



## A Benzimidazole based Colorimetric Chemosensor for Selective Detection of Copper Ions

Manoj V. Patil<sup>a</sup>, Ashok A. Patil<sup>a\*</sup>, Nilesh B. Patil<sup>a</sup> and Vijay S. Patil<sup>b</sup>

<sup>a</sup>P.G. Research Centre, Department of Chemistry, JET's Z. B. Patil College, Deopur, Dhule (M.S)– 424002 India

<sup>b</sup>R.F.N.S. Senior science College, Akkalkuwa, Dist.- Nandurbar, (M.S)–425415 India

\*Corresponding Author Email: [ashabhi@rediffmail.com](mailto:ashabhi@rediffmail.com)

**Abstract** A water-applicable Thiobenzimidazole (TBZ) chemosensor, (6-Methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1*H*-benzimidazole, displayed a selective colour change from colourless to purple in the existence of copper ions. The detection limit was computed as  $4.11 \times 10^{-6}$  M which is substantially lower than the World Health Organisation guideline ( $3.15 \times 10^{-5}$  M) for copper ions. The coordination mode of TBZ to copper ions was demonstrated through Job plot. The complex formed between the chemosensor and  $\text{Cu}^{2+}$  ions forms a 1:1 stoichiometry. The analytical detection limit for  $\text{Cu}^{2+}$  by the naked eye is as low as  $10.0 \times 10^{-5}$  M.

**Keywords** Copper Chemosensor, Thiobenzimidazole, naked eye

### 1. Introduction

Copper, the third-most abundant transition element in the body, plays an important role in various physiological processes such as hemoglobin biosynthesis, bone development, dopamine production, nerve function regulation, gene expression, and the functional and structural enhancement of proteins. Due to its redox-active nature, copper serves as an essential co-factor for a variety of metalloenzymes in living organisms such as cytochrome c oxidase, lysyl oxidase, copper-zinc superoxide dismutase and tyrosinase, which have a significant role in the enzymatic defense against oxygen toxicity. However, at high concentration, its redox properties turn into biologically hazardous materials because of its ability to generate reactive species, which create problems in the cellular metabolism. Apart from the biological and environmental importance, other advantages are that copper is relatively abundant, of low cost, and possess good malleability, electrical conductivity, thermal conductivity, chemical stability as well as germicidal efficiency. All of these properties make copper central to the pharmaceutical and industrial sectors for making alloys, electrical wires, machine parts, batteries, drugs and fertilizers etc. However, with excessive loading,  $\text{Cu}^{2+}$  is highly toxic to living organisms. For example, it's over accumulation in human being leads to various diseases including neurodegenerative diseases such as Alzheimer's disease, Wilson's disease, Menkes disease, prion disease, gastrointestinal disorders, kidney damage, amyotrophic sclerosis, lipid metabolism and inflammatory disorders. The World Health Organization (WHO) have reported that the maximum limit of copper in drinking water should be 2 ppm (30  $\mu\text{M}$ ). Under normal conditions, the average concentration of copper in the blood should not exceed 100-150  $\mu\text{g/dL}$ . However, due to the widespread use of copper in household appliances, industry, agricultural and water-pipes,  $\text{Cu}^{2+}$  pollution has increased immensely throughout the world. Therefore, it is necessary to develop fast, convenient and reliable analytical methods for the qualitative and quantitative detection of copper, particularly in drinking water and in biological samples. Several analytical techniques such as atomic absorption spectrometry (AAS), inductively



coupled plasma mass spectroscopy (ICP-MS), inductively coupled plasma atomic emission spectrometry (ICP-AES) and voltammetry, quantum-dot-based assay have been developed for the qualitative and quantitative detection of  $\text{Cu}^{2+}$  ions at trace levels. These technologies can detect  $\text{Cu}^{2+}$  ion selectively with high sensitivity, but tend to need highly sophisticated and expensive instrumentation, and require tedious sample preparation and highly trained operators. By contrast, naked-eye detection methods permit detection of the target analyte at the micro/submicromolar levels without any need for expensive/sophisticated instrumentation. Therefore, given the importance of and the hazardous roles played by copper, we were encouraged to develop a colorimetric sensor with naked-eye capability for detecting  $\text{Cu}^{2+}$  from pure aqueous media. On surveying the literature, we have noted that most of the reported  $\text{Cu}^{2+}$  selective colorimetric sensors have a number of drawbacks, viz long response times, poor detection limits, tedious synthetic procedures, use of organic solvents, and interference from other transition metal ions [1-32].

