



Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Optical and electrochemical dual channel sensing of Cu^{2+} using functionalized furo[2,3-*d*]pyrimidines-2,4[1*H*,3*H*]-diones



Manoj Kumar^{a,1,2}, Lokesh Kumar Kumawat^{b,1}, Priyanka Bhatt^c, Anjali Jha^c, Shilpi Agarwal^b, Anuj Sharma^a, Vinod Kumar Gupta^{b,*}

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

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

^c Department of Chemistry, GITAM Institute of Science, GITAM University, Visakhapatnam, Andhra Pradesh 530045, India

ARTICLE INFO

Article history:

Received 12 January 2017

Received in revised form 7 March 2017

Accepted 16 March 2017

Available online 18 March 2017

Keywords:

Fuopyrimidinones

MCR

Sensor

Dual channel sensing

ISE

ABSTRACT

Owing to their easy accessibility and high degree of structural and functional diversity, many multicomponent reactions (MCRs) have been a rich source of conjugate π -systems, functionalised chromophores (or fluorophore) and redox active molecules. Despite their high explorative potential and practical benefits, only a few MCR products have been so far investigated for their metal sensing abilities. In the present report, two fuopyrimidinones (FPys) based molecular systems have been synthesized by [4 + 1] cycloaddition based MCR sequence. Designed chemosensors displayed optic (absorption spectra) as well as electroanalytical (ion selective electrode) response toward Cu^{2+} ion in solution and membrane phase respectively (dual channel sensing). Different aspects of both the sensing phenomena such as selectivity, association constants, detection limit, membrane composition etc. were studied in detail using UV–Vis spectroscopy, NMR titration and cell assembly. Both the compounds showed excellent performance characteristics such as high selectivity, acceptable affinity and low detection limits (10^{-7} M) in both sensing assays with potential utility in the area of sample monitoring.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Revelation of novel molecular systems with unique photophysical/electroanalytical attributes is scientifically exciting and intellectually challenging task. Such molecular systems find applications in various domains of research such as energy conversion, light emitting diodes (LEDs), dye-sensitized solar cells (DSSCs) and in sensing arrays [1,2]. Use of receptor organic molecules (or chemical sensor) to identify ecologically and biologically relevant analyte/species such as metal ions is now an established field of research with hundreds of reports every year [3–16].

Among many factors that look decisive for the development of this field is the synthetic accessibility of these systems. Generally, it is highly desirable that these scaffolds originated from a simple, clean and easy synthetic route which also aligns well with the current idea of “green analytical chemistry (GAC)” [17–22]. Moreover, methods that ensure

high degree of structural and functional diversity are an added advantage in studying structure property relationships (SPRs).

In this connection, multicomponent reactions (MCRs) seem to be an obvious choice. MCRs are highly convergent chemical transformations in which three or more reactants form a product derived from all the inputs [23–31]. The majority of MCRs are atom/step economical, operationally simple and provide access to a wide range of functionalized heterocycles. Many of the MCR products contain functional π -electron system, high degree of conjugation or donor atoms such as O, N and S in their framework and/or in attached groups and can be a good starting point for many sensing investigation [23–31]. Recently, two approaches “scaffold” and “chromophore” have been presented for MCR formation of these functionalised systems. In scaffold approach, a starting material itself bears a chromophoric group while in chromophore approach, a new chromophore is generated from MCR itself (i.e. MCR is a chromogenic event).

A recent review by Levi and Müller eloquently outlined many such functional MCR systems [2]. The same reviewers also pointed out that despite several practical benefits and high explorative value; most of these systems are under-explored. Only a handful of MCR products have been so far tested for their metal sensing abilities and there is a large scope for further investigation [32–34].

* Corresponding author.

E-mail addresses: anujsfycy@iitr.ac.in (A. Sharma), vinodg@uj.ac.za (V.K. Gupta).

¹ Contributed equally as co-first authors.

² Present address: Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York-11794, USA.

Our group has a long standing interest in the discovery and design of new chemical sensors for biologically and ecologically relevant metal ions [32–33,35–44]. In light of above discussion, we wish to disclose herein two new furopyrimidine-diones (FPy)s based molecular systems for easy and effective detection of copper (Cu^{2+}). These annulated keto-lactones are easily accessible through [4 + 1] cycloaddition based IMCR sequences [45–51]. In this particular example MCR sequence act as a chromogenic event (chromophoric approach). The synthesized receptors are unique and rare in the sense that they display dual channel (optic/electro-analytic) response toward Cu^{2+} ions with excellent performance characteristics. The purpose of this paper is (1) to recognise the chromophoric portion of the molecules responsible for Cu^{2+} recognition (2) to determine the role of basic molecular framework and substituent pattern in sensing applications (3) to examine the utility of titled compounds in electroanalytic/membrane sensing. If successful, this work can be expanded in multiple directions; notably, a large number of furopyrimidine-diones with suitable substituent patterns can be synthesized and studied for their structural property relationship (SPRs) to get deeper insight into underlying sensing mechanism. Keeping all these things in mind, we decided to explore the sensing properties of hitherto undescribed furo[2,3-*d*]pyrimidines-2,4[1*H*,3*H*]-diones series of compounds.

2. Experimental section

2.1. Chemical and reagents

Reagents such as *N,N'*-dimethylbarbituric acid, Benzaldehyde and isonitriles were purchased from Sigma-Aldrich® India and were used as received. Solvents were purified and dried before use. The detail of all other chemicals (such as grade and supplier) used for membrane fabrication is presented in the table S2 (ESI).

2.2. Instrument detail

^1H and ^{13}C NMR spectra were obtained using a Jeol Resonance ECX-II spectrometer machine (operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR). Chemical shift values were reported in parts per million (ppm) using TMS as an internal standard and $\text{DMSO-}d_6$ as NMR solvent. MestReNova-6 software was used for spectral processing and inspection

of data. Splitting patterns were abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet) and m (multiplet). UV–Vis spectra were recorded using Shimadzu (model UV-2450) spectrophotometer. HRMS data were acquired from calibrated Bruker-daltonics-microTOF-QII® spectrometer operating at ESI mode, with <5 ppm mass error. Origin 6.0 software was used for graphical representation of data and statistical work. pH of the solutions were measured with Eutech-510 pH-meter. Merck®60F254 analytical silica gel TLC plates were used to monitor the progress of the reaction.

