



Glycosyl based *meso*-substituted dipyrromethanes as fluorescent probes for Cd²⁺/Cu²⁺ 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 Cd²⁺ and Cu²⁺ ions. Notably, *meso*-galactosyl dipyrromethane **2** remains silent toward tested metal ions.

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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, Cu²⁺ 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, Cd²⁺ is industrially and agriculturally important element.²¹ Biological and environmental damages caused by Cd²⁺ 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*-glucosyl substituted dipyrromethanes **1** and

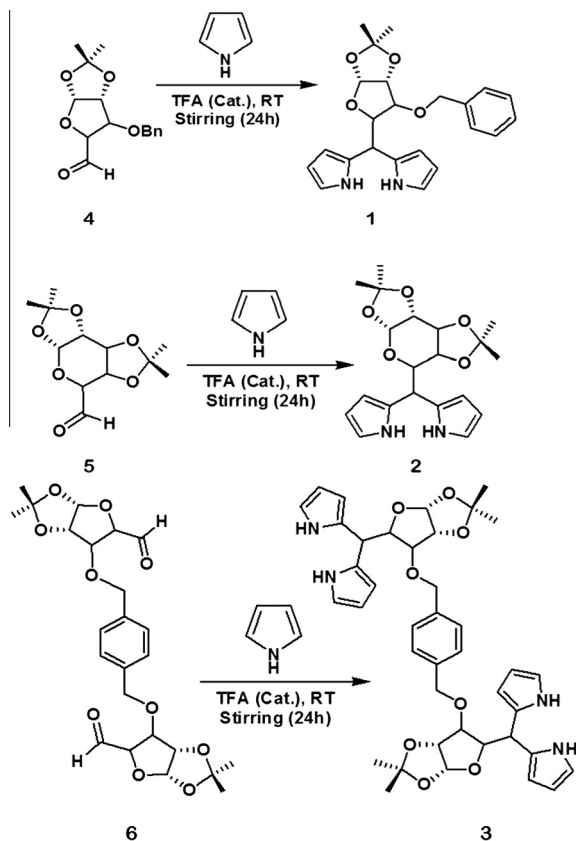
3, wherein **3** is akin to a dimer of **1**. For the sake of disparity at the *meso*-position, we have also prepared a *meso*-galactosyl dipyrromethane **2** and compared the optical and cation recognition properties of **1–3**.

Through this contribution we present the synthesis and characterization of three new glycosyl derivatives, 5-(3-*O*-benzyl-1,2-*O*-isopropylidene- α -D-xylo-pentodialdo-1,4-furanose)-dipyrromethane (**1**), 5-(1,2:3,4-di-*O*-isopropylidene- α -D-galacto-hexodialdo-1,5-pyranose)-dipyrromethane (**2**), and 5-[1',4'-bis(1,2-*O*-isopropylidene- α -D-xylo-pento-dialdo-1,4-furanose-3-*O*-methyl)benzene]-bis(dipyrromethane) (**3**) along with potential applications of **1** and **3** as a new class of chemosensors for Cd²⁺ and Cu²⁺ ions under aqueous conditions (H₂O/EtOH; 1:1, 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-*O*-benzyl-1,2-*O*-isopropylidene- α -D-xylo-pentodialdo-1,4-furanose (**4**), 1,2:3,4-di-*O*-isopropylidene- α -D-galacto-hexodialdo-1,5-pyranose (**5**) and 1',4'-bis(1,2-*O*-isopropylidene- α -D-xylo-pento-dialdo-1,4-furanose-3-*O*-methyl)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 dipyrins 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 (¹H and ¹³C), ESI-MS, absorption and emission spectral studies.

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Scheme 1. Synthesis of 1–3.

^1H NMR spectra (CDCl_3) of both **1** and **3** exhibited two broad resonances at δ 8.93 (1H, $-\text{NH}$) and 8.04 ppm (1H, $-\text{NH}$) associated with pyrrole ring protons (Figs. S1a and S3a, Supplementary information). Notably, the pyrrole ring protons of both the **1** and **3** resonated at almost the same position ($\Delta\delta = 0.89$ ppm). Relatively large downfield shift for one $-\text{NH}$ proton indicated intramolecular H-bonding via only one of the pyrrolic protons, which has further been supported by single crystal X-ray analyses on **1**. Similarly, **2** displays broad signals at δ 8.83 (1H, $-\text{NH}$) and 8.49 (1H, $-\text{NH}$) ppm (Fig. S2a). Rather small downfield shift and signal separation ($\Delta\delta = 0.34$ ppm) relative to **1** and **3** suggested about weak H-bonding in **2**. ^{13}C NMR spectral studies on **1–3** also supported formation of these compounds (Figs. S1b, S2b and S3b). The presence of molecular ion peaks $[\text{M}+\text{H}]^+$ at m/z 395.1979 (Calcd 395.1892), **1**; 375.1923 (Calcd 375.1841), **2**; and 711.3394 (Calcd 711.3315), **3** (Figs. S5a, S7, and S8a) in the ESI-MS spectra strongly supported the formation of **1–3**.

