Sensors & Actuators: B. Chemical 320 (2020) 128285

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

# Au-Pt nanoparticles based molecularly imprinted nanosensor for electrochemical detection of the lipopeptide antibiotic drug Daptomycin

Goksu Ozcelikay[a], Sevinc Kurbanoglu[a], Aysu Yarman[b], Frieder W. Scheller[b], Sibel A. Ozkan[a,*]

[a] Ankara University, Faculty of Pharmacy, Department of Analytical Chemistry, Tandogan, Ankara 06100, Turkey
[b] University of Potsdam, Institute of Biochemistry and Biology, Karl-Liebknecht-Strasse 24-25, 14476 Potsdam, Germany

ARTICLE INFO

*Keywords:*
Molecularly imprinted polymer
Daptomycin
Platinum nanoparticles
gold nanoparticles
modified electrodes

ABSTRACT

In this work, a novel electrochemical molecularly imprinted polymer (MIP) sensor for the detection of the lipopeptide antibiotic Daptomycin (DAP) is presented which integrates gold decorated platinum nanoparticles (Au-Pt NPs) into the nanocomposite film. The sensor was prepared by electropolymerization of *o*-phenylenediamine (*o*-PD) in the presence of DAP using cyclic voltammetry. Cyclic voltammetry and differential pulse voltammetry were applied to follow the changes in the MIP-layer related to rebinding and removal of the target DAP by using the redox marker $[Fe(CN)_6]^{3-/4-}$. Under optimized operational conditions, the MIP/Au-Pt NPs/GCE nanosensor exhibits a linear response in the range of 1-20 pM towards DAP. The limit of detection and limit of quantification were determined to be 0.161pM ± 0.012 and 0.489pM ± 0.012, respectively. The sensitivity towards the antibiotics Vancomycin and Erythromycin and the amino acids glycine and tryptophan was below 7 percent as compared with DAP. Moreover, the nanosensor was also successfully used for the detection of DAP in deproteinated human serum samples.

## 1. Introduction

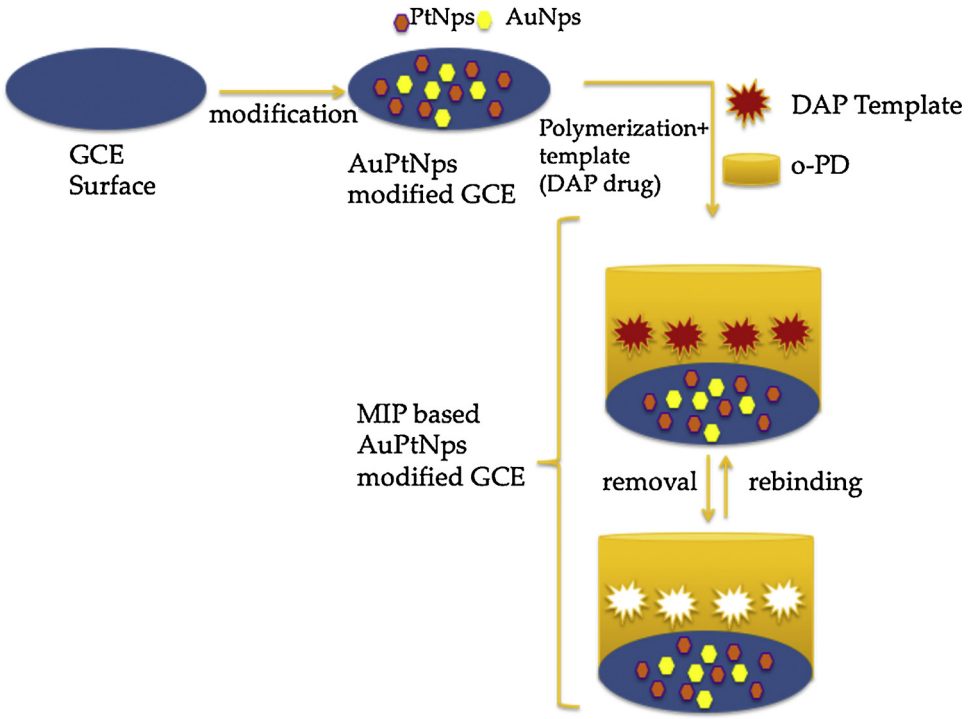
The cyclic lipopeptide DAP was the first approved drug of a new class of antimicrobials [1–3]. DAP presents a broad spectrum of activities against a wide range of gram-positive bacteria. It is composed of a peptide moiety containing 3 D- and 10 L- amino acids [4,5]. It binds to calcium and enters the cytoplasmic cell membrane of gram-positive bacteria, rapidly depolarizing the cell membrane. Depolarization causes inhibition of DNA, RNA and protein synthesis [6,7]. For appropriate application of antibiotics, accurate clinical diagnosis, selection of the most appropriate drug, its dosage and amount are very important [8]. Therefore, its determination in bulk and biological samples has gained great attention. In literature there exist mainly chromatographic methods for the determination of DAP such as HPLC [9–11], LC-MS [12–14] UPLC–PDA [15]. Voltammetric determination of DAP exploiting the electrochemical oxidation of DAP on glassy carbon electrode has been conducted by Brett's group [16] and there is no work in the literature on sensors based on molecularly imprinted polymers for DAP. MIP is biomimetic recognition elements which contain selective recognition sites for a target molecule, the so-called template, in a polymer matrix: They are prepared by polymerizing functional monomers with or without cross-linkers in the presence of the template molecule, which is subsequently removed [17–20]. This process leads to the formation of cavities in the polymer, which are to some extent complementary in size, shape and functionality to the template [17,18,21]. Therefore, it is preferentially rebound even from complex mixtures [17,22–28]. Due to their high selectivity along with their cost-effectiveness, high stability, and versatility MIP-based sensors have been successfully developed for drugs [29–42].

