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A fluorescein-based chemodosimeter for selective gold(III) ion monitoring in aqueous media and living systems

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ABSTRACT

We constructed a turn-on type chemodosimeter based upon a fluorescein scaffold for the rapid, selective detection of gold(III) ions over other metal species. This novel probe structure offers distinct features including high water solubility, a low detection limit, rapid response time and applicability in imaging gold(III) ions in living cells.

1. Introduction

Gold ions possess an unparalleled ability to activate unsaturated functional groups (e.g., alkynes), thereby allowing the synthesis of an array of complex molecular structures. Given their exceptional catalytic features, gold species furthermore outshine other transition metal ion species. For these and other reasons, the number of synthetic methods using gold as a catalyst in recent studies has risen sharply [1–6]. However, products obtained by way of gold catalysis—often candidates for certain drugs and medicines—may nevertheless contain gold impurities and thus pose serious health and environmental concerns. As other recent studies have invariably shown, the accumulation of gold ions, despite their diverse biological and chemical properties, indeed generates toxicity in living organisms [7,8]. As expanding research using gold ions comes to recognize these realities, another strand of research has sought to develop efficient, practical analytical methods of ascertaining gold ion levels in both chemical and biological environments.

In that context, a great deal of attention has focused on developing fluorescent-based assays for probing gold species. In fact, several different types of fluorescent gold ion probes have appeared in literature on the topic, most of them bearing a receptor unit specifically for gold ions, one which translates the binding event into a detectable optical signal [9–19]. Several receptor units, mostly alkynes and some hydrazone derivatives, were shown to have an exceptional affinity for gold ions, and among these units, the alkyne moiety is a particularly excellent receptor candidate for gold ions. In response, fluorescent molecules such as rhodamine [20–23], BODIPY [24,25], fluorescein [26,27] and naphthalimide [28,29] have been rationally modified with alkyne functionalities.

Our research group has recently contributed to the field, by elegantly decorating a spiro derivative of rhodamine dye (**RH-1**) with an alkynyl hydrazone unit to yield a fluorescent probe displaying a distinct and highly selective fluorescence signal response in the presence of gold ions, all as part of a gold ion-mediated ring opening and cyclisation process (Fig. 1a). Rhodamine-based molecules particularly exhibit incomplete water solubility, which generally requires a co-solvent to mitigate, thereby dramatically limiting their applicability in living systems.

Aimed at constructing a water-soluble fluorescent gold ion probe, we chose a fluorescein-based dye as the signal reporter, modified it with an alkyne based recognition unit, and investigated its response to gold ions. Ultimately, the spiro derivatives of fluorescein were accepted as a water-soluble version of their rhodamine analogues with a similar ring-opening equilibrium.

Herein, we explain the design, synthesis, spectral properties, and cell imaging of a water-soluble, fluorescein-based fluorescent probe **FL-1** (Fig. 1b), with a skeleton of both a fluorescein derivative as the fluorophore core and a reactive alkyne unit as the receptor, which allows the detection of gold ions in pure aqueous media.

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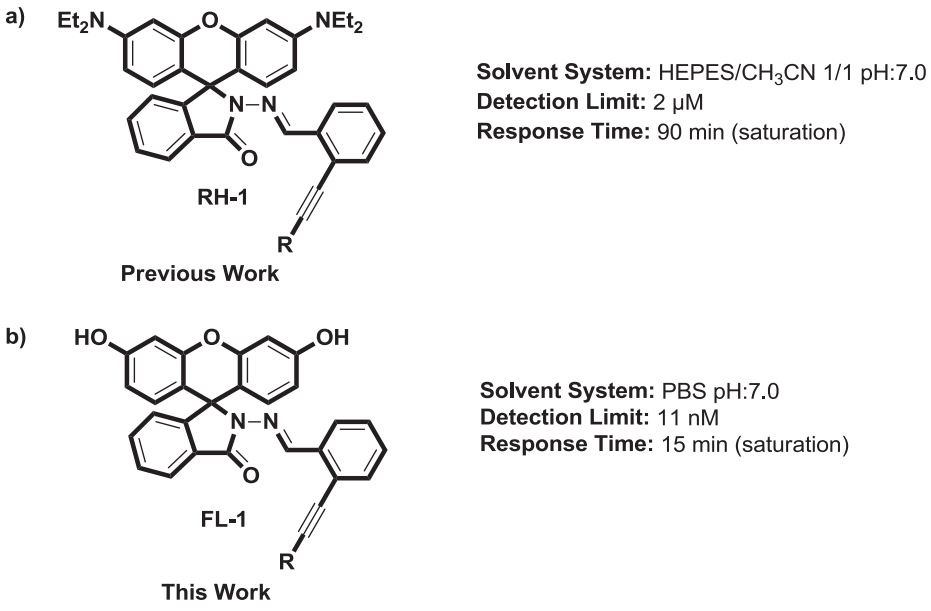