2.3. Microwave irradiation experiment

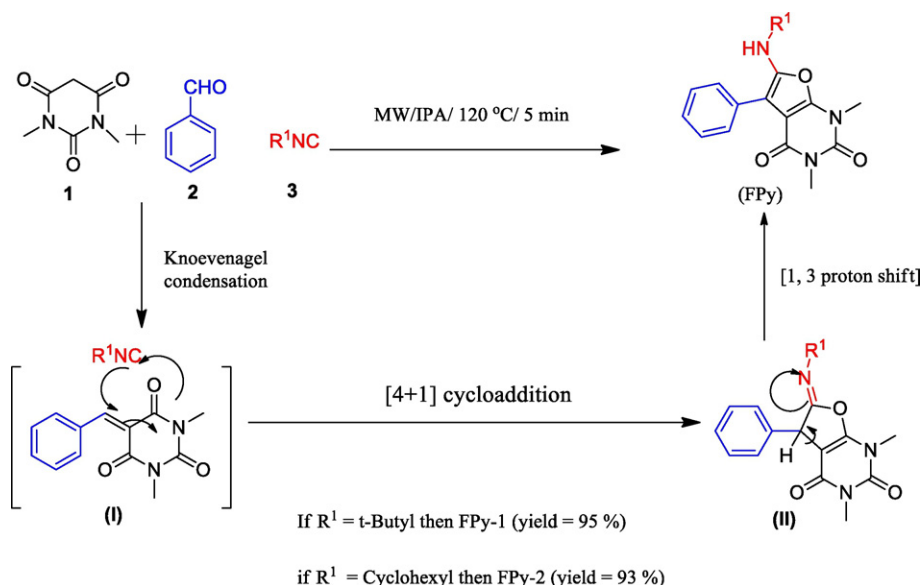
Microwave reactions were conducted using Anton Paar microwave synthesizer-300®. This machine supplies a continuous flow of microwave energy (at 2.455 GHz) with a selectable output power option from 0 to 300 W. All the reactions were carried in a high quality borosilicate process vial, capped with a Teflon (PTFE) septum. At the beginning, Microwave radiations of required power were used to attain a desired temperature. Once this temperature was attained, the reaction vial was held to this temperature for appropriate time. Finally, the reaction mixture was cooled to room temperature by a fast adiabatic air jet.

2.4. General procedure for the microwave-assisted three component reaction

A mixture of *N,N'*-dimethylbarbituric acid **1** (1.0 mmol), benzaldehyde **2** (1.1 mmol) and isonitrile **3** (1.2 mmol) was dissolved in isopropanol with continuous stirring at room temperature. This mixture was then transferred to a G-10 process glass vial and tightly sealed with teflon septum. After a pre-stirring of 1 or 2 min, the vial was subjected to microwave irradiation with the initial ramp time of 2 min at 60 °C. The temperature was then raised to 120 °C with the holding time of 5 min. This solid was filtered and washed with excess of ice cooled IPA/MeOH (2/3, v/v). This solid was pure enough for routine characterization.

2.5. Analytical data

6-(*tert*-butylamino)-1,3-dimethyl-5-phenylfuro[2,3-*d*]pyrimidine-2,4[1*H*,3*H*]-dione (FPy-1).



Scheme 1. Multicomponent synthesis of substituted furo[2,3-*d*]pyrimidines-2,4[1*H*,3*H*]-diones (FPy)s.

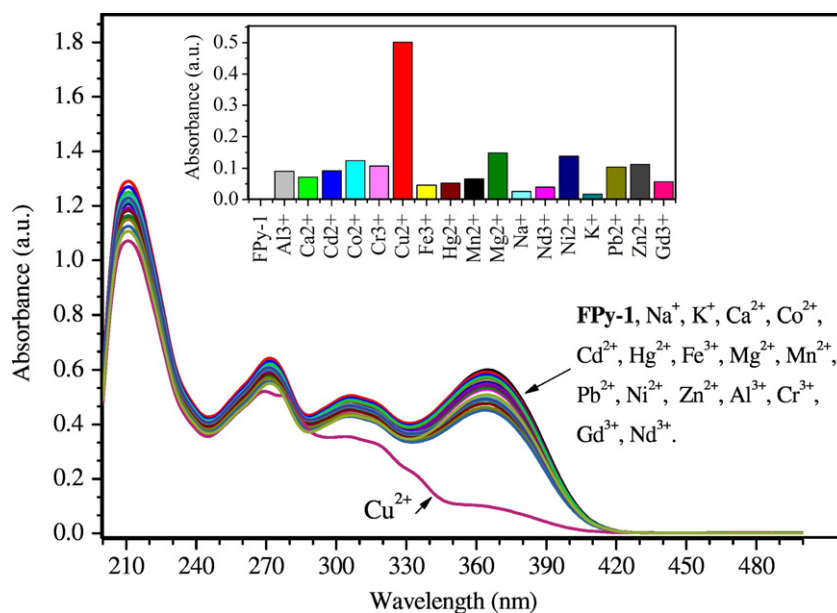


Fig. 1. Absorption spectra of **FPy-1** in the presence of different metal ion [20 μ M, (MeOH/H₂O, 2/8, v/v)]. Band near 375 nm completely disappeared in the presence of Cu²⁺ (equivalent amount).

Yield: 92%; Lemon yellow solid; IR (KBr) ν_{max} cm⁻¹ 3360 (NH), 1707 & 1656 (C=O). ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 1.20 (s, 9H), 2.82 (s, 3H), 2.95 (s, 3H), 3.19 (s, 1H), 7.21 (tt, 1H, *J* = 6.0 & 1.3 Hz), 7.32 (t, 2H, *J* = 6.0 Hz), 7.52 (dd, 2H, *J* = 5.9 & 1.0 Hz). ¹³C NMR: (100 MHz, DMSO-*d*₆): δ (ppm) 28.6, 29.7, 33.4, 55.0, 122.3, 128.7, 129.2, 130.1, 131.6, 131.6, 136.1, 137.1, 138.8, 151.0, 155.5. HRMS (ESI) *m/z* calcd. for (C₁₈H₂₁N₃O₃) [M + Na]⁺: 350.1481, found: 350.1476.

1,3-dimethyl-5-phenyl-6-(2,4,4-trimethylpentan-2-ylamino)furo[2,3-*d*]pyrimidine 2,4(1*H*,3*H*)-dione (**FPy-2**).

Yield: 95%; Pale yellow solid; IR (KBr) ν_{max} cm⁻¹ 3315 (NH), 1710 & 1669 (C=O). ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 1.20 (s, 9H), 1.46 (s, 6H), 1.77 (s, 2H), 3.08 (s, 3H), 3.21 (s, 3H), 3.78 (s, 1H), 7.47 (tt, 1H, *J* = 6.0 & 1.0 Hz), 7.57 (t, 2H, *J* = 6.0 Hz), 7.77 (dd, 2H, *J* = 6.0 & 1.0 Hz). ¹³C NMR: (100 MHz, DMSO-*d*₆): δ (ppm) 28.6, 28.8, 31.6, 33.4, 54.0, 58.2, 126.8, 128.7, 129.2, 130.1, 131.6, 136.9, 137.6, 151.0, 155.5. HRMS (ESI) *m/z* calcd. for (C₂₂H₂₉N₃O₃) [M + Na]⁺: 406.2107, found: 406.2101.

2.6. General detail of UV absorption experiment

For UV absorption spectra, stock solutions of the compounds and metal ions Ag⁺, Al³⁺, Cu²⁺, Cd²⁺, Ca²⁺, Co²⁺, Cr³⁺, Hg²⁺, Mg²⁺, Gd³⁺, Fe³⁺, Mn²⁺, Ni²⁺, Na⁺, Nd³⁺, Zn²⁺ and Pb²⁺ were prepared (1.0 \times 10⁻³ M) in MeOH. For spectral recordings, the stock solutions

were further diluted to 20 μ M. Solutions were added through a Hamilton burette equipped with 1 ml syringe. The light path length of cuvette was 1.0 cm. Spectral data were recorded 90 s after the addition of the ions. The ionic strength of all solutions was adjusted to 0.1 M (KNO₃). Three separate titrations were performed, each including 60–80 points. For determination of selectivity, association constant and LODs standard procedures were used.