Metal nanoparticles have been used in electrochemical nanosensor to increase the surface-to-volume ratio of the recognition layer. Among different nanomaterials, gold nanoparticles (AuNPs) are most frequently used in fabrication of nanosensor. They can easily be immobilized on the surface of electrodes and have high adsorption ability to facilitate the electron transfer [43–45]. Platinum nanoparticles (PtNPs) are promising candidates in nanosensor design showing remarkable catalytic activity, high corrosion resistance [46,47].

In this work, we combine for the first time MIPs with Au-Pt NPs to design an electrochemical molecularly imprinted polymer based nanosensor for the detection of the lipopeptide antibiotic Daptomycin. The MIP was prepared on the Au-Pt NPs modified GCE by the electropolymerization of *o*-PD in the presence of DAP. Subsequent removal of the template led to the formation of selective binding cavities for the rebinding of DAP in the pM concentration range. Moreover, DAP detection using the MIP/Au-Pt NPs/GCE nanosensor in deproteinated human serum sample was tested.

* Corresponding author.
*E-mail address:* ozkan@pharmacy.ankara.edu.tr (S.A. Ozkan).

https://doi.org/10.1016/j.snb.2020.128285
Received 27 January 2020; Received in revised form 30 April 2020; Accepted 10 May 2020
Available online 23 May 2020




**Scheme 1.** Preparation procedure of the MIP/Au-Pt NPs/GCE for DAP.

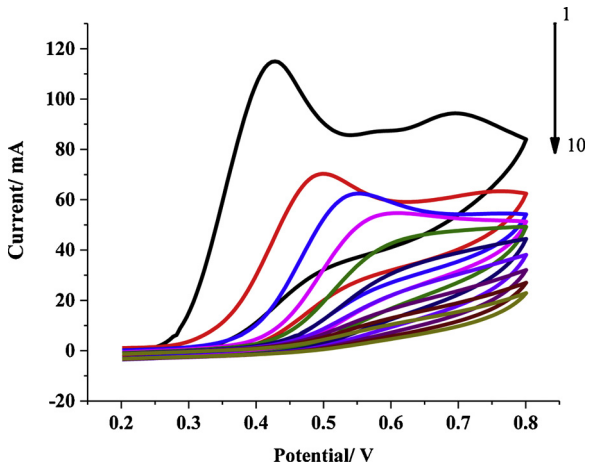



**Fig. 1.** Cyclic voltammograms during electropolymerization of *o*-PD on Au-Pt NPs/GCE.

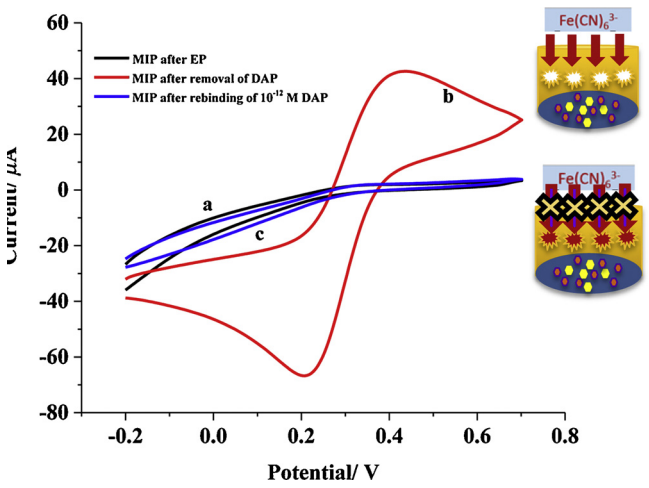



**Fig. 2.** Cyclic voltammograms of a)MIP/Au-Pt NPs/GCE after MIP synthesis b) after removal of DAP c) after rebinding of 1 pM DAP, 5 mM $[Fe(CN)_6]^{3-/4-}$ mixture solution in 100 mM KCl scanning between −0.2 and 0.8 V at a scan rate of 50 mV/s.

