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Tuning glycoconjugates to acquire selectivity for toxic Hg^{2+} ion

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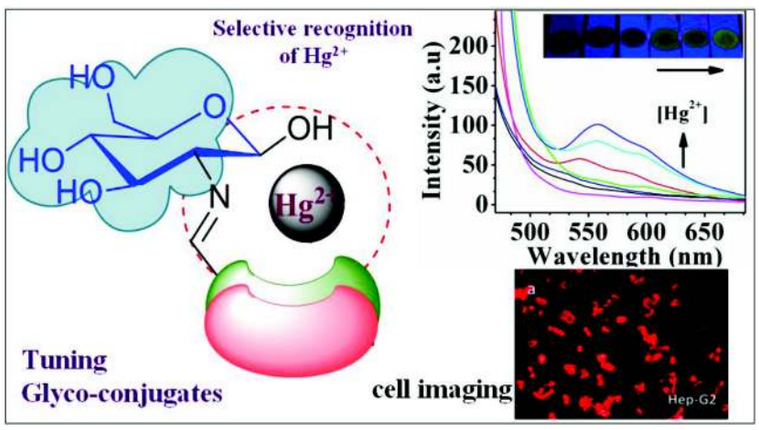
Abstract

The development of probes for Hg^{2+} ion has been an active area of research in recent years because of the ill effects of this ion on the human health and environment. Hence the probe that needs to be developed should be sensitive as well as biologically compatible. This review mainly focuses to provide a comprehensive and comparative view of advances reported over the past ten years of literature, including our own contributions, in the design and application of the carbohydrate-based conjugates as fluorescent sensors for mercury. Therefore, this review covers aspects, such as, Hg^{2+} ion recognition, sensing and complexation by carbohydrate conjugates addressed using different spectral techniques and their critical analysis in a comparative manner.

Graphical Abstract



Keywords. Gluco-conjugates; selective recognition of Hg^{2+}; cation…π interaction, hetero atom coordination, detection limit, DFT computation, fluorescence imaging.

Introduction

Mercury is one of the most widespread heavy metal pollutants and exhibits high toxicity.[1,2] Accumulation of this causes both biological and ecological problems.3 Environmental pollution by mercury is a global problem due to the upsurge in the utility of this in industry and subsequently its discharge into the environment.[4] Thus, mercury (Hg^0 and Hg^{2+}) and some of its species, such as, methylmercury are released into the environment through a variety of anthropogenic activities including industrial ones, as well as natural sources including emissions from volcanoes and forest fires.[5,6] Irrespective of the source, the mercury species would easily pass through the biological tissue and hence affects various organs of the body including the central nervous system.[7-9] The Environmental Protection Agency (EPA) set an upper limit of 2 ppb (10 nM) for Hg^{2+} to be safe in drinking water.[10] Therefore, the development of selective chemo-sensors for the detection of mercury in biological and environmental samples continues to attract a great deal of attention of chemists in particular.[11-14]

There are various conventional techniques used for the detection of Hg^{2+} such as electrochemical detection and chromatographic methods.[15,16] However, all these methods are limited in their applicability. Thus, it is essential for real-time monitoring of environmental samples by simple and inexpensive method for not only detecting but also for quantifying Hg^{2+}. Among the various detection techniques existing, the one that is based on optical signals has proven most important as

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compared to the others. In particular, fluorescence is a rapid detection method and attracted increasing attention during the past two decades because of its high sensitivity, selectivity and low detection limit.

Hence developing new receptor molecules which would detect Hg^{2+} at very low concentrations with high selectivity is still an active field and poses challenges to the synthetic chemists. Another challenging factor that the synthetic chemists need to address is the solubility of the receptor molecule in aqueous medium and its biological compatibility. All these concerns will be taken care, if the carbohydrate-based conjugates are synthetically modified to possess fluorescent probes.

Results and discussion

The main feature of this review is to critically analyze the literature reports appeared during the past 10 years on glyco-conjugates dealing with the recognition and sensing of Hg^{2+} and their tunability for providing easy and selective sensing, while using aromatic and heterocyclic moieties as fluorescence reporters. All the corresponding literature reports have been divided into six different categories based on the nature of their sensing as discussed in this review article.

