# Chemosensing ability of hydroxynaphthylidene derivatives of hydrazine towards Cu$^{2+}$: Experimental and computational studies

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**Abstract.**    2-Hydroxynaphthylidene derivatives of hydrazine, namely **L$_1$**, **L$_2$** and **L$_3$**, were synthesized by going through two-step reactions and the products were characterized. The ion recognition properties of these receptors were studied using fluorescence and absorption spectroscopy. The receptors were found to be sensitive and selective towards Cu$^{2+}$ in methanol solution among the 13 metal ions studied, namely Mn$^{2+}$, Fe$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, Hg$^{2+}$, Pb$^{2+}$, Na$^+$, K$^+$, Ca$^{2+}$ and Mg$^{2+}$, by exhibiting switch off fluorescence. The stoichiometry of the complexed species was found to be 2:1. The fluorescence quenching with Cu$^{2+}$ is in the order of **L$_1$ > L$_2$ > L$_3$**. These conjugates were also found to act as colorimetric sensors for Cu$^{2+}$ in solution by exhibiting visual colour change. The 2:1 complex shows a centrosymmetric structure based on DFT computations.

**Keywords.**    Ion recognition; copper sensor; hydroxynapthylidene derivative of hydrazine; heterocycle; fluorescence quenching.

## 1. Introduction

The development of selective chemosensors to provide signals in response to chemically and biologically important metal ions is an interesting area of contemporary research. In this regard, the development of molecular sensors for Cu$^{2+}$ has received considerable attention due to its biological and environmental implications, including its involvement in neurodegenerative Alzheimer and Wilson's diseases.[1] The Cu$^{2+}$ ion is also involved in the functional part of a number of enzymes.[2] There are reports of Cu$^{2+}$ fluorescent sensors wherein the binding of this ion generally quenches fluorescence emission, though a few are known where enhancement takes place.[3,4] Synthetic carbohydrate-based molecules capable of recognizing metal ions, including Cu$^{2+}$, are also being reported by our group.[5] The naphthalene derivatives with appropriate binding cores and yet possessing the fluorescent probe are of advantage for sensitive detection.[6] Therefore, this paper demonstrates the metal ion recognition properties of napthylidene derivatives of hydrazine using their fluorescence *turn-off* response towards Cu$^{2+}$, where the sensitivity was tuned by varying the derivatization from pyrrole to furan to thiophene moiety.

## 2. Experimental

### 2.1 *Solution studies*

For fluorescence titrations, bulk solutions ($6 \times 10^{-4}$ M) of receptors were freshly made before each set of experiments by dissolving in a small quantity of DMSO (50 $\mu$L) and then preparing with methanol. The metal perchlorate salts were made at $6 \times 10^{-4}$ M concentration in the corresponding solvent. Effective concentration of the receptor was 10 $\mu$M in fluorescence cuvette. For absorption titrations, the effective concentration of receptors was maintained at 33 $\mu$M.

### 2.2 *Synthesis and characterization of L$_1$*

To a solution of 2-acetyl pyrrole (2.5 mL, 24.5 mmol) in 50 mL methanol, hydrazine hydrate (1.14 mL, 24.5 mmol) was added and the reaction mixture was stirred and heated under reflux for 12 h. The cooled reaction mixture was concentrated under reduced pressure and dried. The dry residue (2.85 g, 22.95 mmol) was taken in 50 mL methanol and 2-hydroxy napthaldehyde (3.95 g, 22.95 mmol) was added and refluxed for 12 h. The obtained precipitate was filtered and washed thoroughly with hot methanol to give a yellow solid. Yield: (5.25 g, 83%). M.P. 165–168°C. FTIR:

