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Chemoselective detection of Ag^+ in purely aquatic solution using fluorescence 'turn-on' probe based on crown-containing 4-methoxy-1,8-naphthalimide

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Experimental Section

Materials

Skeletal nickel catalyst was prepared from nickel aluminium alloy (weight percentage of Ni was 50%) according to the known procedure.[S1] All other reagents were purchased from commercial sources. Acetonitrile and DMSO used in spectroscopic studies were of HPLC grade. Phosphate-citrate[S2] and HEPES buffer solutions as well as solutions of perchlorate salts of Cu^{2+}, Zn^{2+}, Pb^{2+}, Cd^{2+}, Ni^{2+}, Ca^{2+}, and Mg^{2+} were prepared in deionized water (18.2 MΩ·cm). $AgClO_4$, $Hg(ClO_4)_2$, and $Fe(ClO_4)_2$ were dissolved in MeCN. The exact concentration of $Hg(ClO_4)_2$ in MeCN was determined by complexometric titration using EDTA and xylenol orange as an indicator. Compound **MNI** was weighted and dissolved in DMSO. Then, the obtained stock solution (2·mM) was added to a deionized water to get diluted 5 μM solution containing 0.2 vol.% of DMSO for optical measurements.

General Methods

Melting points were measured on Melt-temp melting point electrothermal apparatus and were not corrected.

The reaction progress and purity of the final products were monitored by TLC on silica gel (DC-Alufolien Kieselgel 60 F_{254}, Merck). Column chromatography was conducted on silica gel (Kieselgel 60, particle size 0.063-0.200 mm, Merck). Flash chromatography was performed using a Biotage Isolera™ Prime system.

^1H and ^{13}C NMR spectra were recorded on Avance 300 and Avance 400 spectrometers (Bruker). The measurements were performed in DMSO-d_6 and $CDCl_3$ solutions. The chemical shifts (given as δ) were determined with an accuracy of 0.01 ppm relative to the signals corresponding to the residual solvents and recalculated to the internal standard (TMS); the spin-spin coupling constants (J) were measured with an accuracy of 0.1 Hz. The assignment of proton signals H(2)–H(3) and H(5)–H(7) in the naphthalimide fragment of compound **8** (Scheme 1) and **MNI** is based on theoretical calculations carried out in ACD/Labs 6.0 software.

LC-ESI-MS analyses were performed on a Finnigan LCQ Advantage mass spectrometer equipped with octopole ion-trap mass-analyzer, MS Surveyor pump, Surveyor auto sampler, Schmidlin-Lab nitrogen generator (Germany) and Finnigan X-Calibur 1.3 software for data collecting and processing. Isotope patterns were calculated with Molecular Weight Calculator, Version 6.37 (Matthew Monroe).

Synthesis of MNI

***N,N*-Bis(2-chloroethyl)aniline (2)**. *N*-phenyldiethanolamine **1** (20 g, 0.11 mol) was added portionwise to $POCl_3$ (46 g, 0.30 mol). The mixture was heated at 100°C for 1 h, cooled to room temperature, and then, benzene (60 ml) was added. The obtained solution was poured over

ice (100 g). The organic layer was separated, the water phase was extracted with benzene. The extracts were combined and dried over Na_2SO_4. The solvent was removed *in vacuo*. Recrystallization of the residue from MeOH gave product **2** (18.6 g, 77%). M.p. 44–45 °C (41–45 °C *cf.* ref. 3). ^{1}H NMR (400.13 MHz, DMSO-d_6, 19 ºC), δ: 3.71 (s, 8H, 4×CH_2), 6.63–7.15 (m, 3H, ArH), 7.15–7.26 (m, 2H, ArH).

10-Phenyl-1,4-dioxa-7,13-dithia-10-azacyclopentadecane (4). To a refluxing solution of Cs_2CO_3 (8.70 g, 26.7 mmol) in aqueous ethanol (560 ml, 50 vol.% of EtOH) a mixture of dithiol **3** (1.07 g, 5.9 mmol), compound **2** (1.29 g, 5.9 mmol), and EtOH (100 ml) was added dropwise during 1 h. The reaction mixture was stirred at 60 °C for 20 h, the solvent was removed *in vacuo* and then, water (35 ml) was added to a resulting residue. The product was extracted with benzene. After the removal of the solvent, the crude product was purified by column chromatography on SiO_2 using petroleum ether–ethyl acetate gradient mixture as an eluent. M.p. 84–86 °C. ^{1}H NMR (400.13 MHz, DMSO-d_6, 19 ºC), δ: 2.69–2.83 (m, 8H, 4×CH_2), 3.50–3.61 (m, 4H, 2×CH_2), 3.50–3.61 (m, 8H, 4×CH_2), 6.53–6.64 (m, 3H, ArH), 7.10–7.21 (m, 2H, ArH).

