Glycosyl based meso-substituted dipyrromethanes as fluorescent probes for \(\text{Cd}^{2+}/\text{Cu}^{2+}\) ions

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**Abstract**

Synthesis of new glycosyl based meso-substituted dipyrromethanes 1-3 has been described. Crystal structure of the representative compound 1 has been determined by X-ray single crystal analysis. The compounds 1 and 3 exhibit fluorescent ‘Turn-On’ and ‘Turn-Off’ signaling for \(\text{Cd}^{2+}\) and \(\text{Cu}^{2+}\) ions. Notably, meso-galactosyl dipyrromethane 2 remains silent toward tested metal ions.

The chemistry of dipyrromethanes has attracted a great deal of attention because of their potential applications in diverse areas.\(^{1-3}\) The photophysical and photochemical properties of these are governed by substituents at meso-position. In this context, numerous systems containing a variety of meso-substituents have been developed and extensively studied.\(^{4-18}\) Although, some sugar appended porphyrin derivatives have been described in the literature, there are only a couple of reports dealing with the dipyrromethanes containing sugar moieties appended to the pyrrole ring/meso-carbon.\(^{19,20}\) The synthetic strategies for such systems involve substitution at the pyrrole ring of a dipyrromethane using a sugar derivative or as intermediate in the synthesis of meso-substituted porphyrins.\(^{19,20}\) At the same time, their properties have scarcely been investigated.\(^{20}\)

Furthermore, \(\text{Cu}^{2+}\) is an indispensable trace element in biological systems and harmful as well.\(^{21}\) Considering inherent quenching behavior of copper, numerous fluorescent chemosensors have been developed and thoroughly studied. On the other hand, \(\text{Cd}^{2+}\) is industrially and agriculturally important element.\(^{21}\) Biological and environmental damages caused by \(\text{Cd}^{2+}\) are well known, therefore selective chemosensors for its detection are highly demanding.\(^{21}\)

Keeping these points in mind, we have designed and synthesized two new meso-glycosyl substituted dipyrromethanes 1 and 3, wherein 3 is akin to a dimer of 1. For the sake of disparity at the meso-position, we have also prepared a meso-galactosyl dipyrromethane 2 and compared the optical and cation recognition properties of 1–3.

Through this contribution we present the synthesis and characterization of three new glycosyl derivatives, \(5-(3'-\text{O-} \text{benzyl}-1,2,3\text{-isopropylidene-}\alpha-\text{o-xylo-pentodialdo-1,4-furanose})\)-dipyrromethane (1), \(5-(1,2,3,4\text{-di-o-isopropylidene-}\alpha-\text{o-galacto-hexodialdo-1,5-pyranose})\)-dipyrromethane (2), and \(5-[1',4'\text{-bis}(1,2,3\text{-isopropylidene-}\alpha-\text{o-xylo-pento-dialdo-1,4-furanose-3-O-methyl})\text{benzene}]-\text{bis(dipyrromethane)} (3) along with potential applications of 1 and 3 as a new class of chemosensors for \(\text{Cd}^{2+}\) and \(\text{Cu}^{2+}\) ions under aqueous conditions (\(\text{H}_2\text{O}/\text{EtOH}; 1:1, \text{v/v}\)).

In this letter, we have synthesized the glycosyl based dipyrromethanes by an acid catalyzed condensation of pyrrole with respective aldehydes.\(^{3}\) Three different aldehydes \(3'-\text{O-} \text{benzyl}-1,2,3\text{-isopropylidene-}\alpha-\text{o-xylo-pentodialdo-1,4-furanose} (4)\), \(1,2,3,4\text{-di-o-isopropylidene-}\alpha-\text{o-galacto-hexodialdo-1,5-pyranose} (5)\), and \(1',4'\text{-bis}(1,2,3\text{-isopropylidene-}\alpha-\text{o-xylo-pento-dialdo-1,4-furanose-3-O-methyl})\text{benzene} (6)\) were chosen as the key precursor for the synthesis of 1–3.\(^{22,23}\) Simple synthetic strategy adopted for their preparation is depicted in Scheme 1. It is noteworthy to mention that the oxidation of dipyrromethanes 1–3 to respective dipyrrins could not be achieved using DDQ.\(^{2}\) The reluctance of these compounds toward oxidation may be associated with intramolecular H-bonding interactions (vide supra). The compounds 1–3 have been characterized by elemental analysis, IR, NMR (\(^{1}\text{H}\) and \(^{13}\text{C}\)), ESI-MS, absorption and emission spectral studies.

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adopted syn-conformation with respect to each other whereas, O(1) and O(4) assume anti-conformation.

