

RSC Advances



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



Journal Name

ARTICLE

Rational designing of first furoquinolinol based molecular systems for easy detection of Cu²⁺ with potential applications in the area of membrane sensing†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Manoj Kumar,^{a,†} Lokesh Kumar Kumawat,^{a,†} Vinod Kumar Gupta^{a,b} and Anuj Sharma^{a,*}

Two molecular probes based on furoquinolinol (FQ) framework have been rationally designed for the rapid detection and trace level quantification of Cu²⁺ in organic and semi-aqueous mediums. Synthesized FQs were extensively examined for their Cu²⁺ sensing abilities by UV-Vis/fluorescence experiments, NMR titrations and DFT based calculations. Higher binding constant [$2.11 \times 10^4 \text{ M}^{-1}$ (FQ1) and $1.87 \times 10^4 \text{ M}^{-1}$ (FQ2)], Low detection limit [$1.52 \times 10^{-7} \text{ M}$ (FQ1) and $2.13 \times 10^{-7} \text{ M}$ (FQ2)], high selectivity, fast response, wide operational pH range, repeated usability are some of the salient features of the reported sensors. Furthermore, these compounds (FQs) retained their metal detection abilities in thin PVC membranes.

Introduction

Cu²⁺ is an ion of ubiquitous presence in the living system with prominent role in oxidative metabolism and homeostatic regulation.^{1a} The normal functioning of certain enzyme classes such as superoxidedismutase (SOD1), cytochrome-*c*-oxidase (Cyt-O), tyrosinase and ceruloplasmin rely on Cu⁺/Cu²⁺ redox couple.^{1a-1e} While under normal state, this redox chemistry is inevitable for life, under “overexpressed” or “misregulated” state, it becomes equally life threatening. It is believed that excess amount of free Cu²⁺ triggers the production of ROS (reactive oxygen species) by “Fenton” type reaction, which in turn, is responsible for several pathological states including neurodegenerative diseases and disorders such as Wilson diseases, familial amyotrophic lateral sclerosis, Alzheimer’s disease (AD), Parkinson disease (PD) etc.^{1a-1e} Excess free Cu²⁺ concentration is also linked with the reduction of micro-algal biomass and also causes a drastic shift in diatoms/cynobacteria population in aquatic ecosystems.^{1f}

This population change, generally implicated in various forms such as loss of self cleaning, self healing and reprocessing capabilities of water bodies such as ponds and rivers.^{1f-1g} Consequently, detection and trace level quantification of Cu²⁺ in biological and ecological samples is a research goal of significant interest.

Although instrumental methods such as atomic absorption spectroscopy (AAS), inductively coupled plasma mass spectroscopy (ICP-MS) and voltammetry have been traditionally employed for copper detection, but higher operational cost, requirement of expert handling, destructive nature and low portability have seriously compromised their applicability.² Design of small molecular systems, sensitive to metal ions and their potential utility as “probing agent” can be an effective solution. In fact, this is an area of growing interest with hundreds of research reports every year. Fluorescent based sensors are particularly important in this regard owing to their advantageous features such as higher sensitivity, portability, quick response and non destructive nature.³

Till date, several molecular systems have been tested for their Cu²⁺ sensing abilities with varying degree of success.⁴ Most of these chemical probes are the structural modifications of very few typical scaffold classes such as Coumarin,^{4a-4d} bispine-dyeconjugate,^{4e} rhodanine-aldazine,^{4f-4g} diamines,^{4h} thiadiazole,⁴ⁱ Schiff bases^{4j-4k} etc with common limitations such as slow response, off target selectivity, irreversible nature, operation range at non physiological pH etc. Considering these limitations, design and discovery of molecular probes based on novel structural framework, can be a useful exercise.⁴

^a Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee-247667, India

^b Department of Applied Chemistry, University of Johannesburg, Johannesburg, South-Africa

*Corresponding author
Phone: +9113 3228 4751
Fax: +9113 3227 3560
e-mail: anujsharma.mcl@gmail.com, anujfcy@iitr.ac.in

[†] Contributed equally as co-first authors.

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Our group has a longstanding interest in the discovery and design of novel molecular systems with metal sensing abilities.⁵ In the present report, we have introduced two new annulated furanones based chemosensors 3-(4-bromophenyl)-2-((2-morpholinoethyl)amino)furo[3,2-c]quinolin-4-ol (FQ1), 3-(4-chlorophenyl)-2-(pentylamino)furo[3,2-c]quinolin-4-ol (FQ2) for Cu²⁺ detection alongwith their potential applicability in the area of “membrane sensor” and “environment sample analysis”. To best of our knowledge this is the first report of its kind, where metal sensing abilities of amino substituted furoquinolinols (FQs) have been studied in depth.

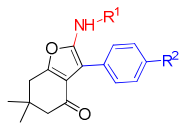
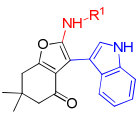
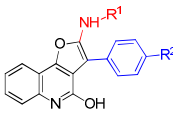
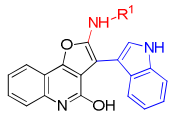
Results and discussion

Our group has recently investigated the Al³⁺ sensing abilities of amino substituted 4-keto-4,5,6,7-tetrahydrobenzofurans.^{5e} During this work, we found that out of 14 compounds studied; only two compounds responded to Al³⁺. Structurally both the compounds were similar and contained “indole moiety” as a substituent. At that point, we got interested to know the contribution of the core scaffold in their ability to metal binding/sensing. It was based upon our belief that had substituent pattern been only responsible for binding, then a change at framework level would not affect the fluorescent response to a large extent.

In order to test our hypothesis, we replaced “dihydrobenzofuranone” by “furoquinolones” not only changed the fluorescent response, but also changed the detection abilities of the compounds. Nearly all the synthesized compounds now sensed Cu²⁺ in place of expected Al³⁺ while indoyl substituted furoquinolones (indoyl-FQs) displayed a very slow turn on fluorescence response towards Al³⁺ alongside turn off fluorescence toward Cu²⁺ (Table 1).