10-(4-nitrosophenyl)-1,4-dioxa-7,13-dithia-10-azacyclopentadecane (5). To a stirring solution of compound **4** (1.22 g, 3.7 mmol) in dilute hydrochloric acid obtained by mixing of 1.1 ml conc. HCl (ρ = 1.18 g ml^{-1}) and H_2O (2.8 ml) an aqueous solution of sodium nitrite (0.28 g, 3.7 mmol) was added dropwise at 0–5°C during 1h. The resulting mixture was stirred at this temperature for 1h and then, sodium carbonate (0.52 g) dissolved in water (6.2 ml) was added at vigorous stirring to yield a dark-green precipitate of the basic form of nitroso compound **5**, which was extracted with DCM. After the removal of DCM, the crude product was chromatographed on SiO_2 column by elution with DCM–MeOH (v : v = 30 : 1) solvent mixture to give **5** (1.04 g, 78%). M.p. 117–118 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6, 21 ºC), δ: 2.69–2.80 (m, 4H, 2×CH_2), 2.82–2.93 (m, 4H, 2×CH_2), 3.58 (s, 4H, 2×CH_2), 3.63–3.73 (m, 4H, 2×CH_2), 3.74–3.86 (m, 4H, 2×CH_2), 6.82 (d, 2H, ArH, ^3J 7.4 Hz), 8.05 (br. s, 2H, ArH). ^{13}C NMR (75.47 MHz, DMSO-d_6, 21 ºC), δ: 29.15, 31.07, 51.80, 69.94, 72.79, 110.88, 153.36, 162.81. ESI MS, calcd, m/z: 357.13; found: 357.14 ([M+H]$^+$).

4-(1,4-dioxa-7,13-dithia-10-azacyclopentadecan-10-yl)aniline (6). Hydrazine hydrate (100 wt.%, 1.0 ml) was added to a refluxed solution of nitroso compound **5** (700 mg, 1.699 mmol) in ethanol (13 ml). Skeletal nickel catalyst prepared from 0.5 g of nickel aluminium alloy (weight percentage of Ni is 50%) was added portionwise to the refluxing reaction mass. After the TLC showed the absence of the starting nitroso compound, the heating was continued for another 1 h. Nickel catalyst was filtered off and the filtrate was evaporated to yield 600 mg of crude

product as a dark oil which was immediately used at the next step without further purification. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 ºC), δ: 2.70–2.79 (m, 4H, 2×CH_2), 2.81–2.91 (m, 4H, 2×CH_2), 3.45–3.56 (m, 4H, 2×CH_2), 3.63 (s, 4H, 2×CH_2), 3.75–3.83 (m, 4H, 2×CH_2), 6.55 (d, 2H, ArH, ^3J 8.9 Hz), 6.64 (d, 2H, ArH, ^3J 8.9 Hz).

2-(4-(1,4-dioxa-7,13-dithia-10-azacyclopentadecan-10-yl)phenyl)-6-nitro-1*H*-benzo-[d,e]isoquinoline-1,3(2*H*)-dione (8). Aza-crown-containing arylamine **6** (600 mg, obtained directly before synthesis, introduced into reaction without any additional purification) was added to suspension of 298 mg (2.23 mM) of 4-nitronaphthalic anhydride **7** in 4 ml of 80% aqueous acetic acid. Reaction mass was heated until boiling, and held like this for 1.5 h, then cooled to room temperature. Precipitate of 4-nitroderivative was filtered and washed with 10% Na_2CO_3, water, and ethanol. The product was dried at 80°C. Yield of **8** was 528 mg (76%). M.p. 259–262 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6, 24 °C) δ: 2.72–2.93 (m, 8H, 4×CH_2), 3.56–3.77 (m, 12H, 6×CH_2), 6.71 (d, 2H, C_6H_4, ^3J 8.9 Hz), 7.15 (d, 2H, C_6H_4, ^3J 8.9 Hz), 8.12 (dd, 1H, H(6), ^3J 7.3 Hz, ^3J 8.6 Hz), 8.58 (d, 1H, H(3), ^3J 8.1 Hz), 8.60 (d, 1H, H(2), ^3J 8.1 Hz), 8.63 (d, 1H, H(7), ^3J 7.3 Hz), 8.75 (d, 1H, H(5), ^3J 8.6 Hz). ^{13}C NMR (100.62 MHz, DMSO-d_6, 27 ºC), δ: 29.01, 30.58, 51.36, 70.04, 73.01, 111.30, 122.84, 123.42, 123.47, 124.29, 127.40, 128.71, 129.57, 130.14, 131.69, 146.53, 149.15, 162.73, 163.53. ESI MS, calcd, m/z: 568.16; found: 568.04 ($[M+H]^+$), 590.06 ($[M+Na]^+$).

