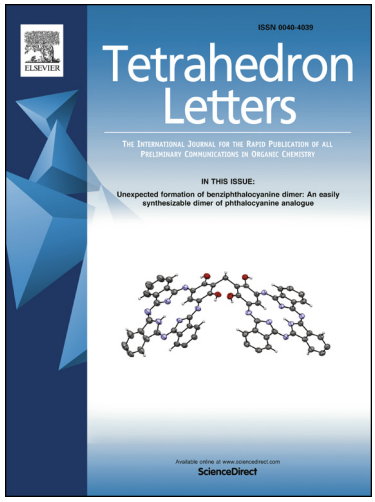

A novel water-soluble AIE-based fluorescence probe with red emission for the sensitive detection of heparin in aqueous solution and human serum samples

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Graphical Abstract

A novel water-soluble AIE-based fluorescence probe with red emission for the sensitive detection of heparin in aqueous solution and human serum samples

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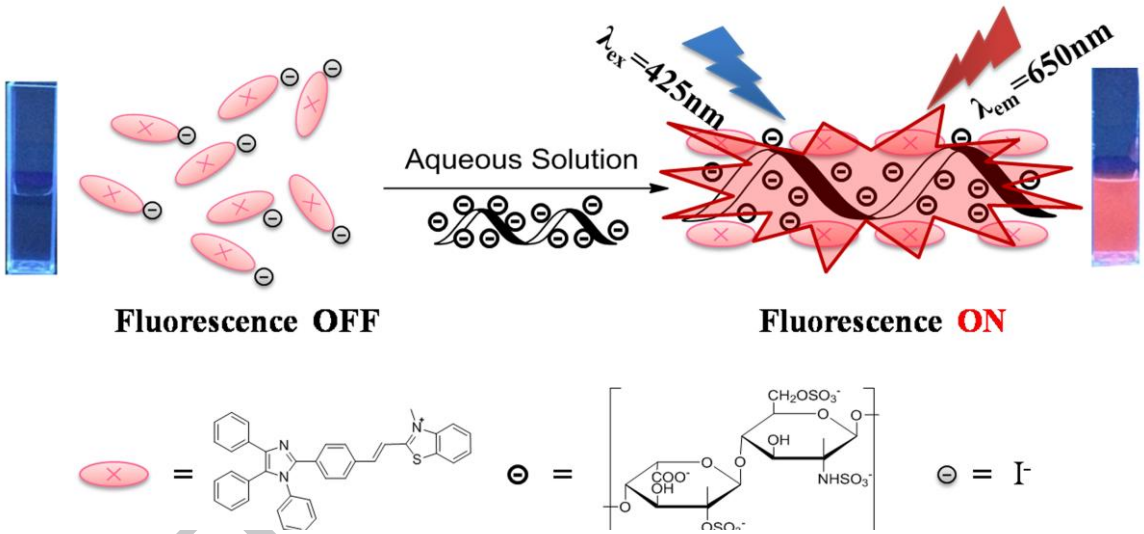

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A novel water-soluble AIE-based fluorescence probe with red emission for the sensitive detection of heparin in aqueous solution and human serum samples

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ABSTRACT

Heparin is widely used to anticoagulation treatment in clinic, while the overdoses of heparin can cause potentially catastrophic complications. Thus, the selective and sensitive detection of heparin is of great importance. Herein, a novel water-soluble AIE-based fluorescent probe (**TIBI)** with red emission (650 nm) has been rationally developed to detect heparin by the electrostatic-interaction and ion replacing strategy. **TIBI** exhibited excellent selectivity and low detection limit (0.08 μM) for detection of heparin. Moreover, **TIBI** was successfully applied to detect heparin in complicated serum samples with satisfactory results. This study holds great promise for real time monitoring heparin in clinical application.

