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Near-neutral pH Sensing by Azoheteroarene Dyes

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# These authors equally contributed to this article and deserves to be considered as the first authors. Supporting information for this article is given via a link at the end of the document.

Abstract: We serendipitously discovered a novel series of azoheteroarene dyes capable of detecting pH variations in near-neutral solutions. These dyes feature thiazole, thiadiazole, triazole, pyrazole, or benzothiazole heteroaryls linked to hydroxyphenyl azo groups. They exhibit distinctive light absorption properties in aqueous solutions and show notable color changes in a narrow pH range, visible to the naked eye. Both experimental data and quantum calculations suggest a plausible mechanism for their function as pH indicators. Additionally, these azoheteroarene dyes effectively monitor pH in complex environments, and we show their use for detecting the pH change of culture medium containing growing cancer cells.

Introduction

pH indicators are widely used in many disciplines of material, environmental, biological, and clinical sciences.[1–6] Broadly, the pH indicators are either based on fluorometry or colorimetry that involves the detection of the change in fluorescence or color from the analyte.[7–15] One major advantage of colorimetry over fluorometry is the ease of detection by naked eye without any instruments and hence is a cost-effective method. Azobenzene dyes are extensively investigated for the development of colorimetric pH indicators and some of them are commercially available for practical applications.[16–21] However, most of the azobenzene dyes show pH detection either in strong acid or alkaline conditions. For instance, pK_a of commercial methyl yellow and alizarin yellow is 3.3 and 11, respectively (Fig. 1). Exceptional case exists as in the case of 4-hydroxy-4'-nitroazobenzene derivatives, which show pK_a 7.2 or 7.9[22, 23] Colorimetric pH indicators that can show distinct color changes in a near neutral pH range are highly advantageous for the detection of pH variation in biological system.[24,25] For instance, tissue/cell culture is a routine experiment in many biology laboratories. When tissue/cells are incubated for several days, the waste products from dying cells can cause a change in pH of culture medium, which can be detected by monitoring the change of indicator color. For this purpose, phenol red (pK_a 7.9, Fig. 1), a non-azo dye, is known. However, it can cause side effect in some culture media,[26] although it is generally inert under most biological conditions.

We serendipitously discovered a new series of azo dyes consisting of heteroaryl motifs, which detect near neutral pH variation. Azoheteroarenes having a five-membered heteroaryl motifs have distinct photophysical characteristics and molecular geometries.[27, 28] Recently, they got much attention as a new category of photoswitches, and we and others have reported photoswitches based on thiazole, pyrrole, pyrazole, imidazole, isoxazole and triazole.[29–34] In our case, the “phenyl azothiazole” photoswitch showed red-shifted maximum absorbance compared to the well-known azobenzene photoswitch, and underwent reversible isomerization by visible-light irradiations. Present study

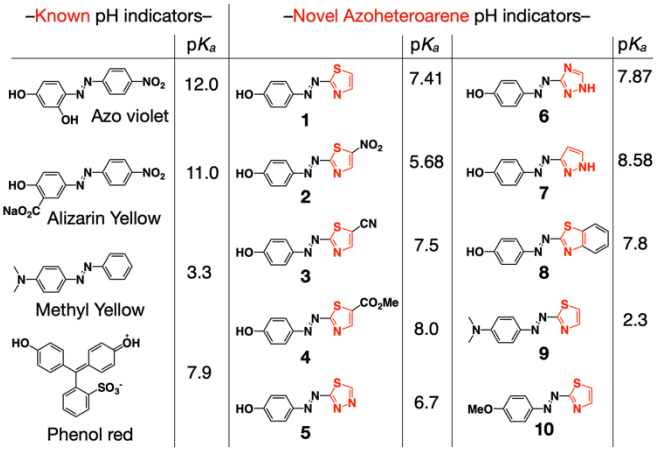


Figure 1. Molecular structures of known and novel azoheteroarenes pH indicators **1**–**10** containing thiazole, benzothiazole, thiadiazole, pyrazole, and triazole moieties along with their p*Ka* values.