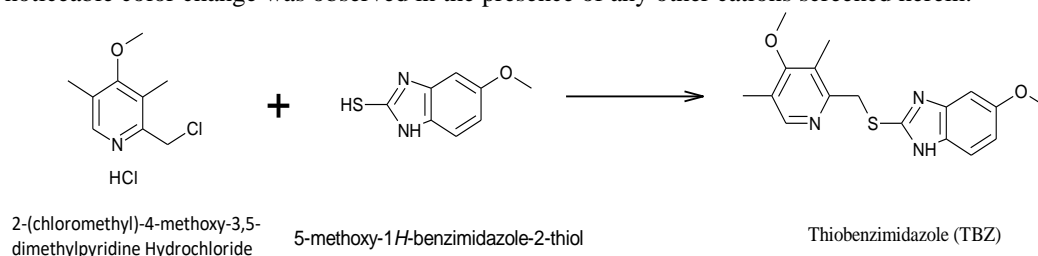
In this study, we reported a Thiobenzimidazole (TBZ), (6-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio)-1*H*-benzimidazole, which can be used as a highly selective colorimetric naked-eye sensor for  $\text{Cu}^{2+}$  in aqueous solution.

## Results and Discussion

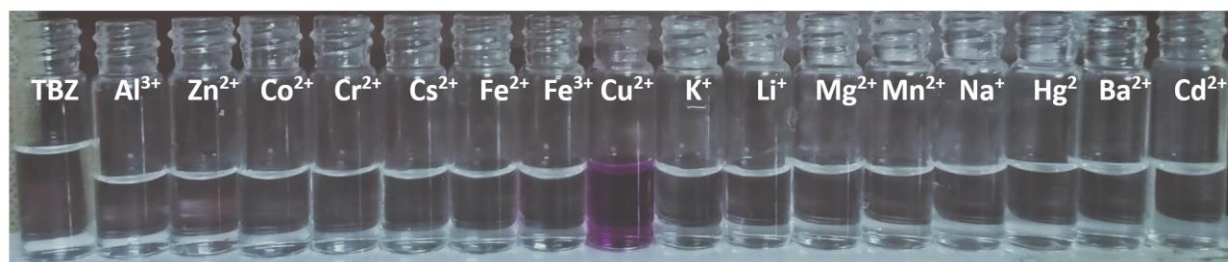
### Naked-eye detection of $\text{Cu}^{2+}$

The synthesis of the Thiobenzimidazole (TBZ) was achieved in one step by the reaction of 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine Hydrochloride and 5-methoxy-1*H*-benzimidazole-2-thiol in presence of sodium hydroxide in water and methanol to give TBZ (**Scheme 1**).

Then, the colorimetric sensing ability of TBZ ( $3 \times 10^{-5}$  M, in Acetonitrile: Water, 10:90, w/w) was tested via the addition of 5 equivalents of various cations ( $1 \times 10^{-2}$  M, in  $\text{H}_2\text{O}$ ). As shown in **Fig. 1**, TBZ exhibits a selective, sensitive and qualitative recognition of  $\text{Cu}^{2+}$  ions in day light/sunlight through a distinct visual color change from colorless to blue. No noticeable color change was observed in the presence of any other cations screened herein.



