Novel Quinoline-Based Thiazole Derivatives for Selective Detection of Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ Ions

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ABSTRACT: New quinoline-based thiazole derivatives QPT and QBT were synthesized and characterized by various spectroscopic and single-crystal X-ray crystallographic studies. The metal-sensing properties of the probes were further examined by absorption and fluorescence spectrometry. The fluorescence intensity of QPT and QBT was remarkably quenched during the addition of Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ ions in THF/H$_2$O (1:1) at pH = 7.4 in HEPES buffer, while the addition of other metal ions did not affect the fluorescence intensity of the ligands. The detection ability of the probes QPT and QBT was further investigated by titration with various equivalents of metal ions, optimized pH ranges for detection, and reversibility with Na$_2$EDTA for biological applications.

INTRODUCTION

Heavy-metal ion detection has been given more attention in recent research because of its toxicity to the environment and living organisms. In particular, iron and copper ions have an important role in enzyme activities and redox processes and are widely used in different fields like biological, agricultural, electronics, industries, etc. Iron is the most essential biologically important element that is present in hemoglobin, myoglobin, and iron–sulfur protein. It also plays an important role in the formation of DNA and RNA in living organisms. Deficiency of Fe$^{2+}$ and Fe$^{3+}$ leads to low blood pressure, anemia, liver and kidney damage, etc. However, excess of the iron leads to the formation of reactive oxygen species and induces cell damage. Therefore, monitoring and detection of the level of iron plays an important role in the biological field.

Copper is an important trace element for essential physiological functions in human beings, animals, plants, and also for insects and microorganisms. It is a cofactor and structural element of various processes such as neurotransmission, enzyme and other protein-requiring metabolic processes, scavenging of free radicals, iron transportation, energy generation, and pigmentation. However, copper deficiency or the over-accumulation of copper in the human body can lead numerous disorders such as liver damage, kidney damage, neurotoxicity, Wilson’s disease, Parkinson’s disease, and Alzheimer’s disease. Furthermore, increased accumulation of copper can lead to severe toxic effects due to oxidative stress caused by redox cycling reactions between copper and cellular reduction-prone species such as biothiols.

Hence, the detection of iron and copper ions with simple methods attracts interest in analytical chemistry. Different analytical instruments such as those of atomic absorption (AAS), emission spectroscopy (AES), inductively coupled plasma mass spectrometry (ICPMS), inductively coupled plasma atomic emission spectrometry (ICP-OES), electrochemical methods, and X-ray fluorescence spectroscopy (XRF) have been used. However, fluorescent and colorimetric detection of metal ions is in demand due to simplicity, lesser time consumption, and cost-effectiveness. Therefore, the development of new Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ sensors with simple instruments is a recent trend in analytical chemistry.

In this context, we have focused on synthesizing a suitable chemosensor for the detection of Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ with several donor atoms like N and S for chelation. Among nitrogen and sulfur-containing heterocycles, quinoline and thiazole analogues were broadly used for the detection of metal complexes. Herein, we have synthesized novel quinoline-based phenyl thiazole (QPT) and benzothiazole (QBT) derivatives. We have examined the detection ability of QPT and QBT chemosensors toward the metal cations Al$^{3+}$, Ca$^{2+}$, Cd$^{2+}$, Co$^{2+}$, Cu$^{2+}$, Fe$^{3+}$, Fe$^{2+}$, Hg$^{2+}$, K$^+$, Mg$^{2+}$, Mn$^{2+}$, Na$^+$, and Pb$^{2+}$.
8.15 for Q-NH, and aromatic protons at 2.83 ppm as a triplet, broad singlets at 3.56 ppm as a multiplet and 3.60 ppm as a singlet. The 13C NMR spectra of QPT show signals for aromatic carbons.  

