



# An easily accessible optical chemosensor for Cu<sup>2+</sup> based on novel imidazoazine framework, its performance characteristics and potential applications

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## ABSTRACT

Despite the fact that a large number of chemical sensors for Cu<sup>2+</sup> have been proposed by different groups in recent past, most of them fall into very few classes of molecular framework with similar utilities and limitations. In order to broaden the scope and to overcome the limitation of present day chemical sensors, design, synthesis and testing of molecular systems based on novel fluoro/chromophore is a research goal of significant interest. In the present report, two novel furan-2-yl substituted imidazoazine based optic chemosensors (**IA-1** and **IA-2**) for Cu<sup>2+</sup> have been disclosed for the first time. Proposed sensors were found to have high association constants (10<sup>4</sup> M<sup>-1</sup>), acceptable detection limits (10<sup>-7</sup> M), high selectivity and reversibility/reusability. Different aspects of this sensing phenomenon were studied using fluorescence spectroscopy and NMR based titrations. Designed probe have shown potential applications in the area of sample monitoring, photo-printing and membrane sensing.

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## 1. Introduction

Copper is one of the indispensable micronutrients with ubiquitous presence in all the life forms from primitive bacteria, fungi to higher plant and mammalian eukaryotic cell [1]. Under physiological conditions, chemistry of this transitional metal is exquisitely governed by Cu<sup>2+</sup>/Cu<sup>+</sup> redox couple, which in turn administers the functions of several biologically relevant enzymes. This unique attribute of copper chemistry is highlighted by its participation in numerous cellular and sub-cellular events such as iron transport, cellular oxidation, electron transport shuttle (ETS), radical detoxification, biosynthesis of several important natural products etc [2–6].

For all this to happen in a well balance manner, a normal level of copper is required in the body. Under ordinary conditions, copper homeostasis remains under the tight control of different copper-enzymes, transporters, carriers, chaperons etc [7,8]. Unfortunately, whenever this control loosens, it is manifested as several disease

conditions such as neurogenetic disorders, sclerosis, ageing, partial anaemia etc. Extreme overexpressed or underexpressed states are even more life threatening [9–11]. Some recent studies have pointed out that the self-healing/self-cleaning capacity of close aquatic ecosystems such as lakes, ponds and other stagnant water bodies very much rely on [Cu<sup>2+</sup>]/[H<sup>+</sup>] ratio [12,13]. Elevated copper concentration has several negative effects on the population, growth and reproduction of aquatic microflora and fauna. In light of all these facts, it is worth recalling that normal copper level is vital for healthy functioning of all living organisms [14,15].

Acknowledging, its important role in various domains and forms of life, qualitative and quantitative estimation of copper at trace level seems to be research task of paramount importance. At present, several instrumental techniques are routinely employed for this purpose such as voltammetry, atomic spectroscopy (AAS and AES), inductively couple plasma hyphenated with mass spectroscopy (ICP-MS) etc [16–20]. Although these sophisticated techniques provides very precise results, yet marred with several limitations such as need of experts handling, high maintenance expenditure, operational complexities, tedious and destructive sample preparation, low portability, unsuitability for “on spot, real time, *in vivo*” experiments. Use of molecular systems

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(chemical sensors) with the ability to demonstrate measurable change (in any of the output signal such as optic/electric/magnetic etc) in the presence of a specific analyte is an effective solution of most of these problems. Indeed, discovery and design of new probing agent/sensing molecule is now a very active area of research with hundreds of reports each year. Because of several advantages such as fast response, higher selectivity and sensitivity, portability etc methods based on optical chemosensors (colorimetric/fluorescence) are particularly mentionable in this regard [21–23].

In recent past, a large number of sensing molecules have been proposed for  $\text{Cu}^{2+}$  ion by different research groups. But a careful survey of the literature revealed that most of these probes are not more than a structural modification of few well established molecular scaffolds such as fluorescein, naphthalimide, anthracene/anthraquinone, quinolones, triazoles, pyrene, BODIPY core [24–53] etc. with similar drawbacks and applicability. Therefore, design and discovery of new sensing molecules with different molecular framework would be a scientifically stimulating and rewarding exercise.

In a continuation of our previous work on chemical sensors [54–62], we herein report two new furan-2-yl functionalized imidazoazines (or Gröebke product) **IA-1** and **IA-2** [63,64] for easy, effective and fast detection of  $\text{Cu}^{2+}$  in mixed aqueous phases. Despite its easy synthetic accessibility presence of donor N and O atoms in attached groups and intense fluorescence nature, this molecular system have never been explored for its metal sensing abilities. This work not only shed light on the different aspects of this particular sensing phenomenon but also explores the practical applicability of these newly disclosed systems in the realm of sample monitoring, membrane sensing and photoprinting.

## 2. Experimental

### 2.1. General information

All solvents and chemicals (analytical grade) were purchased from Sigma-Aldrich® and were used as received. Poly(vinylpyrrolidone) (PVP) and additive for membrane preparation were obtained from Acros Organics (Thermo Fisher Scientific), New Jersey, USA. Progresses of the reactions were monitored by thin layer chromatography (TLC, Merck 60 F<sub>254</sub>). All <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Jeol Resonance ECX-400II spectrometer. Chemical shift values were reported in parts per million (ppm) using TMS as an internal standard. Spectral data were processed using MestReNova<sup>6</sup> software. High resolution mass spectrometry (HRMS) and elemental analysis experiments were carried out using a Bruker Daltonics micrOTOF-QII® (ESI mode of ionization) and Elementar vario MICRO cube respectively. UV–vis absorption and fluorescence spectra were recorded on a Shimadzu UV-2450 spectrophotometer® and Horiba fluoromax-4 spectrofluorometer® respectively. For all the runs excitation and emission slit widths were kept constant at 1.0 nm. ChemDraw Ultra 8.0 was used for drawing structures and Origin 6.0 was used for mathematical and graphical work.

### 2.2. Synthetic procedure

Pyridin-2-amine (1.0 mmol), furan-2-carbaldehyde (1.0 mol) and isonitrile (1.2 mmol) were taken in 5 ml stoppered round bottom flask. This mixture was stirred and heated at 160 °C in an oil bath for about 2 h. Progress of the reaction was monitored by TLC plates. Products were recrystallized from EtOH. Both the compounds were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and HRMS analysis.