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(KBr, cm$^{-1}$): 3439($\upsilon_{OH}$), 1621($\upsilon_{C=N}$), 1604($\upsilon_{C=N}$). Elemental Analysis (% Calc.) C$_{17}$H$_{15}$N$_3$O 73.63, H, 5.45 N, 15.15 Found: C, 72.81; H, 4.98, N, 14.87%.$^1$H NMR (CDCl$_3$, 400MHz, $\delta$ ppm) 2.17 (s, 3H, **CH**$_3$) 7.29 (s, 1H, Pyr-N**H**) 7.59 (d, 1H, Pyr-**H**) 7.61 (t, 1H, Pyr-**H**) 7.63 (d, 1H, Pyr-**H**) 7.81 (d, 1H, Ar-H, J = 8.89 Hz), 7.91 (d, 1H, Ar-**H**, *J* = 8.86 Hz), 8.17 (d, 1H, Ar-**H**, *J* = 8.55 Hz) 9.69 (s, 2H, **H**C=N), 13.04 (s, 1H, Ar-O**H**). $^{13}$C NMR (CDCl$_3$) 161.57 (CH=N), 160.28 (CH=N), 156.4, 151.2, 145.6, 134.7, 132.9, 129.2, 128.09, 123.8, 120.9, 119.3, 114.5, 112.3, 108.9, 15.20. ESI-MS(m/z): 279.2 ([M+H]$^+$, 100%).

## 2.3 *Synthesis and characterization of L$_2$*

This is prepared using the same procedure as that given for **L**$_1$, but by using 2-acetyl furan in place of 2-acetyl pyrrole. Yield: (1.96 g, 89%). M.P. 142–145°C. FTIR: (KBr, cm$^{-1}$): 3439($\upsilon_{OH}$), 1621($\upsilon_{C=N}$), 1604($\upsilon_{C=N}$). Elem. Anal. (% Calc.) C$_{17}$H$_{14}$N$_2$O$_2$: C 73.77, H, 5.07 N, 10.07 Found: C 72.01, H 4.54, N 9.82%. $^1$H NMR (CDCl$_3$, 400MHz, $\delta$ ppm) 2.49 (s, 3H, **CH**$_3$) 7.013 (s, 1H, Fur-**H**) 7.23 (d, 1H, Fur-H) 7.38 (t, 1H, Fur-H) 7.55 (t, 1H, Ar-H, *J* = 7.6 Hz) 7.85 (d, 1H, Ar-**H**, *J* = 8.84 Hz), 8.18 (d, 1H, Ar-**H**, *J* = 8.33 Hz), 9.72 (s, 1H, **H**C=N), 13.60 (s, 1H, Ar-O**H**). $^{13}$C NMR (CDCl$_3$) 161.51 (CH=N), 160.27 (**CH**=N), 156.42, 151.89, 145.59, 134.72, 132.90, 129.27, 128.08, 123.83, 120.24, 119.26, 114.49, 112.29, 108.90, 15.19. ESI-MS(m/z): 280.2 ([M+H]$^+$, 100%).

## 2.4 *Synthesis and characterization of L$_3$*

This is prepared using the same procedure as that used for **L**$_1$, but by using 2-acetyl thiophene in place of 2-acetyl pyrrole. Yield: (4.82 g, 89%). M.P. 150–152°C. FTIR: (KBr, cm$^{-1}$): 3445($\upsilon_{OH}$), 1621($\upsilon_{C=N}$), 1604($\upsilon_{C=N}$). Elem. Anal. (% Calc.) C$_{17}$H$_{14}$N$_2$OS (294.08): C,69.36 H, 4.79 N, 9.52 S, 10.89 Found: C 68.71, H 4.52; N 9.01, S 9.88 %. $^1$H NMR (CDCl$_3$, 400 MHZ, $\delta$ ppm) 2.58 (s, 3H, **CH**$_3$) 7.13 (d, 1H, Thiop-**H**, *J* = 4.9 Hz) 7.39 (t, 1H, Thiop-**H**) 7.48 (d, 1H, Thio-**H**) 7.54 (d, 1H, Ar-**H**), 7.56 (t, 1H, Ar-**H**), 7.78(d, 1H, Ar-**H**, *J* = 8.61 Hz) 7.85 (d, 1H, Ar-**H**, *J* = 8.87 Hz), 8.20 (d, 1H, Ar-**H**, *J* = 8.34 Hz) 9.64 (s, 1H, **H**C=N), 13.6 (s, H, Ar-OH) $^{13}$C NMR (CDCl$_3$) 161.5 (**CH**=N), 159.8 (**CH**=N), 143.3, 134.6, 132.9, 130.1, 129.5, 129.5, 129.3, 128.3, 128.0, 127.9, 123.8, 120.4, 119.3, 108.9, 16.04(-CH$_3$). ESI-MS (m/z): 296.2 ([M+H]$^+$, 100%).