2.7. Fabrication of polymeric membranes

Cragg's method was used for the fabrication of polymeric membranes. PVC films of different compositions were prepared by dissolving and mixing different amount of ionophores (**FPy-1** and **FPy-2**), anionic additives (NaTPB, KBF₄, KTpCIPB and OA), Plasticizer (DBP, DOP, *o*-NPOE, CN, DBBP and THB) in tetrahydrofuran medium (THF, dry). This viscous mixture was poured into polyacrylates rings kept on a smooth glass surface. After slow evaporation polymeric membranes of thickness of about 0.5 mm were obtained [39–42]. These thin membranes were carefully removed from the glass surface and glued to the one end of small pyrex glass tube (this arrangement act as an Ion Selective Electrode, ISE). In this process, viscosities of the solution and evaporation rates were carefully control to ensure the membranes of uniform thickness. A dummy membrane (only PVC as an ingredient) was also fabricated to determine the effect of background noise.

Table 1
Effects of interfering species on the absorbance signal of the optical sensor.^{a,b,c,d}

Interfering ion	Relative error % = ($\Delta A/A_0 \times 100$)	Interfering ion	Relative error % = ($\Delta A/A_0 \times 100$)	Interfering ion	Relative error % = ($\Delta A/A_0 \times 100$)
Na ⁺	-2.7	Hg ²⁺	+0.1	Cd ²⁺	-1.8
K ⁺	+1.3	Pb ²⁺	+1.2	Nd ³⁺	+1.5
Ca ²⁺	-0.8	Mn ²⁺	+0.5	Al ³⁺	+2.2
Mg ²⁺	+0.6	Ni ²⁺	+2.1	Cr ³⁺	-2.1
Co ²⁺	+4.1	Zn ²⁺	+1.3	Fe ³⁺	-1.9
Ag ¹⁺	+3.1	—	—	—	—

^a Concentration of Cu²⁺ and **FPy-1** was kept fix at 20 μ M (pH 6.0);

^b Conc. of all interfering species were keep constant at 10 mM;

^c ΔA is the difference of absorbance before and after exposure to interfering species;

^d MeOH/H₂O (2/8, v/v) was used as a solvent system in all measurements.

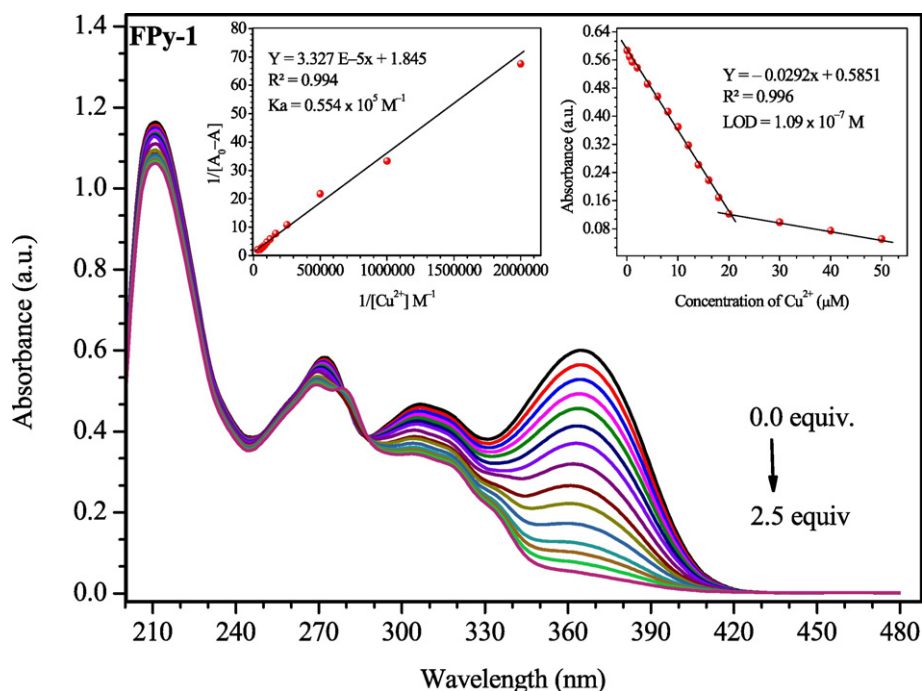


Fig. 2. Effect of increasing Cu^{2+} concentration (from 0 to 2.5 equivalents) on absorption spectra of **FPY-1** [20 μM , (MeOH/ H_2O , 2/8, v/v)]. Inset shows change in absorption intensity at 375 nm as a function of concentration of Cu^{2+} ions.

2.8. Conditioning of the membrane and cell set up for potential measurement

All the membranes were conditioned by keeping them in a solution of 0.01 M CuSO_4 for about 48–56 h. For the measurement of potential, test solutions of varying concentrations in the range of 1.0×10^{-8} M to 1.0×10^{-2} M were used. Following cell assembly was used for the experiments:

SCE//Test solution/PVC membrane/0.01 M CuSO_4 //SCE (cell setup).

3. Results and discussion

3.1. Synthesis of furo[2,3-d]pyrimidines-2,4[1H,3H]-dione **FPY-1** and **FPY-2**

Both the compounds (**FPYs**) were synthesized by microwave assisted three component reaction [45–51] of 1,3-dimethylbarbituric acid **1**, benzaldehyde **2** and respective isocyanides **3** (scheme 1). Initially, a conjugated heterodyne (**I**) is formed by a Knoevenagel condensation of C-H acid **1** and aldehyde **2**. Next step involve a [4 + 1] cycloaddition of heterodine of 5-arylidene-*N,N'*-dimethylbarbituric acid (**I**) with isonitrile to afford an iminolactone intermediate (**II**), which is finally isomerize to furopyrimidine products (**FPYs**) by a 1, 3 proton shift.

acid **1**, benzaldehyde **2** and respective isocyanides **3** (scheme 1). Initially, a conjugated heterodyne (**I**) is formed by a Knoevenagel condensation of C-H acid **1** and aldehyde **2**. Next step involve a [4 + 1] cycloaddition of heterodine of 5-arylidene-*N,N'*-dimethylbarbituric acid (**I**) with isonitrile to afford an iminolactone intermediate (**II**), which is finally isomerize to furopyrimidine products (**FPYs**) by a 1, 3 proton shift.

3.2. Colorimetric sensing of copper

3.2.1. General behaviour and determination of sensing parameters

The absorption spectra of synthesized furopyrimidine systems were characterized by three intense and one broad band centred near 210 nm (intense), 271 nm, 325 nm (broad) and 375 nm (intense) [Fig. 1 and SS1 (ESI)]. The nature of solvent and temperature had a very little or no

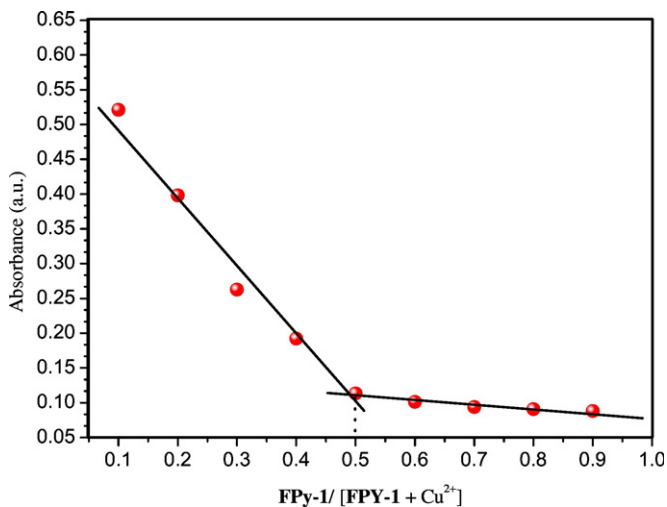


Fig. 3. Job's absorption plot of **FPY-1** with Cu^{2+} in (MeOH/ H_2O , 2/8, v/v). (Total concentration of probe **FPY-1** and Cu^{2+} was kept constant at the level of 20 μM).

