

SYNTHESIS OF A NEW PET BASED BENZANTHRONE PROBE FOR DETERMINATION OF pH AND CUPRUM (II) ION

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ABSTRACT

The paper reports on the synthesis and fluorescence characteristics of a novel benzanthrone fluorophore. It is configured as a “fluorophore-spacer-receptor” system able to act as a pH-probe via PET fluorescence sensing mechanism. Due to the tertiary amine receptor the novel probe shows “off-on” switching properties under transition from alkaline to acid media ($FE = 16.3$). The ability of the probe to detect metal ions in water/DMF (1:1, v/v) is evaluated by monitoring the changes of its fluorescence intensity. The presence of cuprum ion (Cu^{2+}) only, among the tested metal ions (Cd^{2+} , Co^{2+} , Cu^{2+} , Fe^{3+} , Ni^{2+} , Hg^{2+} , Zn^{2+} and Ag^{+}), is efficiently detected by fluorescence quenching mechanism. Due to the remarkable fluorescence changes in the presence of protons, hydroxide anions and Cu^{2+} ions the novel probe is able to act as a disabled-INH logic gate at a molecular scale.

Keywords: a benzanthrone derivative, a charge-transfer, a selective pH sensor, Cu^{2+} sensor.

INTRODUCTION

The environmental analysis applies chemical sensors having the inherent ability to detect on-line and in real time analytes as cations, anions or small molecules in distributed systems [1]. The fluorescent chemical sensors attract particular attention in vitro and in vivo detection of trace amounts of analytes owing to their versatility, high selectivity/sensitivity, reliability and reproducibility, as well as their low limit of detection, low cost, noninvasiveness, and potential application in real-time and real-space analysis [2 - 9].

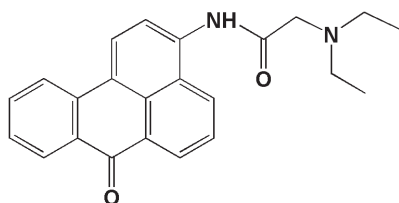
The measurement of pH is very important in biological, chemical and industrial fields [10 - 21]. In recent years, the optical pH sensing technique based on absorption or emission of certain organic compounds of a structural diversity, has received increasing attention because it provides many advantages over the potentiometric method, such as rapid response time and requisite reference electrode absence [22 - 28].

Two common principles for fluorescence sensors

are used: a photoinduced electron transfer (PET) and an internal charge transfer (ICT) [29 - 32]. The PET and ICT process of a variety fluorophores has been studied in details. However the PET based benzanthrone probes are still very rare. Benzanthrone derivatives attract particular interest due to their favorable spectral properties – a large extinction coefficient, a marked Stokes shift, high sensitivity of fluorescence parameters to environmental polarity, etc. [33 - 36]. Derivatives of benzanthrone are well known as fluorophores emitting fluorescence from yellow-green to orange-red. They are used as disperse dyes for textiles, daylight fluorescent pigments, dyes for polymers, lasers, as components in liquid-crystalline systems for electro-optical displays. They can also be used as sensors for biological important metal ions and amines [37 - 41]. Such dyes can be also utilized as suitable sensing probes for checking solvent polarity [42 - 45].

This paper reports on the design and synthesis of novel PET based amidinobenzanthrone fluorophore (1). The photophysical properties of the new compound in

presence of protons and metal cations are also presented.