## 2. Experimental

### 2.1. Reagents

*o*-PD, PtNPs dispersion (3 nm in $H_2O$), were purchased from Sigma-Aldrich. AuNPs were from Nanocos, Canada, with a size of 10 nm and a concentration of 0.01% AuNPs in water solution. DAP (lot 010903A) was supplied from Cubist, Inc., Lexington, MA. Potassium hexacyanoferrate (II) and hexacyanoferrate (III) were obtained from Merck. All reagents were of analytical grade, used without further purification, and double distilled water from a Millipore Milli-Q system was used in all sample preparations. A stock solution of human serum (human male AB plasma) was purchased from Sigma-Aldrich (St. Louis, MO, USA).

### 2.2. Instruments

PalmSens potentiostat (Utrecht, The Netherlands) was used for cyclic voltammetry and differential pulse voltammetry (DPV), with a three electrode system including glassy carbon electrode (GCE) with a diameter of 3 mm as working electrode, an Ag/AgCl (BAS; 3 M KCl) electrode as the reference electrode, and a platinum wire as the counter electrode. pH measurements were carried out by a pH meter Model 538 (WTW, Austria) with a combined glass electrode. The modified electrodes were characterized by SEM and energy dispersive X-ray (EDX) analysis using ZEISS EVO 40 (Merlin, Carl Zeiss).

### 2.3. Preparation of solutions

The nanocomposite solution was obtained by ultrasonication and

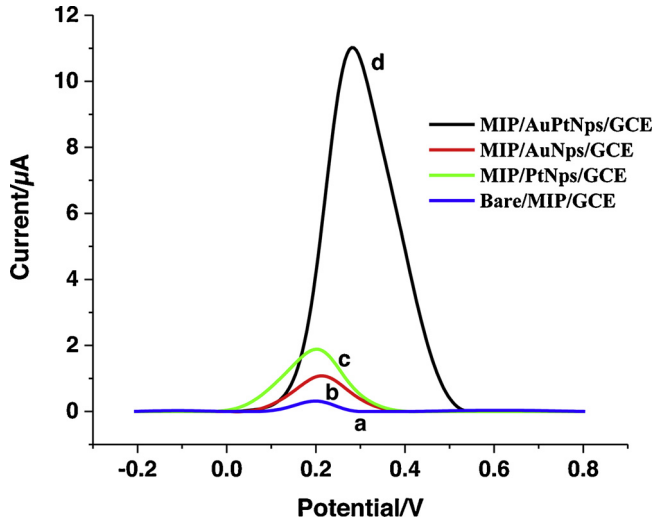



**Fig. 3.** Effect of modification of MIP nanosensors on the DPV of the 5 mM $[Fe(CN)_6]^{3-/4-}$ redox marker after DAP removal a) bare MIP/GCE b) MIP/AuNP/GCE, c) MIP/PtNP/GCE, d) MIP/Au-Pt NPs/GCE.

mixing the dispersions of AuNPs and PtNPs in a ratio of 2 to 1. 100 mM acetate buffer (pH 5.2) was prepared by mixing 2.90 mL acetic acid and 3.281 gr sodium acetate. Stock solution of *o*-PD (10 mM) was prepared in 5 mL acetate buffer (100 mM, pH 5.2) by weighing 9.0 mg *o*-PD. In order to prepare 5 mM $[Fe(CN)_6]^{3-/4-}$ solution, 0.745 gr KCl(0.1 M) was dissolved in ultradistilled water and 82.3 mg $K_3[Fe(CN)_6]$ and 105.6 mg $K_4[Fe(CN)_6].3H_2O$ was added to 0.1 M KCl solution to obtain 5 mM $[Fe(CN)_6]^{3-/4-}$.

