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Quinoline-based ratiometric fluorescent probe for detection of physiological pH changes in aqueous solution and living cells

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ABSTRACT

Herein, a novel quinoline-based fluorescent probe **DQPH** has been developed for ratiometric detection of subtle pH fluctuation in biosystem. Upon altering the pH from 4.50 to 9.00, the emission spectra exhibit a large hypsochromic shift (57 nm) and the ratio of fluorescence intensity ($F_{531\ nm}/F_{588\ nm}$) changes from 0.30 to 1.36 with an ideal pK_a value of 7.18 and a linear pH variation range of 6.35–8.00. The ratiometric response is attributed to the protonation-activable resonance charge transfer (PARCT) process, which has been proved by ^{1}H NMR and NOESY experiment. This probe displayed good solubility, low cytotoxicity, anti-interference capability and reversible pH sensing. Furthermore, **DQPH** was successfully applied for monitoring pH changes in living cells.

1. Introduction

Intracellular pH is one of the significant factors that relate tightly with various physiological processes, including proliferation [1], metabolism [2], endocytosis [3], ion transport and homeostasis [4–6]. Under normal physiological environment, differences in the pH are investigated in distinct cellular regions. For example, the cytosolic pH value is generally 7.20–7.40 [7,8]. Meanwhile, various organelles maintain special pH values due to their unique biological functions, such as the pH in lysosomes and mitochondria is about 4.50–5.50 and 8.00, respectively [9–11]. However, disruption of normal pH homeostasis in these compartments could give rise to cellular dysfunctions, which is a key factor in many diseases, such as cancer [12–14], cardiopathy, and Alzheimer's disease [15,16]. In other words, the regulation and homeostasis of pH are tightly associated with viability of live cells and tissues. Therefore, precise measurement of physiological pH values is extremely necessary and crucial for better understanding the physiological and pathological processes in biological system.

In recent years, a number of approaches were developed to detect intracellular pH such as microelectrodes, absorbance spectroscopy, nuclear magnetic resonance and HPLC-MS technique [17–20]. Compare to these typical methods, fluorescence imaging has been extensively used because of its numerous advantages, including visualization, high sensitivity, spatiotemporal resolution, non-invasive test, and real-time detection [21–23]. And as far as we know, there are two main classes of fluorescent probes have been reported for detection of pH changes. One class is intensity-based probes which detect pH values by increasing or decreasing the fluorescence intensity. But the accuracy of these probes would be inevitably disturbed by instrumental factors and nonuniform distribution of probes within samples [24–36]. Another class is ratiometric probes which could overcome the above-mentioned problems by means of self-calibration of two emission bands [37–51]. Therefore, this kind of ratiometric probes can realize quantitative measurements for accurate detection of pH in vivo and in vitro. Therefore, we summarized several recently reported ratiometric fluorescent probes for pH detection (Table 1). By comparing their characteristics, most of these probes have lower pK_a and used in acidic environment. In addition, the low water solubility is a big obstacle for their biological application. Consequently, the development of highly sensitive and water-soluable fluorescent probes for quantitative monitoring weak acidic to weak basic physiological pH fluctuation, like in cytoplasm, is still urgently demanded.

Recently, several 4-methoxyl quinoline-based fluorescent probes were reported for monitoring metal ions and bioactive molecules [52–54]. These probes displayed ratiometric detection property on account of protonation-activable resonance charge transfer (PARCT) process, which let electron transfer from 4-position electron-donating group to protonated quinolinic nitrogen in aqueous medium (Scheme 1). Consequently,

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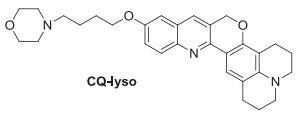
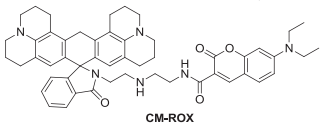
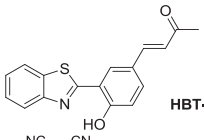
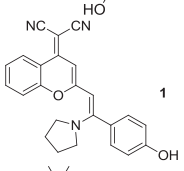
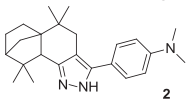
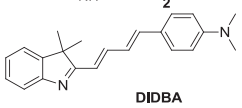
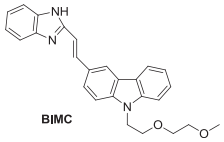
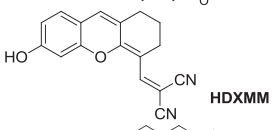
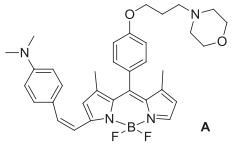
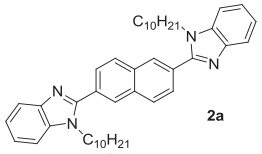
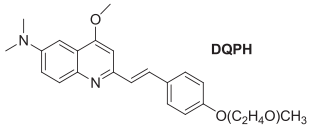
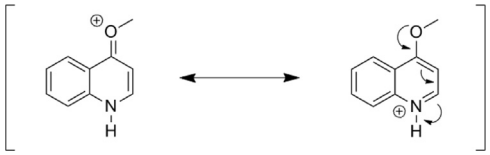
Table 1
Comparison of properties of recently reported probes for pH sensing in ratiometric method.

Probes	λ_{ex} / nm	[a]λ_{em} / nm	pK_a	[b]pH range	Solvent (v: v)	Ref.
 CQ-lyso	470	613 / 560	5.00	4.00–6.00	[c]B-R buffers: CH_3CN = 7: 3	[41]
 CM-ROX	435, 590	475 / 605	5.69	4.50–6.00	Tris HCl buffer: EtOH = 6: 4	[42]
 HBT-O	392	565 / 515	6.73	[d]–	PBS buffer	[43]
 1	380	511 / 439	–	3.80–6.00	EtOH: H_2O = 8: 2	[44]
 2	325	373 / 445	2.59	1.50–4.00	EtOH: H_2O = 8: 2	[45]
 DIDBA	495	697 / 618	4.50	3.50–5.20	Glycerol-EtOH: H_2O = 2: 1	[46]
 BIMC	360	514 / 454	4.46	3.80–5.00	DMSO: H_2O = 1: 4	[47]
 HDXMM	550	572 / 623	7.45	7.00–8.00	PBS buffer: CH_3CN = 10: 1	[48]
 A	470	515 / 665	2.00	–	THF: H_2O = 1: 1	[50]
 2a	325	402 / 472	2.92	–	THF: H_2O = 2: 3	[51]
 DQPH	405	588 / 531	7.18	6.35–8.00	Na_2HPO_4-citrate buffer	This work

[a] Maximum emission wavelength in protonation vs deprotonation state.
[b] linearity range of pH detection.
[c] Britton-Robinson (B-R) buffer solution.
[d] Not reported in the corresponding paper.



Scheme 1. Resonance process of the protonated 4-methoxyquinoline.

this resonance effect would lead to greatly bathochromic shift in both UV–vis absorption and fluorescence emission spectra due to the effect of charge delocalization. These studies demonstrate that regulating the protonation or deprotonation of 4-alkoxy-substituted quinoline derivatives can display distinct photophysical state. Therefore, 4-methoxyquinoline derivatives can be excellent candidates for establishing ratiometric pH-responsive fluorescent probes with two emission bands.