Zn(II) Metal-organic Framework Nanoparticles: Synthesis, Characterization and Application as Optical Biosensor for Prostate-Specific Antigen

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Research Article

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Abstract

PSA, abbreviated of “Prostate-Specific Antigen” is widely used as a considered a significant cancer biomarker for diagnosing prostate cancer. Improvement of a fast, facile, and less cost with high accurate/sensitive/selective methodologies for the PSA determination is still a challenge. In this work, we reported a simple biosensor based on a Zn(II) metal-organic framework nanoparticles (Zn-MOF-NPs) derived from reaction of zinc acetate with nano organic linker. The structure, morphology, and physicochemical properties of the prepared Zn(II)-MOF-NPs were definite using various spectroscopic and microanalytical tools as SEM-EDX, HR-TEM, XRD, XPS, elemental analysis, FT-IR, UV-vis spectroscopy, mass spectroscopy, thermogravimetric Analysis (DSC/TGA), and photoluminescence (PL). Obviously, the results revealed that the Zn(II)-MOF-NPs is chemical stable, highly selective and sensitive to PSA, without interferences with other common interfering analytes. The detection limit for PSA was 0.145 fg/mL, in a wide-linear range of concentrations (0.1 fg/mL-20 pg/mL), with a correlation coefficient 0.983. The Zn(II)-MOF-NPs was successfully used as an up-and-coming biosensor for PSA-monitoring and quantification in biological real samples (plasma/whole blood/serum) at clinical target concentration levels. Moreover, the present approach will help the human-beings from the hazard’s prostatic cancer through early discovery and diagnosis process via the detection of PSA at low limits of concentrations. Meantime, the interaction mechanism between the Zn(II)-MOF-NPs and PSA was well studied and investigated.

Introduction

Recently, prostate cancer, one of the fastest growing types of malignant tumors, has matured in the prostate gland in men [1–3]. Considered the second direct reason for the deaths of the cancer cases in the USA [4]. The symptoms of prostate cancer appeared in the advanced stages in most of cancer cases [3]. So, the early diagnosis of this type of tumor is desirable to minimizing the rate of death through following the therapeutic standard strategies [5]. Recent reports issued by the World Health Organization (WHO) point to the calculated mortality with prostate cancer about 1.7 million per year and may be increased in 2030 by about 0.5 million persons [4][6]. The prostate-specific antigen (PSA) is a glycoprotein secreted by the prostatic gland, consisting of 237 amino acids, and considered an important biomarker for the diagnosis of prostatic cancer via detection of its concentration levels in blood samples [7]. The normal concentration level of PSA in serum samples up to 4.0 ng/mL and increasing the PSA concentration above to 10 ng/mL an indication for the primary stage of prostate cancer [8]. Due to the wide-broad spread of prostate cancer among the male population, many research studies directed development of simple, fast, inexpensive, and accurate methodologies for early prostate cancer diagnosis by detection of PSA. There are numerous analytical methodologies and approaches for PSA-detection such as potentiometric method [6], electrochemical method [9], impedimetric immunosensor [10], voltammetry immune-sensing platform [11], chemiluminescence resonance energy transfer [12], electrochemiluminescence [2, 13, 14], colorimetric aptamer-sensor [15], fluorometric aptamer assay [16], surface plasmon fluorescence [17], time-resolved immunofluorometric assay [18], cooperated signal amplification strategy [19], immunosensor-based photo-electrochemical [20, 21] and sandwich-type
electrochemical [22] assay. However, the above reported techniques or methods each of them has many advantages as well many limitations. Thus, herein, we try to develop a simple fast method to collect the advantages of the above-mentioned methods and decrease the limitations through the applicability, selectivity and sensitivity of nanotechnologies.

