



## A Novel Photoprobe Based On Nano Tris(3-acetylindole)-terbium(III) Complex For The Quantitative Determination of Epinephrine In Blood Samples

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### Abstract

A New photoprobe based on tris(3-acetylindole) terbium (III) complex (TbAcI) doped in polyethylene glycol (PEG) thin-film was synthesized, and employed as a novel, simple, sensitive, accurate, and precise method for the determination of Epinephrine (EPI) in different serum samples. The results obtained from the Stern-Volmer bimolecular quenching analysis was attributed to the presence of EPI in the surrounding of the emissive TbAcI. The calibration plot was prepared for the concentration range of 1-1500 pg/mL of EPI with a correlation coefficient of 0.99 and a detection limit of 0.1 pg/mL. That may aid in assessing the activity of the adrenal gland and then the diagnosis of optimal diseases that may be raised due to the abnormal ranges in human blood.

**Keywords:** Luminescence; Photoprobe; Lanthanides; Epinephrine; Quenching

### 1. Introduction

Catecholamine considered as message transfer in the mammalian central nervous system. It is formed by the adrenal medulla in situations of lower blood sugar levels, also in case of psychological stress [1-3]. Epinephrine (EPI) or Adrenaline as it is known is one of the essential Catecholamine, which plays a critical role in motivating several actions of the sympathetic nervous system (SNS) known as “flight or fight response” [4], also play a crucial role during physical or mental tension of the human body. Any change of EPI concentration in the blood plasma from the range [90–690 pg mL<sup>-1</sup>] [5] may cause several diseases viz. tachycardia [6], Guillain-Barre syndrome [7], renovascular hypertension [6], pheochromocytoma and hypertension. So, the establishment of a highly sensitive and selective analytical method for the quantitative determination of the concentration of EPI in serum and drug samples is an essential task for developing nerve physiological and pharmacological research, especially to remove the current defects in

present methods. EPI could be determined quantitatively using Many techniques such as electrochemical methods [8-10], chemiluminescence [11, 12], high performance liquid chromatography [13- 15], flow injection [16], capillary electrophoresis [17], and spectrophotometry [18]. However, most of these methods suffer from some disadvantages, such as complicated procedures of sample pretreatment and the highly coated reagents and deficient selectivity, which limit its clinical applications. The reported methods showed relatively high limits of detection which restricts their practical applications. Moreover, the measurement of low concentrations of EPI in biological samples along with interference from some biomolecules such as uric acid (UA), ascorbic acid (AA), and folic acid (FA) requires to efficiently improve the sensitivity of electrochemical sensors for practical applications. Therefore, developing a simple method for accurate determination of EPI is still of great significance. Today, the research field with lanthanide complexes get great interest [19-20]. Luminescent optical sensors Tb(3-Acetylindole)<sub>3</sub>

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Receive Date: 26 July 2020, Revise Date: 13 September 2020, Accept Date: 14 September 2020

DOI: 10.21608/EJCHEM.2020.37301.2768

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(TbAcI) complex doped in the polymer matrix have many advantages over the mentioned traditional methods. Terbium ion has sharp and precise emission bands in green light region. The terbium ion is used as photo probe for many analytes with a high selectivity depends on the excitation wavelength of terbium-analyte complex, pH and the type of solvent of the test solution. Doping of the optical sensors in the polymer matrix increases its stability and durability [21-30]. The sensor can provide a constant signal response for two years, which makes it 24-fold better balance compared to the lifetime warranted for the chromatographic and electrochemical methods. The source of error of the present work eliminated as it more stables for a long time; it gives a low standard deviation value. The higher stability of the current sensor can be attributed to the doping of the optical sensor in the polymer matrix.

## 2. Experimental

### 2.1. Apparatus

All fluorescence measurements were recorded with a Meslo-PN (222–263000) Thermo Scientific Lumina fluorescence Spectrometer in the range (190–900 nm). The absorption spectra were recorded with Thermo UV–Visible double-beam spectrophotometer. All pH measurements were made with a pHs-ORION model 290A.

