ORIGINAL ARTICLE

Anthracene-tethered aminomethyl oxadiazole chemosensor: a probe offering selective chromo- and fluorogenic signalings for targeting Cu(II)

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Abstract A new optical chemosensor featuring anthracene as a fluorophore and an aminomethyl oxadiazole moiety as a bidentate chelate has been synthesized. From photophysical studies, we find the probe to offer remarkably selective chromo- and fluorogenic signaling responses towards biologically and environmentally significant Cu^{2+}. In the presence of Cu^{2+}, fluorescence is quenched to the extent of 95%, while the absorbance due to the anthracene chromophore is nearly completely bleached out. On the other hand, Li^+, Na^+, K^+, Ba^{2+}, Ca^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Ag^+, Pb^{2+} and Hg^{2+} even at 10 times higher concentration than Cu^{2+} do not cause detectable photophysical perturbations. The stability constants, $\log K$ for Cu^{2+} were calculated to be 4.36 and 4.76 on the basis of spectrophotometric and fluorimetric titrations, respectively. However, $\log Ks$ for other metal ions are too low (<0.1) to pose any interferences in the optical detection of Cu^{2+}. Though, not fully defined, the uncommon phenomenon of the absorbance bleaching by Cu^{2+} is tentatively explained by invoking the involvement of non-covalent anthracene-Cu^{2+} complex.

Keywords Chemosensor · Colorimetry · Fluorescence · Quenching · Cu^{2+} sensor · Absorbance bleaching · Anthracene-Cu^{2+} interaction

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Introduction

The design of artificial sensors capable of selective detection of biologically and or environmentally significance metal ions is an area of burgeoning interest in supramolecular chemistry [1–4]. Copper is an essential mineral in the human diet with its established role in haemoglobin synthesis, nerve functions, lipid metabolism, electron transfer processes and activation of small molecules [5, 6]. Copper is also a significant environmental pollutant, and its prolong exposure beyond the physiological limits is known to cause gastrointestinal problems and renal dysfunction [7, 8].

Detection of Cu^{2+} has been reported by the classical atomic absorption spectroscopy as well as by inductively coupled plasma spectroscopy [9, 10]. In addition, electrochemical methods, using ligand modified electrodes have also been employed [11, 12]. In past decades, optical spectral techniques, particularly the fluorescence spectroscopy have gained tremendous popularity owing to its high sensitivity, inexpensive instrumentations and the possibility of real time analysis [13–15]. One of the most popular approaches to construct fluorescence sensors is to connect a photoemittive unit to a metal ion selective receptor via a suitable spacer within the fluorophore-spacer-receptor format [4]. This sensor protocol, initiated by de Silva [16] and later extensively exploited by others, work on the principle of photoinduced electron transfer (PET) from the donor ligand to the excited fluorophore. Binding of the metal ion could trigger either fluorescence "on" or "off" modulation, depending upon the diamagnetic/paramagnetic character of the interacting metal ion [1–4, 13–15].

Over past decades, a variety of fluorescence sensors of Cu^{2+} exhibiting either fluorescence "on–off" or "off–on" signaling has been developed. While the Cu^{2+} sensors offering fluorescence quenching response generally operate

via PET mechanism, on the other hand, the fluorescence enhancements in a limited number of Cu sensors arise either via chelation induced blocking of a fluorescence quenching channel or the change over of the nonemittive n-π^* to the emmitive $\pi–\pi^*$ state.[17–29] Note withstanding considerable progress, some of the reported Cu^{2+} sensors suffer from delayed response and minor, but significant competitive binding from one or more of the metal ions such as Zn, Ni, Hg, Cd, Pb and Ag ions [30–36]. In this paper, we have designed a new chemosensor, designated as Anthrox to study its potential as an optical sensor for metal ion(s) of biological/environmental interest.

Since, metal binding selectivity depends mainly upon the nature of the ligand system, it is tempting to manipulate the structures of the chelates in order improve binding characteristics and selectivity towards a target metal ion. We have been interested in the photoemittive diaryloxadiazole as an intrinsic fluorescent ligand and have successfully used this system to designed sensors for targeting biologically significant Zn, Mg, Ca, and Ba ions [37–40]. Besides, a Cd^{2+} selective fluorescence chemosensor has recently reported by Lie et al. by incorporating oxadiazole ring as a part of the chelating ligand [41]. Copper (II) exists as a d^9 metal center of borderline softness, exhibiting binding interactions with nitrogen-based ligands such as amines, imines, and bidentate ligands like aminomethyl pyridine, bipyridine etc [42–45]. Though, oxadiazole ring is known to coordinate with Cu^{2+}, however to our knowledge this ring has not been used to design Cu^{2+} selective fluorescence sensor [46]. We now extend the application of oxadiazole core as one of the binding ligands to develop a new fluorescence sensor, Anthrox. The design of Anthrox is based on the fluorophore-spacer-receptor format, and carries anthracene core as a fluorophore, whereas the aminomethyl oxadiazole moiety constitutes a bidentate metal binding domain. Our photophysical results show the probe to be an effective optical sensor, offering highly selective color bleaching and turn-off signaling response towards Cu^{2+}.

