UNIVERSITAT POLITÈCNICA DE VALÈNCIA

Escuela Técnica Superior de Ingeniería del Diseño

Máster Universitario en Sensores para Aplicaciones Industriales

Selective chromo-fluorogenic chemosensor for Cu^{2+} detection in aqueous solution

Trabajo Final de Máster

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January 2017

Abstract

A simple chemosensor consisted of an Imidazole derivative *(N,N-dimethyl-4-(4,5-di(thiophen-2-yl)-1H-imidazol-2-yl)benzenamine)* was synthesized and characterized. The chemosensor **1** showed a selective colorimetric sensing ability for Cu^{2+} by changing colour from pale yellow to red in aqueous solutions facilitating naked eye detection of Cu^{2+}. The UV/Vis titration in aqueous solutions (MeCN: H_2O, 1:1 (v/v), pH 7.4) showed high sensitivity towards Cu^{2+} with a limit of detection of 4.4 µM which is lower than WHO acceptable limits (31.5 µM) in drinking water. Additionally, the fluorescence of chemosensor **1** in MeCN : H_2O 1:1 (v/v) solutions (1.0×10^{-5} mol dm^{-3}) at pH 7.4 is quenched in the presence of Cu^{2+}.

Keywords: *Chemosensors, Copper (II), Supramolecular chemistry, Molecular recognition.*

1.- Introduction

1.1. Supramolecular Chemistry

In contrast to classical chemistry (the chemistry of covalent bond) supramolecular chemistry study the non-covalent interactions[1] between two or more molecules that formed "supermolecules". The first pioneering works in this new line of chemistry were published by J.M. Lehn[2] at the beginning of the eighties of the twentieth century. Thus, supramolecular chemistry is an interdisciplinary field that study the chemical properties of high complexity molecules which are attached and organized through intermolecular interactions without the participation of any covalent bond. These supramolecular aggregates are based on concepts of coordination chemistry and their theoretical study makes use of physical chemistry, biochemistry and material sciences. Where the characteristic properties of these supermolecules determined by the nature of the intermolecular forces that hold them together. A concept directly related to supramolecular chemistry, that gained attention in the last 20 years, is that of "*Molecular Recognition*"

1.2. Molecular Recognition

Molecular recognition is the selective interaction between a receptor molecule (Host) and a specific substrate (guest) which lead to the formation of a supermolecule.[3] Thus, the receptor is a molecule that has been designed and synthesized to coordinate with a given substrate. In order to achieve this selective coordination, the physical and chemical characteristics of the target substrate should be considered in the synthetic process with the objective of obtaining a receptor with high affinity for the selected guest. This is the concept of *"complementarity"*, [4] which is a key in the synthesis of receptors with high selectivity toward given substrates *(see Figure 1)*. During the design of an appropriate receptor to a given substrate we have to consider a number of features such as the size, charge, the possible formation of hydrogen bonds, the geometry, hydrophobicity and hydrophilicity of that substrate, if the receptor is well designed, a high degree of complementarity with the substrate (similar to that found in most complex biological receptors) could be achieved. The first synthesized receptors in the sixties of the last century, were the crown ethers that were used for the coordination of alkali cations.

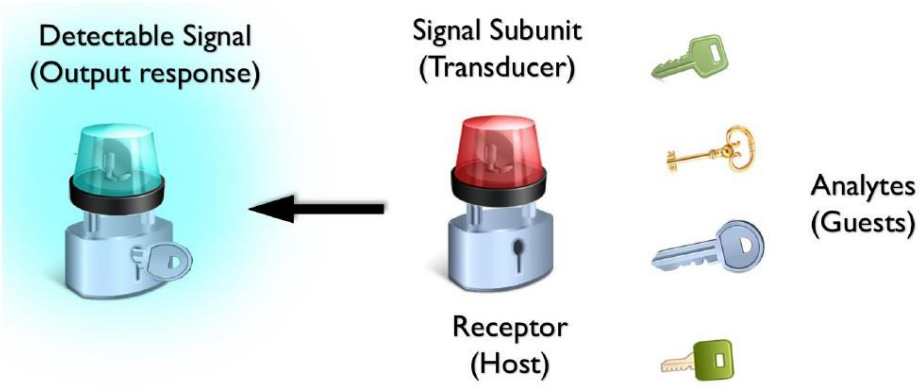


Figure 1: Outlining the molecular recognition event. The receptor subunit of molecular sensor interacts specifically with the complementary analyte. This interaction results in an easily detectable signal produced by the signalling subunit of the molecule

1.3. Molecular chemical sensors

The concepts of the Host-Guest chemistry were used in the synthesis chemical sensors.[5] The sensor is a chemical probe (Host) capable of selectively coordinate with a substrate (Guest) (microscopic event) and report that coordination by an easily measurable signal (macroscopic event). Certain features should be fulfilled by a chemical sensor such as selective recognition, reversible interaction with the guest and fast response in order to carry out real time measurements. As a general trend, chemical sensors are composed mainly by two subunits linked by a covalent bond or by other interactions.

These two units are:

Binding subunit:

This subunit is responsible of the interaction with the substrate (Guest) and must be synthesized in accordance with the properties of the latter in order to obtain a high degree of complementarity.

Signalling subunit:

Their task is related with the transformation of the coordination event into a macroscopic signal. Usually, such signals are changes in optical properties (colour or fluorescence) or modification of redox potentials. Bearing in mind the arrangement of both subunits in the construction of chemical sensors, three different approaches has been described:

Binding site-signalling subunit:

In this method in the chemical sensor, the binding site unit and the signalling unit linked through a covalent bond. The interaction of the guest with the binding site changes the distribution of electrons in the signalling unit which produces a signal that induced a change in the colour or fluorescence. [6] Most chemical sensors are based in this method, for example, Mistri *et al.* *(see Figure 2)* report a mercury sensor in which the interaction of the binding unit of the molecule produced a change in the configuration of receptor ring. [7]

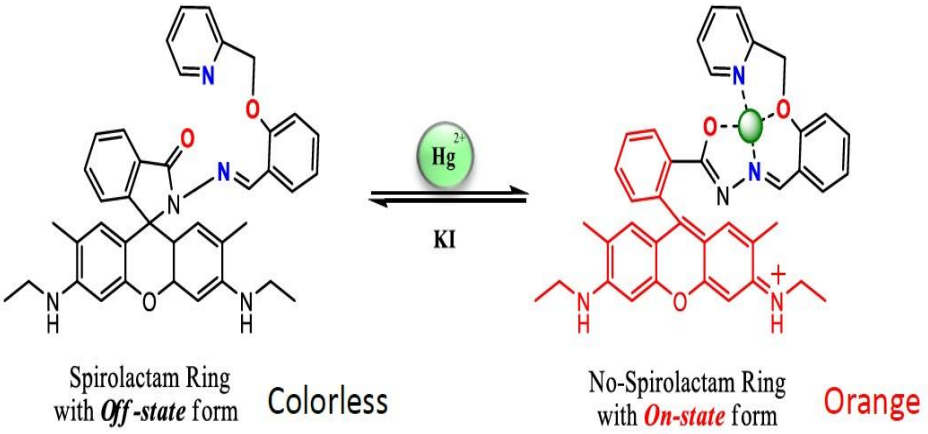


Figure 2: Chromogenic sensor for Hg^{2+} cation detection. as a consequence of coordination, a change of colour from colourless to orange was observed.