2-(4-(1,4-dioxa-7,13-dithia-10-azacyclopentadecan-10-yl)phenyl)-6-methoxy-1*H*-benzo[d,e]isoquinoline-1,3(2*H*)-dione (MNI, 9). A mixture of KOH (85 mg, 1.52 mmol), compound **8** (100 mg, 0.17 mmol) and MeOH (3.0 ml) was refluxed for 20 h. The solvent was removed *in vacuo* to yield a solid residue which was mixed with 2 ml of H_2O and 86 μL of AcOH to neutralize the excess of KOH. The precipitate was filtered off, washed four times with distilled water, dried in air and subjected to column flash-chromatography (silica gel, gradient elution with petroleum ether–ethyl acetate solvent mixture). Yield of **9** was 81 mg (84%). M.p. 233–235°C. ^{1}H NMR (400.13 MHz, DMSO-d_6, 20°C), δ: 2.70–2.93 (m, 8H, 4×CH_2), 3.53–3.78 (m, 12H, 6×CH_2), 4.15 (s, 3H, OMe), 6.68 (d, 2H, C_6H_4, ^3J 8.9 Hz), 7.10 (d, 2H, C_6H_4, ^3J 8.9 Hz), 7.36 (d, 1H, H(3), ^3J 8.3 Hz), 7.79–7.90 (m, 1H, H(6)), 8.47 (d, 1H, H(2), ^3J 8.3 Hz), 8.50 (d, 1H, H(7), ^3J 7.0 Hz), 8.59 (d, 1H, H(5), ^3J 8.5 Hz). ^{13}C NMR (125.76 MHz, DMSO-d_6, 25 ºC), δ: 29.07, 30.62, 51.42, 56.72, 70.08, 73.04, 106.35, 111.32, 114.91, 122.63, 122.96, 124.13, 126.52, 129.04, 129.78, 131.19, 133.39, 136.70, 146.34, 160.39, 163.60, 164.23. ESI MS, calcd, m/z: 661.09; found: 661.13 ($[M+Ag]^+$).

Steady-state optical measurements

The absorption spectra were taken on a Cary 300 spectrophotometer (Agilent Technologies). The fluorescence quantum yield measurements were performed using a Cary 300 spectrophotometer and a Fluorolog3-221 spectrofluorimeter (Horiba Jobin Yvon). Spectral measurements were carried out in air-saturated acetonitrile solutions at ambient temperature. All measured fluorescence spectra were corrected for the nonuniformity of detector spectral sensitivity. Coumarin 481 in acetonitrile (φ^{fl} = 0.08)[S4] was used as reference for the fluorescence quantum yield measurements. The fluorescence quantum yields[S5] were calculated according to the Equation S1:

$$\varphi^{\mathbf{fl}} = \varphi_{\mathbf{R}}^{\mathbf{fl}} \frac{S}{S_{\mathbf{R}}} \cdot \frac{\left(1 - 10^{-A_{\mathbf{R}}}\right) n^2}{\left(1 - 10^{-A}\right) n_{\mathbf{R}}^2} \qquad \text{(S1)}$$

wherein $\varphi^{\mathbf{fl}}$ and $\varphi_{\mathbf{R}}^{\mathbf{fl}}$ are the fluorescence quantum yields of the studied solution and the standard compound respectively; A and $A_{\mathbf{R}}$ are the absorptions of the studied solution and the standard respectively; S and $S_{\mathbf{R}}$ are the areas underneath the curves of the fluorescence spectra of the studied solution and the standard respectively; and n and $n_{\mathbf{R}}$ are the refraction indices of the solvents for the substance under study and the standard compound.