Optical properties of 1–3 have been investigated by UV/vis and fluorescence spectral studies. In its absorption spectra 1 exhibited a shoulder in the high energy region (>260 nm; \( \lambda > 1.71 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1} \)) and a broad band at ~374 nm (Fig. S10). Notably, despite having similar chromophoric framework, 3 displays a strong high energy band at ~294 nm (\( \lambda > 1.38 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1} \)) and a weak structureless shoulder at ~400 nm. In contrast, 2 shows only a single strong band in high energy region (~264 nm; \( \lambda > 1.78 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1} \)). The high energy bands in 1–3 may be ascribed to the dipyrrmethane moiety (intraligand: \( n \rightarrow \pi^* \rightarrow \pi^* \) transitions), whereas low energy bands to the benzoyloxy moieties.24 It is noteworthy to mention that 2 exhibits only a single band below 300 nm as it does not have benzoyloxy moiety.

The interaction studies for 1–3 have been followed in presence of various metal ions (10.0 equiv; c: 10 mM), viz., Li\(^+\), Na\(^+\), Ca\(^{2+}\), Mg\(^{2+}\), Fe\(^{3+}\), Co\(^{2+}\), Ni\(^{2+}\), Cu\(^{2+}\), Zn\(^{2+}\), Cd\(^{2+}\), Pb\(^{2+}\), and Hg\(^{2+}\) in H\(_2\)O/EtOH (1:1, \( v/v \); c: 100 \( \mu \text{M} \)). The absorption spectra of 1 remained almost unaltered except for Cd\(^{2+}\), which induces red shift (\( \lambda > 20 \text{ nm} \)) for the high energy band (~260 nm). On the other hand, high energy band (~294 nm) for 3 displays hyperchromic shift only in the presence of Cu\(^{2+}\) among the tested metal ions. Conversely, 2 does not show significant changes in presence of the tested cations.

To understand binding affinity, titration experiments have been performed. Addition of Cd\(^{2+}\) (0.5 equiv) to a solution of 1 results in a small red shift (~5 nm) in the position of high energy band (~265 nm; \( \lambda > 1.67 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1} \)). It is interesting to note that broad low energy band (~374 nm) remains unchanged. An increase in the concentration of Cd\(^{2+}\) (7.0–8.0 equiv) leads to an appreciable red shift (~20 nm) of the high energy band, which appears at ~280 nm (\( \lambda > 1.59 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1} \), Fig. 2a). The absorption spectral changes for 1 may be ascribed to the formation of 1-Cd\(^{2+}\) complex. Interaction between 3 and Cu\(^{2+}\) has also been investigated by absorption titration studies (Fig. 2b). Addition of Cu\(^{2+}\) (0.5 equiv) to a solution of 3 leads to hyperchromic shift for the high energy band at ~294 nm (\( \lambda > 1.66 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1} \)). In this case too, the low energy band at ~400 nm remains unaltered. Further addition of Cu\(^{2+}\) (8.0–9.0 equiv) results in a considerable hyperchromic shift of the high energy band (\( \lambda > 2.83 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1} \)), indicating enhanced intramolecular charge transfer (ICT) process.
The spectral changes upon interaction with Cu$^{2+}$ may be associated with the formation of 3 Cu$^{2+}$ complex. On the basis of changes taking place only for the high energy bands of 1 and 3, it may be concluded that preferred binding site is nitrogen of the dipyrromethane unit.

The compounds 1–3 display moderate fluorescence [340 nm, $\phi$, 0.05, $\lambda_{ex}$ 280 nm, 1; 385 nm, $\phi$ 0.21, $\lambda_{ex}$ 320 nm, 2; 404 nm, $\phi$, 0.16, $\lambda_{ex}$ 360 nm, 3] in H$_2$O/EtOH (1:1, v/v, 100 µM). It may be related to the lack of extended π-conjugation coupled with chromophores. Further, metal ion interaction studies for 1–3 have been performed under analogous conditions in presence of 10.0 equiv of the tested metal ions (c, 10 mM) (Fig. S13). Probe 1 displays insignificant changes in presence of the tested cations except for Cd$^{2+}$ which leads to fluorescence enhancement (~62%). The fluorescence spectral features of 2 remained unaltered upon addition of various metal ions. Conversely, 3 exhibited fluorescence quenching (~69%) only in the presence of Cu$^{2+}$.

To understand the binding affinity of 1 and 3 toward Cd$^{2+}$ and Cu$^{2+}$, titration experiments have been performed. The addition of Cd$^{2+}$ (0.5 equiv) to a solution of 3 results in fluorescence quenching (~18%). At saturation stage (9.0–10.0 equiv Cu$^{2+}$) it came out to be ~69% ($\phi$, 0.08) (Fig. 3b). The LOD of 3 toward Cu$^{2+}$ has also been determined and found to be ~3 ppm with $R^2$, 0.992 (Fig. S19).