(a) Recognition based on *cation* $(Hg^{2+})...\pi$ interaction: Recently our group reported two water soluble glucosyl-imino-conjugates, one possessing an anthracenyl moiety (L_1) and the other possessing a pyrenyl moiety (L_2) where both are *turn on* fluorescent sensors for Hg^{2+} and the interactions are through *cation*$...\pi$ type (Figure 1).[17] The former receptor (L_1) can function even in the presence of albumin proteins, human blood serum and milk. The L_1 exhibits a twelve-fold fluorescence enhancement against Hg^{2+} among the thirteen metal ions studied and there by provides selectivity in aqueous methanol, with a detection limit of ~50 ± 10 ppb (Figure 1b). Competitive titrations showed that L_1 responds towards Hg^{2+} even in the presence of other metal ions by forming a 1:1 complex that was supported by ESI-MS. The DFT computational modeling revealed that the interaction is through imine as well as *cation*$...\pi$ type and this was further supported by ^{1}H-NMR spectroscopy.

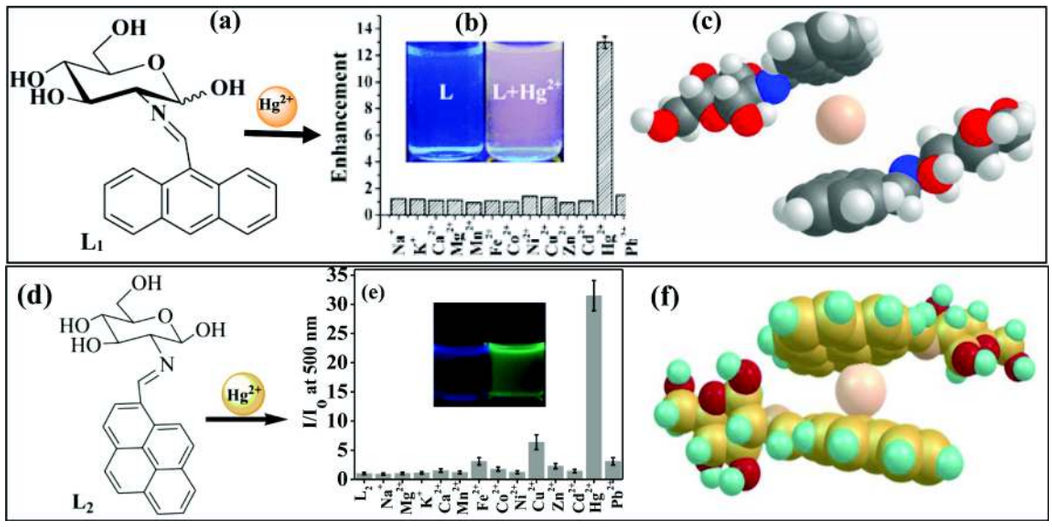

Figure 1. (a) and (d) are the schematic representations of the structures of L_1 and L_2 respectively. (b) and (e) show fluorescence enhancement observed for L_1 and L_2 respectively when titrated with metal ions. The inset photographs show their colour under UV light. (c) and (f) are the DFT-optimized structures of the complex of $[Hg(L_1)_2]$ and $[Hg(L_2)_2]$ respectively.

The fluorescence-based sensitivity increases on going from anthracenyl (**L_1**) to pyrenyl (**L_2**) owing to the greater ***$Hg^{2+}...\pi$*** interaction in the latter that is concomitant to larger aromatic surface area of the pyrenyl moiety over that of the anthracenyl moiety.

The glyco-conjugate (**L_2**) exhibits selective chromogenic as well as fluorophoric property towards Hg^{2+} in a ratiometric manner with ~30-fold enhanced fluorescence emission intensity and a minimum detection limit of 18 ± 2 ppb.[18] The fluorescence enhancement is seen even in the presence of thirteen other competitive metal ions studied (Figure 1e). All the experimental studies carried out supported the formation of 2:1 complex between the conjugate (**L_1** or

L_2) and Hg^{2+} and was proven by ESI-MS. The computationally modeled structures in both the cases showed Hg^{2+} being sandwiched between the two aromatic moieties (Figure 1c, f). The computational studies also showed shorter ***Hg²⁺…π*** distance in case of L_2 as compared to L_1, supporting stronger ***cation…π*** interactions in the case of the L_2 complex. The reversible sensing was demonstrated using Na_2EDTA in the case of L_1 and *n*-Bu4NF in case of L_2 and thereby demonstrated the re-usability of both these receptors.