Compound **1** crystallizes in orthorhombic system with the P_{212121} space group. Crystal structure (Fig. 1) reveals that the pyrrole rings in this molecule are not coplanar. Inter planar angle of 82.63° between the pyrrole rings suggest *gauche*-conformation. The pyrrole ring oriented toward furanosyl oxygen O(3) rotated along C–C bond and gets involved in intramolecular H-bonding $[\text{N}(1)\cdots\text{H}(1)\cdots\text{O}(3); 2.280 \text{ \AA}]$. Rather short H-bonding distance results in the formation of a stable six-membered ring. It is noteworthy to mention that the intramolecular H-bonding takes place only amidst $\text{N}(1)\cdots\text{H}(1)\cdots\text{O}(3)$ though there is a scope for another H-bond formation $\text{N}(2)\cdots\text{H}(2)\cdots\text{O}(4)$. It could not occur probably due to orientation of the other pyrrole ring. The furanose ring represented by C(4)–C(7) and O(3) adopted a tilted envelope where C(6) serves as cover of the envelope. The oxygens O(1) and O(2) from the sugar moiety attached to C(3) of the *iso*-propylidene

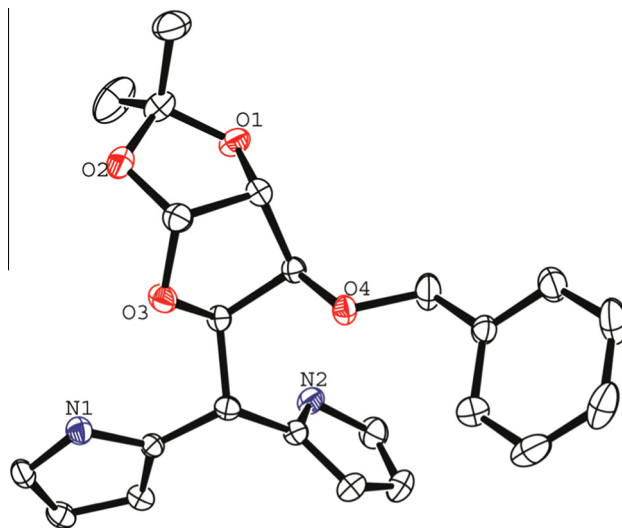


Figure 1. ORTEP view of **1** at 30% thermal ellipsoid probability (H atoms omitted for clarity).

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, ϵ , $1.71 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$) 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 (ϵ , $1.38 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$) and a weak structureless shoulder at ~ 400 nm. In contrast, **2** shows only a single strong band in high energy region (~ 264 nm; ϵ , $1.78 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). The high energy bands in **1–3** may be ascribed to the dipyrromethane moiety (intraligand: $n \rightarrow \pi^*/\pi \rightarrow \pi^*$ transitions), whereas low energy bands to the benzyloxy moieties.²⁴ It is noteworthy to mention that **2** exhibits only a single band below 300 nm as it does not have benzyloxy 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^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+} , Pb^{2+} , and Hg^{2+} in $\text{H}_2\text{O}/\text{EtOH}$ (1:1, v/v; c, 100 μM). The absorption spectra of **1** remained almost unaltered except for Cd^{2+} , which induces red shift ($\Delta\lambda \sim 20$ 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, ϵ , $1.67 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$). 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 (ϵ , $1.59 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$, 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 (ϵ , $1.66 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$). 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 (ϵ , $2.83 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$), indicating enhanced intramolecular charge transfer (ICT) process.