Some important inferences that can be drawn from these observations are (1) Both sensing phenomenon (Al³⁺ and Cu²⁺ sensing) might be operated through either by different kind of mechanisms or different portion of compounds might be involved in these interaction (2) For Al³⁺ sensing “indoyl” substituent was critical for the turn on fluorescence response (series 2 and 4, Table 1), while for Cu²⁺, probably furoquinolone framework itself seemed to be important (series 3 and 4). (3) As expected series 4 (indoyl substituent with furoquinoline ring) sensed both the metals, but because of very long response time of 24-48 hours, it would not be practical to use this series as chemical probe. On the other hand, since compounds of series 3 displayed fast response within 2-3 minutes, hence two representative members of this series FQ1 and FQ2 (FQs) were studied for their potential as chemical probe for Cu²⁺ (Figure 1).

Table 1 Comparison of metal sensing abilities of different amino substituted annulated furanones.

Series 1 ^{5e}	Series 2 ^{5e}	Series 3 (this work)	Series 4
			
Cu ²⁺ (no response)	Cu ²⁺ (No response)	Cu ²⁺ (turn off, fluorescence)	Cu ²⁺ (turn off, fluorescence)
Al ³⁺ (no response)	Al ³⁺ (turn on, fluorescence)	Al ³⁺ (no response)	Al ³⁺ (turn on, fluorescence)
no response	fast response (2-3 min)	fast response (2-3 min)	slow response (24-48 h)
no sensing ability	sensor for Al ³⁺	sensor for Cu ²⁺	Sense both Cu ²⁺ and Al ³⁺ But not practical as a sensor

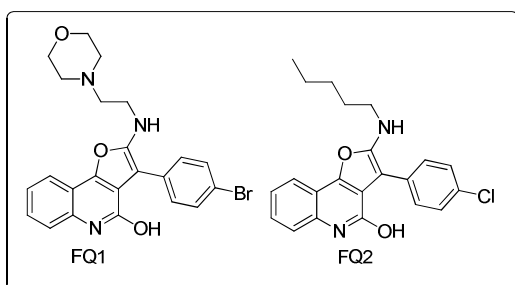
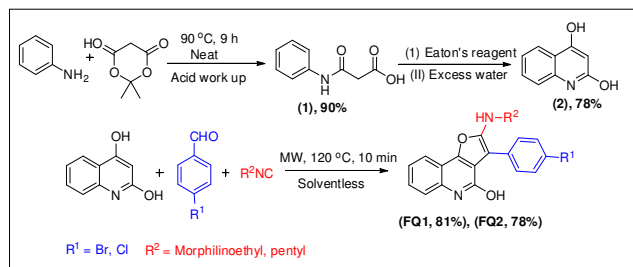


Figure 1 Chemical structure of investigated furoquinolinols (FQs).

Synthesis of ionophore FQs^{6a-6c}

Both FQs were synthesized by a three step procedure (Scheme 1). At the beginning, fusion of aniline and Meldrum acid (Pechmann reaction) at 90 °C for 9 hours afforded half acid N-phenyl-malonic acid (1) after acid work-up. Acid (1) was then cyclized to quinoline-2,4-diol in the presence of Eaton's reagent (P₂O₅ in PPA). Desired furoquinolinols were then synthesized by a microwave assisted multicomponent reaction of C-H acid (2) with respective aldehydes and isocyanide. Mechanistically, this three component condensation relied on

[4+1] cycloaddition between an *in situ* generated enone and isonitrile.



Scheme 1 Three steps synthesis of furoquinolinols (FQs).

Cu^{2+} sensing abilities of sensors FQs

Extensive UV-vis and fluorescence studies were carried out to get insight into Cu^{2+} sensing phenomenon. While representative absorption spectra of synthesized FQs displayed three intense bands centred near 275, 320 and 370 nm, emission spectra had only one broad band at 465 nm in DMSO:MeOH (v/v, 1:9). Addition of 10 equivalents of Li^+ , K^+ , Na^+ , Ca^{2+} , Mg^{2+} , Mn^{2+} , Co^{2+} , Fe^{2+} , Ni^{2+} , Zn^{2+} , Pb^{2+} , In^{3+} , Al^{3+} , Cr^{3+} , Gd^{3+} and Fe^{3+} had no apparent effect on UV absorption/fluorescent spectra. On the other hand, addition of just one equivalent of Cu^{2+} to the solution of FQs (20 μM) totally quenched the emission with slight colour change from yellow to colourless (response time 2-3 min.). These effects were also apparent in corresponding UV-Vis/fluorescence spectra of FQs in the presence of Cu^{2+} (Figure 2-4 and SS7[†]-SS11[†]). FQs retained this distinct behaviour in other organic solvents such as MeOH, ACN, CHCl_3 , DMF and mixed aqueous-organic mixtures such as ACN: Water (v/v, 9:1 to 1:9), MeOH: Water (v/v, 9:1 to 1:9).



Figure 2 Fluorescence responses of FQ1 in the presence of different metal ion in DMSO: MeOH (v/v, 1:9) solution.

Since selectivity is an important performance indicator of a chemical sensor, hence interference effects of other competitive ions on Cu^{2+} -FQs interaction profile were studied. Gratifyingly, presence of other cations didn't produce any noticeable change either in emission spectra or sensing properties of both FQs, indicating the distinct behaviour of FQs toward Cu^{2+} (Figure 5 and SS14[†], SS15[†]).

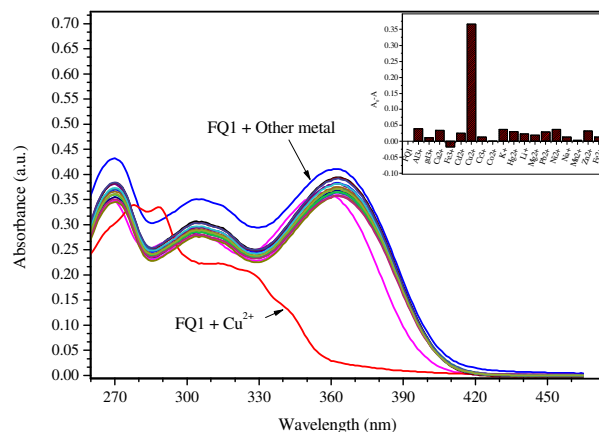


Figure 3 UV-vis Spectra of FQ1 [20 μM in DMSO:MeOH (v/v, 1:9)] in the presence of 10 equiv. of different ions. The distinct behaviour of Cu^{2+} (equimolar) is apparent from figure.