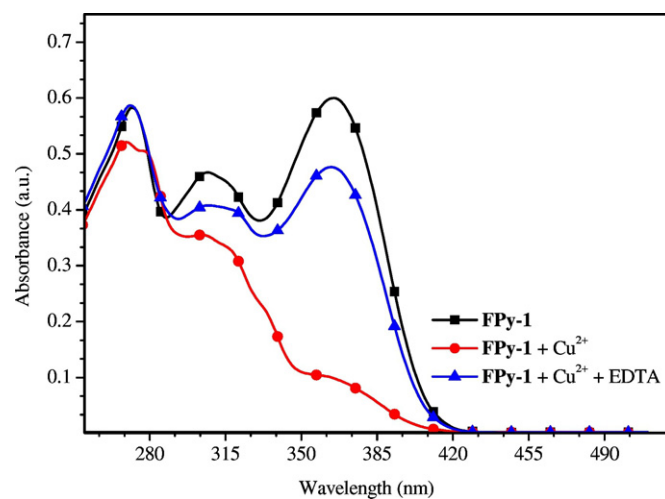


Fig. 4. Reversibility and reusability test of **FPY-1** in the presence of EDTA. **FPY-1** [20 μM , (MeOH/ H_2O , 2/8, v/v)] with equimolar concentration of EDTA and Cu^{2+} .

Table 2
Optimization of membrane composition (effect of plasticizer).

Composition of membrane (Iono./PVC/Add.(KTPCIPB)/plast.) (% w/w)	Memb. No. (FPy-1 as ionophore)	Linear working range	Slope	Response time (sec.)	Memb. No. (FPy-2 as ionophore)	Linear working range	Slope	Response time
0/30/5/65 (DBP)	1	–	–	41	9	–	–	39
15/70/15/0	2	4.10×10^{-4} to 1.0×10^{-2}	24.6	27	10	5.20×10^{-4} to 1.0×10^{-2}	26.6	25
3/30/2/65 (DBBP)	3	5.58×10^{-5} to 1.0×10^{-2}	30.7	20	11	4.90×10^{-5} to 1.0×10^{-2}	28.1	17
3/30/2/65 (DBBP)	4	2.71×10^{-5} to 1.0×10^{-2}	27.9	22	12	3.25×10^{-5} to 1.0×10^{-2}	27.3	15
3/30/2/65 (TEHP)	5	9.28×10^{-6} to 1.0×10^{-2}	27.8	21	13	1.73×10^{-5} to 1.0×10^{-2}	27.9	19
3/30/2/65 (CN)	6	3.09×10^{-6} to 1.0×10^{-2}	30.7	16	14	4.26×10^{-6} to 1.0×10^{-2}	31.1	14
3/30/2/65 (DOP)	7	8.93×10^{-7} to 1.0×10^{-2}	31.2	13	15	1.09×10^{-6} to 1.0×10^{-2}	29.6	21
3/30/2/65 (o-NPOE)	8	1.20×10^{-7} to 1.0×10^{-2}	29.4	11	16	1.40×10^{-7} to 1.0×10^{-2}	24.2	11

effect on the overall spectral pattern and peak positions. Except Cu^{2+} , excess presence of other metal ions didn't create any noticeable change either in band position or in absorbance. Surprisingly, higher wavelength (near 375 nm) band completely disappeared in the presence of equimolar amount of cupric ion with an immediate decolouration from yellow to colourless [Fig. 1 and SS1 (ESI)]. This behaviour was retained in other solvents such as ACN, MeOH and mixed aqueous phases (MeOH/Water, 9/1 to 1/9, v/v). Under UV torch, both the compounds displayed a very dull fluorescence in solution phase, which was not much affected by the presence of Cu^{2+} , hence only absorption studies were carried out to determine the performance characteristics of this sensing phenomenon. Both the probes were found selective toward Cu^{2+} and this sensing behaviour was remained unaffected by

the presence of other cationic species present in the matrix (Table 1, selectivity studies).

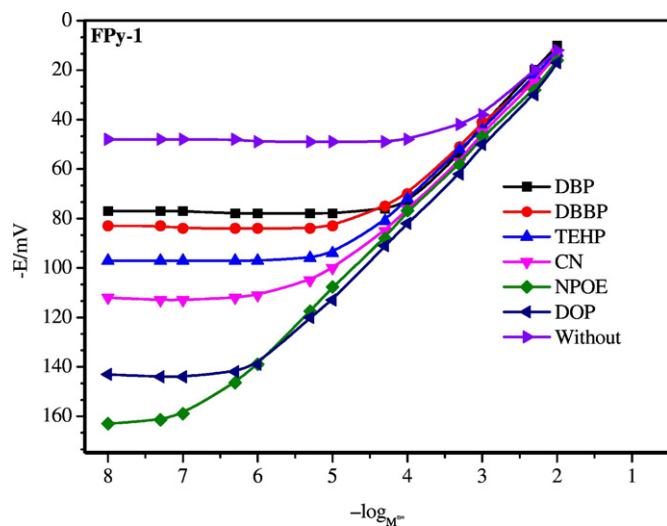
In order to get a thorough understanding of complexometric and stoichiometric aspects of this interaction, absorption titrations were carried out in semi-aqueous medium. In this titration, a gradual decrease in absorbance was observed, with the continued addition of Cu^{2+} . Detection limits (LODs) were calculated by Universal method ($\text{LOD} = 3\sigma/\text{slope}$) and found to be 1.09×10^{-7} and 1.32×10^{-7} M [Fig. 2 and SS2 (ESI)]. In Job's plot, an absorbance minima was found at 0.5 (= 1/2) molar fraction of Cu^{2+} suggesting 1:1 complex between receptor and Cu^{2+} [Fig. 3 and SS3 (ESI)] [52]. In the Benesi–Hildebrand plot [53] association constants for **FPy**- Cu^{2+} were found to be 5.54×10^4 and $4.37 \times 10^4 \text{ M}^{-1}$ suggesting higher affinity of **FPys** toward Cu^{2+} at equilibrium. In both the cases, linear plots with excellent correlation coefficients ($r^2 > 0.99$) were obtained [Fig. 2 and SS2 (ESI)]. Next, we also surveyed the effect of H^+ ion concentration on this sensing interaction. Gratifyingly, both the furopyrimidine systems displayed wide operational pH range indicating their utility in physiological medium.

Finally, recyclability and reusability of synthesized probes were investigated. Sequestering agents (such as EDTA at neutral pH) caused **FPys** to free from the complex and yellow colour of the original solution reappeared again. Free Probing agent was recovered by extraction (95%) and was reused for same sensing assay for 3–4 times with >90% efficiency. This kind of behaviour ensured cost effective practicality of the synthesized chemical sensor [Fig. 4 and SS4 (ESI)].

3.3. Electroanalytical sensing of Cu^{2+} by **FPy** based ion selective electrode (ISE)

We also explored the possibility of furopyrimidines (**FPys**) as a neutral ionophore for Cu^{2+} as a PVC membrane selective sensor. Since the response (selectivity, sensitivity and linearity) of this kind of ion selective electrode (ISE) very much depend on the texture of the membrane, hence membranes were first optimized for their composition.

