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A novel cyanide chemodosimeter based on trifluoroacetamide benzhydrol-2 as binding motif: importance of substituent positioning on intra-molecular charge transfer

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ABSTRACT

The nucleophilic nature of cyanide is used to develop a simple, sensitive, and highly effective sensor. Azo dye **6a** based on 2-(trifluoroacetamide) benzhydrol-2 (2-TFAB) as anions receptor, presents a new way to build molecular color sensors for cyanide in water. The 2-TFAB moiety of the dye **6a** is used as receptor group for cyanides and linked directly by dominant reversible covalent bonding over hydrogen bonding, confirmed by the inactivity of the derivative **6b** toward cyanides.

1. Introduction

Considerable attention has been paid to the design and synthesis of abiotic receptors for anionic species in the past two decades, which makes anion recognition one of the fastest growing disciplines in the field of supramolecular chemistry.[1] In particular, cyanide is one of the most toxic anions and is harmful to the environment and human health. Cyanide is widely used in industrial fields due to its excellent chemical properties.[2] It is used in organic synthesis and in the making of plastics, in the recovery of gold and silver from ores, and in the electroplating of metals, such as silver, gold, platinum, and copper.[3] Cyanide has long been known to be a toxic substance,[4] the toxicity of its salts exploited for many hundreds of years. The detection of cyanides can be done in different ways. There are several methods for the detection and determination of cyanides, such as spectrophotometic methods,[5] electrochemical sensors,[6] and fiber optic sensors,[7] in addition to indication formats, such as chemical displacement[8] or molecular chemodosimetry,[4b,9] which requires an architecture in which the two chemical entities responsible for the key actions of coordination and transduction (i.e., the binding site and the signaling subunit) are integrated into a superstructure.[10]

Optical outputs are especially attractive with respect to the transduction of a modulated signal, because detection can then use cheap, easy-to handle and widely used instrumentation. Besides fluorescence-based systems, colorimetric recognition has gained popularity in recent years because a shift of an absorption band is often intrinsically ratiometric and avoids the necessity for an internal reference and also offers the possibility of so-called 'naked eye detection' for semiquantitative determinations.[11]

However, many receptors for cyanide reported to date have several limitations as follows: (i) poor selectivity, especially in the presence of fluoride or acetate, (ii) requiring specific conditions, such as high temperature or basic media, (iii) not instantaneously registering the addition of cyanide, (iv) requiring the use of instruments, such as luminoscopes, or UV light, (v) running the risk of releasing HCN, (vi) only working in an organic environment, and (vii) complicated synthesis. With these considerations in mind, we now report a simple yet effective colorimetric sensor 2-(trifluoroacetamide) benzhydrol-2 **6a** (2-TFAB), which overcomes the above limitations, and can achieve the so-called 'naked eye' detection of cyanide in an aqueous environment. Our strategy is based on the fact that cyanide is a well known nucleophile and can attack the carbon atom of an electron-deficient trifluoroacetyl group easily by dominant reversible covalent bonding over hydrogen

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bonding (Fig. 1). Compounds 1-(trifluoroacetamide) benzhydrol **6b** (1-TFAB) and 2-(trifluoroacetamide) benzhydrol **6a** (2-TFAB) were also synthesized easily in five steps.

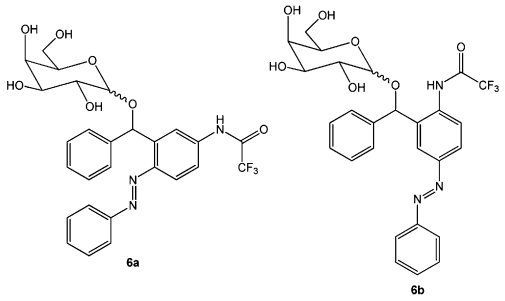
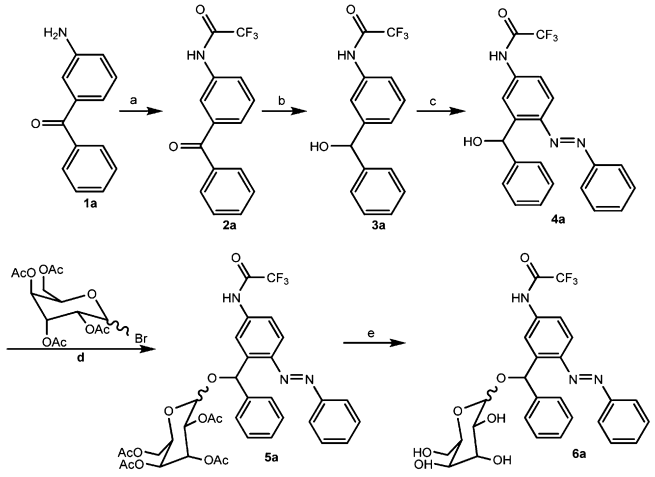


Fig. 1. Structures of (trifluoroacetamide) benzhydrol-2-based receptor 2-TFAB **6a** and reference compound 1-TFAB **6b**.

2. Results and discussions

2.1. Synthesis of chromogenic probes 6a and 6b

Scheme 1 report the synthesis of the azoic dye **6a** possessing (trifluoroacetamide) benzhydrol-2 as cyanide receptor.



Scheme 1. Synthesis of the dye **6a**. Reagent and conditions: (a) $(CF_3CO)_2O$, 80 °C, 1 h (b) $NaBH_4$, EtOH, rt, (c) Aniline, $NaNO_2$, HCl 37%, H_2O, 0 °C to rt, 12 h (d) NaH, THF, rt, 6 h (e) NaOMe, MeOH/CH_3Cl, rt, 16 h.