*Scheme 1: Synthesis of Thiobenzimidazole (TBZ)*



*Figure 1: Naked-eye detectable color change of ions with TBZ in the presence of 5 equivalents of different cations*  
 The concentration dependent naked-eye study was performed (Fig. 1) by addition of various concentrations of TBZ (A =  $1 \times 10^{-3}$  M, B =  $1 \times 10^{-4}$  M, C =  $1 \times 10^{-5}$  M, D =  $5 \times 10^{-5}$ , E =  $1 \times 10^{-6}$  M, F =  $5 \times 10^{-6}$  M and G =  $1 \times 10^{-7}$  M) to a fixed concentration of  $\text{Cu}^{2+}$  ions ( $1 \times 10^{-3}$  M, in  $\text{H}_2\text{O}$ ). The observed color change clearly suggested that the sensor was quite sensitive up to a concentration of  $5 \times 10^{-5}$  M for the detection of  $\text{Cu}^{2+}$  ions. Next, we investigated the effect of changing the concentration of  $\text{Cu}^{2+}$  ions from  $1 \times 10^{-3}$  M to  $1 \times 10^{-7}$  M to a fixed concentration of TBZ ( $1 \times 10^{-4}$  M), which inferred that our sensor was able to detect  $\text{Cu}^{2+}$  up to the concentration of  $1 \times 10^{-5}$  M.



### Cation sensing studies

The cation recognition behavior of sensor TBZ with group I, II and III metal ions ( $\text{Ba}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Cs}^+$ ,  $\text{Li}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Na}^+$ ,  $\text{Al}^{3+}$  and  $\text{K}^+$ ) and transition and heavy metal ions ( $\text{Co}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Hg}^{2+}$ ) was investigated using UV-Vis absorption spectroscopy. The absorption spectrum of sensor TBZ in Acetonitrile: Water, 10:90, w/w) solvent system exhibited one absorption bands centered at 307 nm due to  $\pi\pi^*$  transitions, respectively. Upon addition of 5 equivalents of different cations (50  $\mu\text{L}$ ,  $1 \times 10^{-2}$  M, in water) to a  $5 \times 10^{-5}$  M solution of TBZ in Acetonitrile: Water, 10:90, w/w), only the  $\text{Cu}^{2+}$  ions was able to perturb the absorption spectrum of TBZ effectively. The addition of aqueous  $\text{Cu}^{2+}$  ions to the TBZ solution led to the disappearance of the absorption band at 307 nm and the appearance of a new broad band between 325 nm due to the interaction of the paramagnetic  $\text{Cu}^{2+}$  with TBZ (**Fig. 2**). The appearance of a new charge transfer band was responsible for the naked-eye detectable color change of TBZ. The UV-Vis absorption titration was next performed upon successive addition of 1-10 equivalents of  $\text{Cu}^{2+}$  ions to the solution of TBZ to determine the binding ability and the limit of detection. With the incremental addition of  $\text{Cu}^{2+}$ , the absorbance at wavelength 307nm decreased continuously with the appearance of the new broad peak between 325 nm (**Fig. 3**). The titration resulted in the formation of an isosbestic point at 320 nm, which suggested the formation of a complex between TBZ and copper ions in solution.

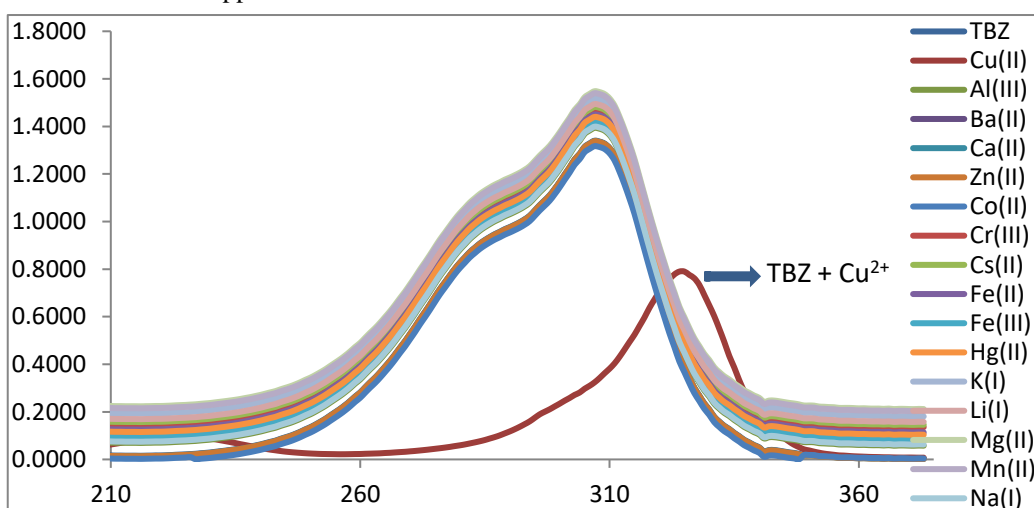


Figure 2: TBZ's absorption spectra when 5 equivalents of various cations are present