EXPERIMENTAL

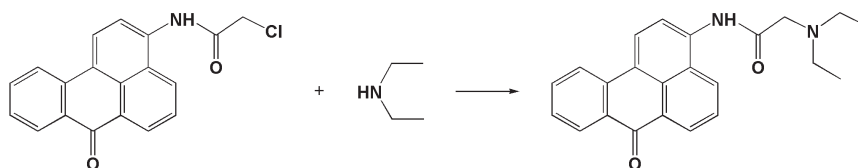
Materials

The synthesis of 2-chloro-N-(7-oxo-7H-benzo[de]anthracen-3-yl)-acetamide as a precursor for the synthesis was carried out in accordance with a method described previously [37]. The solvents used were of p.a. or analytical grade (Fluka). Commercial HEPES (Fisher Chemical) and borate buffer (pH = 9.2, Fisher Chemical) were applied. $\text{Zn}(\text{NO}_3)_2$, $\text{Cu}(\text{NO}_3)_2$, $\text{Ni}(\text{NO}_3)_2$, $\text{Co}(\text{NO}_3)_2$, $\text{Cd}(\text{NO}_3)_2$, $\text{Pb}(\text{NO}_3)_2$, $\text{Fe}(\text{NO}_3)_3$, $\text{Hg}(\text{NO}_3)_2$, and AgNO_3 salts were as sources of metal cations (all were Aldrich salts of a p.a. grade).

Methods

The melting points were recorded on a Büchi 535 apparatus (Switzerland). Tlc were made on silica gel plates (Merck, 60 F 254, 20x20 cm, 0.2 mm thickness, ready-to-use). The pH values were monitored using a 704 pH-meter (Metrohm, Swiss). Electronic spectra were recorded on a Hewlett Packard 8452A UV/vis spectrophotometer; IR - on a Varian 660 instrument (Varian, USA); ^1H -NMR spectra - on DRX-250-Brucker equipment, while the fluorescent spectra - on a spectrometer FS-2 (Scinco).

The fluorescence quantum yields (Φ_F) were measured relatively to Coumarin 6 ($\Phi_F = 0.78$ in ethanol [46]) as a standard. All fluorescence measurements were performed at room temperature (25.0°C). A 1x1 cm quartz cuvette was used for all spectroscopic analyses.



Scheme 1

Very small volumes of hydrochloric acid and sodium hydroxide were used to adjust the pH value. The effect of the metal cations upon the fluorescence intensity was examined by adding portions of the metal cations stock solution (freshly prepared aqueous solutions) to a known volume of the fluorophore solution (10 mL DMF buffered with HEPES or a borate buffer). The addition was limited to 100 μL so that the dilution remains insignificant.

Synthesis of 2-N,N-diethylamino-N-(7-oxo-7H-benzo[de]anthracen-3-yl)-acetamide (1)

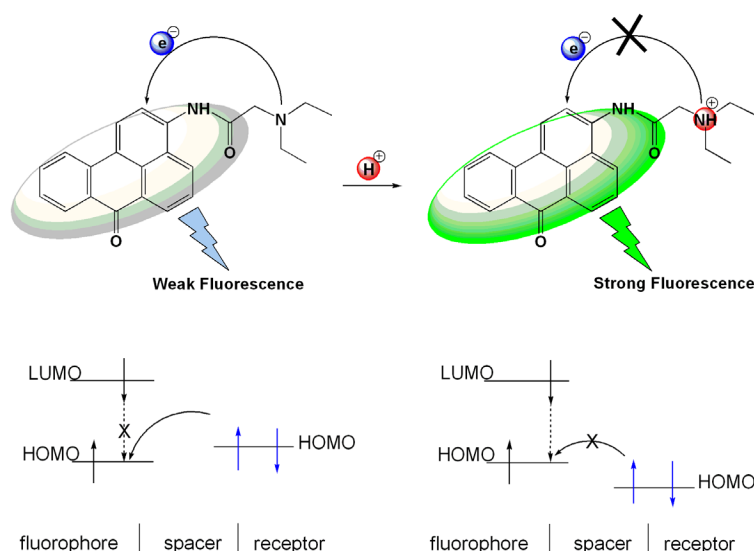
2-Chloro-N-(7-oxo-7H-benzo[de]anthracen-3-yl)-acetamide (3.21 g, 0.01 mol) was dissolved in 30 ml dioxane, then 3.1 ml (0.03 mol) of diethylamine was added and the solution was stirred for 11 h at 80°C. After cooling to room temperature, the precipitate was filtered off, washed with acetone and dried in vacuum at 40°C.

