ijlpr 2020; doi 10.22376/ijpbs/lpr.2021.11.1.L91-101

International Journal of Life science and Pharma Research

Review Article

Chemistry for New drug discovery

A Review on the Development of Spectroscopic Sensors for the Detection of Creatinine in Human Blood Serum

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Abstract: Creatinine measurement is the key parameter in detecting renal, muscular and thyroid dysfunction. The accurate detection of creatinine level may be informative regarding the functional processes of these systems and help in early detection of acute diseases.There are lots of techniques available for detecting creatinine in human blood serum, most of them are of mainly based on spectroscopic (spectrophotometry, colorimetry and fluorimetric). Other techniques are based on electrochemical, impedometrical, Ion Selective Field-Effect Transistor (ISFET) and chromatography techniques. Each method has its own advantages and few limitations(limitation would be better word) regarding selectivity, sensitivity, reproducibility, cost effective, point-of-care level detection etc. Few methods based on electrochemical techniques are recently promising in detecting creatinine at the point-of-care level with adequate sensitivity and selectivity. On the other hand some biosensors based on spectroscopic techniques are recognized as the most promising substitute in recent years. As creatinine levels in the blood serum offer better information about patient status, here in this review it is thoroughly discussed over other biological samples such as urine, saliva.

Keywords: Creatinine, Spectroscopic, Fluorescent, Sensors, Selectivity

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Recieved On 29 May 2020
Revised On 01 June 2020
Accepted On 26 June 2020
Published On 04 January 2021

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Krishanu Sarkar , A Review on the Development of Spectroscopic Sensors for the Detection of Creatinine in Human Blood Serum.(2021).Int. J. Life Sci. Pharma Res.11(1), L91-101 http://dx.doi.org/10.22376/ijpbs/lpr.2021.11.1.L91-101

1. INTRODUCTION

Creatinine (2-amino-1-methyl-2-imidazoline-4-one) is one of the essential components of human blood and one of the important biomoleculesin clinical diagnostics. It is the ultimate product of creatine metabolism in mammals[1] and it is produced by a physiological process that involves adenosine triphosphate, creatine, and phosphocreatine[2]. This process happens in skeletal muscles to release energy[3]. Accurate analysis of creatinine level in human blood and urine is clinically important because it directly reflects the renal, muscular and thyroid functions. Creatine is mainly synthesized upon methylation of glycocyamine by S-adenosyl methionine in the liver. It is then transported to other organs, brain, and muscle and finally produces high-energy compound phosphocreatine[4] via phosphorylation. At the same time, the enzyme creatine kinase catalysed creatine and phosphocreatine to produce Creatinine[5]. Creatinine is excreted through glomerular filtration from the kidneys at a relatively constant rate and accumulated in urine without tubular reabsorption. An increased level of creatinine concentration in blood serum often diagnoses kidney problems, thyroid malfunction or muscular disorders[6]. Therefore it is very important to measure creatinine concentration in blood serum in order to diagnose their functions. Moreover, creatinine concentration is widely used as an indicator for urine dilution[7], and this tool is frequently used in doping tests by anti-doping organizations in sports[8]. In the human body creatinine remains mainly in two forms, 60% of which in phosphorylated form and rest 40% in free form. The normal physiological concentration of creatinine in the blood of a healthy individual is 40-150 μM however it can be less or more according to age and gender[9]. It can go above 1000 μM in certain pathological conditions. Creatinine levels greater than150 μM indicate the need to perform tests, such as creatinine clearance and values greater than 500 μM indicate severe renal disorder which eventually leads to dialysis or transplantation. On the other hand, creatinine levels less than 40 μM indicate decreased muscle mass[10]. Therefore the creatinine level above 150 μM in human serum acts as a biomarker for renal dysfunction and less than 40μM for muscular disorder. Regular creatinine monitoring may help critically ill patients with severe kidney damage and with timely administration of treatment to peritoneal dialysis patients for improving their quality of life[11,12]. Right now different techniques have been adopted for detecting creatinine[13] in human blood serum. Colorimetric methods for measuring creatinine are more common techniques which are primarily based on using either Jaffe's reaction[14] which was the first report (1886) of creatinine detection or the enzymatic colorimetric method[15]. However, many metabolites and drugs in the sample can interfere with these methods[16]. Also the long time consuming nature of this process creates a problem for the critically ill patients[17]. Further this type of colorimetric based techniques which uses Jaffe's reaction are not selective for creatinine and can detect a wide range of biomolecules, such as, urea, uric acid, sugar, pyruvate, and dopamineand have many shortcomings, e.g. pH dependence, low selectivity etc. After a long gap from Jaffe's report, in 1995 Bell et al. developed[18] a creatinine receptor that bind creatinine via host-guest interaction based on colorimetric method. Since then several quantification methods were reported in the literature that are based on electrochemistry[19], chromatography[20], mass spectrometry[21], liquid chromatography-mass spectrometry (LC-MS)[22] surface-enhanced Raman scattering (SERS)[23], potentiometric[24], capillary zone electrophoresis[25], nuclear magnetic resonance (NMR)[26], spectrophotometric[27], colorimetric[28], fluorimetric[29] methods etc. Although these techniques meet the analytical results, these techniques suffer in reproducibility, stability, sensitivity, and selectivity. Most of these methods operate in high analyte concentrations, drastic reaction conditions and suffer from various interferences. The reported costly enzymatic methods[30] are not even good enough for accurate measurement of creatinine. Moreover most of these methods are not very easy to apply in a biological environment (e.g., live cells and tissues) with non-invasive, real-time approach. Recently molecularly imprinted polymers (MIPs) have been reported[31,32] as new generation chemical/biological sensors because of their high adsorption capacity, high selectivity, desirable stability, excellent reusability, low cost and easy preparation methods. However, their low binding affinity, high diffusion barrier, slow mass transfer, improper conductivity and electro catalytic data restrict the use of MIPs[33]. Recently biosensor technology[34] provides many advantages over these techniques for usual creatinine detection, because of its simplicity, specificity, sensitivity, rapid response time, home monitoring advantages, point of care testing (POCT) facility. Sometimes tedious measurement conditions, pH and temperature dependency[35] limits the use of biosensor. In comparison, spectroscopic techniques specially fluorimetric detection technique has been applied as very simple analytical tool for various heavy metal ions[36], biomolecules[37] and disease causing pathogens[38] because of their easy operation, real-time imaging capacity, high spatiotemporal resolution[39] and low limit of detection (LOD)[40]. Here in this review the recent development in spectroscopic sensors for creatinine detection in human blood serum, their mechanistic study, response time, limit of detection and other details were thoroughly discussed starting from 2016 up to the present.