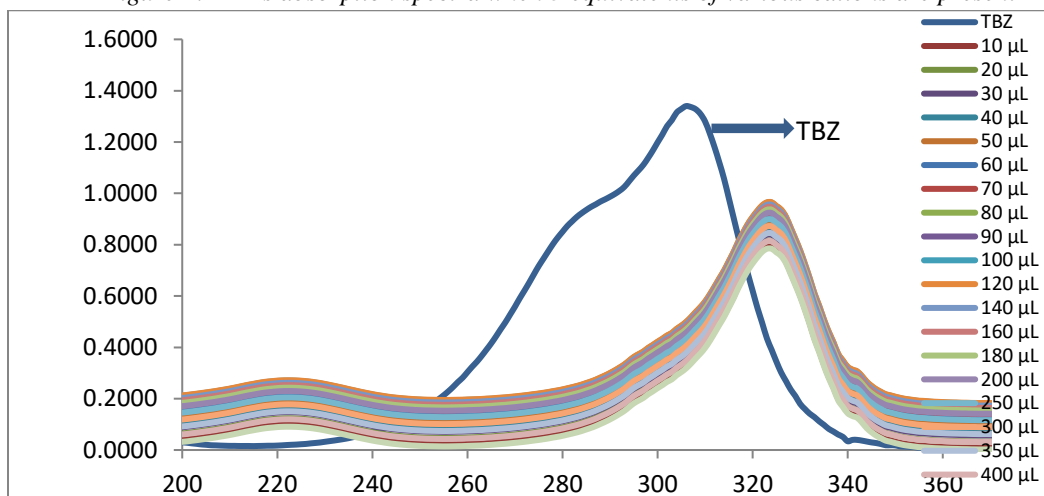


Figure 3: TBZ absorption spectra change as  $\text{Cu}^{2+}$  ions are added in small amounts (1-10 equiv.). A mole ratio plot, or change in the absorption spectrum ( $A$  at  $\text{max}=325$  nm), is shown in the inset as a function of the concentration of  $\text{Cu}^{2+}$  ions



The association constant ( $K_a$ ) was estimated graphically by plotting  $1/\Delta A$  against  $1/[Cu^{2+}]$  (Fig. 4). The data was linear (fitted according to the Benesi–Hilderbrand equation) and the  $K_a$  value was obtained from the slope and intercept of the line. The  $K_a$  value for the TBZ copper complex was found to be  $2.8 \times 10^4 \text{ M}^{-1}$  ( $R^2 = 0.9961$ ). The value suggested that the sensor TBZ has high affinity towards  $Cu^{2+}$  ions. The limit of detection (LOD) and limit of quantification (LOQ) of TBZ were also calculated from the absorption titration data. According to the IUPAC definition, the LOD and LOQ were calculated using the relationship  $LOD = (3.3 \times \text{standard deviation})/\text{slope}$  and  $LOQ = (10 \times \text{standard deviation})/\text{slope}$ . To calculate the relative standard deviation, the absorption measurements of ten blank samples were taken.

As shown in Fig. 4, the absorbance calibration values were normalized between the minimum intensity and the maximum intensity and then a linear regression curve was fitted to these normalized data to get the slope. With this approach, the LOD and LOQ were found to be  $4.11 \times 10^{-6} \text{ M}$  and  $1.24 \times 10^{-5} \text{ M}$ , respectively.