Yield: 93 %. IR (KBr) cm^{-1} : 3249 (NHCO), 3060 (C-H, Ar), 2984 (CH_2), 2967 (CH_3), 2873 (CH_2), 1695 (C=O), 1651 (C=O), 1579 and 1524 (NH), 1503 (C-H, Ar), 1476 (CH_3), 1306 (CH_2), 1258 (C-N), 1206 and 1163 (CH_3). ^1H NMR (DMSO- d_6 , ppm): 10.44 (s, 1H, NH), 8.72–8.69 (d, 1H, ArH), 8.48–8.33 (m, 3H, ArH), 8.22–8.13 (m, 2H, ArH), 7.78–7.72 (t, 1H, ArH), 7.68–7.22 (t, 1H, ArH), 7.47–7.41 (d, 1H, ArH), 3.27 (s, 2H, $-\text{CH}_2-$), 2.78–2.65 (m, 4H, 2 x $-\text{CH}_2\text{CH}_3$), 1.17–1.07 (m, 6H, 2 x $-\text{CH}_2\text{CH}_3$). Elemental analysis: calculated for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2$ (MW 358.4) C 77.07, H 6.19, N 7.82 %; Found C 76.88, H 6.31, N 7.79 %.

RESULTS AND DISCUSSION

Design and synthesis of PET based benzanthrone probe 1

The synthetic route used for the preparation of 2-N,N-diethylamino-N-(7-oxo-7H-benzo[de]anthracen-3-yl)-acetamide **1** is outlined in Scheme 1.



Scheme 2

2-Chloro-N-(7-oxo-7H-benzo[de]anthracen-3-yl)-acetamide is synthesized according to a method described previously [37]. It has an activated chlorine atom, which can be attacked by diethylamine. The final product **1** is obtained by the reaction of 2-chloro-N-(7-oxo-7H-benzo[de]anthracen-3-yl)-acetamide with diethylamine in dioxane at 80°C for 11 h. The resulting orange precipitate of dye **1** is filtrated and washed by acetone and dried under vacuum.

The synthesized benzanthrone **1** is based on the “fluorophore-spacer-receptor” architecture, where the amidobenzanthrone is fluorophore, the electron-donating tertiary amino group is the cation receptor, while the intermediate methylene group serves as spacer that covalently separates the two units. In the absence of a bound cation or proton, the HOMO (highest occupied molecular orbital) of the unbound receptor has a higher energy than that of the half-filled HOMO of the excited fluorophore. This energy difference drives a rapid electron transfer from the receptor to the excited-state fluorophore, thus quenching or “switching-off” the fluorescence. When the receptor is bound to a cation or proton, the energy level of the receptor is lower than that of the HOMO of the excited fluorophore. Therefore, the receptor is stabilized and the electron transfer is not energetically favored. Thus, the fluorescence is “switched on” (as shown in Scheme 2).

pH effect on absorption and fluorescent properties of probe **1**

The compound under study is designed as a fluorescence sensor for determining pH changes over a wider pH scale. This is the reason to investigate the photophysical behaviour of probe **1** in a water/DMF (1:1, v/v) solution at different pH values.

The longest-wavelength absorption band is observed in the range between 340 nm and 510 nm with λ_A maximum at 416 nm in case the UV-VIS spectrum of probe **1** is recorded in an alkaline solution at ca pH 9. This absorption band is typical for the amidobenzanthrone dyes and it is attributed to the internal charge transfer (ICT). It is well known that the photophysical properties of the benzanthrone derivatives are basically related to the polarization of their chromophoric system [45, 47]. Light absorption by this molecule generates a charge transfer interaction between the electron-donor substituent at C-3 position and an electron-acceptor carbonyl group within the benzanthrone molecule which largely depend on the electron-donating power of the substituents at C-3 position. The absorption spectra of probe **1** do not show significant pH-dependent changes in pH window 4 - 9, since the benzanthrone ICT excited states are not affected.