(b) Presence of heteroatom moiety leads to the recognition through ligation: A quinoline-imino-glucosyl conjugate (L_3) was synthesized by connecting the C2-imine of glucose with the carboxaldehyde of quinoline as reported in the literature recently.[19] The Hg^{2+} binds to L_3 as 1:1 (Figure 2) as depicted, based on the data from different spectral methods including ^1H NMR spectroscopy. Further, the ^1H NMR revealed β-$^4C_1$ conformation with the chemical shift of the anomeric proton being observed at 4.9 ppm. However, in the presence of Hg^{2+}, a $^1C_4$ conformation is stabilized by N_2O_2 chelation resulting in a tetrahedral coordination geometry where the anomeric proton signal shifts downfield and is observed at 6.3 ppm (Figure 2a). All this is associated with significant downfield shifts in the signals of the quinoline ring protons. The L_3 shows weak fluorescence emission at 480 nm in aqueous solution with a quantum yield of 0.005. In presence of Hg^{2+}, the emission band is blue shifted to 415 nm with only ~10-fold enhancement in the fluorescence intensity with the formation of 1:1 complex having Ka of $7.14\times104\ M^{-1}$ (Figure 2b). The blue-shift is attributed to photo-induced charge transfer (PCT) from the hydroxyl group to the quinoline moiety, and the fluorescence enhancement to the alleviation of PET.

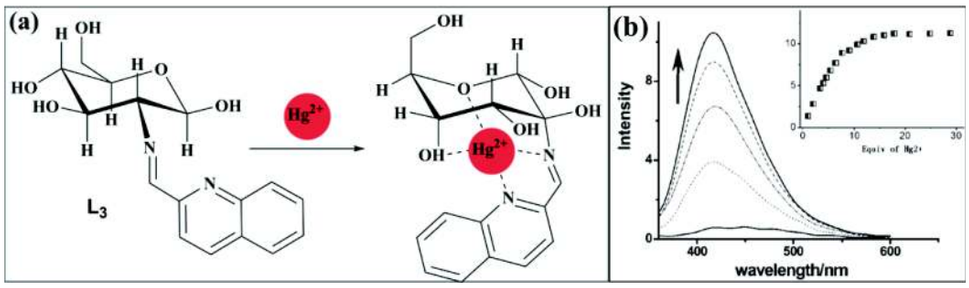

Figure 2. (a) Schematic representation of the structure of L_3 and its proposed Hg^{2+}-bound complex. (b) Fluorescence spectra of aqueous solution of L_3 (10 μM) upon addition of increasing concentrations of Hg^{2+} (λ_{ex} = 315 nm). The inset shows the fluorescence emission intensity at 415 nm.

(c) Larger hetero-aromatic moiety prefers recognition through both *cation (Hg²⁺)…π* as well as ligation: We have recently reported a thiourea-linked anthraquinone conjugate of a carbohydrate (L_4) which exhibits selective chromogenic as well as fluorogenic properties towards Hg^{2+} by showing ~75-fold fluorescence enhancement with a minimum detection limit of 25 ± 4 ppb in buffer with the formation of a 2:1 complex between L_4 and Hg^{2+} (Figure 3d).[20] The computational studies carried out with this complex resulted in ***Hg²⁺…π*** interactions besides binding through 'S' center of the thiourea residue (Figure 3b, c). When coated on silica gel, the receptor L_4 exhibits ~10-fold fluorescence enhancement upon addition of Hg2+ where the fluorescent glow can be seen under UV light (Figure 3e, f). The L_4 senses Hg^{2+} even in blood serum and or in biological fluids by switch on fluorescence as demonstrated by disposable silica sheets coated with L_4 in the Hg^{2+} concentration range of 5 – 60 μM. Thus, the minimum detection limit of 285 ± 15 and 345 ± 17 ppb were observed with L_4 on silica gel sheets for the Hg^{2+} present in *HEPES buffer* and in blood serum solutions respectively.

(d) Dominance of the triazole core coordination over the interaction of the pyrenyl moiety in the recognition: Ribose-based Hg^{2+} fluorescent sensors L_5 and L_6 were synthesized by coupling ethylene ether, ribosyl-, and pyrene-triazole moieties and the results of these were reported recently in the literature (Figure 4).[21] The L_5 exhibits fluorescence quenching of pyrene excimer selectively against Hg^{2+} among the twelve biologically important metal ions studied in CH_2Cl_2/MeOH solution. The minimum detection limits for Hg^{2+} were 10 and 15 μM respectively in the case of L_5 and L_6. The presence of Hg^{2+} ion caused a 2-3 nm red shift in the absorption and this is attributed to the formation of 1:1 complex with association constants of 1.73×105 and $4.44 \times 105\ M^{-1}$ respectively for L_5 and L_6. NMR spectroscopy revealed binding of Hg^{2+} through the triazole nitrogen of each arm. In the computationally