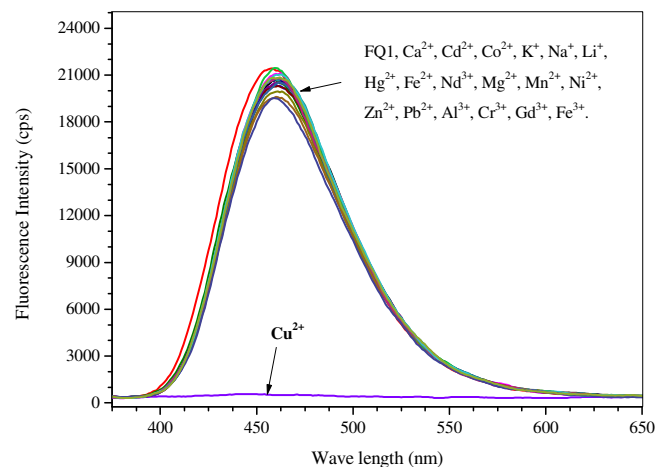


Figure 4 Fluorescence response of FQ1 [20 μM in DMSO:MeOH (v/v, 1:9)] toward different metal ions (10 equivalent). In the presence of equimolar amount of Cu^{2+} peak at 465 nm completely disappeared.

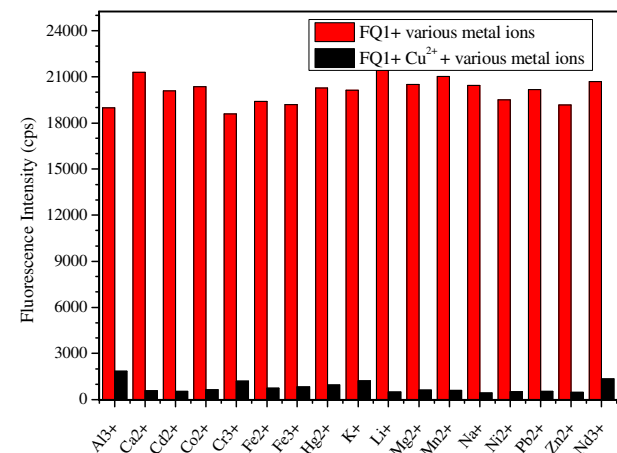


Figure 5 Examination of selectivity of FQ1 [20 μM in DMSO:MeOH (v/v, 1:9)] towards Cu^{2+} in the presence of interfering ions ($\lambda_{\text{ems}} = 465 \text{ nm}$).

When excited at 370 nm both the receptors exhibited high fluorescence quantum yield, $\Phi = 0.3915$ (FQ1), 0.3856 (FQ2) (standard reference: Coumarin-1 in ethyl acetate; $\Phi = 0.99$, $\lambda_{\text{ex}} = 355$ nm). On the other hand, receptor– Cu^{2+} complex exhibited very low fluorescence quantum yield, $\Phi = 0.0253$ (FQ1+ Cu^{2+}), 0.0597 (FQ2+ Cu^{2+}). This data ensured significant quenching of fluorescence during the Cu^{2+} sensing process.

To understand complexometric and stoichiometric aspects of binding, fluorescent titration were carried out (Figure 6 and SS12[†], SS13[†]). Band at 465 nm displayed a gradual decrease in intensity with the incremental addition of Cu^{2+} . Detection limits for Cu^{2+} was calculated 1.52×10^{-7} M (FQ1) and 2.13×10^{-7} M (FQ2) by universal method (LOD = $3\sigma/\text{slope}$) respectively. These results were comparable or better than some of the already known sensors.^{4,8} In Job's plot intensity minima were noticed, when molar fraction of Cu^{2+} approached a value of 0.5, indicating 1:1 stoichiometric relationship (Figure SS17[†] and SS18[†]) and this fact was further confirmed by ESI-HRMS (Figure SS19[†] and SS20[†]). Binding constants for FQ1 and FQ2 were calculated 2.11×10^4 M⁻¹ and 1.87×10^4 M⁻¹ respectively by plotting measured $1/I - I_0$ (at 465 nm) against $1/\text{Cu}^{2+}$ concentrations.⁷ High correlation was observed between data with pearson's coefficients (r^2) of 0.992 and 0.993 respectively (Figure 6 and SS12[†], SS13[†]).

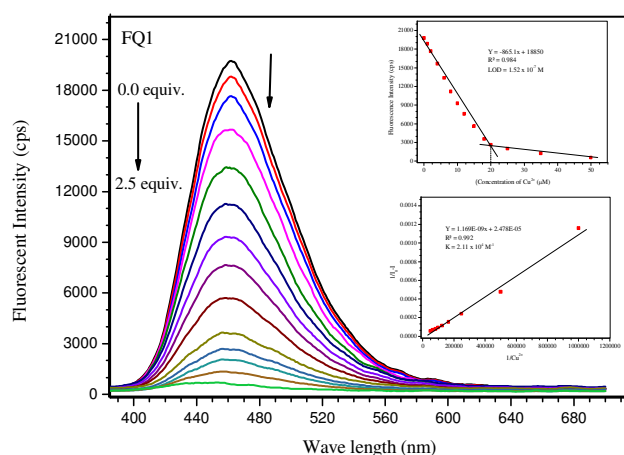


Figure 6 Fluorescent titration of FQ1 [20 μM in DMSO:MeOH (v/v, 1:9)] with Cu^{2+} (from 0.0 equivalent to 2.5 equivalents) at excitation wavelength 370 nm.

Furthermore, fluorescence response of FQs toward Cu^{2+} was found to be pH dependent. Optimum responses were obtained in the pH range of 5.5–10, pointing out that FQs could be utilised in a wide pH range (Figure 7).

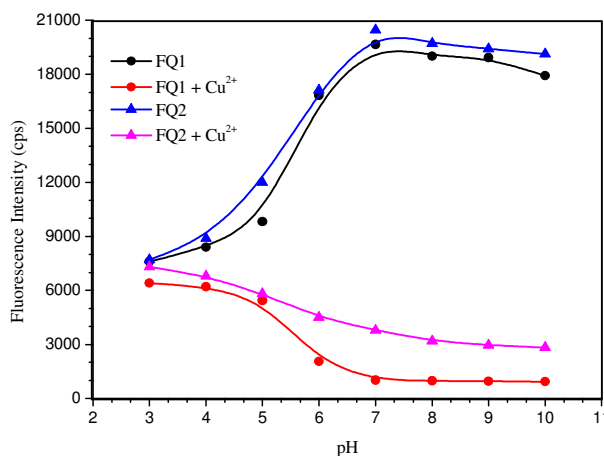


Figure 7 Dependence of fluorescence response of FQs– Cu^{2+} over pH of the medium. ($\lambda_{\text{ems}} = 465$ and 460 nm respectively for FQ1 and FQ2).