## 2.5 *Synthesis and characterization of Cu$^{2+}$ complexes*

To a solution of **L**$_1$, **L**$_2$, or **L**$_3$ (2 mmol) in methanol (5 mL), copper(II) acetate monohydrate (0.2 g, 1 mmol) dissolved in methanol was added drop wise. After stirring for 24 h under reflux, the volume of solution was reduced to half by evaporation and the solid formed was filtered, washed with cold methanol (3 mL) and dried under vacuum to give the corresponding Cu$^{2+}$ complex. Yield of the copper complexes: **L**$_1$ – 0.52 g (77%); **L**$_2$ – 0.54 g (80%) and **L**$_3$ – 0.63 g (87%). Notable $\upsilon_{C=N}$ bands in the FT-IR (KBr, cm$^{-1}$): **L**$_1$ – 1615, 1599 cm$^{-1}$; **L**$_2$ – 1615, 1599 cm$^{-1}$; **L**$_3$ – 1615, 1604. ESI-MS (m/z): 675.24 ([2**L**$_1$+Cu+OAc+H]$^+$, 10%), ESI-MS (m/z): 676.26 ([2**L**$_2$+Cu+OAc+H]$^+$, 20%); ESI-MS (m/z): 727.6 ([2**L**$_3$+Cu+OAc+H$_3$O]$^+$, 25%).

## 3. Results and Discussion

The naphthyledene platform was coupled with pyrrole, furan and thiophene moieties through hydrazine linker to result in the receptor molecules. The receptor molecules, **L**$_1$, **L**$_2$ and **L**$_3$, have been synthesized in two steps with high yields (scheme 1). Reaction of acetyl pyrrole, acetyl furan or acetyl thiophene with hydrazine hydrate yields the corresponding hydrazine derivatives. The hydrazine derivatives, upon further reaction with 2-hydroxynaphaldehyde, resulted in **L**$_1$, **L**$_2$ and **L**$_3$ with good yield. All the compounds yielded satisfactory analytical and spectral results as given in the experimental section (Supplementary information, figure S1).

### 3.1 *Fluorescence titration studies*

Interaction of Mn$^{2+}$, Fe$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, Hg$^{2+}$, Pb$^{2+}$, Na$^+$, K$^+$, Ca$^{2+}$ and Mg$^{2+}$ has been studied with **L**$_1$, **L**$_2$ and **L**$_3$ by fluorescence spectroscopy in methanol, acetonitrile and aqueous acetonitrile. Metal ion binding cores of the types N$_3$O, N$_2$O$_2$ and N$_2$OS were present in **L**$_1$, **L**$_2$ and **L**$_3$, respectively, owing to the presence of two imine nitrogens, naphthylic-OH as well as a heterocycle. The molecules exhibited strong emission from the naphthyl moiety ~500–507 nm in methanol when excited at 400 nm. The metal ions, namely Na$^+$, K$^+$, Ca$^{2+}$ Mg$^{2+}$, Mn$^{2+}$, Fe$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, Hg$^{2+}$ and Pb$^{2+}$ were studied for their binding with **L**$_1$, **L**$_2$ and **L**$_3$ at 10 $\mu$M concentration in methanol by carrying out the titrations as given in the experimental section. The emission intensity for the three receptor molecules in methanol was in the order **L**$_3$ > **L**$_2$ > **L**$_1$. Among
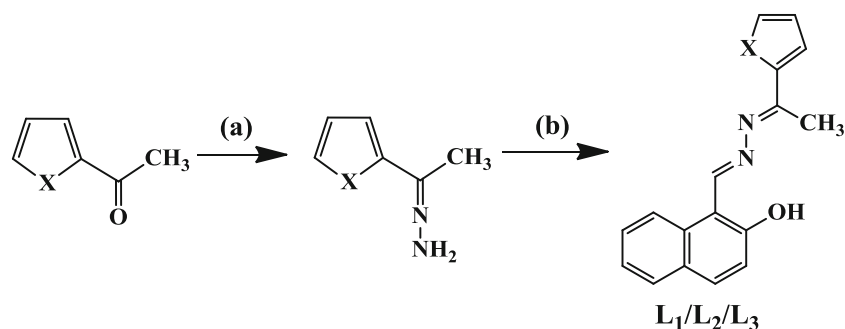
**Scheme 1.** (**a**) NH$_2$-NH$_2$.H$_2$O, MeOH, reflux, 12 h. (**b**) 2-hydroxy-1-naphthaldehyde, methanol, MeOH, reflux, 12 h. X = −NH (**L$_1$**); −O (**L$_2$**); −S (**L$_3$**).