Fig. 1. Molecular structure of **RH-1** and **FL-1**.

2. Experimental details

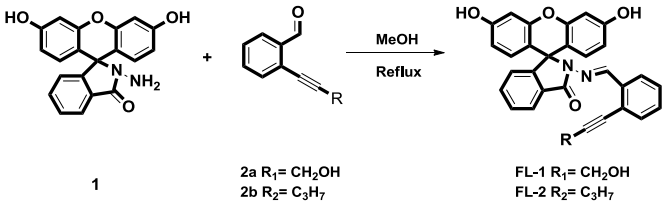
2.1. General methods

All reagents were purchased from commercial suppliers (i.e., Sigma–Aldrich and Merck) and used without further purification. ^{1}H NMR and ^{13}C NMR were measured on a nuclear magnetic resonance spectrometer (VNMRJ 400, Varian Medical Systems), ultraviolet (UV) absorption spectra were obtained with a spectrophotometer (UV-2550, Shimadzu), and fluorescence emission spectra were obtained with a fluorescence spectrophotometer (Cary Eclipse, Varian Medical Systems). Cell imaging was performed with a fluorescence microscope (Axio, Carl Zeiss). Samples were contained in quartz cuvettes (2 mL) with path lengths of 10 mm. Upon excitation at 460 nm, the emission spectra were integrated in the range of 480–700 nm, with excitation and emission slit widths of 5 nm each. The pH was recorded with a pH meter (HI-8014, Hanna). All measurements were conducted in triplicate at least.

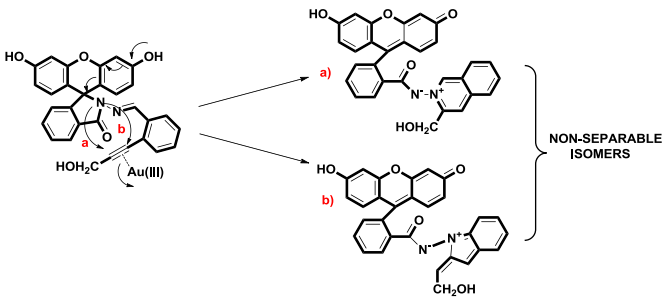
3. Synthesis

3.1. Synthesis of FL-1

Fluorescein hydrazide **1** was prepared according to a previously reported procedure [30]. To a solution of fluorescein hydrazide **1** (114 mg, 0.33 mmol) in absolute ethanol (10 mL), we added compound **2a** (80 mg, 0.50 mmol) and stirred the solution overnight at room temperature. At the end of the reaction the crude mixture was extracted with dichloromethane (DCM) (3 × 10 mL), the organic layers collected were dried over anhydrous $MgSO_4$, concentrated in a vacuum, and purified by way of column chromatography (DCM/MeOH = 10/1) in order to yield 100 mg of compound **FL-1** (62%) as a yellow solid (Scheme 2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.90 (t, J = 9.6 Hz, 2H), 7.40 (quint, J = 6.4 Hz, 2H), 7.20–7.18 (m, 1H), 7.09 (quint, J = 8.4 Hz, 2H), 6.95 (d, J = 6.4 Hz, 1H), 6.66–6.65 (m, 2H), 6.50–6.48 (m, 2H), 6.38 (dd, J = 8.8, 2.0 Hz, 2H), 4.44 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.23, 158.64, 152.07, 151.96, 143.93, 135.63, 133.78, 132.30, 129.32, 128.53, 128.25, 127.75, 127.68, 125.12, 123.57, 123.48, 122.98, 112.63, 109.57, 103.16, 93.76, 81.41, 65.22, 50.93. HRMS: *m/z*: Calcd. for $C_{30}H_{20}N_2O_5$) $(M-H)^+$: 487.1293; found, 487,0966. Anal. cald. for



Scheme 1. Synthesis of **FL-1** and **FL-2**.