Displacement assays:

In this approach the receptor unit form a complex with the signalling molecule where in the presence of the guest displacement occurs accompanied with signalling unit release in the solution. In other cases, the displacement happens with new complex formation (signalling-guest) which have different optical properties of colour or fluorescence. For this method to succeed, it is required that the stability constant of the "receptor-dye" complex is lower than the stability constant of the "receptor-guest" complex. A particular example is a metal form a complex with a dye or fluorophore where a displacement by other metal ion produce colour or/and fluorescence change. Wang *et al.* reported a probe for Ag^+ detection where the displacement of the Ag^+ ion by the iodide produces a change in colour from blue to yellow *(see Figure 3)*. [8]

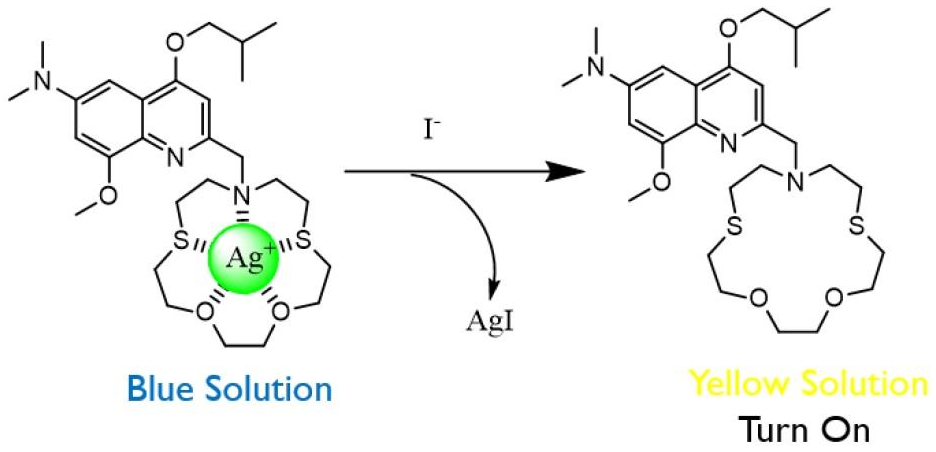


Figure 3: Iodide probe based on the displacement method, the colour change from blue to yellow.

Chemodosimeter:

This assay is based on a specific and generally irreversible chemical reaction between the guest and the probe and usually involves the rupture or formation of covalent bonds. In general, the spectroscopic change that occurs (colour or/and fluorescence) is a consequence of the chemical modifications on the structure of the whole molecule. For example, Xiu *et al*. reported a new cyanide-based Chemodosimeter, where aqueous solutions of the probe were blue and changed to yellow upon addition of the cyanide anion *(see Figure 4)*.[9]

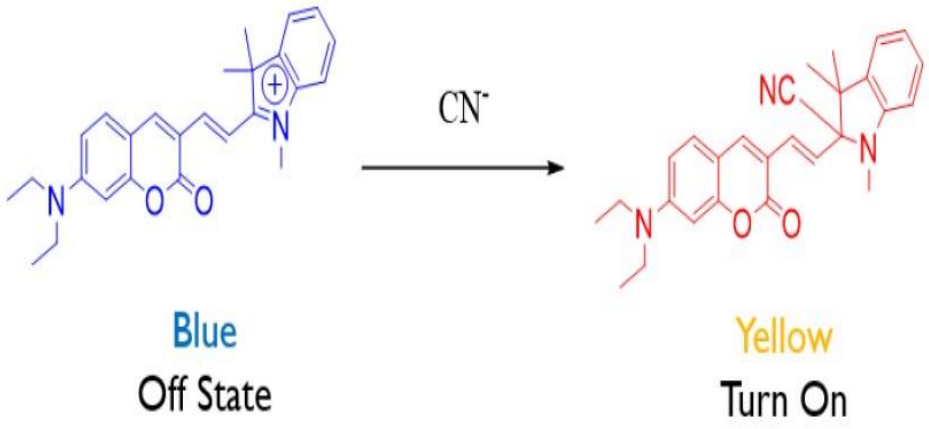


Figure 4: Example of a chemodosimeter for the detection of cyanide, the colour change from blue to yellow**.**

1.4. *Optical sensors*

As discussed in the first part of the introduction, the interaction of a chemical sensor with a target substrate is a process reported by measurable signals.[10] In optical sensors, this interaction is reflected in colour or fluorescence changes. The main advantages provided by the use of optical sensors are:

- Allow rapid and visible detection by naked eye.
- Require a simple instrumentation.
- Non-destructive detection method.
- Require small amount of sample.
- The measurements are carried out in real and short time.

1.5. *Chromogenic sensors*

In chromogenic sensors, the interaction with the analyte ion is reflected in changes in the visible absorption bands that yield colour changes. These sensors have been widely used in detection process because simple equipment was required and also the response could be observed with the "naked eye". Bearing in mind that organic dyes have absorption bands in the region between 380 and 770 nm. For example, it is well established that the conjugated systems of several dyes have the energy difference between HOMO and LUMO that correspond exactly to the visible region of the spectrum and therefore, exhibit naked eye visible colour. However, the more widespread the conjugation system, the smaller the difference between the excited and ground state resulting in a shift of the absorption band to longer wavelengths. Additionally, the absorption band of these organic dyes could be changed by anchoring electron-donating (NR_2, NHR, NH_2, OH^-, OMe) or electron-accepting (NO_2^-, HSO_3^-, SO_3^-, COOH, C=O, CN^-) groups.[11] Apart from organic dyes, there are extensively studies about the use of metal complexes as signalling subunits in the development of chromogenic sensors.[12] These metal complexes are characterized by the presence of partially filled *d* orbitals and, in general, the molecular orbital diagrams of metal complexes are composed mainly of partially occupied *d* orbitals located in the metal and the ligand centred occupied (bonding) and non-occupied (anti-bonding) orbitals. In such systems several types of electronic transitions could be seen:

- *d-d* transitions involving electronic jump between metal *d* orbitals.
- Charge transfer bands of metal-ligand or ligand-metal involving the transfer of electrons from filled orbital of the ligand to unoccupied orbitals of the metal (MLCT bands) or vice versa.

The energy difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) cause the appearance of an absorption band. If a target analyte (T) interacts with acceptor part (A), will produce an increase of electronic conjugation which decrease the energy of interaction, producing a band shift to higher wavelengths (bathochromic effect). However when interact with the donor group, the phenomenon is contrary (hypochromic effect). *(see Figure 5)*

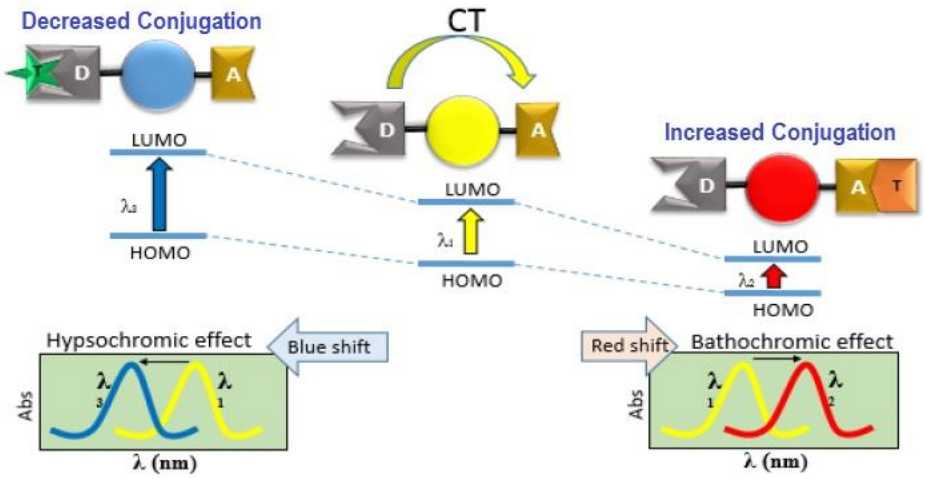


Figure 5: Changes in the absorbance spectrum produced by the interaction of an analyte (T) with the acceptor part of the molecular sensor (A) or with the donor of the molecular sensor (D).

1.6 Fluorogenic sensors

Fluorescence has been used as a versatile tool in the fields of analytical chemistry, biochemistry and cell biology.[13] The variation in the fluorescence intensity after the coordination process has been commonly used as signal response and the position of the emission maximum can also be affected by changes in the molecular structure due to alterations in the energies of the ground and excited states[14]. Besides that, the solvents play an important role in the spectral position and intensity of the fluorescence bands.

2.- Objectives

The aim of this work is the development of a chromo-fluorogenic chemosensor for the optical detection of copper cation in organic solvents and aqueous solutions.