**RESULTS AND DISCUSSION**

Initially, the starting precursor 2,3-dihydro-8-nitro-4-quinolone 1 was synthesized as per the reported procedure. In the next step, 2,3-dihydro-8-nitro-4-quinolone 1 was refluxed with 2-hydrazino-4-phenylthiazole 2 and 2-hydrazinobenzothiazole 3 in the presence of acetic acid in methanol to afford novel N-(8-nitro-2,3-dihydro-1H-quinoline-4-ylidene)-N’-(4-phenyl-thiazole-2-yl)-hydrazine (QPT) and (E)-2-(2-(8-nitro-2,3-dihydroquinolin-4(1H)-ylidene)hydrazinyl) benz[d]thiazole (QBT) (Scheme 1). QPT remains stable in the atmosphere and soluble in acetone, DMF, DMSO, THF, methanol, ethanol, and acetonitrile.

The structures and purity of chemosensors QPT and QBT were confirmed by IR, 1H and 13C NMR, HR mass spectroscopy methods, and X-ray single crystal analysis. In the IR spectrum of QPT, the carbonyl group of quinolone disappeared and characteristic absorption bands for N\textsubscript{H} and aromatic protons at 3389 and 3268 cm\(^{-1}\), the carbonyl group of quinolone at 170.91, thiazole C=N at 150.82, and aliphatic carbons at 147.88 ppm. In the 1H NMR spectrum of QPT, the proton signals of CH\(_2\) protons for quinoline rings appear at 2.83 ppm as a triplet, broad singlets at 3.56 ppm as a multiplet, and 3.60 ppm as a singlet. The 13C NMR spectra of QPT showed the disappearance of the carbonyl group and carbon assignments for thiazole N=C at 176.07, quinoline C=N at 170.91, thiazole C=N at 150.82, and aliphatic carbons at 38.92 and 23.59; all other signals are for aromatic carbons.

**X-ray Crystallographic Studies.** The structure of compounds QBT and QPT were further confirmed by single-crystal X-ray crystallographic analysis.

Molecular Geometry and Crystal Packing of QBT. The compound QBT crystallized in the centrosymmetric monoclinic unit cell with four molecular units. The adopted space group of the crystalline lattice is \(P_{2}_1/n\) and the structure refinement is completed with the \(R\) factor of 5.78\%. The nitro group attached to the 10-membered heterocyclic ring slightly deviated from the mean plane of the 10-membered ring with an angle of 1.2(1)°. According to Cremer and Pople conformational analysis, the six-membered heterocyclic ring (N2/C7/C8/C9/C10/C11) adopted an envelope conformation, the six-membered heterocyclic ring has slightly deviated from the mean plane of the 10-membered ring with an angle of 2.1(1)°.

Molecular Geometry and Crystal Packing of QPT. The compound QPT crystallized in the centrosymmetric monoclinic unit cell with four molecular units. The adopted space group of the crystalline lattice is \(P_{2}_1/c\), and the structure refinement is completed with an \(R\) factor of 4.27\%. The compound is almost flat with two heterocyclic rings and one phenyl ring. The nitro group attached to the quinoline heterocyclic ring has slightly deviated from the mean plane of the ring with an angle of 7.1(1)°. Similarly, the five-membered thiazole ring is making dihedral angles of 6.5(1)° with the mean plane of the 10-membered ring and 8.1(1)° with the phenyl ring. According to Cremer and Pope’s conformational
The six-membered heterocycle ring (N4/C10/C11/C16/C17/C18) adopted an envelope conformation with the puckering coordinates of q2 = 0.2702(3) Å, φ2 = 284.07(1)°, and q3 = 0.1930 Å. The molecular aggregations on the unit cell are almost parallel to the ab plane and the mean plane of the molecule in the asymmetric part is 8.45(3)°.

The hydrogen bonds that are involved in the crystal packing are listed in Table 2, and the packing diagram of the compound is shown in Figure 4. Intermolecular interactions, especially classical and non-classical hydrogen bonds, are playing a crucial role in the formation of crystalline solids and their physiochemical properties. These hydrogen-bonding interactions can be classified and notated with graph-set nomenclature, which is useful in comparing the stability of molecular conformations and crystalline lattices between the similar molecules.