3-Amino benzophenone **1a** and trifluoroacetic anhydride was stirred at 80 °C for 1 h, and then the mixture was filtered and purified via column chromatography to afford compound **2a**. The reduction the carbonyl group of compounds **2a** to the corresponding benzhydrol derivative **3a** is carried out in the presence of $NaBH_4$ in the ethanol. The synthesis of the dye **4a** was carried out by treating the aniline with sodium nitrite in acidic medium at 0 °C to form the corresponding diazonium salt, followed by treatment with the derivative **3a**. The coupling of the bromo acetylated glucose derivative[13] and **4a** in the presence of NaH as base afford the dye **5a**. The chemosensor **6a** was obtained by deprotection of **5a** using NaOMe in methanol in 89% as yield. Both compounds were characterized by ^1H NMR, ^{13}C NMR, elemental analysis, and mass spectra.

2.2. Response to anions

In water, dye **6a** shows a colorless solution with a maximum in the absorption spectrum of 361 nm (ε=32,950 M^{-1} cm^{-1}). Addition of cyanide to a solution of **6a** in water (50 μM) causes a color change from colorless to yellow accompanying a new absorption band at λ_{max}=447 nm (Fig. 2). To further investigate the selectivity of the sensor **6a**, 12 anions of interest, namely, CN^-, F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, HSO_4^-, S^{2-}, CO_3^-, Cl^-, and N_3 were added (as salts) to a solution of **6a** in pure water. It can be seen that only CN^- induced a color change from colorless to yellow, and addition of other anions caused no obvious changes either in color or in the UV–vis spectra, even in a large excess (Fig. 2).

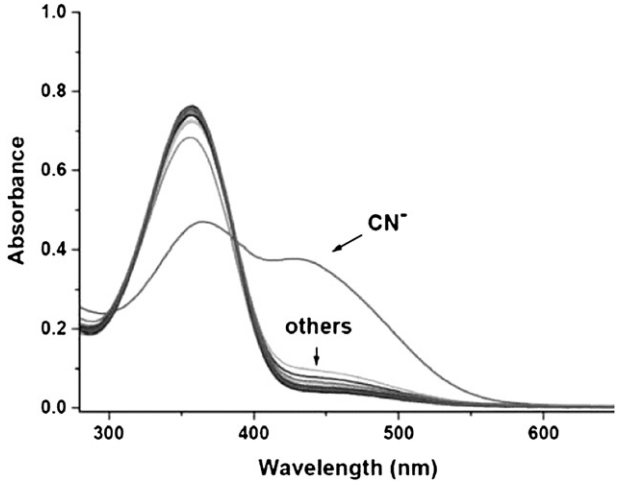


Fig. 2. Absorption spectra when 2-TFAB **6a** (50 μM) was treated with 2.0 equiv of various anions: CN^-, F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, HSO_4^-, S^{2-}, CO_3^-, Cl^-, and N_3 in pure water at pH=7.

The UV–vis spectra changes and the corresponding color changes of **6a** toward anions are highly solvent sensitive, especially to the amount of water present in the medium, probably due to the strong solvation effect in water as demonstrated in our previous studies.[12] Consequently, a pure water system was used as the optimized condition for the titration experiments at room temperature (Fig. 3).

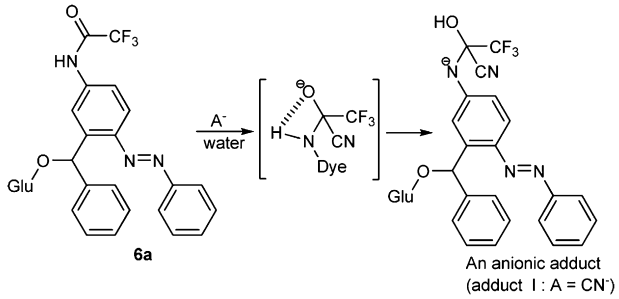


Fig. 3. Suggested mechanism for off–on switching in the presence of CN^- anion.

To confirm the interaction mechanism between the cyanide and the receptor **6a**, ^1H NMR titration experiments were carried out by addition of Bu_4NCN to a DMSO-d_6 solution of **6a** (Fig. 4). All the aromatic protons exhibited an upfield shift, which is compatible with the proposed switching mechanism.

Also, the ^{13}C NMR of the adduct **I** present the disappearance of the amidic *CO* signal at 155.11 of **6a** and the appearance of two new signals at 109.44 and 98.77 corresponding to *CN* and the formed alcohol.

In the case of the reference compound **6b**, addition of cyanide in water produced no obvious color changes even in a large excess, which can be ascribed to the strong intramolecular hydrogen bond between the *NH* and the benzhydrol oxygen forming a six-membered ring; hence the intermediate cyanohydrin cannot be stabilized by the *NH* (Fig. 5).

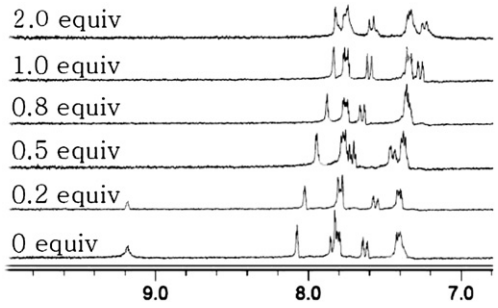


Fig. 4. ^{1}H NMR spectra of a solution of **6a** in DMSO-d_6 upon the addition of Bu_4NCN.

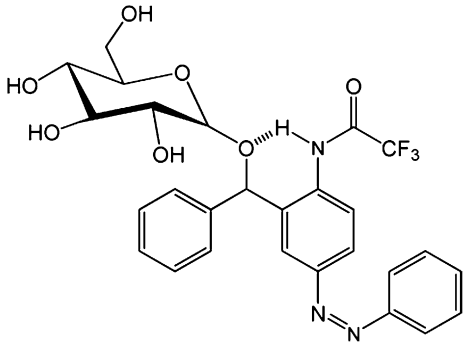


Fig. 5. Intramolecular hydrogen bond between –*NH* and the benzhydrol oxygen of **6b**.

The binding constants calculated from a 1:1 stoichiometry using nonlinear curve fitting analysis (see Supplementary data),[14] based on the absorption spectral changes at λ_{max}=447 nm, yields K=7.21×10^4 M^{-1} (Fig. 6).