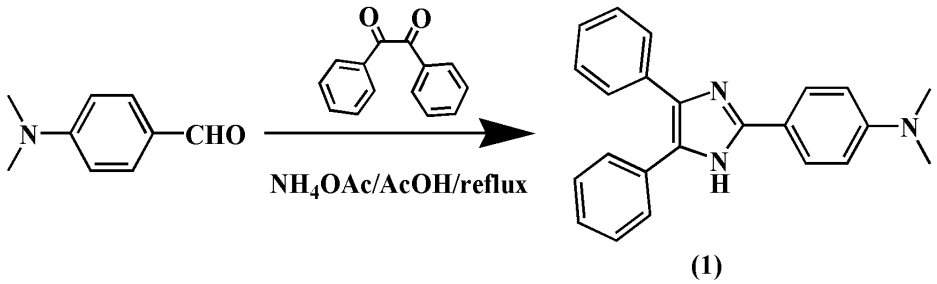
In order to fulfil all the requirements, the chemosensor should present the following features:

- High selectivity for copper cation over other inorganic cations.
- High sensitivity.
- Low limit of detection.
- Recognition in aqueous solution.

3.- Experimental

3. Synthesis of chemosensor 1 *(N,N-Dimethyl-4-(4,5-diphenyl-1H-imidazol-2-yl)benzenamine).*

3.1. Experimental procedure:



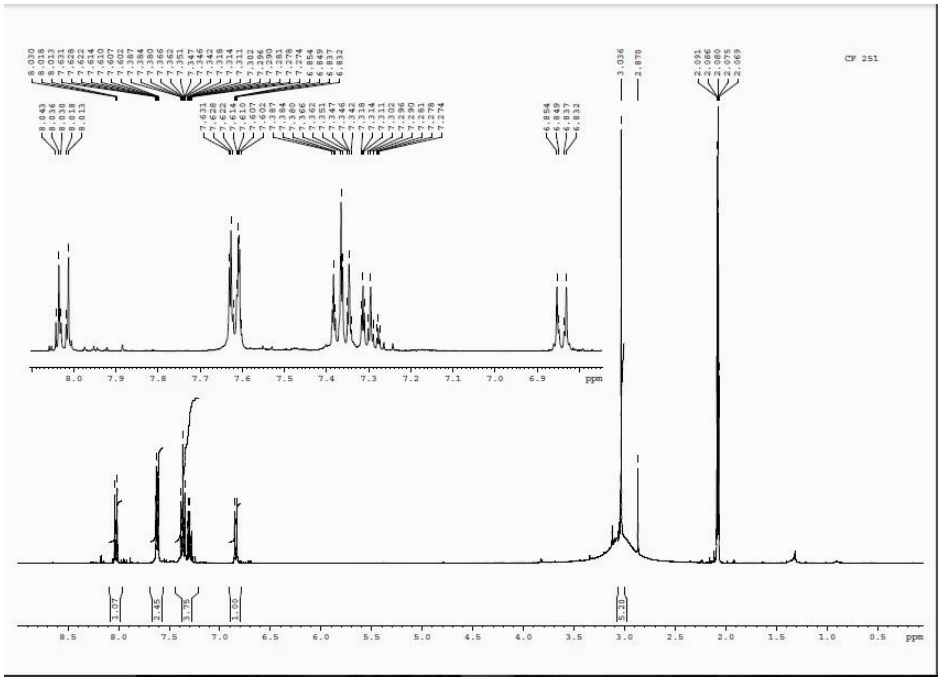
Scheme 1. Synthesis of chemosensor **1**

The chemosensor **(1)** was synthesised by adding *(4-(dimethylamino) benzaldehyde)* (0.15 g,1 mmol), *(diphenylethanedione)* (0.2 g, 1 mmol) and NH_4OAc (20 mmol) to glacial acetic acid (5 mL), followed by stirring and heating at reflux for 8 h. The reaction mixture was then cooled to room temperature, ethyl acetate was added (15 mL) and the mixture was washed with water (3 x 10 mL). After drying the organic phase with anhydrous $MgSO_4$, the solution was filtered and the solvent was evaporated to dryness. The resulting crude product was purified by column chromatography (silica gel, DCM/MeOH (100:01)), Yield (11 mg, 10%) as yellow oil.

3.2. Characterization of chemosensor 1

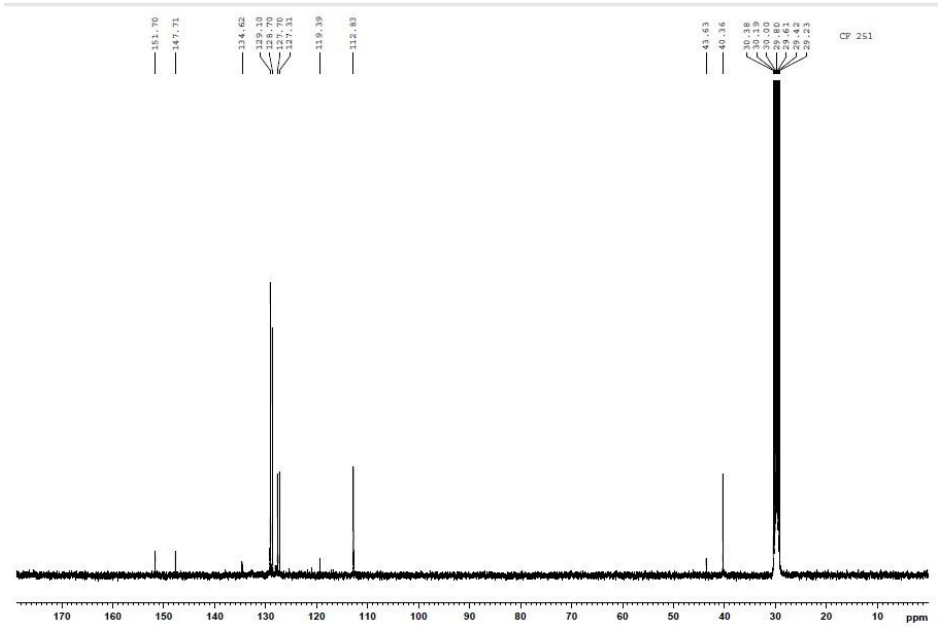
3.2.1.- Nuclear Magnetic Resonance Spectroscopy (^{1}H-NMR)

^{1}H NMR (400 MHz, acetone-d_6): δ = 3.04 (s, 6H), 6.84 (dd, J = 6.8 and 2.0 Hz, 2H), 7.27-7.32 (m, 2H), 7.34-7.39 (m, 4H), 7.61 (d, J = 8.4 Hz, 4H), 8.03 (dd, J = 6.8 and 2.0 Hz, 2H) ppm.



3.2.2.- Nuclear Magnetic Resonance Spectroscopy (^{13}C-NMR)

^{13}C NMR (100.6 MHz, acetone-d_6): δ = 40.36, 112.83, 119.39, 127.31, 127.70, 128.00, 128.20, 128.70, 129.10, 134.62, 147.71, 151.70 ppm.



3.2.3.- Infrared Spectroscopy

IR (liquid film): v = 3420, 2926, 2856, 1692, 1646, 1615, 1549, 1509, 1495, 1446, 1405, 1363, 1250, 1202, 1172, 1124, 1071, 1026, 1002, 966, 945, 822, 766, 696 cm^{-1}.

4.- Results and Discussion

4.1 Copper cation and chemosensors

Much attention has been given in recent years to the development of chemosensors for heavy metal ions due to their environmental harm and biological importance. [15-19] copper as the third most abundant transition metal in the human body, plays vital roles in many fundamental physiological processes. Copper dependent enzymes act as catalysts to help a number of body functions to provide energy for biochemical reactions, transform melanin for pigmentation of the skin, assist the formation of crosslinks in collagen and elastin, and thereby maintain and repair connective tissues.[20-22] However, the excess of Cu^{2+} ion has serious harmful effect on the living systems. The over accumulation in human being leads to various neurodegenerative diseases such as Alzheimer's, Prion, Wilson's, kidney damage, Menkes disease, gastrointestinal disorders, amyotrophic sclerosis, lipid metabolism, and inflammatory disorders. [23-26] Therefore, the rapid and easy detection of Cu^{2+} is very important in environmental and biological systems. However, many of discovered probes require sometimes complicated synthesis and expensive instruments, and some chemosensors are insoluble in aqueous solutions. For practical applications, it is necessary to develop Cu^{2+} sensors that are easily prepared, water-soluble, and shows easy detection without the help of instruments. Hence, colorimetric sensors are very attractive as simple-to-use and naked-eye diagnostic tools.[27, 28]

4.2.- Selectivity of chemosensor 1 in the organic solvents

4.2.1.- UV-Vis Spectroscopy studies

As a first step, the chromogenic behaviour of solution of chemosensor **(1)** in acetonitrile (1.0×10^{-5} mol dm^{-3}) was tested. In the presence of 10 equivalents of selected Cations (*i.e.*, Na^{+}, Mg^{2+}, Al^{3+}, K^{+}, Cr^{3+}, Ca^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Li^{+}, Be^{2+}, Fe^{3+}, Co^{2+}, Hg^{2+}, In^{3+}, Ge^{2+}, As^{3+}, Pb^{2+}, and Ba^{2+}) *(see Figure 6)*. Only the addition of Cu^{2+} induced a remarkable colour modulation from pale yellow to red that was visible to the naked eye *(see Figure 7)*. Other cations tested were unable to induce any such remarkable colour change. In particular, the UV band at 319 nm underwent a bathochromic shift, while a new band appeared at 495 nm upon copper addition due to interaction between Cu^{2+} and the imidazole ring in chemosensor **1**.