On the other hand, the nanomaterials generally and metal-organic frameworks in nano-size-scale (MOF-NPs) especially have many advantages and auspicious properties like chemical and thermal stability, porosity, large surface area, highly magnetic, excellent adsorbent materials ...., etc. [23–32]. Different excellent physicochemical properties of the MOF-NPs make these nanomaterials are very sensitive and selective tools for bonding to biological and organic molecules and can be simply interacted more-effective than bulk state materials [33]. In addition, distinctive properties make MOF-NPs have considerable several applications like sensing, biomedical, drug delivery gas separation/storage, catalysis, etc.[34–39]

In the present work, a novel nanoparticles of Zn(II) metal-organic framework (Zn-MOF-NPs) was prepared via reaction of zinc acetate with nano organic linker previously prepared [37]. The prepared Zn(II)-MOF-NPs was characterized using various micro/analytical techniques for proving the structure and morphology. Then Zn(II)-MOF-NPs was used as a prostatic biomarker (biosensor) for PSA mentoring and quantification based on the results PL-study. The results showed that with raising the concentration of PSA, the Zn(II)-MOF-NPs PL emission spectrum was prociently enhanced. Therefore, the Zn(II)-MOF-NPs could use gainfully as a propitious biosensor for determination of the PSA concentration. Moreover, no interfering with some bio-molecules and common different tumor biomarkers are observed. Furthermore, a contrast between the former reports with the present method is already performed. The comparison proves that the PSA detection based on Zn(II)-MOF-NPs exhibited more: fast, simple, low cost, sensitive, selective, and comfortable to operate. The applicability of the present approach in real serum samples was examined and the analytical and statistical evaluation of the proposed biosensor beside the enhancement mechanism and thermal stability were well investigated.

**Experimental**

**Materials & Instruments**

See the details in “supplementary material file”.

**Procedures**

**Zn(II)-MOF-NPs Synthesis**

The Zn(II)-MOF-NPs was synthesized according to the reaction scheme (Fig. S1), via dropwise addition of zinc acetate (2.0 mmol, 0.489 g) soluble in (15 ml distilled water) to the prepared nano organic linker flask [37], with continued stirring and refluxed for 24 h at 80 °C reaction scheme (Fig. S1). After a few
minutes the solution color changed to brown, then to white precipitate and finally obtained at the end reaction to off-white precipitate. The off-white precipitate was filtered off, washed, and finally dried.

**PL-measurements procedures**

A stock-solution (1 mM) of Zn(II)-MOF-NPs was prepared by dissolving a suitable weight in DMSO. From stock solution, a (10.0 mM) working-solution was prepared via distilled water dilution. The Zn(II)-MOF-NPs (10.0 mM) was examined for PL-measurements at auto-scan mode, then at various excitation wavelengths, and the optimum chosen excitation wavelength based on maximum wavelength emission obtained.

**Determination of PSA using Zn(II)-MOF-NPs & application in real-samples**

The Zn(II)-MOF-NPs PL spectrum (10 mM) against fresh prepared suitable concentrations of PSA, various tumor biomarkers and biomolecules was explored. Upon the optimum conditions of the PL measurements, a relationship (linear curve) was established between the Zn(II)-MOF-NPs PL-intensity at \( \lambda_{\text{em}} = 366 \text{ nm} \) after \( \lambda_{\text{ex}} = 305 \text{ nm} \), in a range of PSA concentration (0.1 fg/mL - 20 pg/ml). The statistic least-squares method was applied for calculation of correlation coefficient and other equation parameters according to the equation: 

\[
Y = a + bX
\]

where \( Y \), is the PL intensity of the Zn(II)-MOF-NPs at \( \lambda_{\text{em}} = 372 \text{ nm} \); \( a \), is the intercept; \( b \), is the slope; and \( X \), is the PSA concentrations”. Additionally, the quantification and detection limits (LOQ and LOD), respectively were estimated from the equations: 

\[
\text{LOQ} = 10 \left( \frac{S}{b} \right) \quad \text{and} \quad \text{LOD} = 3.3 \left( \frac{S}{b} \right \)[40–42] 
\]

where \( S \), is the PL intensity standard-error value; \( b \), is the slopes of the linear-graph”. The PL spectrum of Zn(II)-MOF-NPs also was investigated against different real serum samples spiked with various concentrations of PSA. The serum samples obtained from a disposable sample of a medical lab. The samples were handled, treated affording to typical precautions and guidelines.