Scheme 2. Mechanism for the formation of non-separable isomer products of **FL-1**.

($C_{30}H_{20}N_2O_5$); C, 73.76; H, 4.13; N, 5.73; found; C, 73.95; H, 4.637; N, 5.080.

3.2. Synthesis of FL-2

To a solution of fluorescein hydrazide **1** (114 mg, 0.33 mmol) in absolute ethanol (10 mL), we added compound **2b** (86 mg, 0.50 mmol) and stirred the solution overnight at room temperature. At the end of the reaction the crude product was extracted with dichloromethane (DCM) (3 × 10 mL), the organic layers were collected and dried over anhydrous $MgSO_4$, concentrated in a vacuum, and purified by way column chromatography (DCM/MeOH = 20/1) in order to yield 95 mg of compound **FL-2** (58%) as a yellow solid (Scheme 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.93 (br.s, 2H), 8.78 (s, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.73–7.71 (m, 1H), 7.62–7.54 (m, 2H), 7.31–7.29 (m, 3H), 7.08 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 2.0 Hz, 2H), 6.53–6.51(m, 2H), 6.44 (dd, J = 8.4, 2.0 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 1.59 (sextet, J = 7.6 Hz, 2H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR

(100 MHz, DMSO-d_6) δ: 164.53, 159.13, 152.11, 151.91, 143.99, 135.44, 134.72, 132.95, 130.42, 129.47, 128.63, 127.94, 127.90, 124.26, 123.97, 123.91, 123.83, 112.96, 109.86, 103.09, 96.85, 77.33, 65.11, 22.09, 21.18, 13.96. HRMS: *m/z*: Calcd. for ($C_{32}H_{24}N_2O_4$) (M-H)$^+$: 499.1657; found, 499,1399. Anal. cald. for ($C_{32}H_{24}N_2O_4$); C, 76.78; H, 4.83; N, 5.60 found; C, 74.99; H, 5.004; N, 5.693.

3.3. Cell imaging

Human A549 lung adenocarcinoma cell lines were grown in Dulbecco's modified eagle medium supplemented with 10% foetal bovine serum in an atmosphere of 5% CO_2 at 37 °C. Cells were plated on 12-mm cover glasses in a 6-well plate and allowed to grow for 24 h. Prior to experiments, the cells were washed with phosphate buffer saline (PBS, 0.1 M), incubated with **FL-1** (10 μM) for 20 min at 37 °C, and washed with PBS three times. After incubating with Au^{3+} (50 μM) for 20 min at 37 °C, the cells were rinsed with PBS three times, incubated with 4′,6-diamidino-2-phenylindole (DAPI) for 10 min at 37 °C, and then washed again with PBS three times. Ultimately, fluorescence images were acquired with a fluorescence microscope.

4. Results and discussion

4.1. Synthesis of FL-1 and FL-2

FL-1 and **FL-2** were synthesised by following the synthetic procedure outlined in Scheme 1. Fluorescein hydrazide **1** and alkynyl benzaldehyde derivatives were refluxed in ethanol to give the title compounds, **FL-1** and **FL-2**, in a yield of approximately 60%. The structures of both probes were also unambiguously confirmed by ^{1}H-NMR, ^{13}C NMR, and mass spectroscopy, as detailed in the Supporting Information (SI).