### 2.4. Preparation of MIP/Au-Pt NPs/GCE Nanosensor

Prior to the modifications, the surface of electrode is ultrasonicated in water and ethanol. Then, the surface of the GCE was cleaned with alumina slurry (size of alumina: 1.0 micron) on a polishing pad, rinsed with distilled water and dried in air. After that, nanosensors were prepared by dropping 5 μL of the mixture PtNP-AuNP (2:1) on the surface of the GCE. After drying at ambient room temperature, Au-Pt NPs modified GCEs (Au-Pt NPs/GCE) were used to prepare MIP- and NIP-electrodes (non-imprinted polymer). For preparation of MIP and NIP, 5 mM *o*-PD solution was prepared in acetate buffer pH 5.2 [48–50]. For NIP based nanosensors, 5 mM *o*-PD was electropolymerized on the Au-Pt NPs/GCE by cyclic voltammetry between 0 and 0.8 V with 10 scans at a scan rate of 50 mV/s. DAP-imprinted Au-Pt NPs/GCE were prepared in the same way, but in the presence of 0.5 mM DAP. Template molecules were removed by rotating the electrode in 0.1 M NaOH at room temperature for 3 h at 300 rpm. Rebinding of DAP and its removal were followed by CV in 5 mM $[Fe(CN)_6]^{3-/4-}$solution (in 100 mM KCl) by sweeping between -0.2 and 0.8 V (three scans) at a scan rate of 50 mV/s. The workflow of the electrosynthesis of MIPs and NIPs, template removal and readout is presented in Scheme 1.

### 2.5. Preparation of biological samples

The developed MIP/Au-Pt Nps/GCE sensor was also applied to detect DAP in spiked deproteinated serum samples. For this purpose, standard solutions of human serum derived from human male AB plasma were prepared. By mixing 5.4 mL of acetonitrile, 3.6 mL of the synthetic serum sample and 1.0 mL of 10 nM DAP-solution, the stock solution containing 1 nM DAP was prepared. The purpose of acetonitrile addition was to precipitate the protein residues in the sample. Blank serum is prepared with 5.4 mL of acetonitrile, 3.6 mL of synthetic serum sample and 1.0 mL of 100 mM acetate buffer(pH 5.2). The solutions were centrifuged for 25 min at 3000 rpm and the supernatants were then collected before the experiments. For the electrochemical analysis, aliquot from the stock solution of serum were used for rebinding of DAP.

## 3. Results and Discussion

### 3.1. Design of MIP/Au-Pt NPs/GCE nanosensor

For the preparation of MIP nanosensor, electropolymerization of *o*-PD was performed using cyclic voltammetry as shown in Fig. 1. As control, NIPs were also prepared without DAP. Cyclic voltammograms of the redox marker $[Fe(CN)_6]^{3-/4-}$ for all steps of MIP synthesis and rebinding are demonstrated in Fig. 2.

It can be seen from Fig. 2a that after MIP preparation on the surface of the Au-Pt NPs/GCE the permeation of the redox marker is partially suppressed by the DAP-containing poly-*o*-PD film. Removal of DAP from the Au-Pt NPs/GCE - *o*-PD film by the treatment in NaOH generates cavities which allow the redox marker to reach the electrode surface (Fig. 2b). The following rebinding of DAP decreased the $[Fe(CN)_6]^{3-/4-}$ response in a concentration dependent manner (Fig. 2c).

The influence of the NPs on the performance of the MIP was investigated by DPV. Different nanomaterials such as AgNPs, PtNPs and AuNPs were used to modify the surface of GCE prior the electropolymerization in order to increase the MIP performance. After removal of DAP for 3 h, the peak current of 5 mM $[Fe(CN)_6]^{3-/4-}$ was approximately 27 times higher at the MIP/ Au-Pt NPs /GCE as compared to the bare MIP/GCE which indicates the effect of the increased active surface area by the NPs (Fig. 3, Table SI. 1). This modification was used in the further experiments.

### 3.2. Characterization of the MIP/Au-Pt NPs/GCE nanosensor by scanning electron microscopy and energy dispersive X-ray analysis

Scanning electron microscopy and energy dispersive X-ray analysis techniques were used to characterize and follow the modification of the GCE. SEM images of the MIP/ Au-Pt NPs /GCE before and after removal and after rebinding are presented in Fig. 4A–C. Moreover, the changes in the amount of C, N, O from EDX results indicates the removal (Fig. SI.1) and rebinding of the DAP from the surface of MIP/ Au-Pt NPs/GCE nanosensor and indicates the presence of PtNPs and AuNPs (Fig. 4D).

### 3.3. Analytical performance of the MIP sensor

In order to optimize removal time, MIP/ Au-Pt NPs /GCE and NIP/ Au-Pt NPs /GCE were kept in 0.1 M NaOH solutions for different removal times. 3 h of template removal with rotation at 300 rpm, in 0.1 M NaOH, was optimal. After the template removal the MIP electrode was incubated in 0.5 M acetate buffer (pH 5.2) for rebinding of DAP for different incubation times and 5 min rebinding was found as optimum and used for all studies.

When the MIP/Au-Pt NPs/GCE modified MIP electrode was incubated in solutions containing different concentrations of DAP, the cavities in the film were occupied by DAP, which led to the concentration dependent decrease of the peak current signal produced by the redox marker. $\Delta I = I_0 - I_c$, equation was used where, $I_0$ is the currents after template removal and Ic after rebinding of DAP at related concentration in pM, respectively.