**Results And Discussion**

**Zn-MOF-NPs characterization**

The Zn(II)-MOF-NPs was synthesized via a simple reaction of zinc acetate with nano organic linker according to the reaction scheme (Fig. S1). Off-white precipitate is obtained, filtered, then washed and finally dried. The elucidated suggested structure using the acquired micro/analytical data and were investigated as follows:

**FE-SEM/EDX and HR-TEM spectroscopy**

The Zn(II)-MOF-NPs FE-SEM & EDX images are shown in (Fig. 1 a, b, c). The Zn(II)-MOF-NPs morphology represented by FE-SEM images at diverse magnifications (Fig. 1 a, b) seemed to be aggregates of irregular square shapes (1 a) and almost irregular square wood shapes with average size about 118 nm (1b). Whereas, the mapping analysis using EDX (Fig. 1 c and Table 1) of Zn(II)-MOF-NPs showed the
presence of (carbon/oxygen/nitrogen/zinc) as an elements construction block in each single particle. The excellent distribution of block elements alongside the cross-section displayed by EDX mapping (Fig. 1 c) confirmed the Zn(II)-MOF-NPs structure formation. Likewise, from EDX Table (Table 1) the mapping elements percentage were in a good conformity with the element’s percentage calculated theoretically: Theoretically; C, 40.18; N, 6.83; O, 28.99; Zn, 18.23; Found: C, 40.00; N, 6.57; O, 34.87; and Zn, 18.56. The TEM image of the Zn(II)-MOF-NPs appears irregular square nonosheets with average size about 120 nm, (Fig. 1 d). Whereas, (Fig. 1 e, f) shows the SAED image of 3D nanostructure of square sheets.

**Elemental analysis**

The Zn(II)-MOF-NPs CHN-elemental data compared with obtaining by EDX mapping and theoretically calculated were represented in (Table 1). The results were in an excellent conformity with the proposed chemical formula; the Anal. Calc.(%): C$_{48}$H$_{82}$N$_7$O$_{26}$Zn$_4$, (1434.73 g/mol), C, 40.18; H, 5.76; N, 6.83; found C, 39.96; H, 5.95; N, 6.82; with a reaction yield about 87.8 %.

**Mass spectrum**

The Zn(II)-MOF-NPs mass spectrum (Fig. S2) and suggested fragmentation-scheme (Fig. S3) were represented. Fig. S2, showed the m/z peaks which were completely agreed with the proposed empirical-formula (C$_{48}$H$_{82}$N$_7$O$_{26}$Zn$_4$) theoretically calculated and confirmed from CHN-analysis (molecular ion peak at 1434.73 m/z). The subsequent mass fragmentations as represented in Fig. S3, the ion of m/z = 1434.73 subsequent fragmentation, many main peaks at m/z= 943, 716, 488, 229, 171, 149, 108 and 65 due to losing of (ethanol and water molecules) followed by further decomposition of organic skeleton. Mostly, the sequential fragmentations of the Zn(II)-MOF-NPs were totally consistent with the mass spectrum and with the calculated theoretical fragmentations and with the assumed molecular structure.

**FT-IR and UV-vis spectra**

The Zn(II)-MOF-NPs IR-spectrum compared with nano organic liker is shown in (Fig. S4). The peaks at 3440, 3140, 3018, 2928 and 1157 cm$^{-1}$ are due to stretching of amine groups, water and ethanol molecules of the compound [43]. The peak at 3263 cm$^{-1}$ is apportioned to the stretching of N-H. The sharp-bands at 1640, 1585, 1560, 1476 and 1364 cm$^{-1}$ are apportioned to stretching of C=O, C=N, and C=C [26, 44]. The bands between at 1024 and 771 cm$^{-1}$ are apportioned to CH. The bands at 540 and 418 cm$^{-1}$ apportioned to the coordination and covalent bonding of zinc ion with O and N [$\nu$(Zn–O), (Zn<−N)], respectively [44–46]. The appearing of the above new bands approved the chelation between the zinc ion and nano organic linker through the N and O [44–46]. A comparison of the electronic-reflection spectra (Fig. S5) and bandgap energy (BGE) (Fig. S6) of the Zn-MOF-NPs with nano organic linker were investigated. From Fig. S5, it observed that the Zn-MOF-NPs displays various reflection bands at 235, 271, 330, 385, 408 and 634 nm, these bands may be due to LMCT and intra-ligand $\pi$- $\pi^*$, n-$\pi^*$ [47]. Moreover, from the BGE spectra Fig. S6, it can be noted a decrease in the BGE values of the MOF to 1.79, 2.95, and
3.50 eV than linker due to the conjugation within the organic skeleton of the linker leads to rise of the BEG for HOMO valance [26, 36]