The changes in the fluorescence spectra of compound **1** in a water/DMF (1:1, v/v) solution at different pH values are depicted in Fig. 1. In alkaline media (pH 10)

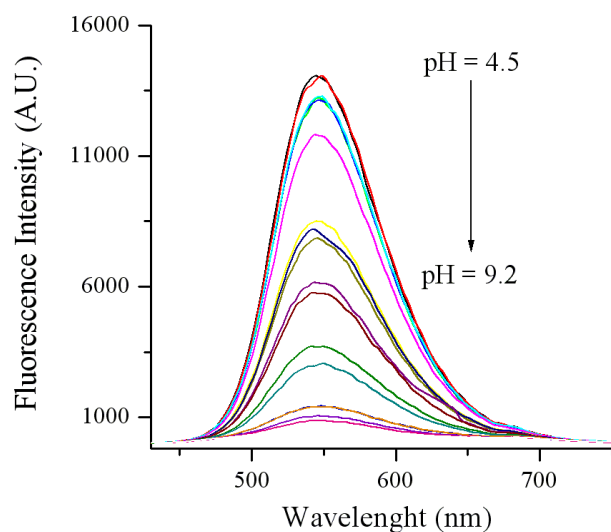


Fig. 1. Fluorescence spectra of probe 1 in a water/DMF (1:1, v/v) solution at different pH values.

benzanthrone **1** shows fluorescence in the range between 450 nm and 700 nm with a maximum at 545 nm. The calculated Stoke's shift value 5692 cm^{-1} for compound **1** is expected for amidinobenzanthrones and does not indicate remarkable changes in the probe's **1** excited state due to the incorporation of the PET receptor fragment. At this pH, the PET process from the tertiary alkylamine receptor to the excited fluorophore quenches the benzanthrone fluorescence emission and the system is in its "on states". The quantum yield of fluorescence $\Phi_F = 0.035$ is calculated using Coumarin 6 ($\Phi_F = 0.78$ in ethanol) as a standard according to Eq. (1) [46], where A_{ref} , S_{ref} , n_{ref} and A_{sample} , S_{sample} , n_{sample} stand for the absorbance at the excited wavelength, the integrated emission band area and the solvent refractive index of the standard and the sample, respectively.

$$\Phi_F = \Phi_{\text{ref}} \left(\frac{S_{\text{sample}}}{S_{\text{ref}}} \right) \left(\frac{A_{\text{ref}}}{A_{\text{sample}}} \right) \left(\frac{n_{\text{sample}}^2}{n_{\text{ref}}^2} \right) \quad (1)$$

The addition of HCl to probe **1** in an alkaline medium converts the amino PET receptor fragment in a quaternary ammonium cation which decreases strongly the electron donating ability of the nitrogen atom in the receptor moiety and cuts off the PET quenching process. Thus, the fluorescence intensity of **1** gradually increases with pH decrease (Fig. 1). The enhancement

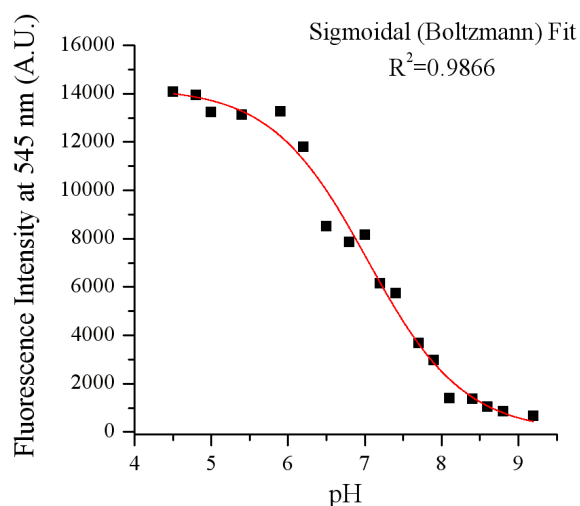


Fig. 2. Effect of pH on the fluorescence intensity of probe 1 at 545 nm in a water/DMF (1:1, v/v).

of the fluorescence emission $FE = 16.3$ is used as a qualitative parameter. The $FE = I/I_0$ is determined as a ratio of the maximum fluorescence intensity I at pH 4.5 and the minimum fluorescence intensity I_0 at pH 10. The calculated quantum yield of fluorescence for probe **1** at pH 4.5 is $\Phi_F = 0.358$.