Heparin is a negatively sulfated polymeric glycosaminoglycan (GAG) with the highest charge density in biological systems, primarily (>70%) consists of trisulfated disaccharide repeating units[1]. Owing to its important role in regulation of diverse biological processes such as cell growth, differentiation, metabolism and inflammation[2], heparin is of great importance in biological studies. It is also capable of binding antithrombin III with high affinity, which powerfully enhances antthrombin's inhibition activity towards coagulation factors such as thrombin[3]. So it has been widely used in both anticoagulation treatment and venous thrombosis conditions clinically. The prescribed therapeutic dosages of heparin are 2-8 U mL^{-1} (17-67 μM) and 0.2-1.2 U mL^{-1} (1.7-10 μM) during cardiovascular surgery and postoperative long-term care, respectively[4]. Unfortunately, overdoses of heparin can cause various potentially catastrophic complications, such as haemorrhaging, osteoporosis and heparin-induced thrombocytopenia[5]. Therefore, the selective and sensitive quantification of heparin during surgery and postoperative therapy are of critical importance.

Up to now, several assays to monitor heparin have been reported, including activated clotting time assay (ACT), activated partial thromboplastin time assay (aPTT), capillary electrophoresis and electrochemical methods[6,7]. However, ACT and aPTT methods are not sufficiently reliable[8]. On the other hand, the electrochemical assays suffer from some limitations, such as low specificity and interference by other charged species in serum[9]. Thus, it is highly desirable to develop new methods for detection of heparin with high accuracy and reliability. In recent years, fluorescent assays have gained considerable attention for monitoring analytes due to the low cost, easy manipulation and high performance. Recently, some fluorescence probes, such as small molecule probes[10], peptide-based probes[11], cationic conjugated polymers[12] and quantum dots[13] have been developed to detect small molecules, biomacromolecule, and microenvironment. However, some of them are based on complicated nano-organic hybrid systems with poor water-solubility and toxicity which limit their practical applications[14]. Meanwhile, the fluorescence emission of some conventional fluorophores, such as coumarin, rhodamine, benzothiazole derivatives and etc, was found to be often partially or completely quenched in aqueous solution, and many of these probes based on the formation of probe/ heparin closely packed complexes, their fluorescence might suffer from self-quenching because of the aggregation caused quenching (ACQ) effect[15]. Therefore, it is still highly demanded to explore fluorescent probes with good water-solubility and superior luminescent property in aqueous solution for heparin detection.

In 2001, Tang and co-workers firstly reported the phenomenon of "aggregation-induced emission" (AIE)[16]. AIE luminogens (AIE-gens) are almost non-luminescent when they are dissolved in a good solvent but emit intensely in a poor solvent[17]. Meanwhile, the AIE-gens have significant advantages, such as bright luminescent in the aggregate state and large Stokes shift, *etc*[18]. Recently, a variety of AIE-based fluorescent probes have been developed for detection of many substances, such as ions, organic small molecules and biomolecules, *etc* [19]. However, the reported AIE-based fluorescent probes for heparin often have short emit wavelength (< 600 nm), which may interfere by the background fluorescence of endogenous biomolecules. Thus it is highly desirable to design AIE-based

fluorescent probe for heparin detection with long wavelength emission.

In previous studies[20], we discovered that the tetraphenyl imidazole derivatives could act as a typical AIE gen, emitting weak fluorescence in dispersed state and turning on its fluorescence in aggregate state. In this work, we successfully designed and synthesized a water-soluble AIE-based cationic fluorescent probe **TIBI** for highly sensitive and selective detection of heparin through an ion pairing mechanism. The design rationale was illustrated in Fig 1. In our strategy, the tetraphenyl imidazole group was treated as the AIE fluorophore, and a 2,3-dimethylbenzo[d]thiazol-3-ium iodide was incorporated through a vinylene bridge to the poly-substituted imidazole core, since the 2,3-dimethylbenzo[d]thiazol-3-ium iodide not only could increase water solubility but also could serve as an electron-withdrawing group to induce a strong intramolecular charge transfer (ICT) transition and thus making the emission wavelength shift to red obviously. The probe **TIBI** exhibited weakly fluorescent in aqueous solution owing to the free intramolecular rotation, when the probe was in the presence of heparin, the electrostatic attractions between the negatively charged groups of heparin with positively charged **TIBI** would lead to the formation of **TIBI**/heparin complex, emitting red bright fluorescence (650 nm) through the restriction of intramolecular motion (RIM).