**XRD and XPS analysis**

The Zn-MOF-NPs XRD spectrum in comparison with Zn-MOF published-reports [48, 49] was introduced in (Fig. 2 a). The Zn-MOF-NPs XRD patterns displayed sharp-peaks proved the Zn-MOF-NPs crystalline-phase was progressed. Furthermore, the diffraction patterns matched with standard ZIF-8 and some prepared Zn-MOFs XRD patterns that demonstrated the efficacy synthesis of Zn MOF-NPs [48, 49]. The details of the XRD data estimated using Scherrer-equation were presented in (Tables S1 and S2). The results revealed that the crystallites size about 120 nm which confirmed SEM and TEM results [50].

The XPS-analysis of the synthesized Zn-MOF-NPs sample is represented in (Fig.2 b:e) proved the presence of C, O, N, and Zn without any impurities in the sample. The XPS spectrum of Zn 2p (Fig. 2b) showed a signal at 1020.92 eV ascribed to Zn(II) 2p3/2 satellite peak to prove the existence of Zn\(^{2+}\) in the Zn-MOF sample [51]. The O 1s spectrum (Fig. 2c) showed 3-peaks of (O-Zn-O, C-O and C=O) at (530.34, 531.25, and 533.22 eV), respectively [52–54]. The N 1s spectrum (Fig. 2d) showed a satellite peak at 398.16 eV. Finally, the C 1s spectrum (Fig. 2e) showed 3-signals at (282.85, 286.52, and 289.59 eV) are appointed to (C-C, C-N, and C=O), correspondingly [51].

**Thermal analysis and thermal stability of the Zn(II)-MOF-NPs**

The thermal behavior of Zn-MOF-NPs (TGA/DSC) plots (Fig. 2f) implied that the Zn-MOF-NPs underwent four breakdowns’ stages. The first and second weight loss due to the loss of \(\text{C}_2\text{H}_5\text{OH}\) and intra/inter H\(_2\)O molecules in a temperature between 65 to 226.0 °C [55]. The third and fourth decomposition stages due to the breakdowns of organic skeleton in a temperature started from 440.0 °C. The remaining residue is zinc about (18.11 %), the discussed data was in conformity with obtaining from mass spectrometry and XRD data [56, 57]. Moreover, from the thermogravimetric behavior of the Zn(II)-MOF-NPs the results indicate the formed MOF is stable thermally at high-temperature reached to 440.0 °C [56, 57].

Based on the above discussed data, it can be deduced the 3D-structure of the Zn-MOF-NPs (Fig. 3 a), and the advanced-molecular-surface (Fig. 3 b).

**Photoluminescence study & applications**

The PL excitation spectrum against an emission spectrum of the Zn-MOF-NPs via auto-scan mode was presented in (Fig. 4a), the PL Zn-MOF-NPs spectrum showed an emission band at 366 nm at excitation wavelength 365 nm. Moreover, the PL spectrum of the Zn-MOF-NPs at different excitation wavelengths was recorded and presented in (Fig. S8). The fluorescent performance of the Zn-MOF-NPs may be due to intra-ligand n/π - π* transition, and molecular-orbital transitions within ligand-metal charge transferring (LMCT). On the other hand, Zn-MOF-NPs were used as optical-biosensors for detection of PSA and quantification. The Zn-MOF-NPs PL spectrum (at \(\lambda_{ex}=305\) nm) (10.0 mM) was investigated against a
series of PSA concentrations and the results were presented in (Fig. 4b). As represented in (Fig. 4b); via increasing the PSA concentrations, the Zn-MOF-NPs PL intensity was remarkably increased in a PSA range of concentration (0.1 fg/ml to 20 pg/ml) with a slight red-shift (6.0 nm) from 366 nm to 372 nm. The results proved that the Zn-MOF-NPs could be considered as a promising biosensor based on spectrofluorimetric phenomena for detection PSA and quantification after considering the method evaluations and statistical parameters.