### 2.3. Analytical data

#### 2.3.1.

##### N-tert-butyl-2-(furan-2-yl)H-imidazo[1,2-a]pyridin-3-amine (**IA-1**)

Yield: = 95%; brownish solid; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) 1.13 (s, 9H), 3.51 (br s, 1H), 6.50 (q, 1H, *J* = 1.5 Hz), 6.72 (t, 1H, *J* = 6.7 Hz), 6.87 (d, 1H, *J* = 3.4 Hz), 7.06–7.13 (m, 1H), 7.45–7.49 (m, 2H), 8.22 (dd, 1H, *J* = 6.9 & 1.0 Hz). <sup>13</sup>C NMR: (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) 29.7, 52.3, 109.1, 110.1, 11.1, 112.6, 117.5, 126.4, 126.7, 138.2, 143.6, 144.0, 159.9. HRMS (ESI) *m/z* calcd. for (C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O) [M+Na]<sup>+</sup>: 278.3048, found: 278.3042. Anal. Calcd for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O; C, 70.56; H, 6.72; N, 16.46 Found: C, 70.62; H, 6.80; N, 16.48.

#### 2.3.2. 2-(furan-2-yl)-N-(2,4,4-trimethylpentan-2-yl)H-imidazo[1,2-a]pyridin-3-amine (**IA-2**)

Yield: = 93%; brownish solid; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) 1.02 (s, 9H), 1.40 (s, 6H), 1.60 (s, 2H), 3.41 (br s, 1H), 6.40 (q, 1H, *J* = 1.5 Hz), 6.61 (t, 1H, *J* = 6.6 Hz), 6.77 (d, 1H, *J* = 3.4 Hz), 6.94 7.30 (m, 1H), 7.30 7.40 (m, 2H), 8.11 (dd, 1H, *J* = 6.8 & 1.0 Hz). <sup>13</sup>C NMR: (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) 28.8, 31.6, 31.9, 54.0, 56.4, 109.0, 110.1, 111.9, 112.6, 117.5, 126.4, 126.7, 138.2, 143.6, 144.0, 161.7. HRMS (ESI) *m/z* calcd. for (C<sub>19</sub>H<sub>25</sub>N<sub>3</sub>O) [M+Na]<sup>+</sup>: 334.4111, found: 334.4106. Anal. Calcd for C<sub>19</sub>H<sub>25</sub>N<sub>3</sub>O; C, 73.28; H, 8.09; N, 13.49 Found: C, 73.32; H, 8.14; N, 13.52.

### 2.4. UV–vis and fluorescent study

For UV and fluorescence studies, stock solutions of the compounds and metal ions Na<sup>+</sup>, Ca<sup>2+</sup>, Cd<sup>2+</sup>, Mg<sup>2+</sup>, Mn<sup>2+</sup>, Co<sup>2+</sup>, Cu<sup>2+</sup>, Ni<sup>2+</sup>, Hg<sup>2+</sup>, Zn<sup>2+</sup>, Pb<sup>2+</sup>, Al<sup>3+</sup>, Cr<sup>3+</sup>, Nd<sup>3+</sup> and Fe<sup>3+</sup> were prepared (1.0 × 10<sup>-3</sup> M) in MeOH/H<sub>2</sub>O (2/8, v/v). For spectral recordings, the stock solutions were further diluted to 2.0 × 10<sup>-5</sup> M. All fluorescence spectra were recorded from 390 to 700 nm in a quartz cell (1 cm path length) at room temperature (1.0 nm excitation and emission slit). Solutions were added through a Hamilton burette equipped with 1 ml syringe. For real time analysis ACN/H<sub>2</sub>O (2/8, v/v) and pH experiments MeOH/H<sub>2</sub>O (2/8, v/v) was used as a solvent.

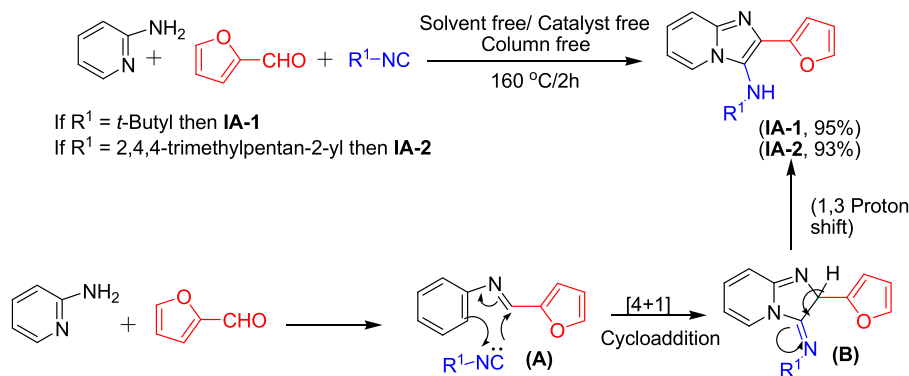
### 2.5. Synthesis of polymeric membrane for sensing

3 mg of ionophore (**IAs**), plasticizers 2-nitrophenyloctyl ether (*o*-NPOE) and dioctylphthalate (DOP) (65 mg), additive NaTPB (around 2 mg) and high molecular weight PVC (30 mg) were dissolved in THF with continuous stirring. This viscous oily substance was then poured into a polyacrylate ring placed on a smooth surface. After evaporation of solvent fluorescent membranes of about 0.5–1.0 mm thickness were obtained which were then cut to the desired size and glued to one end of a 2 cm diameter Pyrex glass tube and kept at the room temperature for full night. Metal solutions of appropriate concentrations can be directly applied to these thin layers [65].