4.2. Au^{3+} sensing properties of FL-1

The spectroscopic behaviour of the probe **FL-1** was investigated towards the addition of various metal cations by way of both UV–vis and fluorescence spectroscopy. We began by examining optimum sensing conditions, namely by screening buffer systems such as HEPES, PBS, and phosphate buffers. Results showed that 10 mM PBS buffer was the most efficient sensing media with 10 μM dye concentration. As expected, **FL-1** was in the fluorescence-off mode (i.e., non-emissive) due to the dominating spirocyclic ring structure. However, upon adding $AuCl_3$ (10 μM), the probe solution (pH = 7.0, 10 mM PBS buffer) immediately turned yellow and started to produce a green emission under the UV light within an exceptionally brief response time (<1 min) (Fig. S1). As Fig. 1 shows, the free dye had no absorbance or fluorescence emission due to the ring-closed structure of the fluorescein moiety. Nevertheless, soon after Au^{3+} was added, a new absorption band appeared at 496 nm along with a strong increase in fluorescence emission at 517 nm (Fig. 2).

Fluorescence titration experiments for **FL-1** in terms of the added Au^{3+} were carefully scrutinised upon their excitation at 460 nm. The emission band at 517 nm increased linearly in response to Au^{3+} over a wide concentration range (10–100 μM). The saturation point was realised when 6 equiv. of Au^{3+} ion were added, with a 175-fold enhancement factor. The detection limit of the probe for Au^{3+} was evaluated as 11 nM, based on the signal-to-noise ratio of 3 (Fig. S4) (Fig. 3).

4.3. Selectivity studies

The selectivity profile of **FL-1** was examined in the presence of various metal cations under optimum sensing conditions. Remarkably, **FL-1** showed no spectral response to alkynophilic metal ions

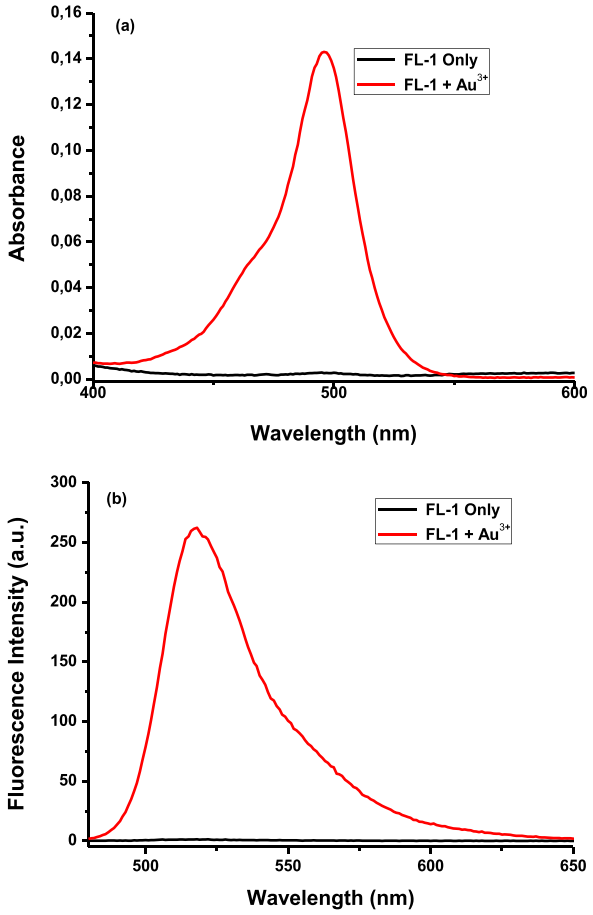


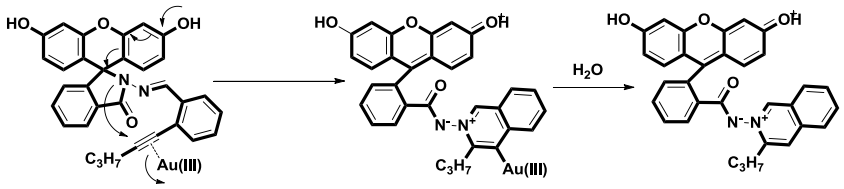
Fig. 2. Absorption and Emission spectra of **FL-1** (10 μM) and Au^{3+} (5.0 equiv.) in PBS at pH = 7.0; (λ_{ex}: 460 nm, at 25 °C).

