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Roymon Joseph, Adersh Asok, Kuruvilla Joseph

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Quinoline appended pillar[5]arene (QPA) as Fe^{3+} sensor and complex of Fe^{3+} (FeQPA) as a selective sensor for F^-, arginine and lysine in the aqueous medium

Roymon Joseph*[1], Adersh Asok[2] and Kuruvilla Joseph[1]

[1]Department of Chemistry, Indian Institute of Space Science and Technology (IIST), Thiruvananthapuram, Kerala, India 695547.

[2]Material Science and Technology Division, National Institute for Interdisciplinary Science and Technology (NIIST) Thiruvananthapuram, India 695019.

Email: royj80@gmail.com. Tel: +918301871153.

Abstract

A quinoline functionalized pillar[5]arene, **QPA** has been prepared and its interaction with biologically relevant ions and molecules in aqueous solution has been demonstrated. The sensor molecule, **QPA** has shown selectivity towards Fe^{3+} among eleven metal ions studied. The Fe^{3+} complex of **QPA** (**FeQPA**) selectively interacts with F^- among halides by ~4 fold fluorescence enhancement. Further, **FeQPA** has shown selectivity towards arginine and lysine among twenty naturally occurring amino acids. The binding of **QPA** with Fe^{3+} has been confirmed by MALDI-TOF and ^{1}H NMR titrations.

Keywords

Fe^{3+} sensor, fluoride sensor, Pillar[5]arene, amino acid detection, fluorescence

1. Introduction

Owing to the indispensable role in various biological processes, the detection and quantification of ions and molecules are of fundamental importance [1-2]. To cite an example; iron the most essential trace element in the human body plays an integral role in many physiological processes such as oxygen transport, electron transfer, and enzyme catalysis [3-8]. The optimum amount of iron present in men and women are 3 and 4 grams respectively and the total iron is disseminated throughout the body in haemoglobin, bone marrow, tissues, muscles, blood proteins, etc [9]. Iron deficiency or overload may impact various biological processes in human body and this abnormal iron content may lead to different diseases such as anemia, Parkinson's syndrome, Alzheimer's disease, and cancer [10-11]. Consequently, the monitoring of iron levels in humans using fluorescent molecules has been elevated to an intriguing area of research in recent years [12-14]. Also, due to the relevance of anions in chemical, biological, and environmental processes several synthetic receptors have been reported in the literature for the selective sensing of anions [15-16]. Among various anions, detection of F^- is of particular concern on account of its vital role in treating osteoporosis and protecting dental health [17]. Nevertheless, excessive fluoride ingestion may lead to urolithiasis and fluorosis [18]. Thus the detection of F^- is paramount in human health.

In addition to cations and anions, amino acids are involved in several crucial functions in cell regulations and metabolism, and they are essential in numerous cellular functions [19-20]. For instance, the basic amino acids such as arginine and lysine play a vital role in the proper functioning of biological systems. Arginine functions as a precursor for the synthesis of agmatine, creatine, glutamate, urea, proline, nitric oxide and polyamines [21-22]. The important biological processes associated with arginine are tissue integrity, reproduction, hormone release, wound healing, etc [23-24]. The ability of arginine to lower blood pressure, reduce blood clots and strokes and its application in the treatment of erectile dysfunction is

well evident from the literature [25-26]. Arginine overdose may lead to life threating allergic reactions, anaphylaxis and increase in the levels of stomach acid [22]. Similarly, lysine also plays vital role in various biological processes. However, it acts as a precursor for protein synthesis and in the biosynthesis of carnitine. Excess amount of lysine in plasma and urine may cause congenital metabolic disorders such as cystinuria or hyperlysinemia [23, 27-28]. Therefore, the selective detection of ions and molecules are of necessity in biology to avert its deficiency or overload and thereby head off several side effects in humans [23-24, 29-31].

