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Fluorescein Based Fluorescent Dye as a Sensor for Transition Metal Ions

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Abstract

Fluorescein based probes serve as a unique tool for sensing due to its unique fluorescent property as well as low detection limit (LOD). This molecule can combine with various metal ions because of its variable pockets developed on the periphery of the molecular system. Research on this particular probe has been sprouted during the past few years. This article reviewed recent progress in fluorescein based probes to sense and detect the various transition metal ions such as Cu^{2+}, Zn^{2+}, Ni^{2+}, Cd^{2+}, Co^{2+}, Au^{3+}, Fe^{3+}, Hg^{2+}, Ag^{+} etc.

Keywords: Fluorescein; Fluorescent; Sensors; Selectivity; Transition metal ion

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Introduction

Due to heavy industrialization and high utilization of various types of metals, the concentration of different metal ions has crossed its permissible limit in environment and reached at a higher toxic level [1]. The high concentration of different metal ions shows carcinogenic as well as toxic effects on human health as well as other living organisms. Among all types of diseases which are produced by extreme concentration of metal ions, cancer is very common now-a-days. Gene regulation and signaling pathway are affected by metals which are responsible for cell growth and differentiation [2]. To find out presence as well as concentration of different metal ions various types of fluorescent dyes have been prepared by researcher across the world. Due to high fluorescent property and compatibility with human body, fluorescein is an important fluorescent molecule which can be used to sense metal ions present at various levels.

Literature Review

In this review, we are summarizing work since 2016 related with fluorescein-based molecules and it's utility to sense various transition metal ions. Adolf von Baeyer synthesized Fluorescein in 1871 for the first time and its derivatives were synthesized in 1887 by various other scientists [3]. Fluorescein molecule absorbs blue light and emits radiation in the green region. The various fluorescein derivatives are fluorescein isothiocyanate, tokyo green, oregon green, carboxy-neptho flourescein. They have excellent potency to be used as a fluorescent probe for detecting various molecules such as metal ions, smaller molecule, anion, bimolecules. Flourescein detect transition metal ions such as cobalt, copper and zinc etc. which are important part of our body system due to its involvement in various enzymatic functions.

Traditional method based on the analysis such as AAS, Inductively coupled plasma (ICP), Ion chromatography (IC) have various disadvantages including expensive instrumentation, sample pretreatments, toxicity of various compounds, so to overcome these limitations we have found that the most promising method is the fluorescence [4].

Fluorescein is a fluorescent molecule which is used in labeling membranes and proteins. This molecule appears in its different form at various pH levels. The fluorescein structure is given below **(Figure 1):**

The chemical structure of fluorescein is divided into three parts:

1. Chromophore (Signal unit)
2. Linker (Spacer)
3. Receptor (Binding unit) [5]

These units are linked with each other and function only when they are present in combined form. When these units combine together as a single unit it leads to the formation of various chemosensors or functional probe. The various units combine together as a functional probe. The lifetime of fluorescein in protonated form is approximately 3 nanoseconds and in deprotonated form is 4 nanoseconds.

Detection of Fe^{3+}

Iron is one of the most chief trace elements found in the human body responsible for various metabolic and biological processes such as transport of oxygen and electron, synthesis and repair of DNA and RNA and haemoglobin formation [6]. Iron is found as ferritin. Its deficiency can cause diabetes, anemia, breathing problem, liver, heart and kidney damage and excess leads to various ailments such as Parkinson's disease, metabolic disorder, Alzheimer disease, haemchromatosis.

Fluorescein based dyes are used for sensing this metal ions. The Fluorescein compounds are triggered when spirocyclic form changes to open cyclic form. A benzothiazole compound which is a fluorescein based fluorescent chemosensor used for the detection of Fe^{3+} ion **(Figure 2).** This optical sensor works on OFF-ON mechanism which is highly selective and sensitive. This probe is used for the detection of Fe^{3+} in aqueous media and also found to enhance the intensity when DMSO/H_2O is mixed together in the ratio of 3:7,HEPES buffered ,pH =7.2 [7].

Porous aromatic framework involving fluorescein molecules as a linker is of great importance and has been used to sense iron in its (III) oxidation state. Due to presence of unique site to accommodate metal ions, this porous material is highly selective and sensitive for the detection of Fe^{3+}. Various scientists synthesized porous framework such as Yang et al synthesized MIL-53 (Al); Zheng et al synthesized Eu–MOF. The porous material used for the detection of Fe^{3+}, (PAF-5CF) proved to be much more beneficial as compared to the metal organic framework [8] **(Figure 3).**

Fluorescein sensor, FLN/OS-LRH is able to detect Fe^{3+} is solution state at low concentration. It is combined form of FLN (2-(6-hydroxy-3-oxo- (3H)-xanthene-9yl) benzoic acid) and OS (1–octane sulfonic acid sodium). LRH includes layered rare earth hydroxides in which R includes various metals such as Tb, Y. LRH is a 2D layer formed by the intercalation of alternatively arranged positive and anionic form. FLN exhibits a great photoactive compound and has a fluorescent property. FLN along with OS act a guest molecule which gets fit into the layered earth metal oxides [9].

A Fluorescein based probe for the sensitive detection of both $Fe^{3+}$and OCl^- was synthesized. It is a dual sensor which is used to detect both $Fe^{3+}$and OCl^- **(Figure 4).** It exhibits a calorimetric response towards the Fe^{3+} and fluorescence turn-on response is shown by OCl^- [10].

Another sensor is Reduced Graphene oxide combined along with poly ethylene amine (PEI-rGO) is a fluorescent sensor for detection of Fe^{3+} [11].

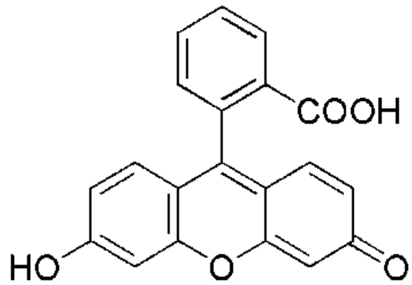


Figure 1 Structure of flourescein.