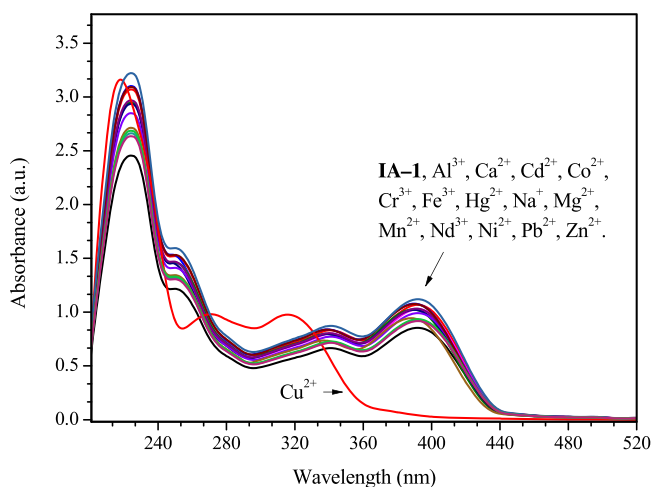
## 3. Results and discussion

### 3.1. Synthesis of furan-2-yl substituted imidazo[1,2-a]-pyridine **IA-1** and **IA-2**

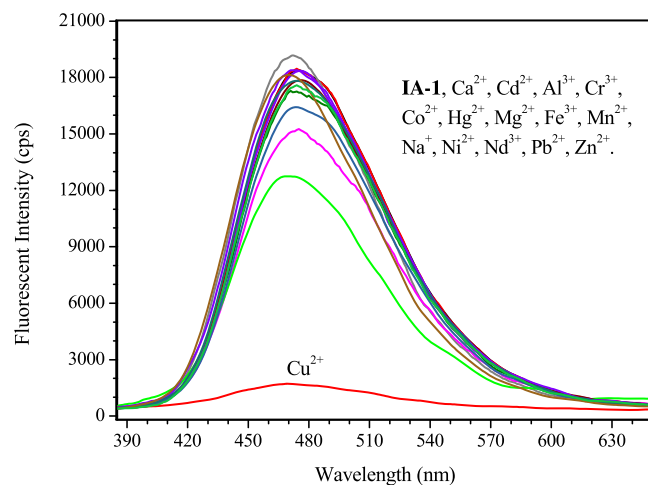
Both functionalized imidazo-azines were synthesized through three components (3-CR) Gröebke–Blackburn–Bienaymé reaction (Scheme 1). This reaction proceed through a Schiff base (A) (from 2-aminoazine with furfuryl), containing both nucleophilic and electrophilic centres. This imine intermediate then undergoes a [4+1] cycloaddition with isocyanide input leading to a bicyclic



**Scheme 1.** Multicomponent synthesis of (furan-2-yl)*H*-imidazo[1,2-*a*]pyridin-3-amine **IA-1** and **IA-2**.



**Fig. 1.** Absorption spectra of compound **IA-1** [20  $\mu\text{M}$  in MeOH/ $\text{H}_2\text{O}$  (2/8, v/v)] in the presence of different metal ions (5 equivalents). Distinct behaviour of  $\text{Cu}^{2+}$  (equivalent amount) is clearly noticeable from figure and higher wavelength peak at 392 nm completely disappeared in the presence of  $\text{Cu}^{2+}$ .



**Fig. 2.** Fluorescence response of **IA-1** [20  $\mu\text{M}$  in MeOH/ $\text{H}_2\text{O}$  (2/8, v/v)] toward different metal ions (5 equivalents). In the presence of equivalent amount of  $\text{Cu}^{2+}$  peak at 473 nm (excitation wave length 365 nm, excitation and emission slit width = 1 nm) completely disappeared.

cycloadduct (B), followed by 1,3-proton shift to a desired aminoimidazole (**IA**s).

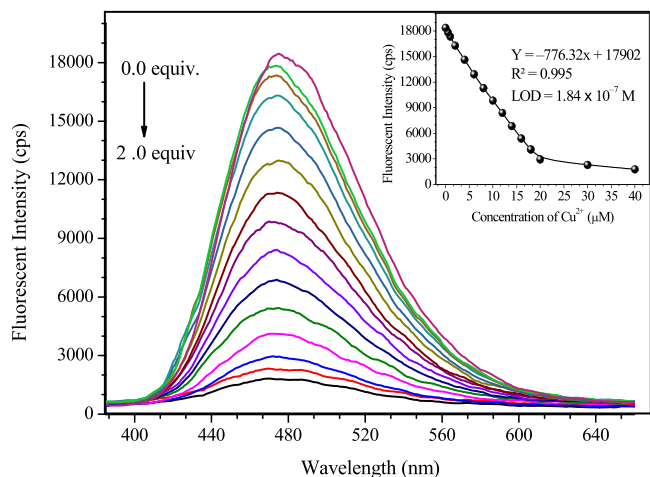
### 3.2. $\text{Cu}^{2+}$ sensing assays

Representative absorption spectra (Fig. 1 and SS1<sup>#</sup>) of synthesized **IA**s in MeOH/ $\text{H}_2\text{O}$  (2/8, v/v) displayed four intense bands centred near 224, 251, 339, 392 nm (**IA-1**) and 222, 311, 342, 377 nm (**IA-2**). While the excess (5 equivalent) presence of other metal ions such as  $\text{Al}^{3+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Na}^{+}$ ,  $\text{Nd}^{3+}$ ,  $\text{Pb}^{2+}$  and  $\text{Zn}^{2+}$  didn't create any significant change in spectral pattern, only equimolar amount of  $\text{Cu}^{2+}$  was adequate to discolour the solution (yellow to colourless) with disappearance of longest wave length absorption maxima [392 nm (**IA-1**) and 377 nm (**IA-2**)] (Fig. 1 and SS1<sup>#</sup>). These cationic species and heavy metal ions are commonly present in the aqueous and environmental samples. So this selectivity study clearly marked the practical applicability of the entitled sensors. Similar effects were also noticed in fluorescence spectra of both the compounds and emission at 473 nm and 453 nm got quenched in the presence of cupric ion in solution phase (Fig. 2 and SS2<sup>#</sup>). Both the probes retained their sensing properties in other organic solvents such as ACN, MeOH, DMSO and mixed aqueous phase such as MeOH/ $\text{H}_2\text{O}$  (1/9 to 9/1, v/v) and ACN/ $\text{H}_2\text{O}$  (1/9 to 9/1, v/v). Since water is a common solvent in most of the biologically and ecologically relevant media, hence it is important to examine the utility of our sensors in aqueous phase. Since our compounds are only partially soluble in the water, hence mixed

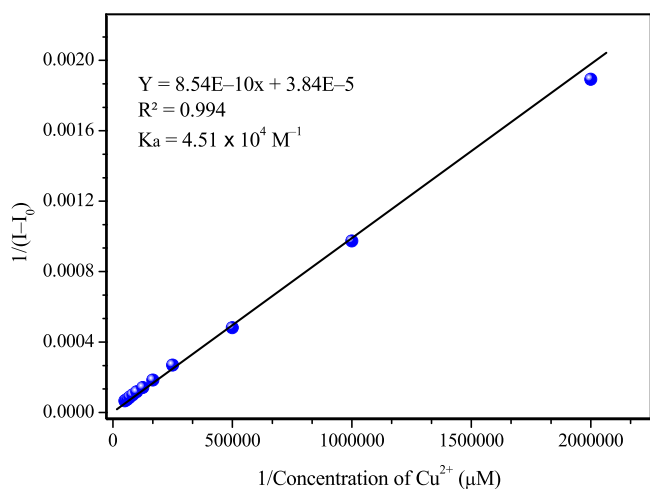
aqueous phase (MeOH/water, 2/8, v/v) was used in our study. Use of organic phase ensures higher availability of probe molecule in medium.

