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COMMUNICATION

Xanthurenic acid: A natural ionophore with high selectivity and sensitivity for potassium ions in aqueous solution

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A simple natural molecule xanthurenic acid (H_3L), a well known tryptophan metabollite involved in the biosynthesis of quinolobactin siderophore, was developed herein as an efficient "turn-on" fluorosensor for potassium ions in aqueous HEPES buffer solution. The natural ionophore H_3L showed high selectivity for K^+ at physiological pH and in the context of interference from other competing metal ions, particularly Na^+, the specific response of H_3L towards K^+ did not change. The detection limit was found to be 53 nM. This study demonstrated the first example in which a non-cyclic system bearing a monocarboxylate functionality was used as an efficient fluorosensor for the detection of K^+ in water.

All microorganisms, fungi and plants have nutritional requirements for different metal ions which they sequester via a range of mechanisms.[1] A classic example of "microbial-metal" interaction involves low molecular weight (200-1500 daltons), powerful chelating molecules termed "siderophores" which are polar and organic in nature. Microbes synthesize and secrete siderophores which have a well-documented role as iron-scavenging materials, chelating Fe(III) ions in the environment whereupon the ferrisiderophores re-enter the bacterial cells by means of dedicated high-affinity cell-surface receptors.[2] Siderophores are water soluble natural products and have tremendous therapeutic and analytical potential (such as chemosensors). More than a decade ago, Palanche et al. were demonstrated elegantly the use of siderophores and its derivatives as chemical sensors for detection of trace levels of Fe(III).[3] Given the high affinity (K_a = 10^{20}–10^{52}) of siderophores for aqueous iron(III), siderophore-based chemosensors are expected to have high selectivity and sensitivity for Fe(III).[4] A good body of reports exist in the literature in which these natural molecules and their derivatives received special attention as Fe(III)-specific chemosensors.[5] However, siderophores can also bind other hard ions indicating opportunity in the chemosensor technology to design receptors derived from these natural molecules.[6] As part of our ongoing endeavor in the design and development of new types of task-specific probes derived from microbial chelators such as siderophores or the intermediates appearing in their biosynthetic pathway, in this work, we have chosen an analogue of 8-hydroxyquinoline, xanthurenic acid (8-hydroxy-4-oxo-1H-quinoline-2-carboxylic acid, **H_3L**, **Fig. 1**) which is an intermediate siderophore presumably involved in the biosynthesis of a quinolone siderophore, quinolobactin.[7]

The ionophore, xanthurenic acid, has three potential binding sites (ONO). Bag et. al. earlier showed that **H_3L** coordinates in a bidentate mode of chelation with different transition metal ions.[8] However, recent crystallographic data showed tridentate mode of coordination by this natural molecule.[9] In eukaryotes and microorganisms, xanthurenic acid and its various derivatives are biosynthesized from tryptophan.[7] The roots of the invasive plant, *Centaurea diffusa*, release 8-hydroxyquinoline (qu), a fluorescent phytosiderophore. Upon reacting aluminium(III) with 8-hydroxyquinoline, resulted in the synthesis of $Al(qu)_3$, which has been used as an emitter and one of the most stable electron-transporting materials and used in Organic-Light-Emitting-Diodes (OLED). Moreover, variations in the substituents on the quinoline rings, the color of the developed OLED also changes.[6e] Attaching diaza-18-crown-6 functionality to 8-hydroxyquinoline resulted in the development of a Mg^{2+}-specific chemosensor.[6b] All these exciting results serve as our inspiration to explore the sensory properties/applications of the analogue of 8-hydroxyquinoline i.e. xanthurenic acid. We observed that the addition of potassium ion to the solution of non-fluorescent **H_3L** causes development of a strong fluorescence.

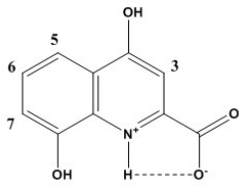

Fig. 1. Structure of the natural ionophore xanthurenic acid (**H_3L**) at physiological pH.

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Electronic Supplementary Information (ESI) available: Experimental details, spectroscopic data (Figs. S1-S5) and Table S1. See DOI: 10.1039/x0xx00000x