Reversibility study

Reversibility studies were performed to examine the recyclability/reusability of the reported sensors. Addition of 1.0 equiv. of Cu^{2+} to the equimolar solution of FQ1 caused the expected loss of fluorescence under UV light. It was then treated with aliquots from 1.0 mM solution of EDTA with the gradual appearance in fluorescence, indicating regeneration of free FQ1. To ensure the reusability of FQ1, this mixture was washed with brine solution two times followed by extraction with excess of ethyl acetate and dried over MgSO_4 . The fluorescent of recovered (90 % recovery) FQ1 was again quenched by Cu^{2+} and again reappeared by EDTA. The binding constants for both fresh and recovered FQ1 were found comparable, indicating the reversibility of interactions. Slight excess of EDTA displaced Cu^{2+} from its site of interactions with the regeneration of fluorescence. Similar results were obtained for other fluorophores FQ2. These results ensured the repeated applicability of the sensors for Cu^{2+} detection (Figure 8).

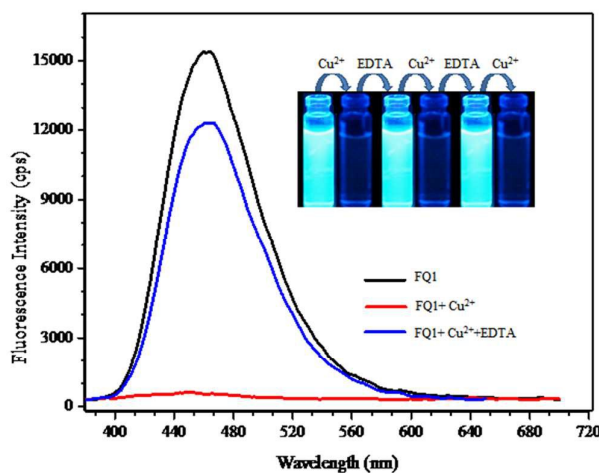


Figure 8 Reversibility and reusability test of FQ1 in the presence of EDTA.

Moreover this cyclic response of FQs towards Cu^{2+} / EDTA is similar to a molecular switch and can be best explained with the help of suitable truth table and logic gate. Two input signal were input-1 (Cu^{2+}) and input-2 (EDTA), presence and absence of an input was denoted by "1" and "0" respectively. The resultant fluorescence response could be used as an output (fluorescence on = 1, fluorescence off = 0) with the condition that presence of Cu^{2+} alone will quench the fluorescence. This behaviour can be epitomised by "OR" gate with a "NOT" at input-1 (Figure 9).

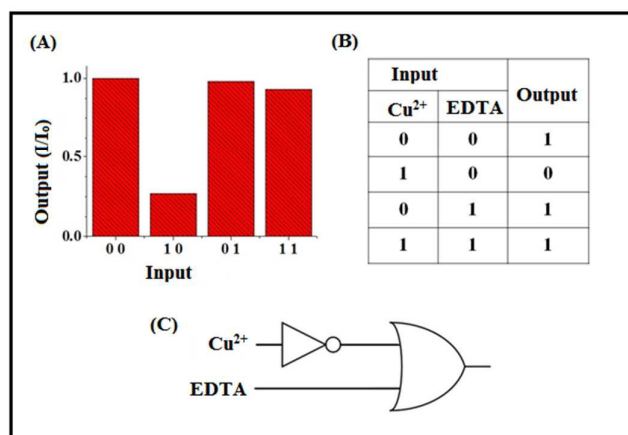


Figure 9 Output response (a) truth table (b) and respective logic gate diagram (c) for reversibility test.

^1H NMR titrations

Two probable metal binding sites "site A" (with furan oxygen), "site B" (with quinolinone carbonyl) are shown in figure 10. In order to get a deeper insight into binding a ^1H NMR titrations were performed.

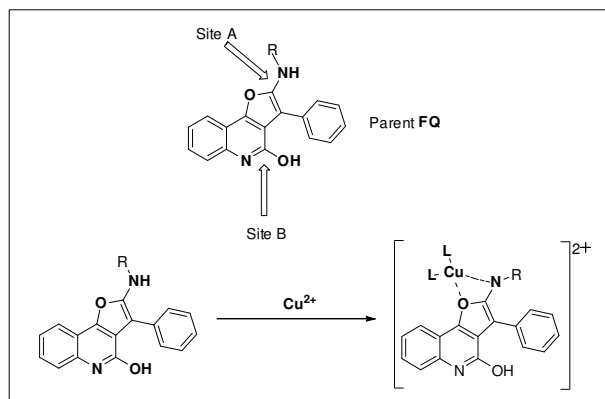


Figure 10 Two possible coordination sites A and B with result appeared from NMR titration.

Cu^{2+} is paramagnetic in nature and is known to have a significant effect over NMR signals of vicinal/coordinating

groups. NMR spectra were recorded in the presence (0.25 equivalent to 1.0 equivalent) and absence of copper in DMSO-d_6 (Figure 11 and SS22^{\dagger} , SS23^{\dagger}). Signal of NH proton (morpholinoethylamino group) at 6.32 ppm gradually diminished with some initial broadening. Finally this signal completely disappeared at equimolar level of Cu^{2+} , indicating the direct involvement of this peripheral nitrogen in coordination with metal ion. The proton signal of four proton of morpholinoethylamino group of FQ1 at 2.47 also displayed a slight downfield shift toward 2.50 ppm and ultimately merged with DMSO protons. As compare to these protons, aromatic protons ($\delta_{\text{H}} = 7-8$) and quinolinone NH proton at 11.62 ppm largely remained unchanged during NMR titration. This titration unambiguously proved that site A was directly involved in coordinating with Cu^{2+} and in satisfying its secondary valency.