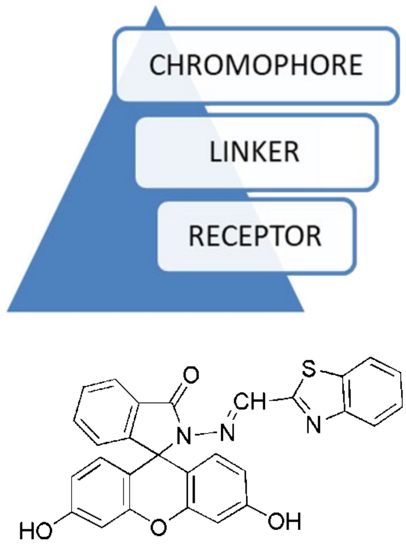


Figure 2 Structure of Fe^{3+} ion sensor.

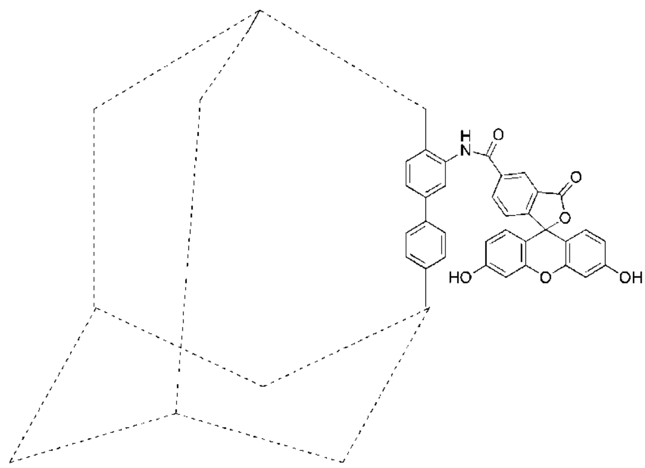


Figure 3 Structure of Fe^{3+} sensor [PAF-5CF].

Detection of Hg^{2+}

Mercury is liquid at room temperature. It is a pollutant released in the atmosphere by various activities such as coal combustion, mineral extraction [12]. It is highly toxic and gets biomagnified in aquatic and terrestrial forms [13]. It can be produced from natural as well as artificial sources.

Diarylethene derivative has been used as a fluorescein derivative for the detection of Hg^{2+}. The fluorescent probe is highly selective and sensitive for Hg^{2+} and its intensity is enhanced by the addition of Hg^{2+} **(Figure 5).** It works on OFF-ON-OFF mechanism. The colour change is observed when the Hg^{2+} is added to it [14].

N- (Flourescein) lactam-N'-methylethlidene (FLA) is a naked eye sensor for the detection of Hg^{2+} **(Figure 6).** Different proportion of acrylamide (AAm), 2-hydroxyethyl methacrylate (HEMA) and methyl methylacrylate (MMA) were copolymerized with FLA which act as a functional monomer, N,N'-methylenebisacrylamide (MBA) as a crosslinker to prepare hydrogel sensors. Using various solvent such as water or DMSO, it is capable to respond to different colours of Hg^{2+}. This sensor is highly selective and sensitive towards the detection of $Hg^{2+}$and can be reused after the treatment with ethylenediamine (EDA) solution [4].

Fluorescein amino acid unit have been synthesized Boc-Ser (TBDMS)-OH or Boc-Cys (4-MeBzl)-OH and considered as luminescent compound to sense various metal ions such as Na^+, K^+, Hg^+, Ag^+, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^2, Al^{3+}, Fe^{3+}, Ga^{3+}, Cr^{3+}. But these probes were synthesized successfully for Hg^{2+} and trivalent metallic ions **(Figure 7).** Its binding with the Hg^{2+} is based on CHEF mechanism [15].

A Fluorescein derivative acryloyl Fluorescein hydrazine (ACFH) was synthesized for sensing Hg^{2+}. This probe forms weaker intermolecular hydrogen bond but ACFH binding was increased when Hg^{2+} bound to it [16] **(Figure 8).**

Detection of Nickel ion

Nickel is an important trace element which is silver white in color and leads to various complications if inhaled in excess amount can cause various respiratory problems, cancer, asthma, pneumonitis, respiratory system cancer, and disorders of central nervous system. We have recognized a fluorescein derivative which is used as a sensor for the detection of Ni^{2+} ion. The Fluorescein molecule is immobilized on the surface of amines modified by silica magnetic core shell nanoparticles. The

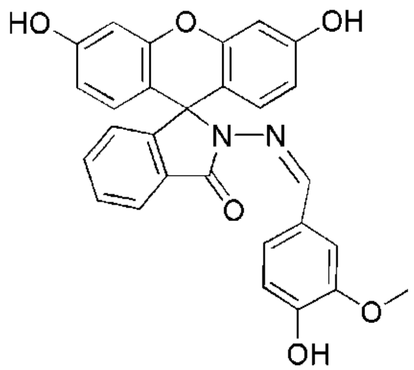


Figure 4 Structure of Fe^{3+} and OCl^- sensor.

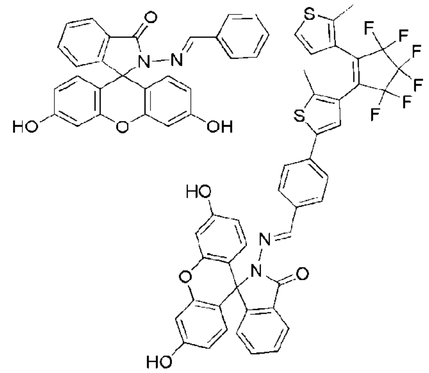


Figure 5 Structure of Hg2+ ion sensor.