**Method validation and analytical merits**

The full calibration curve linking the PL intensity of Zn-MOF-NPs at $\lambda_{em}=372$ nm, and the concentration of PSA in a range between 0.1 fg/ml to 20 pg/ml were represented in (Fig. S9). Under ideal conditions for PL measurements, the linear-dynamic relationship for Zn-MOF-NPs PL biosensor (Fig. 4c) was obtained. From (Fig. 4c), the spectral PL intensities were strongly dependent on the rising in concentration of PSA. The calibration graph showed a well relationship (linear curve) over a range between (0.1 – 1000.0 fg/mL). The fitting enhancement equation can be stated as:

$$\text{Zn-MOF-NPs PL intensity} = 523.01 + 105.21 \log[\text{PSA}]$$

with $r^2 = 0.983$.

The LOD for Zn(II)-MOF-NPs optical photoluminescence biosensor was estimated to be 0.145 fg/mL, while the LOQ was 0.438 fg/mL. The brief of the analysis of PL regression data is presented in Table S3. From Table data, the LOD / LOQ low values and wide linear concentration ranges for the proposed optical photoluminescence biosensor a validation for sensitivity. Additionally, comparing the performances of the current biosensor with other previous literature reports for the PSA quantification and determination was presented in (Table 2). From this Table, the present optical photoluminescence biosensor showed a lower LOQ / LOD, and wide linear detection PSA ranges in comparison with previous methods.

The selectivity of the present optical photoluminescence Zn(II)-MOF-NPs based biosensor was investigated to evaluate its ability to respond primarily to PSA in the existence of interfering analytes as some tumor biomarkers and different biomolecules. The PL spectrum of Zn(II)-MOF-NPs (10 mM) was measured against PSA (0.1 pg/mL), CEA “carcinoembryonic antigen” (10 ng/mL), AFP “alpha-fetoprotein” (10 ng/mL), CK-T “creatine kinase total” (10.0 ng/mL), CK-MB “creatine kinase muscle\brain” (10.0 ng/mL), glucose (100 mg/dL), uric acid (10 mg/dL), starch (10.0 M), bilirubin (10.0 mg/mL), cholesterol (10.0 mg/mL), mixture of matrix. The results of selectivity study were summarized and presented in a histogram (Fig. 4d). From the histogram it can be noted that a remarkable enhancement in the Zn(II)-MOF-NPs PL intensity with slight redshift was observed in case of PSA whereas, no observed any response for the different interfering matrix. Therefore, we can conclude that the Zn(II)-MOF-NPs is exceptionally specific and selective for PSA over other interfering matrices.

The precision, accuracy, recovery, and applicability of proposed optical photoluminescence biosensor based Zn(II)-MOF-NPs to detection of PSA and quantification in real serum samples was investigated. This study was performed via spiking of different concentrations of PSA standard (1.0, 100.0, 500.0, 1000.0 and 2000.0 fg/mL) to real serum samples and each test repeated three times, and the results of
investigation were summarized in (Table 3). From the Table data and statistical evaluations of results, the mean values (X) were in target, the lower values of relative-error present (RE %) average 1.01% and relative standard deviation (SD) average 4.27 % reflect the accuracy and precision of the proposed method. Additionally, the average percent recoveries (RC %) was about 99.02% and this means that the current optical photoluminescence biosensor may be used for the detection of PSA as an important cancer biomarker diagnosis for prostate at ultra-low concentration levels with sufficient accuracy and precision.

**Conclusion**

This work present optical photoluminescence biosensor based on a novel promising Zn(II)-MOF-NPs, which was synthesized and well characterized. The morphology of the synthesized Zn(II)-MOF-NPs appeared to be irregular square wood shapes with average size about 118 nm (1b). As well the thermal stability results showed a significant stability of the Zn(II)-MOF-NPs. The photoluminescence study results revealed that Zn(II)-MOF-NPs could use as an auspicious optical biosensor for determination of PSA concentration in real samples (serum samples). The evaluation of the current approach overall was fit for purpose statistically. The PSA LOD was 0.145 fg/mL, over range (0.1 fg/mL – 20.0 pg/mL), with r² of 0.983. Comparison of this work with the others published-reports revealed that it’s faster, simpler, and costless. Also, highly sensitive and selective, as well lower LOQ and LOD, and apply for real serum samples. The results revealed a promising future crucial tool for monitoring and quantification of PSA, which is a vital early diagnostic tool for a most common cancer (prostate cancer) among men in all the world and helps to monitor public men’s human health issues.