Potassium ions, the most abundant physiological metal ions in living organisms, play numerous crucial roles in biology. Other than maintaining cellular osmotic pressure and suitable pH equilibrium, it also involved in different sensory transduction cascades throughout the nervous system.[10] This ion makes up about 0.4 % of the mass in the human body and functions diverse roles in biological processes associated with the regulation of blood pressure, muscle contraction, nerve transmission, heartbeat, and kidney function.[10b] An imbalance of potassium concentrations triggers certain diseases such as stroke, anorexia, hypertension, alcoholism, heart disease, renal disease, diabetes and many more.[11] In view of the aforesaid significances of potassium ions, there have been several continuing attempts to develop analytical techniques such as atomic absorption spectrometry, inductively coupled plasma atomic emission spectrometry, and spectrophotometry, etc., for accurate and selective detection of K^+. Of them, colorimetry and spectrofluorometry, has gained increasing attention in the past decades due to their sensitivity, selectivity, and enhanced resolution.[12-16] Major challenges in the design and development of the sensor for the measurement of potassium ions in aqueous solution are the high hydration energy of the metal ion and no pH interference in physiological pH range. Furthermore, presence of the large excess of Na^+ poses serious confront in developing K^+-selective chemosensors.[12a] Below, we describe the results of studies that have led to the development of a natural receptor, **H_3L**, which is highly sensitive and selective for potassium ions in aqueous solution even in presence of large excess of sodium ions.

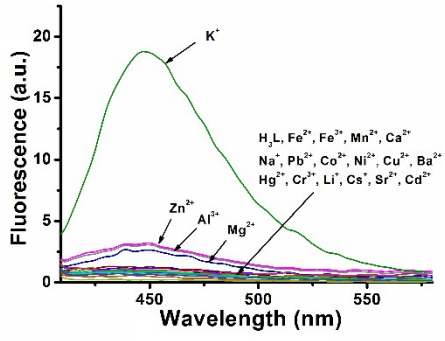

Fig. 2. Emission spectra of xanthurenic acid (10 µM) upon excitation at 360 nm in aqueous HEPES buffer medium (pH 7.2) upon addition of different metal ions (1 equivalent).

H_3L in aqueous solution is non-fluorescent and colourless in visible light to the naked eye. The photophysical properties of **H_3L** were explored in aqueous HEPES buffer (50 mM) at pH 7.2. In this medium, the free **H_3L** showed two absorption bands at 244 (ε, 31200 $Lmol^{-1}cm^{-1}$) and 339 nm (ε, 6750 $Lmol^{-1}cm^{-1}$) attributed to the π-π* transitions; the second one probably results from an intra-ligand charge transfer, **Fig. S1** (see ESI†). The perchlorate salts of several metal cations (Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Fe^{3+}, Mn^{2+}, Ba^{2+}, Sr^{2+}, Cr^{3+}, and Al^{3+}) were used to evaluate the metal ion binding properties of **H_3L**. Alkali, alkaline earth metal, and transition/heavy metal (HTM) ions did not show change in the absorption properties of **H_3L**. Fluorescence emission spectra of the receptor **H_3L** were recorded upon excitation at 360 nm to understand the nature of the interactions in the excited state, **Fig. S1** (see ESI†). A sharp increase in the fluorescence intensity at 448 nm (**Fig. 2**) was observed upon addition of 10 µM K^+. The fluorescence intensity of **H_3L** underwent a ca. 18-fold (F/F_0, ratio of the fluorescent intensity peak values at 448 nm) enhancement upon addition of K^+. All other metal ions, particularly Na^+, did not show any significant change in the emission spectra of the ionophore **H_3L**. Attempt to use ionophore at a concentration lower than 10 µM, did not work, as at this low **H_3L** concentration the higher fluorescence response upon K^+ addition cannot be described quantitatively, due to low signal-to-noise ratio at this low concentration.

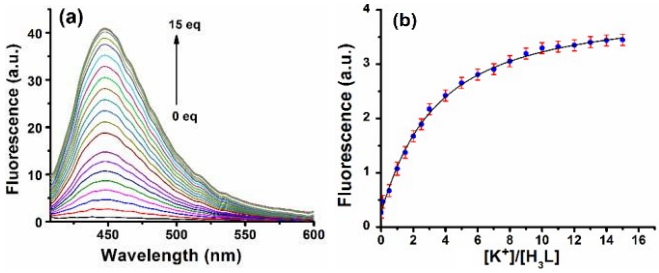

Fig. 3. (a) Spectrofluorometric titration of **H_3L** (10 µM in aqueous HEPES buffer) in presence of increasing concentrations of K^+ at 25 °C and (b) non-linear curve fitting of emission maxima of **H_3L** as a function of K^+ concentration. Each data points indicate the average of three values and the error bars represent the standard deviations.