The crystalline lattice features intra- and intermolecular classical N–H⋯O hydrogen bonds. Further, non-classical C–H⋯N and C–H⋯O interactions are supporting the crystalline assembly. The classical intramolecular hydrogen bond leads to a self-associated S(6) motif. Another classical intermolecular N–H⋯O hydrogen bond [N2–H2N⋯O2] leads to a zigzag chain C(9) motif extending along the b axis of the unit cell. A non-classical C–H⋯O interaction [C3–H3⋯O1] leads to a straight-chain C(15) motif extending along the b axis of the unit cell. These two infinite chain motifs intersect to form a ring R3(21) motif (Figure 5).

**UV–Visible and Fluorescence Studies. Detection of Fe³⁺, Fe²⁺, and Cu²⁺ by QPT and QBT.** The absorption spectrum of the compound QPT showed intense bands at 279, 338, and 464 nm and the compound QBT showed absorption bands at 281, 338, and 464 nm in THF/H₂O (50:50, v/v buffered at pH 7.4). Initially, we have examined absorbance changes of QPT and QBT toward metal ions Al³⁺, Ca²⁺, Cd²⁺, Co²⁺, Cu²⁺, Fe²⁺, Fe³⁺, Hg²⁺, K⁺, Mg²⁺, Mn²⁺, Na⁺, Ni²⁺, Pb²⁺, and Zn²⁺ in THF/H₂O (50:50, v/v buffered at pH 7.4) at room temperature. Addition of Al³⁺, Ca²⁺, Cd²⁺, Co²⁺, Hg²⁺,
K+, Mg2+, Mn2+, Na+, Ni2+, Pb2+, and Zn2+ had no effect on the absorption spectrum. However, upon the addition of Fe3+, Fe2+, and Cu2+ both QPT and QBT showed significant enhancement at the range of 281–338 nm. Additionally, an immediate color change of the QPT and QBT solution from bright red to dark brown was obtained within 10 s upon the addition of Fe3+, Fe2+, and Cu2+ ions. The results suggest that QPT and QBT could serve as a potential detector of Fe3+, Fe2+, and Cu2+ ions (Figure 6).

Further, the fluorescence spectra of the compounds QPT and QBT were recorded at pH 7.4 [HEPES (10 μM)—THF with H2O (50:50)], and the emission wavelength was observed at 310 nm. Initially, we examined the fluorescence changes of QPT and QBT toward Al3+, Ca2+, Cd2+, Co2+, Cu2+, Fe2+, Fe3+, K+, Mg2+, Mn2+, Na+, Ni2+, Pb2+, and Zn2+ had no effect on the absorption spectrum. However, upon the addition of Fe3+, Fe2+, and Cu2+ both QPT and QBT showed significant enhancement at the range of 281–338 nm. Additionally, an immediate color change of the QPT and QBT solution from bright red to dark brown was obtained within 10 s upon the addition of Fe3+, Fe2+, and Cu2+ ions. The results suggest that QPT and QBT could serve as a potential detector of Fe3+, Fe2+, and Cu2+ ions (Figure 6).

Figure 4. Packing of the molecules showing flat aggregations along the $ab$ plane in the monoclinic unit cell viewed along the $a$ axis. H-bonds are shown as dashed lines.

Figure 5. Self-associated ring S(6), infinite chain C(9), and C(15) motifs along [010] and ring R$_3^{3(21)}$ motifs. H-bonds are shown as dashed lines.

Figure 6. (a) UV−vis changes of QPT and (b) UV−vis changes of QBT (2 × 10$^{-4}$ M) with various metal ions (2 × 10$^{-4}$ M) in THF/H2O (1:1) at pH = 7.4 in HEPES buffer.
Hg$^{2+}$, K$^+$, Mg$^{2+}$, Mn$^{2+}$, Na$^+$, Ni$^{2+}$, Pb$^{2+}$, and Zn$^{2+}$ in THF/H$_2$O (50:50, v/v) buffered at pH 7.4 at room temperature. The fluorescence emission spectra of both QPT and QBT displayed maximum fluorescence quenching effects with Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$. However, fluorescence intensities of chemosensors QPT and QBT did not show any remarkable changes with other metal cations (Figure 7).