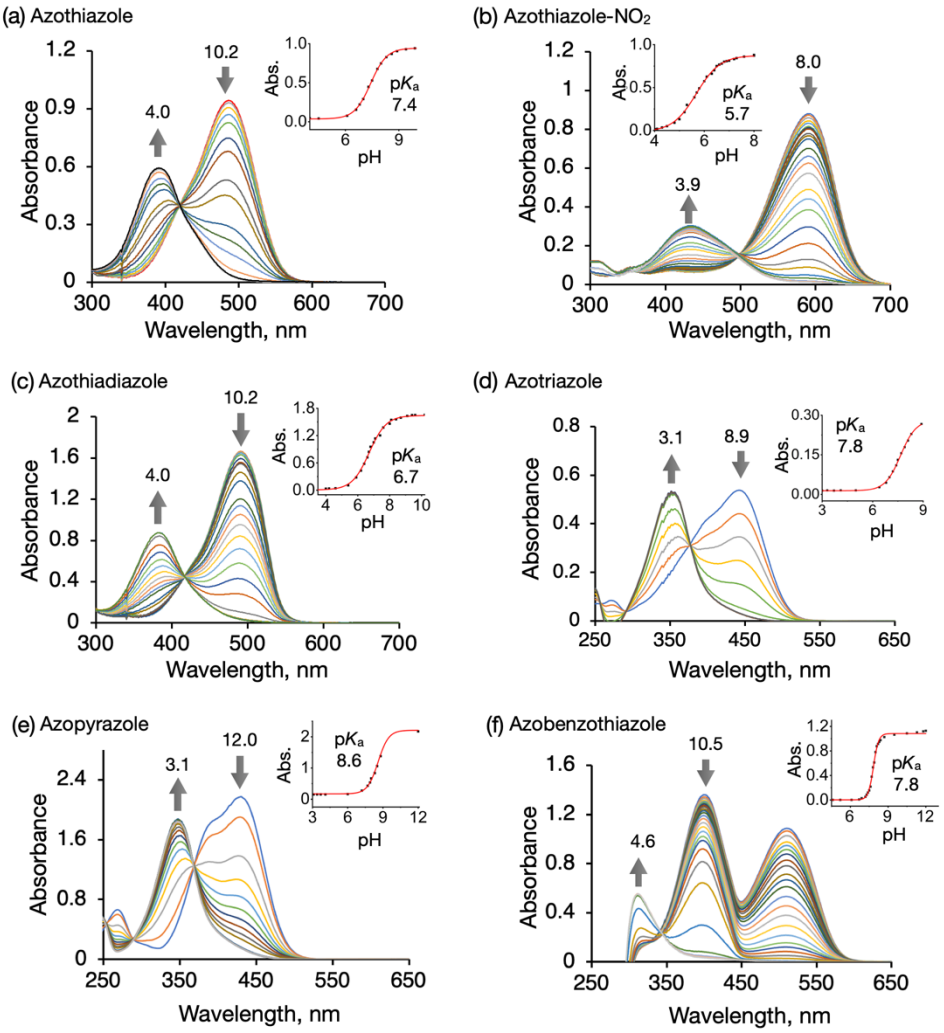


Figure 2. Absorption spectra of **1** (a), **2** (b), **5** (c), **6** (d), **7** (e), and **8** (f) in water or 0.1M HEPES buffer (pH adjusted with 0.1M NaOH) at 25 °C upon titration with 1M HCl between pH ranges mentioned in each graph. A new spectral band appeared at lower wavelength over decrease in pH value and become saturated at pH 3.1–4.6. Non-linear fitting of the pH dependent absorbance changes at λ_{max} along with the pK_a values (insets).

reports the development of near-neutral pH indicators based on azoheteroarenes. We envisioned that thiazole, benzothiazole, thiadiazole, pyrazole, and triazole heteroarene should have a favorable effect to increase the electron delocalization and may exhibit unique color in aqueous medium containing H^+/OH^-. We indeed found that the azo dyes composed of heteroaryl motifs and hydroxyl substituent at *para* position on the phenyl ring display significant color changes observable by naked eye in a narrow pH range. We also demonstrated that the azoheteroarene dye can precisely monitor the pH even in a complex environment such as cell culture medium. Further, we show the potential use of the azoheteroarene dyes for detecting the pH change of culture medium containing growing cancer cells.