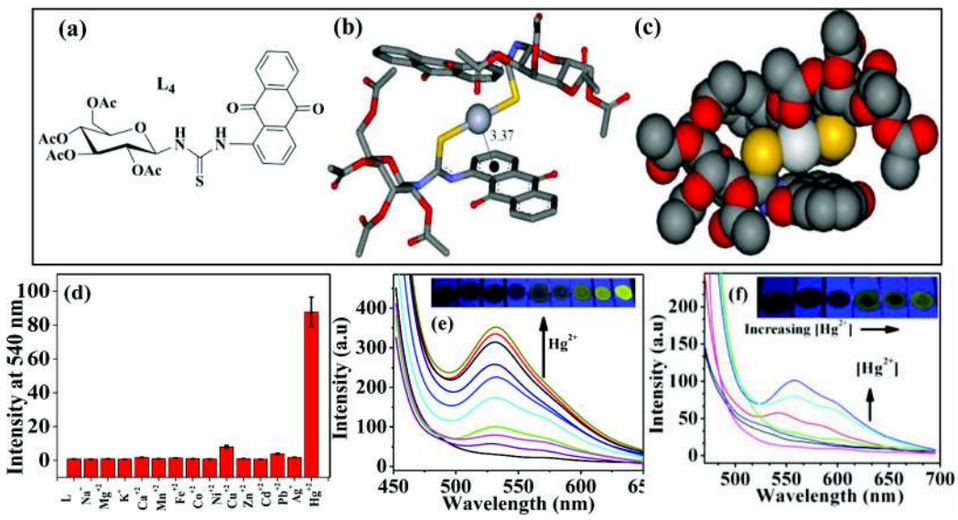

Figure 3. (a) Schematic representation of the structures of L_4. The B3LYP/LANL2DZ-optimized structures: (b) $[(L_4)_2Hg^{2+}]$ complex, and (c) space-filling representation of the complex $[(L_4)_2Hg^{2+}]$. (d) Histogram showing the number of folds of fluorescence enhancement (I/I0) in the titration of L_4 with Mn+ (λ_{em} = 540 nm). Spectra obtained in the fluorescence titration of L_4 (λ_{ex} = 430 nm) with Hg^{2+} on the silica gel solid support in presence of, (e) HEPES buffer and (f) blood serum. Insets in both (e) & (f) are photographs of all the samples under 365 nm UV light.

modeled [$\mathbf{L_5}$+Hg^{2+}] complex, the Hg^{2+} ion is bound by N_4 core where each of the triazole extends coordination through two of its nitrogens and thereby pushing the two pyrene moieties apart from each other.

(e) Recognition through coordination by triazolyl-naphthyl derivative and the metal ion-induced affinity to form gels: A triazole-linked per-acetylated glucose based naphthalene derivative $\mathbf{L_7}$ has been synthesized and demonstrated for its gelation property in the literature (Figure 5a).[22] The organogelator $\mathbf{L_7}$ showed good gelating ability and better affinity towards Hg^{2+} even at 10 μM concentration when compared with other cations. The fluorescence studies showed quenching for both Cd^{2+} and Pb^{2+} but it was maximal for Hg^{2+} and the complex formation was supported by absorption spectroscopy. The downfield shift observed in the triazole- and the anomeric protons supports the coordination with the glyco-conjugate. Addition of Cd^{2+} and Pb^{2+} to $\mathbf{L_7}$ caused only a minimum change in the gel state as compared to that of Hg^{2+}. The morphological changes are significant when Hg^{2+} was added to $\mathbf{L_7}$ resulting in the formation of gel as studied by FESEM and HRTEM (Figure 5b, c).

f) Recognition through reactivity followed by cell imaging: A sugar conjugate of rhodamine ($\mathbf{L_8}$) has been reported as probe for Hg^{2+} in aqueous solution (Figure 6).[23] Upon addition of Hg^{2+} to $\mathbf{L_8}$, typical absorption and emission spectra of ring-opened rhodamine were obtained (Figure 6b). This happens through the formation of a 1:1 complex and exhibits a detection limit of 1 ppb which is below the recommended 2 ppb level in drinking water by EPA.