such as Au^+, Ag^+, Ni^{2+}, Pd^{2+}, Fe^{3+}, and Hg^{2+} or to other metals, including Na^+, K^+, Ba^{2+}, Ca^{2+}, Cd^{2+}, Mg^{2+}, Mn^{2+}, Zn^{2+}, Pb^{2+}, Cu^{2+}, and Cr^{3+}. The probe could furthermore discriminate Au^{3+} from Au^+ ions, which could aid in investigating different oxidation states of gold species (Fig. 4). Au^{3+} species are known to interact with thiol species forming thiol complexes of gold ions. As such, it could be highly challenging to realize gold species in biological environments where biological thiols are present at high concentrations. Thus, it is highly essential to investigate the spectral response of the probe toward Au^{3+} in the presence of reactive biothiol species, such as cysteine, the most nucleophilic and chemically reactive of the common amino acids. The results from the competition experiments showed that **FL-1** could smoothly detect Au^{3+} ions in the presence of biological thiols such as cysteine and in the mixtures of other related metal species (Fig. S2).

Since we anticipated the overall sensing process to be irreversible, we introduced an excess amount of CN^- (KCN) into the solution (**FL-1** + Au^{3+}), with the expectation of extracting gold species and reversing the reaction or revealing a possible binding complex. Clearly, no spectral changes were observed upon adding CN^- ions, which verified the irreversibility of the sensing mechanism.

4.4. Reaction mechanism

The product of the reaction between **FL-1** and Au^{3+} was isolated in order to clarify the pathway of the sensing process. The progress of that reaction was routinely monitored by thin layer chromatography (TLC), as was the formation of two major products with close



Scheme 3. Proposed mechanism for the formation of **FL-2P**.

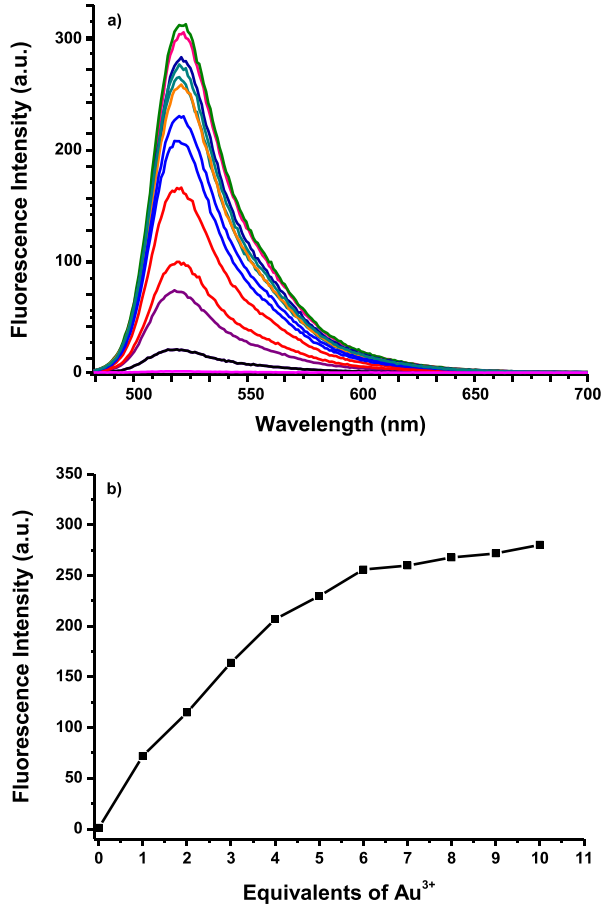


Fig. 3. Fluorescence spectra of **FL-1** (10 μM) in PBS at pH = 7.0 in the presence of Au^{3+} (mole equivalents = 0–10).