the metal ions studied, addition of Cu$^{2+}$ quenches the emission intensity of all three molecules. No other metal ion showed any significant change in the emission intensity of these. Figure 1 shows selective fluorescence quenching of the receptor molecule upon Cu$^{2+}$ addition and the quenching is to an extent of 92–96%. Thus, the extent of quenching follows a trend **L$_1$** > **L$_2$** > **L$_3$**, which is just the reverse of the fluorescence intensity of the simple receptor molecules. The titrations carried out in other solvents, such as CH$_3$CN (quenching of 64–79%) and CH$_3$CN/H$_2$O (75:25 v/v) (quenching of 67%) (figure 2), also showed quenching of emission in case of all these three molecules, but the extent of quenching is lower than that observed in methanol. Thus, methanol is suited for a higher sensitivity for Cu$^{2+}$ as compared to the other two solvents. The association of Cu$^{2+}$ with **L$_1$**, **L$_2$** and **L$_3$** yielded K$_a$ = 33557 ± 988, 29832 ± 600 and 27853 ± 780 M$^{-1}$, respectively, as determined using the fluorescence data.

To evaluate the recognition efficiency of the receptors **L$_1$**, **L$_2$** and **L$_3$** towards Cu$^{2+}$ in the presence of other metal ions, competitive fluorescence titrations were carried out. Fluorescence spectra were recorded for **L$_1$**, **L$_2$** and **L$_3$** upon addition of Cu$^{2+}$ in presence of 30 equivalents of Na$^+$, K$^+$ or Ca$^{2+}$, which are biologically relevant ones. The competitive ion titrations carried out in the presence of excess equivalents of other metal ions such as Na$^+$, K$^+$, Ca$^{2+}$ or Mg$^{2+}$ did not affect the quenching by the Cu$^{2+}$, supporting that these molecules recognize Cu$^{2+}$ in the presence of other metal ions. To determine the minimum detection limit of these three receptor molecules towards Cu$^{2+}$, fluorescence experiments were carried out at varying concentrations, keeping metal ion to ligand ratio as 1:2 in all cases. The minimum detection limits for Cu$^{2+}$ are 0.6, 1.9 and 0.9 ppm, respectively, for **L$_1$**, **L$_2$** and **L$_3$**.

### 3.2 *Absorption titration studies*

The UV-visible absorption titrations were carried out with the three receptor molecules by Cu$^{2+}$ at a concentration of 33 $\mu$M in methanol showed increase in the