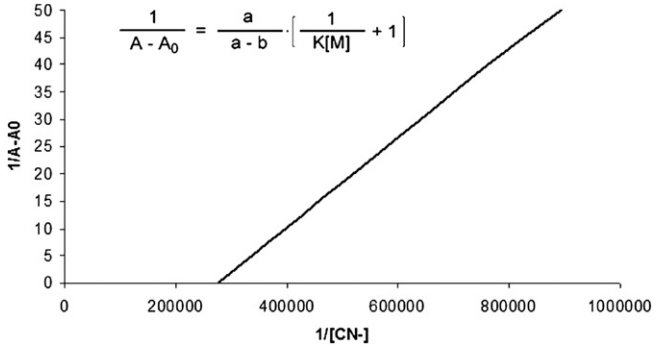


Fig. 6. A plot of $1/(A-A_0)$ versus $1/[CN^-]$ at 447 nm in water. The concentration of the chemosensor was 5 μM.

The colorimetric titration of probe **6a** with CN^- (0–30 equiv) gave an interesting quenching result, as inferred from a plot of $(A-A_0)$ versus equivalent of the cyanide ion. Fig. 7 show a near linear correlation between intensity difference absorption $(A-A_0)$ and CN^- concentration in water at room temperature. This demonstrates the potential utility of sensor **6a** for calibrating and determining cyanide ion concentration in water in the presence of other halide ions, which did not cause any changes in the absorption of **6a**.

The absorption spectra measured for the titration solutions with increasing amounts of cyanide for the solutions containing 5, 10, 20, and 30 equiv of CN^-, respectively showed little spectral changes from that of **6a**, and only gradual hypsochromic shifts and very small changes in the intensity were observed. Although further experiments, such as luminescence lifetime measurements depending on the concentration of quenchers can provide valuable information on the quenching mechanism, we tentatively suggest

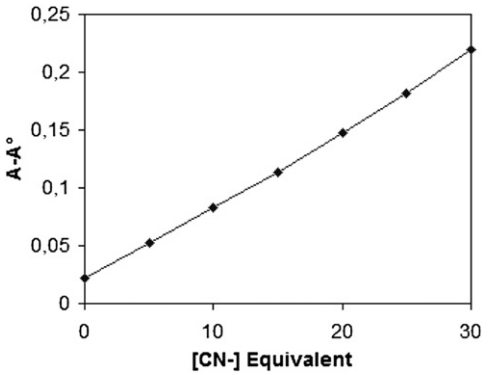


Fig. 7. The plot of $A-A_0$ versus equivalent of $[CN^-]$ for the titration of **6a** (50 μM) with CN^- (0–30 equiv) in water at 25 °C and pH=7.

that dynamic quenching is a dominant process for the latter region because molecular interactions other than collision are hard to imagine between the adduct **I** and cyanide. The Stern–Volmer plot shown in Fig. 7 suggests that the dynamic quenching process may be dominant but not exclusive.[9u,v] This absorbance intensity behavior depending on the cyanide equivalent also supports the formation of a 1:1 adduct species **I**, and, furthermore, the absorbance quenching is mainly due to the adduct formation.

Cyanide has the strongest carbonyl carbon affinity among the anions examined, whereas anions, such as AcO^- and F^- have lower affinity and other anions have very weak affinity.[12] The formation of adduct **I** should be dependent on the anion's carbonyl carbon affinity, which led to the observed absorbance behavior dependent on the anions. The fact that probe **6a** recognizes anions through reversible covalent adducts (RCA), not through H-bonding interactions, the most widely used paradigm in molecular recognition and sensing, suggests that we may achieve a selectivity pattern completely different from the absorbance probes based on H-bonding interactions in water. We have shown that cyanide is preferably recognized by the 2-(trifluoroacetamide) benzhydrol-2-based chemodosimeter. In addition, cyanide has poor H-bonding ability compared to F^- and AcO^-. Both properties suggest that CN^- may be completely discriminated from the competing F^- and AcO^- if we use aqueous solvents. Indeed this is the case. When probe **6a** was titrated with the anions in water, only CN^- showed significant absorbance quenching, and the competing anions F^- and AcO^- showed no changes (Fig. 2).

The response time upon exposure to cyanide is instantaneous, and the selectivity over F^- and AcO^- is high (Fig. 8). This is very important because F^- and AcO^- are the main interfering ions in cyanide sensing.

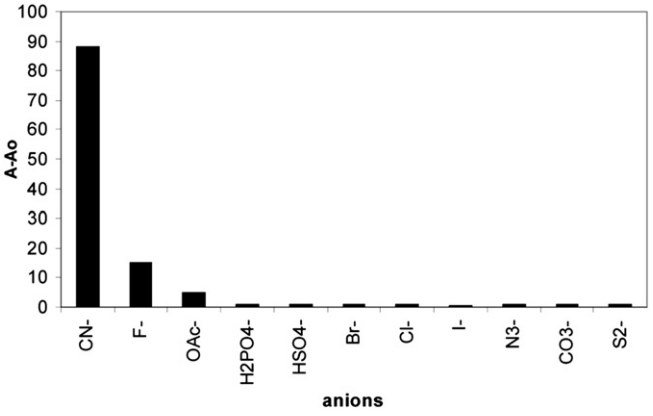


Fig. 8. Absorbance value changes $(A-A_0)$ of **6a** (50 μM) at 447 nm in the presence of 30.0 equiv of selected anions in water at pH=7. From the left: **6a** only, CN^-, F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, HSO_4^-, S^{2-}, CO_3^-, Cl^-, and N_3.

The detection limit[15] of cyanide in aqueous environment has been calculated (see Supplementary data). Fig. 9 shows the plot of $A-A_0$ versus the cyanide concentration in water. A linear response was observed in the 0 to 1 cyanide equiv range. A detection limit as low as 0.33 μM, the sensor **6a** can be used to detect the WHO suggested maximum allowed cyanide concentration in drinking water[16] (1.9 μM).