### 2.2. Materials and reagents

NaCl, KCl, albumin, uric acid, urea, Folic acid and glucose were purchased from Stanbic Co. and Fluka CO. (Fluka, AG, Buchs, Switzerland). The pH of all solutions was adjusted at 6.5 using Phosphate Buffer. Human samples have been collected from the New Al-Kasr-El-Aini Teaching Hospital Cairo University and Ain Shams Specialized Hospital, Ain shams University, Cairo, Egypt following WHO (World Health Organization) approved protocol for human specimen collection and the use of this material and related clinical information for research purposes. [All patients are consented and approved the use of their clinical samples in the research work]. All Solvents, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), ethanol, and acetonitrile, were purchased from Spectrochem Pvt. Ltd. (Mumbai, India). The standard stock solution of EPI (1.00 g

mL<sup>-1</sup>) was prepared using deionized water. All working solutions of different EPI concentrations were prepared by diluting the stock solution with the requisite volume of ethanol. Stock and all of the moving solutions were stored at 0–4 °C when not used.

### 2.3. Preparation of TbACI optical sensor doped in PEG.

A stock solution of  $1 \times 10^{-2}$  mole /L of Tb (NO<sub>3</sub>)<sub>3</sub> .6H<sub>2</sub>O was prepared by dissolving 0.113 g into 25 mL Ethanol solvent. Also, a stock solution of 3-Acetyleneindol was prepared by dissolving 0.039 g into 25 mL Ethanol, a solution of  $1 \times 10^{-2}$  mole/L concentration was obtained. An equal molar ratio was diluted by different solvent for searching for a more effective solution using a different solvent such as DMSO, DMF, ETOH, Acetonitrile, and deionized water. The molar ratio between Tb (III) ion as a metal and 3-Acetylene indole as a ligand was checked by physically mixing of different volumes of the stock solutions of both Tb(III) ion solution and 3-acetyleneindole then diluted by acetonitrile solvent which is the best medium to form the complex. The thin films were prepared by dissolving 0.1 g of the solidified and seamless complex in 3 mL ethanol and then adding 10 mL of viscose freshly prepared PEG with stirring for about one hour until a homogenous solution was obtained. A thin film was fabricated by spin-coating on a small quartz slide (width 8.5 mm, height 25 mm) to outfit the cuvette of the spectrofluorometer. First, the substrate slide was washed with distilled water and surfactant, then ultrasonically for 30 min in distilled water and surfactant, followed by ultrasonic cleaning for 10 min in acetone. Finally, it was boiled for 10 min in 2-propanol. Before spin-coating, the substrate was washed with 2-propanol and spun until the film was sufficiently dry to make sure that there are no interfering pollutants on the surface of the thin film. Then, the polymer solution was dropped onto a cleaned substrate with a micropipette and was spun at 3000 rpm for 30 sec.

### 2.4. Recommended Procedure.

An appropriate volume (100 µL) of various standard concentrations of EPI should be diluted to 3 mL with acetonitrile. The dilute solution was mixed with a thin film of optical sensing TbAcI doped in PEG matrix in the quartz cell of a spectrofluorometer. The luminescence spectra were recorded at the excitation wavelength  $\lambda_{ex} = 325$  nm, and the excitation/emission slit wades were 10 nm of each. After each measurement, the optical sensor was washed with

acetonitrile, and the calibration curve was built by applying the Stern's Volmer equation by plotting  $(F/F_0)$  at  $\lambda_{em} = 545$  nm on the y-axis versus the EPI concentration in ng/mL on the x-axis.

### 2.5. Proposed method for epinephrine.

A 0.2 mL portion of each human serum sample was mixed with 10 mL of acetonitrile, and the mixture was centrifuged for 15 min at 3000 rpm to separate serum proteins, and then the supernatant was collected. The optical sensor, TbAcI doped in PEG matrix thin film, was immersed in 2 mL of each serum solution in the measuring cuvette. The emission intensity was measured at  $\lambda_{em} = 545$  nm against the reagent blank before and after serum addition, and the optical sensor thin film was washed with acetonitrile after each measurement. So, the EPI concentration can be determined by comparing the measured intensity with the calibration plot.