Equilibrium Constant Determination

Complex formation of compound **MNI** (**9**) with Ag^+ was studied by spectrofluorometric titration.[S6,7] The ratio of **NI1** to Hg^{2+} was varied by adding aliquots of a solution of mercury (II) perchlorate in acetonitrile of known concentration to a solution of ligand **NI2** in water – methanol mixture (40 vol.% MeOH) of known concentration at pH 4.7 (acetate buffer, 5 mM). The fluorescence spectrum of each solution was recorded, and the stability constants of the complexes were determined using the SPECFIT/32 program (Spectrum Software Associates, West Marlborough, MA). The following equilibria were considered in the fitting (Eq. S2 and Eq. S3, L = **NI1**; M^{2+} = Hg^{2+}):

$$\mathbf{L} + \mathbf{M}^{2+} \rightleftarrows (\mathbf{L}) \cdot \mathbf{M}^{2+} \qquad \text{(S2)}$$

$$2\mathbf{L} + \mathbf{M}^{2+} \rightleftarrows (\mathbf{L})_2 \cdot \mathbf{M}^{2+} \qquad \text{(S3)}$$

In doing so, it was found that the experimental data corresponded to the theoretical ones only if the Eq. S2 was taken into account, while the formation of complexes with the

composition of 2 : 1 was not observed. The fitting curve used to calculate the complex stability constant is shown in Figure S7.

Computational details

The three dimentional structure of **MNI** was built with MOPAC 2016 program package using PM6 semiempirical method.[S8] The calculations were performed at optimized geometries, which reached gradient variations less than 0.01 kcal mol^{-1}. The solvent effect was included in geometry optimizations following the 'COnductorlike Screening Model' (COSMO) implemented in MOPAC. A dielectric constant of ε = 65 and a refraction index of solvent (n) such that n^2 = 2 were used.

Figures S1–S7

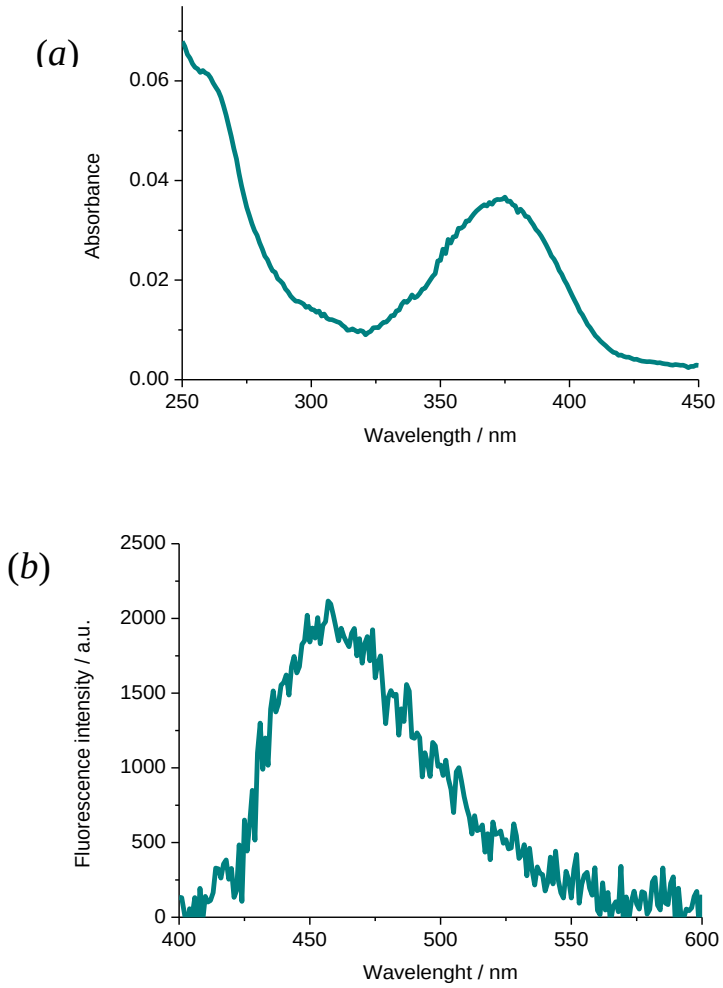

Figure S1 Steady state (*a*) absorption and (*b*) emission spectra of **MNI** (1.33×10^{-6} M) in aqueous solution containing 40 vol.% of MeOH. Excitation wavelength was 375 nm.

