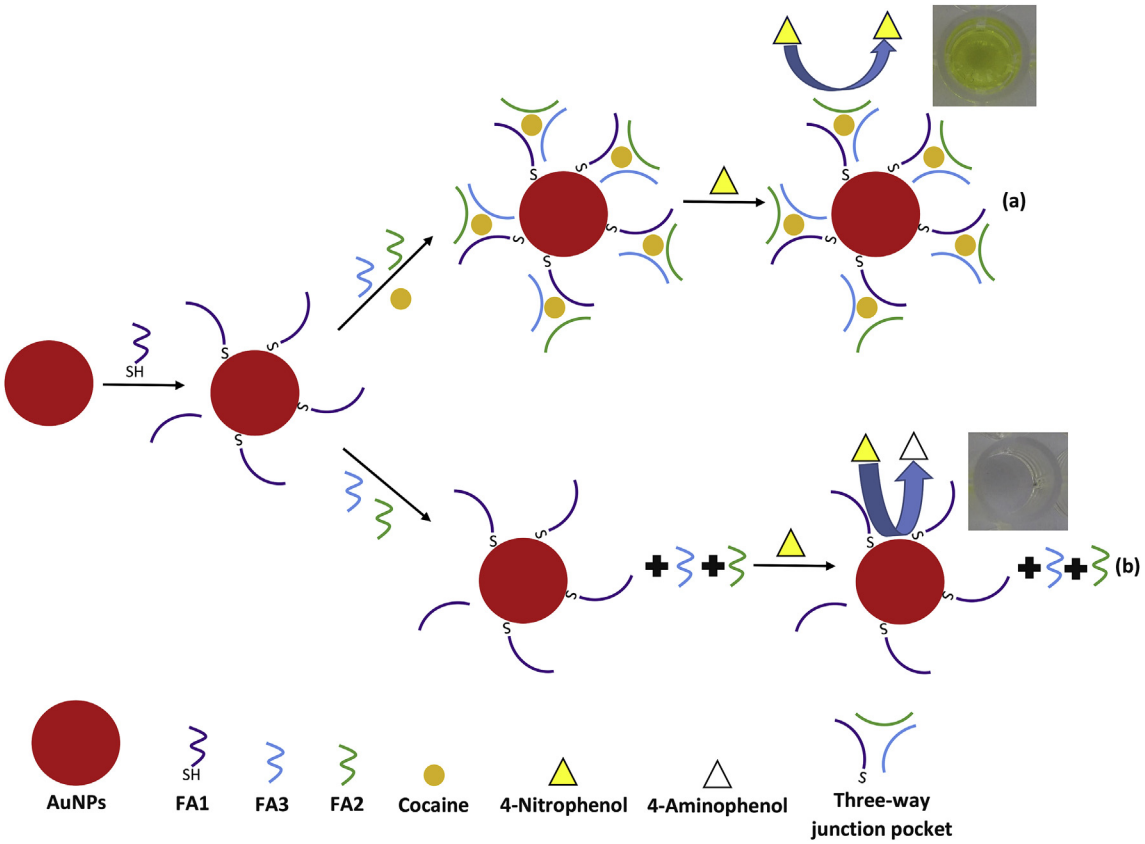

Fig. 7. Schematic diagram of cocaine detection by the three-way junction pockets-based colorimetric aptasensor. Reprinted with permission from Ref (Abnous et al., 2018b).

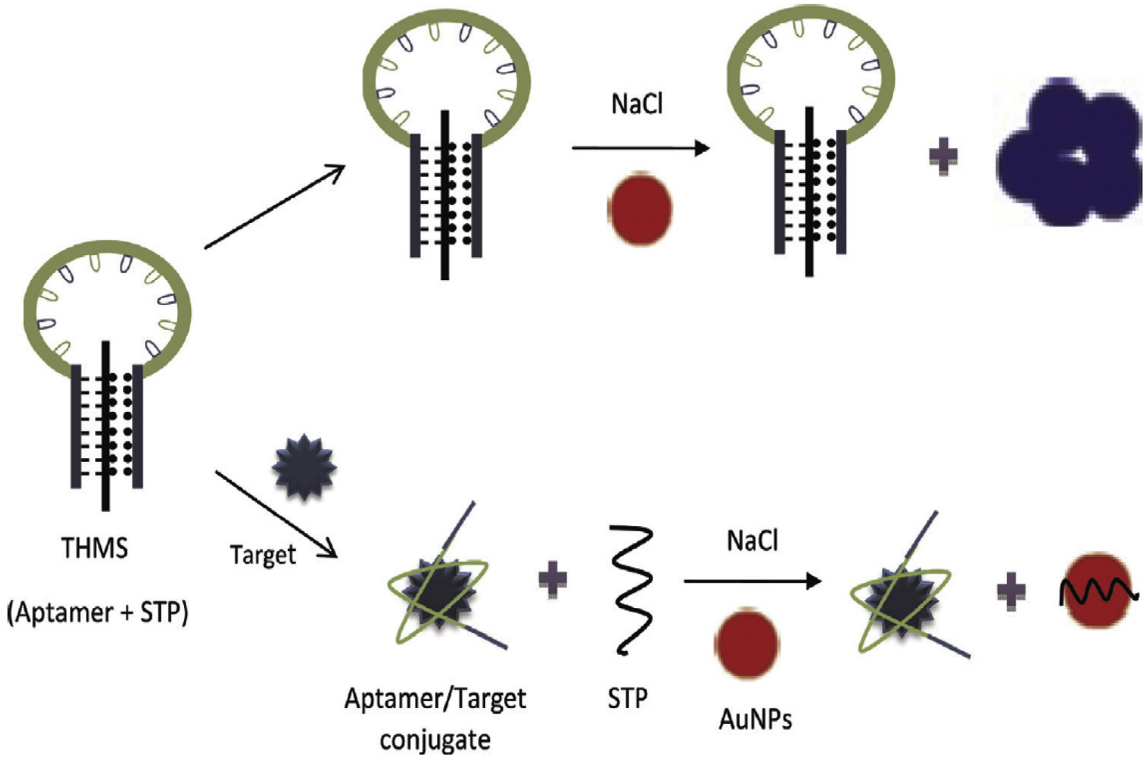

Fig. 8. Schematic description of tetracycline by the colorimetric aptasensor detection based on based on THMS and AuNPs. Reprinted with permission from Ref (Ramezani et al., 2015).

user (Haghighi-Podeh and Bhattacharya, 1996).