Results and Discussion

Synthesis and absorption spectral studies.

We synthesized compounds **1**–**10** via a direct azo coupling reaction, as reported previously (Schemes S1 and S2,[26] and unambiguously characterized using a variety of analytical methods (^{1}H NMR, ^{13}C NMR, and mass spectroscopy) (Fig. S1–14). In organic solvents (CH_3CN or DCM), the compounds **1**–**10** exhibited absorption bands (λ_{max} = 338–490 nm) assignable to the $\pi \rightarrow \pi^*$ electronic transition (Fig. S15). In aqueous solvents, the compounds exhibited a significantly red-shifted absorption bands depending on the solution pH (Figs. 2, S16). For instance, compound **1**, exhibited an absorption band (λ_{max} = 479 nm, pH 10.2, water) that seemingly contain both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transitions (Fig 2a, red). We then performed UV-vis titration of the compounds for a range of pH. Fig 2a shows the absorption spectra of compound **1** (20

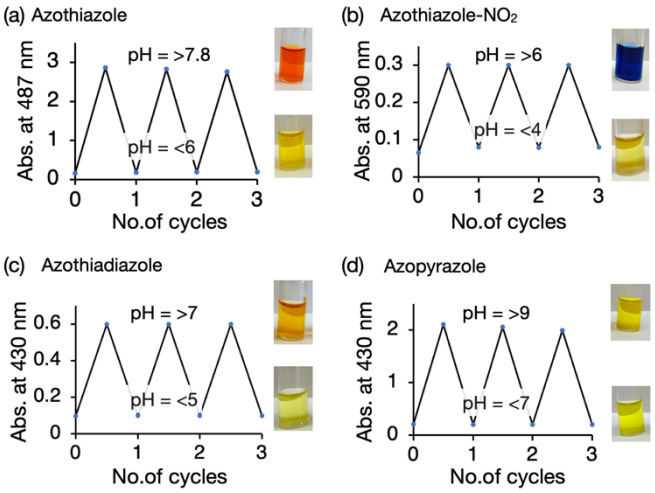


Figure 3. Reversibility of the absorption spectral changes of **1** (a), **2** (b), **5** (c), and **7** (d), for pH variation between <4 or 6 and >9. Images showing the changes in solution color of 1 (a; pH 6 [yellow] – 7.8 [red]), 2 (b; pH 4 [yellow] – 6 [blue]), 5 (c; pH 5 [pale yellow] – 7 [orange]), and 7 (d; pH 7 [pale yellow] – 9.1 [yellow]) are displayed.

μM, pH 10.2 to 4) in aqueous solution where the absorption band at 487 nm (λ_{max}) gradually decreased with the emergence of new absorption band at 391 nm (λ_{max}) that became dominant over the pH 7. The isosbestic point at ~420 nm indicated the existence of two species in equilibrium as the pH changed. The pK_a value calculated from the absorbance changes at 487 nm was 7.4. Accordingly, the color of the aqueous solution at pH 6 and 7.8 observable to the naked eye was yellow and red, respectively (Figs. 3a, S18). Repeated switching of solution pH gave yellow (pH <6) and red (pH >7.8) colors without any deterioration indicating excellent reproducibility. The presence of substituent at the thiazole segment, as in the case of **2**–**4**, significantly affected their light absorption properties and colors in aqueous solution. For instance, the compound **2**, having an electron withdrawing NO_2 substituent on the thiazole ring, showed absorption bands (λ_{max}) at 435 nm in low pH (<4) and at 590 nm in high pH (>6) aqueous solutions with yellow and deep blue colors, respectively (Figs. 2b, 3b, S19). The pK_a value was 5.7 at 25 °C with a pH detection range of 4.2–5.9. The light absorption properties and pH detection range can be further adjusted to near neutral (λ_{max} = 604 nm in high pH; pK_a 6.3) by introducing electron donating methoxy group at the phenyl segment (Figs. S15, S16, S24, S26). The compounds **3** and **4**, having CN and CO_2Me substituents, respectively, showed nearly identical spectral characteristics in acid and base solutions with pK_a values 7.5 (**3**) and 8.0 (**4**) (Figs. S16a, c, S20, S21).