To evaluate compound **1** for pH sensing purposes, the calibration curve is constructed and the acidity constant is determined. As seen from Fig. 2, the probe response to pH is characterized by a "S" shaped calibration curve. The sensitivity of probe **1** to pH is followed in the pH interval from 5 to 8.5. The pK_a value of probe **1** is calculated on the ground of Eq. (2) [48] using the section of the graph in Fig. 2 located between pH 6 and 8. The value obtained is equal to 7.06 ± 0.10 . It is in the physiological region suggesting the potential of PET based amidinobenzanthrones to serve as a pH probe for bioimaging.

$$\log[(I_{F\text{max}} - I_F) / (I_F - I_{F\text{min}})] = \text{pH} - pK_a \quad (2)$$

Effect of metal cations on the fluorescence intensity of probe 1

The signaling fluorescent properties of compound **1** in presence of transition metal cations (Co^{2+} , Cu^{2+} , Fe^{3+} , Ni^{2+} , Pb^{2+} , Cd^{2+} , Zn^{2+} , Hg^{2+} and Ag^+) are investigated. The metal cations effect is studied in an organic solvent

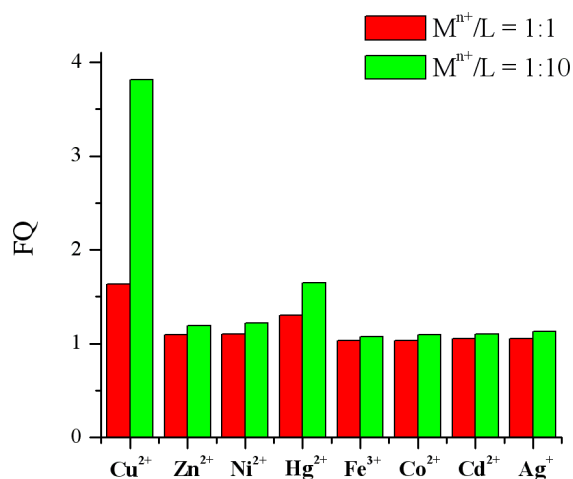


Fig. 3. Effect of metal cations ($c = 1 \times 10^{-5} \text{ mol l}^{-1}$ and $c = 1 \times 10^{-4} \text{ mol l}^{-1}$) on the fluorescence of probe **1** ($c = 1 \times 10^{-5} \text{ mol l}^{-1}$) in a DMF solution buffered with 10 μM HEPES ($\text{pH} = 7.2$).

aiming to avoid an aggregation process and the establishment of a more complicated equilibrium. To maintain a constant pH value, the experiments are performed in DMF in presence of a borate buffer ($\text{pH} 9.2$) and in DMF in presence of HEPES buffer ($\text{pH} 7.2$). The borate buffer of $\text{pH} = 9.2$ is used because the PET process is feasible at this pH and compound **1** is in “off-state”. Furthermore, the HEPES buffer is chosen because it ensures pH in the physiological range ($\text{pH} = 7.2$), which is a presumption for applications in living organisms.

It is found that the addition of a metal ion solution up to $1 \times 10^{-4} \text{ mol L}^{-1}$ concentration to DMF solution of probe **1** ($1 \times 10^{-5} \text{ mol L}^{-1}$) does not cause any photophysical change in presence of 10 μM borate buffer ($\text{pH} = 9.2$). This suggests that the synthesized compound **1** is not a suitable probe for metal cation determination in alkaline media. Probably at this pH the examined metal ions form rapidly hydroxides and in fact do not interact with probe **1**.

In contrast to the above, a fluorescence quenching is observed on addition of metal cations (up to $1 \times 10^{-4} \text{ mol L}^{-1}$) to DMF solution of probe **1** ($1 \times 10^{-5} \text{ mol L}^{-1}$) buffered with 10 μM HEPES ($\text{pH} = 7.2$). The quenching (FQ) of the fluorescence emission is used as a qualitative parameter. The $FQ = I_0/I$ is determined from the ratio

of the maximum fluorescence intensity (I_0 – a solution free of metal cations) and the fluorescence intensity in presence of metal cations (I). Fig. 3 presents the calculated FQ results for probe **1**. As seen from the figure, the novel probe **1** exhibits sensor selectivity. A strong fluorescence quenching is observed only upon addition of Cu^{2+} , while the remaining ions have a negligible effect. The well pronounced quenching effect of Cu^{2+} is probably due to the better complexation and paramagnetic properties of Cu^{2+} referring to the resulting unspecific fluorescence quenching by energy or electron transfer [49,50]. It is found that the addition of 1 equivalent of Cu^{2+} cations results in $FQ = 1.6$, while the addition of 10 equivalents of Cu^{2+} quenches the emission with $FQ = 3.8$. The higher quenching effect of Cu^{2+} present in a high concentration suggests the ability of probe **1** to bind more than 1 equivalent of Cu^{2+} .