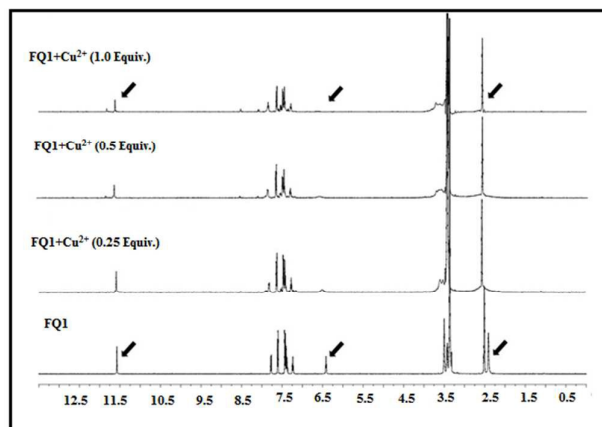


Figure 11 Disappearance of NH peak at 6.32 ppm and shift of aliphatic proton at 2.47 ppm during ^1H NMR titration (DMSO-d_6 was used as NMR solvent and TMS as internal standard).

Theoretical investigation

We believe that quenching response of FQs in the presence of Cu^{2+} can be best explained by some electron transfer process (ET) that is also in agreement with some of the previous reports. To confirm this possibility, DFT calculations based on B3LYP/6-31G(d,p) methods were performed (Figure 12 and SS25^{\dagger}).

The relevant molecular orbitals (HOMOs and LUMOs) of free FQs and FQ-Cu^{2+} were explored for this purpose. From figure 12, it is obvious that while frontier orbitals of FQs were localised over rigid and conjugated furoquinolinol moiety which acts as actual fluorophore. After coordination with Cu^{2+} , charges were redistributed and most of the electron density was transferred to the receptor site "A", leaving the rigid fluorophore electron deficient. This flow of charge/ electrons from fluorophore to receptor-quencher chelating site is

sometimes termed as CHEQ (Chelation Enhanced Fluorophore Quenching) and seemed to be operative in present case.

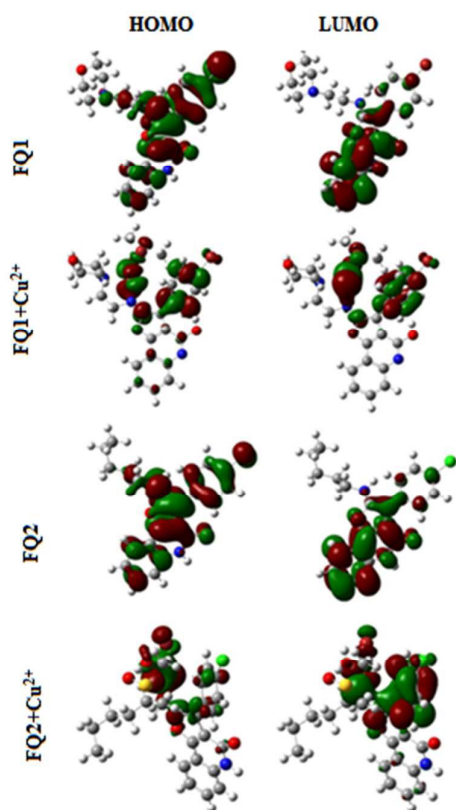


Figure 12 Frontier orbitals and charge distribution of FQs and their coordinated product with Cu^{2+} .

Comparative study

With good binding constant of 10^4 and high LOD of 10^{-7} order of magnitude FQs are well comparable or better than most of the recently reported Cu^{2+} sensors. High selectivity, instantaneous response, wide operation pH range and repeated usability make FQs a perfect sensor for several important purposes. All these facts are evident from table SS1[†] (see also table SS2[†] for comparison of sensing properties of two sensors).

Applications of the proposed sensors

Real sample analysis

Practical utility of the synthesized sensors were demonstrated by determining Cu^{2+} concentration of samples collected from different localities of Roorkee city (India), Industrial waste water, canal and tap water were used for this purpose (Table 2). Spike solutions were prepared by adding different known conc. of Cu^{2+} . Solvent used for dilution was a mixture of MeOH and aqueous buffer Na_2CO_3 and NaHCO_3 (v/v, 1:9, pH = 7.4). Fluorescent intensity at the band near 465 (FQ1) were recorded and calibration curve (1/ fluorescence intensity vs.

Concentration of added Cu^{2+}) thus obtained was used for the calculation of the concentration of unknown samples. In all the cases, triplicate reading were recorded and average values were taken for used (Table 2). Results were in good agreement with that obtained by AAS (atomic absorption spectroscopy, result A) with relative error less than $\pm 3.0\%$, indicating the utility of proposed sensors in environmental sample monitoring.

Table 2 Real time analysis of water samples for Cu^{2+} concentrations using reported sensor FQ1 [concentration (A) obtained from AAS, concentration (B) is determined from Fluorescence measurement].

Sample	Concentration (A)	Concentration (B)	Relative error in % (B-A/A) × 100
Tap water	5.2×10^{-6} M	5.3×10^{-6} M	+1.92
Canal water	10.46×10^{-6} M	10.24×10^{-6} M	-2.10
Industrial waste water	32.08×10^{-6} M	32.48×10^{-6} M	+1.24

Membrane sensing

Very thin fluorescent membranes of 0.5 mm thickness were prepared using high polymeric weight PVC, plasticizer, additive and FQs (Detail of PVC membrane preparation is given in the experimental section). A solution of Cu^{2+} ion (in DMSO or MeOH) was applied on to the film. After drying, fluorescence completely disappeared, indicating the utility of these films in Cu^{2+} detection. It is important that these membranes can be stored for 15-20 days without any significant loss of their sensitivity. These thin films, because of their low cost, easy preparation, long storage life of 15-20 days, can be used as handy sensors for real time applications (Figure 13).

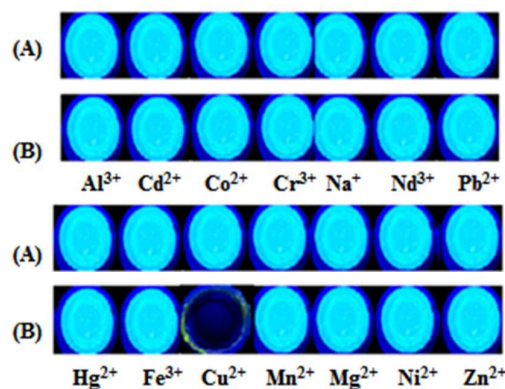


Figure 13 Response of PVC membrane based sensor (FQ1) toward different metal ion; Row (A) shows the initial fluorescence state; Row (B) developed after immersion of film into different metal ion solution. Distinct behaviour towards Cu^{2+} is apparent from the figure.