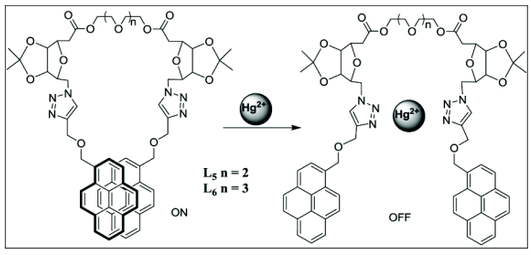

Figure 4. (a) Schematic representation of the structure of L_5 and L_6 and its proposed Hg^{2+} bound complex.

The reversible sensing of $\mathbf{L_8}$ was demonstrated using NaI or Na_2S (Figure 6c). When HeLa cells along with 10 μM $Hg(NO_3)_2$ were incubated with $\mathbf{L_8}$, a significant fluorescence increase was observed in the perinuclear region of the cytosol, hence $\mathbf{L_8}$ is useful in cell imaging (Figure 6d).

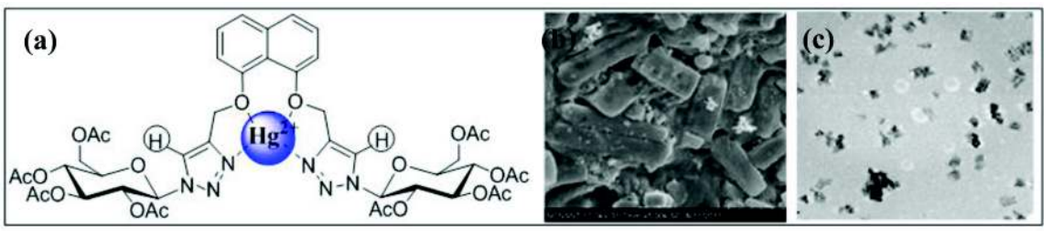

Figure 5. (a) Schematic representation of the proposed structure of Hg^{2+} bound complex of L_7. FESEM images of (b) L_7 and (c) L_7 in presence of Hg^{2+}.

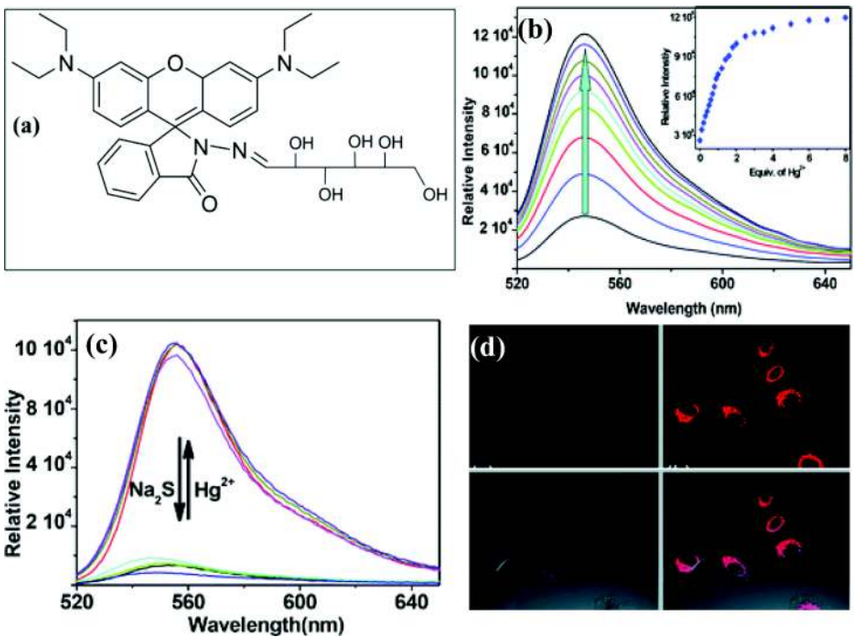

Figure 6. (a) Schematic representation of the structures of L_8. (b) Fluorescence spectra and the relative intensity (the inset) for the titration of L_8 by Hg^{2+}. (c) Fluorescence spectra showing the reversibility of Hg^{2+} coordination to L_8 by Na_2S. (d) Fluorescence imaging of cancer cells in presence of L_8 followed by Hg^{2+}.

