

Chemical Sensors towards Environmental Toxic Molecule Monitoring: Fluorescent Probes for Detection of Thiophenol

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Abstract Thiophenols, a family of important industrial chemicals, is highly toxic for aquatic organisms and human beings. Developing new chemical sensors with the merit of fast, low cost, portable, selective and sensitive, as well as visualizable signal output for efficient detection of thiophenols, is highly desirable. This spotlight article reviewed and discussed the current trend and statement of thiophenols-specific fluorescent probes. Moreover, the future outlook in this field was also stated.

Keywords fluorescent probes, thiophenols, toxic small molecules, environmental analysis, eco-toxicology study

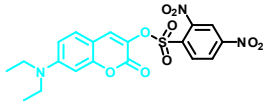
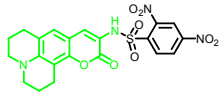
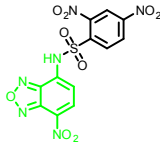
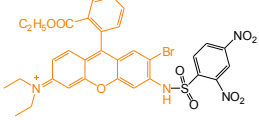
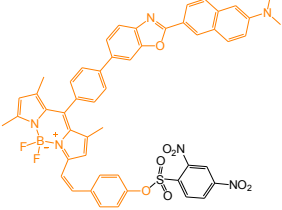
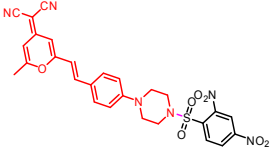
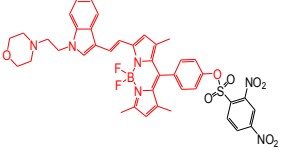
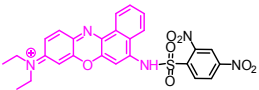
Thiophenols, a family of important industrial chemicals, is utilized to produce dyes, chemical intermediates, as well as polymers.^[1] They are toxic to aquatic organisms, human beings and animals (LD₅₀ ~46.2 mg·kg⁻¹ to mouse), low dose can bring about central nervous system (CNS) injury, muscular weakness and coma,^[2] which made them highly important environmental pollutants (EPA waste code P014, environment protection agency of USA).^[3] Thus, developing efficient method for monitoring thiophenols in environmental samples and living cells is highly demanded.

To date, a number of thiophenol-specific fluorescent probes have been reported (Table 1). Most of them were designed on the basis of aromatic nucleophilic substitution reaction (thiolysis) between thiophenol and dinitrobenzenesulfonyl amides/esters attached to fluorophores, which could subsequently alter the related intramolecular charge transfer (ICT) properties and cause obvious color or fluorescence change.^[4] Various fluorescent probes were prepared with good selectivity to thiophenols against aliphatic thiols, their working (emission) wavelength covered a wide range of spectrum (493–675 nm). In the region of blue-green emission, firstly prepared 7-nitro-2,1,3-benzoxadiazole (NBD)-based probes showed good selectivity to thiophenols with fluorescent “turn-on”, but the high detection limit at millimolar level restricted its application.^[5] Comparatively, coumarin-based probes with dinitrobenzenesulfonyl amide/ester at 3-position^[6] have lower detection limit (nanomolar level) and adjustable wavelength (495–535 nm). Long wavelength probes, especially near infrared (NIR) one, could minimize background fluorescence interference and benefit for non-invasive deep tissue imaging of thiophenols *in vivo*.^[7] Many long wavelength probes for thiophenols are working at yellow-orange emission region (560–600 nm), few red/NIR fluorescent probes (> 610 nm) have been developed.^[8,9] Recently, we one-step synthesized a NIR fluorescent probe NB-DN (675 nm) to detect thiophenols and visualize detoxification process of H₂O₂ to thiophenol in HeLa cells.^[10] Moreover, dinitrobenzene-sulfonyl ester-bearing probes possess relatively quicker responses than their dinitrobenzenesulfonyl amide counter-

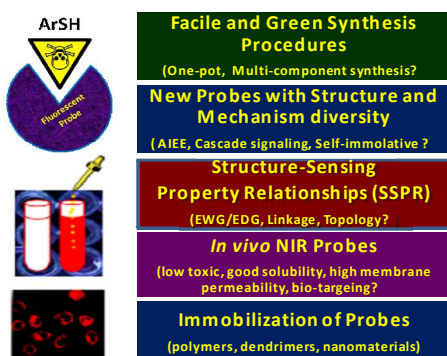
parts,^[6a,9b] due to their faster S_N_Ar reaction rate. Besides, the reported probes demonstrated pseudo-first-order reaction kinetics to thiophenol in solution.^[9,10] Although the above remarkable progress was obtained, most of the reported probes still work in the mixture of buffer solution with organic solvent, and their synthetic routes are tedious and redundant. Moreover, rational design and synthesis of thiophenol-specific fluorescent probes with desired sensing properties and mechanisms are not achieved and still remain a big challenge.