2. CLASSIFICATION OF SPECTROSCOPIC SENSOR

Spectroscopic sensor mainly includes colorimetric sensor, spectrophotometric sensor and fluorimetric sensor. Advanced developments of these three types of sensor reported by different renowned groups were discussed below.

2.1 Colorimetric Sensor

Colorimetric sensor based on gold nanoparticle for the selective determination of creatinine was designed by Du and his coworker[41]. With the help of synergistic coordination chemistry of adenosine and creatinine with silver ion (Fig 1) on a gold nanoparticle surface, this system shows an excellent selectivity towards creatinine over other biomolecules. The same group previously reported[42] an AuNP system based on synergistic coordination effect of creatinine and uric acid to $Hg^{2+}$for selective recognition of creatinine in body fluid samples with a distinct naked-eye red-to-blue colour change. But in this report the potential toxicity of mercuric ion was overcome by introducing Ag^{+} instead of Hg^{2+} and adenosine instead of uric acid. Here Ag^{+} shows not only low toxicity but it can also exhibit some kind of bactericidal capability[43] at low concentration along with excellent sensitivity and selectivity towards creatinine.

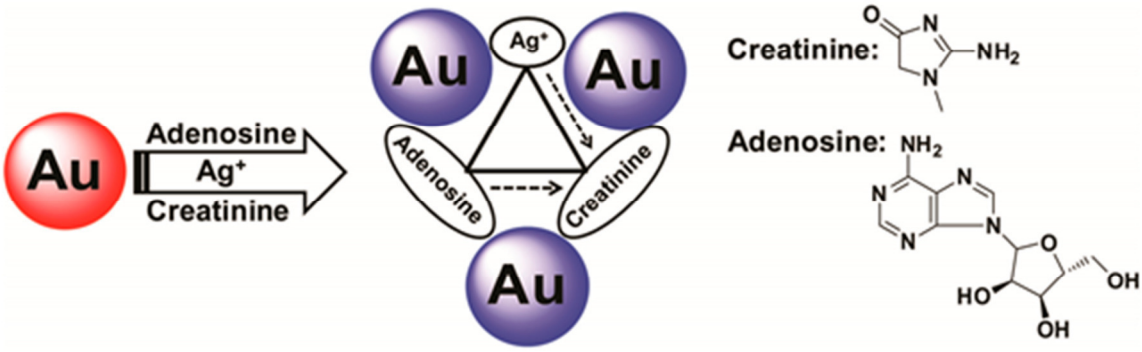

Fig 1. Colorimetric sensing of creatinine based on AuNPs via synergistic coordination chemistry of creatinine with adenosine and Ag^+. Adapted with permission from ref. 41. Copyright ©2016, American Chemical Society.

Because of the presence of distinct surface plasmonic resonance (SPR) property in plasmonic gold nanoparticles this type of colorimetric based sensor shows 1000-fold more absorption extinction coefficient than usual dyes[44,45]. Again gold nanoparticle facilitates the synergistic coordination effect of the various functional species and produces cumulative advantages of all. Adenosine/Ag^+ composite on the gold nanoparticle surface can recognize creatinine because creatinine possesses similar active sites as cytosine which is always used for Ag^+ detection[46] and both creatine and adenosine could form stable complex with Ag^+ in aqueous solution. Here in this process the creatinine-involved complexes act as receptors and Au NPs are transducers. Plasmonic gold nanoparticle (diameter 13 nm) gives a red color with a typical localized surface plasmon resonance (LSPR) band at 520 nm. But in addition creatinine results in a decrease of LSPR intensity at 520 nm while a new peak appears at around 630 nm and as a result a red-to-blue color change could be observed by the naked eye within one minute. The detection limit (LOD) of this system reaches up to 12.7 nM (calculated by 3σ/slope), which is sensitive enough for both qualitative and quantitative detection of creatinine in real samples. Later, Menon and his group[47] developed a silver nanoparticle (Ag NPs) based colorimetric sensor for the quantification of creatinine. Here some modification over traditional Jaffe's method was employed by coating AgNPs with picric acid which can selectively detect creatinine. This Ag NPs based colorimetric sensor selectively recognizes creatinine because of the strong complex forming ability of picric acid with creatinine (Fig 2).