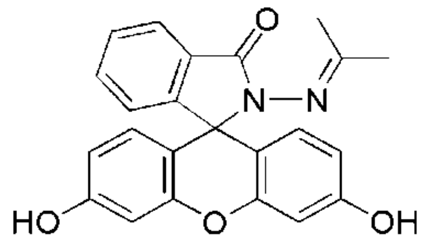


Figure 6 Structure of Hg^{2+} ion sensor [FLA].

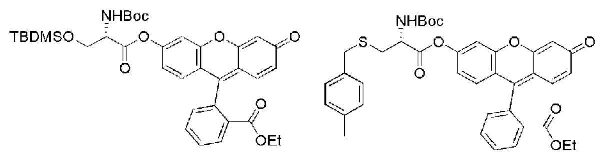
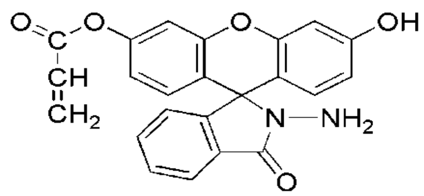


Figure 7 Structure of Hg^{2+} ion sensor a and b.



(ACFH)

Figure 8 Structure of Hg^{2+} ion sensor (ACFH).

quenching of fluorescein molecule in neutral aqueous media is used as a mechanism for the detection of Ni^{2+}, fluorescein dye is quenched by the addition of Ni^{2+} ion. If the sensor is imbibed by Fe_3O_4 @SiO_2-NH_2-flourescein it enhances the sensor activity [17] **(Figure 9).**

Detection of Copper ion

Copper is considered as one of the most important crucial micronutrient for plants and animals. It plays pivotal role in neural signal transmission in the body. It is important for immune system and for various enzymes such as Cytochrome C oxidase, copper amine oxidase, Cu and Zn superoxide dismutase [18]. It is involved in various proteins such as chaperones, transcriptional regulators [19]. It can be used as a fungicide, bactericide in agricultural production. A higher dose of copper can cause various gastrointestinal disorders, neural disorders such as Parkinsons, Alzeheimer, Wilsons, Menkes syndrome and its deficiency can cause coronary cardiovascular disease, anaemia and arteriosclerosis.

A chemosensor for the detection of copper ion using various fluorescent families' rhodamine, coumarin, fluorescein, dansyl and anthracene. But at last we have found a fluorescein compound N- (3'6'-DIHYDROXY-oxo-3, 3a-dihydrospiro [isoindole-1, 9'-xanthene] 2 (7ah)-yl)-1-naphthamide (FNH) which is detecting heavy transition metal ion effectively. It shows higher selectivity of Cu^{2+} ion due to chelation enhanced florescence phenomenon (CHEF) [20] **(Figure 10).**

Fluorescein based sensor named FR-L **(Figure 11**) a new fluorescent indicator made up of 5–aminoisopthalic acid methyl ester and fluorescein was synthesized for the detection of Cu^{2+}. This FR-L sensor worked on the quenching phenomenon after the addition of Cu^{2+} ion, quenching leads to the interaction between the Cu^{2+} and the FR-L sensor. This sensor is selective towards other metal ions and works by the phenomenon of absorption [21].

A new probe for the detection of copper ions were established by using a fluorescein based sensor 2-hydroxy-5 methoxybenzaldehyde fluorescein hydrazone (5-HMBA-FH) and 2-hydroxy-3-methoxybenzaldehyde (3-HMBA-FH). These two molecule act as a sensor for Cu^{2+} ion, but the selectivity of two is different from one another and (5-HMBA-FH) is more selective over (3-HMBA-FH) [22].

A FBO Sensor which is linked with fluorescein hydrazide combined to form 2-acetyl pyridine, works on the 'TURN-ON' mechanism. As the binding of the Cu^{2+} with FBO takes place it results in the opening of the spirolactam ring. In the presence of Cu^{2+} ion, FBO sensor **(Figures 12-14)** turns its color from colorless to deep yellow state. This sensor works under the acidic condition [23].

The coupling of fluorescein hydrazide with 3,5 dinitrosalicyldehyde forming a molecule of fluorescein hydrazone (FDNS),this sensor shows an absorption maxima at a wavelength of around 495 nm and also increases its binding capacity with the Cu^{2+} [24].

The chromophoric fluorescent probes are of great importance and have high water solubility, high quantum yield, and high molar extinction coefficient. Due to the colorless spirocyclic ring form much metal ions bind to the structure of fluorescein in its opened form. A fluorescent probe 5–chlorosalicyldehyde fluorescein hydrazone (CFSH) which is a calorimetric probe shows higher binding with Cu^{2+} ion. The absorption intensity as well as color intensity increases by the addition of metal ion Cu (II) into it. It is a highly selective and sensitive sensor. As the metal ion is added to it color change is also being observed from colorless to yellow. A specialized fluorescent probe was synthesized named

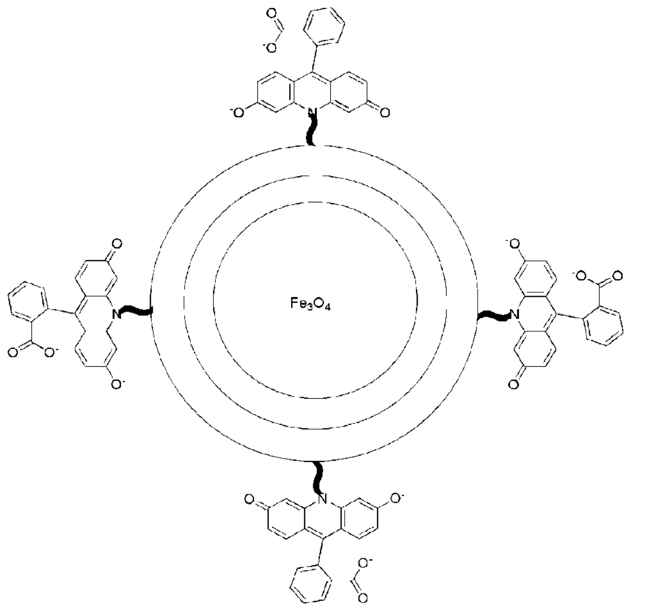


Figure 9 Structure of Ni^{2+} ion sensor [Fe_3O_4 @SiO_2-NH_2-flourescein].