Under optimized operational conditions, the decrease of the DPV peak current of the MIP/Au-Pt NPs/GCE nanosensor depended on the DAP concentration from 1 to 20 pM DAP (Fig. 5A). The regression equation for DAP is $\Delta I$ (μA) = 0.228 (μA.pM$^{-1}$)c + 0.355 (μA, n = 3) and the regression coefficient (R) is 0.996.

The electrochemical sensitivity from dividing the slope of the concentration dependency (Fig. 5B) by the geometric surface area of the electrode was found as 3.257 μA/pM cm$^2$.

On the other hand, incubation of the NIP-sensor in DAP-containing

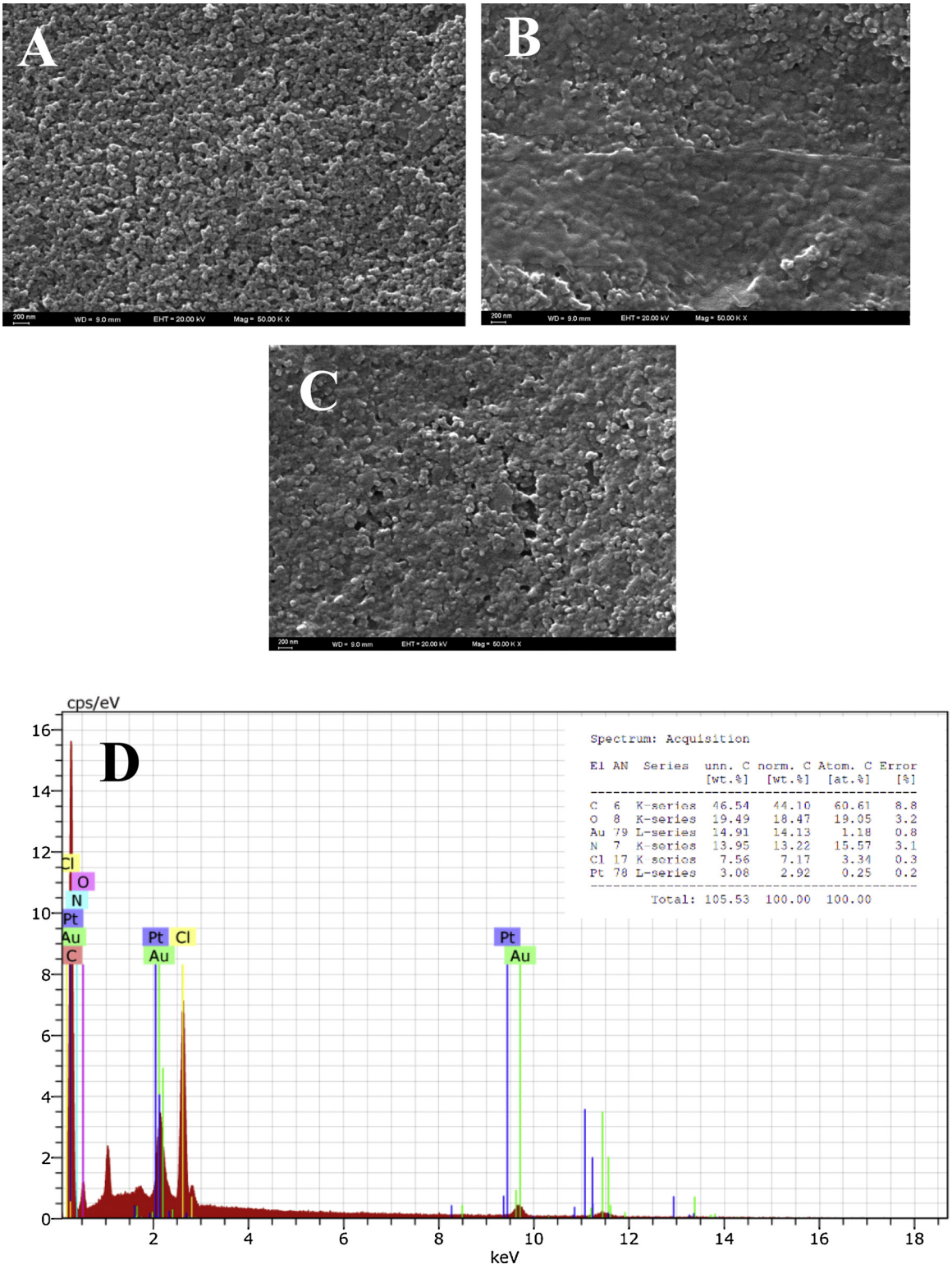



**Fig. 4.** SEM images of MIP a) before and b) after template removal c) after rebinding d) EDX results of MIP after rebinding. (All images were taken at a magnification level of 50,000×).

solution had only a very small effect on the peak current of the redox marker. At 20 pM the MIP electrode showed a 5.81-fold higher signal as compared with the NIP i.e. the imprinting factor is 5.81.