In the fluorescence titration experiments, Fe$^{3+}$ (0–100 equiv), Fe$^{2+}$ (0–100 equiv), and Cu$^{2+}$ ions (0–75 equiv) were titrated with QPT and QBT in THF at room temperatures. The fluorescence intensity was gradually quenched upon the addition of Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ (Figures 8 and 9). From the fluorescence titration data, the association constant $K_a$ values of QPT and QBT with Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ were calculated by using the Benesi–Hildebrand equation (eq 1). The fitting curves showed a good linear pattern with high correlation coefficients. The calculated $K_a$'s of QPT with Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ are 2.5116 × 10$^4$, 3.2578 × 10$^4$, and 1.9990 M$^{-1}$. The $K_a$ values of QBT with Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ are 1.9625 × 10$^4$, 3.4606 × 10$^4$, and 1.2405 × 10$^4$ M$^{-1}$.

$$\frac{1}{I_0 - F} = \frac{1}{K(F_0 - F')[M]} + \frac{1}{F_0 - F}$$  (1)

where $F_0$ is the intensity of fluorescence of the fluorophores without metal ions (M), $F$ is the intensity with a particular concentration of metal ions (M), $F'$ is the intensity at the maximum concentration of metal ions (M) used, and K is the binding constant.

The calibration curve between fluorescence intensities of QPT and QBT versus the concentrations of Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ ions were plotted and showed a good linear relationship with good correlation coefficients. The detection limits of the compound were calculated using the formula $3\sigma/x$ and were found to be 3.1201 × 10$^{-4}$ M for QPT-Fe$^{3+}$, 4.4079 × 10$^{-4}$ M for QPT-Fe$^{2+}$, 3.1740 × 10$^{-4}$ M for QPT-Cu$^{2+}$, 2.9763 × 10$^{-4}$ M for QBT-Fe$^{3+}$, 3.8395 × 10$^{-4}$ M for QBT-Fe$^{2+}$, and 2.9169 × 10$^{-4}$ M for QBT-Cu$^{2+}$.

The complexation stoichiometry of QPT and QBT was further confirmed by Job plot analysis. The values of QPT-Fe$^{3+}$, QPT-Fe$^{2+}$, QPT-Fe$^{2+}$, QPT-Cu$^{2+}$, and QPT-Cu$^{2+}$ reached the maximum when the molar fraction was 0.5, which indicated that the complexation stoichiometry ratio was 1:1 (Figure 10).

To examine the ability of QPT and QBT to resist the interference of other metal ions, the competition experiments were conducted where 100 equiv of metal cations Al$^{3+}$, Ca$^{2+}$, Cd$^{2+}$, Co$^{2+}$, Hg$^{2+}$, K$^+$, Mg$^{2+}$, Mn$^{2+}$, Na$^+$, Ni$^{2+}$, Pb$^{2+}$, and Zn$^{2+}$ was mixed with QPT and QBT then 100 equiv of Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ was added to all the mixtures. The emission spectra of QPT-Fe$^{3+}$, QPT-Fe$^{3+}$, QPT-Fe$^{2+}$, QPT-Fe$^{2+}$, QPT-Cu$^{2+}$, and QPT-Cu$^{2+}$ remain the same in the presence of other metal ions (Figure S1).

Additionally, to examine the reversibility of chemosensor QPT from its Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ complex, EDTA titration experiments were performed. Upon addition of Na$_2$EDTA (100 equiv) to the QPT-Fe$^{3+}$, QPT-Fe$^{3+}$, QPT-Fe$^{2+}$, QPT-Cu$^{2+}$, and QPT-Cu$^{2+}$ mixtures, the fluorescence intensity was enhanced and reached the intensities of QPT and QBT (Figure S2). This cycle was repeated many times and the results suggest that the Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ recognition by QPT and QBT is a reversible process. The time dependence of the complexation experiment indicates the binding phenomena of chemosensors QPT and QBT completely binding with Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ in 3 min.