We then studied the absorption spectral changes in different solution pH for the compounds **5**–**8** that has thiadiazole, triazole, pyrazole or benzothiazole "heteroaryls" connected to the *para* hydroxy phenyl azo segment. Both the λ_{max} and pK_a altered significantly depending on the type of "heteroaryls" present in the compound (Figs. 2c-f, Table 1). The compound **5** having thiadiazole heteroaryl showed near-neutral pK_a value 6.71 with distinct solution colors of pale yellow (pH <5.2) and orange (>7.2) (Fig. 3c). However, in the case of compounds **6** (pK_a 7.87) and **7** (pK_a 8.58) having triazole and pyrazole heteroaryls, respectively, we observed only a marginal change in the solutions colors from pale yellow to yellow in different solution pH (Figs. 3d, S23, S24). The compound **8** having benzothiazole heteroaryl showed identical spectral changes to that of compound **1** with pK_a 7.8 and distinct solution colors of yellow (pH <6.6) and red (>8.2) (Figs. 2f, S25, Table 1).

We also studied the effect of substituent at *para* position on the phenyl ring by replacing the electron donating OH group with NMe_2 (compound **9**) or OMe (compound **10**) group. Compound **9** showed spectral changes and color only in a highly acidic solution (pH 1.5–3.0; pK_a 2.3) (Figs. S16e, S26). On the other hand, compound **10** with OMe substituent did not show any spectral changes for different solution pH in our experimental conditions (Fig S16g). These results indicate the importance of OH group at the *para* position on the phenyl ring together with heteroaryl segments for showing the near-neutral pH detection.

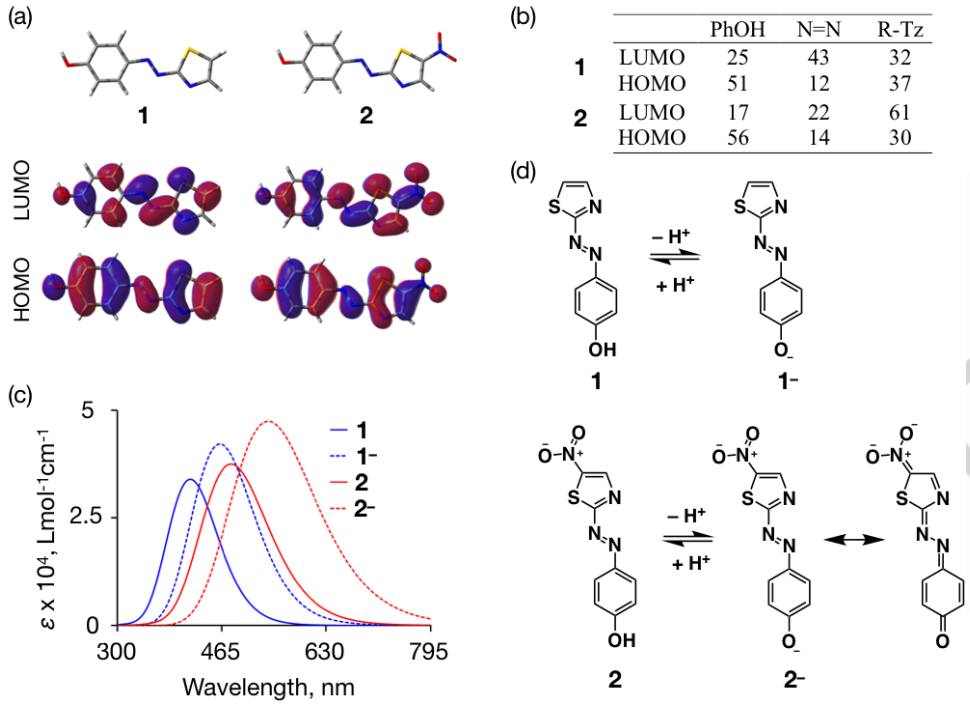
Table 1. Spectral parameteres and solution colors of **1**–**10**.