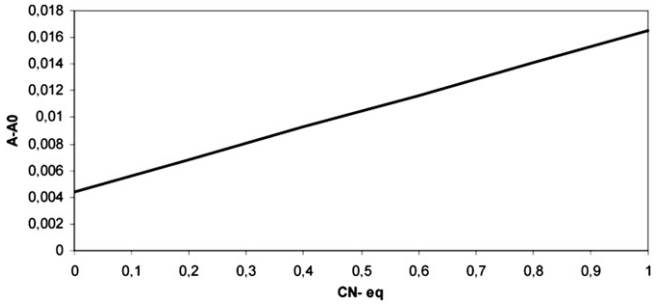


Fig. 9. A plot of $(A-A_0)$ versus CN^- concentrations at 447 nm in water at pH=7. The concentration of the chemosensor was 50 μM.

As reported in previous study,[17] the trifluoroacetyl group should also interact with aliphatic amines or alcohols via nucleophilic attack (Fig. 10).

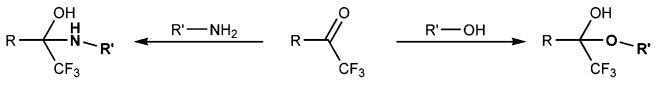


Fig. 10. Nucleophilic attack of the alcohol and amine on the trifluoroacetyl group.

For this purpose, the sensing ability of **6a** in water in the presence of 2-propanol, Ethanol as alcohols and 1-propylamine as amine was evaluated. The addition of the 2-propanol, Ethanol, and 1-propylamine aqueous solutions (10^{-2} M) to the solution of chromogenic probes **6a** does not exhibit any significant shift, insensitive to warming, stirring, powdering, and microwaving. Thus, the chromogenic probe **6a** can be used as water soluble chemodosimeter for selective cyanide detection in pure water.

To evaluate the reversibility of adduct **I**–CN^- system, adduct **I** was treated by increasing amounts of MeOH/H_2O: 10/1 (0.25, 0.5, 0.75, 1.25, 1.5, and 2 mL). The complete disappearance of the absorbance spectrum at 447 nm and the appearance of the absorption bond at 361 nm prove the transformation of adduct **I** to **6a** (Fig. 11).

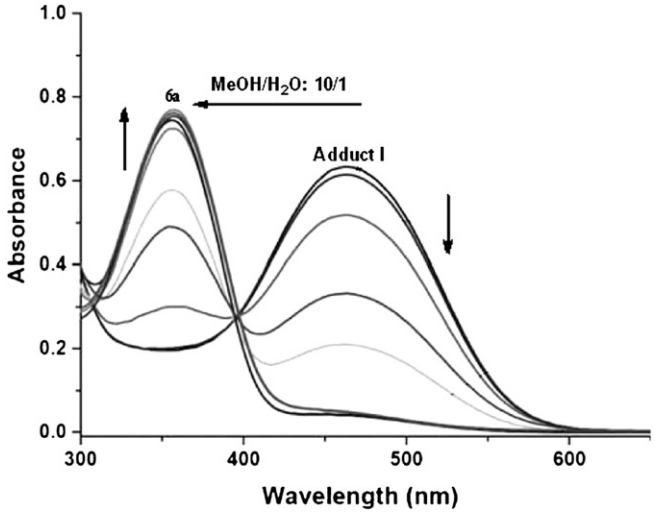


Fig. 11. Absorption spectra when adduct **I** was treated with increasing amounts of MeOH/H_2O.

Because of the reversibility of the nucleophilic addition of the CN^- to the carbonyl group, the treatment of the adduct **I** with MeOH/H_2O causes the transformation of the cyanohydrins to the carbonyl group by hydrolysis and the reformation of the double bond between oxygen and carbon.

3. Conclusion

In summary, we have reported the use of 2-(trifluoroacetamide) benzhydrol-2 as a chemodosimeter for the sensing of cyanide. The probe recognizes cyanide through the formation of reversible covalent adducts, and gives selective absorbance quenching in water among various anions examined. Our method is safe, fast, simple to use, and inexpensive. The probe is easy to synthesize and allows sensitive and highly selective detection of very low concentrations of cyanide in an aqueous environment.

4. Experimental

4.1. Chemicals and materials

All chemicals and solvents obtained from commercial sources were analytical pure and used without further purification. TLC was carried out on silica gel pre-coated plates (Merck; 60 Å F_{254}) and spots located with (a) UV light (254 and 366 nm), (b) ninhydrin (solution in acetone), (c) fluorescamine, (d) I_2 or (e) a basic solution of permanganate [$KMnO_4$ (3 g), K_2CO_3 (20 g), and NaOH (0.25 g) in water (300 mL)]. Flash column chromatography (FCC) was carried out on Merck silica gel 60 (230–400 mesh) according to Still et al.[18] ^1H and ^{13}C NMR spectra were recorded at 200 MHz with Varian spectrometers in deuteriated solvents and are reported in parts per million (ppm) with the solvent resonance used as the internal reference. Mass spectra were recorded with a Thermo Fisher LCQfleet ion-trap instrument (the spectra reported were also using the ESI $+c$ technique). Elemental analysis was carried out with a Perkin–Elmer 240C Elemental Analyzer. UV–vis spectra were recorded with a Cary-4000 Varian spectrophotometer. The anions CN^-, F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, HSO_4^-, S^{2-}, CO_3^-, Cl^-, and N_3 are coming from their corresponding salts KCN, KF, AcONa, $Na(H_2PO_4)$, KCl, KBr, KI, $KHSO_4$, Na_2S, Na_2CO_3, and NaN_3.

4.2. UV–vis titrations

Stock solutions (1 mM) of the salts of (CN^-, F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, HSO_4^-, S^{2-}, CO_3^-, and N_3) in water were prepared. Stock solutions of chemodosimeter (0.1 mM) were prepared in water. Test solutions were prepared by placing 4–40 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each anion, and diluting the solution to 4 mL with water. All the experiments were carried out at 20±2 °C and pH=7. After each addition the UV–vis spectra were taken and the absorbance values were collected in water.