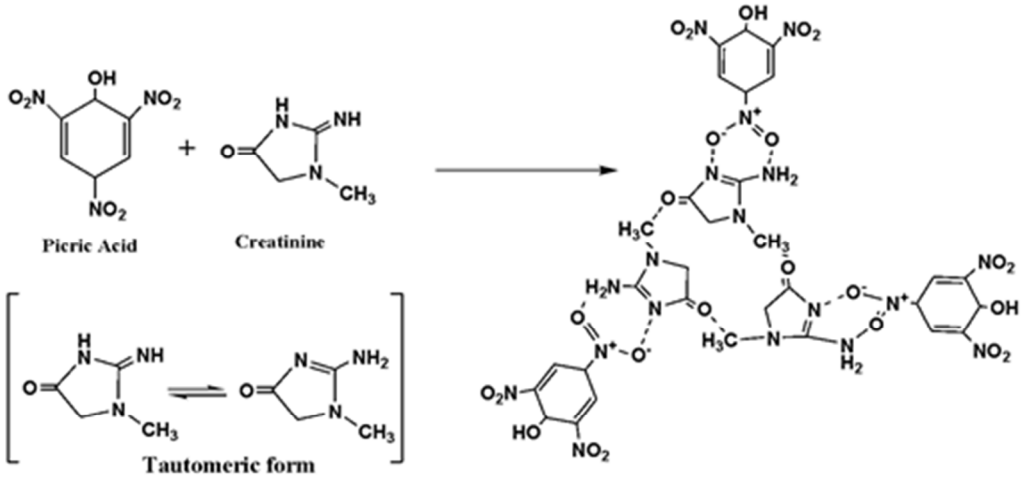

Fig 2. Proposed mechanism for the colorimetric detection of creatinine.

Silver nanoparticles (Ag NPs) were chosen because of its easy synthesis process, high thermal conductivity, high resistance to oxidation, antifungal and antibacterial activity[48] and its use in diagnostic and therapeutic application. UV-Vis spectra showed an absorption maximum at 410 nm characteristic for surface plasmon Ag NPs. The PA capped yellow colour Ag NPs solution showed an intense surface plasmon band at about 395 nm. After interaction with creatinine the absorption maxima shifted from 395 nm to 500 nm and the color changed from fluorescent yellow to dark orange. PA capped Ag NPs show high stability at room temperature without any aggregation. The lower detection limit (LOD) of creatinine was found 8.4 nM. This simple, low-cost and high selective colorimetric method finds application in detecting creatinine in icteric and hemolyzed blood and other body fluids. In 2018, Kumar et al.[49] reported a simple and cost effective colorimetric protocol based on L-cysteine stabilized copper nanoparticles (L-cys-CuNPs) ensembles for the quantification of creatinine.

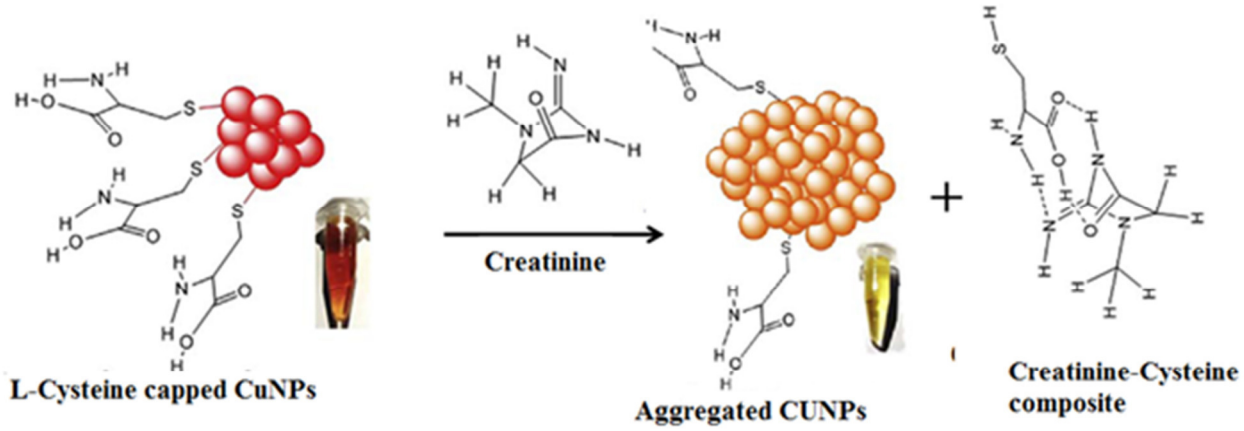

Fig 3. Aggregation induced sensing mechanism of creatinine. Adapted with permission from reference 49.Copyright ©2017, Elsevier.

During the treatment of L-cys-CuNPs with creatinine, a red to yellow colour change along with a change in spectral profile of L-cys-CuNPs from blue-shifted band to red-shifted band with less intensity was noticed (Fig 3). This change in spectral profile in presence of creatinine may be due to aggregation of L-cys-CuNPs within the solution[50]. UV-Vis absorption spectrum of L-cys-CuNPs showed maximum absorbance at about 563 nm. Observed absorption peak is due to localized surface plasmon resonance (LSPR) of L-cys-CuNPs in narrow shape confirming the crystalline nature and uniform particle distribution in the solution.

2.2 *Spectrophotometric Sensor*

On the other hand, Babuet al.[51] reported a novel fluorescent based optical sensor for the detection of creatinine in both normal and abnormal physiological condition. Here a non-enzymatic sensing material was developed in several steps. First carbon nanodots (CNDs) were synthesized from water melon pulp. Then by reducing $HAuCl_4$ by CNDs produced fluorescent carbon-gold (C-Au) nanocomposites (NC) and finally functionalized with bovine serum albumin (BSA) resulted (C-Au-BSA) the fluorescent based creatinine sensor where BSA acts as the sensing material (Fig 4).