Experimental Section

All solvent were distilled prior to use and all chemicals were purchased from sigma-Aldrich[®] and used without further purification. All NMR spectra were recorded on a Jeol Resonance ECX-400II spectrometer. Chemical shifts are reported in parts per million and are referenced to TMS. Spectra were processed using MestReNova-6 software. Mass spectrometry (HRMS) was performed using a Bruker daltronics microTOF-QII[®] spectrometer using ESI ionization, with less than 5 ppm error for all HRMS analyses. IR spectra were recorded on a PerkinElmer FT-IR spectrometer in the range 4000–400 cm⁻¹. The UV–Vis absorption spectra were recorded on a Shimadzu UV-2450 spectrophotometer and the Fluorescent spectra on a ShimadzuRF-5301PC spectrofluorophotometer Analytical Thin layer chromatography (TLC) was performed on a silica gel plate (Merck[®] 60F₂₅₄). For statistical analysis and graphical representation of data Origin 6.0 software was used.

Microwave Irradiation Experiment

All microwave experiments were carried out in a dedicated Anton Paar Monowave 300 reactor[®], operating at a frequency of 2.455 GHz with continuous irradiation power of 0 to 300 W. The reactions were performed in a G-4 Borosilicate glass vial sealed with Teflon septum and placed in a microwave cavity. Initially, microwave of required power was used and temperature was being ramped from room temperature to a desired temperature. Once this temperature was attained, the process vial was held at this temperature for required time. The reactions were continuously stirred. Temperature was measured by an IR sensor. After the experiments a cooling jet cooled the reaction vessel to ambient temperature.

Synthetic procedures

Synthesis of *N*-Phenyl-malonamic acid (1)

Aniline (1.86 gm, 20 mmol) and meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione, 2.88 gm, 20 mmol) was fused at 90 °C for about 12h. After cooling, this reaction mixture was dissolved in ethyl acetate and extracted with bicarbonate. This aqueous layer was then acidified to pH = 1-2 with Conc. HCl and again washed with excess of DCM. The combined DCM layers were dried over anhydrous MgSO₄. Removal of DCM layer under vacuum provided analytically pure product (1) in 90% yield.

Synthesis of Hydroxy-2-quinolone (2)

A mixture of *N*-Phenyl-malonamic acid (1) (15 mmol, 2.67 gm) was dissolved in 20 ml. of Eaton's reagent (P₂O₅ in PPA) under argon atmosphere. This mixture was heated for 70 °C for about 6h. Excess ice cold water was then added into the reaction mixture with continuous stirring. Solid participate was

deposited, which was filtered by suction and air dried to yield pure crystalline product (2) in 78% yield.

Synthesis of 2-(alkylamino)-3-arylfuro[3,2-*c*]quinolin-4-ol (FQs)

Hydroxy-2-quinolone (2) (1.0 mmol), respective aryl-aldehyde (1.0 mmol) and isonitrile (1.2 mmol) was mixed well in a G10 process vial capped with Teflon septum. After a pre-stirring of 1 or 2 minutes, the vial was subjected to microwave irradiation with the initial ramp time of 1 minute at 70 C. The temperature was then raised to 120 °C with the holding time of 5 minutes. After completion of the reaction, the ethanol:water (1:4) or isopropanol:water (1:4) was added into it and the precipitated solids (FQs) were filtered.

Analytical data

3-(4-bromophenyl)-2-((2-morpholinoethyl)amino)furo[3,2-*c*]quinolin-4-ol (FQ1).

Yellow solid (81%), mp (decomp.) = 258-259°C, IR (KBr, cm⁻¹): ν_{\max} = 3369, 2963, 2864, 2821, 1655, 1602, 1498. ¹H NMR (400 MHz, CDCl₃): δ_{H} = 2.47 (br s, 4H), 2.61 (br s, 2H), 3.48 (br s, 2H), 3.66 (br s, 4H), 5.26 (br s, 1H), 7.21–7.29 (m, 3H), 7.38 (td, 1H, J = 7.3 & 1.2 Hz), 7.54 (s, 4H), 7.82 (d, 1H, J = 7.8 Hz), 10.49 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_{C} = 37.2, 48.5, 52.8, 62.2, 89.9, 103.3, 106.0, 115.1, 117.7, 120.0, 123.6, 125.9, 126.6, 128.5, 130.4, 141.0, 155.0, 155.4, 160.8. HRMS (ESI) m/z calcd. for C₂₃H₂₂BrN₃O₃ [M-H]⁺ : 466.0760, found: 466.0765.

3-(4-chlorophenyl)-2-(pentylamino)furo[3,2-*c*]quinolin-4-ol (FQ2).

Yellow solid (78%), mp = 218-220 °C, IR (KBr, cm⁻¹): ν_{\max} = 2827, 1661, 1606, 1500, 1416. ¹H NMR (400 MHz, CDCl₃): δ_{H} = 0.87–0.94 (m, 3H), 1.36 (m, 4H), 1.64 (quint, 2H, J = 7.2 Hz), 3.39 (t, 2H, J = 7.1 Hz), 4.38 (br s, 1H), 7.14–7.26 (m, 2H), 7.32 (m, 2H), 7.39 (d, 2H, J = 8.5), 7.58 (dt, 2H, J = 8.5 & 1.8 Hz), 7.82 (d, 1H, J = 7.8 Hz), 11.17 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_{C} = 14.0, 22.9, 29.2, 29.8, 42.6, 94.6, 107.9, 110.7, 122.4, 124.6, 128.2, 129.9, 130.4, 130.9, 131.3, 133.0, 145.7, 159.6, 160.1, 165.4. HRMS (ESI) m/z calcd. for C₂₂H₂₁ClN₂O₂ [M+H]⁺ : 379.1207, found: 379.1207.