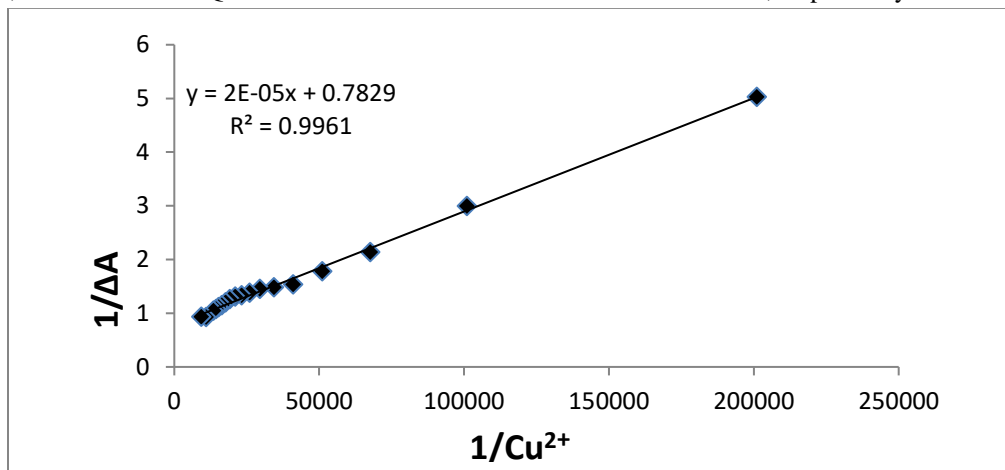


Figure 4: The Benesi-Hilderbrand plot of the chemosensor TBZ with the  $Cu^{2+}$  ion is used to determine the association constant or binding constant. (where,  $\Delta A$  is at  $\lambda_{max} = 307 \text{ nm}$ ).

The 1:1 binding stoichiometry for the complexation between TBZ and  $Cu^{2+}$  was determined using a Job's plot experiment (Fig. 5). Furthermore, more direct evidence for the formation of this 1:1 complex was obtained from the ESI-MS spectra of TBZ in the presence of 1.0 equivalent of  $Cu^{2+}$  in Acetonitrile: Water, 10:90, w/w) (Fig. 3).

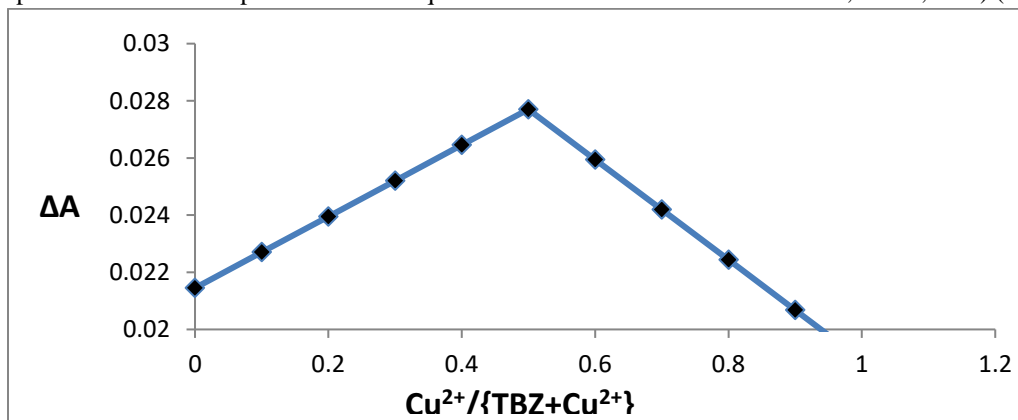


Figure 5: Job's plot for the determination of a 1:1 stoichiometry upon complexation of TBZ with  $Cu^{2+}$  ions (where,  $\Delta A$  is at  $\lambda_{max} = 325 \text{ nm}$ ).

The chemosensor TBZ can bind to the  $Cu^{2+}$  ion via binding sites consisting of an amine and a Sulfide group. All the crystal structures reported for complexes with similar ligands show the coordination through amino nitrogen and sulphur of Sulfide group [33-38]. Thus, the lone pair of electrons on the nitrogen atoms of the amino and Sulfide groups of the sensor TBZ are delocalized to the vacant orbital localized on the  $Cu^{2+}$  as shown in the Fig. 6. This electron donation or charge transfer gave rise to a color change from colorless to blue. The charge of the copper is +2



and hence there should be two negative charges in our proposed structure for charge neutrality. Therefore, we propose the deprotonation of -NH group and the inclusion of  $\text{ClO}_4^-$  counter ion in the complex formula.