Another receptor **L_9**, possessing two triazole-cores appended with glucose and rhodamine has been reported (Figure 7). The **L_9** is colorless and is weakly fluorescent (λ_{em} = 552 nm, λ_{ex} = 500 nm).[24] However, upon addition of Hg^{2+}, a 20-fold enhancement was observed in the fluorescence emission. The emission intensity is linearly proportional to the amount of Hg^{2+} added, and the limit of detection is 7.35 $\times 10^{-8}$ M. The Job's plot and ESI MS supported a 1:1 complex between the **L_9** and Hg^{2+} and the binding mode was derived based on 1H NMR studies. The hepatoma cancer cells give fluorescence imaging when treated with **L_9** followed by Hg^{2+} and the imaging is cell selective as understood when the studies were extended to HepG2, HeLa and HCT-116 (Figure 7). This study provides unique insights into the cell-selective imaging of specific intracellular species using sugar as targeting agent.

A peracetylated glycosyl moiety that is connected to rhodamine B through a triazole residue (**L_{10}**) recognizes Hg^{2+} ratiometrically among various metal ions studied in 80:20 H_2O:CH_3CN solution (Figure 8).[25] The Hg^{2+} opens spirolactam ring of **L_{10}** resulting in the formation of a strong 1:1 chelated complex with Ka = 1.4×106 M^{-1}, where the **L_{10}** coordinates through the triazole-nitrogen, ether-oxygen and carbonyl-oxygen as demonstrated by absorption, ESI MS and ^{1}H NMR spectroscopy. Upon

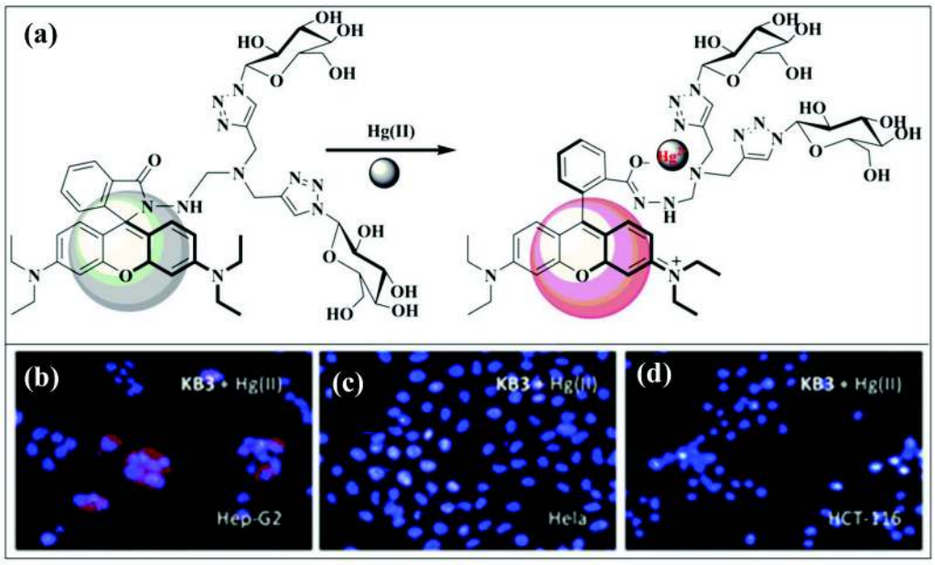

Figure 7. (a) Schematic representation of the structure of L_9 and its proposed Hg^{2+} bound complex. Fluorescence imaging of different cancer cells in presence of Hg^{2+}: (b) HepG2, (c) Hela and (d) HCT-116.

interaction with Hg^{2+}, the $\mathbf{L_{10}}$ exhibits ~38-fold enhancement in the intensity via fluorescence resonance energy transfer (FRET) where the acetyl glycoside acts as a donor and the complex acts as an acceptor and provides a minimum detection limit of 7.6×10^{-8} M.

Ferrier carbocyclization reaction of Hg^{2+} with a synthetic resorufin-C1-glycoconjugate ($\mathbf{L_{11}}$) resulted in a fluorescent moiety resorufin (Figure 9a), so that $\mathbf{L_{11}}$ act as a turn-on fluorescent probe that is sensitive and selective to detect Hg^{2+} in aqueous medium (Figure 9b).[26] When excited at 570 nm, the emission intensity at