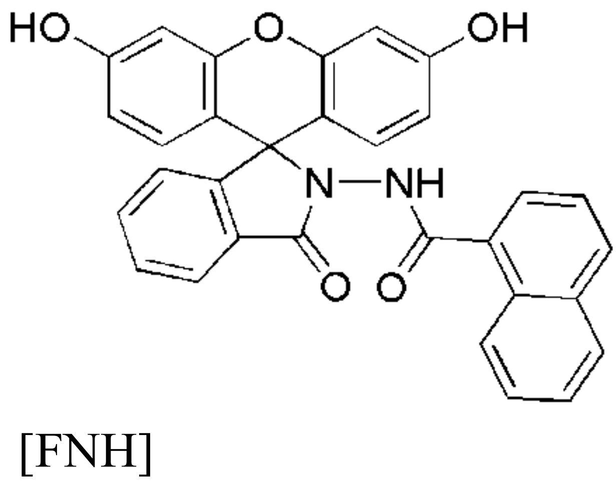


Figure 10 Structure of Copper ion sensor [FNH].

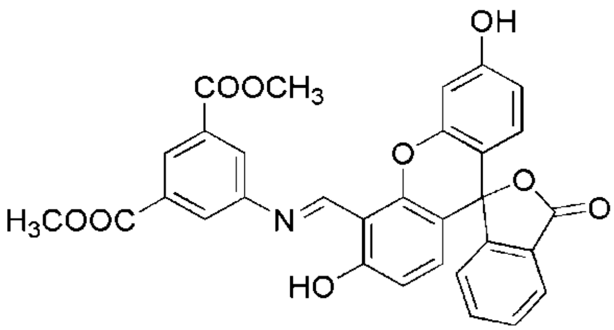


Figure 11 Structure of copper ion sensor [FR-L].

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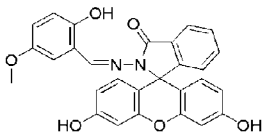
as 1-phenyl-3-methyl-5-hydroxypyrazole-4-benzoyl by Li et al for the quick detection of Cu^{2+}. With the reaction between aldehyde group and phenolic hydroxyl group of salicyldehyde a new CFSH can be synthesized named as 5-chlorosalicyldehyde Fluorescein hydrazone. The binding of Cu^{2+} ion with CFSH molecule is though carbonyl O, amido N and hydroxyl O as donors [25] **(Figures 15 and 16).**

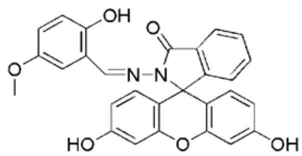
A NBD based chemidosimeter having fluorescein derivative has been used for the detection of Cu^{2+}. The spirolactam structure is very weak fluorescent molecule and in open amide form the fluorescent property is enhanced. NBD- flourescein hydrazide in conjugation can be used as a chemodosimeter which has a unique fluoremetric response towards Cu^{2+} [26] **(Figure 17).**

Paper based diagnostic assay is an important for the detection of Cu^{2+}. The sensor is a fluorescent probe **(Figure 18)** which is a fluorescein molecule constructed by changing in the naphthalene units F1 fluorescein, F2 naphtha fluorescein, F3 seminaphthaflourescein, F4 dinaphthafluorescein and the corresponding probes are FN1 –FN4 [27].

The derivative of flourescein (E)-2- [(1H-pyrrol-2-yl) methylene) amino)] 3’6’ dihydrooxyspiro [isoindole-1,9’-xanthene]-3-one

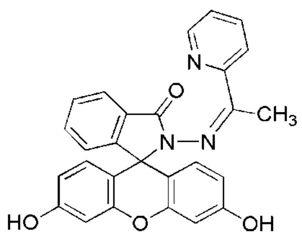


[12.1] 3-HMBA-FH



[12.2] 5-HMBA-FH

Figure 12 Structure of Copper ion sensor [3-HMBA-FH], 12.2 Structure of Copper ion sensor [5-HMBA-FH].



[FBO]

Figure 13 Structure of copper ion sensor [FBO].

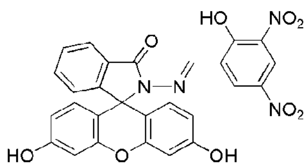


Figure 14 Structure of copper ion sensor [FDNS].

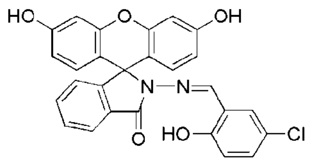


Figure 15 Structure of copper ion sensor [CFSH].

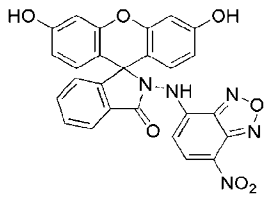
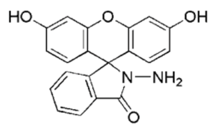
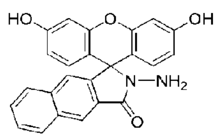


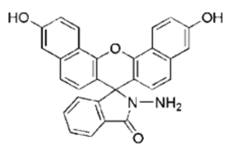
Figure 16 Structure of copper ion senor.



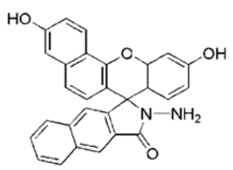
17.1



17.2



17.3



17.4

Figure 17 (17.1) Structure of copper ion sensor [FN1]; (17.2) Structure of copper ion sensor [FN2]; (17.3) Structure of copper ion sensor [FN3]; (17.4) Structure of copper ion sensor [FN4].