The synthesizing route of **TIBI** was shown in **Scheme 1**. Firstly, the **TIB** was prepared as reported in the literature via one-pot reaction method[21], then **TIB** was further reacted with 2,3-dimethylbenzo[d]thiazol-3-ium iodide to generate the probe **TIBI** in 52%yield. (see ESI for more details, Scheme S1-S3). Molecular structure of the probe **TIBI** was confirmed by ^{1}H NMR, ^{13}C NMR and HR-MS analysis in the supporting information (Fig. S2-S4).

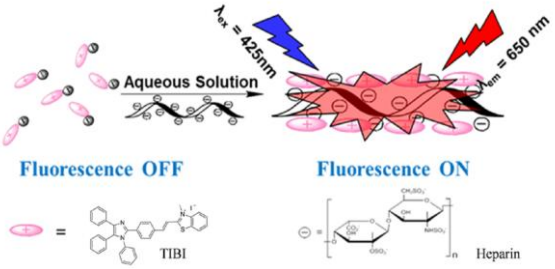
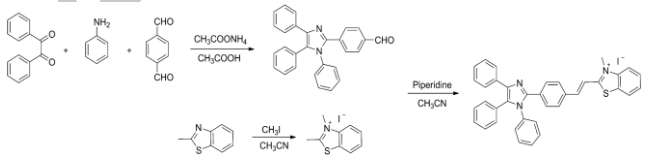


Fig 1. Illustration of the proposed mechanism of interaction between **TIBI** and heparin.



Scheme 1. Synthesizing route of **TIBI**

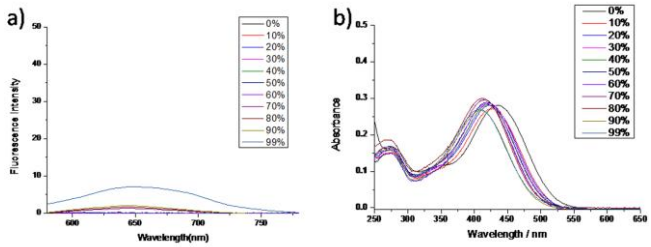


Fig 2. (a) Fluorescence emission and (b)absorption spectra of 10μM **TIBI** in DMSO/PBS mixtures with different PBS contents (λex = 425 nm).

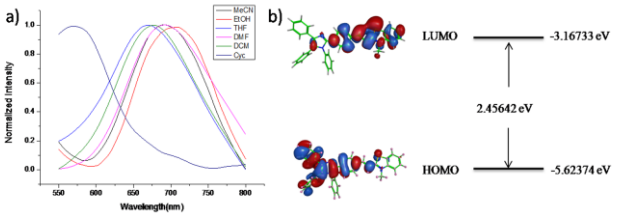


Fig 3. (a) Normalized fluorescence spectra of **TIBI** in different solvents. Cyc, cyclohexane; THF, tetrahydrofuran; DCM, dichloromethane; MeCN, acetonitrile; MeOH, methanol; DMF, N,N-dimethylformamide; Concentration: 10 μM; λex = 425 nm; b) Molecular orbital amplitude plots of HOMO and LUMO of TIBI (Iodide ion was omitted, and the meaning of red and blue color is the distribution of high-density electronic cloud.)

We then measured the fluorescence spectra of **TIBI** in different water fractions. As shown in Fig 2a, when the water fraction in the mixture was lower than 99%, **TIBI** was nearly non-fluorescent. The phenomenon of non-fluorescent might be due to the TIBI could be dissolved in DMSO solution easily, and the good solubility of **TIBI** could make the molecule undergo dynamic intramolecular rotations, reducing the luminescence. However, when the fraction of water was higher than 99%, a weak fluorescence signal in 650 nm was recorded (Φ=0.01). The abnormal fluorescence emission suggested the generation of a loose aggregation state. Unlike the dense aggregation states, the loose aggregation state made the **TIBI** compounds have enough free space to consume the radiative energy, resulting in nearly no fluorescence. Meanwhile, owing to its heavy-atom effect, iodine was a well-known effective fluorescent quencher, which could help to accelerate the rate of intersystem crossing and hence promoted the collision of the fluorophore, resulting in non-radiative relaxation[22]. Based on the reasons as mentioned above, the fluorescent signal of **TIBI** in aqueous solution was very weak. Moreover, the UV absorption spectra of **TIBI** in different water fractions were also measured. As shown in Fig 2b, in pure DMSO solution, the absorption peak of **TIBI** located around 440 nm. Upon the water content increase to 99%, a significant blue shift was observed and a new maximum absorption peak appeared at 420 nm which attributed to the ICT transition of the entire molecule and the production of H-aggregates[23]. The influence of ICT effect was proved by the fluorescence spectra of TIBI in different solvents, As the solvent polarity increased (from n-hexane to methanol), the emission bands of TIBM showed gradual red-shifting from 575 nm to 710 nm (Fig. 3a). The results indicated that the electron-donating tetraphenyl imidazole and the electron-withdrawing 2,3-dimethylbenzo[d]thiazol-3-ium iodide group offer an ICT process in the molecule. Moreover, the influence of ICT effect was further proved via the computational