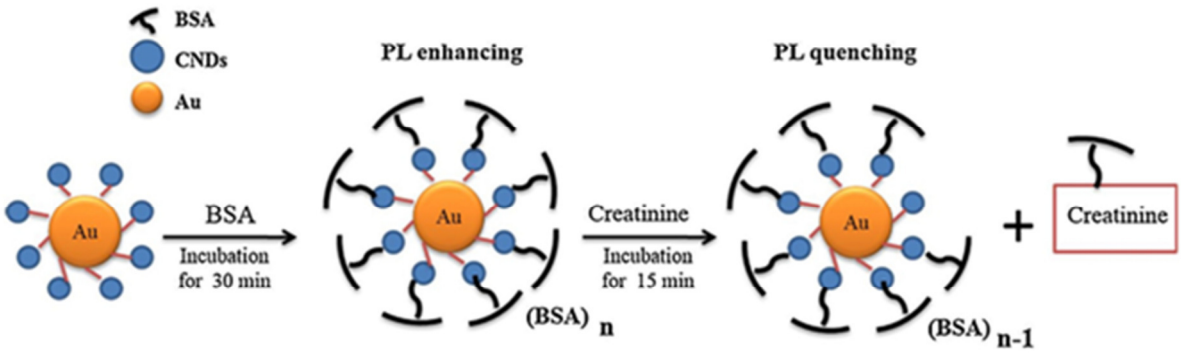

Fig 4. Fluorescence quenching mechanism of creatinine. Adapted with permission from reference 51. Copyright © 2017, Elsevier.

The presence of various functional groups on CNDs facilitates simultaneously on the reduction process and also capping by BSA. Additionally the functional groups that are present in the CNDs may contribute to the absorption and fluorescence phenomena. The typical strong absorption band of CNDs in the UV region (268 nm) having a shoulder is due to the π-π* transition of the aromatic C-C bonds, while the shoulder at 300 nm is ascribed to the n-π* transition of C=O functional group[52]. Apart from optical sensors this C-Au NC can be used for multiple applications such as fluorescence probe, cellular imaging imagining etc. They explored nontoxic and biocompatible behavior of C-Au NC towards HeLa and L929 cell lines. The sensor showed excellent limit of detection towards creatinine and was found to be 200 µg/ml.Very recently Bhalla and his team[53] reported the aggregation induced emission enhancement (AIEE) active supramolecular ensemble of a fluorescent derivative (Fig 5) and Fe^{2+} ions which exhibited extremely sensitive "on-on" response toward creatinine (Fig 6) in human blood serum having a detection limit in picomolar range. This is the first report of metallic iron-induced modulation of self assembly where transformations from H-type aggregates to J-type aggregates were noticed.

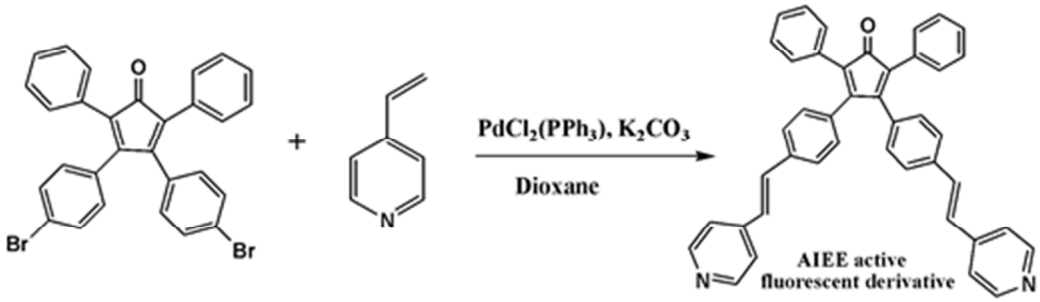

Fig 5. Synthesis of AIEE active fluorescent probe.

In this targeted synthesis of AIEE active fluorescent derivative, cyclopentadiene scaffold portion was responsible for AIEE phenomena and the peripheral pyridyl group for binding with soft Fe^{2+} ion. The derivative formed fluorescent aggregates in H_2O:DMSO (6:4, v/v) solvent mixture because of its AIEE characteristics. These aggregates showed strong binding affinity towards Fe^{2+} ions, and the resulting supramolecular ensemble exhibited an "on-on" response toward creatinine.

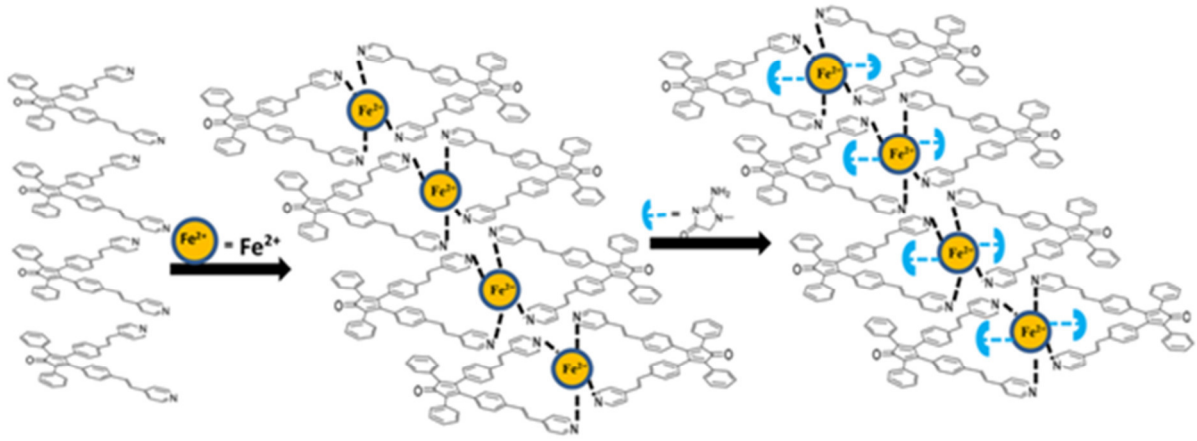

Fig 6. Sensing mechanism of Fe^{2+}supramolecular ensemble. Adapted with permission from ref 53. Copyright © 2019, American Chemical Society.