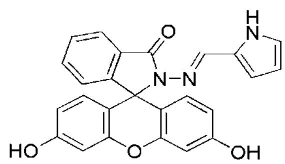


Figure 18 Structure of copper ion sensor.

(FLPY) in DMSO/HEPES (3:1,Ph-7.2) is a highly selective and sensitive sensor for the detection of Cu^{2+} [28] **(Figure 19).**

Copper (II) ions and biothiols were also detected by using fluorescence by on-off-on mechanism. Probe **(Figure 20)** was synthesized bearing a fluorescein unit in 100% HEPES buffer which sense Cu^{2+} by fluorescence quenching [29].

Foster Resonance Energy Transfer (FRET) OFF-ON chemosensor consisting of a fluorescein acceptor and phenanthroline donor is used as a sensorfor the detection of Cu^{2+} [30] **(Figure 21).**

Bio-conjugated fluorescein acts as a linker to develop MOF containing Eu^{3+} as a cationic center via cation exchange reaction. This artificially fabricated entity, Eu^{3+}@BIO-MOF has been used to sense Cu^{2+}. In the presence of Cu^{2+} the fluorescence intensity is quenched and it is enhanced by Eu^{3+} [31].

A chemo sensor derived from benzo [f]fluorescein was synthesized named as3'6'dihydroxy-2- [(2hydroxynaphthalene-1-yl)methylene)amino)-6-methyl-4-(p-tolyl)spiro [benzo [f] isoindole-1,9xanthene]-3 (2H)-one (BFFNH) **(Figure 22)** for sensing Cu^{2+} ion. The probe is highly selective for Cu^{2+} ion. The kinetics and thermodynamics study also proved this fact that Cu^{2+} have higher binding capacity with the sensor [32].

1, 4bis (1-flourescein)-2, 3diaza-1,3butadiene (FNSB) is a Fluorescein derived Schiff base sensor which gives high efficient binding with Cu^{2+}. It is a calorimetric as well as fluorometric probe in which the color is changed from colorless to yellow as the metal ion binds to this fluorescent probe [33].

Detection of Zinc

It is the second most abundant element involves in normal human growth and development [34]. The insufficiency of zinc leads to immune dys-functioning, impaired cognition, Alzheimer disease, Parkinson's disease, epilepsy and cerebral ischemia [35]. It is very important element as it involves transportation of many enzymes, neural signal transmission, gene expression and cell functioning [34].

There are various sensors for Zn^{2+} ions. Schiff bases are one of them because nitrogen atom has the capacity to bind metal ion. Schiff bases derived from fluorescein hydrazine and phenol via condensation reaction has high importance due to its capability to sense Zn^{2+}. The receptors L when binds with zinc metal increases its "turn-on" activity with twenty three times **(Figures 23 and 24).** The selective detection of metal ions in turn-on mode has been explained by chelation enhance fluorescein (CHEF) mechanism as well as photo induced electron transfer (PET) mechanism [36].

Fluorescein based nano-particles derived from N- (3'6'-dihydroxy-3oxospiro [isoindole-1, 9' xanthene]-2-yl) 2-hydroxybenzamide (FB) is an interesting molecular system having ability to detect Zn^{2+} ion in presence of various analytes. This nano-system shows turn-on sensing behavior in aqueous system. It works on the chelation enhanced fluorescence (CHEF) [37].

A Fluorescein based fluorescent probe has been designed and synthesized, bearing special sites for detecting Zn^{2+} and ATP molecule together with its high selectivity and sensitivity. It works on "turn-on" mechanism via involving opening and closing of spiro-ring of newly derived molecular system [38] **(Figure 25).**

Fluorescein dye having an imidazole ring shows binding with Zn^{2+}. The fluorescent probe shows highly calorimetric turn on response towards the binding of Zn^{2+}, and the colour changes from colorless to yellow [39] **(Figure 26).**

Azofluorescein **(Figure 27)** consist of a fluorescein moiety which act as a fluorophore unit consisting of a linker (-N=N-) and

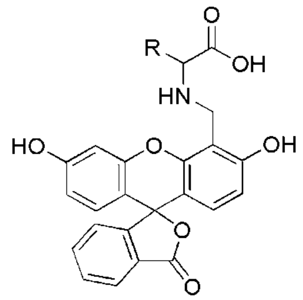


Figure 19 Structure of copper ion sensor (R=H (1), Bn(2)).

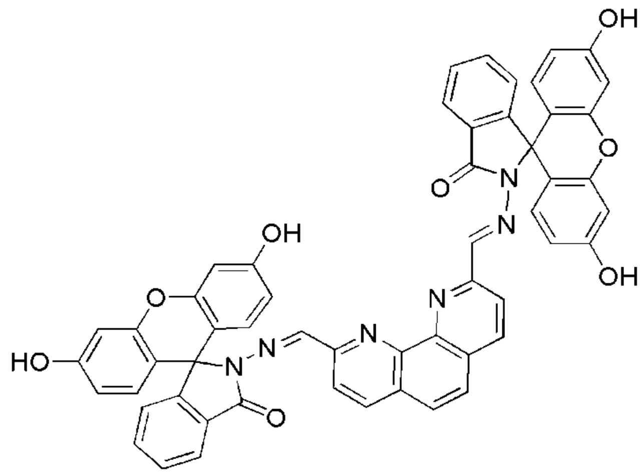


Figure 20 Structure of copper ion sensor.

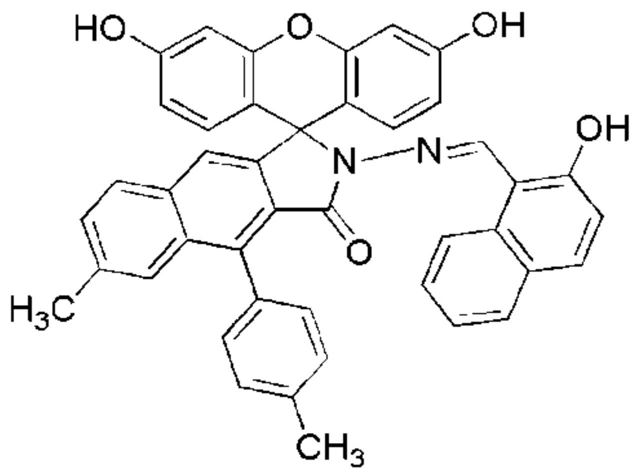


Figure 21 Structure of copper ion sensor (BFFNH).

