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1-(D-Glucopyranosyl-2′-deoxy-2′-iminomethyl)-2-hydroxynaphthalene as chemo-sensor for Fe^{3+} in aqueous HEPES buffer based on colour changes observable with the naked eye

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ABSTRACT

A new glucose-based C2-derivatized colorimetric chemo-sensor (L_1) has been synthesized by a one-step condensation of glucosamine and 2-hydroxy-1-naphthaldehyde for the recognition of transition metal ions. Among the eleven metal ions studied, viz., Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+}, L_1 results in visual colour change only in the presence of Fe^{2+}, $Fe^{3+}$and Cu^{2+} in methanol. However, in an aqueous HEPES buffer (pH 7.2) it is only the Fe^{3+} that gives a distinct visual colour change even in the presence of other metal ions, up to a concentration of 280 ppb. The changes have been explained based on the complex formed, and the composition has been determined to be 2:1 between L_1 and Fe^{3+} based on Job's plot as well as ESI MS. The structure of the proposed complex has been derived based on HF/6-31G calculations.

Iron is the most abundant transition metal ion present in the earth's crust. It is also an important biological element owing to its diverse functions. Some of these functions are driven based on the concentration of the ions.[1] Though iron can exhibit a variety of oxidation states, the most prominent ones are +3 and +2. To our knowledge, the literature reports on the detection of Fe(III) have been based mainly on techniques such as fluorescence, potentiometry and redox titrations.[2] The early studies of photometric determination of Fe(III) carried out using a variety of reagents were mainly effective at millimolar concentrations though there were few suitable for low concentrations.[3] Among these, the reagents that may have some chemical relevance to the present study include salicylic-[3f,g,k]/sulfosalicylic[3f,h,j] acid derivatives and also those based on phenolic-OH, viz., tiron indicator[3a] The chemo-sensor receptors that work through colour changes at micro- or sub-micromolar levels were most in demand owing to the easy visual detection of the colour change that occurs in the presence of guest species with the naked eye.[4] Therefore, the design of synthetic receptors for the selective recognition of biologically and environmentally relevant ions, especially those of transition metal ones including iron, is currently of great importance. The applicability of such synthetic receptors will be broadened if these were built with chemical species having water-solubility and biocompatibility. Carbohydrates possess both these properties, and hence can act as useful platforms for making such molecular receptors. Therefore, this Letter deals with the synthesis and characterization of a glucose-based 2-hydroxy-1-naphthylidene derivative linked through imine, viz., 1-(D-glucopyranosyl-2′-deoxy-2′-iminomethyl)-2-hydroxynaphthalene (L_1), and its selective visual recognition towards Fe^{3+} against a number of other metal ions in an aqueous HEPES buffer (pH 7.2) at biological pH. To our knowledge, this is the first Letter on the visual recognition of Fe^{3+} in a buffer, based on a biologically benign molecular receptor. The derivative L_2, possessing a salicylidene moiety, viz., 1-(D-glucopyranosyl-2′-deoxy-2′-iminomethyl)-2-hydroxybenzene, is less effective and hence acts as a control system in the present study.

Both the chemo-sensor (L_1) and the control (L_2) molecules have been synthesized by a one-step simple condensation[5] of C2-deoxy-C2-amino-glucose (glucosamine) with 2-hydroxy-1-naphthaldehyde/salicylaldehyde as shown in Scheme 1. The products were characterized by analytical and spectral techniques[6] (SI 01). Similar to the binding core observed with the 4,6-di-O-protected[7] glucose-based derivatives, even L_1 and L_2 are capable of exhibiting an ONO binding core.

In order to explore the chemo-sensor properties of L_1 and L_2, these molecules were titrated against a number of metal ions, viz., Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+}, in methanol as well as in an aqueous HEPES buffer (pH 7.2). The titrations were monitored qualitatively by observing the colour change with the naked eye. In order to observe visual colour changes, if any, studies were carried out[8] by mixing L_1 or L_2 with