In the UV-Vis absorption studies the fluorescent probe shows an absorption band at 312 nm in mixed solvent and in presence of Fe^{2+} a red shift from 312 nm to 330 nm and during creatinine sensing a new hump is observed at 488 nm, which was attributed to the generation of supramolecular ensembles. On the other hand in fluorescent studies,the emission spectra of the derivative upon interaction with Fe^{2+} ions, the intensity of 450 nm band was decreased along with an increase of a new band at 525 nm. But during interaction with creatinine the band at 525 nm disappeared and a new band appeared at 475 nm. The detection limit of this sensing protocol of creatinine was remarkable and was found to be 10 picomolar. Moreover, this system showed comparable results with existing Jaffe's method in terms of efficiency and cost.Very recently, in 2020. Sierra and his group[54] designed a novel supramolecular optical sensor for creatinine and its derivative hexylcreatinine. Calix[4]pyrrolephosphonate-cavitands (1) and its dansyl derivative (2) were used as receptors and pyridyl-N-oxide moiety as binding motifs of the indicator guests (3, 4) (Fig 7).

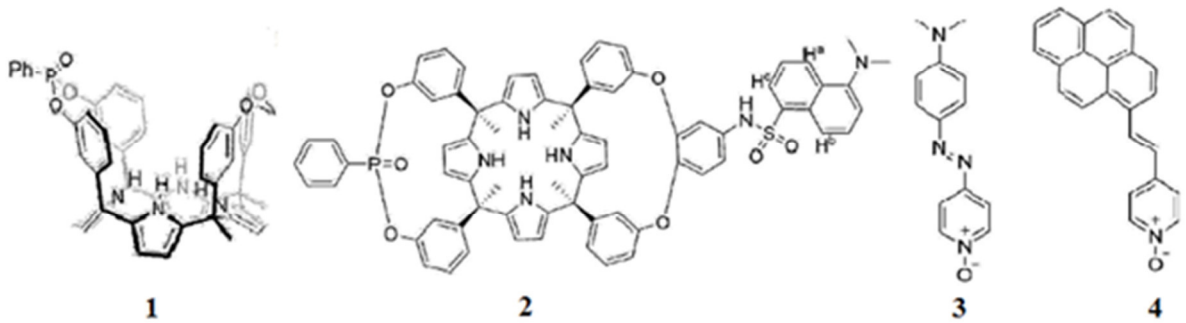

Fig 7. Molecular structure of receptor 1, 2 and indicator guest 3, 4. Adapted with permission from reference 54. Copyright © 2020, American Chemical Society.

The sensing mechanism is based on indicator displacement assays (IDA) of an inherently fluorescent guest dye (4) or a black-hole indicator quencher (3) from the receptor's cavity by means of competition with the creatinine and its derivative For the use of the black-hole indicator dye, the calix[4]pyrrole was modified with a fluorescent dansyl chromophore as signaling unit which facilitates. Förster resonance energy transfer (FRET) process with the indicator dye resulting quenching of fluorescence. But upon interaction with creatinine by indicator displacement assay process by inhibiting FRET process and resulting regaining fluorescence of the signalling fluorophore. Alternatively fluorescent dye remains in quenched state by reacting with receptor moieties but with interacting creatinine by IDA process the dye gets displaced and regains its fluorescent property (Fig 8).

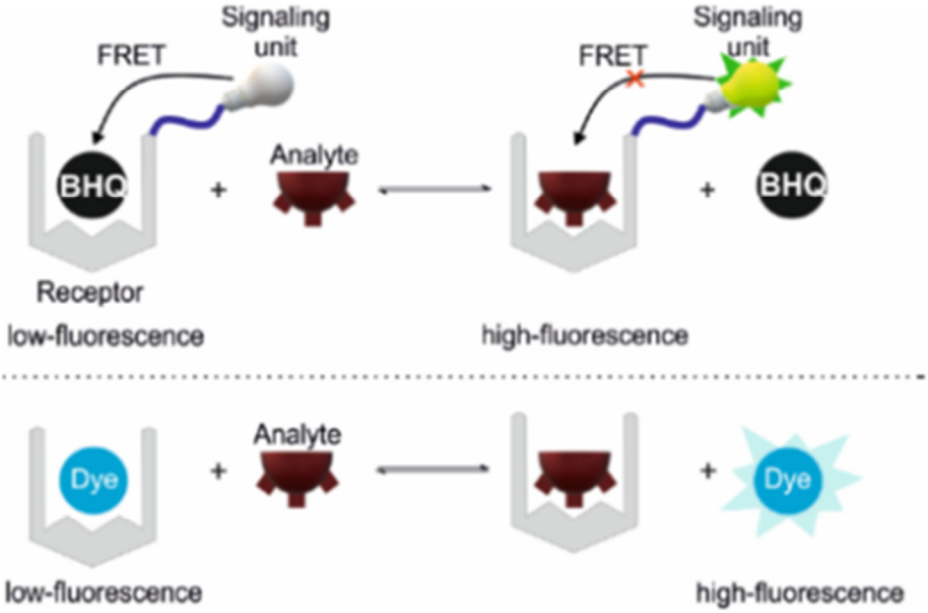

Fig 8. Schematic approaches to optical supramolecular sensing of creatinine using calix[4]pyrrole scaffold.Top: Displacement of a black-hole quencher (BHQ) and deactivation of FRET quenching. Bottom: Displacement of a fluorescent dye. Adapted with permission from ref 54. Copyright © 2020, American Chemical Society.