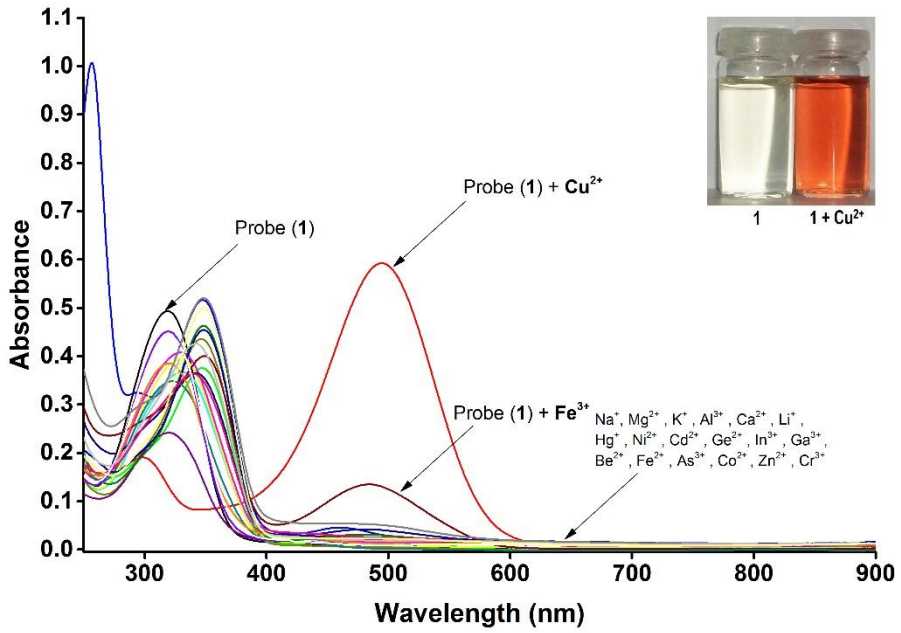


Figure 6: UV-visible spectra of chemosensor **1** (1.0 x 10^{-5} mol dm^{-3} in acetonitrile) in the presence of various metal ions (10 equiv.) Inset: colour of solutions of **1** in acetonitrile observed in the absence and in the presence of Cu^{2+} .

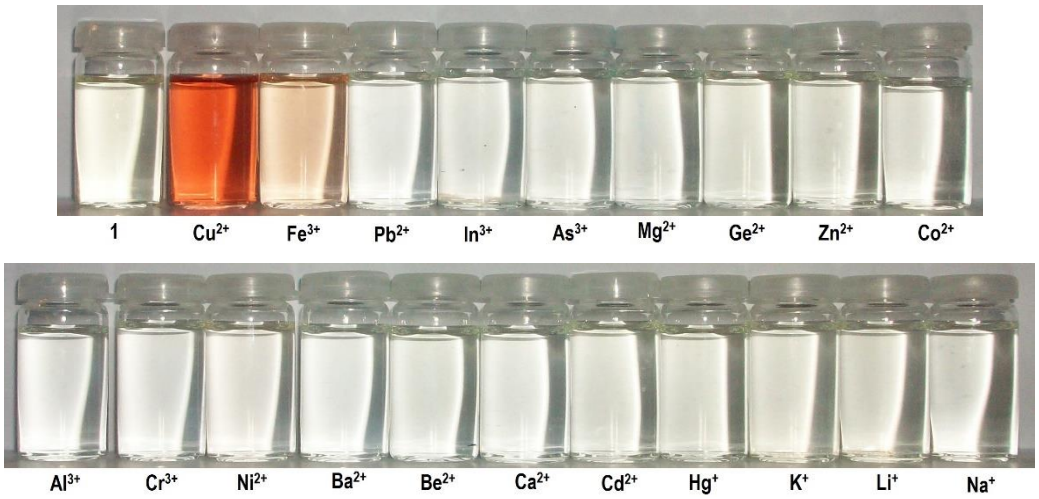


Figure 7: Colour changes observed in acetonitrile solutions of **1** (1.0 × 10^{-5} mol dm^{-3}) upon addition of 10 equiv. of selected metal cations.

(*Figure 8)* Shows that addition of Cu^{2+} to **1** induced a significant absorption changes at 495 nm, whereas addition of the other cations induced negligible modifications.

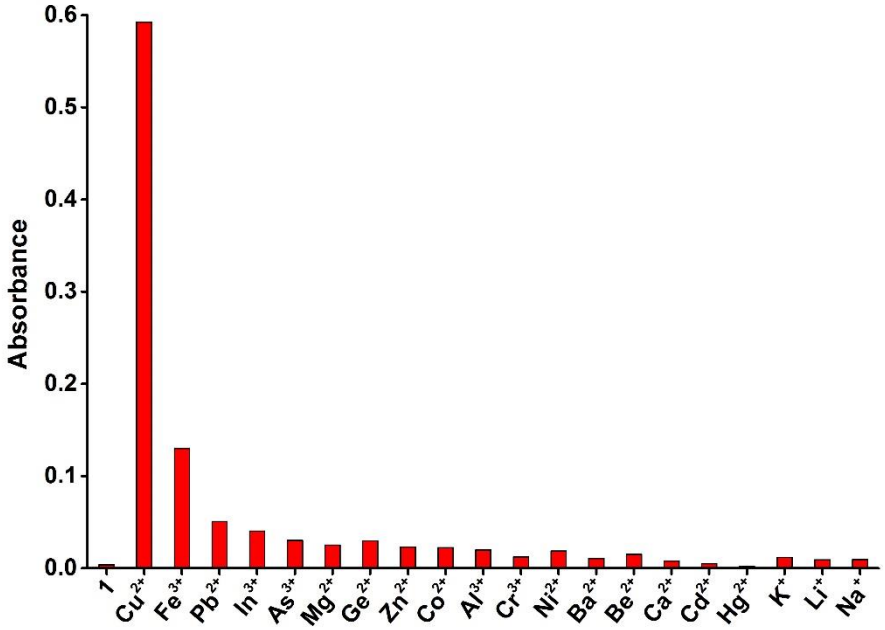


Figure 8: Absorbance at 495 nm of chemosensor **1** (1.0×10^{-5} mol dm^{-3} in acetonitrile) in the presence of 10 equiv. of various metal ions.