calculations. As shown in Fig 3b, in the highest occupied molecular orbital (HOMO), the higher density of electron cloud was distributed on electron-donating imidazole group, while in the lowest unoccupied molecular orbital (LUMO), they tended to be denser located around electron-withdrawing 2,3-dimethylbenzo[d]thiazol-3-ium iodide unit.

As mentioned above, a weak fluorescence could be observed when **TIBI** was dissolved in aqueous solutions. However, as shown in Fig S1a, a bright red fluorescence "turn on" in 650 nm was observed after the addition of heparin to a 10 μM **TIBI** PBS solution (pH = 7.4, 10 mM) (Φ=0.16), which might attributed to the fluorescence quenching iodide ion was availably displaced by the negative charge of heparin, meanwhile, the aggregation of **TIBI** driven by electrostatic interaction between the positively charged 2,3-dimethylbenzo[d]thiazol-3-ium iodide and the negatively charged heparin limited the free intramolecular motion. As shown in Fig 4a,4b with an increasing amount of added heparin, the fluorescence intensity of the **TIBI** at 650 nm was enhanced gradually and could be directly observed by naked eye under excitation of the UV lamp (λex = 365 nm**).** Analysis of the fluorescence emission intensity data revealed that the intensity increased linearly with the increasing concentrations of heparin in the range of 0 -10 μM, which covered the clinical dosage level (1.7-10 μM), and a good linear correlation coefficient (R^2 = 0.9906) can be obtained (Fig 4c). The calculated detection limit for heparin with fluorescent methods based on 3δ/s can reach 0.08 μM under this condition. Furthermore, as shown in Fig S1b and Fig 4d, upon the addition of heparin in **TIBI** solution, the UV-Vis absorption spectra of **TIBI** exhibited a decrease in absorption intensity (at 420 nm) and a slight red-shift in the absorption maximum(at 425 nm), which also proved the formation of a new aggregation state.

The selectivity of **TIBI** for heparin was assessed by measuring the fluorescence intensity in the presence of main relevant species, including glucose, adenosine triphosphates (ATP), bovine serum albumin (BSA), cysteine, phosphate ion (Na_3PO_4), chondroitin-4-sulfate (Chs) and hyaluronic acid (HA). As shown in Fig 5, among these molecules, only the addition of heparin in **TIBI** system resulted in an obvious increase in the fluorescence emission intensity. It was worth pointing out that the heparin analogues Chs and HA also did not produce distinguished fluorescence enhancement when using **TIBI** as the tested probe. These phenomena suggested that the probe **TIBI** was highly selective for the detection of heparin, not suffering from interferences from other ions and biomolecules. The high selectivity of **TIBI** might attribute to the electrostatic interactions between probe **TIBI** and heparin. Compared with other molecules, heparin possessed more negatively charged groups, so it had much stronger electrostatic interactions than other molecules, and exhibited outstandingly affinity toward heparin.

