

Chemoselective detection of alkyl halides via an iridium(III) luminescent probe

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ABSTRACT

The high reactivity of alkyl halides towards nucleophiles renders them as acutely toxic and mutagenic agents. Therefore, it is urgent to develop simple, sensitive, and selective methods for the detection of alkylating agents in a wide range of scenarios. Herein, we have designed and synthesized a novel cyclometalated iridium(III) complex **Ir_1** as a rapid and effective chemosensor for a range of alkyl halides based on cycloaddition reaction. **Ir_1** displayed an enhanced luminescence with the increase of BnBr-thiourea concentration, within a linear range of 0.8–8 μM BnBr-thiourea, and the detection limit at a signal-to-noise ratio of 3 was as low as 0.39 μM.

1. Introduction

Alkyl halides, such as benzyl bromide (BnBr) and methyl iodide, are widely used as alkylating reagents for the construct of drug molecules in organic synthesis. However, their high reactivity towards nucleophiles renders them as acutely toxic and/or mutagenic agents [1–4]. Consequently, rigorous detection regimes are required to ensure that pharmaceutical agents contain no alkylating agents for human consumption [5]. Alkylating agents in trace amounts are also present in the environment due to their uses as soil sterilizers [6], anti-cancer agents [7], and chemical warfare agents [8]. Therefore, it is urgent to develop simple, sensitive, and selective methods for the detection of alkylating agents in a wide range of scenarios [9,10].

Fluorescent sensors previously reported for alkyl halides have generally used fluorescently-conjugated amines, which react with electrophilic alkyl halides to form ammonium salts [11–15]. This type of reaction could decrease quenching by photoinduced electron transfer (PET) from the lone pair on the amine to the attached fluorophore, resulting in an increase in fluorescence intensity [16]. A pyridinium cation- π interaction sensor has also been used for the fluorescent detection of alkyl halides [17]. As most detection methods rely on the nucleophilic substitution reaction between alkyl halides and *N*-containing sensors [18], it

would be valuable to develop new types of reactions, to enrich the detection routes available to detect alkyl halides.

Cyclometalated iridium(III) complexes have emerged as potential alternatives to fluorescent probes in sensing applications due to their large Stokes shifts, long luminescence emission lifetimes and tunable luminescence emission wavelengths [19–23]. Recently, we reported the development of an iridium(III) complex as the chemosensor for sensing thiourea, which underwent a cycloaddition reaction with a 1,10-phenanthroline-5,6-dione recognition unit on the metal complex [24]. This reaction affects the metal-to-ligand charge-transfer (MLCT) state of the iridium(III) complex, leading to change its emission properties. But because of the low reactivity of thiourea, only a 3.3-fold enhanced luminescence was observed. Interestingly, thiourea can also react with alkyl halides, such as benzyl bromide (BnBr), to form a *S*-benzylthiuronium bromide adduct. Compared with thiourea, the cyclization reactivity of *S*-benzylthiuronium bromide is higher [25]. Therefore, we hypothesized that alkyl halides could be captured by thiourea to form a *S*-alkylthiuronium salt, which could be recognized by the iridium(III) complex sensor (**Ir_1**), bearing the 1,10-phenanthroline-5,6-dione *N,N* ligand, through a cycloaddition with the dione unit. Thus, the combination of **Ir_1** and thiourea can work as a sensitive luminescent chemosensor for alkyl halides (Scheme 1).

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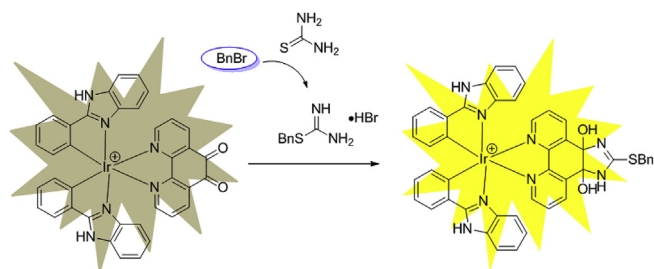
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Scheme 1. Reaction-based iridium(III) complex chemosensor for the luminescent detection of benzyl bromide.