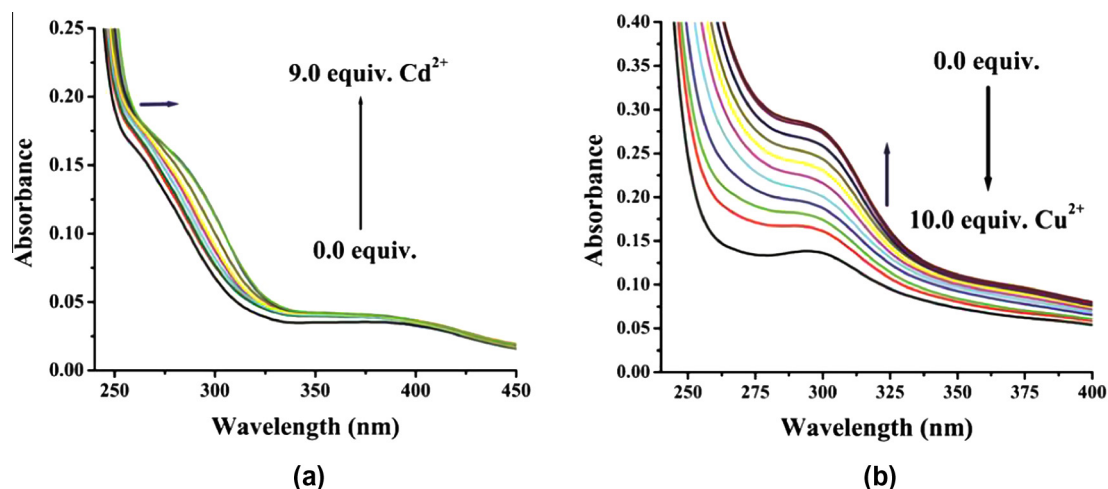


Figure 2. UV/vis titration spectra of (a) **1** with $\text{Cd}(\text{NO}_3)_2$ and (b) **3** with $\text{Cu}(\text{NO}_3)_2$ in $\text{H}_2\text{O}/\text{EtOH}$ (1:1, v/v; c, 100 μM).

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**, which is associated with dipyrromethane moiety, it may be concluded that preferred binding site is nitrogen of the dipyrromethane unit.

The compounds **1–3** display moderate fluorescence [340 nm, ϕ , 0.09, λ_{ex} , 280 nm, **1**; 385 nm, ϕ 0.21, λ_{ex} , 320 nm, **2**; 404 nm, ϕ , 0.16, λ_{ex} , 360 nm, **3**] in $\text{H}_2\text{O}/\text{EtOH}$ (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 ($\sim 62\%$). The fluorescence spectral features of **2** remained unaltered upon addition of various metal ions. Conversely, **3** exhibited fluorescence quenching ($\sim 69\%$) 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 **1** enhances the emission intensity by $\sim 21\%$ which upon addition of ~ 7.0 – 8.0 equiv of Cd^{2+} became saturated and intensity enhanced to $\sim 62\%$ (Fig. 3a). The quantum yield (ϕ) increased to 0.19. The LOD of **1** has been determined to be ~ 20 ppm with R^2 , 0.983 (Fig. S18). On the other hand, addition

of Cu^{2+} (0.5 equiv) to a solution of **3** results in fluorescence quenching ($\sim 18\%$). At saturation stage (9.0–10.0 equiv Cu^{2+}) it came out to be $\sim 69\%$ (ϕ , 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 $4.25 \times 10^2 \text{ mol}^{-1}$ and $1.8 \times 10^5 \text{ mol}^{-1}$, 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 $[\text{M}+\text{H}]^+$ 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 $[\text{M}+\text{H}]^+$ 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 $\text{Cd}^{2+}/\text{Cu}^{2+}$ 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