4.3. General procedures

*4.3.1. General procedure A: synthesis compounds **2a** and **2b**.* Derivatives (**1a** or **1b**) were (1 equiv) dissolved in trifluoroacetic anhydride (10 mL) and the resulting mixture was stirred at 80 °C for 1 h. Then the mixture was filtered and purified via column chromatography (AcOEt/PE: 10/3) to afford the desired compounds **2a** or **2b**.

*4.3.1.1. N-(3-Benzoylphenyl)-2,2,2-trifluoroacetamide (**2a**).* The product **2a** was prepared according to the general procedure A using the following quantities: **1a** (1.00 g, 4.13 mmol), in trifluoroacetic anhydride (10 mL). The crude material was purified by FCC (EtOAc/petroleum ether, 10:3) to afford **2a** (1.38, 99%). R_f=0.63.

^{1}H NMR (200 MHz, $CDCl_3$): δ=8.05–7.65 (m, 9H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=193.5, 155.2, (*C*O), 144.1, 140.1, 138.1, 132.8, 132.3, 130.2, 128.5, 126.7, 125.5, 119.9 (ArH), 115.5 ppm. MS (ESI): *m*/*z*=294.07.16 $[M+1]^+$. $C_{15}H_{10}F_3NO_2$ (293.07): calcd C, 61.44; H, 3.44, found, C, 61.49; H, 3.48.

*4.3.1.2. N-(2-Benzoyl-5-nitrophenyl)-2,2,2-trifluoroacetamide (**2b**).* The product **2b** was prepared according to the general procedure A using the following quantities: **1b** (1.00 g, 4.13 mmol), in trifluoroacetic anhydride (10 mL). The crude material was purified by FCC (EtOAc/petroleum ether, 10:3) to afford **2b** (1.32, 95%). R_f=0.65. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.06–7.65 (m, 9H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=193.6, 155.3, (*C*O), 139.4, 138.6, 132.8, 132.1, 130.2, 128.7, 127.6, 125.5, 124.6, 119.9 (ArH), 115.5 ppm. MS (ESI): *m*/*z*=294.19 $[M+1]^+$. $C_{15}H_{10}F_3NO_2$ (293.07): calcd C, 61.44; H, 3.44, found, C, 61.47; H, 3.49.

*4.3.2. General procedure B: synthesis compounds **3a** and **3b**.* To a solution of **2a** or **2b** derivatives (1 mol) was dissolved in ethanol (10 ml), $NaBH_4$ (1 mol) was added and the resulting mixture was stirred under reflux. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite. The filtrate was evaporated under vacuum and the residue was taken into chloroform, washed twice with 80% saturated brine solution and finally with water. The organic layer was dried over anhydrous sodium sulfate and evaporation of the organic layer was followed by purification either by column chromatography, to yield the desired products **3a** or **3b**.

*4.3.2.1. N-(3-Benzoyl-5-aminophenyl)-2,2,2-trifluoroacetamide (**3a**).* The product **3b** was prepared according to the general procedure B using the following quantities: **2b** (1.00 g, 3.24 mmol), $NaBH_4$ (0.13 g, 3.24 mmol). The crude material was purified by FCC (EtOAc/petroleum ether, 2:1) to afford **3b** (0.94, 95%). R_f=0.55. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.76–7.13 (m, 9H), 5.77 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=155.1 (*C*O), 143.3, 143.2, 139.5, 129.6, 129.1, 128.5, 126.4, 123.2, 120.7, 119.2 (Ar–H), 115.5, 70.2 ppm. MS (ESI): *m*/*z*=296.13 $[M+1]^+$. $C_{15}H_{12}F_3NO_2$ (295.08): calcd C, 61.02; H, 4.10, found, C, 61.06; H, 4.14.

*4.3.2.2. N-(2-Benzoyl-5-aminophenyl)-2,2,2-trifluoroacetamide (**3b**).* The product **3b** was prepared according to the general procedure B using the following quantities: **2b** (1.00 g, 3.24 mmol), $NaBH_4$ (0.13 g, 3.24 mmol). The crude material was purified by FCC (EtOAc/petroleum ether, 2:1) to afford **2b** (0.94, 95%). R_f=0.57. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.77–7.11 (m, 9H), 5.76 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=155.8 (*C*O), 144.4, 143.1, 136.6, 129.5, 128.7, 128.2, 126.6, 126.2, 124.9, 115.9, 115.2, 70.1 ppm. MS (ESI): *m*/*z*=309.33 $[M+1]^+$. $C_{15}H_{11}F_3N_2O_2$ (308.26): calcd C, 58.45; H, 3.60, found, C, 58.53; H, 3.67.

*4.3.3. General procedure C: synthesis compounds **4a** and **4b**.* To a solution aniline (1 mol) in 15 mL of water/HCl 1 N: 15/1.5, a solution of $NaNO_2$ (1.4 mmol) in water (2 mL) was added dropwise at 0 °C and the resulting mixture was stirred for 30 min. The diazonium salt solution previously prepared was added dropwise to the solution of **3a** or **3b** (1 mol) in methanol (3 ml) and the combined solutions was maintained at 0 °C for 6 h with stirring. After this time, the pH was adjusted to 8 and the resulting mixture was diluted with chloroform (20 ml), the formed product was isolated by filtration and washed with chloroform to afford the corresponding azo dyes **4a** or **4b**.

*4.3.3.1. Azo dye **4a**.* The product **4a** was prepared according to the general procedure C using the following quantities: aniline (0.5 g, 5.20 mmol), **3a** (1.50 g, 5.20 mmol), $NaNO_2$ (0.47 g, 6.24 mmol), in HCl 1 N/water (10 mL), to afford **4a** (1.84 g, 89%). ^{1}H NMR (200 MHz, DMSO-d_6): δ=8.11–7.94 (m, 4H), 7.71–7.39 (m, 9H), 5.77 (s, 1H) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ=155.1 (*C*O), 152.0, 149.1, 146.4, 143.0, 141.3, 137.6, 130.2, 129.7, 129.2, 128.4, 126.6, 123.4, 123.1, 120.7, 116.2, 115.1, 71.4 ppm. MS (ESI): *m*/*z*=400.18 $[M+1]^+$. $C_{21}H_{16}F_3N_3O_2$ (399.12): calcd C, 63.16; H, 4.04, found, C, 63.21; H, 4.08.