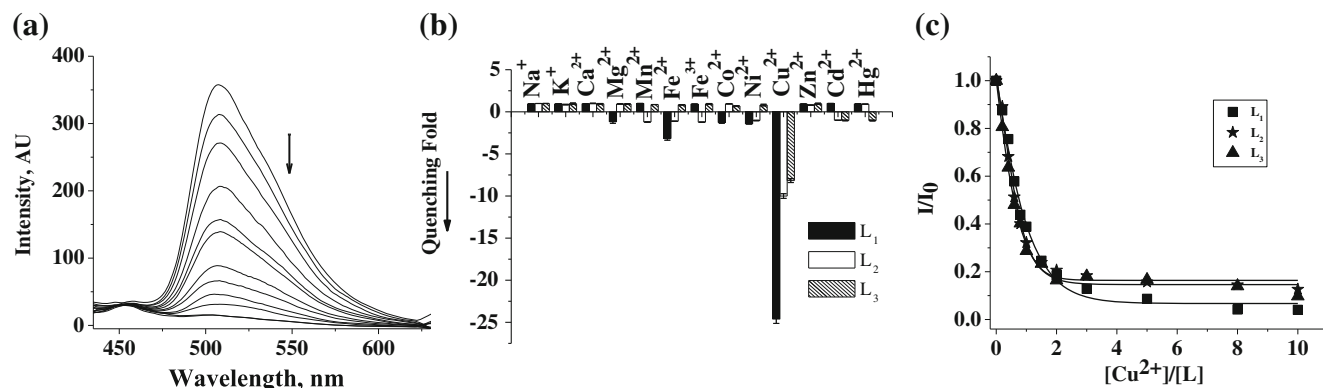**Figure 1.** (**a**) Fluorescence spectral traces of the titration of **L$_1$** as a function of added Cu$^{2+}$ to result in [Cu$^{2+}$]/[**L**] mole ratio from 0 to 10.0 in methanol. Arrow indicates the direction of decrease of fluorescence intensity upon increased Cu$^{2+}$ addition. (**b**) Histogram of highest I/I$_o$ ratio indicating quenching fold (negative scale) for the titration of different metal ions with **L$_1$**, **L$_2$** and **L$_3$**. (**c**) Relative fluorescence intensity (*I/I$_o$*) vs. Cu$^{2+}$/[**L**] mole ratio.