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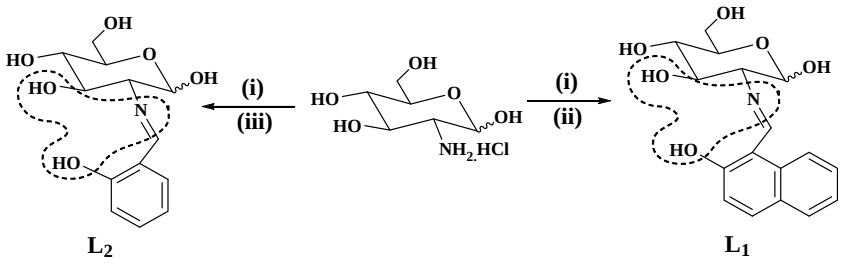
metal ions in a 1:1 mole ratio in methanol, and the corresponding results are shown in Figure 1. Distinct visual colour changes were noticed only in the presence of Fe^{2+} and Fe^{3+} with both the ligands, wherein these ions are light and dark purple, respectively, to differentiate the presence of iron in the +2 and +3 oxidation states. The other ion that turns the solution colour of L_1 and L_2 to light green was Cu^{2+}. The presence of all other ions exhibited practically no change in the colour of the ligand solution.

Though L_1 and L_2 seem to recognize Fe^{2+} and Fe^{3+} with high visual clarity, Cu^{2+} can also be recognized by these only by a marginal colour variation that is barely noticed. The results shown in Figure 1 are suggestive of L_1 being more sensitive towards metal ions than L_2. Since L_1 and L_2 are sensitive towards both Fe^{2+} and Fe^{3+}, the selectivity of these ions has been addressed by challenging the persistence of the colour in the presence of other metal ions as competitive ones, and the results are shown in Figure 2. The titration of $\{L_1 + Fe^{2+}\}$ with other M^{2+} results in the fading away of the original colour, and hence the resulting solutions cannot be distinguished. However, the original colour of $\{L_1 + Fe^{3+}\}$ persists even after the addition of other M^{2+} ions including that of Cu^{2+}. Thus, the results shown in Figure 2 are clearly suggestive of the selective recognition of Fe^{3+} by L_1 even in the presence of other M^{2+} ions with the naked eye and not so in the case of Fe^{2+}. Similar competitive metal ion titrations carried out in the case of the salicylidene derivative, L_2, did not result in colour changes that are distinguishable either with Fe^{2+} or with Fe^{3+} (SI 02), and hence L_2 is not selective towards either of these ions in methanol.

Titrations carried out between $\{L_1 + Cu^{2+}\}$ or $\{L_2 + Cu^{2+}\}$ and other ions (Fig. 3) resulted in the fact that Cu^{2+} can still be recognized in the presence of other ions except Fe^{3+}; however, the over-



Scheme 1. Synthesis of glucose-based derivatives, viz., L_1 and L_2.[6] (i) Triethylamine [$N(CH_2CH_3)_3$], (ii) 2-hydroxy-1-naphthaldehyde and (iii) salicylaldehyde. The enclosed portions exhibit an ONO core.

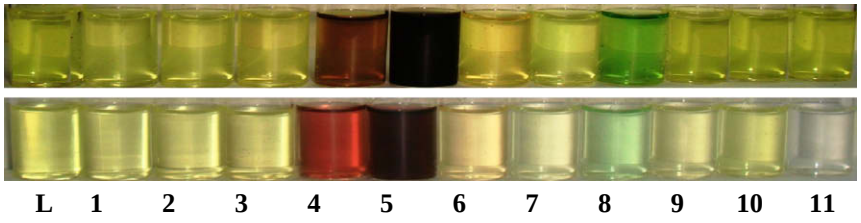


Figure 1. Colour of the methanolic solutions of L_1 (top row) and L_2 (bottom row) in the presence of different metal ions at a 1:1 mole ratio: Vial L is a simple ligand; Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} are present in vials 1–11, respectively.

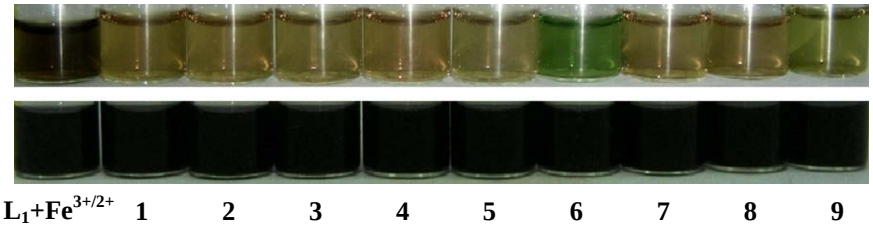


Figure 2. Competitive ion titration of $\{L_1 + Fe^{3+}\}$ (bottom row) or $\{L_1 + Fe^{2+}\}$ (top row) with different metal ions in methanol: Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} are present in vials 1–9, respectively.