In another study a colorimetric aptasensor was fabricated by our team for selective and sensitive detection of tetracycline as a broad-spectrum antibiotic which could have severe side effects on human health and emergence of bacterial resistance to antibiotics in both human and veterinary (Moreira et al., 2010; Tan et al., 2013). This sensing system was based on THMS and AuNPs. The three most important features of this analytical approach include: i) strong binding of ssDNA (STP) to AuNPs, ii) very low interaction of THMS with AuNPs and iii) target-induced release of STP from Apt. In the lack of tetracycline, the structure of THMS (Apt + STP) is unchanged, resulting in the aggregation of AuNPs by adding salt and a clear color change from red to blue. Upon addition of tetracycline, a conformational change occurs and Apt-target conjugate is formed. Thus, STP leaves the THMS and adsorbs on the surface of AuNPs by electrostatic interaction between the negatively charged AuNPs and the positively charged bases of STP (Chang et al., 2013; Liu et al., 2014). As a result, the AuNPs are stable against salt-induced aggregation with a red color (Fig. 8). In this system, the corona shield effect of AuNPs is also observed as a major challenge. The introduced aptasensor indicated high specificity for tetracyclines with a LOD of 266 pM and linear range of 0.3–10 nM toward tetracycline (Ramezani et al., 2015).

The LODs and linear ranges of the aforementioned optical aptasensors are summarized in Table 2.

3. Conclusion and future perspectives

In this review, we comprehensively summarized the developments in DNA origami-based aptasensors using both electrochemical and optical methods. In order to overcome the obstacles of traditional analytical methods including high cost and long detection procedures, researchers have been trying to introduce easy and fast analytical systems with great sensitivity and specificity. Aptamers have been able to make significant contributions to this matter due to their high sensitivity, simplicity and high affinity for their targets. In addition, ease of labeling and modification and high chemical and thermal stability compared to antibodies have made aptamers a valuable tool for using in biosensors. In the meanwhile, the DNA-origami based aptasensors have obtained a lot of attention and have made many advances.

In addition to the usual methods of DNA origami-based biosensors, such as electrochemical or optical methods, new and more advanced techniques have been introduced in the field of sensors, including DNA origami nanopores. They can be used as a new tool in nanotechnology in the field of biosensors, especially when combined with aptamers. This idea is to further target the system and allow screening of drugs capable of interacting with a specific molecular anchor receptor on the DNA origami nanopore (Bell et al., 2011; Feng et al., 2016; Hernández-Ainsa and Keyser, 2014).

Generally, DNA origami-based aptasensors are more sensitive compared to other sensors, but they have been composed of multiple sequences, increasing the cost of their fabrication and this could be considered as a drawback for DNA origami-based aptasensors. On the other hand, the aptasensors face some challenges for application and commercialization. The selectivity and performance of aptasensors depends on the sample conditions such as pH, temperature, ionic strength and viscosity. Moreover, it is difficult to isolate aptamers against small molecules and some interactions of them with the sample matrix cannot be avoided. Perhaps the main obstacle to the use of aptamer in diagnostics can be considered the lack of standardized protocols. In the other words, the different aptamers produced in laboratories against the same target will vary in their affinity, specificity, primary structure and other chemical features. As a result, the protocols developed for one aptamer may not be applicable for other oligonucleotides and taregts. This circumstance makes an obstacle for aptamer application in the diagnosis of human disease which can be resolved via creating standardized kits and protocols based on well-characterized aptamers with optimum features (Lakhin et al., 2013). It should be noted, some of the current presented aptasensors in this review are expected to have the potential to become commercially available in the future.

Table 2
LODs and linear ranges of the optical aptasensors.

Sensing technique	Method	LOD	Linear range	Analyte	Reference
Fluorescent aptasensor	Based on the formation of a DNA pyramid nanostructure	0.135 nM	0.3–10 nM	Ochratoxin A	Nameghi et al. (2016)
Fluorescent aptasensor	Based on the formation of three-way junction structure and ATMND as a fluorescent probe	1.5 pg/mL	4.5 pg/mL to 30 ng/mL	Carcinoembryonic antigen	Danesh et al. (2018)
Colorimetric aptasensor	Based on the formation of three-way junction pockets on the surfaces of gold nanoparticles	440 pM	2–100 nM	Cocaine	Abnous et al. (2018b)
Colorimetric aptasensor	Based on the formation of triple-helix molecular switch structure	266 pM	0.3–10 nM	Tetracycline	Ramezani et al. (2015)

Conflict of interest

There is no conflict of interest about this article.

CRediT authorship contribution statement

Elham Sameiyan: Writing - original draft, Writing - review & editing. **Elnaz Bagheri:** Writing - original draft, Writing - review & editing. **Mohammad Ramezani:** Writing - original draft, Writing - review & editing. **Mona Alibolandi:** Writing - original draft, Writing - review & editing. **Khalil Abnous:** Writing - review & editing, Project administration, Conceptualization. **Seyed Mohammad Taghdisi:** Writing - review & editing, Project administration, Conceptualization.

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.

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