4.2.2.- Job's plot of 1 in acetonitrile using UV/Vis

Moreover, in order to determine the binding stoichiometry between **1** and Cu^{2+}, Job's plots were performed using UV- Visible *(see Figure 9)*. It shows the formation of chemosensor-cation complex with 1:1 stoichiometry (only the set of spectra obtained at low metal cation concentrations was used for the estimation of the stability constant). Based in the Job's plots the corresponding stability constants for the formation of $[M\ (1)]^{2+}$ complexes were determined using the OriginPro 9.0 software and adjusting the data to the equilibrium equation:

$$M^{2+} + L \leftrightharpoons [M(L)]^{2+}$$

Equation (1)

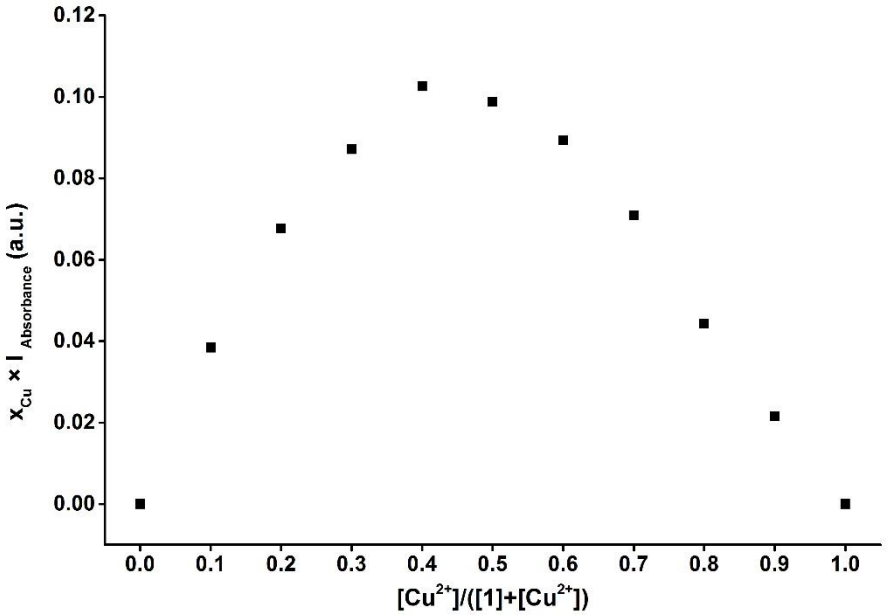


Figure 9: Job's plot for complexation between chemosensor **1** and Cu^{2+} at 318 nm in acetonitrile, the total concentration of **1** with Cu^{2+} was 30 µM.

4.2.3.- UV-Vis Spectra titration of chemosensor 1

Having assessed the highly selective response of **1** toward Cu^{2+} cation, we studied the sensitivity of the chemosensor by monitoring the UV/Vis changes at 25 °C in acetonitrile solutions upon the addition of increasing quantities of Cu^{2+}. The UV/Vis profile obtained in the presence of Cu^{2+} *(is shown in Figure 10)*. As observed, the addition of increasing amounts of Cu^{2+} induced a progressive decrease at λ=319 nm together with simultaneous growth of a new band at λ =495 nm with clear isosbestic points at λ =330 and 390 nm. The appearance of the new absorption band at λ =495 nm was responsible for the pale yellow-to-red colour modulation observed.

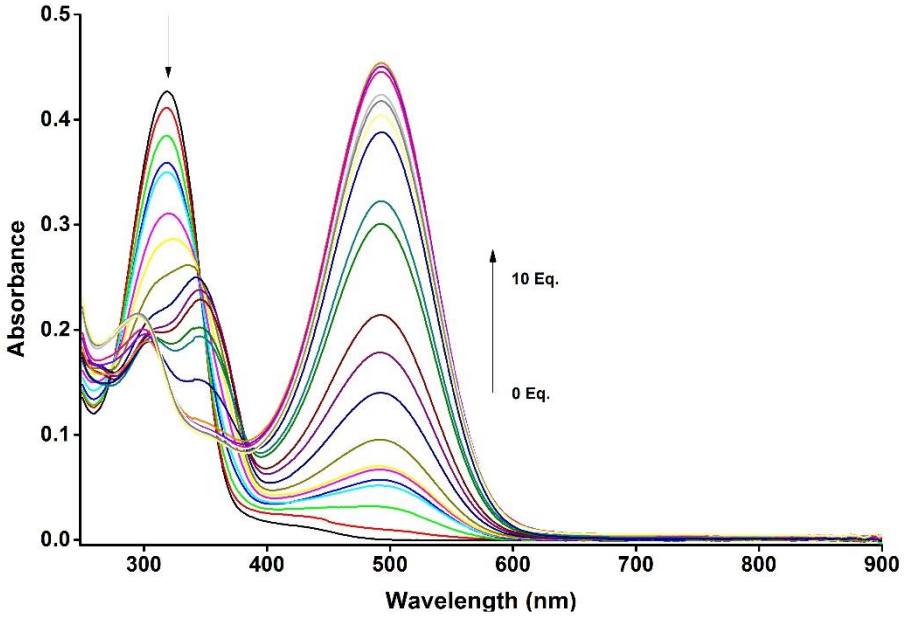


Figure 10: UV-visible profile of the titration of chemosensor **1** (1.0×10^{-5} mol dm^{-3} in acetonitrile) upon addition of increasing quantities of Cu^{2+} cation (0 -10 equiv.).

As shown in *(Figure 11)* the absorbance at 495 nm enhanced gradually with increasing concentration of Cu^{2+} ions. When the addition amount reached 3 x 10^{-5} M, which was three equivalent relatives to **1**, the absorbance was almost constant and was accompanied with an obvious colour change from pale yellow to red. From the obtained titration profile *(Figure 12)* we calculate the stability constant ***(log $K^{[a]}$ > 10)*** and limit of detection (LOD) of Cu^{2+} ***(4.6 µM)***.

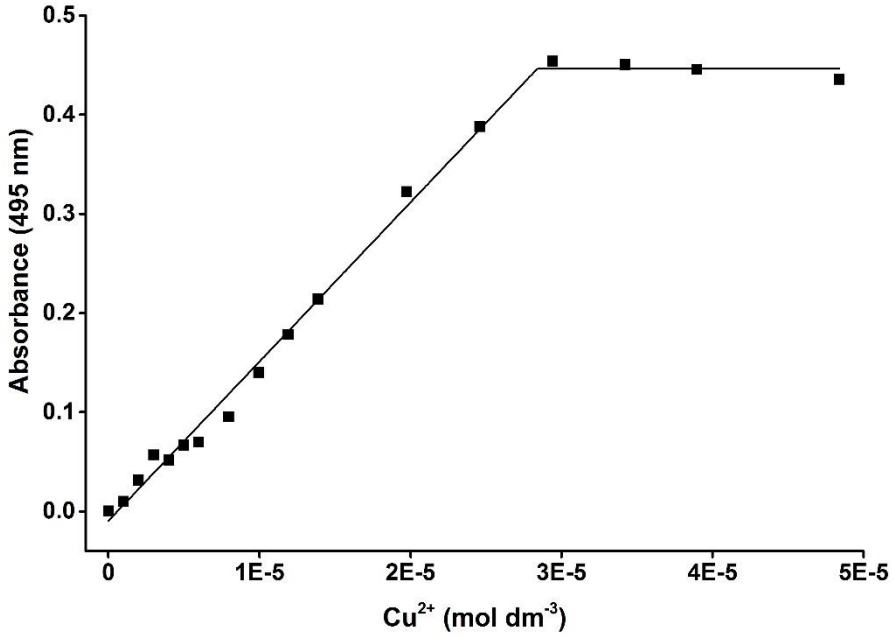


Figure 11: Calibration curve for Cu^{2+} Cation using acetonitrile solution of chemosensor **1** (1.0 x 10^{-5} mol dm^{-3}).

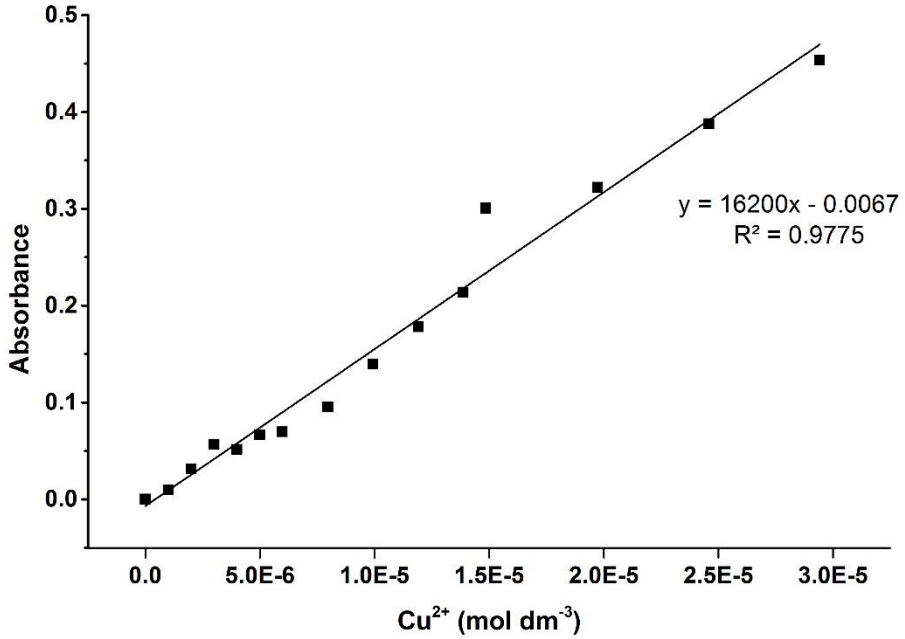


Figure 12: The plot of absorbance changes of **1** (10 µM) in acetonitrile solution against 0–3 µM of Cu^{2+}.