In order to examine the best pH region for the selectivity of **H_3L** to K^+, the influence of pH in a range between 2 and 12 was studied next. No apparent changes in the emission spectra were observed for **H_3L** alone however, **Fig. S2** showed that the detection of K^+ can work fine in the pH range of 7-12. Thus, in this study, all spectral analyses were accomplished in HEPES buffer solution at pH 7.2, prepared in water. **Fig. 3** showed the arrays in the emission spectra of **H_3L** (10 µM) against variable concentrations of K^+ under identical conditions. As can be further seen from **Figs**. **3a** and **3b**, the fluorescence intensity of the emission maximum reached a plateau i.e. fluorescence signal gets saturated at 140 µM of K^+. Non-linear fitting of the data points from the systematic fluorescent titrations, performed at 25 °C (**Figs. 3a** and **3b**), resulted in an association constant, *Ka* = 0.4 x 10^5 M^{-1} (calculated from the following equation).[17] To explore the practical applicability, the limit of detection (LOD) of this natural ionophore was calculated from 3σ/S model[18] (**Fig. S3**) which showed a value of 53 nM. Using the emission spectroscopic data, the binding stoichiometry between **H_3L** and K^+ was found to be 2:1 (ionophore:K^+) which was established by Job's plot (**Fig. S4**). This result was also confirmed by HR-MS, where a peak at *m/z* 447.0230 corresponding to the 2:1 complex formation between **H_3L** and K^+, provided further direct evidence in support of above stoichiometry (**Fig. S5**).

$$F = F_0 + \frac{F_{max} - F_0}{2}\left\{\left(1 + \frac{[M]}{C_L} + \frac{1}{C_L K}\right) - \sqrt{\left(1 + \frac{[M]}{C_L} + \frac{1}{C_L K}\right)^2 - 4 * \frac{[M]}{C_L}}\right\}$$

To further elucidate the binding stoichiometry of **H_3L** with K^+, ^1H NMR titration spectra were recorded in DMSO-d_6. As showed in **Fig. 4** and **Table S1**, the signal at 10.68 ppm originating from the intramolecularly hydrogen bonded N^+—H moiety, was found to shift downfield (10.71 ppm) upon addition of 0.25 equiv of K^+. As expected, further downfield movement of the N^+—H peak was observed with the increasing addition of K^+ and exactly at 1:0.5 (**H_3L**:K^+) stoichiometry, the signal shifted maximum (10.77 ppm) in the low-field direction and remained

unaffected with additional rise in K^+ fraction. This clearly indicates the rupturing of intramolecular hydrogen bonding (**Fig. 1**) upon gradual addition of K^+ to the probes solution. Therefore, the enhancement of fluorescence signal after potassium addition is likely on account of the decrease of the intramolecular hydrogen bond assisted fluorescence quenching of the 8-hydroxyquinoline fluorophore moiety upon addition of K^+.

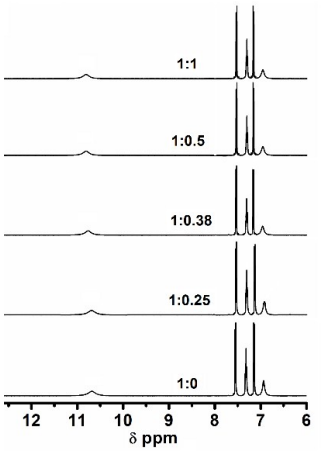

Fig. 4. ^{1}H NMR titration of **H_3L** in DMSO-d_6. Solution stoichiometry of **H_3L** (2 mmol) and K^+ is shown for each spectrum.

Optical properties for several potassium ion selective and water soluble chemosensors have been summarized in Table 1 which provides a bench mark to compare the title K^+-selective natural ionophore (i.e. **H_3L**) with literature reported data. This is aimed at serving researchers a reference point for designing new sensors targeted for the significant improvement of aqueous soluble efficient K^+-sensors. Table 1 clearly reveals that all these aqueous soluble K^+-specific chemosensors are cyclic ethers or cryptands in nature such as crown, azacrown, cryptand, azacryptand, calix or calix-crown based. The binding constant in most of the cases are quite moderate, in the range 10^4-10^6 M^{-1}. The crown ether fluoroionophores, developed by Yamauchi et al., upon constructing supramolecular network structures with γ-cyclodextrin were reported to form 2:1 complexes with K^+ with a high binding affinity ($Ka \approx$ 4-6 x10^9 M^{-2}).[13c] On the other hand there is potassium sensor with binding constant as low as 11 M^{-1}.[12m] The determination of LOD of these K^+-selective chemosensors has been paid no interest in the literature. Only one report is available with LOD of 16 μM while **H_3L** with a very low LOD (53 nM) is remarkable in this context.