At the beginning, the effect of plasticizer on the performance characteristics of the membrane was studied. Six plasticizers with different dielectric constants [DBBP ($\epsilon = 4.6$), TEHP ($\epsilon = 4.8$), CN ($\epsilon = 5$), DOP

**Fig. 5.** Variation in membrane potential (membrane with different plasticizer were used) with Cu^{2+} concentration.**Table 3**
Optimization of membrane composition (effect of additives).

Membrane No.	Composition	Additive	Working range	LODs	Response time (sec.)
17	FPy-1 :PVC:o-NPOE (% w/w) 3:30:65	–	4.1×10^{-4} to 1.0×10^{-2}	2.45×10^{-4}	19
8		KTPCIPB	1.2×10^{-7} to 1.0×10^{-2}	1.08×10^{-7}	11
18		NaTPB	4.9×10^{-7} to 1.0×10^{-2}	2.64×10^{-7}	13
19		KBF ₄	1.8×10^{-6} to 1.0×10^{-2}	1.39×10^{-6}	13
20		OA	5.4×10^{-6} to 1.0×10^{-2}	4.60×10^{-6}	17
21		FPy-2 :PVC:o-NPOE (% w/w) 3:30:65	–	5.6×10^{-4} to 1.0×10^{-2}	4.50×10^{-4}
16	KTPCIPB		1.5×10^{-7} to 1.0×10^{-2}	1.32×10^{-7}	11
22	NaTPB		2.9×10^{-7} to 1.0×10^{-2}	2.05×10^{-7}	18
23	KBF ₄		1.8×10^{-6} to 1.0×10^{-2}	1.15×10^{-6}	15
24	OA		6.1×10^{-6} to 1.0×10^{-2}	5.43×10^{-6}	17

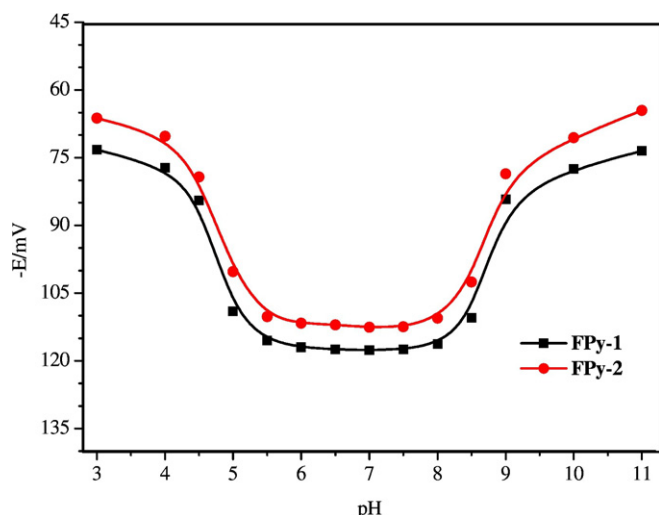


Fig. 6. pH response study of FPy-1 and FPy-2 based best selective and responsive membrane sensors (sensor no. 8 and 16).

($\epsilon = 5$), DBP (6.4) and *o*-NPOE ($\epsilon = 24$)] were examined. From Table 2, it is clear that membranes containing *o*-NPOE are better than other plasticizers with largest operational range and low response time [Fig. 5 and SS6 (ESI)]. In the second set of experiments, role of anionic additive was examined. Different additive NaDBP, KTpCIPB, OA and KBF_4 were used while keeping all other variables constant (Table 3). KTpCIPB at 2% (w/w) relative to the total membrane composition displayed best results. Hence all the further studies were carried out using *o*-NOPE/KTpCIPB pair only (table 3).

Next we also studied the effect of H^+ ion concentration (pH) and non-aqueous medium on to the performance of the membrane. The potential remained constant over a pH range of 5–8.5 (adjusted with HCl/NaOH solution), which may be taken as operational pH range of the synthesized sensor (Fig. 6). Performance characteristics of the membranes in some non-aqueous mediums are listed in table SS1 (ESI). This table indicate that up to 15% non-aqueous content no major change occur in working range, response time and the slope of the response curve. However, above this concentration (>15% non-aqueous, v/v) working range significantly reduced. So for practical purposes, synthesized ionophore can be used up to 15% non-aqueous content. Finally, the synthesized membrane was examined for its general response and selectivity. Formation constants ($\log \beta_{\text{FPy}}$) for different set of metal-ionophore complexes were determined using the method of polarized sandwich membranes [54] and are included in Table 4. The elapsed time between sandwich fusion and contact to ion solution was <1 min. Standard deviations (SD) were obtained by performing each experiment in triplicate. Cu^{2+} has significantly higher formation constant than other tested metal ions.

For Cu^{2+} ion, membranes displayed wide concentration working range, low LOD, high selectivity and Nernstian compliance. For all other metals, a very poor response in the concentration range of 1.0×10^{-8} M to 1.0×10^{-2} M with lower potential slope (than expected

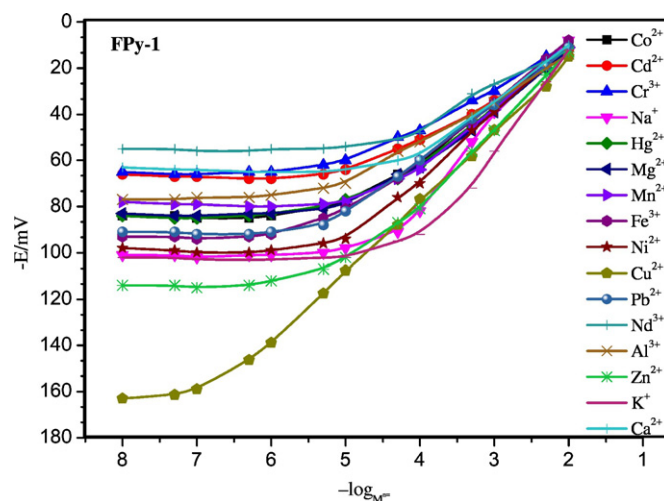


Fig. 7. Response study of membrane sensors (based on FPy-1, membrane no. 8) against different metal ions.

slope of 59, 29.5 and 20 mV/per decade of activity respectively for mono, di and trivalent metal ion) were observed [Fig. 7 and SS7 (ESI)]. The membrane could be used over a period of 2 months without significant loss of effectiveness for Cu^{2+} .

3.4. ^1H NMR titration

Cu^{2+} is paramagnetic in nature and its interaction with probe molecule will surely affects the vicinal electronic environment and NMR signal of protons. A study of these changes in pattern/position/shape can provide valuable information about the possible site of interaction. Proton NMR spectra of probe FPy-1 is recorded in the presence and absence of Cu^{2+} in $\text{DMSO}-d_6$ (Figs. 8 and 9). Following changes were observed: (1) at higher concentration of Cu^{2+} (0.5 Equiv. or more) a slight distortion in baseline is observed (Fig. 9). (2) While the position of the peaks at aliphatic region remained largely unchanged, peaks of aromatic protons displayed a slight downfield shift (Fig. 9). (3) the most notable change was observed in the peak of alkylamino “NH” proton. This proton exhibited considerable broadening with increased Cu^{2+} concentration and eventually completely disappeared at equimolar amount of Cu^{2+} (Fig. 9).

These observations clearly indicated that furan oxygen atom and alkylamino NH group directly involve in coordination with Cu^{2+} and this seems to be the probable binding site for metal (Fig. 8).