The anticipated fluorescent probes for thiophenols detection should be highly selective and sensitive, fast response, with large Stokes shift, visualizable color output and high quantum yield. To fulfill the optimized applicability,^[11] as a future perspective, we suggested the following issues (Scheme 1) need to be further addressed: (1) Facile, low cost, green and high efficient synthesis procedures (e.g., one-pot or multi-component reactions)^[12] need to be developed and employed to prepare new fluorescent probes; (2) To satisfy different thiophenol analytes and further optimize the sensing efficiency, new sensing mechanisms-based (e.g., AIEE, cascade-signaling, self-immolative) probes^[13] need to be rationally designed and their molecular diversity need to be expanded; (3) Probe structure-sensing property relationships (SSPR), especially, the contribution of molecular factors (e.g., topology, linkage bonds, electrodonating/withdrawing groups (EDG/EWG), as well as flexibility/ rigidity) to the relevant sensing properties, need to be systematically studied; (4) For *in vivo* imaging and monitoring of thiophenols and toxicological analysis, new NIR probes (650–800 nm) possess low cytotoxicity, good water solubility and high cell membrane permeability, is highly demanded. Notably, *in vivo* NIR probes should avoid the risk of competition reaction of aliphatic biothiols (e.g., cysteine, homocysteine and glutathione) to thiophenols under enzyme catalysis in body fluid and cytoplasm; (5) For practical application, it is highly desirable to develop immobilized fluorescent probes by using functional polymers/dendrimers/nanomaterials as supporter or scavenger, through covalent or non-covalent surface modifica-

Table 1 Several representative thiophenol-specific fluorescent probes

Probes	($\lambda_{\text{ex}}/\lambda_{\text{em}}$)/nm	Detection Limit	Response time	Detection media	Ref.
	380/493	7.3×10^{-9} M	1 min	HEPES-THF buffer solution (V/V = 7/3, pH 7.4)	[6a]
	380/535	4.5×10^{-9} M	30 min	phosphate buffer solution (pH 7.4)	[6c]
	465/555	2.0×10^{-6} M	10 min	phosphate buffer solution (pH 7.3)	[5]
	540/570	3.7×10^{-8} M	30 min	DMSO/HEPES buffer solution (V/V = 1/1, pH = 7.4)	[7b]
	420/586	4.9×10^{-9} M	30 min	PBS/EtOH buffer solution (V/V = 1/1, pH 7.4)	[9a]
	454/613	8.3×10^{-9} M	15 min	DMSO/HEPES buffer solution (V/V = 3/7, pH = 7.4)	[8]
	595/634	9.8×10^{-9} M	8 min	PBS/DMSO buffer solution (V/V = 7/3, pH 7.4)	[9b]
	620/675	1.8×10^{-9} M	12 min	PBS/EtOH buffer solution (V/V = 3/2, pH = 7.4)	[10]

Scheme 1 Possible future directions for the R&D of thiophenol-specific fluorescent probes

tion.^[14]

We believe that, in the near future, based on the dedicated works from chemists and biochemists worldwide, more and more efficient fluorescent probes for thiophenols detection will be created, optimized and employed in the fields of environmental analysis, eco-toxicology study, and *in vivo* bio-imaging.

Acknowledgement

We appreciate ARDITI-Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação, through the project M1420-01-0145-FEDER-000005-Centro de Química da Madeira-CQM⁺ (Madeira 14-20), ARDITI-2017-ISG-003, FCT-Fundação para a Ciência e a Tecnologia (project PEst-OE/QUI/UI0674/2019, CQM, Portuguese Government funds), and project PROEQUI PRAM-Reforço do Investimento em Equipamentos e Infraestruturas Científicas na RAM (M1420-01-0145-FEDER-000008).

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Received August 19, 2019

Accepted September 16, 2019