For the biological applications, the suitable pH was investigated for QPT/QBT and its Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ complexes. The fluorescence intensities of QPT, QBT, QPT-Fe$^{3+}$, QPT-Fe$^{3+}$, QPT-Cu$^{2+}$, QPT-Cu$^{2+}$, and QPT-Cu$^{2+}$ varied at different pH values, ranging from 1 to 12. However, the emission intensity remains almost the same in the pH range of 6–8 (Figure S3). Based on the results from the studies, a physiological pH value of 7.4 was chosen for all the fluorescence studies.

**CONCLUSIONS**

In conclusion, new quinoline-based thiazole derivatives QPT and QBT were successfully synthesized, which showed a fluorescence quenching effect with Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ at pH 7.4 in THF/H$_2$O. The Job plots demonstrated a 1:1 complex formation of QPT and QBT with Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ metal ions. The detection ability of QPT and QBT was further investigated by titration with various equivalents of metal ions and competitive experiments of Fe$^{3+}$, Fe$^{2+}$, and Cu$^{2+}$ in the presence of other metal ions, and pH ranges for detection and reversibility with Na$_2$EDTA were investigated for biological applications.

**EXPERIMENTAL SECTION**

Chemicals and Instrumentation. All the chemicals and reagents were of analytical grade and purchased from Sigma-
Aldrich and used without purification. A JASCO FT IR 4100 spectrometer was used to record the absorption frequencies for the compounds. Bruker Advance instruments (400 MHz for $^1$H and 100 MHz for $^{13}$C) were used to record the $^1$H and $^{13}$C NMR spectra using DMSO-$d_6$ as solvent. The reactions were monitored by using silica gel-precoated TLC F254 Merck plates. A Shimadzu UV-240 spectrophotometer and JASCO FP-8200 spectrofluorimeter were used to record absorption and fluorescence spectra of the compounds using standard quartz cuvettes of 1 cm in path length. The recorded excitation and emission slit width was 5.0 nm at 24 ± 1 °C temperature. A PerkinElmer 2400 series II Elemental CHNS analyzer was used to perform the elemental analysis. Mass spectra of the compounds were obtained on an HR mass spectrometer.

**Synthesis of Chemosensors QPT and QBT.** Equal mole ratios of 2,3-dihydro-8-nitro-quinolone (1 mmol) and 2-hydrazino phenylthiazole/hydrazino benzothiazole (1 mmol) were dissolved in 10 mL of methanol, and a catalytic amount of glacial acetic acid was added to the mixture. The reaction mixture was refluxed for 2−4 h at 80 °C. The reaction mixture was cooled to room temperature; the pure products QPT and QBT were obtained as crystals.

$N$-(8-Nitro-2,3-dihydro-1H-quinolin-4-ylidene)-$N'$-(4-phenyl-thiazol-2-yl)-hydrazine QPT. Red solid, mp: 210−
212 °C; IR (cm⁻¹): ¹H NMR (400 MHz, DMSO-δ₆) δ: 11.42 (s, 1H, N-NH), 8.39 (s, 1H, Q-NH), 8.19 (d, 1H, J = 7.2 Hz, Ar-H), 8.08 (d, 1H, J = 8.4 Hz, Ar-H), 7.88 (d, 2H, J = 6.8 Hz, Ar-H), 7.41 (t, 2H, J = 7.2 Hz, Ar-H), 7.35 (m, 2H, Ar-H), 6.77 (t, 1H, J = 8 Hz, Ar-H), 3.51 (s, 2H, Q-CH₂), 2.84 (s, 2H, Q-CH₂); ¹³C NMR (100 MHz, DMSO-δ₆) δ: 176.488, 156.960, 146.660, 144.782, 143.678, 140.004, 139.487, 138.635, 133.018, 131.413, 127.040, 122.980, 116.237, 115.766, 115.382, 108.671, 39.133, 23.134; HRMS: C₁₈H₁₅N₅O₂S m/z [M + H] 366.10350.