3.5. Analytical application of the proposed sensor

Analytical utility of synthesized FPy sensors were evaluated by comparative estimation of Cu^{2+} in different real samples. The results of Absorbance titration and ISE based experiments were compared. Method of Haraguchi and Fuwa [55] was used to prepare sea water in laboratory (artificially made sea water). Different salts NaCl (2.67 g),

Table 4
Formation constant for different set of metal ligand complex (membrane no. 8 and 16).

Cation	Membrane no. 8 $\log \beta_{\text{FPy-1}} \pm \text{SD}$	Membrane no. 16 $\log \beta_{\text{FPy-2}} \pm \text{SD}$	Cation	Membrane no. 8 $\log \beta_{\text{FPy-1}} \pm \text{SD}$	Membrane no. 16 $\log \beta_{\text{FPy-2}} \pm \text{SD}$
Na^+	0.54 ± 0.05	0.84 ± 0.05	Zn^{2+}	2.91 ± 0.12	3.61 ± 0.24
K^+	0.61 ± 0.04	0.67 ± 0.05	Co^{2+}	3.54 ± 0.15	3.94 ± 0.15
Ag^+	1.29 ± 0.16	1.54 ± 0.17	Cr^{3+}	3.21 ± 0.25	2.54 ± 0.22
Cu^{2+}	6.54 ± 0.19	6.78 ± 0.32	In^{3+}	4.21 ± 0.34	4.54 ± 0.37
Pb^{2+}	2.54 ± 0.25	2.91 ± 0.19	Ca^{2+}	3.54 ± 0.17	2.94 ± 0.25
Cd^{2+}	2.61 ± 0.15	2.46 ± 0.15	Al^{3+}	2.54 ± 0.15	2.57 ± 0.14

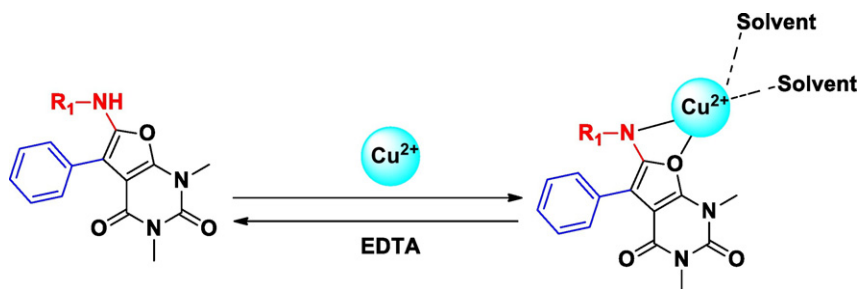


Fig. 8. Possible binding interactions between FPYs and Cu^{2+} .

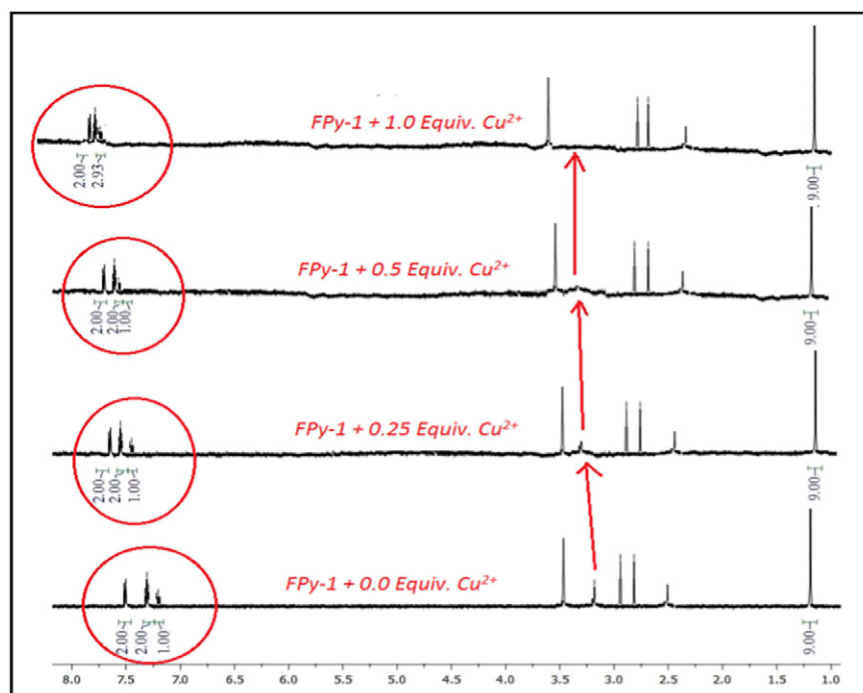


Fig. 9. ^1H NMR spectra of compound FPY-1 in the presence of different concentration of Cu^{2+} .

MgCl_2 (0.54 g), KCl (0.08 g with 3.40% salinity) and CaCl_2 (0.11 g) were dissolved in deionized water with the addition of 1 ml (15 mg/ml) of Cu^{2+} solution and total final content was transferred in to a 100 ml volumetric flask. Known solutions of Cu^{2+} (10%, 25%, 35%, 50%, w/v, mg/ml) were prepared and a concentration of Cu^{2+} was directly determined by ISE. In absorbance titrations ACN/water (1/9, v/v) was used for the solution preparation, because of the poor solubility of the probe in water alone. The absorption band near 365 nm (FPY-1) were recorded and calibration curve (1/absorbance vs. concentration of added Cu^{2+}) thus obtained was used for the calculation of the concentration. All the experiments were performed in triplicate. Both the results were good agreement with the relative error less than $\pm 3.5\%$ indicating the practical utility of sensor for real sample analysis (Table 5) [56–61].

4. Conclusion

In summary, two new furopyrimidinones based chemosensors have been synthesized by a microwave assisted three component condensation of 1,3-dimethylbarbituric acid, benzaldehyde and respective isocyanides. Designed chemosensors displayed dual channel (optic and electroanalytical) response toward Cu^{2+} in solution and membrane phase with excellent performance characteristics. Proposed systems can be used for monitoring of samples of biological and ecological relevance.

Declaration of interest

The authors have no competing interests to declare.

Table 5
performance of membrane in non-aqueous medium (membrane no. 8 and 16).

Sample no. (A)	Memb. no. 8 (ISE) (B)	% Recovery = $B/A \times 100$	Absorption titration (FPY-1) (C)	% Recovery = $C/A \times 100$
1 (10 mg/ml)	9.74 ± 1.2	97.4	9.86 ± 0.7	98.6
2 (25 mg/ml)	24.40 ± 1.1	97.6	24.32 ± 0.9	97.2
3 (35 mg/ml)	34.15 ± 0.7	97.5	34.10 ± 1.2	97.5
4 (50 mg/ml)	48.14 ± 1.1	96.3	48.05 ± 1.2	96.1

Acknowledgements

Authors MK and LKK would like to acknowledge CSIR-New Delhi (India) and University of Johannesburg (South Africa) respectively for JRF (Ext.) and GES-UJ Postdoctoral fellowships. The authors are also thankful to departmental Instrumentation labs (IITR, UJ and GITAM) for providing necessary facilities.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.saa.2017.03.034>.