The stoichiometry of the complexation between Cu^{2+} cation and probe **1** is determined using the continuous variations method (Job’s method). The Job’s plot referring to the emission at 545 nm (Fig. 4B) shows a maximum near 0.50 and an inflection point at approximately 0.67 which can be attributed to the existence of 1:1 and 2:1 (Probe **1**: Cu^{2+}) complexes, respectively, in the solution [51]. The linear section is found to range at 20 μM $Cu^{2+} \sim 65 \mu\text{M}$ Cu^{2+} with a correlation coefficient of $R^2 = 0.991$. The limit of detection (LOD) is calculated to be $23 \times 10^{-6} \text{ mol/l}$ according to formula $LOD = 3\sigma/b$, where σ is the standard deviation, while b is the slope of the calibration plot (Fig. 4A, the inset). [52] The fluorescence intensity of probe **1** in absence of Cu^{2+} is measured 10 times and the standard deviation is determined.

The Stern-Volmer plot suggests a simultaneous effect of static and dynamic quenching. The linear plot ($R^2 = 0.98$) observed at concentrations less than 55 μM Cu^{2+} with Stern-Volmer constant of 5856 M^{-1} is contributed to the static quenching (formation of a ground-state non-fluorescent complex), while the upward curvature (Fig. 5) outlined at higher concentrations is related to the dynamic quenching realized through the collisions in the system.

Furthermore, the formation of the ground-state binding complex between probe **1** and Cu^{2+} is confirmed by the changes of **1** in presence and absence of Cu^{2+} ions. It is found that the addition of 1 equivalent of Cu^{2+} does

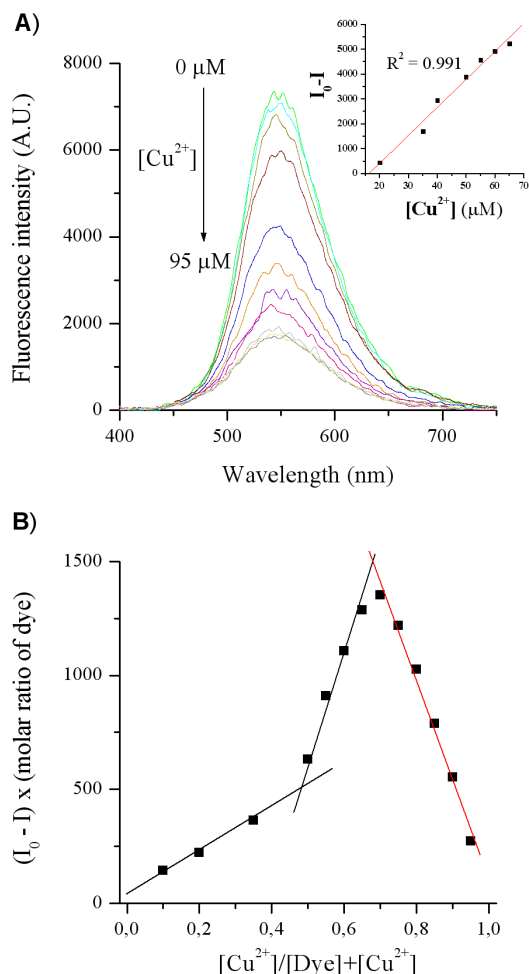


Fig. 4. Fluorescence changes (A) and Job's plot (B) of a DMF solution (buffered with 10 μM HEPES) of probe 1 (1×10^{-5} M) in presence of Cu^{2+} .