	π–π^* (*acid*) λ_{max}, nm	π–π^* (*base*) λ_{max}, nm	π–π^* (*organic*)* λ_{max}, nm	pK_a (25 °C)	pH range	Color *(acid)*	Color *(base)*
1	391	487	397	7.41	6.1–7.9	Yellow	Red
2	435	590	448**	5.68	4.2–5.9	Yellow	Blue
3	378	562	374	7.5	6.6–7.8	Yellow	Violet
4	382	542	374	8.0	6.6–8.2	Yellow	Violet
5	385	491	393**	6.71	5.2–7.2	Pale yellow	Orange
6	356	442	345	7.87	6.0–8.2	Pale yellow	Yellow
7	347	430	338	8.58	7.0–8.8	Pale yellow	Yellow
8	401	512	399	7.8	6.6–8.2	Yellow	Red
9	583	516	490	2.30	1.5–3.0	Violet/ Pink	–
10	393	399	388	–	–	Orange	Orange

* CH_3CN, ** DCM

Theoretical calculations.

Density functional theory (DFT) calculations were performed to understand the effect of the charge transfer on the pK_a using compounds **1** and **2**. The basis set 6-31+G(d,p) with Becke's three-parameter hybrid exchange and the Lee-Yang-Parr's correlation functional (B3LYP) including Grimme dispersion correlation in aqueous medium was used. Energy optimized structures of **1** and **2** showed a planar structure in the ground state (Fig. 4a). In **1** and **2**, the electron density in highest occupied molecular orbital (HOMO) was localized on the hydroxyphenyl part, while in lowest unoccupied molecular orbital (LUMO) the



		PhOH	N=N	R-Tz
1	LUMO	25	43	32
	HOMO	51	12	37
2	LUMO	17	22	61
	HOMO	56	14	30

Figure 4. (a) The geometry optimized structures and the frontier molecular orbitals (HOMO and LUMO) of **1** and **2** in the ground state. (b) Table showing HOMO and LUMO electron distribution (%) in different moieties (hydroxy phenyl [PhOH], azo bond [N=N], and thiazole [R-Tz]; R = H/NO_2) of **1** and **2**. (c) Theoretically calculated absorption spectra of **1** (blue curve) and **2** (red curve) in the neutral (solid curve) and anion (dotted curve) forms in aqueous medium. (d) Plausible changes in the chemical structures of **1** and **2** in acid ($+H^+$) or base ($-H^+$) solutions.