Limit of quantification and limit of detection values were determined as 0.489 pM ± 0.012 and 0.161 pM ± 0.012, according to 3.3ss/m and 10ss/m equations, respectively [51]. The dependence of the DPV responses on the concentration of Daptomycin for NIP/Au-Pt NPs/GCE is presented in Fig. 5B.

Furthermore, rebinding studies were performed using different concentrations of DAP in deproteinated human serum samples. In human serum sample studies, differential pulse voltammograms of DAP were recorded in 5 mM $[Fe(CN)_6]^{3-/4-}$ mixture in 0.1 M KCl. In order to characterize the effect of serum, control experiments were performed using DAP-free human serum sample as a blank. The current after

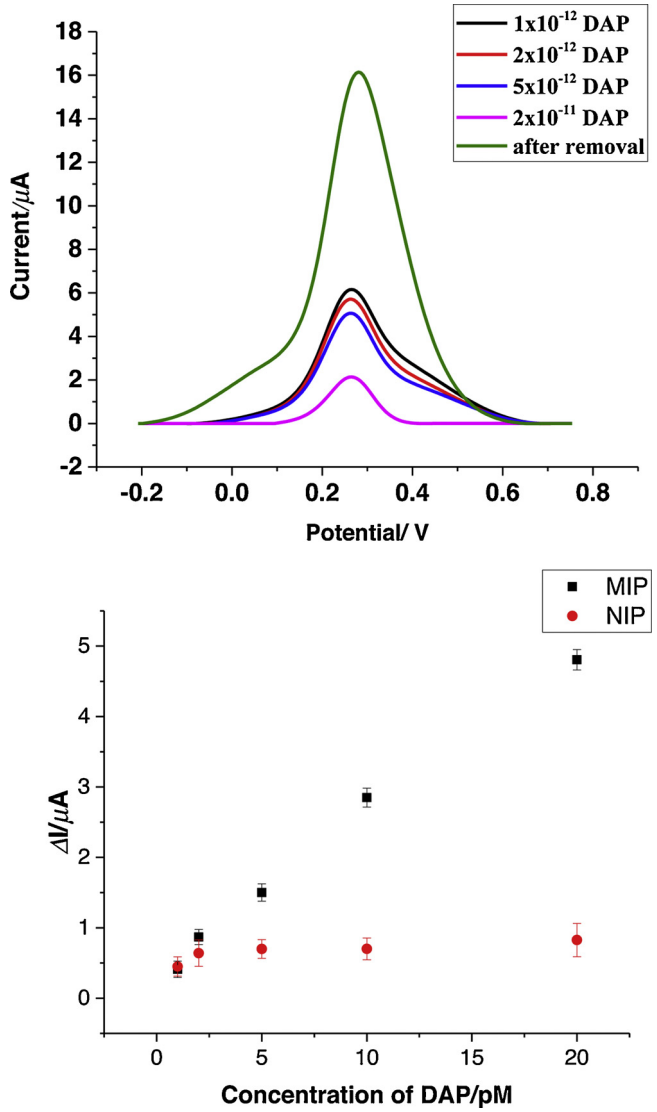



**Fig. 5.** DPVs of the MIP/Au-Pt NP/GCE after immersion in different DAP concentration from 1 pM to 20 pM(A) and Dependence of current decrease ΔI of MIP/Au-Pt NPs/GCE and NIP/Au-Pt NPs/GCE (B).

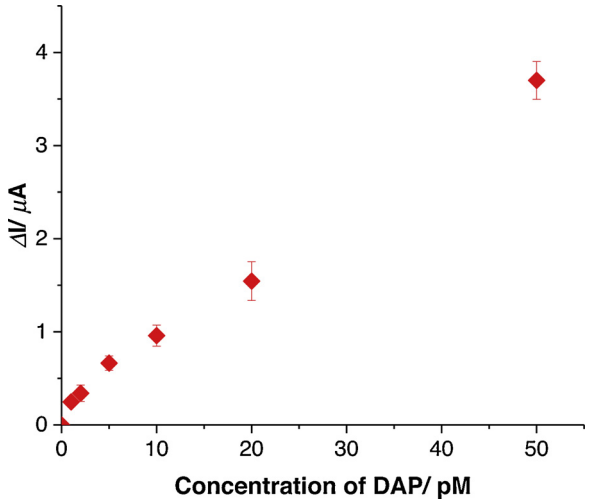



**Fig. 6.** Linear calibration curve of ΔI with DAP concentrations in human serum using the MIP/Au-Pt NPs/GCE.

template removal decreased on addition of human serum from 4.46 μA to 4.02 μA and this value was used as the blank. With increasing concentration of DAP, the difference to the blank increased in the range of 1–50 pM (Fig. 6). The regression equation for the concentration dependence is ΔI (μA) = 0.069(μA.pM$^{-1}$)c + 0.227 (μA, n = 3) and the regression coefficient (R) is 0.999.