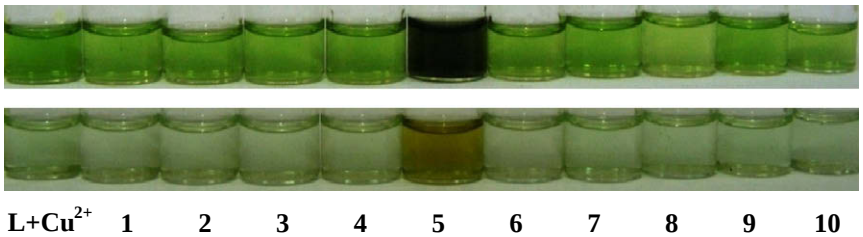


Figure 3. Competitive ion titration of $\{L_1 + Cu^{2+}\}$ (top row) or $\{L_2 + Cu^{2+}\}$ (bottom row) with different metal ions in methanol: Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} are present in vials 1–10, respectively.

all sensitivity is low. Thus, in a methanolic solution, L_1 can clearly sense Fe^{2+} and Fe^{3+} largely and Cu^{2+} to a reasonable extent by simple visual colour changes that can be noticed with the naked eye. However, in the presence of other ions, it is only Fe^{3+} that can be sensed by L_1 and not by L_2.

Similar experiments have been carried out in an aqueous HEPES buffer at pH 7.2. Even in a buffer medium, it is only Fe^{2+} and Fe^{3+} which show distinguishable colour changes mainly with L_1 and to a little extent with L_2 that have already been noticed even in the methanolic solution (Fig. 4). The colour changes observed with Cu^{2+} were only marginal.

Competitive metal-ion titrations carried out between $\{L_1 + Fe^{2+}\}$ or $\{L_2 + Fe^{2+}\}$ and other metal ions in the HEPES buffer (pH 7.2) exhibited no distinguishable colour change, as the original colour of the solution does not persist in the presence of other ions (SI 03). However, the experiments carried out between $\{L_1 + Fe^{3+}\}$ or $\{L_2 + Fe^{3+}\}$ and other metal ions could not bleach out the original colour developed by Fe^{3+} at least in the case of L_1 as evident from Figure 5.

Thus, L_1 can distinctly recognize only Fe^{3+} even in the presence of other metal ions in the HEPES buffer (pH 7.2) by producing visual colour changes which are noticed with the naked eye, and hence L_1 can act as a selective and biologically benign molecular sensor for Fe^{3+}. The selectivity of L_1 is increased towards Fe^{3+} in the HEPES buffer (pH 7.2) as compared to that in the methanol medium.

In order to quantify the visual colour changes that occurred upon mixing L_1 with metal ions and also to establish the complex formation between these, titrations were carried out by measuring the absorption spectra.[9] Several metal ions, viz., Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} ,exhibited either no change in the absorption spectra and/or no new band formation during their titrations (SI 04). The ions, viz., Fe^{2+}, Fe^{3+} and Cu^{2+}, showed considerable changes in the absorption spectra (Fig. 6) in methanol.

Among Fe^{2+} and Fe^{3+}, it is the latter that exhibits great changes in the absorption spectra. The changes observed with 300, 420 and 550 nm bands are suggestive of the metal ion complex formation (Fig. 6, SI 04). Even the d→d transitions (Fig. 6, inset) have supported the formation of the complex between L_1 and these ions. Greater changes were noticed in the presence of Fe^{3+} as compared to those in the presence of Fe^{2+}. These results are in accordance with those observed by the visual colour changes.

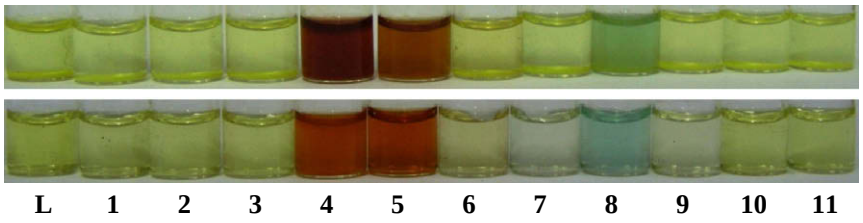


Figure 4. Colour of the HEPES buffer solutions of L_1 (top row) and L_2 (bottom row) in the presence of different metal ions at a 1:1 mole ratio: vial L is a simple ligand; Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} are present in vials 1–11, respectively.