## 3. Results and discussion

### 3.1. absorption spectra

Figure 1 shows that the absorption spectrum of 3-acetylindole in acetonitrile (black line). It displays one band at 286 nm in the ultraviolet region, which refers to the  $\pi - \pi^*$  transition. The Tb(III) has forbidden f-f transitions, which make  $Tb^{3+}$  ion suffer from weak light absorption. Also, most of the lanthanides have molar absorption coefficients ( $\epsilon$ ) smaller than  $10 \text{ L mol}^{-1}\text{cm}^{-1}$ , while upon addition of  $Tb^{3+}$  (as terbium nitrate) to 3-acetylindole the absorption band enhanced and shifted to 288 nm (red shift) with the appearance of a new band at 252 nm which related to LMCT between 3-acetylindole and  $Tb^{3+}$  which indicate that the complexation between 3-acetylindole and Tb(III) ion formed successfully. The addition of different concentrations of EPI to the  $Tb^{3+}$  ion, a blue shift was occurred for 288 nm band gradually to 283 nm, which refers to the hydrogen bond formation between EPI and ligands of TbAcI complex. This will increase the complex rigidity and the ligand rotation was forbidden. At the same time, the other band at (252 nm) went to red shift to (261 nm), which means that the energy transfer from ligand to metal was affected upon introducing EPI in the surrounding, which results in luminescence quenching of the TbAcI complex, which will be discussed in details later.

### 3.2. Emission spectra

Because of the forbidden f-f transition of trivalent  $Tb^{3+}$  ion, it is inflexible to absorb light directly. Generally, trivalent lanthanides have low molar

absorption coefficients ( $\epsilon < 10 \text{ L mol}^{-1}\text{cm}^{-1}$ ), and we can overcome the limiting absorption by coupling Ln(III) with a highly absorbing organic ligand that can contribute to efficient light absorption and energy transfer processes which called "antenna effect." In the present photoprobe, Tb (III) ions are covalently surrounding with three molecules of 3-Actyle indole ligand, which is responsible for light absorption then energy transfer to  $^4D_5$  state of Tb (III) ion. In the case of the TbAcI complex, the maximum excitation wavelength was (325 nm) that recorded regarding the maximum emission wavelength in of TbAcI complex at 545 nm refers to  $^5D_4 - ^7F_5$ . The emission of the TbAcI complex contains four intense specific bands, belongs to transitions between  $^5D_4 - ^7F_J$  ( $J = 6,5,4$  and  $3$ ) [31-35]. Addition of different concentrations of EP to the TbAcI photo prop leading to a notifying fluorescence quenching (as shown in figure 2). The most pronouncedly quenched peak was that at 545 nm. The most probable is that the presence of EPI in the surrounding of the optical sensor an energy transfer process happens from the excited state of the TbAcI complex to EPI molecule by electrostatic collision.

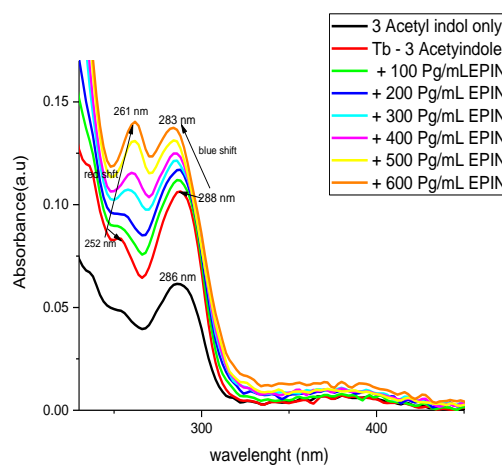


Figure 1: UV-Vis. absorption spectrum of 3-Acetylindole and TbAcI complex in the absence and presence of different concentrations of EPI in acetonitrile solvent at 296 K.