electron density distribution changed to N=N bond or thiazole ring (Fig. 4a). The electron density distribution in different moieties in the frontier molecular orbitals are displayed in Figure 4b. The calculated absorption spectrum of **1** and **2** gave λ_{max} at 416 nm and 480 nm, respectively (blue and red curves; Fig. 4c). In the case of **2**, calculation indicated a significant charge transfer from donor (hydroxyphenyl moiety) to the acceptor (nitrothiazole moiety) in the excited state, which can be attributed to the absorption λ_{max} at longer wavelength. We then calculated absorption spectra in the anionic forms $\mathbf{1}^-$ and $\mathbf{2}^-$, which gave much red-shifted λ_{max} at 462 and 539 nm, respectively (dotted blue and dotted red curves; Fig. 4c). This result indicates that a stronger donor to acceptor charge transfer in the anionic form as compared to the neutral form of **1** and **2**. The theoretically calculated pK_a of **1** and **2** was 8.4 and 3.4, respectively. Importantly, we observed the similar tendency of red-shifted absorption (**1**: λ_{max} = 487 nm, pK_a = 7.41; **2**: λ_{max} = 590 nm, pK_a = 5.68) experimentally when solution pH was increased suggesting the existence of anionic forms $\mathbf{1}^-$ and $\mathbf{2}^-$ (Fig. 4d). The plausible changes in the chemical structures of **1** and **2** in acid or base solutions are shown in Figure 4d. At low pH solution, **1** exhibits a yellow color. With an increase in pH, the proton is lost, resulting in negative charge ($\mathbf{1}^-$) that can delocalize throughout the molecule and hence show a red-shifted absorption spectra and red color in solution. In the case of **2**, increase in pH cause a loss of proton and the resulting negative charge ($\mathbf{2}^-$) delocalizes throughout nitrothiazole moiety, exhibiting a deep blue color. These pH dependent color changes enable the new azoheteroarenes to be used as pH indicator dyes.

Biological studies.

We then checked whether heteroarene compounds could detect pH variations in cell culture media incubated with growing cancer cells. A key requirement is stability in a reductive environment. Compounds **1**–**8** exhibited stability in the presence of reductants, as no decrease in absorbance was observed when they were incubated in a glutathione-containing aqueous solution (Fig. 5b and S38). Additionally, the compounds should show distinct color changes within a narrow near neutral pH range. While compounds **1** and **3**–**5** met these criteria, compound **1** was selected to demonstrate the pH-sensing ability of the novel heteroarenes.

We first confirmed that **1** can detect the pH variation in cell-free culture medium (IMDM) containing serum protein (10%) with pK_a 7.5, which was identical to the pK_a observed in aqueous solution

(Fig 5a). To check the detection of pH variation in a growing cancer cell, HeLa cells were seeded in a 96-well plate (15 x 10^4 cells/well) and incubated 24 hours at 37 °C and 5% CO_2. Then the medium was replaced with new medium containing **1** (6.25–50 μM) and further incubated for 53 hours without CO_2. Absorbance was measured directly on the culture plate. For comparison, culture plates that contain only DMEM medium without HeLa cells were made under similar experimental conditions.