*4.3.3.2. Azo dye **4b**.* The product **4b** was prepared according to the general procedure C using the following quantities: aniline (0.5 g, 5.20 mmol), **3b** (1.50 g, 5.20 mmol), $NaNO_2$ (0.47 g, 6.24 mmol), in HCl 1 N/water (10 mL), to afford **4b** (1.82 g, 88%). ^{1}H NMR (200 MHz, DMSO-d_6): δ=8.11–7.93 (m, 4H), 7.73–7.37 (m, 9H), 5.76 (s, 1H) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ=155.7 (*C*O), 152.3, 148.4, 144.5, 143.8, 138.5, 130.4, 129.8, 129.4, 128.4, 126.5, 123.6, 123.1, 121.7, 115.1, 108.3, 71.2 ppm. MS (ESI): *m*/*z*=400.21 $[M+1]^+$. $C_{21}H_{16}F_3N_3O_2$ (399.12): calcd C, 63.16; H, 4.04, found, C, 63.19; H, 4.07.

*4.3.4. General procedure D: synthesis of compounds **5a** and **5b**.* To a solution of **4a** (1 mol) in 15 mL of THF, a solution of NaH (1 mol) in THF (2 mL) was added dropwise at 0 °C and the resulting mixture was stirred for 30 min. The glucose derivative (1 mol) in THF (3 ml) was added and the resulting mixture was stirred at room temperature for 6 h. After this time, the reaction mixture was filtered through Celite. The filtrate was evaporated under vacuum and the residue was taken into chloroform, washed twice with 80% saturated brine solution and finally with water. The organic layer was dried over anhydrous sodium sulfate and evaporation of the organic layer was followed by purification either by column chromatography, to yield the desired products **5a** or **5b**.

*4.3.4.1. Azo dye **5a**.* The product **5a** was prepared according to the general procedure D using the following quantities: **4a** (0.5 g, 1.25 mmol), NaH (0.03 g, 1.25 mmol), glucose derivative (0.51 g, 1.25 mmol) to afford **5a** (0.82 g, 88%). ^{1}H NMR (200 MHz, DMSO-d_6): see Table 1 for glucidic part and δ=8.11–7.92 (m, 4H), 7.74–7.38 (m, 9H), 5.77 (s, 1H), 2.25 (s, 12H) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): see Table 2 for glucidic part and δ=170.4 (*C*O) 155.3 (*C*O), 152.1, 149.3, 146.4, 143.2, 141.4, 137.3, 130.5, 129.5, 129.6, 128.1, 126.2, 123.6, 123.2, 120.7, 116.3, 115.3, 71.1, 21.4 (*C*H$_3$) ppm. MS (ESI): *m*/*z*=730.26 $[M+1]^+$. $C_{21}H_{16}F_3N_3O_2$ (729.21): C, 57.61; H, 4.70, found, C, 57.66; H, 4.75.

*4.3.4.2. Azo dye **5b**.* The product **5b** was prepared according to the general procedure D using the following quantities: **4b** (0.5 g, 1.25 mmol), NaH (0.03 g, 1.25 mmol), glucose derivative (0.51 g, 1.25 mmol) to afford **5b** (0.83 g, 89%). ^{1}H NMR (200 MHz, DMSO-d_6): see Table 1 for glucidic part and δ=8.13–7.93 (m, 4H), 7.74–7.37 (m, 9H), 5.75 (s, 1H), 2.26 (s, 12H) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): see Table 2 for glucidic part and δ=170.2 (*C*O), 155.5 (*C*O), 152.3, 148.3, 144.5, 143.7, 138.5, 130.5, 129.8, 129.5, 128.4, 126.4, 123.6, 123.1, 121.7, 115.1, 108.2, 71.4, 21.1 (*C*H$_3$) ppm. MS (ESI): *m*/*z*=400.24 $[M+1]^+$. $C_{21}H_{16}F_3N_3O_2$ (399.12): calcd C, 63.16; H, 4.04, found, C, 63.20; H, 4.08.

*4.3.5. Generale procedure E: synthesis of **6a** and **6b**.* The compounds **6a** and **6b** were then deprotected using the classic sodium methoxide in MeOH method (1 equiv) stirring at room temperature for 16 h. Chloroform was used as a co-solvent where necessary for complete solvation. Acidic ion-exchange resin (Amberlite IR-120) was then added and at neutralization was filtered off and washed with MeOH. The solvent was then evaporated off to afford the products **6a** and **6b**.

*4.3.5.1. Azo dye **6a**.* Hydrolysis of **5a** (0.60 g, 0.83 mmol) with sodium methoxide in MeOH (5 mL) by the procedure E afforded **6a** (0.45 g, 98% yield) as a mixture of α- and β-pyranosic anomers in

the ratio of 40:60, calculated on the basis of the relative C-1 signal intensities. ^{1}H NMR (200 MHz, DMSO-d_6): δ=8.11–7.92 (m, 4H), 7.74–7.37 (m, 9H), 5.8 (d, 1H, J=9.3 Hz), 5.76 (s, 1H), 5.55 (m, 2H), 5.22 (dd, 1H, J=10.3, 3.3 Hz), 4.2 (m, 3H) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): see Table 3 for glucidic part and δ=155.4 (CO), 152.1, 149.2, 146.5, 143.2, 141.3, 137.5, 130.5, 129.5, 129.6, 128.1, 126.2, 123.6, 123.2, 120.6, 116.3, 115.4, 71.2 ppm. MS (ESI): m/z=562.22 $[M+1]^+$. $C_{27}H_{26}F_3N_3O_7$ (561.17): calcd C, 57.75; H, 4.67, found, C, 57.79; H, 4.71.