### 3.3. Molar ratio, Solvent and pH effect

Measuring of the luminescence of different molar ratios between metal (Tb III) ion and ligand (3-Acetylindol) used as a tool to declare a perfect ratio of them to form a stable complex. The electronic

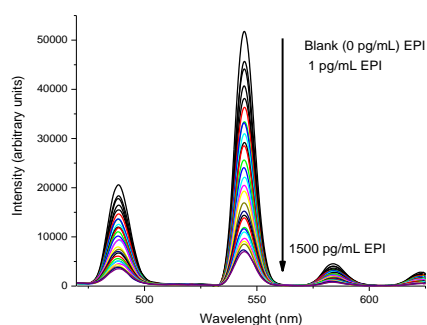


Figure 2: Luminescence spectrum of TbAcI complex optical sensor doped into PEG polymer in absence and presence of EPI with different concentrations

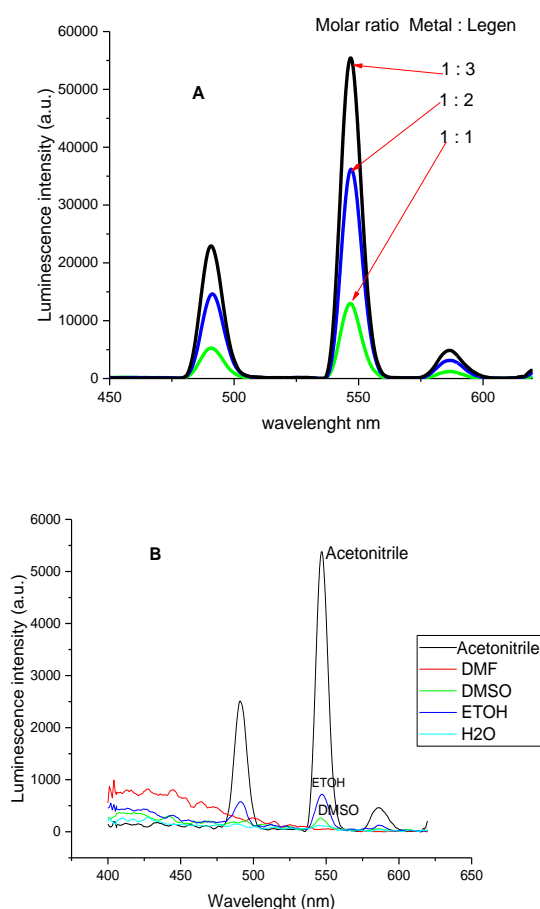


Figure 3: a) Luminescence spectrum of different molar ratio between Tb(III) ion and 3-Actylindol legend b) luminescence spectrum of TbAcI complex in different solvents.

configuration of Tb(III) Ion  $[Xe] 4f^6 5d^0 6s^2$  enables Tb(III) ion to form up to six coordination bonds and more with donating sites of the ligand. So, as shown in Fig. 3(a) the intensity of emission enhanced by increasing the ratio of Tb:3-Acetylindol till 1:3, respectively. Therefore, the perfect molar ratio used to prepare the TbAcI complex was 1:3. Figure 3(b) shows the solvents effect on the luminescence quantum yield of TbAcI complex, by measuring the luminescence emission of TbAcI complex in different solvents such as ethanol, water, dimethyl sulfoxide (DMSO), dimethylformamide (DMF) and acetonitrile, the results declare that the solvent polarity significantly influences the fluorescence intensity. TbAcI complex has high fluorescence quantum yield in acetonitrile solvent of a moderate polarity rather than in DMSO and DMF (aprotic solvent) and ethanol and water (H<sub>2</sub>O) (protic solvent). And this is attributed to the formation of an anhydrous solvation to TbAcI complex by introducing acetonitrile solvent molecules in its primary coordination sphere which leads to enhancing all the emission bands of the complex especially the highest intensity band related to transition from ( $^3D_4 - ^7F_5$  at 545 nm), due to the absence of vibrational energy transfer to quenchers (OH oscillators) in hydroxyl solvents. [36-42]