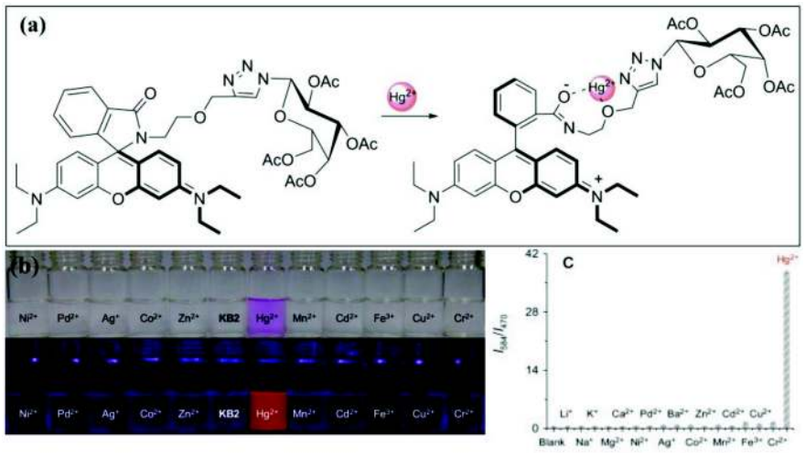

Figure 8. (a) Schematic representation of the structure of L_{10} and its proposed Hg^{2+}-bound complex. (b) Photograph of color changes of L_{10} in the presence of various transition metal ions under 365 nm UV light. (c) Ratiometric fluorescence intensity (I584/I470) change of L_{10} in the presence of various metal ions.

594 nm increases by ~25-fold upon increasing the concentration of Hg^{2+} and the limit of detection works out as 1 μM. The probe was also successfully applied to the imaging of Hg^{2+} ions in A549 cells and zebrafish, which is valuable in studying Hg^{2+} uptake, bioaccumulation and bioavailability in living organisms (Figure 9c).

Critical analysis

Critical analysis of all these reports clearly supports the selective recognition of Hg^{2+} ion upon appropriately derivatizing the carbohydrate platform. A well suited design for such receptors is to connect the fluorophore to the glycose in order to provide some coordination sites in addition to the presence of aromatic moiety and

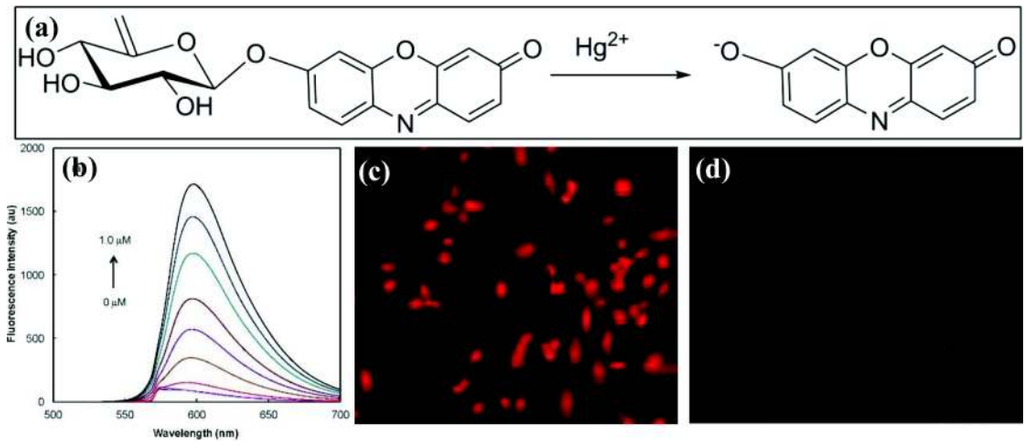

Figure 9. (a) Schematic representation of the structure of L_{11} and its sensing mechanism Hg^{2+}. (b) Fluorescence titration spectra (λ_{ex}=570 nm) of probe L11 (20 μM in pure water) with Hg^{2+} from 0 to 1.0 μM. Fluorescence images of Hg^{2+} ions with probe L11: (c) A549 cells and (d) zebrafish.

a typical design is given in Figure 10. Thus, the use of anthracenyl and pyrenyl moieties provide the aromatic region, the use of quinoline, anthraquinone, triazole, etc., can provide either the coordination site or the π-cloud or both. Even pre-organized binding core and/or reactive moiety are suitable enough to act as sensitive and selective sensors if the simple interaction or the reaction by Hg^{2+} can spontaneously generate fluorescent species with several folds of enhancement in the intensity. The carbohydrate platform is further useful to give water solubility and biological compatibility. Thus, this review clearly explains the inherent advantage of glyco-conjugates for the selective recognition of Hg^{2+} and brings out significant aspects upon critically analyzing the literature in appropriately tuning the glyco-conjugates. Some of these are as follows.