2. Materials and methods

2.1. Materials

Reagents, unless specified, were purchased from Sigma Aldrich (St. Louis, MO) and used as received. Iridium chloride hydrate ($\text{IrCl}_3 \cdot x\text{H}_2\text{O}$) was purchased from Precious Metals Online (Australia).

2.2. Alkyl halide detection

Equal amounts of alkyl halide and thiourea were mixed for 30 min at 25 °C in *N,N*-dimethylformamide (DMF) to achieve a 25 mM stock concentration. Afterwards, different concentrations of the mixture were added to DMF/water (H_2O) (9:1, v/v) containing complex **Ir_1** (4 μM) in 1.5 mL tubes, and the solutions were finally transferred to a cuvette for emission measurement. Luminescence emission spectra were recorded on a PTI QM-1 spectrofluorometer (Photon Technology International, Birmingham, NJ) at 25 °C, with the slits for both excitation and emission set at 2.5 nm. UV–Vis absorption spectra were recorded on a Cary UV-300 spectrophotometer (double beam).

2.3. Synthesis of **Ir_1**

A solution of [1,10-phenanthroline-5,6-dione] (25.2 mg, 0.12 mmol) and the dichloro-bridged $[\text{Ir}(\text{pbi})_2\text{Cl}]_2$ (68.8 mg, 0.056 mmol) in dichloromethane (4 mL) and methanol (4 mL) was stirred at 65 °C overnight. After the reaction completed, an excess of solid ammonium hexafluorophosphate (NH_4PF_6) was added and stirred for another 0.5 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent, methanol/dichloromethane, 1/20, v/v) to yield **Ir_1** as an orange powder. Yield: 57%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.99 (s, 2H), 8.69–8.67 (m, 1H), 8.27 (dd, $J = 5.4, 1.3$ Hz, 1H), 7.94–7.87 (m, 4H), 7.59 (d, $J = 8.1$ Hz, 2H), 7.23 (t, $J = 7.8$ Hz, 2H), 7.04 (dd, $J = 10.9, 4.2$ Hz, 2H), 6.94 (t, $J = 7.9$ Hz, 2H), 6.84 (td, $J = 7.5, 1.2$ Hz, 2H), 6.17 (d, $J = 7.5$ Hz, 2H), 5.78 (d, $J = 8.3$ Hz, 2H) ppm; ^{13}C NMR (101 MHz, DMSO) δ 173.71, 164.00, 155.61, 154.27, 153.44, 148.94, 139.19, 136.26, 135.64, 134.06, 133.13, 132.37, 131.78, 129.13, 125.20, 123.53, 122.29, 114.05, 112.87 ppm. MALDI-TOF-HRMS: Calcd. for $\text{C}_{38}\text{H}_{24}\text{F}_6\text{IrN}_6\text{O}_2\text{P}$ $[\text{M} - \text{PF}_6]^+$: 789.1586, found: 789.1598.

3. Results and discussion

3.1. Screening of iridium(III) complexes

To test our hypothesis, complexes **Ir_1–6** were synthesized according to the literature methods [26], and were characterized by ^1H NMR, ^{13}C NMR, and high resolution mass spectrometry (HRMS) spectrometry (Fig. 1a). Details of the synthesis and characterization data of the complexes are given in the ESI. A previous work by our group has reported the sensing of thiourea by a similar iridium(III) complex,