Though there are several synthetic fluorescent receptors known for the selective detection of ions and amino acids, a single system which recognizes all the three species; cations, anions and amino acids are rather rare [32-33]. In the search for a suitable molecular system which can function as a platform for functionalization, ease of synthesis, tuning solubility, hydrophobic and hydrophilic cavity we have come across a relatively new supramolecular system, pillar[5]arenes. Pillar[*n*]arenes are first reported by Ogoshi and co-workers in 2008 and the functionalized pillar[*n*]arenes are known for various applications in the areas of host-guest recognition, fluorescence sensing, supramolecular aggregates, biomedical applications, etc [34-41]. Hence, in this paper we have demonstrated the synthesis of a novel quinolone appended pillar[5]arene (QPA) through a triazole linkage and its selective detection of Fe^{3+} using fluorescence spectroscopy. Further, the iron complex of **QPA** (**FeQPA**) has been used for the sensing of F^- among all the halides and arginine and lysine among the twenty naturally occurring amino acids by fluorescence spectroscopy.

2. Experimental Section

2.1. Materials and physical methods

The salts used for the present study, *viz.*, $Mn(ClO_4).6H_2O$, $Fe(ClO_4)_2.xH_2O$, $Fe(ClO_4)_3.6H_2O$, $Co(SO_4)_2.7H_2O$, $Ni(ClO_4)_2.6H_2O$, $Cu(ClO_4)_2.6H_2O$, $Zn(ClO_4)_2.6H_2O$,

$NaClO_4.H_2O$, $KClO_4$, $Ca(ClO_4)_2.4H_2O$ and $Mg(ClO_4)_2.6H_2O$, were procured from Sigma Aldrich Chemical Company. Salts of anions, *viz.*, Bu_4NF and Me_4NCl were procured from Otto Chemie Pvt. Ltd. and Bu_4NBr, Bu_4NI were procured from Spectrochem Pvt. Ltd. India. All the 20 naturally occurring amino acids, except lysine (TCI Chemicals (India) Pvt. Ltd.) and histidine (Avra Synthesis Pvt. Ltd. India), were procured from Spectrochem Pvt. Ltd. India. ^1H and ^{13}C NMR spectra were measured on a Brucker Ascend^{TM} 400 spectrometer working at 400 MHz. The mass spectra were recorded on Bruker UltrafleXtreme MALDI-TOF mass spectrometer. The absorption and steady-state fluorescence spectra were measured on Varian Cary 100 Bio and Horiba Scientific FluoroMaz-4 respectively. The elemental analysis was carried out using PerkinElmer 2400 SeriesII CHNS.

2.2. General procedure for fluorescence experiments

All the fluorescence titrations were carried out in HPLC grade solvents. The bulk solution of **QPA** (6×10^{-4} M) was prepared in DMSO and the salts of cations and anions, and the amino acids were dissolved in water. During the fluorescence titration the final concentration of **QPA** was kept at 10 μM and the concentration of metal salts was increased gradually to get requisite mole ratios of **QPA**:M^{n+}. All the titrations were conducted in 1:1 H_2O: CH_3CN solvent. The limit of detection (LOD) was calculated from the fluorescence titration of host and guest species. The standard deviation of the blank (σ) was determined by measuring the fluorescence intensity of the probe without analyte at least 10 times. Then, the fluorescence intensity of the probe has been measured upon addition of increasing concentrations of analyte (3 times). The slope of the linearity plot (m) has been obtained by

plotting the average value of fluorescence intensity of the probe versus concentration of analyte. Finally the LOD was calculated using the equation, LOD = $3\sigma/m$.

2.3. Synthesis of QPA and its precursors

Synthesis of 1a. A mixture of hydroquinone (5.0 g, 45 mmol), potassium carbonate (28.2 g, 0.20 mol) and 1,6-dibromohexane (21 mL, 0.14 mol) in acetone (120 mL) were refluxed for 24 h under nitrogen atmosphere. The reaction mixture was cooled to 25 °C, filtered and the filtrate was evaporated under vacuum. The product was purified by chromatography (silica gel; petroleum ether/dichloromethane) followed by recrystallization from ethyl acetate to afford **1a** (8.2 g, 43%) as white solid. ^{1}H NMR ($CDCl_3$): δ = 6.81 (s, 4H, Ar*H*), 3.90 (t, *J* = 6.3 Hz, ArOCH_2, 4H), 3.42 (t, *J* = 6.3 Hz, CH_2Br, 4H), 1.92-1.85 (m, CH_2, 4H), 1.80-1.73 (m, CH_2, 4H), 1.54-1.44 (m, CH_2, 8H) ppm. ^{13}C NMR (100 MHz): δ 153.2, 115.5, 68.4, 33.9, 32.8, 29.3, 28.0, 25.4 ppm. HRMS (ESI) calcd for $C_{18}H_{30}Br_2O_2$ ($[M+Na]^+$) 459.03332, found 459.03399.