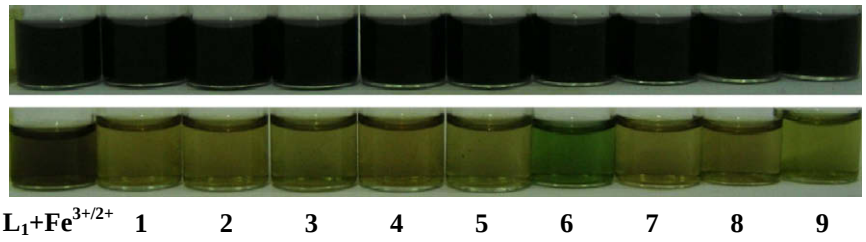


Figure 5. Competitive ion titration of $\{L_1 + Fe^{3+}\}$ (top row) or $\{L_1 + Fe^{2+}\}$ (bottom row) with different metal ions in an aqueous HEPES buffer (pH 7.2): Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} are present in vials 1–9, respectively.

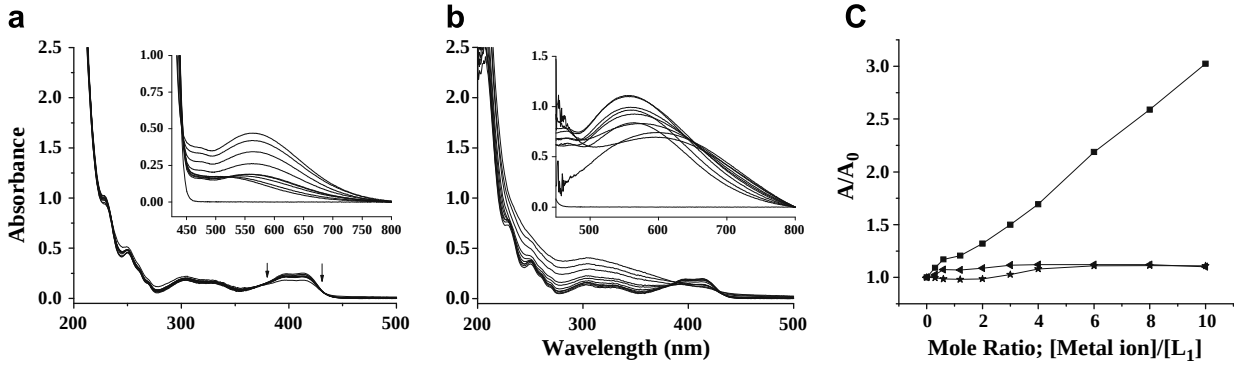


Figure 6. Absorption spectral data during the titration of L_1 with metal ions in methanol: Spectral traces in the case of (a) Fe^{2+} and (b) Fe^{3+}. (c) Relative absorbance (A/A_0) plots of 303 nm band as a function of the mole ratio of [Metal ion]/[L_1]. The symbols, ◄, ■ and ★ are for Fe^{2+}, Fe^{3+} and Cu^{2+}, respectively. Insets given in (a) and (b) are the spectra in visible region at a higher concentration.

Titrations carried out between the receptor molecules L_1 and Fe^{2+}, Fe^{3+} or Cu^{2+} in the aqueous HEPES buffer (pH 7.2) exhibited changes in the absorption spectra, and these changes were found to be greater in the case of Fe^{3+} titration (Fig. 7, SI 04), supporting the formation of a complex between L_1 and Fe^{3+} in methanol as well as in the HEPES buffer (pH 7.2). The stoichiometry of the complex formed between L_1 and Fe^{3+} has been found to be 2:1 based on Job's plot[10] (SI 05). This has been further confirmed by the mass spectral peak observed at $m/z = 720$ in ESI MS, and the presence of iron in this has been augmented by the isotope peak pattern (SI 06).

In order to establish the lowest concentrations of Fe^{3+} that can be detected visually by L_1 in methanol as well as in the HEPES buffer (pH 7.2), titrations were carried out by keeping the mole ratio between L_1 and Fe^{3+} as 2:1 and it was found that L_1 and L_2 can detect up to a concentration of 5×10^{-6} M (280 ppb) (SI 07). At this concentration, the HEPES buffer (pH 7.2) solution is darker as compared to the methanol one.