Next, some complexometric and stoichiometric titrations were performed to determine different performance characteristics of this sensing phenomenon. In MeOH/ $\text{H}_2\text{O}$  (2/8, v/v), there was a gradual decrease in fluorescence intensity [473 nm (**IA-1**) and 453 nm (**IA-2**)], with the continuous addition of  $\text{Cu}^{2+}$  from 0.0 to 2.0 equivalents (Fig. 3 and SS3<sup>#</sup>). Detection limits (LOD) for **IA-1** and **IA-2** were found to be  $1.84 \times 10^{-7}$  M and  $3.14 \times 10^{-7}$  M respectively by universal method (LOD = 3s/slope) (Fig. 3 and SS3<sup>#</sup>). For many ecological and biological samples, these detection limits are quite acceptable, indicating the potential utility of these systems (annulated azines) in trace level analysis.

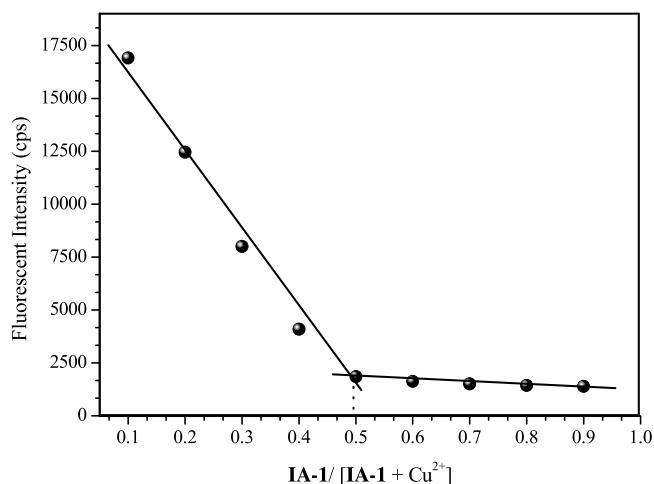
In Benesi–Hildebrand plots [66] (between  $1/I - I_0$  and  $1/[\text{Cu}^{2+}]$ , for 1:1 stoichiometry) a linear relationship with excellent correlation coefficient (>0.99) were obtained for both compounds (Fig. 4 and SS4<sup>#</sup>). Association constants for **IA**s- $\text{Cu}^{2+}$  were calculated to be  $4.51 \times 10^4 \text{ M}^{-1}$  (**IA-1**) and  $1.99 \times 10^4 \text{ M}^{-1}$  (**IA-2**) reflecting higher affinity of furanyl imidazoazines toward  $\text{Cu}^{2+}$  at equilibrium. In Job's method [67], Intensity minima was observed at 0.5 molar fraction of  $\text{Cu}^{2+}$ , suggesting 1:1 binding between probe and ion under investigation (Fig. 5 and SS5<sup>#</sup>). This fact was further confirmed by high resolution mass spectra of the complex in methanol/acetonitrile (5/5, v/v) (see spectra in electronic Supporting information). For some biological studies, it is highly desirable that chemosensor must have a wide operation pH range.



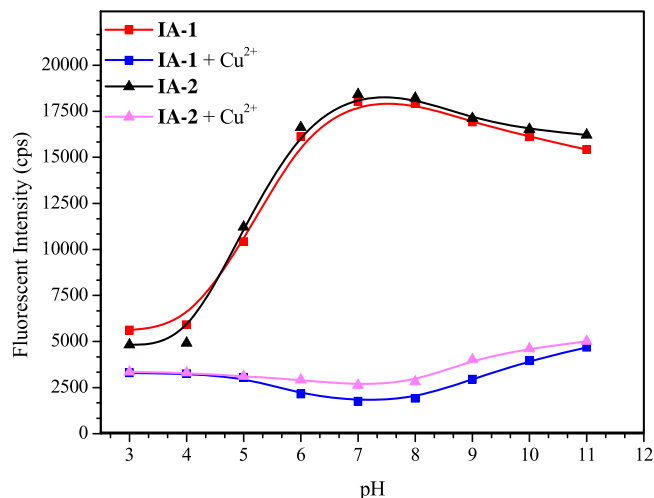
**Fig. 3.** Fluorescent titration of **IA-1** [20 μM in MeOH/H<sub>2</sub>O (2/8, v/v)] with Cu<sup>2+</sup> (from 0.0 equivalent to 2.5 equivalents) at excitation wavelength 365 nm (excitation and emission slit width = 1 nm).



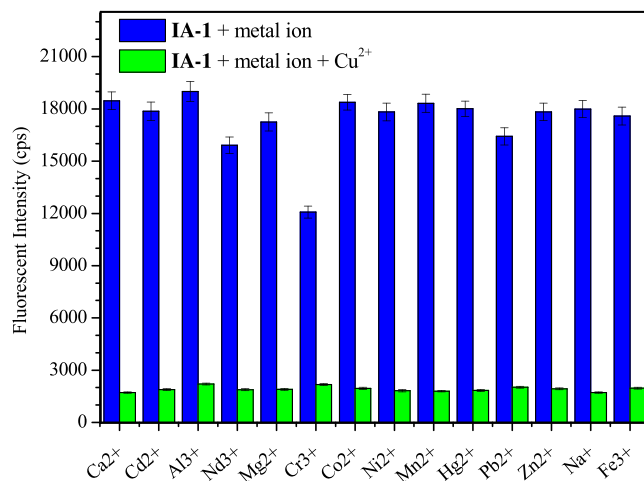
**Fig. 4.** Relevant Benesi–Hildebrand plots for fluorescence titration of **IA-1** against Cu<sup>2+</sup> shown in Fig. 3.



**Fig. 5.** Job's plot for determination of stoichiometry of complex (minima at 0.5 indicate 1:1 stoichiometry between **IA-1** and Cu<sup>2+</sup>).



**Fig. 6.** Dependence of fluorescence response over pH of the medium. Titrations were performed in MeOH/H<sub>2</sub>O (2/8, v/v) solution.