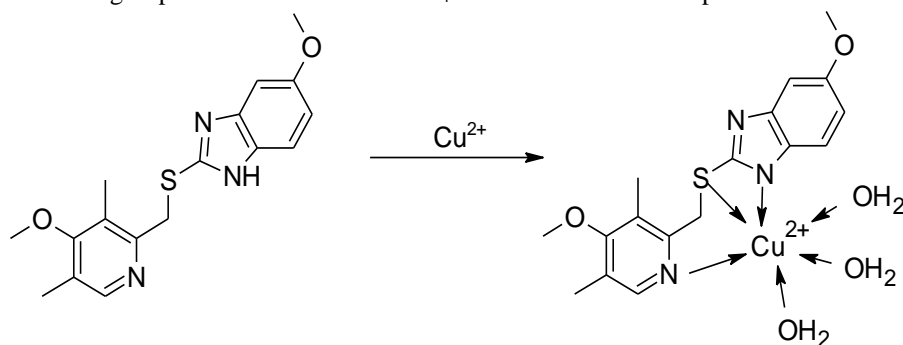


Figure 6: Proposed mode of binding of  $\text{Cu}^{2+}$  ion with TBZ as shown by the color change

Practical applications of analytical applicability of TBZ were first tested by performing competitive experiments. The absorption and color changes caused by the mixture of  $\text{Cu}^{2+}$  with the other metal ions was similar to that caused by  $\text{Cu}^{2+}$  alone, which indicates that the other metal ions did not interfere with the binding of the chemosensor TBZ with  $\text{Cu}^{2+}$ . Secondly, the reversibility of TBZ for the detection of  $\text{Cu}^{2+}$  was examined. To perform the reversibility test, a stock solution of TBZ ( $1 \times 10^{-3}$  M) was first treated with 1 equivalent of  $\text{Cu}^{2+}$ . The color of the solution changes from colorless to Purple. To the same solution, the reverse color change from purple to colorless was observed upon addition of 4 equivalents of aqueous EDTA solution. This result demonstrated the reversibility of the sensor TBZ. The sensing of  $\text{Cu}^{2+}$  by TBZ worked very well on a solid support (Fig. 7). In this experiment, the silica gel (60–120 mesh, 10.0 g, colorless) was soaked with TBZ (in methanol, 50 mL,  $1 \times 10^{-2}$  M) and then dried to afford a faint pink color silica gel due to the adsorption of the sensor on the surface. When the treated silica gel was added to a 10 mL aqueous solution of  $\text{Cu}^{2+}$  ( $1 \times 10^{-3}$  M), the faint pink color promptly turned to a dark greenish/yellow color (supporting video). The instantaneous color change of the solid silica gel in aqueous solution clearly inferred the practical application of TBZ for the qualitative detection of  $\text{Cu}^{2+}$  in aqueous medium. Then, the TBZ supported silica gel was treated with different concentrations of  $\text{Cu}^{2+}$  ( $\text{B} = 1 \times 10^{-3}$  M,  $\text{C} = 1 \times 10^{-4}$  M,  $\text{D} = 1 \times 10^{-5}$  M,  $\text{E} = 1 \times 10^{-6}$  M), which indicated that the silica gel can be used to detect  $\text{Cu}^{2+}$  up to  $1 \times 10^{-5}$  M by a visually detectable color change (Fig. 8). The results indicate that we can use this silica supported method not only in the determination of  $\text{Cu}^{2+}$  ions from water but also in the extraction / separation of  $\text{Cu}^{2+}$  ions from water. In another approach, the practical utility of TBZ for the detection of  $\text{Cu}^{2+}$  was studied by developing a TLC strips. The TLC strips was dipped in the methanolic solution of TBZ ( $1 \times 10^{-2}$  M) followed by drying in air to prepare the desire test strip. When this strip was dipped into an aqueous solution of  $\text{Cu}^{2+}$  ( $1 \times 10^{-3}$  M), the colorless strip sharply turned to a purple. The rapid color change of the TLC strip in solution clearly inferred the practical application of TBZ for the qualitative detection of  $\text{Cu}^{2+}$  in aqueous medium.