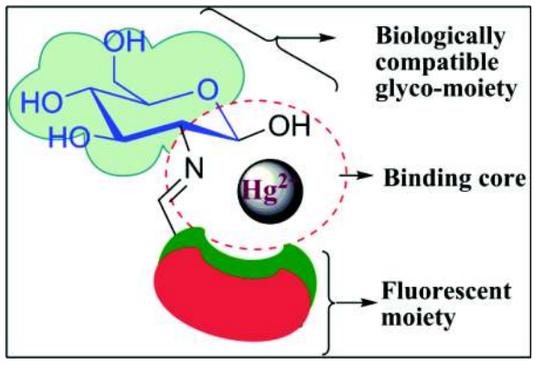

Figure 10. Typical design of a probe molecule for sensing Hg^{2+}.

(i) The conjugates of glucose bearing an anthracene moiety in conjunction with imine functionality *turns-on* the fluorescence emission in the presence of Hg^{2+}. This is by blocking the PET process when it interacts with both the imine moiety (by binding) as well as the aromatic moiety (through cation…π interaction). However, the fluorescence-based sensitivity seems to increase upon increasing the area of the aromatic region, i.e., for example on going from anthracenyl to pyrenyl, due to the presence of shorter Hg^{2+}…π distances, and thereby exhibits stronger interaction in the case of pyrene derivative (2.7 Å) as compared to the anthracenyl derivative (3.2 Å).

(ii) Once a hetero atom is introduced into the conjugate, the binding is preferred as coordination type through heteroatom rather than through ***cation…π*** type, unless the surface area of the π-system is large. This means that a heteroatom center directs the coordination over π type interaction as confirmed in the case of

quinolyl derivative, i.e., $\mathbf{L_3}$. However, when the surface area of the π-component is large, both the binding through the heteroatom and also the ***cation…π*** interactions were observed simultaneously, as noticed in the case of the conjugate possessing anthraquinone, i.e., $\mathbf{L_4}$. Thus, an increase in the number of aromatic rings increases the cation…π interaction and the presence of heteroatom tends to dictate coordination and when both are present, a combination of both these are observed simultaneously. Introduction of a hetero atom into the rings and/or into the derivatization such as that present in the triazole-pyrene moiety, leads to coordination only. This is true even with a triazole-naphthalene moiety.

(iii) The presence of rhodamine allows metal ion attack followed by opening the spirolactam ring leading to the binding of hetero atoms to Hg^{2+}. This is true in the case of conjugates, $\mathbf{L_8}$, $\mathbf{L_9}$ and $\mathbf{L_{10}}$. Since these conjugates possess glyco moieties, these were targeted to cells. Owing to their reactivity towards Hg^{2+}, fluorescence imaging of cells had become possible and based on the derivatization these acquire selectivity towards specific cancer cells over the others.

(iv) When the fluorescence intensity enhancement of **L1** and **L2** with Hg^{2+} is 13- and 30-fold respectively, their minimum detection limit changes from ~50 ± 10 and 18 ± 2 ppb. While both these receptors are selective towards Hg^{2+} over other metal ions studied, the sensitivity increases by ~3 times in the case of $\mathbf{L_2}$ as compared to $\mathbf{L_1}$.

(v) The silica gel sheets coated with $\mathbf{L_4}$ can be used to detect Hg^{2+} with a detection limit 285 ± 15 and 345 ± 17 ppb respectively in the presence of albumin-proteins and even the blood serum and thus $\mathbf{L_4}$ is a potential sensor for Hg^{2+}.

(vi) The EPA limit for Hg^{2+} is 2 ppb in drinking water. At this level of concentration, all the receptors, viz., $\mathbf{L_1}$, $\mathbf{L_2}$, $\mathbf{L_4}$, $\mathbf{L_8}$, $\mathbf{L_9}$ and $\mathbf{L_{10}}$ show at least >25 % of enhancement in their fluorescence intensity. All these would find wide range of applications including those of environmental concern. However, the $\mathbf{L_5}$ and $\mathbf{L_6}$ shows higher detection limit of 10 and 15 μM respectively.

(vii) Reversibility and reusability are important factors for the development of devices to sense the ion and in this case it is, Hg^{2+}. The reversible sensing of Hg^{2+} and reusability of $\mathbf{L_1}$, $\mathbf{L_2}$ and $\mathbf{L_8}$ receptors have been demonstrated by using Na_2EDTA, *n*-Bu_4NF and Na_2S respectively.

Thus, the literature clearly reveals that judicially designed derivatization of carbohydrate platform would lead to selective as well as sensitive detection of Hg^{2+}. It is indeed a matter of the desired level of sensitivity and the nature of the application that drive the specific design, followed by its synthesis and the execution.

Acknowledgements

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