**Fig. 7.** Examination of selectivity of **IA-1** towards Cu<sup>2+</sup> (20 μM) in the presence of various metal ions (5 equiv.), such as Ca<sup>2+</sup>, Cd<sup>2+</sup>, Al<sup>3+</sup>, Cr<sup>3+</sup>, Co<sup>2+</sup>, Ca<sup>2+</sup>, Mg<sup>2+</sup>, Mn<sup>2+</sup>, Ni<sup>2+</sup>, Na<sup>+</sup>, Pb<sup>2+</sup>, Nd<sup>3+</sup>, Fe<sup>3+</sup> and Zn<sup>2+</sup> in MeOH/H<sub>2</sub>O (2/8, v/v).

Gratifyingly, our amino substituted imidazoazine displayed optimum pH response in the range of 5–11, suggesting its utility in physiological mediums (Fig. 6).

### 3.3. Selectivity studies

For a scaffold to be labelled as sensor it must have higher degree of selectivity towards a particular analyte/ion and this response should largely remain unaffected by the presence of other interfering species or ions. Determination of matrix effects and selectivity studies are thus very important for sensing applications. In a series of experiments, fluorescence intensities of probe **IA**s were recorded in the presence and absence of other metal ion such as Al<sup>3+</sup>, Cd<sup>2+</sup>, Co<sup>2+</sup>, Cr<sup>3+</sup>, Hg<sup>2+</sup>, Mg<sup>2+</sup>, Fe<sup>3+</sup>, Mn<sup>2+</sup>, Ni<sup>2+</sup>, Na<sup>+</sup>, Nd<sup>3+</sup>, Pb<sup>2+</sup> and Zn<sup>2+</sup>. Recorded data (Table 1) and graphs (Fig. 7 and SS6<sup>#</sup>) suggested that synthesized probe **IA**s were successful in retaining their selectivity towards Cu<sup>2+</sup> even in the excess presence of other metal ions.

While the presence of commonly occurring anionic species such as AcO<sup>-</sup>, Br<sup>-</sup>, Cl<sup>-</sup>, F<sup>-</sup>, I<sup>-</sup>, NO<sub>3</sub><sup>-</sup>, SCN<sup>-</sup> and SO<sub>4</sub><sup>2-</sup> in MeOH/H<sub>2</sub>O (2/8, v/v) didn't produce any observable change in **IA**s-Cu<sup>2+</sup> selectivity, a sharp increase in fluorescent intensity was observed in the presence of S<sup>2-</sup> (Fig. 8 and SS7<sup>#</sup>) In fact, 1.5 equimolar amount of S<sup>2-</sup> was found sufficient for complete removal of the quenching effect



**Table 1**  
Effects of interfering species on the fluorescence signal of the optical sensor<sup>a,b,c,d</sup>.

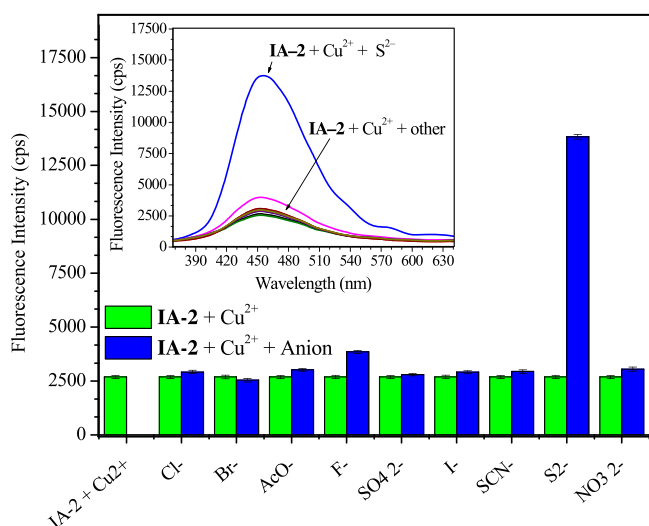
Interfering ion	Relative error in%	Interfering ion	Relative error in% $(\Delta F/F_0 \times 100)$	Interfering ion	Relative error in% $(\Delta F/F_0 \times 100)$
Na <sup>+</sup>	+1.7	Hg <sup>2+</sup>	+0.2	Cd <sup>2+</sup>	-2.3
K <sup>+</sup>	+1.3	Pb <sup>2+</sup>	+1.1	Nd <sup>3+</sup>	+2.7
Ca <sup>2+</sup>	-0.88	Mn <sup>2+</sup>	+0.7	Al <sup>3+</sup>	+3.9
Mg <sup>2+</sup>	+0.67	Ni <sup>2+</sup>	+1.9	Cr <sup>3+</sup>	-1.7
Co <sup>2+</sup>	+4.9	Zn <sup>2+</sup>	+2.7	Fe <sup>3+</sup>	-2.1

<sup>a</sup> Concentration of Cu<sup>2+</sup> and IA-1 was kept fix at 20 μM (pH 6.0).

<sup>b</sup> Conc. of all interfering species were keep constant at 10 mM.

<sup>c</sup> ΔF is the difference of fluorescence intensities before and after exposure to interfering species.

<sup>d</sup> MeOH/H<sub>2</sub>O (2/8, v/v) was used as a solvent system in all measurements.



**Fig. 8.** Determination of selectivity of IA-1 towards Cu<sup>2+</sup> (20 μM) in the presence of various anionic species (5 equiv.), such as AcO<sup>-</sup>, Br<sup>-</sup>, Cl<sup>-</sup>, F<sup>-</sup>, I<sup>-</sup>, NO<sub>3</sub><sup>-</sup>, SCN<sup>-</sup>, SO<sub>4</sub><sup>2-</sup> and S<sup>2-</sup> in MeOH/H<sub>2</sub>O (2/8, v/v).

produced by cupric ion. This observation was in consistency with some of the previous reports, where fluorescent effect produced by Cu<sup>2+</sup> in solution phase, was removed by sulphide ions [68–72].

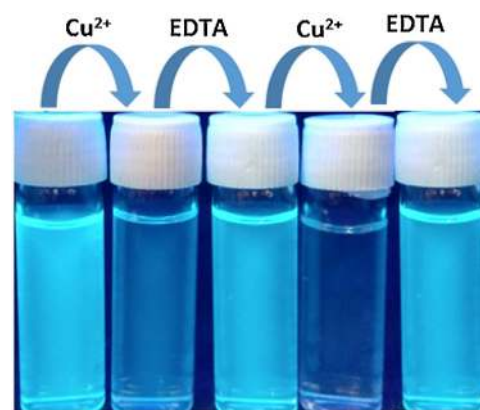
### 3.4. Reversibility studies

For several practical reasons, reversible nature of bonding between designed probe and ligand is important because it ensure the recyclability and reusability of the probe. When 1.5 equivomolar amount of EDTA, a sequestering agent (at neutral pH), was added to a quenched solution of IAs-Cu<sup>2+</sup>, re-emergence of fluorescence was observed. From this solution Probe IAs can be a recovered again (90% recovery) and can be used for cupric ions sensing without losing much efficiency. These experiments can be repeated 3–4 times while retaining the same level of efficiency (Figs. 9 and 10). Slight excess of EDTA probably displaced Cu<sup>2+</sup> from its interaction sites with the regeneration of fluorescence. Similar reversibility experiments can be performed using S<sup>2-</sup> in place of EDTA.