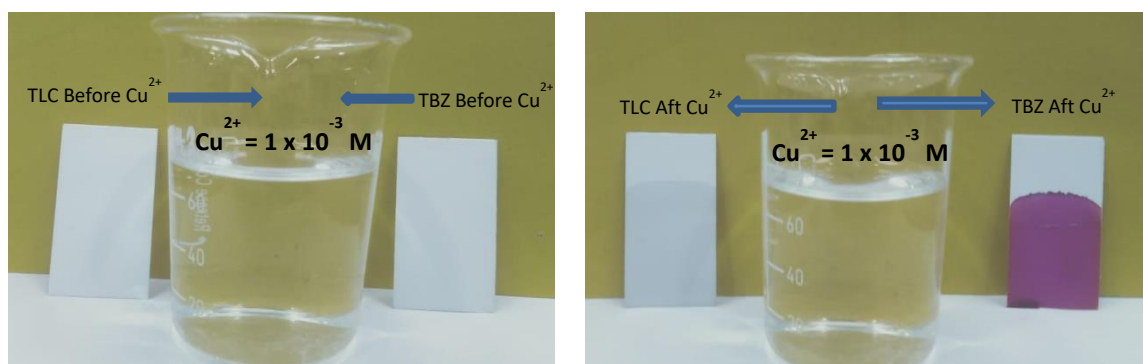


Figure 7: Application of sensor TBZ on supported silica, and color changes of silica gel with / without TBZ and  $\text{Cu}^{2+}$  solution (before and after the addition).





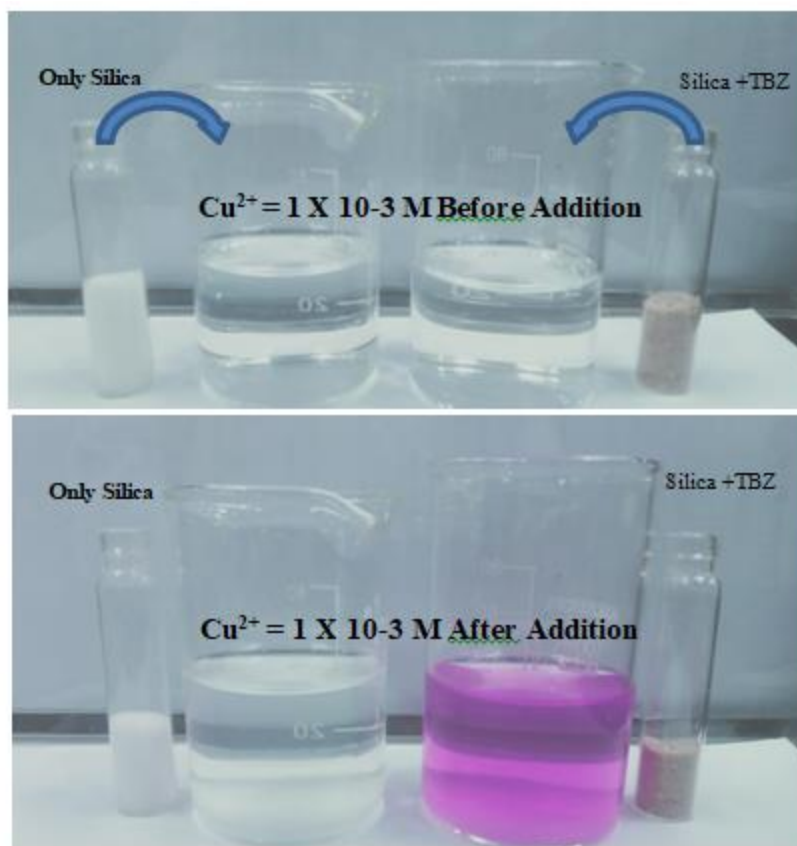


Figure 8: TBZ supported silica gel was treated with different concentrations of  $\text{Cu}^{2+}$ . A=silica without TBZ +  $1 \times 10^{-3} \text{ M Cu}^{2+}$  as control.