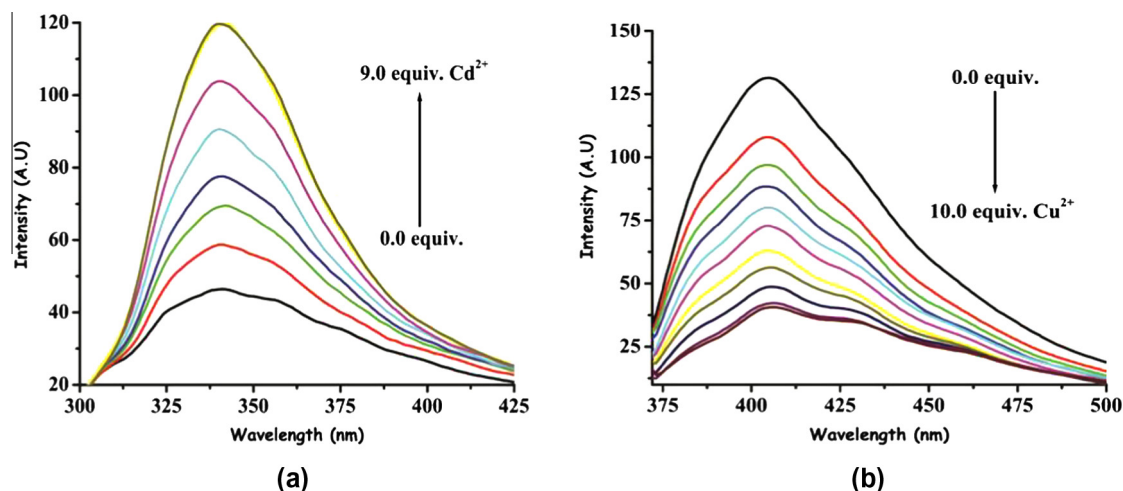
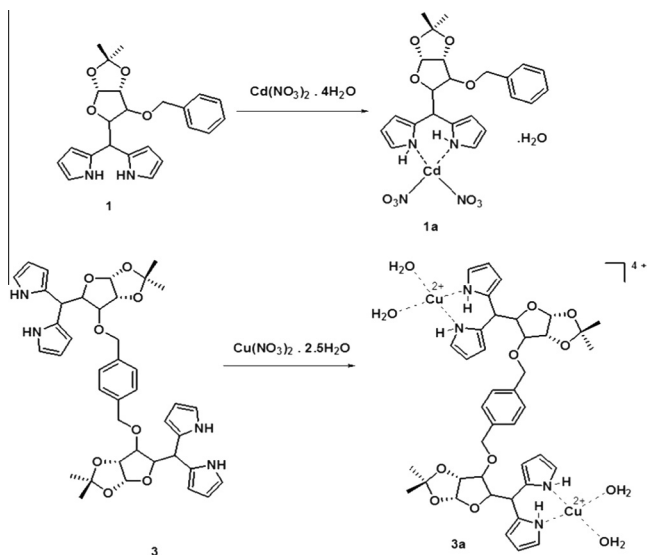


Figure 3. Fluorescence titration spectra of (a) **1** with $\text{Cd}(\text{NO}_3)_2$ and (b) **3** with $\text{Cu}(\text{NO}_3)_2$ in $\text{H}_2\text{O}/\text{EtOH}$ (1:1, v/v; c, 100 μM).



Scheme 2. Plausible binding mode of **1**/ Cd^{2+} and **3**/ Cu^{2+} .

enhancement. Further, addition of EDTA to the solution of **1**+ Cd^{2+} lead to quenching to some extent (41%) indicating reversible interaction of **1** with Cd^{2+} . On the other hand, 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 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 $-\text{O}-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-\text{O}-$ 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 kcal/mol. Upon interaction with two Cu^{2+} ions through its *cis*-dipyrromethane units steric crowding is increased between two metal ions and their co-ligands (H_2O) in the resultant complex.

Based on overall results it is obvious that **1** exhibits fluorescence enhancement in the presence of Cd^{2+} whereas **3** induces quenching upon interaction with Cu^{2+} ions despite interactions

through same site (pyrrolic nitrogens in both the cases). It may be associated with the 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 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 Cd^{2+} ions owing to larger size, rather interacts with smaller metal ion 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 Cd^{2+} while **3** as 'turn-off' toward 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, ^1H and ^{13}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>.

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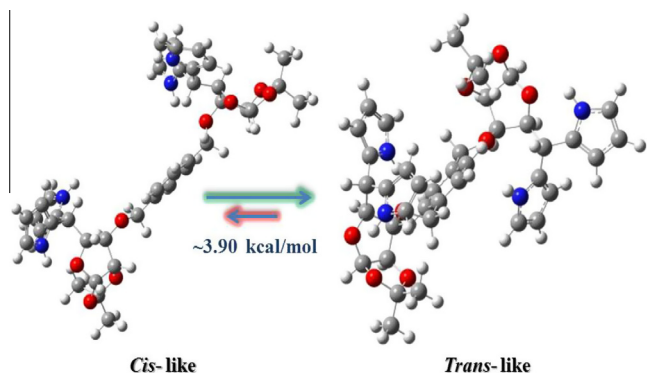


Figure 4. Optimized energy comparison between *cis*- and *trans*-like structures for **3**.

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