Both receptor-indator and receptor-analyte i.e. host-guest species formed 1:1 complexes and these were thermodynamically and kinetically very stable. Here combination of hydrogen bond, π-π and CH-π interactions acted as driven forces for the molecular recognition process. The limits of detection of these systems were very low and one of the systems reached submicromolar ranges (110 nM).

2.3 Fluorimetric Sensor

Meanwhile, Dhara et al.[55] for the first time reported a naphthalimide-based single molecular fluorescence light-up probe for selective detection and quantification of creatinine in human blood serum in PBS buffer of pH 7.2 at 37 °C. Here they designed the probe in such a way that after coordinating with Pd^{2+}, the fluorescent ligand exhibits very weak fluorescence because of the quenching effect the heavy Pd^{2+} ion.

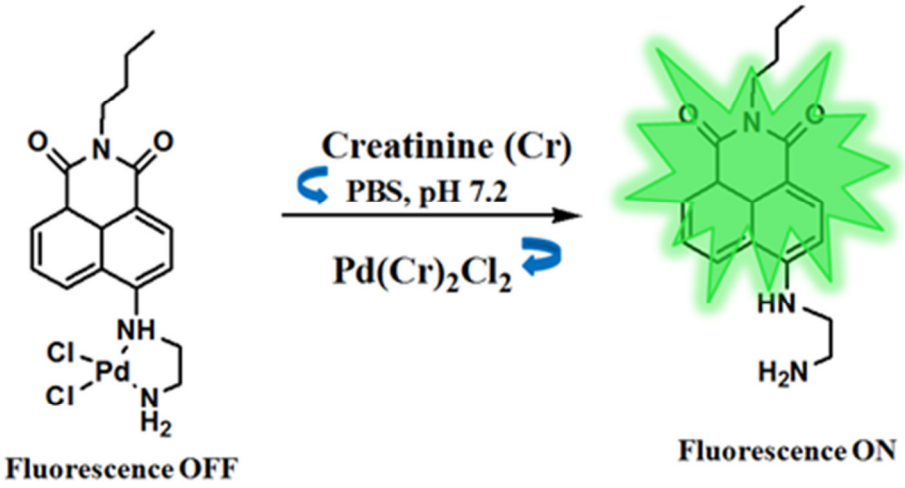

Fig 9. Proposed mechanistic route for creatinine detection using fluorogenic probe.

The inhibition in fluorescence behaviour may also be favoured by the combined effect of photoinduced electron transfer (PET) process that operated from naphthalimide fluorophore to the Pd^{2+} ion and the intramolecular charge transfer (ICT) process. But in presence of creatinine, the Pd^{2+} ion of the fluorescence probe-Pd complex readily reacted with creatinine to produce $[Pd(Cr)_2Cl_2]$ complex[56] (where Cr=creatinine), and made the fluorescent ligand free with subsequent enhancing the fluorescent intensity (Fig 9). From the fluorescence spectrum of this probe it was clear that the probe triggered a 'turn-on' fluorescence response to creatinine with 27 times enhancement of fluorescence intensity of the emission spectrum centered at 530 nm when excited at 440 nm. Further, the UV-Vis absorption spectrum of this probe showed maximum centered at 535 and 345 nm which resemble the complexation of Pd^{2+} and ligand. Upon interaction with creatinine the absorption bands at 535 and 345 nm were gradually decreased and two new bands at 270 and 440 nm gradually increased. The selectivity assay of this probe was tested over a variety of interfering metal ions and/or anions and various biologically important species that may hamper the sensing study. This fluorogenic probe is capable of detecting creatinine as 0.30 μM significantly lower than the normal level in human blood serum samples. After that an alternative approach for non- enzymatic fluorescence turn-on sensing of creatinine (Crn) based on Crn-mediated fluorescence enhancement of thioglycolic acid (TGA) capped ZnS-Mn/ZnS core shell quantum dots (QDs) in aqueous medium reported by Tajarrod and his group[57]. TGA capped ZnS: Mn/ZnS core shell QDs have been prepared via co-precipitation method. The probable sensing mechanism of the designed fluorescence probe for Crn detection was shown in Fig 10. The fluorescence emission spectrum of TGA capped ZnS: Mn/ZnS QDs, showed a considerable increase in emission intensity in presence of creatinine. The gradual enhancement in emission intensity is attributed to the passivation of surface trap states of QDs due to the binding of Crn with QDs surface resulting in new radiative electron-hole recombination centers.