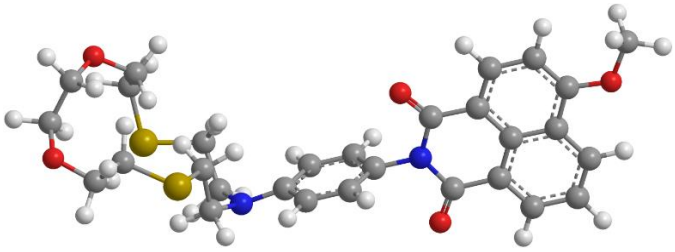

Figure S2 Optimized ground state geometry of compound **MNI** (Method PM6). Dihedral angle between the naphthalimide and benzene ring is 89°.

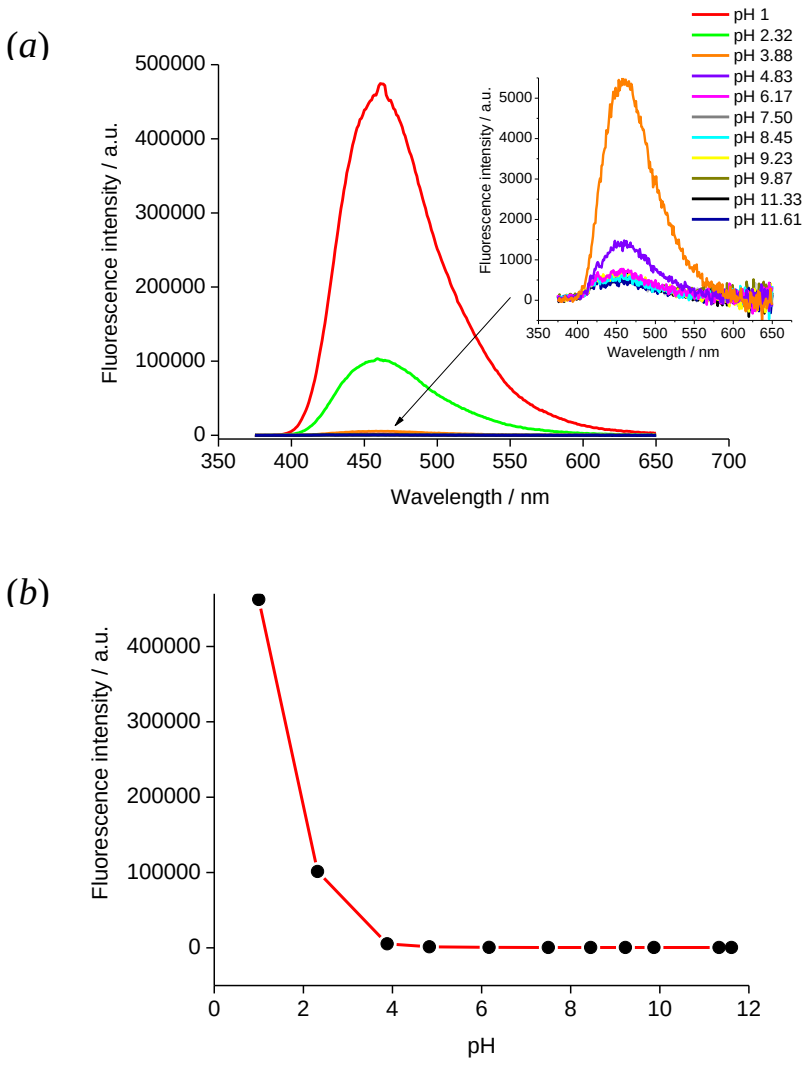

Figure S3 (*a*) Fluorescence spectra of **MNI** at different pH and (*b*) fluorescence intensity of **MNI** at 460 nm versus pH in water–methanol mixture (40 vol.% MeOH). Concentration of **MNI** was 5 μM. Excitation wavelength was 375 nm. pH was maintained by phosphate-citrate buffers (6.7 mM).

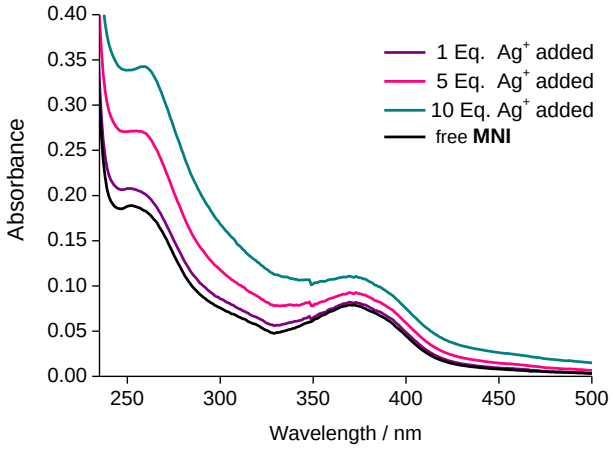

Figure S4 Absorption spectra of compound **MNI** (5 μM) upon addition of Ag^+ in water at pH 7.3 (10 mM HEPES buffer).