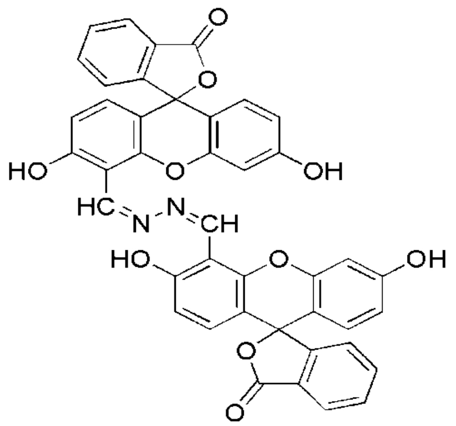


Figure 22 Structure of copper ion sensor (FNSB).

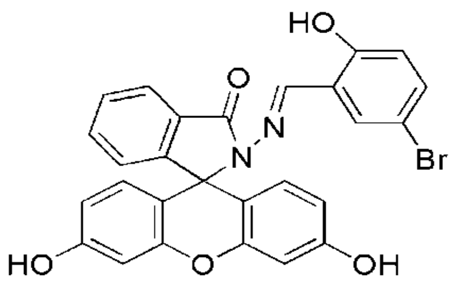


Figure 23 Structure of Zn^{2+} ion sensor.

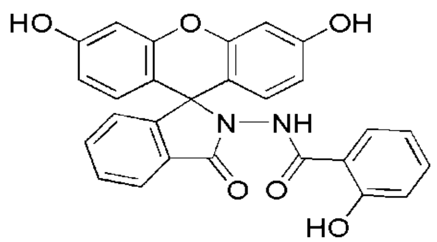


Figure 24 Structure of Zn^{2+} ion sensor (FB).

ionophores which is formed by linker (-N=N-) with phenoxyl and carboxyl functional groups to create a binding pocket of [2]Madan Mohan Malaviya University of Technology, Gorakhpur, Uttar Pradesh, India . It works on the photoinduced electron transfer mechanism (PET) [40].

Detection of Cobalt

Cobalt is considered one of most important nutrient for human body an plays an pivotal role in various biological processes. This ion of cobalt containing co-enzyme and water soluble vitamin are responsible for myelin sheath formation, protein synthesis and production of RBC's. Excess of cobalt ion causes impaired lung function, bronchial asthma, panic–anxiety attack, cardiotoxicity and low cardiac output [41].

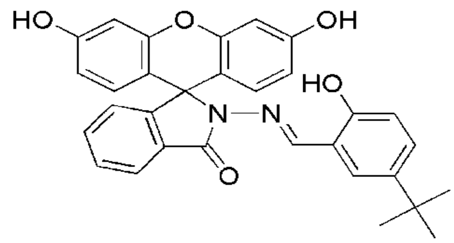


Figure 25 Structure of Zn^{2+} ion sensor.

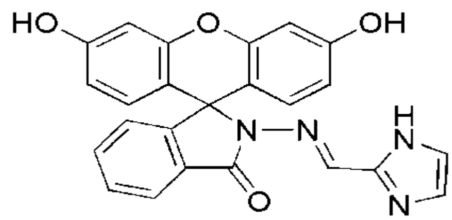


Figure 26 Structure of Zn^{2+} ion sensor.

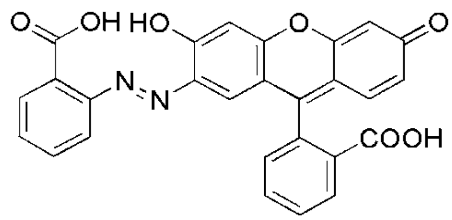


Figure 27 Structure of Zn^{2+} ion sensor [Azofluorescein].

Flourescein and its derivatives 4'5dibromoflourescein, 2'7'dichloroflourescein and 2'4'5'7' tetrabromoflourescein can be efficiently used as a chemoluminiscent sensor for the detection of Co^{2+} ion. Chemoluminiscent has been used extensively to determine the various inorganic and organic elements. The flourescein and its derivatives include the reaction with the luminol molecule in alkaline medium to produce chemoluminiscence. Luminol is popular liquid phase chemoluminiscent agent in alkaline condition. [40]

Detection of Cadmium

Cadmium is one of the most toxic elements. Cadmium can cause various urinary, reproductive and respiratory disorders. Cadmium which is a trace element leads to biomagnification,bioaccum ulation and ground water contamination [43]. It is hazardous as it leads to chronic toxicities on renal tubules and then the metabolism of bones is disturbed [44]. Diarylethene derivative with flourescein-quinoline was synthesized for the detection of Cd^{2+}. The sensor **(Figure 28)** for the detection of Cd^{2+} is operated by the turn on mechanism [45].

Detection of Gold

Gold have anticancer and antitumour properties. Phosphine

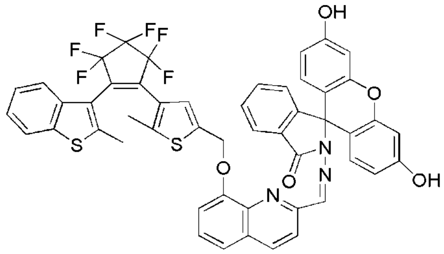


Figure 28 Structure of Cd^{2+} ion sensor.