Having determined the composition of the complex formed as 1:2 between Fe^{3+} and L_1 based on ESI MS and absorption data, the species has been modelled based on the HF/6-31G level of calculations using the GAUSSIAN 03 package.[11] The optimized structure (SI 08) was found to be a neutral complex, viz., $Fe(L_1)_2$, with a square pyramidal geometry at Fe^{3+}, wherein one of the ligands acts as a di-anionic tridentate and the other as a mono-anionic bi-dentate (Fig. 8a). Both the ligands use phenolate-O^- and C3-O^- of the carbohydrate. The fifth coordination is extended from the imine nitrogen of the tri-dentate ligand. The tri-dentate ligand exhibited an equi-planar conformation between the plane of the phenyl moiety and the average plane of the carbohydrate moiety (Fig. 8b). Thus, one of the ligands exhibited an ONO binding core and the other exhibited an OO binding core. Indeed, the di-O-protected glucosyl derivatives mainly exhibited ONO binding cores in their metal ion complexes of *cis*-VO_2^+, *cis*-MoO_2^{2+}, *trans*-UO_2^{2+}, Ni^{2+} and Cu^{2+} expect in the case of Zn^{2+} where the ligand exhibited only an ON binding core. [12] Even the un-protected galactosyl derivative also exhibited a ONO binding core with Cu^{2+}.[5a]

Thus, the glucose-based 2-hydroxy-1-naphthalidene derivative linked through imine, viz., 1-(D-glucopyranosyl-2′-deoxy-2′-iminomethyl)-2-hydroxynaphthalene (L_1), has been found to be selective towards Fe^{3+} in an aqueous HEPES buffer (pH 7.2) based on visual colour changes, absorption spectroscopy and ESI MS. The same molecular receptor (L_1) exhibited recognition towards Fe^{2+}, Fe^{3+} and Cu^{2+} in methanol owing to their coordination preferences as judged from the charge transfer transition noticed in the corresponding absorption spectra. The 2:1 complex formed between L_1 and Fe^{3+} has been further supported by computational calculations to result in a square pyramidal Fe^{3+} bound through both the phenolate-O^-, C3-O^- and imine nitrogen only from one of the ligands. Such tri-dentate binding through the ONO core has already been shown by us in the past in the case of transition metal ion complexes of the 4,6-di-O-blocked-glucosyl- as well as the free-galactosyl-based derivatives. To our knowledge, this is the first letter on the selective recognition of Fe^{3+} by a biologically benign carbohydrate receptor in a buffer medium where the recognition can be noticed through a visual colour change. The literature reports on Fe^{3+} recognition were mostly in alcohol, though a few were in water, but the receptors were non-carbohydrate derivatives.

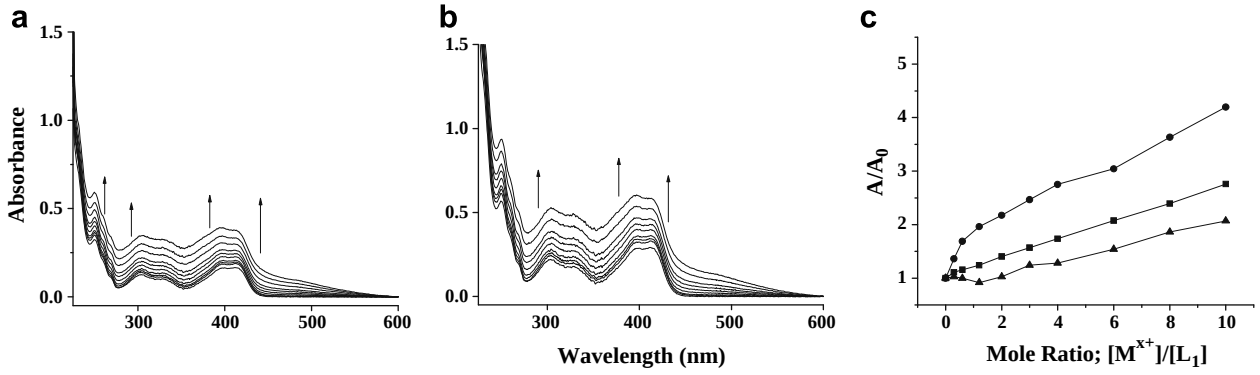


Figure 7. Absorption spectral data during the titration of L_1 with metal ions in an aqueous HEPES buffer: Spectral traces in the case of (a) Fe^{2+} and (b) Fe^{3+}. (c) Relative absorbance (A/A_0) plots of a 303 nm band as a function of the mole ratio of [metal ion]/[L_1]. The symbols, ■, ● and ▲ are for Fe^{2+}, Fe^{3+} and Cu^{2+}, respectively.