Synthesis of 1b. To a solution of **1a** (6.3 g, 14.4 mmol) and paraformaldehyde (1.37 g, 45.6 mmol) in dichloroethane (120 ml) was added $BF_3.OEt_2$ (2.0 mL, 15.9 mmol) under inert atmosphere and the reaction mixture was stirred at 25 °C for 2 h. Water (200 ml) was then added and the organic layer was separated. The solution was again extracted with dichloromethane (2 × 50 mL) and the combined organic layers were washed with water (2 × 100 mL), brine (2 × 100 mL) and dried with Na_2SO_4 and the solvents evaporated. The product was purified by column chromatography (silica gel; petroleum ether/dichloromethane) to afford **1b** (3.1 g, 48%) as white solid. ^{1}H NMR ($CDCl_3$): δ 6.87 (s, Ar*H*, 10H), 3.91 (br, OCH_2, 20H), 3.76 (s, ArCH_2Ar, 10H), 3.24 (br, CH_2N_3, 20H), 1.81-1.60 (br, CH_2, 40H), 1.44-1.28 (br, CH_2, 40H) ppm. ^{13}C NMR (100 MHz): δ 149.6, 128.2, 114.6,

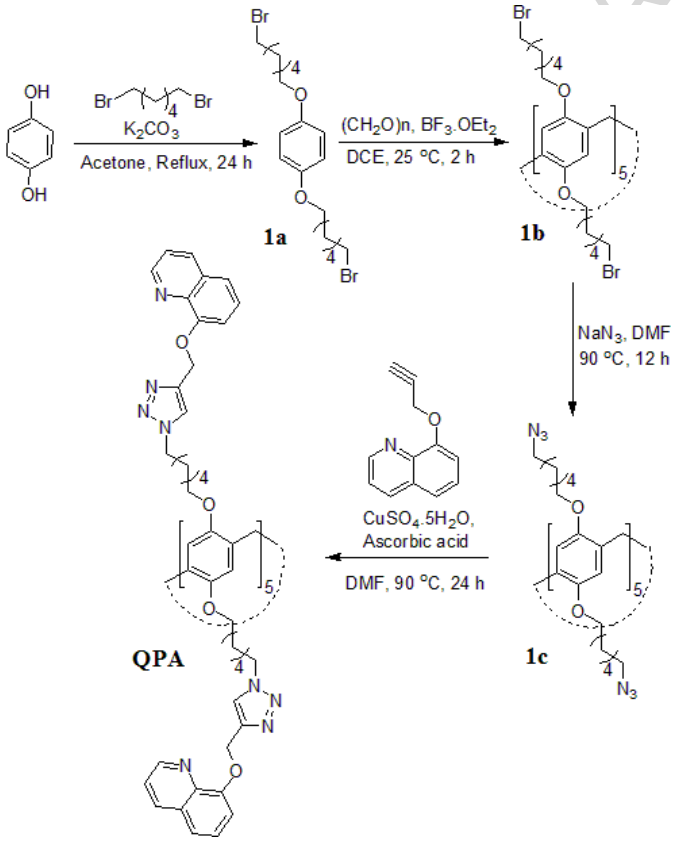
68.0, 33.9, 32.6, 29.8, 29.5, 28.1, 25.5 ppm. Anal. Calcd for $C_{95}H_{140}Br_{10}O_{10}.12.7H_2O$: C, 46.2; H, 6.75. Found C, 45.96; H, 6.51.