Crystallographic Data Collection and Refinement. The slow solvent evaporation solution growth technique is adopted to get the X-ray quality crystals. Block-type single crystals were taken away from the crop, and the X-ray intensity

Figure 9. Fluorescent changes of QBT with different concentrations of (a) Fe³⁺ (100 equiv) with its (b) Benesi–Hildebrand plot, (c) Fe²⁺ (100 equiv) with its (d) Benesi–Hildebrand plot, and (e) Cu²⁺ (75 equiv) with its (f) Benesi–Hildebrand plot in THF/H₂O (1:1) at pH = 7.4 in HEPES buffer.
data collection was done with an X-ray wavelength of 0.71073 Å at room temperature. A Bruker AXS KAPPA APEX-2 diffractometer equipped with a graphite monochromator was employed. The details of parameters regarding the data collection and structure solution are given in Table 3. The structure was solved by direct methods and refined by full-matrix least-squares calculations using SHELXL-2014. The ORTEP view of the molecule drawn in 50% probability thermal-displacement ellipsoids with the atom numbering scheme is shown in Figure 1.

Fluorescent Studies. Stock solutions of QPT and QBT (2 × 10⁻⁴ M) were prepared in THF/H₂O (50:50 v/v) buffered at pH 7.4. The fluorescence test solutions for metal selectivity were prepared from 2 mL of QPT/QBT with 2 mL of each metal stock solution. The excitation wavelength was at 310 nm.

Table 3. Crystallographic Details of the Compounds

| QPT | QBT |
|-----|-----|
| molecular formula | C₁₈H₁₅N₅O₂SC₁₆H₁₃N₅O₂S |
| formula weight | 365.41 | 339.37 |
| temperature | 296 K | 300 K |
| wavelength | 0.71073 Å | 0.71073 Å |
| crystal system | monoclinic | monoclinic |
| space group | P2₁/c | P2₁/c |
| unit cell dimensions | a = 12.8882(12) Å; α = 90° | a = 13.888(2) Å; α = 90° |
| | b = 16.8832(15) Å; β = 106.261(3)° | b = 4.7349(8) Å; β = 91.509° |
| | c = 7.8668(7) Å; γ = 90° | c = 23.274(4) Å; γ = 90° |
| volume | 1643.3(3) Å³ | 1529.9(4) Å³ |
| Z | 4 | 4 |
| density (calculated) | 1.477 mg/m³ | 1.473 mg/m³ |
| absorption coefficient | 0.222 mm⁻¹ | 0.232 mm⁻¹ |
| F(000) | 760 | 704.0 |
| index ranges | h = 16, k = 21, l = 10 | h = 19, k = 6, l = 2 |
| CCDC no. | 1957058 | 1961067 |

Mn²⁺, Na⁺, Ni²⁺, Pb²⁺, and Zn²⁺ ions (2 × 10⁻⁴ M) were prepared in THF/H₂O (50:50 v/v) buffered at pH 7.4. The fluorescence test solutions for metal selectivity were prepared from 2 mL of QPT/QBT with 2 mL of each metal stock solution. The excitation wavelength was at 310 nm.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03445.

Interference studies of QPT and QBT with other metal ions, reversibility experiment of QPT and QBT, pH-dependent fluorescence changes of QPT and QBT, and IR ¹H and ¹³C NMR and HR mass analysis (PDF)

Figure 10. Job plots for the complexes of (a) QPT with Fe³⁺, (b) QPT with Fe²⁺, (c) QPT with Cu²⁺, (d) QBT with Fe³⁺, (e) QBT with Fe²⁺, and (f) QBT with Cu²⁺ ions in THF/H₂O (1:1) at pH = 7.4 in PBS buffer.
Crystallographic data of C_{6}H_{12}N_{5}O_{2}S (CIF)
Crystallographic data of C_{10}H_{13}N_{5}O_{2}S (CIF)