The detection limit of DAP was 0.310 pM ± 0.007 and LOQ value of 0.940 pM ± 0.007. The parameters of the calibrations plots are summarized in Table SI. 2. The LOD of the designed nanosensor indicates that our proposed method could potentially be employed to monitor DAP concentration with high sensitivity. In the current work MIP/Au-Pt Nps/GCE shows a wide linear concentration range and lower LOD than reported values for DAP drug at different modified electrodes as presented in Table 1.

The MIP-sensor has been tested in a medium, which is typically used in HPLC analyses of biological samples. The reason for the required "sample pretreatment" is the presence of of highly abundant proteins in the millimolar concentration region whilst protein biomarker or drugs are in the nanomolar range. Since MIP-sensors represent only one "separation plate", it is challenging to reach the required selectivity in non-pretreated biological samples. Therefore, testing of MIP-sensors in semi-synthetic serum or artificial urine is generally reported in literature [52].

### 3.4. Selectivity studies

The selectivity of the MIP/ Au-Pt NPs /GCE nanosensor, which is the most important validation parameter, was characterized by comparing the binding of 10 pM DAP, Vancomycin and Erythromycin which are DAP-like structured antibiotics, and the amino acids glycine and tryptophan, which are found in DAP structure (Fig. SI.2). The sensitivity towards the antibiotics Vancomycin and Erythromycin and the amino acids glycine and tryptophan was below 7 percent as compared with DAP (Fig. 7).

## 4. CONCLUSION

In this work, the first MIP based nanosensors were developed for the sensitive electrochemical detection of Daptomycin. DPV and CV techniques of the redox marker ferrocyanide/ferricyanide were used to monitor all steps of MIP-synthesis and subsequent target binding. Integration of gold decorated platinum nanoparticles into the DAP-imprinted poly o-PD layer (MIP/Au-Pt NP/GCE) resulted in a 26 fold increase of the current signal after template removal. Under optimized operational conditions, the MIP/Au-Pt NP/GCE sensor exhibits a linear response between 1 pM and 20 pM DAP with LOQ and LOD values of 0.489 ± 0.012 pM and 0.161 ± 0.012 pM, respectively. The MIP electrode has an almost 5.81 fold higher sensitivity towards DAP as compared with the NIP and structurally related antibiotics or amino acids gave below 7 percent smaller signals than the target DAP. It was also successfully used for the detection of DAP in deproteinated diluted human serum samples.

### Declaration of Competing Interest

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

### CRediT authorship contribution statement

**Goksu Ozcelikay:** Writing - original draft, Writing - review & editing. **Sevinc Kurbanoglu:** Writing - original draft, Writing - review & editing. **Aysu Yarman:** Writing - original draft, Writing - review & editing. **Frieder W. Scheller:** Writing - original draft, Writing - review & editing. **Sibel A. Ozkan:** Writing - original draft, Writing - review &

**Table 1**
Comparison studies of various published electrochemical sensors for DAP with the present work

| Electrode/ Column | Technique | Linearity range | LOD | Reference |
|---|---|---|---|---|
| GCE | DPV | 0.5–7.5 μM | 0.32 μM | [16] |
| MIP/Au-Pt Nps/GCE | DPV | $1.62 \times 10^{-9}$-$3.24 \times 10^{-8}$ mg $mL^{-1}$ | $2.61 \times 10^{-10}$ mg $mL^{-1}$ | This Work |
| C18, 250 × 4.6 mm, 5 μm | HPLC-UV | 5 − 100 $mgL^{-1}$ | 1.65 $\mu gmL^{-1}$ | [14] |
| Zorbax Eclipse XDB-C8 column | HPLC-UV | 3.5 -350 $\mu gmL^{-1}$ | 0.5 $\mu gmL^{-1}$ | [9] |
| X Terra RP-18 | RP-LC | 0.5-12 $\mu gmL^{-1}$ | 0.1176 μg $mL^{-1}$ | [10] |
| Agilent Zorbax C18 analytical column (4.6 × 150 mm, 5 μm) | HPLC | 20-70 $\mu gmL^{-1}$ | 1.87 μg $mL^{-1}$ | [11] |
| Acquity UPLC TM HSS T3, 1.8 μm, 2.1 × 150 mm | UPLC-PDA | 0.781- 200 μg $mL^{-1}$ | 0.195 μg $mL^{-1}$ | [15] |