not change remarkably probe's **1** absorption spectrum (Fig. 6). Obviously, the first equivalent of Cu^{2+} binds the tertiary amino receptor in probe **1** preventing its effect on the ICT process in the chromophoric system. However, the addition of another 1 equivalent of Cu^{2+} (2 equivalents) induces a bathochromic shift of the absorption maximum ($\Delta\lambda_A = 10$ nm) due to complexation with probe **1**. This indicates that the benzanthrone carbonyl group is subjected to a second coordination of probe **1** with Cu^{2+} cations. It is well known that the light absorption properties of the benzanthrone derivatives are basically related to the polarization of their chromophoric system. The cation coordination in the benzanthrone carbonyl group increases partially the push-pull character of the ICT state and leads to a red shift.

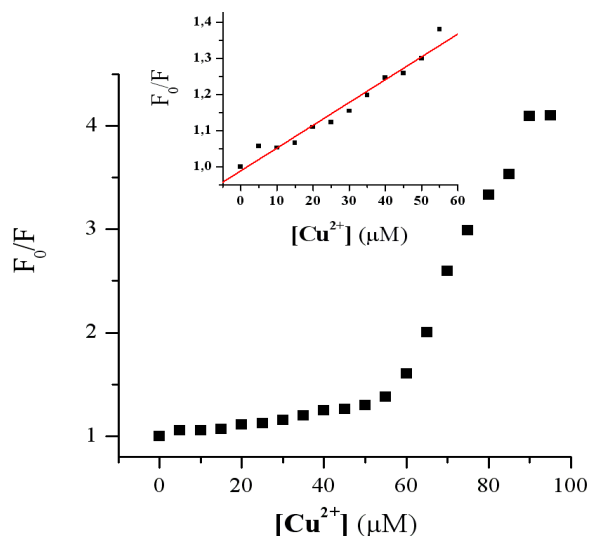


Fig. 5. Stern-Volmer plot for probe 1 (1×10^{-5} M, a DMF solution buffered with 10 μM HEPES) in presence of increasing concentrations of Cu^{2+} .

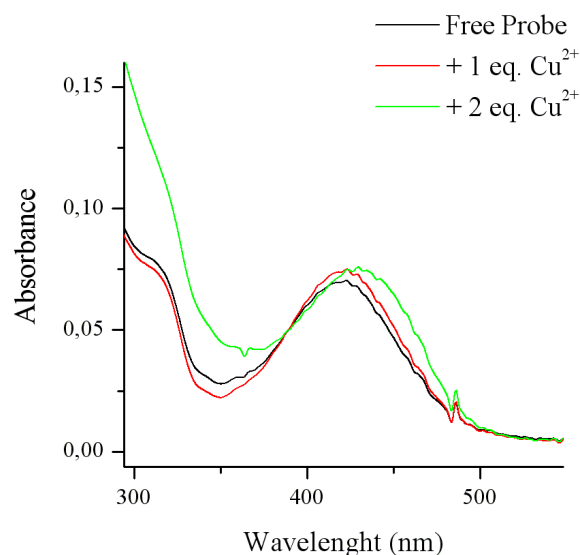


Fig. 6. Effect of the concentration of Cu^{2+} on the absorbance of compound **1**.

Probe's **1** based molecular computing

Probe **1** ($C = 10^{-5}$ mol L^{-1}) can act as a single output combinatorial logic circuit with three chemical inputs due to its remarkable fluorescence changes in presence of H^+ (0.01 M HCl), OH^- (0.01 M NaOH) and Cu^{2+} ($C = 2 \times 10^{-5}$ mol L^{-1}). An input₃-disabled-INH gate at a molecular scale is obtained by monitoring the emission output at 545 nm (Fig. 7) of probe **1**, where Cu^{2+} is the disabling Input 3, while H^+ and OH^- are Input 1 and Input 2, respectively. It is worth adding that this procedure