Synthesis of 1c. Sodium azide (0.73 g, 11 mmol) was added to a solution of **1b** (2.0 g, 0.89 mmol) in DMF (30 mL) under inert atmosphere and the reaction mixture was kept at 90 °C for 12 h. After cooling to 25 °C, water (150 mL) was added and the precipitate was filtered and dried under vacuum to afford **1c** as white solid (1.5 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, Ar*H*, 10H), 3.89 (br, ArOCH_2, 20H), 3.76 (s, ArCH_2Ar, 10H), 3.10 (br, CH_2N_3, 20H), 1.81 (br, CH_2, 20H), 1.47-1.32 (m, CH_2, 60H) ppm. ^{13}C NMR (100 MHz): δ 149.7, 128.3, 114.7, 68.1, 51.4, 29.8, 29.5, 28.7, 26.6, 25.9 ppm. Anal. Calcd for $C_{95}H_{140}N_{30}O_{10}.5.6C_3H_7ON$: C, 59.11; H, 7.95; N, 21.95. Found C, 58.58; H, 8.01; N, 22.48.

Synthesis of QPA. A mixture of **1c** (0.25 g, 0.13 mmol), 8-(prop-2-ynyloxy)quinoline [42] (0.37 g, 2.0 mmol), $CuSO_4.5H_2O$ (8.0 mg, 32 μmol) and ascorbic acid (42 mg, 0.21 mmol) in DMF (25 mL) were kept at 90 °C for 24 h. The reaction mixture was cooled to 25 °C and evaporated. The solid was treated with water and extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried with Na_2SO_4 and the solvents evaporated. The product was purified by chromatography (silica gel; dichloromethane/methanol) to afford **QPA** as brown solid (0.31 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (br, Ar*H*, 10H), 8.26 (m, Ar*H*, 20H), 7.47-7.43 (m, Ar*H*, 30H), 7.34-7.32 (m, Ar*H*, 10H), 6.78 (s, Ar*H*, 10H), 5.28 (s, OCH_2, 20H), 4.35 (t, *J* = 6.8 Hz, OCH_2, 20H), 3.95 (br, ArCH_2Ar, 10H), 3.63 (br, NCH_2, 20H), 1.83-1.69 (m, CH_2, 40H), 1.49-1.46 (m, CH_2, 20H), 1.31-1.28 (m, CH_2, 20H) ppm. ^{13}C NMR (100 MHz): δ 154.3, 149.5, 149.3, 142.9, 140.2, 136.2, 129.5, 128.3, 127.1, 125.0, 122.3, 120.4, 114.4, 110.4, 68.2, 62.3, 49.8, 30.1, 29.5, 29.2, 26.3, 25.7 ppm. Anal. Calcd for $C_{215}H_{230}N_{40}O_{20}.10CH_2Cl_2.10C_3H_7ON$: C, 58.07; H, 6.11; N, 13.28. Found C, 57.74; H, 6.47; N, 13.61.

3. Results and Discussion

The receptor molecule **QPA** has been synthesized by four known steps starting from commercially available material hydroquinone as given in Scheme 1. Alkylation of hydroquinone was carried out with 1,6-dibromohexane using potassium carbonate in acetone to afford dibromo derivative, **1a**. The cyclized derivative of pillar[5]arene, **1b** was obtained by the reaction of **1a** with paraformaldehyde and boron trifluoride diethyletherate in dichloroethane. Reaction of **1b** with sodium azide resulted in the formation of azido derivative of pillar[5]arene, **1c**. Finally, the sensor molecule, **QPA** was synthesized by the 1,3-dipolar cycloaddition reaction using **1c** and the 8-(prop-2-ynyloxy)quinoline. **QPA** and its precursor molecules were well characterized by ^{1}H and ^{13}C NMR, high-resolution mass spectroscopy (HR-MS) and elemental analysis (Fig. S1-S4 in supplementary Data).