Job’s plot analysis reveals 1:1 and 1:2 stoichiometries for 1/Cd$^{2+}$ and 3/Cu$^{2+}$ systems (Fig. S16). Association constants for 1/Cd$^{2+}$ and 3/Cu$^{2+}$ have been worked out using the Benesi–Hildebrand method and it converged to 4.25 × 10$^2$ mol$^{-1}$ and 1.8 × 10$^5$ mol$^{-1}$, respectively (Fig. S17). The formation of more fluorescent complex 1a (Scheme 2, Figs. S5b and S6) may be attributed to chelation of Cd$^{2+}$ to 1 through pyrrole ring nitrogen. Conversely, 3 serves as ‘turn-off’ probe for Cu$^{2+}$ leading to formation of almost nonfluorescent complex 3a. The ESI-MS of 1a shows molecular ion peak [M+H]$^+$ at $m/z$, 648.2298 (calcd 648.8996) followed by loss of the associated water ($m/z$, 631.1279, 568.0834) (Figs. S5b and S6). On the other hand, 3a displays [M+H]$^+$ at $m/z$ 909.4235 (calcd 909.9683). It further showed peaks at $m/z$ 891.7044 and 874.7165 due to the loss of coordinated water molecules from the complex 3a (Figs. S8b and S9).

To have insight into reversibility of the systems fluorescence changes in 1 and 3 have been investigated in the presence of Cd$^{2+}$/Cu$^{2+}$ followed by addition of a strong chelating agent EDTA in large excess (150 equiv). In this context, Cd$^{2+}$ (9.0 equiv) was added to a solution of 1 which results in a 62% fluorescence...
enhancement. Further, addition of EDTA to the solution of 1\(\text{Cu}^{2+}\) lead to quenching to some extent (41%) indicating reversible interaction of 1 with \(\text{Cu}^{2+}\). On the other hand, \(\text{Cu}^{2+}\) (10 equiv) was added to a solution of 3 which causes 69% quenching in the presence of EDTA (150 equiv) leading to regeneration of the fluorescence associated with 3 to a considerable extent (49%). It also suggests reversible interaction between 3 and \(\text{Cu}^{2+}\) (Fig. S15).

To have an idea about chemosensing behavior of 3 and since there is a conflict with the orientation of the two dipyrromethane moieties about \(-\text{OCH}_2\text{CH}_4\text{H}_2\text{CH}_2\text{O}\)– unit, which serves as a linker, we have performed quantum chemical calculations. In this context, both cis- and trans-forms of 3 were optimized independently. Our results revealed that irrespective of the initial structure, optimized structures seem to be gauche-like with respect to the linker. It is worth mentioning that two dipyrromethane moieties remain in either trans- or cis-orientation as they were initially in the starting structure (Fig. 4).

However, the optimized structure for trans- is slightly more stable relative to cis-form by \(~3.90 \text{kcal/mol}\). Upon interaction with two \(\text{Cu}^{2+}\) ions through its cis-dipyrromethane units steric crowding is increased between two metal ions and their co-ligands (\(\text{H}_2\text{O}\)) in the resultant complex.

Based on overall results it is obvious that 1 exhibits fluorescence enhancement in the presence of \(\text{Cd}^{2+}\) whereas 3 induces quenching upon interaction with \(\text{Cu}^{2+}\) ions despite interactions through same site (pyrrolic nitrogens in both the cases). It may be associated with the \(\text{Cd}^{2+}\) (d\(^{10}\)) system which is reluctant in participating any photoinduced charge transfer transitions and displays ‘Turn-On’ fluorescence response. On the other hand \(\text{Cu}^{2+}\) is a d\(^{9}\) system, thus promotes photoinduced charge transfer and leads to the fluorescence quenching. One can see that though the dipyrromethane interaction site is the same both in 1 and 3, but the adjacent environment is quite bulky in case of 3 (please see theoretically calculated structures of 3). Therefore, it does not preferably interact with \(\text{Cd}^{2+}\) ions owing to larger size, rather interacts with smaller metal ion \(\text{Cu}^{2+}\) and results in fluorescence quenching. On the other hand, the metal ion silent nature of 2 may be associated with the presence of galactosyl moiety instead of glucosyl at the meso-position.

Through this work, we have described the synthesis, characterization and optical properties of a new class of meso-substituted dipyrromethanes 1–3. Further, crystal structure of any glycosyl based dipyrromethane has been presented for the first time. The compounds 1–3 are fluorescent among which 1 serves as a ‘turn-on’ probe for \(\text{Cd}^{2+}\) while 3 as ‘turn-off’ toward \(\text{Cu}^{2+}\) ion. The present work may open new avenues toward photophysical chemistry of sugar based dipyrromethanes/dipyrins.

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## Supplementary data

Supplementary data (contains experimental section, \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra, ESI-MS, UV/vis spectra, fluorescence spectra, Job’s plot analysis and B–H plot) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.126.

## References and notes