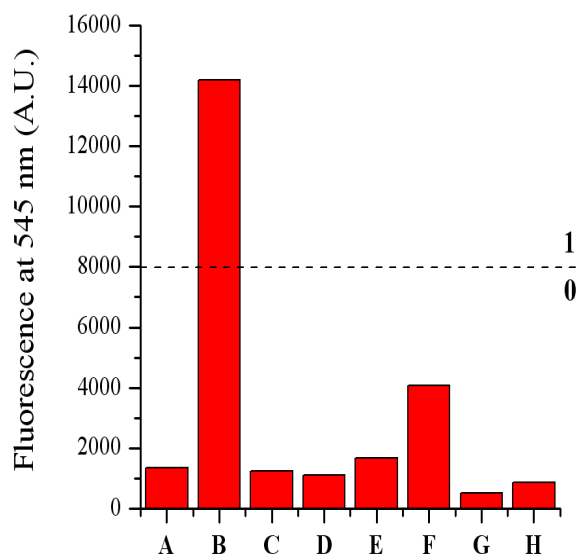
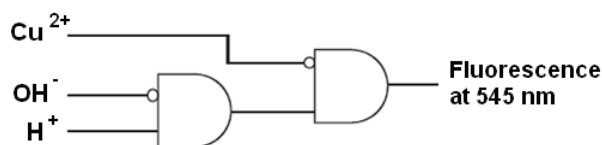


Fig. 7. The changes in fluorescence intensity at 545 nm of probe **1** ($C = 10^{-5}$ mol L $^{-1}$) in presence of NaOH ($C = 10^{-2}$ mol L $^{-1}$), Cu $^{2+}$ ($C = 2 \times 10^{-5}$ mol L $^{-1}$) and HCl ($C = 10^{-2}$ mol L $^{-1}$) as chemical inputs.

starts at pH = 8, where probe **1** is in its “off-state”.

It is seen that the fluorescence of **1** is high at 545 nm (coded for binary 1) only in presence of an acid (Table 1), which cuts off the PET quenching process in **1**. The presence of OH $^{-}$ alone does not affect probe's **1** fluorescence output and the system shows low emission (coded for binary 0). The simultaneous introduction of acid and base results in their annihilation generating the initial low emission at 545 nm. This behavior mimics INH logic gate. At the same time probe **1** fluorescence is always quenched in presence of Cu $^{2+}$ and the action of the above INH gate is prevented. This behavior correlates very well with a three-input disabled INH gate [53]. The logic behavior of probe **1** could be summarized through the electronic representation in Scheme 3 on the basis of the results obtained in the present study.



Scheme 3

Table 1. The truth table for the operation of compound **1**.

| | Input 1 | Input 2 | Input 3 | Output 1 |
|---|----------|-----------|------------|-------------|
| | H $^{+}$ | OH $^{-}$ | Cu $^{2+}$ | Fl $_{545}$ |
| A | 0 | 0 | 0 | 0 |
| B | 1 | 0 | 0 | 1 |
| C | 0 | 1 | 0 | 0 |
| D | 1 | 1 | 0 | 0 |
| E | 0 | 0 | 1 | 0 |
| F | 1 | 0 | 1 | 0 |
| G | 0 | 1 | 1 | 0 |
| H | 1 | 1 | 1 | 0 |

CONCLUSIONS

The synthesis and characterization of a new 2-N,N-diethylamino-N-(7-oxo-7H-benzo[de]anthracen-3-yl)-acetamide is described. The novel compound is designed in a “fluorophore-spacer-receptor” format providing its action as a molecular fluorescence PET-based pH probe. Its photophysical properties are studied in a water/DMF (1:1, v/v) solution and subsequently discussed. The emission intensity of novel compound is enhanced in the pH range from 9 to 4.5 (FE = 16.3). The determined pK $_a$ value of 7.06 ± 0.10 indicates that it can act as an efficient “off-on” switch for pH. The novel probe shows also sufficient sensor selectivity towards metal ions. It quenches its fluorescence intensity (FQ = 3.8) in presence of Cu $^{2+}$. The formation of 1:1 and 2:1 complexes in presence of Cu $^{2+}$ is observed. These results demonstrate the potential of the novel benzanthrone derivative to detect metal ions of pronounced selectivity towards Cu $^{2+}$. The logic behaviour of sensor **1** is also examined using Cu $^{2+}$, H $^{+}$ and OH $^{-}$ as chemical inputs and a three-input disabled INH gate is achieved at a molecular level.

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