Scheme 1. Synthesis of quinolone derivative of pillar[5]arene, **QPA.**

The pillar[5]arene derivative, **QPA** has been studied for its interaction with various biologically relevant metal ions using fluorescence spectroscopy in aqueous acetonitrile (1:1). The **QPA** has been excited at 320 nm and followed its emission band at 400 nm. Among the eleven metal ions studied, **QPA** showed a significant decrease in fluorescence intensity upon interaction with Fe^{3+} (Fig. 1a). None of the other metal ions, *viz*., Na^{+}, K^{+}, Ca^{2+}, Mg^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}, showed fluorescence changes except Cu^{2+} which shows minimal changes (~7 fold) upon the titration with **QPA** (Fig. 1b). The amount of fluorescence quenching observed during the titration of **QPA** with Fe^{3+} is ~31 fold. Hence, **QPA** can be a selective sensor for the detection of Fe^{3+} among all the biologically relevant ions reported in this paper. The lowest amount of **QPA** required to detect Fe^{3+} in a sample using the current fluorescence technique in aqueous acetonitrile solution is 157 ppm. The stoichiometry of the complex between **QPA** and Fe^{3+} were determined based on MALDI-TOF studies. The molecular ion peak observed at m/z = 781.32 {m/5 of 3906.60 of [**QPA** + $2Fe^{3+}$ + $ClO4]^{5+}$} indicates the 1:2 complex formation between **QPA** and Fe^{3+} (Fig. S5 in Supplementary Data). The isotopic peak pattern observed is characteristic for the presence of iron in the complex. The complex formation of **QPA** with Fe^{3+} has been further supported by UV-Vis spectroscopy and ^{1}H NMR experiments (Fig S6-S7 in Supplementary Data). Upon the addition of Fe^{3+} into a solution of **QPA** in DMSO-d_6, the proton signals corresponding to triazole ring and quinoline experience considerable broadening along with marginal chemical shift. The changes observed in the ^{1}H NMR experiments supporting the binding of Fe^{3+} with **QPA**.

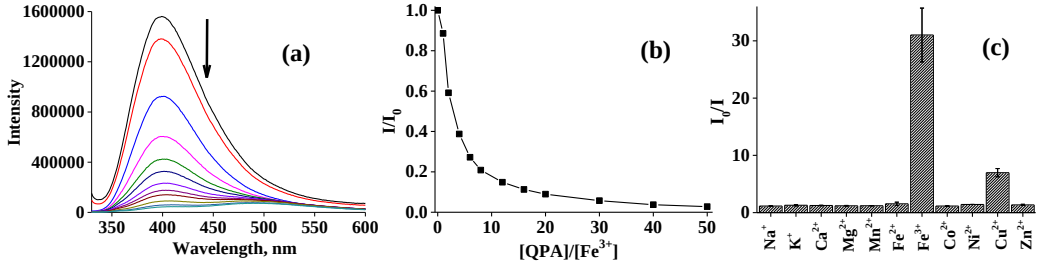


Fig. 1 (a) Fluorescence spectral traces obtained during the titration of **QPA** (10 μM) with increasing concentrations of Fe^{3+}, (b) plot of relative fluorescence intensity with mole ratio of Fe^{3+}, and (c) histogram representing relative fluorescence intensity of **QPA** upon the addition of 50 equivalents of different metal ions.

A competitive metal ion titration has been carried out to demonstrate the efficiency of **QPA** to detect Fe^{3+} in the presence of other competing ions. An *in-situ* prepared mixture of **QPA** with 10 equivalents of metal ions other than Fe^{3+} was titrated with various concentrations of Fe^{3+} resulted in the fluorescence quenching of **QPA** indicating the selectivity of **QPA** towards Fe^{3+} over other ions (Fig. 2). During the competitive titration of {**QPA**+Cu^{2+}} with Fe^{3+}, the initial fluorescence intensity of the receptor was quenched ~4.2 fold by the presence of Cu^{2+} and as a result, the total quenching fold obtained after the addition of Fe^{3+} was only 7.4 fold.

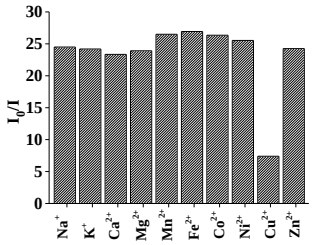


Fig. 2 Relative fluorescence intensity of **QPA** obtained during the addition of 50 equivalents of Fe^{3+} in the presence of 10 equivalents of M^{n+}

Since **QPA** showed selective quenching towards Fe^{3+} among other biologically relevant ions, we further explored the utility of *in-situ* prepared **QPA** and Fe^{3+} complex (**FeQPA**) as a secondary sensor for anions and amino acids. The **FeQPA** complex was prepared by mixing **QPA** and Fe^{3+} in a 1:10 ratio in aqueous acetonitrile solution. The stability of **FeQPA** complex in acidic and alkaline environment has been monitored by analysing the fluorescence spectral traces of **FeQPA** at different pH ranges. It has been found that FeQPA is stable in the pH ranges 3.5 to 10 (Fig. S8 in Supplementary Data).