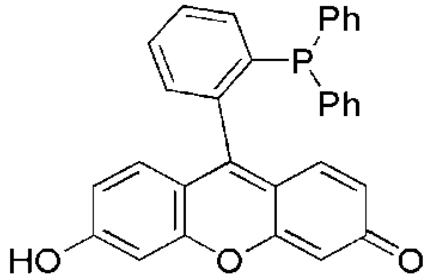


Figure 29 Structure of gold ion sensor.

decorated molecule along with fluorescein molecule is used to sense the gold. Phosphine gold has an increased tendency of fluorescence as compared to free metal ions. This probe works on the double turn on mechanism [46] **(Figure 29**).

Fluorescein based fluorescent probe FL-1 **(Figure 30)** works on turn-on mechanism to sense Au (III) [47]. Notable point is that the molecule is able to detect even at very low concentration of glod ion in aqueous system in presence of other ions. It is also useful to show its utility to sense the ion at cellular level.

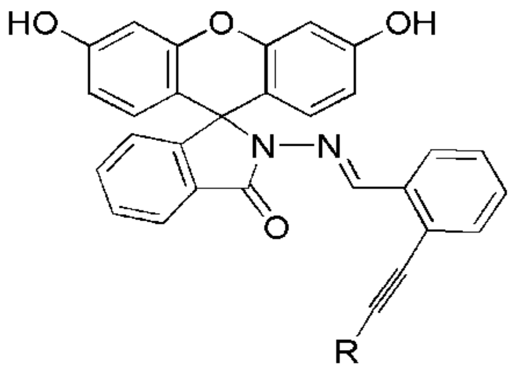
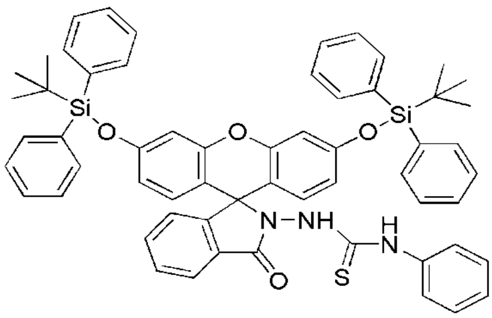


Figure 30 Structure of gold ion sensor [FL-1; FL-1 R_1= CH_2OH], Structure of gold ion sensor [FL-2; R= C_3H_7].

Dual Sensors

Detection of Hg^{2+} and F^{-1}

Mercury is the most heavy metal which is poisonous. It enters the human body through the food chain and its excess leads to the dysfunctioning of central nervous system. And Fluoride anion is most difficult anion to detect. It is widely used in toothpaste and many medicines. However, its higher doses can cause flourosis, urolithiasis or even death. Detection of Hg^{2+} was done on the basis of 'AND' logic gate which is a Flourescein based probe ie (FPSi) **(Figure 31).** It was constructed when the tert-butyl diphenylsilyl thiosemicarbazide was added to the skeleton of fluorescein for detection of Fluoride and Hg^{2+}. No fluorescence is produced when fluoride and Hg^{2+} were added separately in the solution but when added together, F^-cleaves the Si-O bond and the Hg^{2+} catalyze the irreversible desulfurization reaction leading to the formation of spirocyclic and opencyclic changes causing yellow green fluorescence [48].



[FPSi]

Figure 31 Structure of Hg^{2+} and F^- [FPSi].

Detection of Cd^{2+} AND Co^{2+}

Cobalt is an essential trace element whose excess can cause threat to heart and thyroid gland. The detection of cobalt is restricted by various competitors such as Ni (II),Cu (II) and Zn (II) but the extreme toxicity is caused due to Cd (II) as found by Irving William series. To create a chemosensor for the detection of cadmium and cobalt ion using Cu (I) assisted alkyne azide (CuAAC) cycloadditon reaction to form a 1, 2, 3 triazole. This 1, 2, 3 triazole acts as a sensor working on the ON-OFF mechanism **(Figure 32).** The fluorescein dye backbone creates a phenomenon framework for the synthesis of multiple input probes [5].

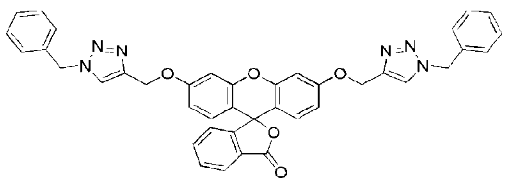


Figure 32 Structure of Cadmium and Cobalt ion sensor [1,2,3 triazole].

Detection of Fe^{3+} and Hg^{2+}

A novel visually detectable fluorescein based ratiometric

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fluorescent chemosensor, which is a ferrocene appended fluorescein moiety connected through triazole linker has been designed for the simultaneous detection of Fe^{3+} and Hg^{2+}. This sensor has been synthesized by introducing fluorescein with an alkyne via [$^{2+}$3] cycloaddition reaction and ferrocene with an azide appendage. This chemosensor is specific towards Fe^{3+} and Hg^{2+} ions and can be detected through through naked eye as well as via ratiometric fluorescence emission at a very low limit of detection, zero wait response time and high binding constant [49] **(Figure 33**).

Detection of Al^{3+} and Zn^{2+}

Aluminium is considered to be the most abundant metal on the earth's crust. It is essential for the growth and development. Zinc is the second most abundant transition element. Deficiency of Zinc leads to various problems such as Alzeheimer disease, Parkinson's disease and Friedrich's ataxia. Fluorescein hydrazone, cyanuric chloride and salicyldehyde chromone combine together to form fluorophore unit (FHCS) **(Figure 34).** When chelation was done with metal ions such as Al^{3+} and Zn^{2+} than FHCS sensor works via turn on mechanism. FHCS with Al^{3+} and Zn^{2+} were confirmed to form a 5 member co -6 member condensed ring. A single sensor for multiple metals has gained much attention due to its cost effective. FHCS is highly effective for the metal ions Al^{3+} and Zn^{2+} [50].