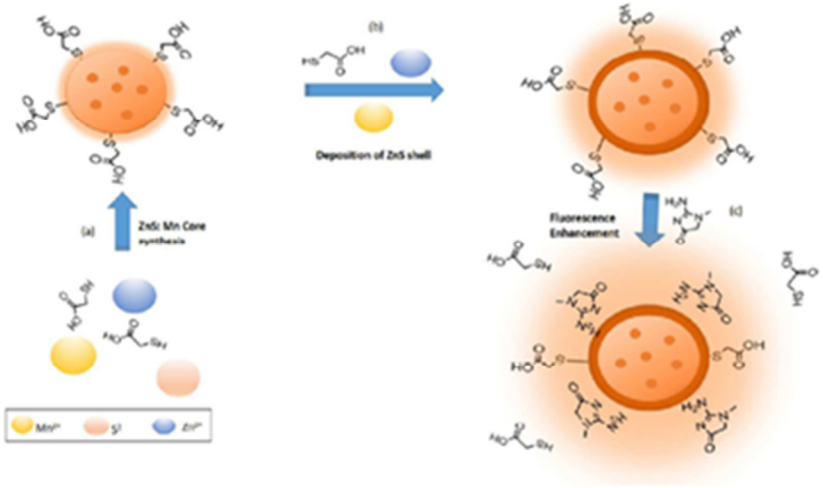

Fig 10. Probable turn-on fluorescence mechanism of the probe for Creatinine detection. Adapted with permission from ref 57.

This novel method offered several advantages such as high sensitivity, short analysis time, low cost and ease of operation for the analysis of creatinine (Crn) content in human serum and urine and the limit of detection was found to be 7.25 nM. Within one year of the previous report Mathew and Joseph developed[58] a novel turn-on fluorescent sensing of creatinine method based gluten stabilized gold quantum clusters (AuQC@gluten) with picric acid (PA) acting as a quencher. Gluten, a cysteine-rich protein, acts not only as an effective stabilizing agent but also as a reducing agent. Sensing experiments were performed at basic medium because of the stability of PA-creatinine complex. During addition of PA to the AuQC@gluten, red fluorescence of AuQC@gluten at 680 nm (excitation at 380 nm) readily quenched due to the interaction PA with the amino group of gluten. But when creatinine was introduced into AuQC@gluten-PA mixture, a steady recovery of quenched fluorescence of PA was observed because of the higher binding affinity of PA and creatinine than gluten and PA (Fig 11).

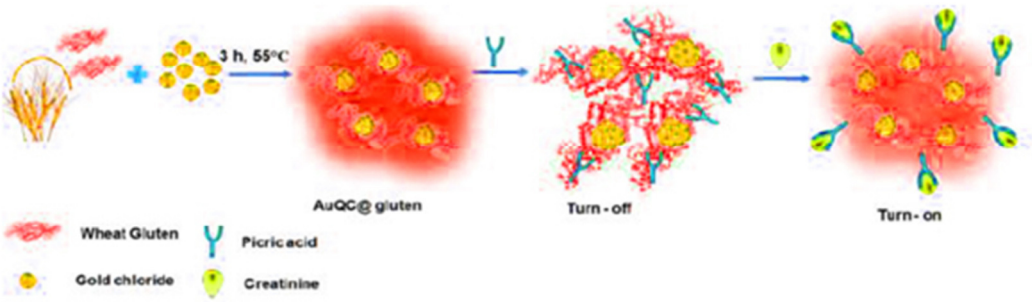

Fig 11. Fluorescent quenching mechanism of AuQC@gluten in presence of PA and successive turn-on sensing of creatinine. Adapted with permission from reference 58. Copyright© 2017, American Chemical Society.

The detection limit is calculated based on 3σ/K where σ is the standard deviation from the blank measurement in the absence of creatinine and K is the slope of the calibration plot. The detection level of creatinine was estimated to be 2 nM, which is much lower than the normal level of creatinine found in human blood serum. Thus this green one pot highly selective, sensitive and cost effective novel water-soluble fluorescent gold quantum clusters finding its potential application in the biomedical field.For the first time, Sundaram et al.[59] developed a highly emissive fluorescent chalcone (E)-3-(pyren-2-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (PTP) biosensor for the selective detection of creatinine in human blood serum. In presence of creatinine, PTP undergoes Michael adduct formation with unique photophysical interaction and because of this, PTP was used as a chemodosimeter for the selective quantification of creatinine in blood serum. UV-Vis spectrum of PTP chalcone shows two distinct absorption maxima at 297 & 407 nm corresponds to π-π* and n-π* transitions respectively, while exciting at 407 nm, two emission peaks appeared around 473 and 587 nm. But upon interaction with creatinine a ratiometric response was observed along with blue shifts of 23 nm in both absorption spectra which clearly supports the internal charge transfer (ICT) mechanism between creatinine and PTP chalcone. On the other hand in fluorescence study during interaction with creatinine the peak intensity at 587 nm gradually decreased whereas the peak intensity at 473 nm gradually in a ratiometric way along with a 60 nm blue shift of the peak from 587 nm to 527 nm. This significant blue shift may be attributed to the ICT mechanism operated between donor and acceptor part of PTP chalcone. As a colorimetric biosensor, the probe can detect the creatinine concentration as low as 0.3959 mg/dL and as a fluorimetric biosensor, it could detect creatinine with an excellent limit of detection of 0.00000065 mg/dL. The sensing behaviour of this biosensor implies that this probe could be applied for clinical diagnosis of muscle and kidney disorder. Within one year Jayasree and his co-workers developed[60] a quantum dot (Qd) based nanosensor for the simultaneous detection of copper and creatinine. In the synthetic strategy, first nanosensor was prepared by using cysteine capped cadmium selenide quantum dots (Qds). Then the Qds were further functionalized with picric acid through 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). Picric acid was judiciously chosen as a potential candidate for creatinine sensing. EDC serves as a spacer and functional moiety that binds picric acid with Qd to form the multianalyte sensor PAd. The probable sensing mechanism of PAd sensor was shown in Fig 12. Fluorescence spectroscopy study showed that in presence of creatinine the emission peak centred at 440 nm showed fluorescence enhancement upon excitation at 290 nm could detect creatinine level in the range from 3 nM to 0.003 mM. On the other hand, upon exciting at 390 nm fluorescence quenching of the 531 nm peak occurs and could detect copper ranged from 20.5 μM to 3.3 mM. Thus PAd acts as both turn-on and turn-off sensor for creatinine and copper respectively based on the fluorescence enhancement and quenching properties i.e. the sensor PAd, can detect both creatinine and copper simultaneously. Moreover, a simple image based detection of creatinine using the sensor strips by means of a mobile camera was developed with acceptable results as point of care detection.