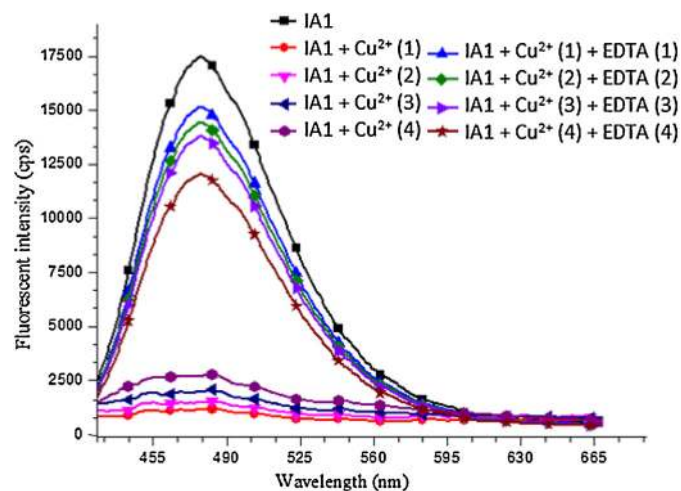
### 3.5. NMR titration and complementary studies

In order to locate the possible binding site, <sup>1</sup>H NMR titrations and complementary experiments were carried out. Furan-2-yl oxygen (from aldehyde) and aminoalkyl nitrogen (from isocyanide) atoms of both the synthesized imidazoazines (IA-1 and IA-2) seemed critical for this binding event, because compounds (IA-3 to IA-6) lacking these atoms didn't display any interaction with Cu<sup>2+</sup> (Table 2).

These observations were further supported by <sup>1</sup>H NMR titrations (Fig. 11 and SS8<sup>#</sup>). Since Cu<sup>2+</sup> is paramagnetic in nature, it would surely affect the electronic environment and peak



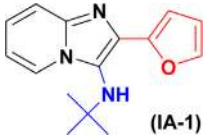

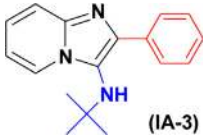
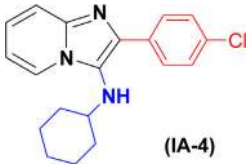
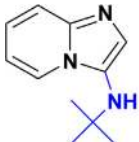
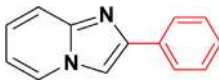
**Fig. 9.** Reversible nature of binding between IA-1 and Cu<sup>2+</sup>. Sequestering agent such as EDTA can be used to remove Cu<sup>2+</sup> from its binding site and free probe can be reused for sensing purpose.

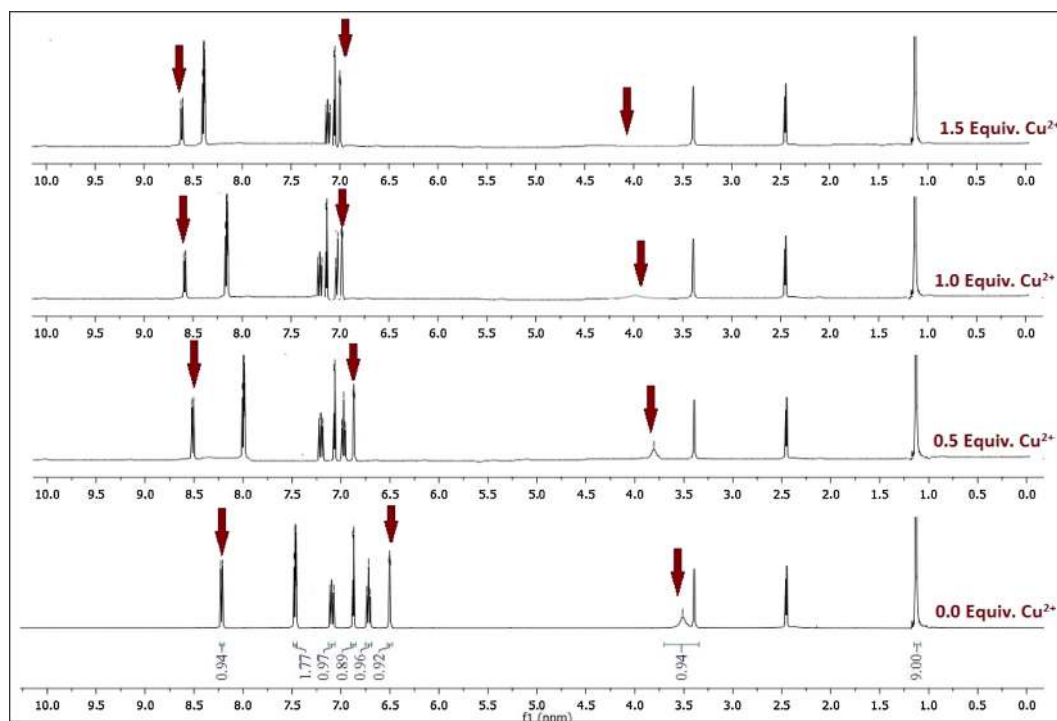


**Fig. 10.** Reversibility experiment of IA-1 [20 μM in MeOH/H<sub>2</sub>O (2/8, v/v)] with EDTA and Cu<sup>2+</sup> (1.5 equivalents amount of Cu<sup>2+</sup> and EDTA was used).

position of the coordinated protons. Proton NMR spectra of both the compounds were recorded in the absence and presence of Cu<sup>2+</sup> in DMSO-*d*<sub>6</sub>. While aliphatic protons remained unchanged in their peak positions, aromatic protons in the region 6–8.5 ppm displayed a slight downfield shift. The most noticeable change was observed in NH proton (at 3.49) of aminoalkyl substituents. These protons displayed a gradual broadening with a significant downfield shift in the area of 3.9–4.5 ppm and at about 1.5 equivalent concentration of Cu<sup>2+</sup>; NH proton completely merged with the base line and disappeared (Fig. 11 and SS8<sup>#</sup>). These observations clearly marked the role of NH proton in Cu<sup>2+</sup> coordination and in satisfying secondary valency (Fig. 12). Less basicity of the imidazole ring nitrogens and possible construction of six membered ring with furanyl oxygen

**Table 2**  
Response of different imidazoazines (**IA-1** to **IA-6**) toward MeOH/H<sub>2</sub>O (2/8, v/v) solution of Cu<sup>2+</sup>.