which was ascribed to the cycloaddition reaction of the dione with thiourea [24]. In the present work, three dione-containing iridium(III) complexes (**Ir_1–3**) with different C $^{\text{N}}$ ligands were initially tested for their luminescence enhancement in the presence of a BnBr-thiourea mixture. Encouragingly, the luminescence intensities of all three complexes were all significantly enhanced upon addition of BnBr-thiourea (Fig. 1b). However, when complexes **Ir_4–6** without the dione unit on the N $^{\text{N}}$ ligand were treated with BnBr-thiourea, no obvious enhancement was observed. These results suggest that the luminescence enhancement effect is associated with reactions with the dione units on the N $^{\text{N}}$ ligands. Overall, **Ir_1** showed the highest luminescence enhancement, and was taken forward as the lead candidate for further studies. The conversion of **Ir_1** to the cycloaddition product **Ir_1a** was monitored by infrared spectroscopy (IR), which revealed a significant decrease in the carbonyl signal at 1697 cm^{-1} after the reaction (Figs. S2a and S2b). Moreover, obvious shifts in characteristic peaks could also be observed by ^1H NMR and ^{13}C NMR spectroscopy (Figs. S2c and S2d). Finally, HRMS spectra revealed the formation of the anticipated adduct at $m/z = 955.3749$ (expected m/z : 955.2149) (Fig. S2e). Importantly, **Ir_1a** showed much stronger luminescence intensity (Fig. 1c) and a longer luminescence lifetime compared to complex **Ir_1** (Fig. S2f).

3.2. Alkyl halides sensing

The maximum emission wavelength of **Ir_1** was detected at 580 nm upon excitation at 320 nm, giving a Stokes shift of approximately 260 nm which is much larger than those typically exhibited by organic chemosensors. Moreover, the presence of BnBr-thiourea in **Ir_1** could also be observed by the naked eye under UV illumination (Fig. 1c). The response of the probe was investigated in different organic solvents (Fig. S3) and varying percentages of water (H_2O) in dimethyl sulfoxide (DMSO) (Fig. S4). From these experiments, the most optimum solvent system was determined to be *N,N*-dimethylformamide (DMF)– H_2O (9:1 v/v). A time-course experiment showed that the luminescence reached steady-state within 3 min upon the addition of 0.1 mM BnBr-thiourea at 25 °C (Fig. S5). The luminescence of the system increased with BnBr-thiourea concentration and achieved maximum intensity at 80 μM , with a ca. 25-fold enhancement (Fig. 2a). A linear relationship ($R^2 = 0.996$) between luminescence intensity and BnBr-thiourea concentration was established in the range of 0.8–80 μM BnBr-thiourea, and the detection limit at a signal-to-noise ratio of 3 was as low as 0.39 μM (Fig. 2b). The emission spectra of **Ir_1** upon addition of BnBr-thiourea at the calculated detection limit is presented in Fig. S6.

To demonstrate the potential of iridium(III) complexes as luminescent sensor towards other types of alkylating agent, we screened a range of commonly used electrophiles in the presence of thiourea. In each case, a large luminescence enhancement was observed (4–25 fold increase), demonstrating that **Ir_1** could be used to sense a wide range of alkylating agents (Table 1, Entries 1–7). As expected, PhBr showed no obvious enhancement with thiourea, as the C(sp 2)-Br bond is highly resistant to nucleophilic attack (Table 1, Entry 8). Moreover, no luminescence of **Ir_1** was observed with BnBr alone or thiourea alone (Table 1, Entries 9 and 10), indicating that the combination of BnBr and thiourea to form the *S*-benzylthiuronium bromide adduct is essential for the subsequent cycloaddition reaction with the dione unit to take place. However, when BnBr was directly added into the (**Ir_1** + thiourea) mixture, no obvious luminescence intensity increase was detected even after 4 h (Table 1, Entry 11). This may be attributed to a possible interaction between **Ir_1** and thiourea, hindering the reaction between BnBr and thiourea. We also investigated the selectivity of **Ir_1** by introducing a 25-fold excess of other common anions and amino acids into a solution of **Ir_1** (Fig. 3). However, **Ir_1** did not significantly respond to the other anions or amino acids, indicating the high selectivity of the probe for BnBr-thiourea.