*4.3.5.2. Azo dye **6b**.* Hydrolysis of **5b** (0.60 g, 0.83 mmol) with sodium methoxide in MeOH (5 mL) by the procedure E afforded **6a** (0.47 g, 99% yield) as a mixture of α- and β-pyranosic anomers in the ratio of 40:60, calculated on the basis of the relative C-1 signal intensities. ^{1}H NMR (200 MHz, DMSO-d_6): δ=8.13–7.94 (m, 4H), 7.74–7.38 (m, 9H), 5.82 (d, 1H, J=9.3 Hz), 5.76 (s, 1H), 5.56 (m, 2H), 5.24 (dd, 1H, J=10.2, 3.3 Hz), 4.2 (m, 3H) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): see Table 3 for glucidic part and δ=155.4 (CO), 152.2, 148.3, 144.5, 143.7, 138.6, 130.4, 129.9, 129.5, 128.4, 126.4, 123.6, 123.1, 121.7, 115.2, 108.3, 71.4 ppm. MS (ESI): m/z=562.21 $[M+1]^+$. $C_{27}H_{26}F_3N_3O_7$ (561.17): calcd C, 57.75; H, 4.67, found, C, 57.80; H, 4.72.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.04.059.

References and notes

1. (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609; (b) Beer, P. D. *Acc. Chem. Res.* **1998**, *31*, 71; (c) Fabbrizzi, L.; Licchelli, M.; Pallavicini, P. *Acc. Chem. Res.* **1999**, *32*, 846; (d) Fabbrizzi, L.; Licchelli, M.; Rabaioli, G.; Taglietti, A. *Coord. Chem. Rev.* **2000**, *205*, 85; (e) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 487; (f) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 3118; (g) Martınez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419; (h) Kubik, S.; Reyheller, C.; Stuwe, S. *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, *52*, 137; (i) Bowman-James, K. *Acc. Chem. Res.* **2005**, *38*, 671; (j) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465; (k) Anzenbacher, P., Jr.; Nishiyabu, R.; Palacios, M. A. *Coord. Chem. Rev.* **2006**, *250*, 2929; (l) Katayev, E. A.; Ustynyuk, Y. A.; Sessler, J. L. *Coord. Chem. Rev.* **2006**, *250*, 3004.
2. Hachiya, H.; Ito, S.; Fushinuki, Y.; Masadome, T.; Asano, Y.; Imato, T. *Talanta* **1999**, *48*, 997.
3. Baskin, S. I.; Brewer, T. G. In *Medical Aspects of Chemical and Biological Warfare*; Sidell, F., Takafuji, E. T., Franz, D. R., Eds.; TMM publications: Washington, 1997; pp 271–286.
4. (a) Lindsay, A. E.; Greenbaum, A. R.; O'Hare, D. *Anal. Chim. Acta* **2004**, *511*, 185; (b) Badugu, R.; Lakowicz, J. R.; Geddes, C. D. *J. Am. Chem. Soc.* **2005**, *127*, 3635; (c) Ishii, A.; Seno, H.; Watanabe-Suzuki, K.; Suzuki, O.; Kumazawa, T. *Anal. Chem.* **1998**, *70*, 4873; (d) Meriya, F.; Hashimoto, Y. *J. Forensic Sci.* **2001**, *46*, 1421; (e) Vennesland, B.; Comm, E. E.; Knownles, C. J.; Westly, J.; Wissing, F. *Cyanide in Biology*; Academic: London, 1981.
5. (a) Deep, B.; Balasubramanian, N.; Nagaraja, K. S. *Anal. Lett.* **2003**, *36*, 2865; (b) Geetha, K.; Balasubramanian, N. *Anal. Lett.* **2001**, *34*, 2507; (c) Wang, M.; Luo, D. L. *Chin. J. Anal. Chem.* **2000**, *28*, 519; (d) Haj-Hussein, A. T. *Talanta* **1997**, *44*, 545; (e) Ishii, H.; Kohata, K. *Talanta* **1991**, *38*, 511.
6. (a) Keusgen, M.; Kloock, J. P.; Knobbe, D.-T.; Jünger, M.; Krest, I.; Goldbach, M.; Klein, W.; Schoning, M. J. *Sens. Actuators, B* **2004**, *103*, 380; (b) Lindsay, A. E.; O'Hare, D. *Anal. Chim. Acta* **2006**, *558*, 158; (c) Hassan, S. S. M.; Marzouk, S. A. M.; Mohamed, A. H. K.; Badawy, N. M. *Electroanalysis* **2004**, *16*, 298; (d) Abbaspour, A.; Asadi, M.; Ghaffarinejad, A.; Safaei, E. *Talanta* **2005**, *66*, 931; (e) Shan, D.; Mousty, C.; Cosnier, S. *Anal. Chem.* **2004**, *76*, 178; (f) Lee, J. I.; Karube, I. *Biosens. Bioelectron.* **1996**, *11*, 1147; (g) Ikebukuro, K.; Miyata, A.; Cho, S. J.; Nomura, Y.; Chang, S. M.; Yamauchi, Y.; Hasebe, Y.; Uchiyama, S.; Karube, I. *J. Biotechnol.* **1996**, *48*, 73; (h) Siontorou, C. G.; Nikolelis, D. P. *Anal. Chim. Acta* **1997**, *355*, 227.
7. (a) Jawad, S. M.; Alder, J. F. *Anal. Chim. Acta* **1991**, *246*, 259; (b) Freeman, M. K.; Bachas, L. G. *Anal. Chim. Acta* **1990**, *241*, 119; (c) Bentley, A. E.; Alder, J. F. *Anal. Chim. Acta* **1989**, *222*, 63.