Measuring of the luminescence intensity of TbAcI complex of molar ratio between metal to legend was 1:3 respectively in acetonitrile in different pHs searching about the optimal pH that not affect the sensor efficiency. The results show that the sensor emission proficiency is significantly affected by changing pH of the solvent, in highly basic medium  $pH \geq 8.5$  the sensor was completely quenched by the effect of quenching hydroxyl ion and the Tb will be precipitated as metal hydroxide. Also, the emission intensity completely quenched at  $pH \leq 3$  as at low pHs and the TbAcI complex dissociated. The most suitable pH founded of high intensity values was  $pH = 6.5$ . Finally, in this part we are notifying that the optimal conditions of the working TbAcI complex sensor to work with high efficiency and low quenching interferences were to prepare the complex with molar ratio 1:3 of metal and ligand respectively in acetonitrile solvent at constant  $pH = 6.5$ .

### 3.4. calibration curve

Quenching mechanism could be checked by applying the Stern-Volmer equation,

$$(F_0/F) - 1 = K_{sv} [EPI]$$

Where  $F_0$  and  $F$  are the fluorescence intensities in the absence and presence of quencher of concentration [EPI]; thus, Stern-Volmer quenching rate constant ( $K_{sv}$ ) could be obtained as the slope of the linear plot of  $(F_0/F) - 1$  versus [EPI]. By applying the Stern-Volmer and plotting  $(F_0/F) - 1$  on the X-axis and the concentration of EPI in Pg/mL on the Y-axis (as shown in figure 4), a linear line was obtained over a wide range from 1 pg/mL to about 1500 pg/mL. From the graph, we can determine the stern-Volmer constant as it equal to the slope of the linear line, the  $K_{sv} = 0.00425 \text{ mL pg}^{-1}$ , which equivalent to  $K_{SV} = 7.8 \times 10^8 \text{ L mol}^{-1}$ . The enormous  $K_{SV}$  value indicates that a robust dynamic quenching was occurred by the charge transfer between the excited state of the TbAcI complex and the EPI molecule by the electrostatic collision, which leads to relaxing of the photosensor without emission of photons.

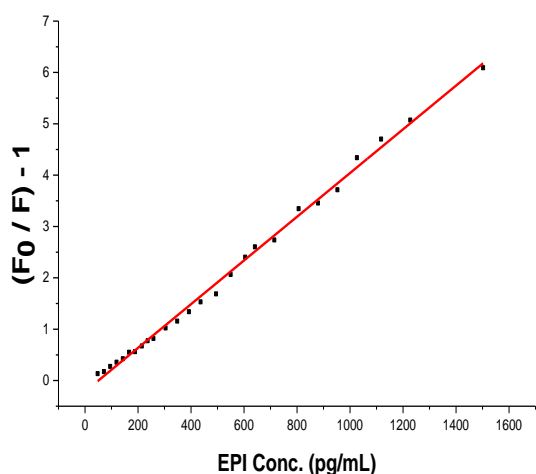


Figure 4: Stern-Volmer plot of data of (Fig. 2) at the 545 nm band.

### 3.5. Method validation

Table 1 shows some results of the analytical parameters obtained at the following. The fluorescence intensity of TbAcI complex doped in PEG was quenched by increasing of EPI concentration over a linear range 1-1500 pg/mL with a correlation coefficient equal to 0.99. Also, the limit of detection (LOD) and the limit of quantification (LOQ) were

calculated according to ICH guidelines. [43] where  $LOD = 0.1$ , and  $LOQ = 0.3$ . Comparing the results obtained versus the reported methods, declare that the current method has lower LOD and LOQ. The selectivity and the validity of the current method were examined by studying the effect of different interfering hormones and protein, for example, T3, T4, TSH, cortisol, Dopamine, Norepinephrine, Albumin, Folic acid, Ascorbic acid, uric acid ( $0.08 \text{ g L}^{-1}$ ), urea ( $0.06 \text{ g L}^{-1}$ ) and glucose ( $0.08 \text{ g L}^{-1}$ ), on the fluorescence spectrum of TbAcI complex doped in PEG thin film after the addition of [EPI]. The tolerable limit is the concentration of the added species individually, causing a deviation lower than 4.5% of the fluorescence intensity under the optimum conditions of the photoprobe. The results indicated no significant observed effect on the intensity. (as shown in figure 5).