Compound/Code	Response to Cu <sup>2+</sup>	Compound/Code	Response to Cu <sup>2+</sup>
 ( <b>IA-1</b> )	Turn off fluorescence Turn off colorimetric	 ( <b>IA-2</b> )	Turn off fluorescence Turn off colorimetric
 ( <b>IA-3</b> )	No response (No furan-2-yl oxygen)	 ( <b>IA-4</b> )	No response (No furan-2-yl oxygen)
 ( <b>IA-5</b> ), [90]	No response (No furan-2-yl oxygen)	 ( <b>IA-6</b> ), [91]	No response (No aminoalkyl nitrogen)



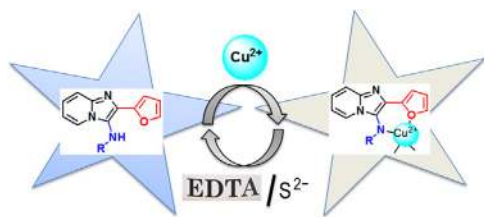
**Fig. 11.** <sup>1</sup>H NMR spectra of **IA-1** in the presence of different conc. of Cu<sup>2+</sup>. Disappearance of NH peak at 3.54 ppm and slight downfield shift of aromatic protons are obvious from figure (DMSO-*d*<sub>6</sub> was used as NMR solvent and TMS as internal standard).

and alkylamino nitrogen, seem to be critical factor for Cu<sup>2+</sup> binding.

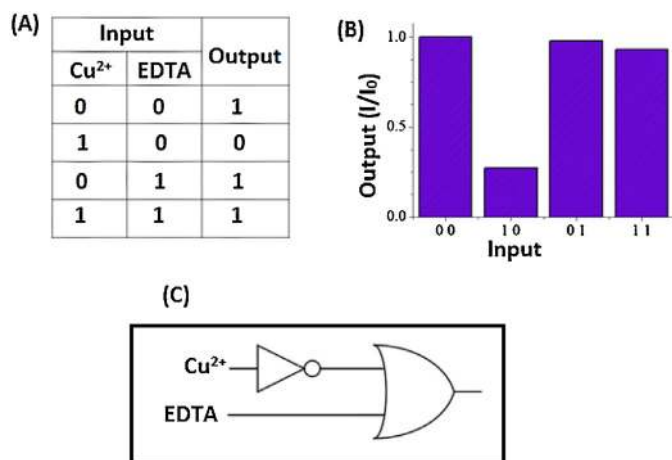
### 3.6. Logic gate representation

Cyclic response of **IAs** towards Cu<sup>2+</sup>/EDTA and Cu<sup>2+</sup>/S<sup>2-</sup> is similar to the behaviour of molecular switch and hence can be represented by suitable logic gate and truth table (Fig. 13). Two

inputs are Cu<sup>2+</sup> and EDTA or S<sup>2-</sup> and their presence and absence can be marked as “1” and “0”. At output *on* and *off* states of fluorescence can be labelled as “1” and “0” respectively. Presence of Cu<sup>2+</sup> alone is responsible for quenching of fluorescence, while addition of EDTA/S<sup>2-</sup> in this quenched state again regenerate fluorescence. This behaviour can be epitomised by “OR” gate with a “NOT” at input-1 (Fig. 13).



**Fig. 12.** Binding interaction between **IAs** and  $\text{Cu}^{2+}$ ; Furan-2-yl oxygen (from aldehyde) and aminoalkyl nitrogen (from isocyanide) atom are involve in binding interaction with cupric ion.



**Fig. 13.** Truth table (A), Output response (B) and respective logic gate diagram (C) for **IA-1**/ $\text{Cu}^{2+}$ /EDTA reversibility experiment (**IA-1**/ $\text{Cu}^{2+}$ / $\text{S}^{2-}$  recyclability can also be symbolized by same logic gate expression).

**Table 3**

Comparison of reported **IAs** with some of the recently developed sensors for  $\text{Cu}^{2+}$ .

S.No.	Sensor/probe	Interaction	Association constant ( $K_a$ ) $\text{M}^{-1}$	LOD in M	pH range
1	IAs (This work)	Turn off (fluor and color) Reversible	$4.51 \times 10^4$ $1.99 \times 10^4$	$1.84 \times 10^{-7}$ $3.14 \times 10^{-7}$	5–11
2 [22]		Conc. dependent Turn off (fluor)	$6.82 \times 10^4$	$4.0 \times 10^{-7}$	–
3 [25]		Turn off (fluor) Irreversible	–	$0.5 \times 10^{-7}$	5–7
4 [26]	<b>PQs</b>	Turn on (fluor) irreversible	–	$1.5 \times 10^{-6}$	7–9
5 [34]		Turn off (fluor)	–	$1.27 \times 10^{-4}$	–
6 [37]		Turn off (fluor)	$5.0 \times 10^4$	$1.5 \times 10^{-6}$	4–11
7 [39]		Turn on (fluor)	$1.1 \times 10^{10}$	$0.15 \times 10^{-6}$	–

Fluor = fluorescence, color = colorimetric.

### 3.7. Comparative studies

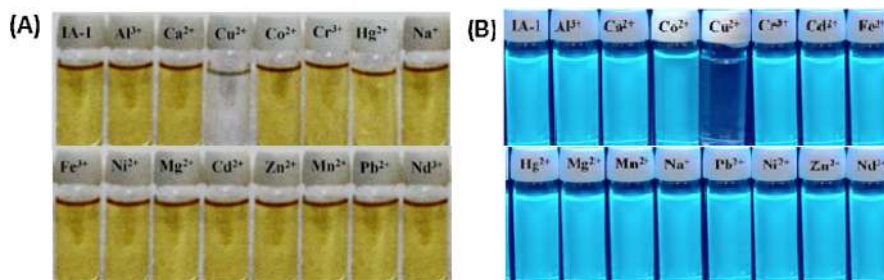
Proposed sensors (**IA-1** and **IA-2**) have very high association constants ( $10^4 \text{ M}^{-1}$ ) and low LOD ( $10^{-7} \text{ M}$ ). These results are comparable to or better than most of the recently reported systems (Table 3). Instantaneous response, higher selectivity, recyclability, reusability and wide operation pH range make these furan-2-yl containing Gröbke products a perfect choice for several important sensing applications.