To investigate the practical application of **Ir_1**, we further explored whether **Ir_1** could be employed for the detection of alkyl halides in

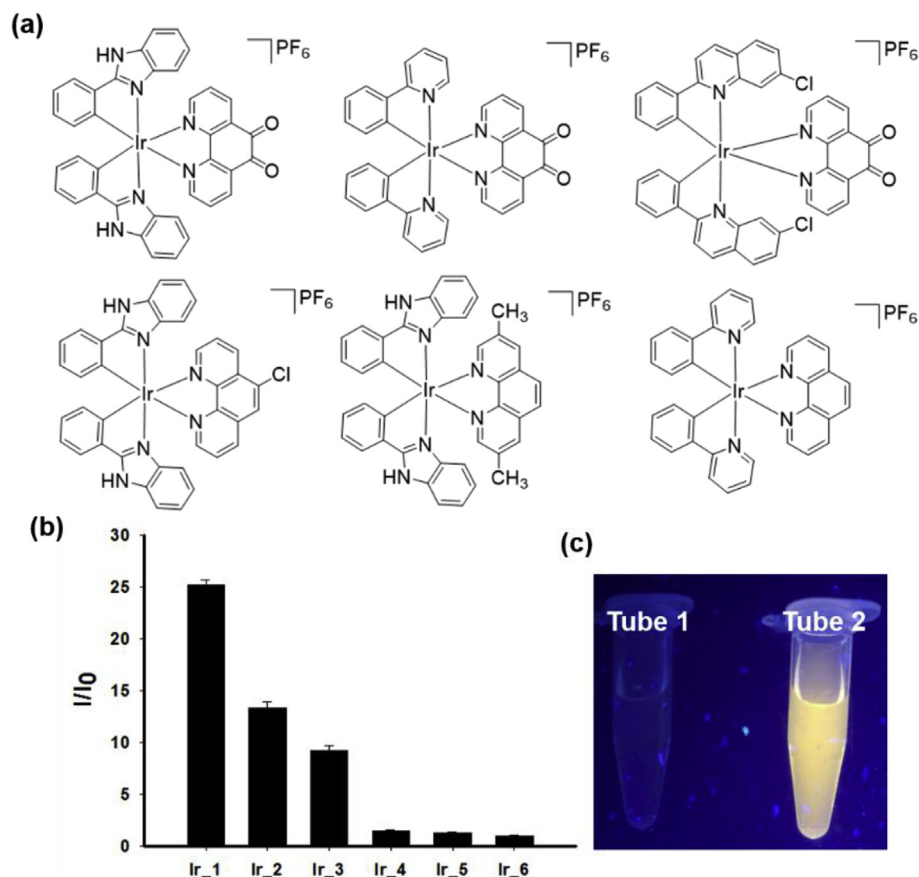


Fig. 1. (a) Chemical structures of Ir₁–6. (b) Fold change of complexes Ir₁–6 (4 μM) in the presence of BnBr-thiourea (0.1 mM, 1:1) in DMF–H₂O (9:1 v/v). (c) Photographic images of Ir₁ (4 μM) in the absence (Tube 1) and presence (Tube 2) of 0.1 mM BnBr-thiourea under UV illumination at 365 nm.

serum. As illustrated in Fig. S7, Ir₁ (4 μM) displayed an increasing luminescence intensity with increasing concentration of BnBr-thiourea (0–380 μM, 1:1) in DMF–10% serum (9:1 v/v). More importantly, further application in 10% aqueous serum has also been demonstrated using Ir₁ (4 μM) for BnBr-thiourea (0–300 μM, 1:1) detection in Fig. S8, indicating the potential of Ir₁ as a luminescent probe in practical application in serum.