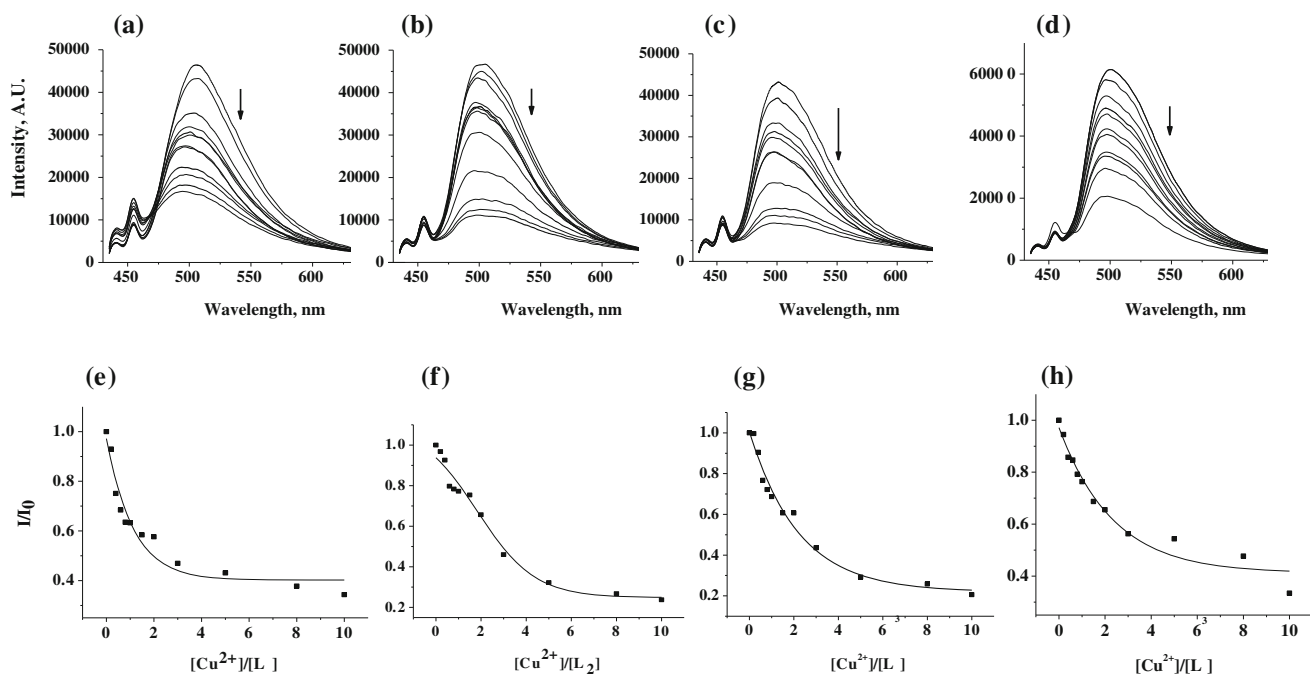
**Figure 2.** Fluorescence spectral traces of (**a**) $L_1$, (**b**) $L_2$ and (**c**) $L_3$ as a function of added $Cu^{2+}$ in $CH_3CN$. (**d**) Fluorescence spectral traces of $L_3$ as a function of added $Cu^{2+}$ in $CH_3CN/H_2O$(75:25 v/v). The plots shown in (**e**) to (**h**) are the fluorescence intensity ratio plots corresponding to (**a**) to (**d**), respectively.
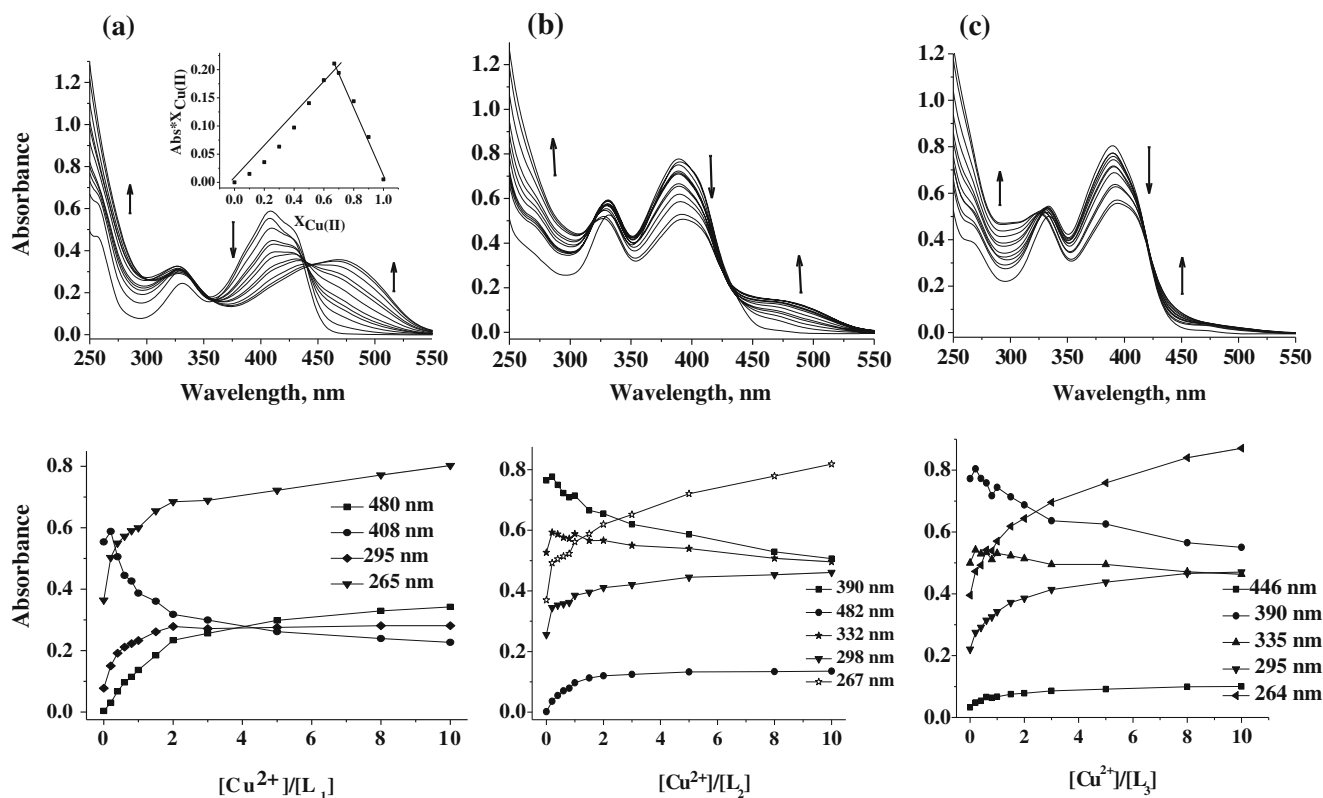