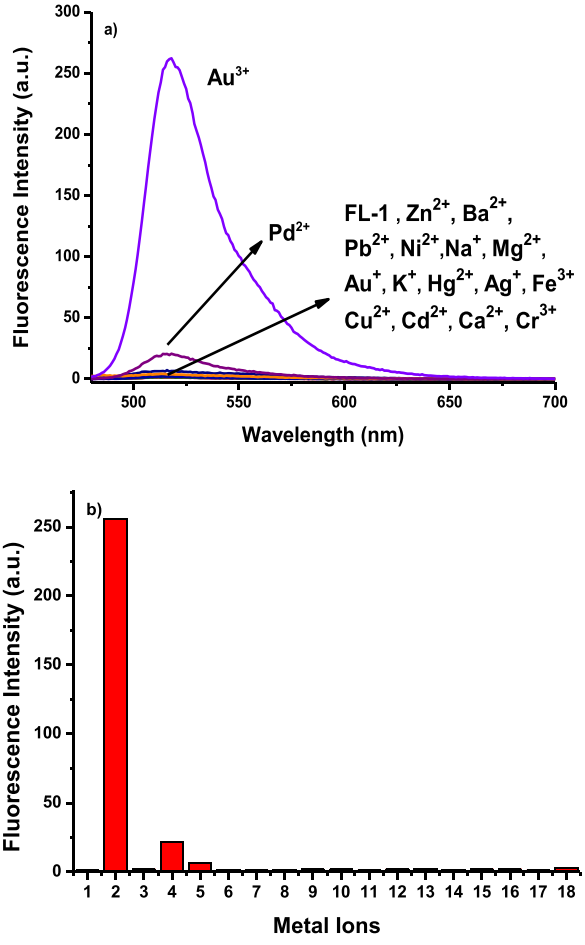
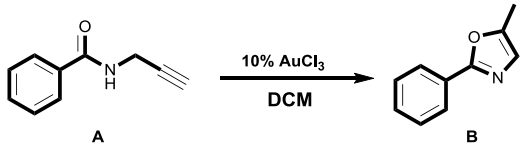


Fig. 4. Fluorescence intensities of **FL-1** (10 μM) in PBS at pH = 7.0 in the presence of 50.0 equivalent of the cations interest: (λ_{eks}: 460 nm). 1, **FL-1**; 2, Au^{3+} (5.0 equiv.); 3, Au^{+}; 4, Pd^{2+}; 5, Ag^{+}, 6, Cd^{2+}; 7, Cr^{3+}; 8, Cu^{2+}; 9, Fe^{3+}; 10, Hg^{2+}, 11, K^{+}; 12, Ca^{2+}; 13, Mg^{2+}; 14, Na^{+}; 15, Ni^{2+}; 16, Pb^{2+}; 17, Ba^{2+}; 18, Zn^{2+}.

R_f values. Despite our efforts, we could not separate the products by chromatography. The ^1H NMR spectrum of the product mixture (S9, SI) suggested the formation of two cyclization products arising from an endo-dig cyclisation, which could yield a six-membered ring, or an exo-dig cyclisation, which could yield a five-membered one (Scheme 2).

To create an alternative to probe **FL-1**, we prepared probe **FL-2**, which bore an alkynyl benzaldehyde derivative with a pentyne moiety (**FL-2**). **FL-2** issued a highly similar fluorometric response to Au^{3+} ions under the same sensing conditions. Moreover, treating **FL-2** with Au^{3+} selectively afforded **FL–2P** as the single product, as confirmed by ^1H NMR, ^{13}C NMR, and high-resolution mass spectroscopy analysis (S10 and S12, SI). The structure of the isolated product revealed that the receptor unit had undergone a highly selective endo-dig intramolecular cyclisation process to yield a six-membered ring isoquinoline derivative. As Scheme 3 shows, the reaction was initiated by activating the alkyne after coordinating the gold ions, which preceded the nucleophilic attack of imine nitrogen in order to form the intermediate complex's structure.



Scheme 4. $AuCl_3$ catalysed cyclization reaction of propargyl amide.

The proto-demetallation of the intermediate complex yielded the isoquinoline fluorescein derivative.