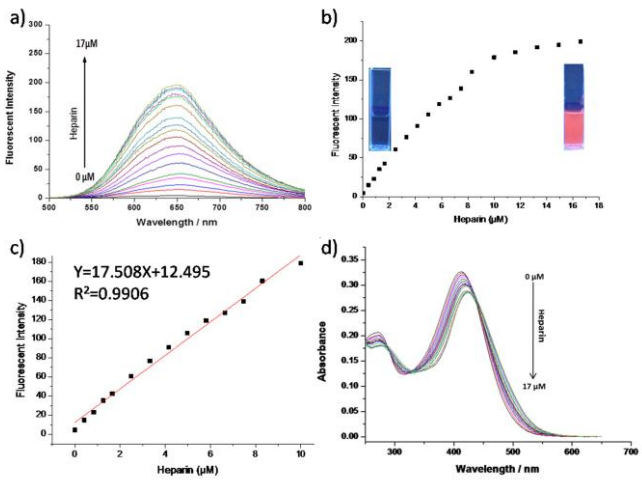


Fig 4. a) Fluorescence spectra of 10 μM **TIBI** in the presence of different amounts of heparin (0-17 μM) in PBS buffer solution (pH = 7.4, 10 mM) with λex= 425 nm; b) Fluorescence spectra of 10 μM **TIBI** at 650nm in the presence of different amounts of heparin (0-17 μM) in PBS buffer solution (pH = 7.4, 10 mM) with λex= 425 nm. Inset shows the photos of the solution of 10 μM **TIBI** in the absence and presence of 8 μM heparin under illumination of portable light; c)Plots of emission intensity in 650 nm against the concentration of heparin with λex = 425 nm; d) Absorption spectra of 10μM **TIBI** in the presence of different amounts of heparin (from 0 to17 μM) in PBS buffer solution(pH = 7.4, 10 mM).

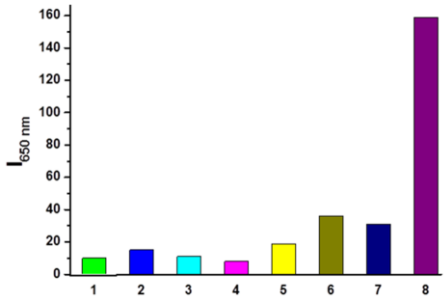


Fig 5. Fluorescence intensities of **TIBI** (10 μM) upon addition of heparin (4 μM) or other different ions and biomolecules (50 μM) (1. Glucose, 2. ATP, 3. BSA, 4. Cysteine, 5. Na_3PO_4, 6. HA, 7. Chs, 8. Heparin).

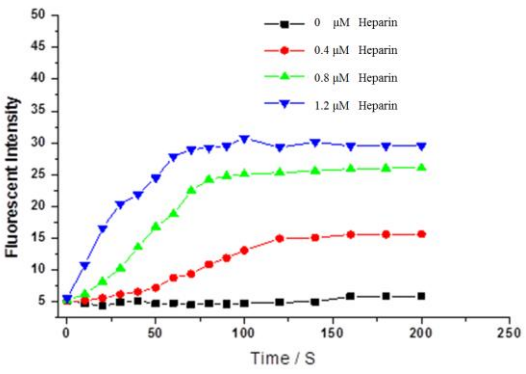


Fig 6. Time-dependent fluorescence intensity changes of 10 μM **TIBI** in PBS buffer solution (pH = 7.4, 10 mM) at 650 nm upon addition of varying concentrations of heparin with λex = 425 nm.

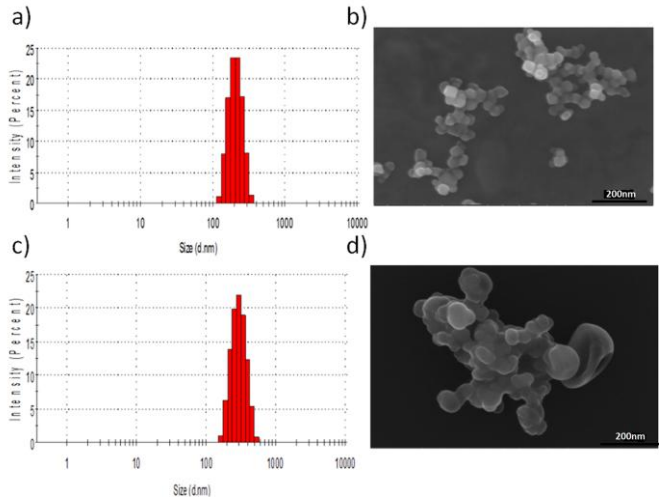


Fig 7. DLS analyses the assemblies of **TIBI** (10 μM) in PBS buffer solution (pH = 7.4, 10 mM) in the absence (a) and presence (c) of heparin (8 μM). SEM analyses the assemblies of **TIBI** (10 μM) in PBS buffer solution (pH = 7.4, 10 mM) in the presence (d) and absence (b) of heparin (8 μM).