4. Conclusions

In the present study, we have designed and synthesized a novel cyclometalated iridium(III) complex Ir₁ as a rapid and effective

chemosensor for a range of alkyl halides. Ir₁ contains a dione moiety in the N[∞]N donor ligand, which can undergo a cycloaddition reaction with *S*-benzylthiuronium, the intermediate formed from the reaction of alkyl halides with thiourea. A linear relationship ($R^2 = 0.996$) between the luminescence intensity of Ir₁ and BnBr-thiourea concentration was established in the range of 0.8–8 μM BnBr-thiourea with a detection limit of 0.39 μM. Moreover, Ir₁ showed high selectivity for a wide range of alkyl halides. To the best of our knowledge, this is the first report that an iridium(III) complex has been used for the luminescent detection of alkyl halides. We are currently making an effort on the design of new complex architectures that we envisage will enable alkylating agents to be detected in the gas phase.

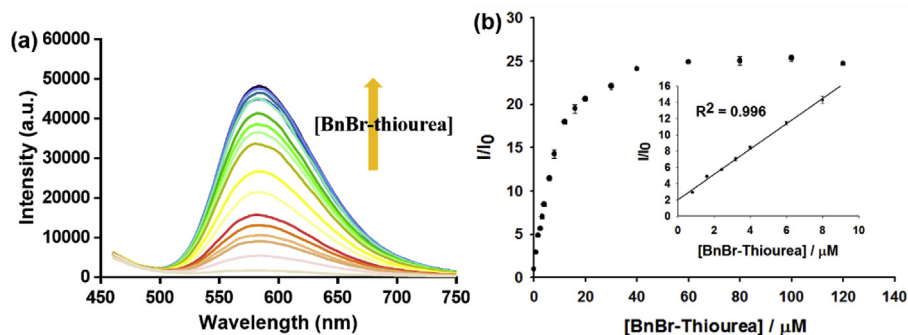


Fig. 2. (a) Luminescence spectra of Ir₁ (4 μM) upon addition of increasing concentrations of BnBr-thiourea (0–120 μM, 1:1) in DMF–H₂O (9:1 v/v). (b) The relationship between luminescence intensity and BnBr-thiourea concentration.

Table 1
Luminescence response of Ir_1 (4 μ M) in the presence of various alkyl halides-thiourea (0.1 mM).^a

Entry	Additive	I_{\max}/I_0	Time
1	BnBr-Thiourea	25.3	5 min
2	BnCl-Thiourea	24.9	7 min
3	AllylBr-Thiourea	24.8	7 min
4	PropargylBr-Thiourea	23.0	7 min
5	EtOCOCH ₂ Br-Thiourea	19.6	9 min
6	MeI-Thiourea	22.0	7 min
7	EtI-Thiourea	14.5	2 h
8	PhBr-Thiourea	1.1	^{-b}
9	BnBr	1.0	^{-b}
10	Thiourea	1.2	^{-b}
11	BnBr	1.4	^{-b,c}

^a n Alkyl halide-thiourea mixture was added to DMF/H₂O containing complex Ir_1 unless specified.

^b No obvious luminescence intensity increased even after 4 h incubation.

^c BnBr was added to the (Ir_1 + thiourea) mixture.

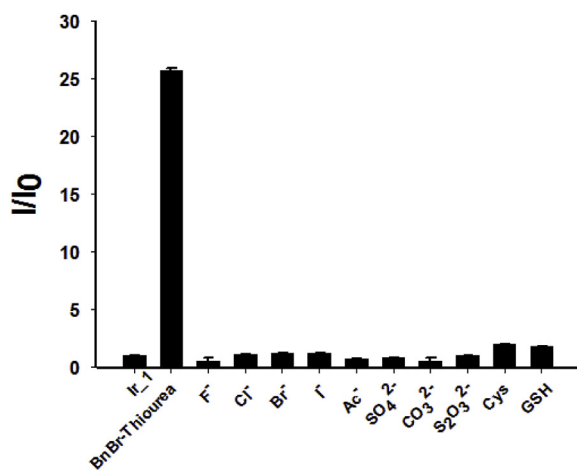


Fig. 3. Luminescence response of Ir_1 (4 μ M) upon addition of BnBr-thiourea or 25-fold excess of common anions or amino acids in DMF–H₂O (9:1 v/v).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.dyepig.2018.07.029>.

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