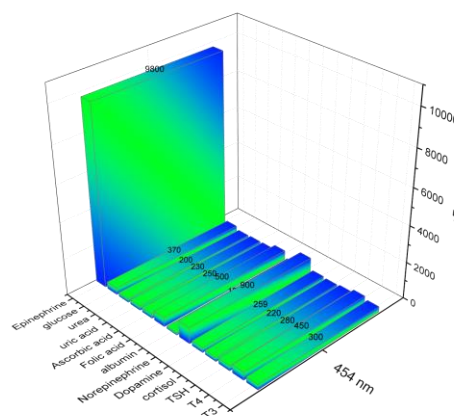


Figure 5: effect of the interfering ion concentration on the luminescence of TbAcI complex doped in PEG.

**Table 1 Sensitivity and regression parameters for the optical sensor.**

Parameter	Method
$\lambda_{em}$ , nm	545
Linear range, (pg/mL)	1-1500
Limit of detection (LOD), (pg/mL)	0.1
Limit of quantification (LOQ), (pg/mL)	0.3
Intercept (a)	$-0.21 \pm 0.02$
Slope (b)	$28.6 \pm 2.7$
Standard deviation	0.87
Regression coefficient (r)	0.99

#### 3.6.1. Accuracy and Precision of the Method

The accuracy and precision of the proposed method were evaluated by ringing the assessment three times in a day to determine the intraday precision and three times in different days to determine the average values

for verifying the interday accuracy and precision of the method. These measurements were performed on four control and six test samples of the serum of patients. The results of this study are summarized in Table 2. The percentage relative standard deviation (% RSD) values of the proposed method were  $\leq 0.1-0.8\%$  (intraday) and  $\leq 0.2-1.2\%$  (interday). These results approved the high precision of the proposed method. Accuracy was assessed as percentage relative error (% RE) between the measured mean concentrations and the taken concentrations of EPI. % RE values of  $\leq 0.4-3.3$  (intraday) and  $\leq 0.3-2.6$  (interday) demonstrate the high accuracy of the proposed method.

### 3.6.2. Application

The analytical utility and applicability of the proposed method were tested by the assessment of EPI concentration in some serum samples (five samples of healthy persons and other five samples of patients with renovascular hypertension, pheochromocytoma, and hypertension diseases in the age range of 25–65 years). The obtained average values by the proposed method match well with those obtained by the standard method, as shown in Table 2.

**Table 2. Analytical results of the serum samples of healthy and patients analyzed by the standard (A) and the developed spectrofluorimetric (B) methods and statistical comparison of the results with the reference method. Evaluation of intra-day and inter-day accuracy**