In the detection of anions, the ensemble **FeQPA** was titrated with varying concentrations of halide ions, *viz.*, F^-, Cl^-, Br^- & I^-. The initial fluorescence intensity of the ensemble **FeQPA** has been quenched due to the presence of Fe^{3+}. During the titration with anions, the fluorescence band of **FeQPA** at 400 nm has been increased significantly upon the interaction with F^- and no changes were observed with other anions (Fig. 3). The reversal of fluorescence during the titration of **FeQPA** by the addition of F^- leads to the displacement of Fe^{3+} from the binding core of **FeQPA** and leaving the sensor **QPA** alone. The free Fe^{3+} forms a stable complex with F^- ($[FeF_6]^{3-}$) and the fluorescence intensity of the **QPA** has been restored [43-44]. The chemosensor ensemble **FeQPA** exhibited ~4 fold fluorescence enhancement upon interaction with F^-. Therefore, it clearly demonstrates the ability of **FeQPA** to detect F^- selectively among all the halide ions. The detection limit of F^- by **FeQPA** has been found to be 289 ppm. Absorption titrations were also carried out to support the secondary sensing of FeQPA with F^- and the corresponding results were summarised in the Fig. S9 of supplementary data. The displacement mechanism of **FeQPA** in the sensing of F^- has been further supported by ^1H NMR titrations by adding 10 equivalents of F^- to an *in-situ* prepared complex of **FeQPA**. During the titration, the proton signals of triazole ring and the quinoline were marginally shifted and moved toward simple **QPA** (Fig. S10 in

Supplementary Data). The regeneration of ^{1}H NMR spectra of **QPA** upon the addition of F^- supports the displacement of Fe^{3+} from the binding core of **FeQPA** complex.

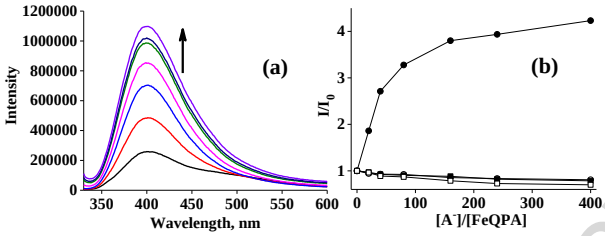


Fig. 3. (a) Fluorescence spectral traces obtained during the titration of *in-situ* prepared **FeQPA** with increasing concentrations of F^-, and (b) plot of relative fluorescence intensity of **FeQPA** with mole ratios of halides. Symbols corresponds to ● = F^-, ○ = Cl^-, ■ = Br^-, □ = I^-.

Selective detection of amino acids using **FeQPA** has been investigated by fluorescence spectroscopy. The complex **FeQPA** has been titrated with increasing concentration of twenty naturally occurring amino acids and the corresponding fluorescence intensity was monitored. None of the amino acids, except arginine and lysine, have shown any change in the fluorescence intensity of **FeQPA** during the titration (Fig. 4). It indicates that **FeQPA** interacts selectively with arginine and lysine among all the amino acids reported in this paper. The fluorescence enhancement observed for arginine and lysine were 3.9 and 4.3 fold respectively (Fig. S11 in Supplementary Data). The **FeQPA** detects arginine and lysine among the naturally occurring amino acids to the lowest concentration of 3.57×10^3 and 3.17×10^3 ppm respectively. Similar to the detection of anions, a displacement mechanism is responsible for the fluorescence enhancement of the sensor molecule when it interacts with basic amino acids. During the absorption titration of **FeQPA** with arginine and lysine, the absorption band observed at 300 nm exhibited a marginal increase in the absorbance while the absorption band at 250 nm showed marginal decrease in the absorbance (Fig. S12-S13 in Supplementary Data). The displacement strategy for the detection of amino

acids has been verified by ^{1}H NMR titration. Upon the addition of 10 equivalents of lysine or arginine to a solution of *in-situ* prepared **FeQPA** resulted in the formation of ^{1}H NMR spectra corresponds to free **QPA** (Fig. S14 in Supplementary Data). Therefore, **FeQPA** is a secondary sensor for lysine and arginine among twenty naturally occurring amino acids.