Table 1. Recovery results of real sample measurements

Sample	Added (μM)	Measured (μM)	Recovery (%)	RSD (%, n=3)
10% diluted human serum	0	Not found	-	-
	2.5	2.42	96.8	2.8
	5.0	5.25	105.0	3.5
	10.0	10.17	101.7	1.7

The time-dependent fluorescent spectrum of probe **TIBI** with heparin was further investigated. As shown in Fig 6, when a low concentration of heparin (0.4 μM) was added, the emission intensity of probe **TIBI** at 650 nm gradually increased and reached the plateau at about 120 s. When the concentration of heparin was increased to1.2 μM, the emission intensity of **TIBI** could reach the maximum in 100s and remains stable in a long time. These results showed that the probe **TIBI** could detect heparin in a remarkably short time with high stability.

We further investigated the recognition mechanism of fluorescent probe **TIBI** for detection of heparin by the dynamic light scattering (DLS) and scanning electron microscope (SEM) experiments. As shown in Fig 7a, before the addition of heparin into the probe system, DLS experiments revealed the aggregates of **TIBI** with a mean diameter of 251nm in PBS buffer solution (pH = 7.4, 10 mM). The SEM images further showed that **TIBI** self-assembled into spherical or square-like structures (Fig 7b). However, when 8 μM of heparin was added into the PBS buffer solution (pH = 7.4, 10 mM) containing **TIBI** (10 μM), the DLS experiments showed that the aggregates of **TIBI** have an average size of about 323 nm (Fig 7c), which was apparently bigger than that in PBS buffer solution (pH = 7.4, 10 mM) without heparin. Moreover, SEM images of **TIBI** in the presence of heparin are shown in Fig 7d, suggesting that the loosely packed aggregates of **TIBI** turned into tightly packed aggregates. It was demonstrated that heparin could interact with the positive charge of **TIBI** through electrostatic interaction, and the formation of nanoaggregates could restrict the intramolecular rotation effectively, resulting in "turn-on" detection of heparin.

Based on the superior luminescent property of **TIBI** as mentioned above, we further applied the probe **TIBI** for detection of heparin in human serum samples to evaluate its validity. According to the report's methods[24], the human serum samples were analyzed using spiking standard heparin samples at different concentrations (0, 2.5, 5.0 and 10.0 μM). The results obtained were listed in Table 1, the measured recoveries of heparin was ranged from 96 to 105% with less than 5.0% RSD under the optimal conditions, which showed the probe **TIBI** has the potential applicability to detect heparin in complex biological systems.

In conclusion, we have developed a simple, effective fluorescent turn-on probe **TIBI** for detection of heparin based on the synergistic strategy of AIE and electrostatic interaction. The results indicated that probe **TIBI** exhibited good water-solubility, excellent selectivity, very low detection limit (0.08 μM) and long wavelength emission (650 nm). In addition, **TIBI** was successfully used to detect heparin in human blood serum samples. The superior detection ability made it a potential analytical tool for detection of heparin in complex clinical samples.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version.

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Highlights

A novel water-soluble AIE-based fluorescence probe with red emission for the sensitive detection of heparin in aqueous solution and human serum samples

Shuqi Yang[1], Tang Gao[1], Jie Dong[1], Huan Xu[2], Feng Gao[2], Qian Chen[2], Yonghong Gu[2], Wenbin Zeng[1,*]

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1. An novel AIE-based compound **TIBI** was successfully designed and synthesized.

2. **TIBI** exhibited great solubility in aqueous solution.

3. **TIBI** could detect heparin with very low detection limit (0.01U mL^{-1}).

4. **TIBI** could exhibit red light emission (650 nm) while interacting with heparin.

5. **TIBI** could be successfully applied to detect heparin in human serum samples.