Sample	reading	Average Found X	Standard method Average $\pm$ RSD (%)	Intra-day accuracy and precision (n=3)			Inter-day accuracy and precision (n=3)			
				Average recovery $\pm$ RSD (%)	Average Found* $\pm$ CL	%RE	%RSD	Average Found* $\pm$ CL	%RE	%RSD
Healthy (1)	254.5, 256.1, 255.5	255.3	256.8 $\pm$ 0.5	99.4 $\pm$ 0.3	255.3 $\pm$ 1.9	0.6	0.3	257.5 $\pm$ 2.5	0.3	0.4
Healthy (2)	304.7, 305.6, 304.5	304.9	302.4 $\pm$ 0.3	101 $\pm$ 0.2	304.9 $\pm$ 0.9	0.8	0.2	303.5 $\pm$ 3.7	0.4	0.5
Healthy (3)	160.1, 160.7, 161.4	160.7	162.0 $\pm$ 0.9	99.1 $\pm$ 0.4	160.7 $\pm$ 1.5	0.8	0.4	163.3 $\pm$ 2.0	0.8	0.5
Healthy (4)	513.9, 512.1, 512.7	512.9	515.0 $\pm$ 0.3	99.5 $\pm$ 0.2	512.9 $\pm$ 2.2	0.4	0.2	511.7 $\pm$ 3.8	0.6	0.3
Healthy (5)	420.3, 420.5, 421.4	420.7	418.0 $\pm$ 0.2	100.6 $\pm$ 0.1	420.7 $\pm$ 1.5	0.6	0.1	422.1 $\pm$ 2.0	1	0.2
Patient (1)	45.5, 45.7, 46.2	45.7	45.1 $\pm$ 0.7	101.3 $\pm$ 0.8	45.7 $\pm$ 0.9	1.3	0.8	44.4 $\pm$ 0.9	1.6	0.9
Patient (2)	60.1, 60.4, 60.5	60.3	61.5 $\pm$ 0.5	98 $\pm$ 0.35	60.3 $\pm$ 0.5	1.9	0.35	63.1 $\pm$ 1.1	2.6	0.7
Patient (3)	74.8, 74.6, 75.0	74.5	77.1 $\pm$ 1.1	96.6 $\pm$ 0.56	74.5 $\pm$ 0.9	3.3	0.56	76.4 $\pm$ 2.2	0.9	1.2
Patient (4)	83.4, 83.1, 84.3	83.9	85.6 $\pm$ 0.4	98 $\pm$ 0.8	83.9 $\pm$ 1.7	1.9	0.8	86.3 $\pm$ 0.8	0.8	0.4
Patient (5)	92.2, 92.5, 92.9	92.2	90.7 $\pm$ 1.3	101.6 $\pm$ 0.6	92.2 $\pm$ 1.2	1.6	0.6	89.2 $\pm$ 1.9	1.6	0.9

[% RE: relative error percentage, % RSD: percentage relative standard deviation, and CL =  $\pm tS/\sqrt{n}$ : confidence limits. t is the tabulated value = 4.303, at the confidence level = 95%; n = number of measurements; and S = standard deviation.

#### 4. Conclusion

The complex formation between the terbium ion and 3-Acetyldindole was resulted in highly sensitive and characteristic emission peaks in acetonitrile due to an energy transfer from the antenna 3-Acetyldindole to the excited states of terbium ion. Optical sensor of TbAcI in doped PEG was successfully established as a highly sensitive and selective photoprobe of EPI in serum samples over a long linear range (1-1500 pg/mL) and with a very low LOD (0.1 pg/mL).

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**مجس ضوئي جديد من التريبيم ثلاثي (3-أستيل إندول) للتعين الكمي  
للايبينيفرين في عينات الدم  
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قسم الكيمياء - كلية العلوم - جامعة عين شمس - القاهرة - مصر.  
تم تخليق مجسة ضوئية جديدة تعتمد على مترابك ثلاثي (3-أستيل  
إندول) تيربيوم (TbAcI) (III) ومطعم في طبقة رقيقة من البولي إيثيلين  
جلايكول (PEG) وتم توصيفه واستخدامه كطريقة جديدة وبسيطة  
وحساسة ودقيقة تعيين كمية الايبينيفرين (EPI) المخدر في عينات دم  
مختلفة. وتم توصيف الطبقة الرقيقة المكونة من مركب النانو سول-هلام  
TbAcI المطعم في PEG باستخدام الفحص المجهرى الإلكتروني  
(SEM). والنتائج التي تم الحصول عليها من تحليل نتائج التنشيط  
باستخدام معادلة شتيرن-فولمر Stern-Volmer حيث يعزى التنشيط إلى  
وجود EPI في محيط TbAcI الباعث للضوء. تم تعيين مخطط للمعايرة  
في نطاق التركيز من 1-1500 جزء من النيكوغرام/مل من EPI مع  
معامل ارتباط قدره 0.99 وحد الكشف 0.1 جزء من البيكوغرام / مل.  
وبمساعدة ذلك في تقييم نشاط الغدة الكظرية ثم تشخيص الأمراض التي قد  
تظهر في دم الإنسان.