4.2.4.- Fluorescence studies of 1 with Cu^{2+}

In addition to the absorbance changes, the fluorescence was studied upon excitation at the isosbestic point observed in the course of the emission titration between **1** and Cu^{2+} (λ_{ex}=330 nm) *(see Figure 13)*. Addition of increasing amounts of Cu^{2+} induced the progressive quenching of the fluorescence intensity at λ= 440 nm.

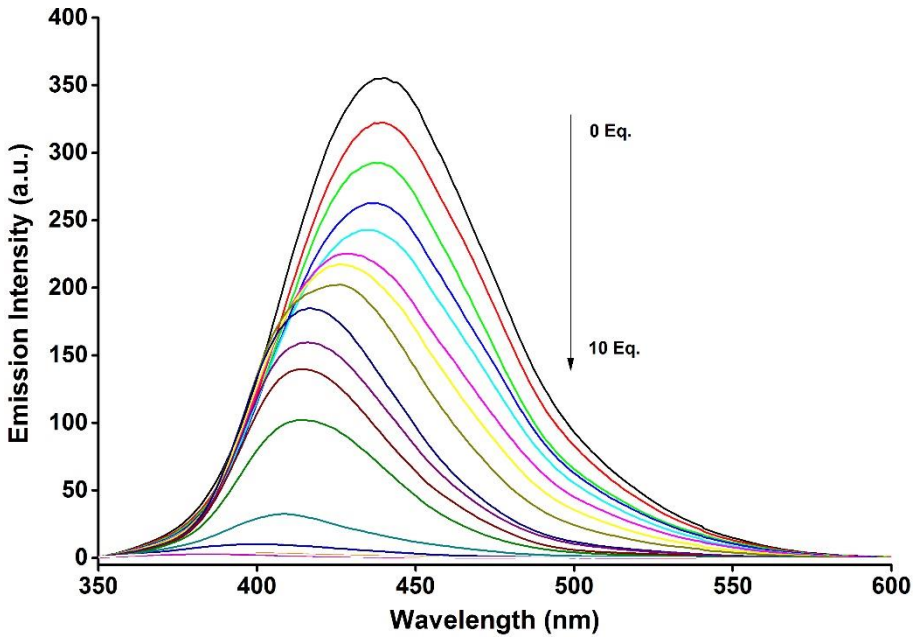


Figure 13: Fluorescence spectral titration of chemosensor **1** (1.0 x 10^{-5} mol dm^{-3} in acetonitrile) upon addition of increasing quantities of Cu^{2+} cation (0-10 equiv.).

4.2.5.- Job's plot of 1 in acetonitrile using fluorescence spectroscopy

The binding stoichiometry between **1** and Cu^{2+} was studied, job's plots were performed by emission studies *(see Figure. 14)* and shows the formation of chemosensor-cation complex with 1:1 stoichiometry.

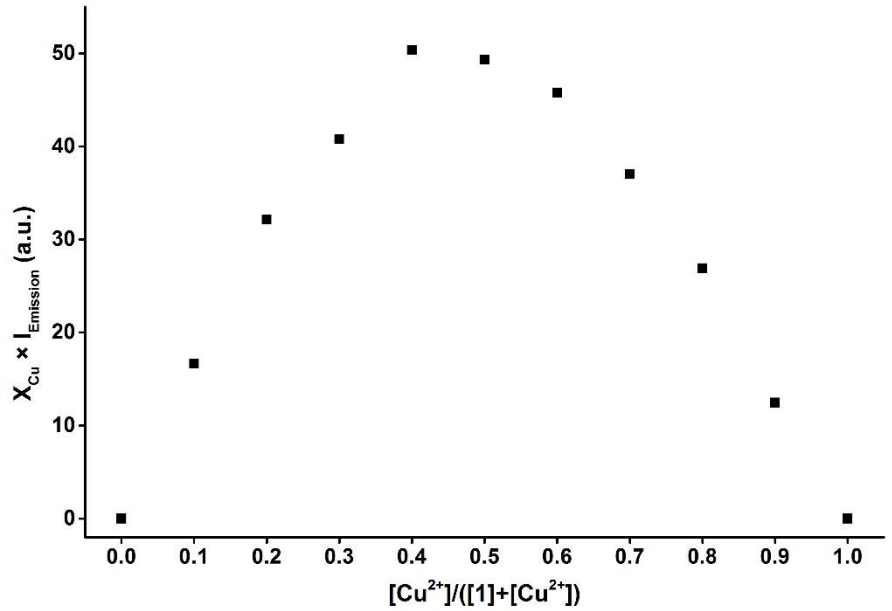


Figure 14: Job's plot for complexation between chemosensor **1** and Cu^{2+} at 438 nm in acetonitrile, the total concentration of **1** with Cu^{2+} was 30 µM.

From a titration profile of Cu^{2+} ions in acetonitrile, chemosensor 1 induce a change in the emission intensity at 440 nm upon addition of increasing quantities of Cu^{2+} cation *(see Figure 15).*

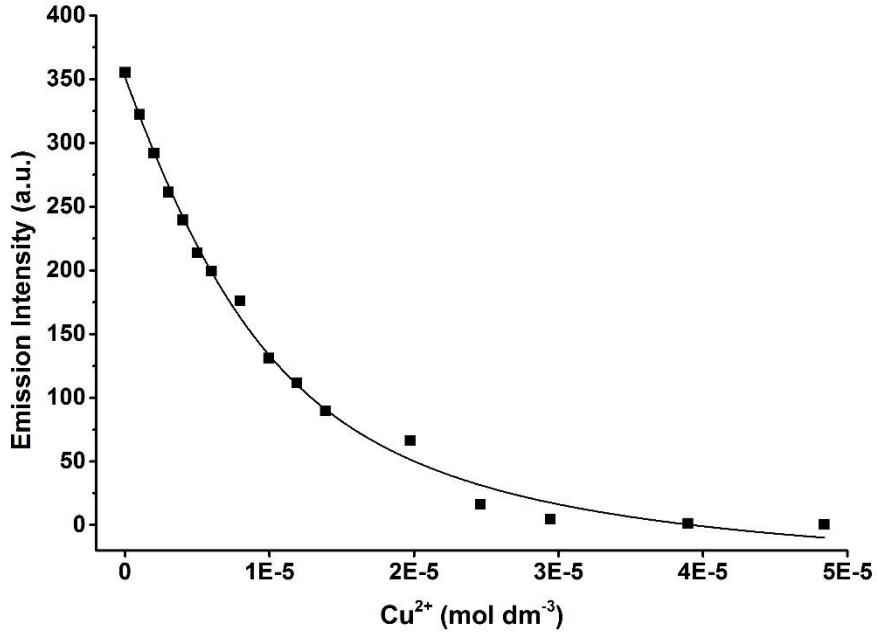


Figure 15: Fluorescence calibration curve for Cu^{2+} Cation and chemosensor **1** (1.0×10^{-5} mol dm^{-3}) in acetonitrile.

From UV-visible and fluorescence emission, the limits of detection **(LOD)** of chemosensor **1** for detecting Cu^{2+} in acetonitrile were evaluated by using the IUPAC regression approach in the micromole µM range. The estimated values of **log *K*** obtained by UV-visible and emission titration profile data are shown in Table 1.

Table 1. LOD values and logarithms of binding constants for the interaction of of chemosensor **1** with Cu^{2+} in acetonitrile.

Limit of detection $[M]^{2+}$		Log $K^{[a]}$	
UV/Vis [μM]	Emission [μM]	UV/Vis	Emission
4.6	2.9	>10	5.3 ± 0.2

[a] Log *K* values for the formation of 1:1 chemosensor – metal complexes [Eq. (1)] .