**Figure 3.** UV-visible absorption spectral traces of (**a**) $L_1$ (Inset: Job's plot for the titration of $L_1$ by $Cu^{2+}$), (**b**) $L_2$ and (**c**) $L_3$ during titration against $Cu^{2+}$. The plots given below corresponds to the absorbance *vs.* $[Cu^{2+}]/[L]$ mole ratio for different bands of the spectra given in (**a**), (**b**) and (**c**), respectively.

absorbance of the 290-nm band in all the three cases (figure 3).

A new band was observed at 475 nm that is attributable to ligand to metal charge transfer in case of $L_1$ and $L_2$. Clear-cut isobestic points were observed for $L_1$, $L_2$ and $L_3$ at 440 nm, 427 nm and 422 nm, respectively, indicating the presence of a complex formation with $Cu^{2+}$. However, in the case of $L_3$, the increase in the absorbance observed at 450–475 nm is not as high as that observed in other cases. The Job's plots indicated 1:2 stoichiometry for the complex formed between $Cu^{2+}$ and $L_1$, $L_2$ or $L_3$ (inset of figure 2a). The mass spectral studies carried out with isolated $Cu^{2+}$ complexes of $L_1$, $L_2$ and $L_3$ confirmed the formation of 1:2 complexes in all the three cases. The absorption data show more pronounced spectral changes in case of $L_1$ as compared to $L_2$ and $L_3$.

### 3.3 *Colorimetric recognition of $Cu^{2+}$*

The receptor molecules $L_1$, $L_2$ and $L_3$ show orange-brown colour upon recognition of $Cu^{2+}$ in methanol, while no other ion, such as $Na^+$, $K^+$, $Ca^{2+}$, $Mg^{2+}$, $Mn^{2+}$, $Fe^{2+}$, $Co^{2+}$, $Ni^{2+}$, $Zn^{2+}$, $Cd^{2+}$ and $Hg^{2+}$, shows such colour change (figure 4).

### 3.4 *Characterization of the isolated complexes*

The $Cu^{2+}$ complexes of $L_1$, $L_2$ and $L_3$ were isolated and characterized. The strong band observed at 3360 cm⁻¹ supports the presence of lattice water in case of the complexes of $L_2$ and $L_3$. These complexes showed a decrease in the stretching frequency for $-C=N$ bond from 1621 cm⁻¹ and 1604 cm⁻¹, suggesting the coordination of Cu(II) to the imine moiety. In case of the pyrrole complex ($L_1$) of copper, the pyrrole N-H stretching vibration is unaltered even in the complex, suggesting that the heterocyclic part of the ring is not involved

in binding to the metal center. Even the vibrations corresponding to the heterocyclic ring were largely unaltered, suggesting the nonbinding nature of the heterocyclic moieties in all the three complexes. The ESI-MS of these complexes exhibited peaks corresponding to 1:2 ($Cu^{2+}$: $L$) complex formed in all the three cases (Supplementary information, figure S2) and the presence of copper can be identified based on the isotopic peak pattern obtained.

### 3.5 *Computational studies*

As all the studies clearly suggested the formation of 1:2 complexes between $Cu^{2+}$ and the receptor molecules, computational modeling was performed to obtain the structural features of these complexes. The 1:2 species were optimized by density functional theory (DFT) using 6–31+G(d,p) basis set for C, H, O, N, S (non-metal atoms) and LANL2DZ basis set for heavy Cu atom. No imaginary frequency was observed for any of the lowest-energy structures. All the computations were performed using GAUSSIAN 09 suite of programs.[7] The optimized structures of the receptors and the 2:1 complexes of $Cu^{2+}$ are given in figure 5.

While the naphthyl and heteroatom rings are almost in the same plane in the unbound molecules, these, when bound to $Cu^{2+}$, exhibited a considerable rotation such that the heteroatom ring is inclined at 38–40° with respect to the napthyl moiety in all the three complexes. The 1:2 complexes thus optimized exhibit center of symmetry about the $Cu^{2+}$ in all three cases where $Cu^{2+}$ is tetra-coordinated by $N_2O_2$ core arising from the two receptor molecules together. When these structures were optimized in methanol and acetonitrile, no substantial changes were observed in the binding nature, the geometry or the metric data of the complex. Even the angle of inclination between the naphthyl ring and the hetero atom ring remains almost same as that observed in the gas phase.
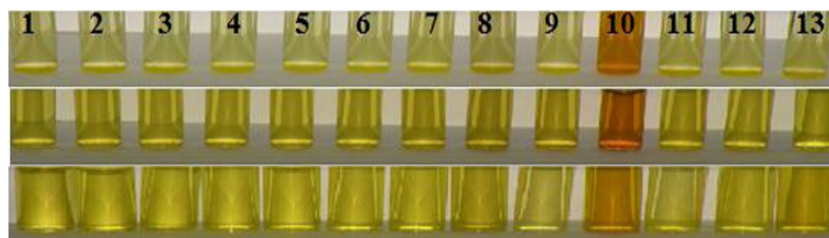