References

- [1] M. Saleem, K.H. Lee, Optical sensor: a promising strategy for environmental and biomedical monitoring of ionic species, *RSC Adv.* 5 (2015) 72150–72287.
- [2] L. Levi, T.J.J. Müller, Multicomponent syntheses of functional chromophores, *Chem. Soc. Rev.* 45 (2016) 2825–2846.
- [3] E. Oliveira, C. Núñez, H.M. Santos, J.F. Lodeiro, A.F. Lodeiro, J.L. Capelo, C. Lodeiro, Revisiting the use of gold and silver functionalised nanoparticles as colorimetric and fluorometric chemosensors for metal ions, *Sensors Actuators B Chem.* 212 (2015) 297–328.
- [4] J. Wang, H.-B. Liu, Z. Tong, C.-S. Ha, Fluorescent/luminescent detection of natural amino acids by organometallic systems, *Coord. Chem. Rev.* 303 (2015) 139–184.
- [5] A.T. Aron, K.M.R. Torres, J.A. Cotruvo, C.J. Chang, Recognition- and reactivity-based fluorescent probes for studying transition metal signaling in living systems, *Acc. Chem. Res.* 48 (2015) 2434–2442.
- [6] X. Qian, Z. Xu, Fluorescence imaging of metal ions implicated in diseases, *Chem. Soc. Rev.* 44 (2015) 4487–4493.
- [7] H. Zhu, J. Fan, B. Wang, X. Peng, Fluorescent, MRI, and colorimetric chemical sensors for the first-row d-block metal ions, *Chem. Soc. Rev.* 44 (2015) 4337–4366.
- [8] R. Yan, S. Qiu, L. Tong, Y. Qian, Review of progresses on clinical applications of ion selective electrodes for electrolytic ion tests: from conventional ISEs to graphene-based ISEs, *Chem. Speciat. Bioavailab.* 28 (2016) 72–77.
- [9] K.P. Carter, A.M. Young, A.E. Palmer, Fluorescent sensors for measuring metal ions in living systems, *Chem. Rev.* 114 (2014) 4564–4601.
- [10] R. Saini, N. Kaur, S. Kumar, Quinones based molecular receptors for recognition of anions and metal ions, *Tetrahedron* 70 (2014) 4285–4307.
- [11] V.K. Gupta, N. Mergu, L.K. Kumawat, A.K. Singh, A reversible fluorescence “off-on-off” sensor for sequential detection of aluminum and acetate/fluoride ions, *Talanta* 144 (2015) 80–89.
- [12] K. Mariappan, A.G. Sykes, The chemistry of constrained crown ring systems and fluorescence sensor applications, *J. Incl. Phenom. Macrocycl. Chem.* 75 (2013) 23–30.
- [13] Y. Guo, L. Zhang, S. Zhang, Y. Yang, X. Chen, M. Zhang, Fluorescent carbon nanoparticles for the fluorescent detection of metal ions, *Biosens. Bioelectron.* 63 (2015) 61–71.
- [14] W.E. Bazzelle, Applications of ion-selective electrodes, *Anal. Chim. Acta* 54 (1971) 29–39.
- [15] V.K. Gupta, A.K. Singh, L.K. Kumawat, A turn-on fluorescent chemosensor for Zn²⁺ ions based on antipyrine schiff base, *Sensors Actuators B Chem.* 204 (2014) 507–514.
- [16] V.K. Gupta, R. Prasad, R. Mangla, P. Kumar, New nickel (II) selective potentiometric sensor based on 5,7,12,14-tetramethyldibenzotetraazaannulene in a poly (vinyl chloride) matrix, *Anal. Chim. Acta* 420 (2000) 19–27.
- [17] M. Koel, Do we need Green Analytical Chemistry? *Green Chem.* 18 (2016) 923–931.
- [18] Green analytical chemistry: theory & practice, in: M. de la Guardia, S. Armenta (Eds.), *In Series Comprehensive Analytical Chemistry*, 57, Elsevier, 2011 (pp. 244).
- [19] K. Danzer, Analytical chemistry—today's definition and interpretation, *Fresenius J. Anal. Chem.* 343 (1992) 827–828.
- [20] P.T. Anastas, J.C. Warner (Eds.), *Green chemistry: theory and practice*, Oxford University Press, New York, 1998.
- [21] C.J. Welch, N. Wu, M. Biba, R. Hartman, T. Barkovic, X. Gong, R. Helmy, W. Schafer, J. Cuff, Z. Pirzada, L. Zhou, Greening analytical chromatography, *Trends Anal. Chem.* 29 (2010) 667–680.
- [22] M. Kaljurand, M. Koel, Recent advancements on greening analytical separation, *Crit. Rev. Anal. Chem.* 41 (2011) 2–20.
- [23] J.D. Sunderhaus, S.F. Martin, Applications of multicomponent reactions to the synthesis of diverse heterocyclic scaffolds, *Chem. Eur. J.* 15 (2009) 1300–1308.
- [24] H. Eckert, Diversity oriented syntheses of conventional heterocycles by smart multi component reactions (MCRs) of the last decade, *Molecules* 17 (2012) 1074–1102.
- [25] A.U. Lesanko, D.G. Hall, Wanted: new multicomponent reactions for generating libraries of polycyclic natural products, *Curr. Opin. Chem. Biol.* 9 (2005) 266–276.
- [26] E. Ruijter, R. Scheffelaar, R.V.A. Orru, Multicomponent reaction design in the quest for molecular complexity and diversity, *Angew. Chem. Int. Ed.* 50 (2011) 6234–6246.
- [27] J.D. Sunderhaus, C. Dockendorff, S.F. Martin, Applications of multicomponent reactions for the synthesis of diverse heterocyclic scaffolds, *Org. Lett.* 9 (2007) 4223–4226.
- [28] B. Ganem, Strategies for innovation in multicomponent reaction design, *Acc. Chem. Res.* 42 (2009) 463–472.
- [29] L. Weber, K. Illgen, M. Almstetter, Discovery of new multi component reactions with combinatorial methods, *Synlett* 3 (1999) 366–374.
- [30] A. Domling, Isocyanide based multi component reactions in combinatorial chemistry, *Comb. Chem. High Throughput Screen.* 1 (1998) 1–22.
- [31] J.E.B. Hough, A. Younai, J.T. Shaw, Recent advances in multicomponent reactions for diversity-oriented synthesis, *Curr. Opin. Chem. Biol.* 14 (2010) 371–382.
- [32] M. Kumar, L.K. Kumawat, V.K. Gupta, A. Sharma, 2-(Alkylamino)-3-aryl-6,7-dihydrobenzofuran-4 (5H)-ones: improved synthesis and their photophysical properties, *ChemistryOpen* 4 (2015) 626–632.
- [33] L.K. Kumawat, M. Kumar, P. Bhatt, A. Sharma, M. Asif, V.K. Gupta, An easily accessible optical chemosensor for Cu²⁺ based on novel imidazoazine framework, its performance characteristics and potential applications, *Sensors Actuators B Chem.* 240 (2017) 365–375.
- [34] J.M. Khurana, A. Chaudhary, A. Lumb, B. Nand, An expedient four-component domino protocol for the synthesis of novel benzo[a]phenazine annulated heterocycles and their photophysical studies, *Green Chem.* 14 (2012) 2321–2327.