4.3.- Sensing of Cu^{2+} with chemosensor 1 in aqueous media

4.3.1.- UV-visible spectroscopy studies

The UV-visible behaviour of chemosensor **1** toward copper cation Cu^{2+} in the mixture of (H_2O – MeCN 1:1 v/v, pH 7.4), upon addition of increasing quantities of this cation was studied. At this respect, addition of increasing quantities of copper induced the progressive appearance of new absorption bands centred at 390 nm *(see Figure 16)*.

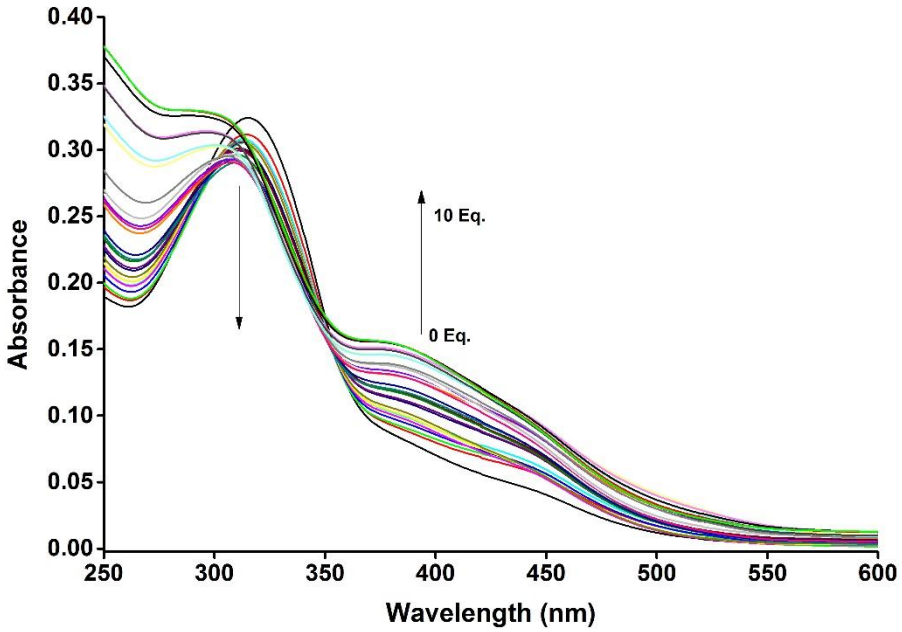


Figure 16: UV-visible profile of chemosensor **1** (1.0×10^{-5} mol dm^{-3} in H_2O– MeCN 1:1 v/v at pH 7.4) on addition of increasing quantities of Cu^{2+} cation (0 -10 equiv).

From the titration profile obtained we calculate the stability constant and the limit of detection. **(See Table 2).**

4.3.2.- Job's plot of 1 in aqueous media using UV/Vis

To determine the binding stoichiometry between chemosensor **1** and Cu^{2+} cation in the mixture of (H_2O – MeCN 1:1 v/v) at pH 7.4, Job's plots were carried out and showed the formation of 1:1 chemosensor – Cu^{2+} complexes *(see Figure 17)*.

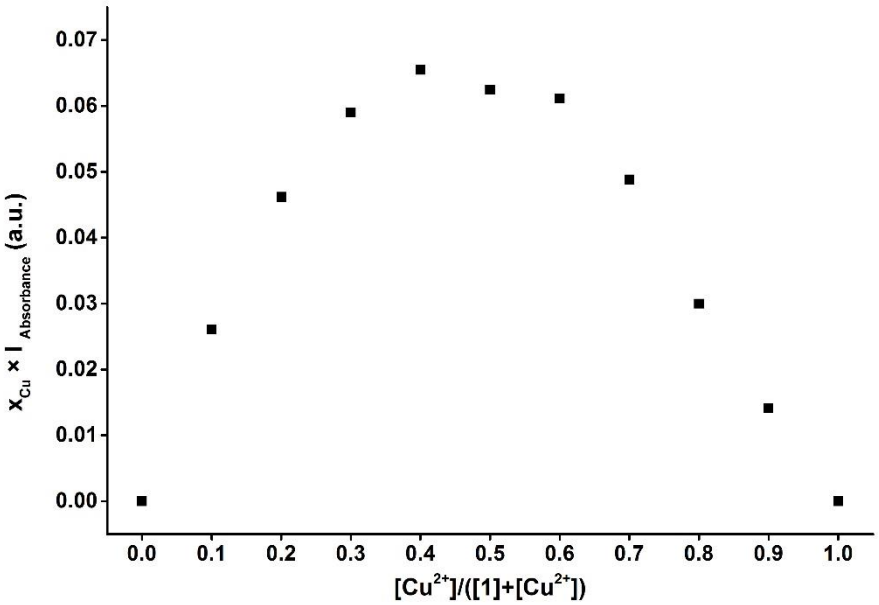


Figure 17: Job plot of chemosensor **1** and Cu^{2+} in (H_2O - MeCN 1:1, v/v, pH = 7.4, the total concentration of **1** with Cu^{2+} was 30 µM.

While up on increasing the amount of Cu^{2+} added as shown in *(Figure 18)*, the absorbance at 390 nm enhanced gradually with increasing concentration of Cu^{2+} ions.

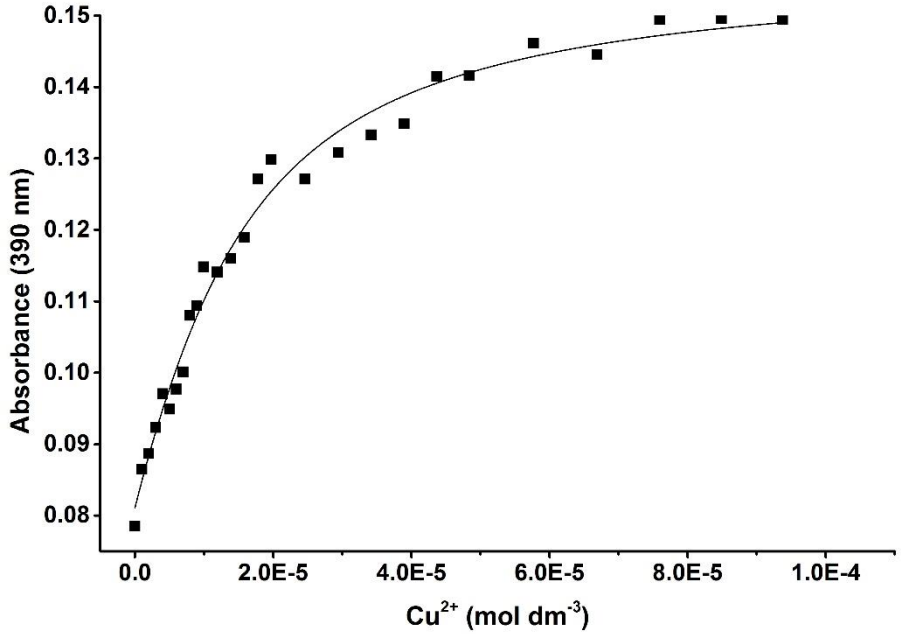


Figure 18: Calibration curve for Cu^{2+} Cation (H_2O: MeCN 1:1 v/v, pH = 7.4) and chemosensor **1** (1.0×10^{-5} mol dm^{-3}).