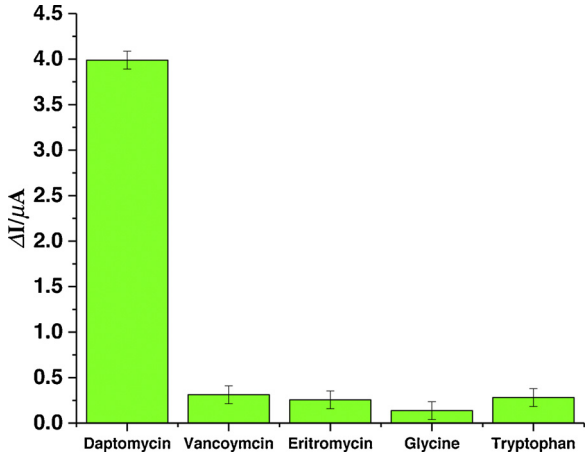



**Fig. 7.** Selectivity of the MIP/Au-Pt NPs/GCE for DAP, Vancoymcin, Erythromycin, Glycine and Trytophan in 5 mM $[Fe(CN)_6]^{3-/4-}$ solution prepared in 100 mM KCl.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.snb.2020.128285.

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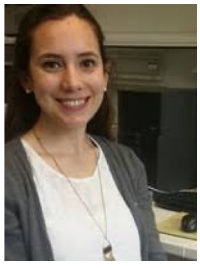

**Goksu Ozcelikay** was graduated from Hacettepe University, Faculty of Science, Ankara in 2013. She received her M.S. degrees in Faculty of Pharmacy, Department of Analytical Chemistry, from Ankara University in 2016. Since 2016, she has been a Ph.D. student at same department under the supervisor of Prof. Sibel A. Ozkan. She involved in a project related with molecularly imprinted polymers for enzyme determination in Frieder W. Scheller Research Group, Germany. Moreover, she was also visiting researcher during PhD, in Prof. Dr. José Pingarrón Research Group at Complutense University, Spain.

**Sevinç Kurbanoğlu** was graduated from Middle East Technical University, Ankara in 2008.. She received her PhD degree in Analytical Chemistry, from Pharmacy Faculty of Ankara University in 2016 under the supervisor of Prof. Sibel A. OZKAN. Related with her PhD thesis topic, she conducted researches about tyrosinase inhibition through drugs and pesticides. For postdoctoral studies now, she is in collaboration with Prof. Dr. Frieder W. Scheller about molecularly imprinted polymers for drug analyses from Department of Analytical Biochemistry at Potsdam University.

**Aysu Yarman** received her M.Sc. in Analytical Chemistry from the Yildiz Technical University (Turkey) and worked as a research assistant at the Department of Anayltical Chemistry. She developed new bio(mimetic) sensors at the Fraunhofer Institute for Biomedical Engineering and received her doctoral degree in Analytical Biochemistry from the University of Potsdam. After her Postdoc at University of Potsdam, she worked for two years as an Assistant Professor at Turkish-German University (Turkey). Currently she works on the development of molecularly imprinted polymer-based sensors for proteins and drugs as a Postdoc in the Cluster of Excellence UniSysCat at University of Potsdam.

**Frieder W. Scheller** has been Professor of Analytical Biochemistry at the University of Potsdam since 1993. He received his diploma in chemistry from the Technical College of Merseburg and his PhD from the Humboldt University of Berlin. For many years he headed the Department of Bioelectrochemistry/Biosensors at the Central Institute of Molecular Biology of the German Academy of Sciences, Berlin-Buch. In 2001 and 2002 he was President of the German Society of Biochemistry and Molecular Biology. He published more than 500 papers. His current research interests include enzyme electrochemistry and biomimetic sensors based on molecularly imprinted polymers

**Sibel A. Ozkan** is a Professor at Ankara University, Faculty of Pharmacy, in Turkey. She obtained her PhD from Ankara University-Faculty of Pharmacy, Department of Analytical Chemistry in 1994. Her current research interests include nanosensor, biosensor, drug assay, electroanalytical studies, LC studies, validation of drug assay. She is a editor of Journal of Pharmaceutical and Biomedical Analysis. She is a member of Editorial Board of Journal of Research in Pharmacy, Turkish Journal of Chemistry, Cogent Chemistry, Sensors International. She received Ankara University Scientific Promotion Award in 2003 and Turkish Pharmaceutical Association, Academy of Pharmacy Science Award in 2008. She is author or co-author of more than 300 published papers.