An important characteristic of any metal ion-specific chemosensor is its exclusive selectivity towards the cation over other competing metal ions, particularly, transition metal ions. Table 1 clearly reveals that the response of all these literature reported water soluble K^+-specific chemosensors were irregularly explored in presence of alkali and alkaline metal ions such as Li^+, Na^+, Ca^{2+} and Mg^{2+}. However, the transition metal ions whether interferes in the selectivity process is overlooked by large. Therefore, in a separate experiment, a mixture of five equiv excess each of the other challenging metal ions, such as transition/heavy metal ions or alkali/alkaline metal ions, were added to a solution of **H_3L** + K^+ to explore any interference from other competing metal ions. The results are displayed in **Fig. S6** which showed comparable changes in the emission spectra as that of K^+ alone, illustrating indubitably the unique ability of the natural ionophore, **H_3L**, as a K^+-specific chemosensor. **Fig. S6** clearly exposed that even in presence of 50-fold excess of Na^+, the selective response of **H_3L** towards K^+ remain unperturbed. Furthermore, miscellaneous counter anions with varying sizes and shapes did not affect the spectral feature of **H_3L** with K^+.

Table 1. Summary of optical parameters of different water soluble K^+-selective chemosensors.

Receptor/ Ref	K_a [a] (M^{-1})/ LOD	Interferences[b]	Buffer/Excitation (nm)
H_3L/This work	0.4x10^5/ 53 nM	No interference	HEPES-Water/360
C3- γ-CyD/ 13c	3.8x10^9 M^{-2}/16 μM	No selectivity with Na^+	HEPES-Water/330
C5-γ-CyD/ 13c	5.8x10^9 M^{-2}/NA[c]	NA[c]	HEPES-Water/330
KS1/15b	1x10^2/ NA[c]	NA[c]	HEPES-Water/450
Eu-KPhen/ 12c	26x10^6/ NA[c]	No selectivity with Li^+, Na^+, Ca^{2+} & Mg^{2+}	Acetate-Water/267
TAC-Red/ 12l	NA[c]/ NA[c]	No interference	HEPES-Water/480
Sensor 1/ 12i	200/ NA[c]	No selectivity with Na^+ & Ca^{2+}	Tris-HEPES-Water/470
KS2/ 12m	11/ NA[c]	No interference with Na^+, Ca^{2+} & Mg^{2+}	HEPES-Water/561
ddTAC-Red/ 15a	NA[c]/ NA[c]	No interference with Na^+, Cs^+ & Rb^+	HEPES-Water/480
Calix-crown/12h	2.8x10^4/ NA[c]	NA[c]	Water/350
ddTAC-Lime/15a	NA[c]/ NA[c]	No interference with Na^+, Cs^+ & Rb^+	HEPES-Water/500

[a]K_a denotes binding constant; [b]selectivity studies (interference studies) in presence of other competing metal ions; [c]data not available from the reported literature

In conclusion, we have reported a simple and natural K^+-selective chemosensor, xanthurenic acid (**H_3L**), which is the key precursor appears in the biosynthetic pathway of a microbial iron chelator, quinolobactin. The selectivity of this intermediate siderophore for K^+ over other metal ions is remarkably high and its sensitivity is nearly 53 nM in aqueous HEPES buffer solutions at physiological pH. Moreover, the effect of other competing metal ions has almost no effect on the selectivity of K^+ by this natural ionophore. Even in the presence of large surplus of sodium ions, **H_3L** can detect K^+ very efficiently. Incidentally, all the small organic molecule based K^+-selective fluoroionophores reported to date are derived by integrating crown ethers, azacrown ethers, cryptands, azacryptands and calixes to a suitable signalling unit i.e. fluorophore. To the best of our knowledge, the remarkable observation reported herein

constitutes the first example of a potassium specific natural ionophore which is devoid of any polyether (crown and azacrown) and/or cryptand and azacryptand functionalities. Due to our limitations, we could not perform the bio-imaging application of this natural ionophore in cell-lines. However, efforts in further tailoring of this metabolite, particularly the effect of introducing sulfonic acid group into **H_3L** is currently underway.

Experimental

Xanthurenic acid, different metal perchlorate salts, HEPES, and other analytical reagents were purchased from Aldrich and were used as received. ^{1}H NMR spectra (500 MHz) were acquired in a Bruker Avance II 500 FT-NMR spectrometers using TMS (δ_0) as internal reference. The UV/vis spectra were recorded using Cary 500 scan UV-vis-NIR spectrophotometer. The fluorescence spectra were recorded using Edinburgh instruments Xe900 (µF 920H) spectrofluorimeter. The HR-MS in the negative ion mode were measured on a Micromass Q-ToF micro™. Solutions pHs were measured using Thermo Scientific Orion Versastar Advanced Electrochemistry meter at 298 K.

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Table of Contents

Synopsis: A well-known tryptophan metabolite xanthurenic acid, a natural non-fluorescent intermediate siderophore, showed very selective turn-on response to K^+ over other competing metal ions and the detection limit of this natural ionophore was found to be 53 nM at physiological pH.