**Figure 4.** Colour of the methanolic solutions $L_1$ (top), $L_2$ (middle) and $L_3$ (bottom) in the presence of different metal ions at a 1:1 mole ratio: Sample vial No: 1 is a simple receptor; vials 2 to 13 are in the presence of (2) $Na^+$, (3) $K^+$, (4) $Mg^{2+}$, (5) $Ca^{2+}$,(6) $Mn^{2+}$,(7) $Ni^{2+}$,(8) $Fe^{2+}$, (9) $Co^{2+}$, (10) $Cu^{2+}$; (11) $Zn^{2+}$; (12) $Cd^{2+}$, (13) $Hg^{2+}$, respectively.
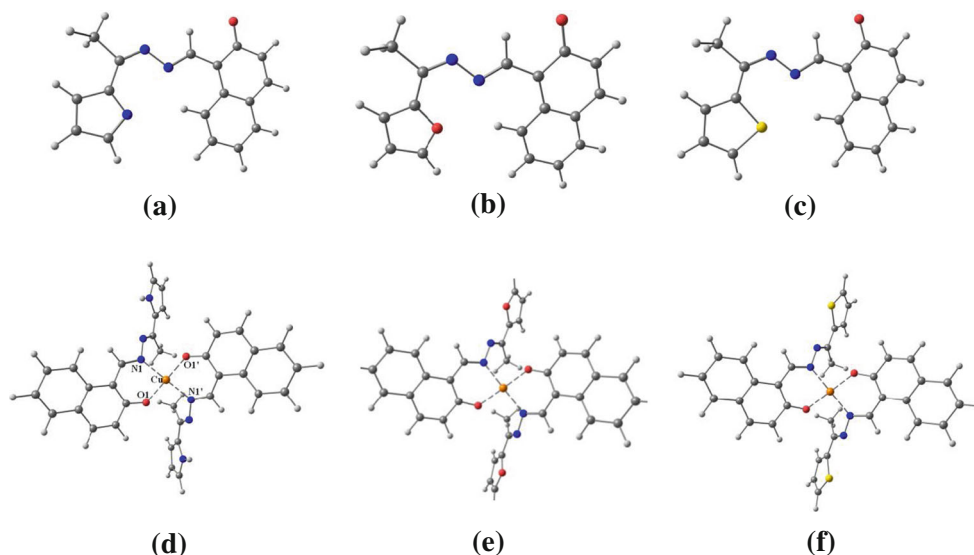
**Figure 5.** B3LYP optimized geometries (in gas phase) of (**a**) $L_1$, (**b**) $L_2$ and (**c**) $L_3$. The 1:2 $Cu^{2+}$ complexes of these receptors (**d**) $Cu^{2+}$: $2L_1$; (**e**) $Cu^{2+}$ : $2L_2$; (**f**) $Cu^{2+}$: $2L_3$.

## 4. Conclusions

In summary, the chemosensing characteristics of $L_1$, $L_2$ and $L_3$ were investigated by fluorescence and absorption measurements. All the three receptors were found to be selectively recognizing $Cu^{2+}$ by *switch-off* fluorescence. The quenching fold order during addition of $Cu^{2+}$ was found to be $L_1 > L_2 > L_3$. The effect of solvent on quenching of emission intensity of these three receptors by $Cu^{2+}$ was studied. The quenching rate was highest in methanol among the solvents studied. The minimum detection limits for $Cu^{2+}$ are 0.6, 1.9 and 0.9 ppm, respectively, for $L_1$, $L_2$ and $L_3$. Based on the emission, absorption, colour of the solution and the minimum detection limits, $L_1$ is the most sensitive among these three derivatives. UV-vis absorption titration data indicate complex formation by exhibiting clear isobestic points. The complex was found to be 2:1 based on the Job's plot as well as by the mass spectral data obtained for the isolated complexes. The structures of all the three 2:1 complexes were optimized using DFT computational studies and found that the centrosymmetric structures are favoured energetically over the non-centrosymmetric ones. While the heterocyclic unit in the receptor molecules occupies the same plane as that of the naphthyl ring, it exhibited a tilt (38–40°) when it complexed with $Cu^{2+}$. No direct interaction was noticed between the hetero atom of the heterocyclic moiety and the metal ion centre; however, the sensitivity towards $Cu^{2+}$ detection alters by a factor of two to three among these.

## Supplementary information

The electronic supporting information can be seen at www.ias.ac.in/chemsci.

## Acknowledgements

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