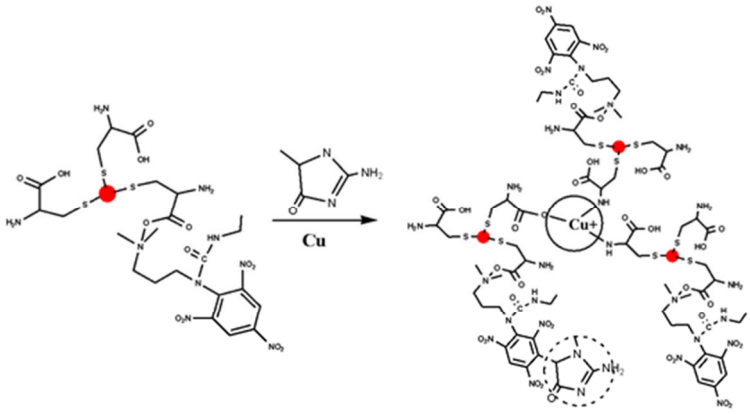

Fig 12. Simultaneous recognition of copper and creatinine by PAd. Solid circle shows the bonding with copper, the dashed circle shows the bonding with creatinine. Adapted with permission from reference 60.Copyright © 2019, Elsivier.

Again Du and his group[61] designed a robust fluorescent turn-on probe for creatinine detection in aqueous solution based on the palladium-catalyzed reaction. The sensing methodology was similar as reported by Dhara et al.[55] but they made the probe water soluble by introducing hydrophilic 2-(2-aminoethoxy)ethanol moiety with the naphthalic anhydride fluorophore. Here also probe-Pd complex displayed weak fluorescence because of heavy Pd^{2+} ion quenching effect and photo induced electron transfer (PET) effect but in presence of creatinine, the probe-Pd complex dissociates and subsequently regains the fluorescence due to exclusion of the heavy atom quenching effect and prevention of the PET effect (Fig 13).

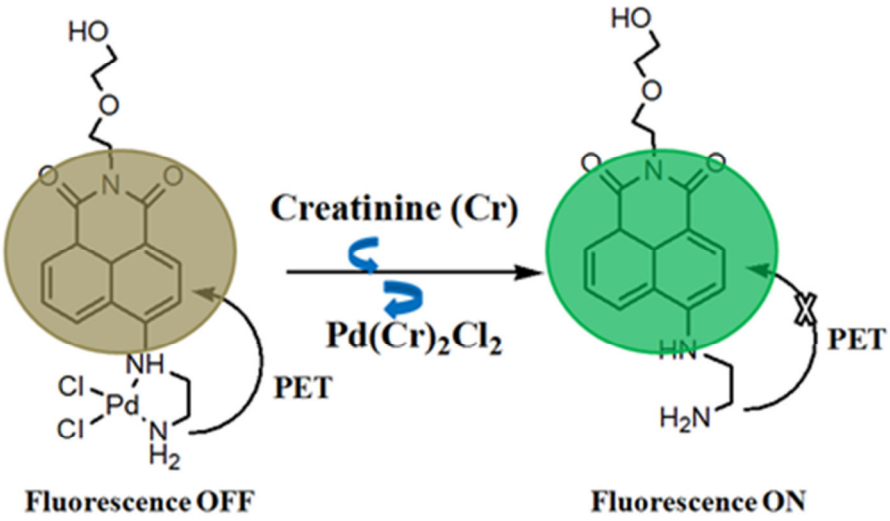

Fig 13. Schematic illustration of the probes' structure and their response towards creatinine.

This probe-Pd complex displayed excellent detecting capacity towards creatinine with a low detection limit of 0.16 μM. Additionally, this sensor displayed excellent membrane permeability with low cytotoxicity resulting in its potential application for the detection of creatinine in biological systems.

3. CONCLUSION

Modern creatinine sensing technologies based on spectroscopic approaches that mainly include colorimetric, spectrophotometric and fluorimetric techniques reported in the last five years were thoroughly discussed. Most of the reports met the demands for facile, selective, sensitive, rapid and cost effective nature of the sensory material. Only some fluorescence based biosensor, AIEE active supramolecular ensembles selectively detects creatinine in picomolar range. One sensor based on fluorescence chemodosimeter can recognize creatinine and Cu simultaneously. Furthermore some sensors showed good membrane permeability and low cytotoxicity and thereby found its potential application in biological systems. But in the majority case of the sensors reported there were some constraints to be used at point of care (POC) level. So still this field is on prime focus in the development of creatinine sensors and its true POC applications in healthcare. Again some biological fluids such as saliva and interstitial fluid (ISF) that have great potential for creatinine detection are not yet fully explored. There are few reports for the direct detection of creatinine in whole blood but to date none of the reported strategies are suitable. . Paper analytical devices in sensing have attracted prime attention of clinical diagnosis because of its simplicity, low cost, minimal quantity of analyte, low limit of detection and disposable nature. However, there is no report of this type device for the detection of creatinine. Therefore special attentions on the development of portable automatic devices for creatinine detection are highly desirable in future.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

5. REFERENCES

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