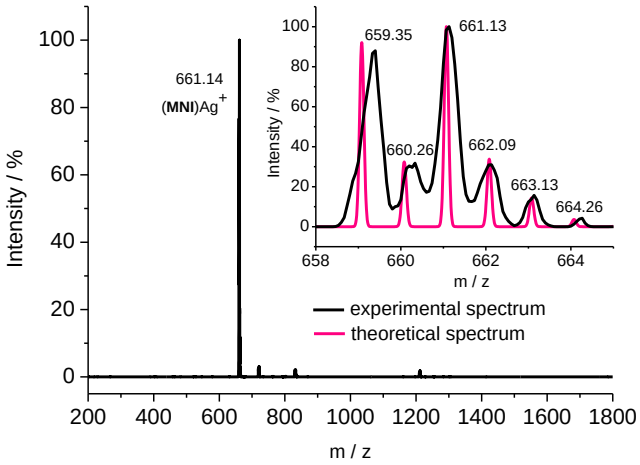

Figure S5 ESI MS spectrum of **MNI** solution (25 μM) in MeCN containing 1 equiv. of $AgClO_4$. The inset shows theoretical and experimental spectra in the zoomed area corresponding to the cation [**MNI**+Ag]$^+$.

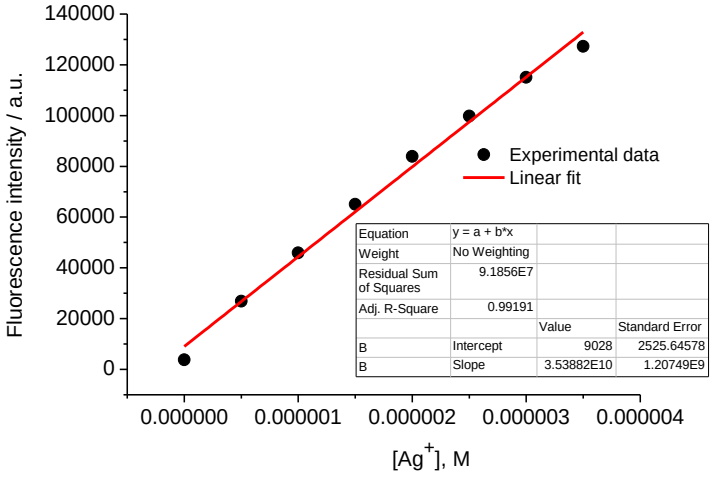

Figure S6 Plot of fluorescence intensity of **MNI** (5 μM) at 460 nm *vs.* increasing concentration of Ag^+ (0–3.5 μM) used for the calculation of detection limit. Excitation wavelength was 375 nm. The inset shows the fitting parameters.

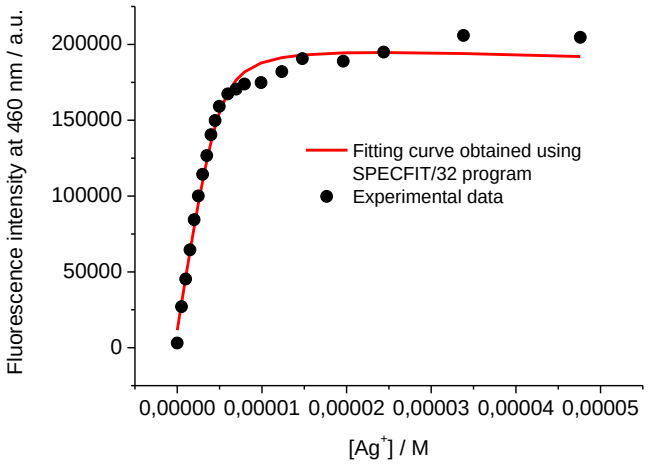

Figure S7 Plot of fluorescence intensity of **MNI** (5 μM) at 460 nm *vs.* increasing concentration of Ag^+ (0–50 μM) and fitting curve obtained using the SPECFIT/32 program. Excitation wavelength was 375 nm.

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