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# REFERENCES

(1) Gumpu, M. B.; Sethuraman, S.; Krishnan, U. M.; Rayappan, J. B. A review on detection of heavy metal ions in water - An electrochemical approach. Sens. Actuators B Chem. 2015, 213, 515–533.
(2) Xu, W.; Tian, J.; Luo, Y.; Zhu, L.; Huang, K. A rapid and visual turn-on sensor for detecting copper (II) ion based on DNAzyme coupled with HCR-based HRP concatemers. Sci. Rep. 2017, 7, 43362.
(3) Ji, Y.; Dai, F.; Zhou, B. Designing salicylaldehyde isonicotinoyl hydrazones as Cu(II) ionophores with tunable chelation and release of copper for hitting redox Achilles heel of cancer cells. Free Radical Bio. Med. 2018, 129, 215–226.
(4) Kundu, M.; Krishnan, P.; Kothala, R. K.; Sumana, G. Recent developments in biosensors to combat agricultural challenges and their future prospects. Trends Food Sci. Technol. 2019, 88, 157–178.
(5) Abbaspour, N.; Hurrell, R.; Kelishadi, R. Review on iron and its importance for human health. J Res Med Sci. 2014, 19, 164–174.
(6) Praveen, L.; Reddy, M. L. P.; Varma, R. L. Dansyl-styrylquinoline conjugate as divalent iron sensor. Tetrahedron Lett. 2010, 51, 6626–6629.
(7) Gong, X.; Zhang, H.; Jiang, N.; Wang, L.; Wang, G. Oxadiazole-based ‘on-off’ fluorescence chemosensor for rapid recognition and detection of Fe^{3+} and Fe^{2+} in aqueous solution and in living cells. Microchem. J. 2019, 145, 435–443.
(8) Dixon, S. J.; Stockwell, B. R. The role of iron and reactive oxygen species in cell death. Nat. Chem. Biol. 2014, 10, 9–17.
(9) Wang, J.; Hwang, M. P.; Choi, M.; Seo, Y.; Jo, Y.; Son, J.; Hong, J.; Choi, J. Sensitive detection of copper ions via ion-responsive fluorescence quenching of engineered porous silicon nanoparticles. Sci. Rep. 2016, 6, 1.
(10) Zhang, Y.; Liu, Z.; Yang, K.; Zhang, Y.; Xu, Y.; Li, H.; Wang, C.; Lu, A.; Sun, S. A ruthenium(II) complex as turn-on Cu(II) luminescent sensor based on oxidative cyclization mechanism and its application in vivo. Sci. Rep. 2015, 5, 8172.
(11) Kumar, V.; Kalita, J.; Bora, H. K.; Misra, U. K. Temporal kinetics of organ damage in copper toxicity: A histopathological correlation in rat model. Regul. Toxicol. Pharmacol. 2016, 81, 372–380.
(12) Lu, J.; Zheng, Y. L.; Wu, D. M.; Sun, D. X.; Shan, Q.; Fan, S. H. Trace amounts of copper induce neurotoxicity in the cholesterol-fed mice through apoptosis. FEBS Lett. 2006, 580, 6730–6740.
(13) Ou, S.; Miyagawa, K.; Honma, Y.; Harada, M. Copper induces hepatocyte injury due to the endoplasmic reticulum stress in cultured cells and patients with Wilson disease. Exp. Cell Res. 2016, 347, 192–200.
(14) Kim, J.; Oh, S. B.; Kim, J.; Kim, K.; Ryu, H. S.; Kim, M. S.; Ayton, S.; Bush, A. J.; Lee, J. Y.; Chung, S. J. Association of metals with the risk and clinical characteristics of Parkinson’s disease. Parkinsonism Relat. Disord. 2018, 55, 117–121.
(15) Barnham, K. J.; Bush, A. I. Metals in Alzheimer’s and Parkinson’s diseases. Curr. Opin. Chem. Biol. 2008, 12, 222–228.
(16) Kepp, K. P.; Squitti, R. Copper imbalance in Alzheimer’s disease: Convergence of the chemistry and the clinic. Coord. Chem. Rev. 2019, 397, 168–187.