Although similar in performance and in substitution pattern, there is a basic difference between annulated furanones and imidazoazines in binding site (Table SS1<sup>#</sup>). In annulated furanones, interacting oxygen atom is a part of main scaffold itself [61,62], while in bicyclic imidazoazine this oxygen atom comes from attached furan-2-yl substituent. As a result, while almost all amino substituted furanones display detection abilities to  $\text{Cu}^{2+}$  irrespective to the nature of attached aldehydic group, only furan-2-yl (furan-2-carbaldehyde or aldehydes with oxygen atom at this position) containing imidazoazines can be used as a probe for this purpose.

### 3.8. Applications of the proposed sensors

#### 3.8.1. Naked eye detection of copper

As mention earlier, both the probes can be used for naked eye detection of copper in solution phase. Addition of trace amount of  $\text{Cu}^{2+}$  in yellowish solution (in MeOH) of **IA-1** or **IA-2** immediately made it colourless with the quenching of fluorescence (Fig. 14 and SS9<sup>#</sup>). **IAs** retained this distinct behaviour in other organic solvents such as ACN, DMSO and mixed aqueous-organic phases such as ACN/ $\text{H}_2\text{O}$  (8/2 to 2/8, v/v), MeOH/ $\text{H}_2\text{O}$  (8/2 to 2/8, v/v).



**Fig. 14.** Colorimetric (A) and fluorescence (B) response of **IA-1** in the presence of different metal ion in MeOH/H<sub>2</sub>O (2/8, v/v) solution.

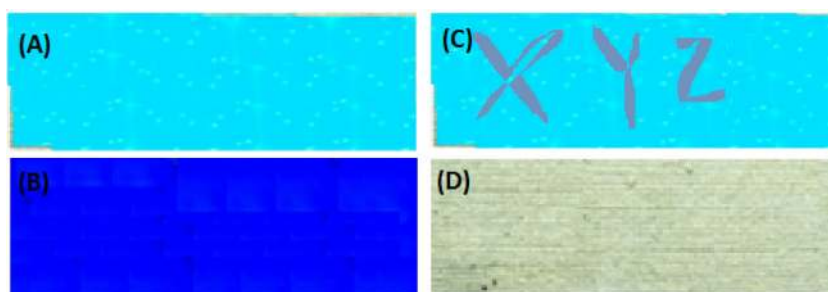
**Table 4**

Real time applications of sensor **IA-1** in determination of Cu<sup>2+</sup> conc.

Added (A) μg/lit	Found (B) μg/lit	% recovery = B × 100/A	Added (A) μg/lit	Found (B) μg/lit	% recovery = B × 100/A
30 (distilled water)	29.7 ± 0.6	99	50 (canal water)	51.9 ± 0.6	103.8
30 (canal water)	31.6 ± 0.9	105.33	100 (distilled water)	99.4 ± 0.6	99.4
50 (tap water)	50.8 ± 0.7	101.6	100 (canal water)	101.8 ± 0.4	101.8



**Fig. 15.** Response of membrane sensors toward different metal ions. Distinct behaviour towards Cu<sup>2+</sup> is apparent from the figure.



**Fig. 16.** Photoprinting application of synthesized probe (A) Filter paper displayed fluorescence after spraying with methanolic solution of **IA-1** under UV light. (B) Disappearance of fluorescence after applying Cu<sup>2+</sup> solution on surface under UV light (dip-strip experiment). (C) Printing of words "XYZ" on fluorescent filter paper using Cu<sup>2+</sup> inks under UV light. (D) Same filter paper under visible light; no change was observed under day light.

### 3.8.2. Real sample application

Proposed sensor can be successfully used for trace level detection of Cu<sup>2+</sup> in organic and organo-aqueous medium under laboratory condition. Compound **IA-1** was dissolved in acetonitrile/water (2/8, v/v), because of the poor solubility of imidazoazine in water alone. These samples were spiked with different known concentration of copper and standard addition method was used to cancel out any matrix effect. Added and found Cu<sup>2+</sup> concentration

with recovery percentage (in different water sources) is given in Table 4.

### 3.8.3. Membrane sensing applications [100]

Polymeric membrane of thickness 0.5–1.0 mm was prepared by mixing PVC, suitable plasticizer, additive and **IA**s (detail of preparation method is given in the Experimental section). Under UV light, these membranes display an intense fluorescence, which can



be removed by spraying/applying it with  $\text{Cu}^{2+}$  solution (other metals shows no response) and hence can be used for detection of  $\text{Cu}^{2+}$  (Fig. 15). These membrane sensors retain their efficiency for about one month. Because of their easy preparation, long storage time, light weight and fast response time, these membranes have some practical benefits over direct solution phase use of IAs.

#### 3.8.4. Photo-printing applications

Square strips of ordinary Whatman filter papers ( $3.5 \times 1.5 \text{ cm}^2$ ) were sprayed with a IAs solution containing small amount of PVP (IA-1 0.5% wt of PVP and 0.5 gm of PVP in MeOH). After air drying, these strips displayed an intense fluorescence under long wavelength UV torch.

Dilute methanolic solution of  $\text{Cu}^{2+}$  can be used as an ink and some pattern, design, word or number can be drawn on to this fluorescent surface. These pattern or words can be visualized under UV light again because of the different intensity of fluorescence in these area than that of the remaining surface (Fig. 16). These patterns/designs didn't disappear even after 15 days. Because of high dilution, these filter papers didn't display any patterns/designs in day light and can be used for as invisible/hidden ink.

## 4. Conclusions

For the first time, two furan-2-yl substituted Gröbke multicomponent products IA-1 and IA-2 have been identified as an effective molecular sensor for  $\text{Cu}^{2+}$  ion in variety of solvents. Both the imidazoazine products displayed high association constants ( $10^{+4} \text{ M}^{-1}$ ), acceptable detection limits ( $10^{-7} \text{ M}$ ), high selectivity, reversibility, wide pH operational range and fast response in fluorescence based experiments. Designed systems have multiple applications in the domain of trace level quantification, sample monitoring, photo-printing and membrane sensing.

## Declaration of interest

The authors have no competing interests to declare.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.snb.2016.08.184>.

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