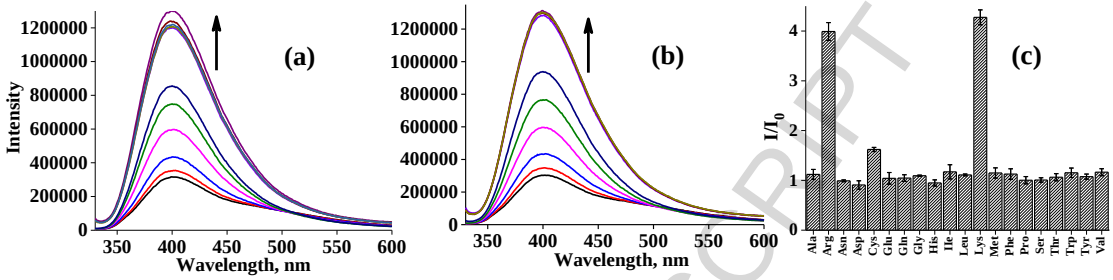


Fig. 4. Fluorescence spectral traces obtained during the titration of *in-situ* prepared **FeQPA** with increasing concentrations of (a) arginine, (b) lysine, and (c) histogram representing relative fluorescence intensity of **FeQPA** upon the addition of 50 equivalents of different amino acids.

4. Conclusions

In conclusion, quinoline appended pillar[5]arene, **QPA** selectively detects Fe^{3+} and its *in-situ* prepared Fe^{3+} complex, **FeQPA** exhibits secondary sensing towards F^{-}, and arginine and lysine. The sensing of Fe^{3+} has been monitored by the decrease in the fluorescence emission band of **QPA** at 420 nm while the detection of F^{-}, lysine and arginine have been observed by the fluorescence enhancement of **FeQPA** at 420 nm. The ion and molecular interactions have been monitored by fluorescence spectroscopy and the complexation was further supported by ^{1}H NMR titration and MALDI-TOF experiments. The **QPA** detects Fe^{3+} to the lowest concentration of 157 ppm and **FeQPA**'s detection limits are 289, 3.57×10^{3} and 3.17×10^{3} ppm towards F^{-}, arginine and lysine respectively.

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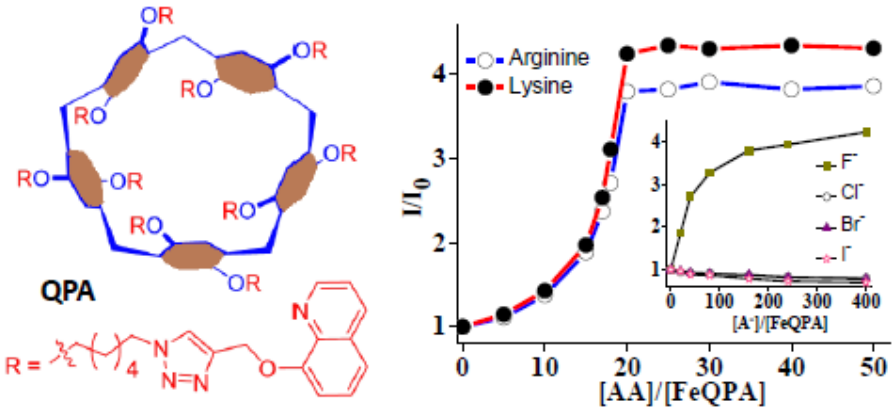

QPA as Fe^{3+} sensor and its Fe^{3+} complex (**FeQPA**) as a sensor for F^-, lysine & arginine

Graphical abstract

Highlights

Selective sensing of Fe^{3+} by novel pillar[5]arene derivative, **QPA**

Fe^{3+} complex of **QPA** (**FeQPA**) detects F^- among all halides

FeQPA selectively detects arginine and lysine among twenty amino acids