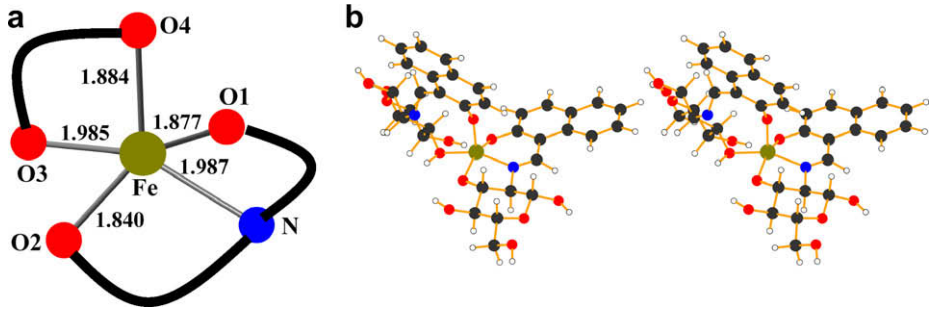


Figure 8. (a) Primary coordination sphere about iron in the complex, $Fe(L_1)_2$ optimized at HF/6-31G level. (b) A stereo view of the optimized $Fe(L_1)_2$ complex. Bond distances are given in the figure in Å. The bond angles (°) are O1–Fe–N = 88.4; O1–Fe–O2 = 151.3; O1–Fe–O3 = 87.2; O1–Fe–O4 = 103.4; N–Fe–O2 = 84.5; N–Fe–O3 = 154.2; N–Fe–O4 = 103.3; O2–Fe–O3 = 87.2; O2–Fe–O4 = 105.3 and O3–Fe–O4 = 102.5.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.116.

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6. (a) Glucosamine hydrochloride (0.215 g, 1 mmol, **1**) salt has been neutralized with triethylamine in ethanol before it is used in the synthesis. To this, an ethanolic solution of 2-hydroxy-1-naphthaldehyde (0.172 g, 1 mmol) was added. The reaction mixture was refluxed for 6 h at 60 °C. The solid product formed, L_1, (0.896 g) was filtered and washed with ethanol several times followed by diethyl ether at the end which was dried under a vaccum. Yield = 89%. ^{1}H NMR (DMSO-d_6, ppm): δ 3.12–3.75 (m, 5H, C2–H, C3–H, C–4H, C5–H and C6–H), 4.46–5.38 (m, 4H, C1–OH, C3–OH, C–4OH, C6–OH), 5.62 (d, H, C1–H, $^3J_{C1-H-C2-H}$ 5.2 Hz), 6.60–8.12 (6H, Ar-H), 8.90 (d, H, CH=N), 13.60 (t, H, Aromatic-OH). ESI MS m/z = 334 ([M+H]$^+$, 100%).(b) L_2 has been synthesized similarly by using salicylaldehyde (0.15 ml; 1 mmol) in place of 2-hydroxy-naphthaldehyde. Yield = 0.23 g (81%). ^{1}H NMR (DMSO-d_6, ppm): 3.25–3.80 (m, 5H, C2–H, C3–H, C4–H, C5–H), 4.54–4.95 (4d, 4H, C1–OH, C3–OH, C4–OH and C6–OH), 5.16–5.18 (d, H, C1–H, $^3J_{C1-H-C2-H}$, 5.5 Hz), 6.19–7.59 (2d, 2t, 4H, Ar-OH), 8.6 (S, H, CH=N), 13.2 (S, H, Ar-OH). ESI MS m/z = 284 ([M+H]$^+$, 100%).
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8. The visual colour detection experiments were carried out by using 10^{-2} M. Methanolic solutions of the ligand and metal ions (as hydrated perchlorate salts) added together to give a mixture with a 1:1 mole ratio wherein the final concentration is 5×10^{-3} M. The ligand was initially dissolved in a minimum volume (100 μL) of DMSO and then the volume was made up to the mark by using dry methanol.
9. A stock solution of 10^{-3} M was prepared both for the ligand and for the metal ions in order to carry out absorption spectral titrations. The requisite volume of the metal ion solution was added to a 50 μL ligand solution to get the corresponding ligand to metal ion mole ratio by making the total volume to 3 ml using MeOH.
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