## Experimental

### Chemicals and Instrumentations

Unless otherwise stated, all chemicals used for the synthesis of TBZ were of AR grade and were purchased either from spectrochem and Avra chemicals. All solvents were of spectroscopic grade and were used without further treatment. The aqueous stock solutions of cations ( $1 \times 10^{-2} \text{ M}$ ) such as  $\text{Al}^{3+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Cs}^{2+}$ , and  $\text{Zn}^{2+}$  were prepared from their perchlorates salts;  $\text{K}^{+}$  and  $\text{Na}^{+}$  were prepared from their nitrate salts;  $\text{Hg}^{2+}$  from its chloride salt and  $\text{Li}^{+}$  from its bromide salt. After making a stock solution of TBZ ( $1 \times 10^{-3} \text{ M}$ ) in methanol, the solution was diluted to  $5 \times 10^{-5} \text{ mol L}^{-1}$  using acetonitrile: water (10:90 w/w). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at ambient temperature in  $\text{CDCl}_3$  with TMS as internal standard and chemical shifts reported in ppm. Mass spectra were recorded on a Bruker Compact HD mass spectrometer. The IR spectra were recorded on a Perkin Elmer FTIR spectrophotometer by using KBr discs and the IR bands are expressed in frequency ( $\text{cm}^{-1}$ ). Absorption spectra were recorded on a Perkin Elmer U 3900 Co, USA UV/Visible double beam spectrophotometer. The purity of the compound and progress of the reaction was monitored by means of a thin layer chromatography (TLC). Pre-coated silica gel 60 F254 (Merck) on alumina plate ( $7 \times 3 \text{ cm}^2$ ) was used and visualized by using either an iodine or a short UV/Visible lamp. Melting points were recorded on the Celsius scale by open capillary method and are uncorrected. Synthesis of TBZ The chemosensor TBZ was synthesized by following the reported method [38-48]. In single step as depicted in Scheme 1. Added compound A (10 g, 1.0 eq.) and compound B (8.1 g, 1.0 eq.) to the 100 ml of toluene and stirred. Added Sodium hydroxide solution (4.5 g NaOH and 10 ml of Water) to the reaction mass. Heated reaction mass to the  $60\text{--}65^\circ\text{C}$ . Stirred for 4-5 h. Completion of reaction checked by TLC. Reaction mass was cooled to  $20\text{--}30^\circ\text{C}$ . 50 ml of water was added to the reaction mass and stirred. Layer was separated. Organic layer



was washed with 1% aqueous acetic acid solution (50 ml). Partial toluene was distilled off from the reaction mass. Cool the reaction mass to 20-30 °C. Reaction mass was filtered off after maintaining 10-12 hrs at RT. Then solid washed with 10 ml of toluene. After drying we got TBZ (12.2 g.)

Yield: 82.9 %; Physical Nature: Pale yellow solid; Melting Point: 108-110 °C; IR (cm<sup>-1</sup>) [KBr]: 2958, 1635, 1593, 1456, 1436, 1404, 1344, 1263, 1190, 1155, 1080, 1029, 837, 806, 657cm<sup>-1</sup>. MS: m/z 330.2 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm): δ 2.39 (s, 3H), 2.42 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 4.38 (s, 2H), 6.79 (m, 1H), 7.03 (d, 1H, J = 2.5), 7.39 (d, 1H, J = 8.5), 8.24 (s, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, δ ppm): δ 160.08, 154.72, 154.60, 150.61, 147.68, 139.96, 136.09, 122.22, 117.20, 110.38, 109.23, 102.10, 60.65, 56.03, 31.59, 12.64, 10.03

### Acknowledgement

We gratefully acknowledge Chairman, the Director and Principal JET's Z.B. Patil College, Dhule for providing lab facilities, constant encouragement and useful suggestions.

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