8. (a) García-Acosta, B.; Albiach-Martí, X.; García, E.; Gil, L.; Matínez-Máñez, R.; Rurack, K.; Sancenón, F.; Soto, J. *Chem. Commun.* **2004**, 774; (b) Ros-Lis, J. V.; Martínez-Máñez, R.; Rurack, K.; Sancenón, F.; Soto, J.; Spieles, M. *Inorg. Chem.* **2004**, *43*, 5183; (c) Jiménez, D.; Martínez-Máñez, R.; Sancenón, F.; Ros-Lis, J. V.; Soto, J.; Benito, A.; García-Breijo, E. *Eur. J. Inorg. Chem.* **2005**, 2393; (d) Wiskur, S. L.; Aït-Haddou, H.; Lavigne, J. J.; Anslyn, E. V. *Acc. Chem. Res.* **2001**, *34*, 963; (e) Jiménez, D.; Martínez-Máñez, R.; Sancenón, F.; Ros-Lis, J. V.; Benito, A.; Soto, J. *J. Am. Chem. Soc.* **2003**, *125*, 9000; (f) Ros-Lis, J. V.; García, B.; Jiménez, D.; Martinez-Máñez, R.; Sancenón, F.; Soto, J.; Gonzalvo, F.; Valldecabres, M. C. *J. Am. Chem. Soc.* **2004**, *125*, 4064; (g) Ros-Lis, J. V.; Martínez-Máñez, R.; Soto, J. *Chem. Commun.* **2002**, 2248; (h) Ros-Lis, J. V.; Martínez-Máñez, R.; Soto, J. *Chem. Commun.* **2005**, 5260.
9. (a) Kim, Y.-H.; Hong, J.-I. *Chem. Commun.* **2002**, 512; (b) Liu, H.; Shao, X.-B.; Jia, M.-X.; Jiang, X.-K.; Li, Z.-T.; Chen, G.-J. *Tetrahedron* **2005**, *61*, 8095; (c) Chow, C.-F.; Lam, M. H. W.; Wong, W.-Y. *Inorg. Chem.* **2004**, *43*, 8387; (d) Zelder, F. H. *Inorg. Chem.* **2008**, *47*, 1264; (e) Zeng, Q.; Cai, P.; Li, Z.; Qin, J.; Tang, B. Z. *Chem. Commun.* **2008**, 1094; (f) Todd, W.; Gabbaı, F. P. *J. Am. Chem. Soc.* **2007**, *129*, 3635; (g) Jin, W. J.; Fernandez-Argüelles, M. T.; Costa-Fernández, J. M.; Sanz-Medel, A. *Chem. Commun.* **2005**, 883; (h) Touceda-Varela, A.; Stevenson, E. I.; Galve-Gasión, J. A.; Dryden, D. T. F.; Mareque-Rivas, J. C. *Chem. Commun.* **2008**, 1998; (i) Kim, Y. K.; Lee, Y.-H.; Lee, H.-Y.; Kim, M. K.; Cha, G. S.; Ahn, K. H. *Org. Lett.* **2003**, *5*, 4003; (j) Tomasulo, M.; Raymo, F. M. *Org. Lett.* **2005**, *7*, 4633; (k) Chung, Y. M.; Raman, B.; Kim, D.-S.; Ahn, K. H. *Chem. Commun.* **2006**, 186; (l) Yang, Y.-K.; Tae, J. *Org. Lett.* **2006**, *8*, 5721; (m) Tomasulo, M.; Sortino, S.; P. White, A. J.; Raymo, F. M. *J. Org. Chem.* **2006**, *71*, 744; (n) Chen, C.-L.; Chen, Y.-H.; Chen, C.-Y.; Sun, S.-S. *Org. Lett.* **2006**, *8*, 5053; (o) Lee, K. S.; Lee, J. T.; Hong, J.-I.; Kim, H.-J. *Chem. Lett.* **2007**, *36*, 816; (p) Sessler, J. L.; Cho, D.-G. *Org. Lett.* **2008**, *10*, 73; (q) Lee, K. S.; Kim, H.-J.; Kim, G.-H.; Shin, I.; Hong, J.-I. *Org. Lett.* **2008**, *10*, 49; (r) Ekmekci, Z.; Yilmaz, D.; Akkya, E. U. *Org. Lett.* **2008**, *10*, 461; (s) Miyaji, H.; Kim, D.-S.; Chang, B.-Y.; Park, E.; Park, S.-M.; Ahn, K. H. *Chem. Commun.* **2008**, 753; (t) Sun, S. S.; Lees, A. J. *Chem. Commun.* **2000**, 1687; (u) Miyaji, H.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 154; (v) Gimeno, N.; Li, X.; Durrant, J. R.; Vilar, R. *Chem.—Eur. J.* **2008**, *14*, 3006; (w) Anzenbacher, P., Jr.; Tyson, D. S.; Jursıkova, K.; Castellano, F. N. *J. Am. Chem. Soc.* **2002**, *124*, 6232.
10. Fabbrizzi, L.; Poggi, A. *Chem. Soc. Rev.* **1995**, *24*, 197.
11. Rurack, K.; Resch-Genger, U. *Chem. Soc. Rev.* **2002**, *31*, 116.
12. Isaad, J.; Perwuelz, A. *Tetrahedron Lett.* **2010**, *51*, 5810.
13. Mahon, E.; Aastrupb, T.; Barboiu, M. *Chem. Commun.* **2010**, 2441.
14. (a) Bourson, J.; Pouget, J.; Valeur, B. *J. Phys. Chem.* **1993**, *97*, 4552; (b) Inoue, Y.; Yamamoto, K.; Wada, T.; Everitt, S.; Gao, X.-M.; Hou, Z.-J.; Tong, L.-H.; Jiang, S.-K.; Wu, H.-M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1807; (c) Liu, S.-Y.; He, Y.-B.; Wu, J.-L.; Wei, L.-H.; Qin, H.-J.; Meng, L.-Z.; Hu, L. *Org. Biomol. Chem.* **2004**, *2*, 1582.
15. Zhu, M.; Yuan, M.; Liu, X.; Xu, J.; Lv, J.; Huang, C.; Liu, H.; Li, Y.; Wang, S.; Zhu, D. *Org. Lett.* **2008**, *10*, 1481.
16. *Guidelines for Drinking-Water Quality*; The World Health Organization: Geneva, Switzerland, 1996.
17. Mohr, G. J.; Demuth, C.; Spichiger-Keller, U. E. *Anal. Chem.* **1998**, *70*, 3868.
18. Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1985**, *50*, 2394.