**Declarations**

**Acknowledgements**

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**Declaration of interests**

- 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.

- The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Tables

Table 1: Theoretically elemental calculated, elemental analysis and EDX analysis of the Zn(II)-MOF-NPs.
### Table 2: Comparison between the Zn(II)-MOF-NPs biosensor and some existing methods for the determination of PSA.

<table>
<thead>
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<th>Element</th>
<th>Theoretically calculated</th>
<th>Found CHN elemental analysis</th>
<th>Found EDX analysis</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight %</td>
</tr>
<tr>
<td>C</td>
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<td>39.96</td>
<td>40.0</td>
</tr>
<tr>
<td>H</td>
<td>5.76</td>
<td>5.95</td>
<td>—</td>
</tr>
<tr>
<td>N</td>
<td>6.83</td>
<td>6.82</td>
<td>6.57</td>
</tr>
<tr>
<td>O</td>
<td>28.99</td>
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</tr>
<tr>
<td>Zn</td>
<td>18.23</td>
<td>—</td>
<td>18.56</td>
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<tr>
<td>Method</td>
<td>Linear detection range</td>
<td>LOD</td>
<td>Reference</td>
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<td>--------------------------------</td>
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<td>Impedimetric immunosensor</td>
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<td>Voltammetry immunosensing platform</td>
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<td>Chemiluminescence resonance energy transfer (CRET)</td>
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<td>Electro chemiluminescent immunosensor</td>
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<td>Optical photoluminescence biosensor based Zn(II)-MOF-NPs</td>
<td>0.1 fg/ml to 20 pg/ml</td>
<td>0.145 fg/mL</td>
<td>The present work</td>
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**Table 3.** Determination of PSA in serum real sample using Zn(II)-MOF-NPs biosensor and evaluation of accuracy, and precision.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Spiked PSA (fg/mL)</th>
<th>Found (fg/mL)</th>
<th>X</th>
<th>SD</th>
<th>RE %</th>
<th>R%</th>
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<tr>
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<td>0.999</td>
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</table>
Figures

Figure 1

(a, b) The field-emission scanning electron microscopy images of the Zinc(II) metal–organic framework nanoparticles (Zn(II)-MOF-NPs) at different magnification, (c) Energy-dispersive X-ray analysis with a single point EDX mapping analysis of Zn(II)-MOF-NPs, and (d, e, and f) The transmission electron microscopy image (TEM) of and SAED images of 3D nanostructure the of the Zn(II)-MOF-NPs.
Figure 2

(a) The powder XRD patterns zinc(II) metal–organic framework nanoparticles (Zn(II)-MOF-NPs), (b) to (e) The XPS analysis of the Zn(II)-MOF-NPs: [(b) Zn 2p, (c) O 1s, (d) N 1s, and (e) C 1s]; (f) The thermogravimetric analysis (TGA-DSC) of the Zn(II)-MOF-NPs.
Figure 3

(a) The 3D Structural representation of the Zn(II)-MOF-NPs monomeric unit, (b) Advanced molecular surface representation of the Zn(II)-MOF-NPs monomeric unit.

Figure 4

(a) Excitation (Blue line) and emission (black line) spectra of Zn(II)-MOF-NPs, (b) The photoluminescence spectra response for behavior of Zn(II)-MOF-NPs towards different concentrations of PSA, (c) A Linear relationship (calibration graph) between the photoluminescence intensity of Zn(II)-MOF-NPs and the
logarithm PSA concentrations (log [PSA]), and (d) The photoluminescence intensity of the Zn(II)-MOF-NPs toward the PSA against different types of interfering analytes histogram.

**Supplementary Files**

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