- [35] L.K. Kumawat, M. Kumar, P. Bhatt, A. Jha, V.K. Gupta, A. Sharma, Structure property studies revealed a new indoyl furanone based bifunctional chemosensor for Cu²⁺ and Al³⁺, *Anal. Methods* 8 (2016) 7369–7379.
- [36] V.K. Gupta, A.K. Singh, L.K. Kumawat, N. Mergu, An easily accessible switch-on optical chemosensor for the detection of noxious metal ions Ni(II), Zn(II), Fe(III) and UO₂(II), *Sensors Actuators B Chem.* 222 (2016) 468–482.
- [37] L.K. Kumawat, V.K. Gupta, Highly selective dual channel chemosensor based on benzo[d]thiazole for detection of Zn²⁺ ions, *Int. J. Electrochem. Sci.* 11 (2016) 8861–8873.
- [38] L.K. Kumawat, N. Mergu, A.K. Singh, V.K. Gupta, A novel optical sensor for copper ions based on phthalocyanine tetrasulfonic acid, *Sensors Actuators B Chem.* 212 (2015) 389–394.
- [39] M. Ghaedi, S.Y.S. Jaber, S. Hajati, M. Montazerzohori, M. Zarr, A. Asfaram, L.K. Kumawat, V.K. Gupta, Preparation of iodide selective carbon paste electrode with modified carbon nanotubes by potentiometric method and effect of CuS-NPs on its response, *Electroanalysis* 27 (2015) 1516–1522.
- [40] V.K. Gupta, A.K. Jain, G. Maheshwari, Novel aluminum (III) selective potentiometric sensor based on morin in poly (vinyl chloride) matrix, *Talanta* 72 (2007) 1469–1473.
- [41] V.K. Gupta, A.K. Singh, M. Al. Khayat, B. Gupta, Neutral carriers based polymeric membrane electrodes for selective determination of mercury (II), *Anal. Chim. Acta* 590 (2007) 81–90.
- [42] V.K. Gupta, A.K. Jain, S. Agarwal, G. Maheshwari, An iron (III) ion-selective sensor based on a m bis (tridentate) ligand, *Talanta* 71 (2007) 1964–1968.
- [43] L.K. Kumawat, N. Mergu, M. Asif, V.K. Gupta, Novel synthesized antipyrine derivative based “Naked eye” colorimetric chemosensors for Al³⁺ and Cr³⁺, *Sensors Actuators B Chem.* 231 (2016) 847–859.
- [44] V.K. Gupta, A.K. Singh, L.K. Kumawat, Thiazole schiff base turn-on fluorescent chemosensor for Al³⁺ ion, *Sensors Actuators B Chem.* 195 (2014) 98–108.
- [45] M.B. Teimouri, R. Bazhrang, Shaken not stirred: a facile synthesis of 1,4-bis(furo[2,3-d]-pyrimidine-2,4(1H,3H)-dione-5-yl)benzenes by one-pot reaction of isocyanides, N,N'-dimethylbarbituric acid, and terephthalaldehyde, *Bioorg. Med. Chem. Lett.* 16 (2006) 3697–3701.
- [46] A. Shaabani, M.B. Teimouri, S. Samadi, K. Soleimani, Microwave-assisted three-component condensation on montmorillonite K10: solvent-free synthesis of furopyrimidines, furocoumarins, and furofuranones, *Synth. Commun.* 35 (2005) 535–541.
- [47] M.T. Maghsoodlou, G. Marandi, N. Hazeri, S.M.H. Khorassami, A.A. Mirzaei, Synthesis of 5-aryl-1,3-dimethyl-6-(alkyl- or aryl-amino) furo [2,3-d]pyrimidine derivatives by reaction between isocyanides and pyridinecarbaldehydes in the presence of 1,3-dimethylbarbituric acid, *Mol. Divers.* 15 (2011) 227–231.
- [48] Y. Ito, H. Kato, T.A. Saegusa, New approach for stereoselective synthesis of γ -butyrolactones, *J. Organomet. Chem.* 47 (1982) 741–743.
- [49] N. Chatani, M. Oshita, M. Tobisu, Y. Ishii, S. Murai, S., A GaCl₃-catalyzed [4+1] cycloaddition of unsaturated carbonyl compounds and isocyanides leading to unsaturated γ -lactone derivatives, *J. Am. Chem. Soc.* 125 (2003) 7812–7813.
- [50] M. Oshita, K. Yamashita, M. Tobisu, N. Chatani, Catalytic [4+1] cycloaddition of α,β -unsaturated carbonyl compounds with isocyanides, *J. Am. Chem. Soc.* 127 (2005) 761–766.
- [51] M. Kumar, T. Kaur, V.K. Gupta, A. Sharma, A green, catalyst-free, solvent-free, high yielding one step synthesis of functionalized benzo[f]furo- [3,2-c]chromene-4-(5H)-ones and furo[3,2-c]-quinolin-4-(5H)-ones, *RSC Adv.* 5 (2015) 17087–17095.
- [52] E.J. Olson, P. Buhlmann, Getting more out of a Job Plot: determination of reactant to product stoichiometry in cases of displacement reactions and n:n complex formation, *J. Organomet. Chem.* 76 (2011) 8406–8412.
- [53] H.A. Benesi, J.H. Hildebrand, A spectrophotometric investigation of the interaction of iodine with aromatic hydrocarbons, *J. Am. Chem. Soc.* 71 (1949) 2703–2707.
- [54] Y. Qin, Y. Mi, E. Bakker, Determination of complex formation constants of 18 neutral alkali and alkaline earth metal ionophores in poly(vinyl chloride) sensing membranes plasticized with bis(2-ethylhexyl)sebacate and o-nitrophenyloctylethe, *Anal. Chim. Acta* 421 (2000) 207–220.
- [55] H. Haraguchi, K. Fuwa, Marine analysis by atomic absorption spectrometry, in: J.E. Cantele (Ed.), *Atomic Absorption Spectrometry*, Elsevier, New York 1982, p. 97.
- [56] V.K. Gupta, A. Nayak, Shilpi Agarwal, Barkha Singhal, Recent Advances on Potentiometric Membrane Sensors for Pharmaceutical Analysis, *Combinatorial Chemistry & High Throughput Screening* 14 (4) (2011) 284–302.
- [57] V.K. Gupta, M.R. Ganjali, P. Norouzi, H. Khani, A. Nayak, Shilpi Agarwal, Electrochemical Analysis of some Toxic Metals and Drugs by Ion Selective Electrodes, *Critical Reviews in Analytical Chemistry* 41 (2011) 282–313.

- [58] V.K. Gupta, B. Sethi, R.A. Sharma, Shilpi Agarwal, Arvind Bharti, Mercury Selective Potentiometric Sensor based on Low Rim Functionalized thiacalix [4] arene as a Cationic Receptor, *J. Mol. Liq.* 177 (2013) 114–118.
- [59] V.K. Gupta, S. Kumar, R. Singh, L.P. Singh, S.K. Shoor, B. Sethi, Cadmium (II) ion Sensing through p-tert-butyl calix[6]arene Based Potentiometric Sensor, *J. Mol. Liq.* 195 (2014) 65–68.
- [60] S. Karthikeyan, V.K. Gupta, R. Boopathy, A. Titus, G. Sekaran, A new approach for the degradation of aniline by mesoporous activated carbon as a heterogeneous catalyst: Kinetic and spectroscopic studies, *J. Mol. Liquids* 173 (2012) 153–163.
- [61] V.K. Gupta, L.P. Singh, R. Singh, N. Upadhyay, S.P. Kaur, B. Sethi, A novel copper (II) selective sensor based on Dimethyl 4,4'-(o-phenylene) bis(3-thioallophanate) in PVC matrix, *J. Mol. Liq.* 174 (2012) 11–16.