UV-vis and Fluorescence Study

For UV and fluorescence studies, stock solutions of the compounds and metal ions Li⁺, K⁺, Na⁺, Ca²⁺, Mg²⁺, Mn²⁺, Co²⁺, Fe²⁺, Ni²⁺, Zn²⁺, Pb²⁺, In³⁺, Al³⁺, Cr³⁺, Gd³⁺ and Fe³⁺ were prepared (1000 μ M) in DMSO : MeOH (v/v, 1:9). For spectral recordings, the stock solutions were further diluted to 20 μ M. All fluorescence spectra were recorded from 390 to 700 nm in a quartz cell (1 cm path length) at room temperature (0.4 nm excitation and emission slit). Solutions were added through a Hamilton burette equipped with 1 ml syringe.

Quantum yield calculations

Quantum yields of samples were determined by using standard reference solution of Coumarin-1 ($\Phi_r = 0.99$ in ethyl acetate at an excitation wavelength of 355 nm) and quantum yield is calculated by using following equation:

$$\frac{\Phi_s}{\Phi_r} = \frac{I_s}{I_r} \times \frac{1 - 10^{-A_r}}{1 - 10^{-A_s}} \times \frac{\eta_s^2}{\eta_r^2}$$

Φ_s and Φ_r are the quantum yields of sample and the reference respectively, A_r and A_s are the respective absorbance of the reference and the sample, I_s and I_r are the areas of emission for sample and reference respectively, η_r and η_s are the refractive indices of the sample and reference solutions.

Synthesis of polymeric membrane

5 mg of ionophore (FQ1), plasticizer (*o*-NPOE), additive NaTPB and high molecular weight PVC were dissolved in THF with continuous stirring. This viscous glue like mixture was then poured into a polyacrylate ring placed on a smooth surface. After evaporation of solvent a fluorescent membrane of about 0.5 mm thickness were obtained.

Theoretical calculations

DFT calculations were carried out using Gaussian 09 software package.¹¹ Initially, free FQs and FQ-Cu²⁺ were optimized using B3LYP exchange function followed by TD-DFT. For FQ-Cu²⁺ LanL2DZ effective core potential (ECP) basic set was employed, while all other atoms were subjected to ordinary 6-31G-(d, p) set. For input-output visualization and for plotting purpose GaussView 5.0 was used.

Conclusion

In summary, two new annulated furanones based chemosensors (FQs) were synthesized by an isocyanide based three component condensation. The synthesized probes displayed higher affinity (10^{+4} M^{-1}), greater selectivity and micromolar detection (10^{-7} M) for Cu²⁺ in organic and semi-aqueous solvents. NMR titrations and DFT based calculations predicted the possibility of CHEQ (Chelation Enhanced Fluorophore Quenching) mechanism. The utility of reported systems were demonstrated in the area of PVC based membrane sensing.

Acknowledgements

MK and LK would like to thank CSIR and UGC, New Delhi for the award of research fellowship. The authors also thank the departmental Instrumentation lab (IITR) and Institute Instrumental Centre (IIC) for providing the instrumental facilities.