4.3.3.- Fluorescence studies of 1 with Cu^{2+} in aqueous media

In addition of the sensitivity of chemosensor **1** in acetonitrile, further studies have been done in aqueous solution (H_2O – MeCN 1:1 v/v, pH 7.4). where the intensity of the emission band at 458 nm decreased upon addition of increasing quantities of Cu^{2+} *(see Figure 19).*

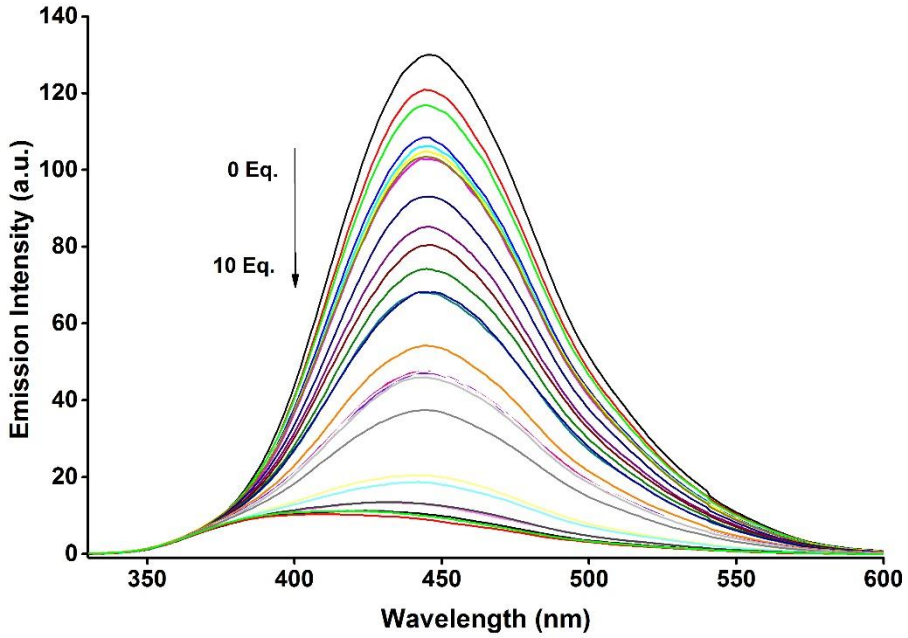


Figure 19: Fluorescence profile of chemosensor **1** (1.0 x 10^{-5} mol dm^{-3} in H_2O – MeCN 1:1 v/v at pH 7.0) upon addition of increasing quantities of Cu^{2+} cation (0 -10 equiv).

4.3.4.- Job's plot of 1 in aqueous media using fluorescence spectroscopy

Using the emission studies, the binding stoichiometry between chemosensor **1** and Cu^{2+} cation in the mixture of (H_2O – MeCN 1:1 v/v) at pH 7.4 was determined, Job's plots prove the formation of 1:1 chemosensor – cation complexes *(see Figure 20).*

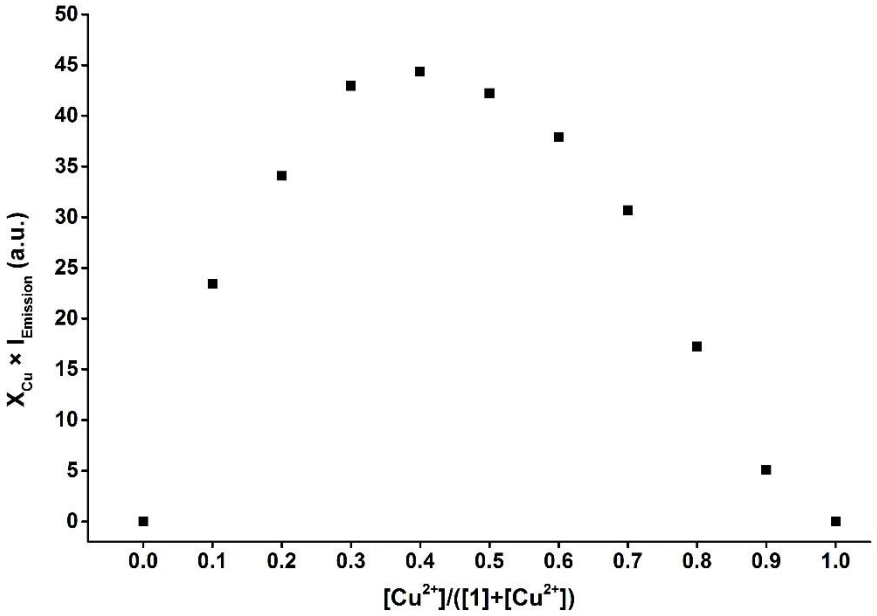


Figure 20: Job plot of chemosensor **1** and Cu^{2+} in acetonitrile/water (1:1, v/v) pH = 7.4, the total concentration of 1 with Cu^{2+} was 30 µM.

From fluorescence emission studies *(see Figure 21)* of chemosensor **1** in aqueous solution (H_2O – MeCN 1:1 v/v, pH 7.4), the limit of detection **(LOD)** and the stability constant **log K** were obtained Table 2.

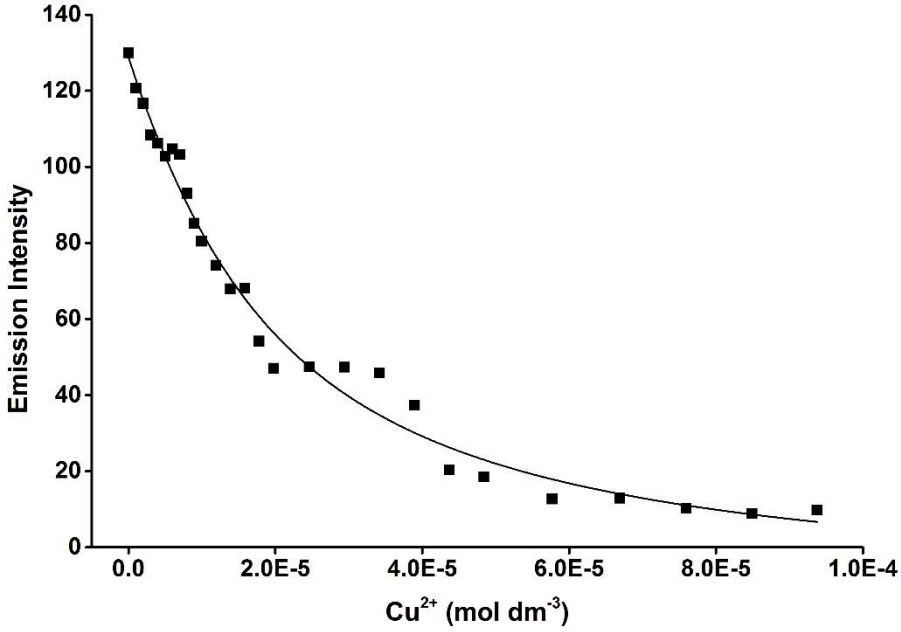


Figure 21: Fluorescence calibration curve for Cu^{2+} Cation in H_2O– MeCN 1:1 v/v at pH 7.4 solution of chemosensor **1** (1.0×10^{-5} mol dm^{-3})

Table 2. LOD values and logarithms of binding constants for the interaction of chemosensor **1** in H_2O – MeCN 1:1 v/v at pH = 7.0 with Cu^{2+} cation.

Limit of detection [M^{2+}]		Log $K^{[a]}$	
UV/Vis [μM]	Emission [μM]	UV/Vis	Emission
4.4	3.19	5.06 ± 0.06	4.84 ± 0.06

[a] Log *K* values for the formation of 1:1 chemosensor – metal complexes [Eq. (1)] .

5.- Conclusions

In summary, we prepared a chromo-fluorogenic chemosensor containing an imidazole derivative bearing two phenyl rings. The chromo-fluorogenic properties of this chemosensor were studied in the presence of several cations using UV-visible and fluorescence titrations. A selective response toward Cu^{2+} was observed in acetonitrile where the solution colour changed from pale yellow to red and a limit of detection in this medium was calculated of 4.6 µM, while in the aqueous solutions (H_2O – MeCN, 1:1 v/v, pH 7.4), the same colour change was observed and a 4.4 µM limit of detection was determined in this mixture. However, from the emission studies, the limit of detection was 2.9 µM in acetonitrile and 3.19 µM in the aqueous solutions.

6.- Acknowledgments

Prima facie, I am grateful to the God for the good health and wellbeing that were necessary to complete this work

Firstly, I would like to express my sincere gratitude to
Prof. Ramón Martínez Máñez for the honour given to me to work with him.

I am grateful to *prof. Félix Sancenón Galarza* for the continuous support and for the daily help

And special thanks for our Academic Director *Prof. M. Dolores Marcos Martínez*

I want to say for the whole team of IDM thanks for your treatment, time, patience and support provided during this work, it has been a pleasure working with everyone.

I wish to express my gratitude to Generalitat Valencia for my fellowship (GRISOLIA/2015/039).

And finally thanks a lot to my family my father Essam Okda,

my mother Amal Rakha, my twin Mohammed, my sister Noha

And all love to my wife Shaimaa and my daughter Lana

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