Detection of $Hg^{2+}$and Ag^{+}

The two heavy transition metal ions, Hg^{2+} and Ag^{+} are released in a greater amount in the environment. Ag^{+} is released from electrical industry and imaging industry. Mercury is extremely hazardous especially for pregnant women and children. Mercury acts as a neurotoxin. The derivative of Fluorescein named as FLTC was synthesized which act as a fluorescent chemosensor to detect Hg^{2+} in ethanol-H_2O (HEPES buffer Ph-7.15) **(Figure 35).** After the complex is made with Hg^{2+} FLTC form complex with Ag^{+} [51].

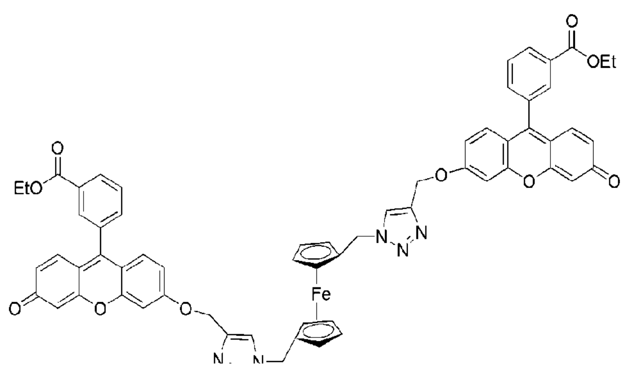

Figure 33 Structure of Fe^{3+} and Hg^{2+}.

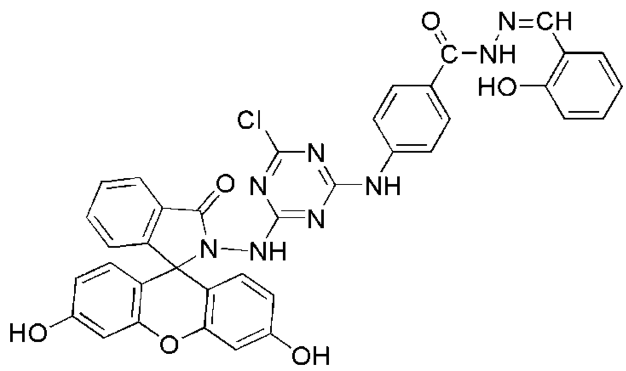

Figure 34 Structure of Al^{3+} and Zn^{2+} sensor [FHCS].

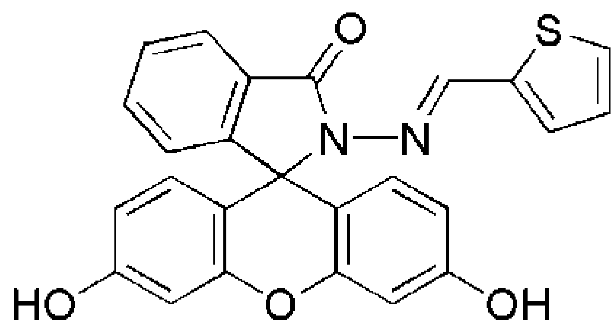

Figure 35 Structure of Hg^{2+} and Ag^{+} ion sensor.

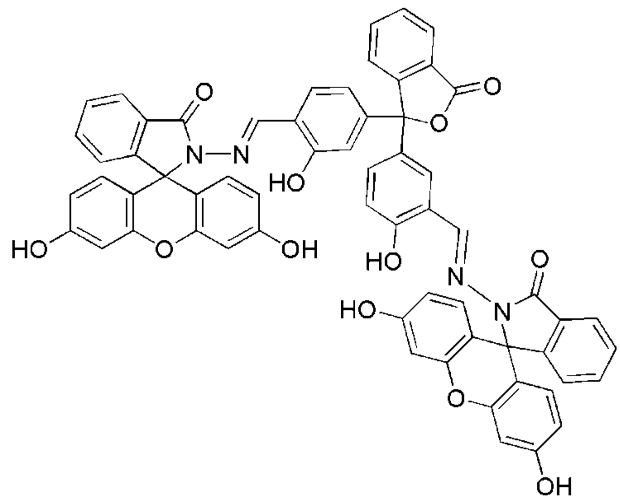

Figure 36 Structure of Hg^{2+} and Zn^{2+} ion sensor.

Detection of Hg^{2+} and Zn^{2+}

A sensor which is used to detect the Hg^{2+} and Zn^{2+} is a derivative of Fluorescein named as Phenolphthalein–fluorescein dye derivative. This probe is highly selective for two cations Hg^{2+} and Zn^{2+} [52] **(Figure 36).**

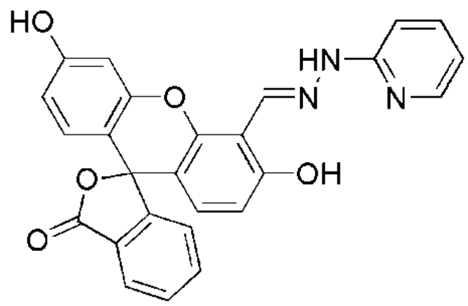

Figure 37 Structure ofAl^{3+} and Cu^{2+}ion sensor.

Detection of Al^{3+} and Cu^{2+}

A fluorescein probe was synthesized for the dual sensing of Al^{3+} and Cu^{2+}. There is a single sensor for the detection of these ions. This probe functions in turn-on mode for the Al^{3+} and Cu^{2+} sensing [53] **(Figure 37).**

Conclusion

There are various fluorescent probes discovered in the past years, but we have focused here on the fluorescein dye as it has attained extreme importance due to its properties. In this review article fluorescein based fluorescent probes for detection of various transition metals were reported. The sensing phenomenon is based on various mechanisms mainly PET, CHEF, etc. Various fluorescein derivatives have been used to detect number of metal ions of high importance such as Cu^{2+}, Zn^{2+}, Ni^{2+}, Cd^{2+}, Co^{2+}, Au^{3+}, Fe^{3+}, Hg^{2+}, and Ag^{+}. It will be highly useful for researchers across the world to get accumulated data on sensing of various transition metal ions in one window.

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