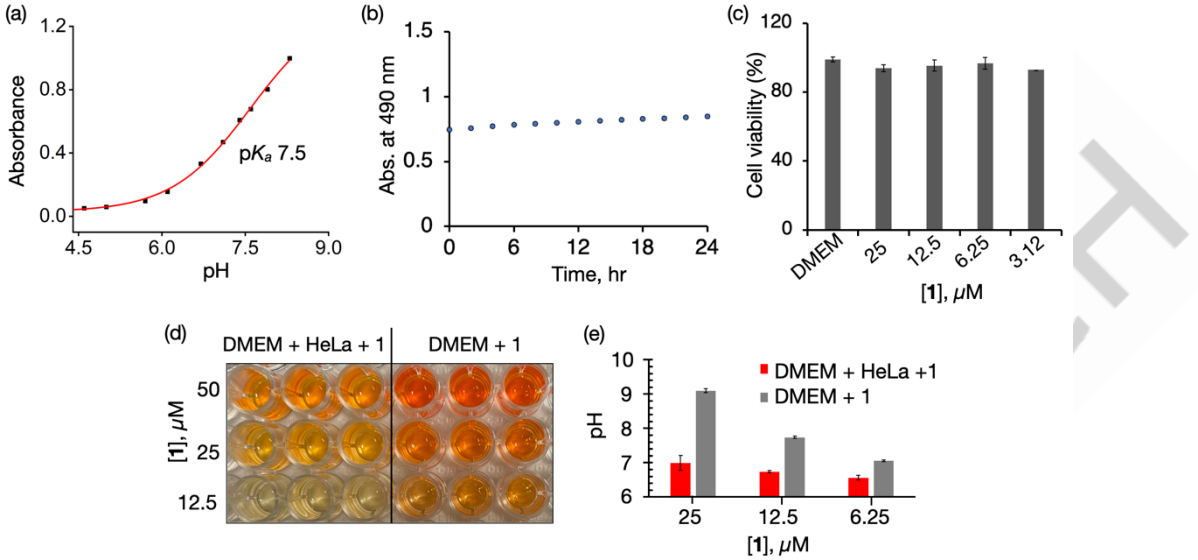


Figure 5. (a) Graph showing the non-linear fitting of the pH dependent absorbance changes of **1** at λ_{max} in IMDM culture medium [pK_a 7.5]. (b) Absorbance changes of **1** over time after incubation for 24 hours at 37 °C in aqueous solution containing glutathione (1 mM) reductant. (c) Bar graph showing the cell viability of HeLa cells after incubation of **1** (3.12–25 μM) in DMEM medium for 48 hours (n = 3 wells). (d) Image showing a part of the culture plate containing DMEM medium after incubation of **1** (12.5–50 μM) in the presence (left) and absence (right) of HeLa cells. (e) Bar graph showing the change in pH of DMEM medium after incubation of **1** (6.25–25 μM) in the presence (red bar) and absence (gray bar) of HeLa cells (n = 3 independent experimental sets).

Interestingly, the medium color of the well that contain cells was changed from red to orange indicating the pH decrease (Fig 5d). The color change was observable by naked eye even for relatively low concentration range ([**1**] = 12.5 μM), which corresponding to a pH change from 7.7 (red) to 6.7 (orange) (Fig 5e). On the other hand, the well plate that contain only DMEM medium did not show any color change. These results indicate that the overgrown HeLa cells cause a pH variation (<7) in culture medium, which are detected by **1** as a color change from red to orange. Finally, we checked the cytotoxicity of **1** by using Cell Counting Kit in HeLa cells (5 x 10^3 cells/well). As seen in Figure 5c, no cytotoxicity was observed for the concentration range used in our experiments.

Conclusion

In conclusion, we have found a novel series of azoheteroarene dyes containing thiazole, thiadiazole, triazole, pyrazole, or benzothiazole heteroaryls capable of detecting pH variations in aqueous solutions. They exhibit distinctive light absorption properties in aqueous solutions and show notable color changes in a narrow pH range, visible to the naked eye. Among these, compounds containing thiazole or thiadiazole heteroarene can detect pH variations in near-neutral aqueous solutions. Both experimental data and quantum calculations indicated a plausible mechanism of pH indicators. We also demonstrate the effectiveness of **1** in monitoring pH levels of culture medium containing cancer cells. Based on the distinct color changes observed in our study, further research can find the the potential of these new azoheteroarene dyes for distinguishing cancerous tissue (pH 6.4–7.0) from normal tissue (7.2–7.5).

Supporting Information. The authors have cited additional references (34–45) within the Supporting Information.

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Keywords: pH indicators • Photoswitches • Azobenzene • Azo dye • Heteroaryl

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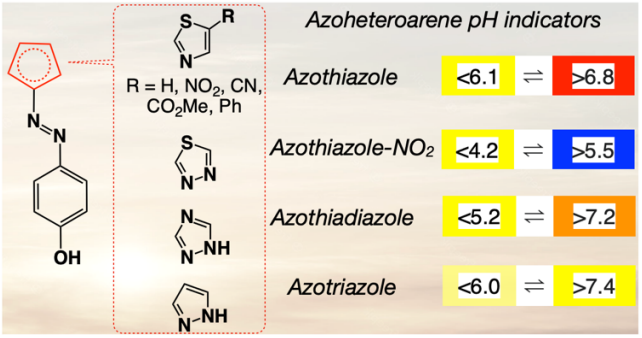

Discovered a novel series of azoheteroarene dyes with thiazole, thiadiazole, triazole, pyrazole, or benzothiazole heteroaryls that detect pH changes in near-neutral aqueous solutions. They exhibit unique light absorption and notable color changes within a narrow pH range, visible to the naked eye.

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