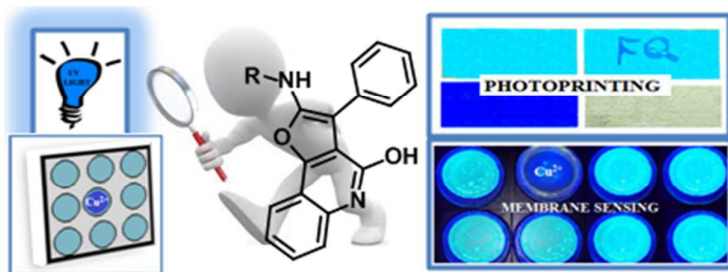
Notes and references

- (a) P. Verwilst, K. Sunwoo and J. S. Kim, *Chem. Commun.*, 2015, **51**, 5556-5571; (b) M. C. Linder and M. H.-Azam, *Am. J. Clin. Nutr.*, 1996, **63**, 797S-811S; (c) L. M. Gaetke, H. S. C. Johnson and C. K. Chow, *Arch Toxicol.*, 2014, **88**, 1929-1938; (d) Z. L. Harris and J. D. Gitlin, *Am J ClinNuir*, 1996, **63**, 836S-41S; (e) C. Shen and E. J. New, *Metalomics*, 2015, **7**, 56-65; (f) C. A. Flemming and J. T. Trevors, *Water, Air, and Soil Poll*, 1989, **44**, 143-158; (g) Y. Zhao, X.-B. Zhang, Z.-X. Han, L. Qiao, C.-Y. Li, L.-X. Jian, G.-L. Shen and R.-Q Yu, *Anal. Chem.*, 2009, **81**, 7022-7030.
- (a) J. A. Cotruvo, A. T. Aron, K. M. R.-Torres and C. J. Chang, *Chem. Soc. Rev.*, 2015, **44**, 4400; (b) N. Pourreza and R. Hoveizavi, *Anal. Chim. Acta*, 2005, **549**, 124-128; (c) A. P. S. Gonz ales, M. A. Firmino, C. S. Nomura, F. R. P. Rocha, P. V. Oliveira and I. Gaubeur, *Anal. Chim. Acta*, 2009, **636**, 198-204; (d) J. S. Becker, M. V. Zoriy, C. Pickhardt, N. P.-Gallagher and K. Zilles, *Anal. Chem.*, 2005, **77**, 3208-3216; (e) V. Beni, V. I. Ogurtsov, N. V. Bakunin, D. W. M. Arrigan and M. Hill, *Anal. Chim. Acta*, 2005, **552**, 190-200; (f) A. A. Ensafi, T. Khayamian, A. Benvidi and E. Mirmomtaz, *Anal. Chim. Acta*, 2006, **561**, 225-232.
- (a) D. Karak, S. Lohar, A. Sahana, S. Guha, A. Banerjee and D. Das, *Anal. Methods*, 2012, **4**, 1906-1908; (b) Y. J. Zheng; J. Orbulescu, X. J. Ji, F. M. Anreopoulos, S. M. Pham and R. M. J. Leblanc, *J. Am. Chem. Soc.*, 2003, **125**, 2680-2686; (c) Y. J. Zheng, X. H. Cao, J. Orbulescu, V. Konka, F. M. Andreopoulos, S. M. Pham and R. M. Lebac, *Anal. Chem.*, 2003, **75**, 1706-1712; (d) Y. T. Li and C. M. Yang, *Chem. Commun.*, 2003, 2884-2885; (e) D. Karak, A. Banerjee, S. Lohar, A. Sahana, S. K. Mukhopadhyay, S. S. Adhikari and Debasis Das, *Anal. Methods*, 2013, **5**, 169-172; (f) I. Majumder, P. Chakraborty, S. Das, H. Kara, S. K. Chattopadhyay, E. Zangrando and D. Das, *RSC Adv.*, 2015, **5**, 51290-51301; (g) G. Sivaraman, T. Anand and D. Chellappa, *Analyst*, 2012, **137**, 5881-5884; (h) G. Sivaraman, T. Anand and D. Chellappa, *RSC Advances*, 2012, **28**, 10605-10609; (i) G. Sivaraman, B. Vidya, and D. Chellappa, *RSC Adv.*, 2014, **58**, 30828-30831; (j) S. Adhikari, S. Mandal, A. Ghosh, S. Guria and D. Das, *Dalton Trans.*, 2015, **44**, 14388-14393; (k) S. Adhikari, A. Ghosh, S. Mandal, A. Sahana and D. Das, *RSC Adv.*, 2015, **5**, 33878-33884; (l) M. Iniya, D. Jeyanthi, K. Krishnaveni and D. Chellappa, *RSC Adv.*, 2014, **48**, 25393-25397; (m) A. Misra, P. Srivastava and Mohammad Shahid, *Analyst*, 2012, **137**, 3470-3478; (n) M. Shahid, P. Srivastava and A. Misra, *New J. Chem.*, 2011, **35**, 1690-1700; (o) A. Biswas, R. Pandey, D. Kushwaha, M. Shahid, V. K. Tiwari, A. Misra and D. S. Pandey, *Tetrahedron Lett.* 2013, **32**, 4193-4197.
- (a) H. S. Jung, P. S. Kwon, J. W. Lee, J. I. Kim, C. S. Hong, J. W. Kim, S. Yan, J. Y. Lee, J. H. Lee, T. Joo, and J. S. Kim, *J. Am. Chem. Soc.*, 2009, **131**, 2008-2012; (b) Y. Shan, Y. Sun, N. Sun, R. Guan, D. Cao, K. Wang, Q. Wu, Y. Xu, *Inorg. Chem. Commun.*, 2015, **59**, 68-70; (c) S. Areti, J. K. Khedkar, S. Bandaru, R. Teotia, J. Bellare and C. P. Rao, *Anal. Chim. Acta*, 2015, **873**, 80-87; (d) S. S. Razi, P. Srivastava, R. Ali, R. C. Gupta, S. K. Dwivedi and A. Misra, *Sens. Actuator B*, 2015, **209**, 162-171; (e) D. Brox, P. Comba, D.-P. Hertena, E. Kimmle, M. Morgen, C. L. R uhl, A. Rybina, H. Stephan, G. Storch and Hubert Wadepohl, *J. Inorg. Biochem.* 2015, **148**, 78-83; (f) Y. Fang, Y. Zhou, Q. Rui and Cheng Yao, *Organometallics* 2015, **34**, 2962-2970; (g) Q. Meng, R.

- Zhang, H. Jia, X. Gao, C. Wang, Y. Shi, A. V. E.-Dass and Z. Zhang, *Talanta*, 2015, **143**, 294–301; (h) L. Qu, C. Yina, F. Huob, Y. Zhang and Y. Li, *Sens. Actuator B*, 2013, **183**, 636–640; (i) O. Çimen, H. Dinçalp and C. Varlikli, *Sens. Actuator B*, 2015, **209**, 853-863; (j) U. N. Yadav, P. Pant, S. K. Sahoob and G. S. Shankarling, *RSC Adv.*, 2014, **4**, 42647-42653; (k) Z. Chen, L. Wang, G. Zou, J. Tang, X. Cai, M. Teng and L. Chen, *Spectrochim Acta A*, 2013, **105**, 57-61.
- 5 (a) V. K. Gupta, N. Mergu, L. K. Kumawat, *Sens. Actuator B*, 2016, **223**, 101-113; (b) V. K. Gupta, N. Mergu, L. K. Kumawat, A. K. Singh, *Talanta*, 2015, **144**, 80-89; (c) V. K. Gupta, A. K. Singh, L. K. Kumawat, *Sens. Actuator B*, 2014, **204**, 507-514; (d) L. K. Kumawat, N. Mergu, A. K. Singh and V. K. Gupta, *Sens. Actuator B*, 2015, **212**, 389-394 (e) M. Kumar, L. K. Kumawat, V. K. Gupta and A. Sharma, *ChemistryOpen*, 2015, **4**, 626-632. (f) V. K. Gupta, A. K. Singh, L. K. Kumawat, N. Mergu, *Sens. Actuator B*, 2016, **222**, 468-482.
- 6 (a) M. Kumar, T. Kaur, V. K. Gupta and A. Sharma, *RSC Adv.*, 2015, **5**, 17087-17095; (b) M. Kumar, S. Bagchi and A. Sharma, *RSC Adv.*, 2015, **5**, 53592-53603; (c) S.-J. Park, J.-C. Lee and K.-I. Lee, *Bull. Korean Chem. Soc.*, 2007, **28**, 1203-1205.
- 7 H. A. Benesi, J. H. Hildebrand, *J. Am. Chem. Soc.*, 1949, **71**, 2703-2707.
- 8 (a) J. Wang and Q Zong, *Sens. Actuator B*, 2015, **216**, 572-577; (b) H. Ye, F. Ge, Y.-M. Zhou, J.-T. Liu, B.-X. Zhao, *Spectrochim Acta A*, 2013, **112**, 132-138.
- 9 V. K. Gupta, A. K. Singh and L. K. Kumawat, *Electrochimica Acta*, 2013, **95**, 132–138.
- 10 L. Liu, A. Wang, G. Wang, J. Li and Y. Zhou, *Sens. Actuator B*, 2015, **215**, 388-395.
- 11 M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, Jr. J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision A.02, Gaussian Inc., Wallingford, CT, 2009.

Rational designing of first furoquinolinol based molecular systems for easy detection of Cu^{2+} with potential applications in the area of membrane sensing

Graphical Abstract



Two highly selective furoquinolinol based molecular systems for Cu^{2+} have been designed with potential application in areas of membrane sensing.