4.5. Quantitative detection of residual Au^{3+}

The analytical performance of the probe has been established through the quantification of trace gold species in synthetic end products. A chemical transformation utilizing $AuCl_3$ as the active

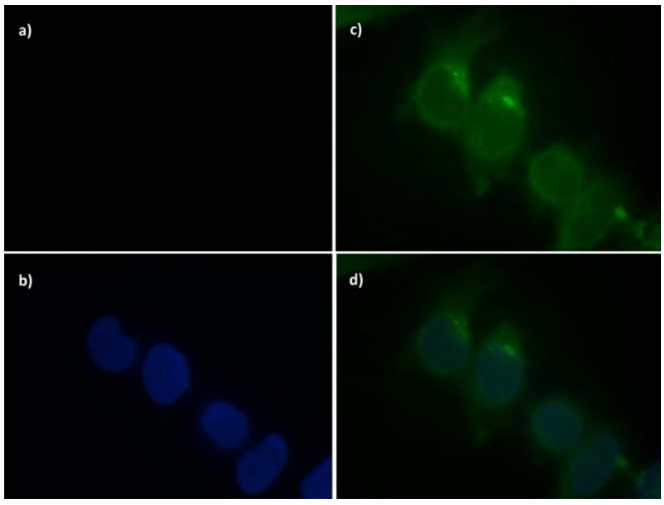


Fig. 5. Images of A-549 cells: **(a)** Cells were incubated with **FL-1** (10 μM) in the absence of Au^{3+} **(b)** cells are detected with DAPI nuclear counter-stain (control) **(c)** cells were incubated with **FL-1** (10 μM) and Au^{3+} (50 μM).

catalyst (10 mol%) was performed as a model reaction (Scheme 4) [31].

The crude product of the chemical reaction was subjected to chromatographic purification using silica as the stationary phase and dichloromethane as an eluent. A defined amount of the purified sample (2 mg) was added to the solution of **FL-1** (10 μM in PBS at pH = 7.0). Immediately, a distinct change in colour and fluorescence could be monitored in the probe solution indicating the presence of gold species in the solution.

By the aid of fluorescence measurements the gold content in the sample solution was measured to be 4.8×10^{-7} mol mg^{-1} based on a standard calibration curve (Fig. S4). This result was also consistent with that obtained by inductively coupled plasma-mass spectrometry (ICP-MS) analysis (5.2×10^{-7} mol mg^{-1}). With this experiment we unambiguously confirmed the viability of **FL-1** for quantitative gold analysis.

4.6. Cell imaging

The promising properties of **FL-1**, including high solubility in water, a low detection limit, and rapid response encouraged us to further monitor Au^{3+} ions in living cells. To that end, we incubated A549 human lung adenocarcinoma cells at 37 °C with **FL-1** (10 μM) for 20 min, followed by adding 50 μM of Au(III) and further incubation for another 20 min. The cells were then stained with nucleus staining dye DAPI (1.0 mM) for another 10 min. The fluorescence images were taken with the aid of fluorescence microscopy before and after adding Au^{3+} ions. To our surprise, the same turn-on response was obtained from **FL-1** in living cells. Notably, throughout the cell-imaging process, the cells remained intact and showed both a healthy spread and adherent morphology. These preliminary results thus revealed that **FL-1** can be efficiently used for imaging Au^{3+} in living cells (Fig. 5).

5. Conclusion

In sum, we have demonstrated the synthesis, spectroscopic investigation, and cell imaging application of a turn-on type fluorescent probe for monitoring Au^{3+} ions in solutions and living milieus. The probe is built upon a fluorescein scaffold in order to improve its solubility in pure aqueous media. The probe exhibited remarkably high selectivity to Au^{3+} ions, as well as a remarkably low detection limit and rapid response time.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.snb.2016.04.158.

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Biographies

Ceyla Çetintaş is MSc. candidate in Chemistry Department of Izmir Institute of Technology. Her research interests include the development of new chemosensors based on fluorescein dyes.

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Mustafa Emrullahoğlu received his Ph.D. degree in Organic Chemistry from Middle East Technical University (METU) in 2009 under the supervision of Prof. Dr. Ayhan S. Demir. He joined Izmir Institute of Technology as an Assistant Professor in 2010. Since 2014, he has been an Associate Professor in Chemistry Department of Izmir Institute of Technology, Turkey. His research interest covers many aspects of Organic and Supramolecular Chemistry. His current research interest is mainly focused on the development of new fluorescent probes for metal ions and biologically significant species.