(17) Zhang, J.; Duan, D.; Xu, J.; Fang, J. Redox-Dependent Copper Carrier Promotes Cellular Copper Uptake and Oxidative Stress-Mediated Apoptosis of Cancer Cells. ACS Appl. Mater. Interfaces 2018, 10, 33010–33021.
(18) Wang, M.; Leung, K. H.; Lin, S.; Chan, D. S. H.; Kwong, D. W. J.; Leung, C. H.; Ma, D. L. A colorimetric chemosensor for Cu^{2+} ion detection based on an iridium(III) complex. Sci. Rep. 2014, 4, 6794.
(19) Wu, C.; Wang, J.; Shen, J.; Zhang, C.; Wu, Z.; Zhou, H. A colorimetric quinoline-based chemosensor for sequential detection of copper ion and cyanide anions. Tetrahedron 2017, 73, 5715–5719.
(20) Wang, W.; Wei, J.; Liu, H.; Liu, Q.; Gao, Y. A novel colorimetric chemosensor based on quinoline for the sequential detection of Fe^{3+} and PPi in aqueous solution. Tetrahedron 2017, 58, 1025–1029.
(21) Mahalingam, M.; Irlapann, M.; Kasirajan, G.; Subramaniam, M. P.; Ramasamy, S.; Unnisa, N. Synthesis of bisbenzimidazo quinoline fluorescent receptor for Fe^{2+} ion in the aqueous medium - An experimental and theoretical approach. J. Mol. Struct. 2015, 1099, 257–265.
(22) Kia, Y.; Osman, H.; Kumar, R. S.; Basiri, A.; Murugaiyah, V. Synthesis and discovery of highly functionalized mono- and bis-spiro-pyrrolidines as potent cholinesterase enzyme inhibitors. Bioorg. Med Chem Lett. 2014, 24, 1815–1819.
(23) Karmakar, M.; Bhatta, S. R.; Giri, S.; Thakur, A. Oxidation-induced differentially selective turn-on fluorescence via photoinduced electron transfer based on a ferrocene-appended coumarin-quinoline platform: Application in cascaded molecular logic. Inorg. Chem. 2020, 59, 4493–4507.
(24) Meghdadi, S.; Khodaverdian, N.; Amirnasr, A.; Mirzamajdi, A. Multicolor redox-dependent copper probes via oxidative cyclization and ring opening: Application in biology. Bioorg. Med Chem Lett. 2020, 30, 11246–11251.
(25) Siddaramappa, S.; Vivek, R.; Saravanan, A.; Arasakumar, T.; Suresh, T.; Athimoolam, S.; Mohan, P. S. A novel 8-nitro quinoline- and PPi in aqueous solution. Bioorg. Med Chem Lett. 2014, 24, 1815–1819.
(26) French, P. J.; Royen, M. E. V.; Wiemer, E. A. C.; Amirnasr, M. A new fluorescent probe as on-off fluorescent and colorimetric sensor for Cu(II) in aqueous solution. J. Mol. Struct. 2015, 1099, 257–265.
(27) Shyamsivappan, S.; Vivek, R.; Saravanan, A.; Arasakumar, T.; Suresh, T.; Athimoolam, S.; Mohan, P. S. A novel 8-nitro quinoline-based on-off fluorescent sensor for Cu(II) and Fe(III) ions in aqueous solution. Bioorg. Med Chem Lett. 2014, 24, 1815–1819.
(28) Meghdadi, S.; Khodaverdian, N.; Amirnasr, A.; Mirzamajdi, A. Multicolor redox-dependent copper probes via oxidative cyclization and ring opening: Application in biology. Bioorg. Med Chem Lett. 2020, 30, 11246–11251.
(29) Shyamsivappan, S.; Vivek, R.; Saravanan, A.; Arasakumar, T.; Suresh, T.; Athimoolam, S.; Mohan, P. S. A novel 8-nitro quinoline-based on-off fluorescent sensor for Cu(II) and Fe(III) ions in aqueous solution. Bioorg. Med Chem Lett. 2014, 24, 1815–1819.
(30) Meghdadi, S.; Khodaverdian, N.; Amirnasr, A.; Mirzamajdi, A. Multicolor redox-dependent copper probes via oxidative cyclization and ring opening: Application in biology. Bioorg. Med Chem Lett. 2020, 30, 11246–11251.