Result and discussion

Synthesis of Anthrox was readily achieved in two easy steps as outlined in Scheme 1. Condensation of chloro-acetyl chloride with the known 4-t-butylphenyl hydrazide in the presence of phosphorus oxychloride afforded chloromethyl oxadiazole **2**. N-alkylation of **2** with the known N-benzyl aminomethyl anthracene under acetone/K_2CO_3 condition, followed by SiO_2 column chromatographic purification afforded the target molecule, Anthrox as a yellow, crystalline solid in about 30% overall yield. The structure of the probe is fully characterized on the basis of spectral data and elemental analysis.
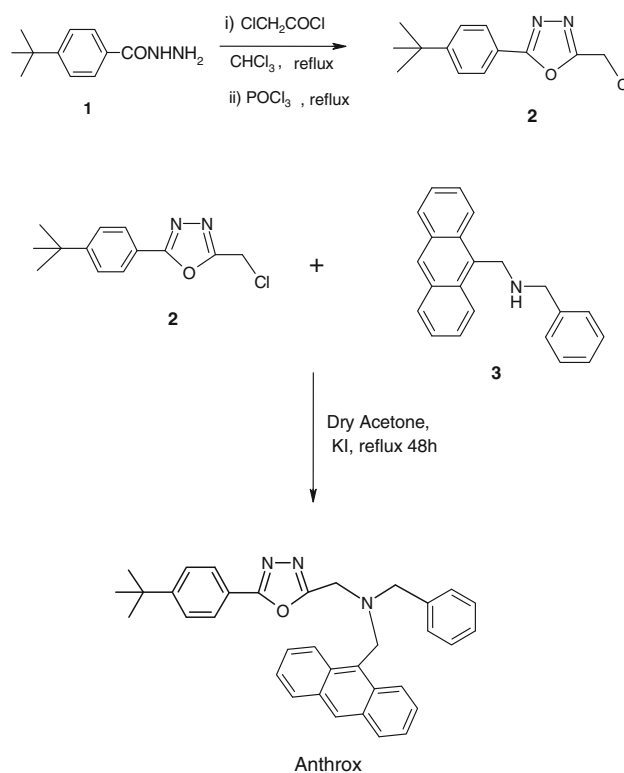
Scheme 1 Synthesis of the chemosensor, Anthrox

Absorption studies and titrations

Photophysical sensitivity of Anthrox towards selected metal ions of biological and or environmental relevance viz Li^+, Na^+, K^+, Ba^{2+}, Ca^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Ag^+, Pb^{2+} and Hg^{2+} were investigated in CH_3CN (ACN) solvent both spectrophotometrically and fluorimetrically. All the metal ion titration experiments were uniformly carried out by adding ACN solution of the known concentration of metal ions perchlorates into the ACN solution of Anthrox. The UV–vis spectrum of Anthrox displayed absorption maxima, characteristic of anthracene chromophore at 348, 366 and 386 nm, with the molar extinction coefficient, ε_m of ca. 0.921×10^4 M^{-1} cm^{-1}. As depicted in Fig. 1, the absorbance of the probe decrease marginally by 5–15% upon adding Li^+, Na^+, K^+, Ba^{2+}, Ca^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Ag^+, Pb^{2+} and Hg^{2+} up to 1000 equiv with respect to a fix concentration of Anthrox (2.83×10^{-5} M). However, the energies of the absorption maxima remained essentially invariant to the added perchlorates of the above metal ions. Since, the probe is not a typical donor–acceptor chromophore, the lack of significant changes in the absorbance profile of the probe does not imply the absence of significant metal ion binding interaction.

By contrast, addition of Cu^{2+} caused progressive decline in the molar absorbance with increasing concentration of
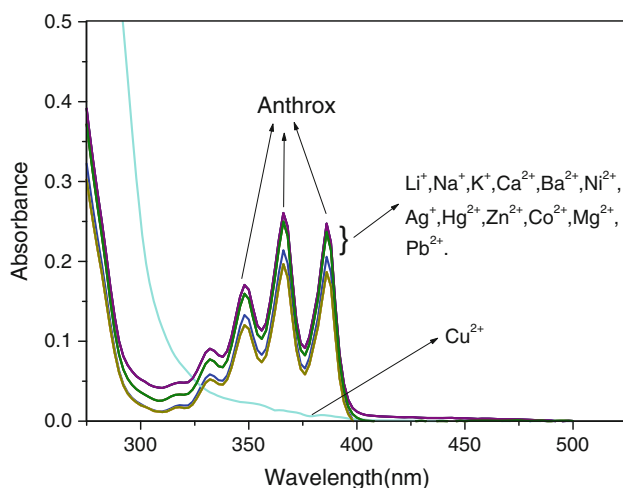
Fig. 1 Absorption spectra of Anthrox (2.83×10^{-5} M) in absence and presence of each of Li^+, Na^+, K^+, Ba^{2+}, Ca^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Ag^+, Pb^{2+} and Hg^{2+} (2.83×10^{-2} M) and Cu^{2+} (2.83×10^{-3} M) in CH_3CN

Cu^{2+}. The spectrophotometric titration revealed linear decrease in the absorption maxima due to the anthracene chromophore, with virtually complete bleaching being observed after the addition of ca. 100 equiv of Cu^{2+}. The loss of anthracene absorption occurred immediately upon mixing the ACN solution of Anthrox and Cu^{2+}, turning the deep yellow solution into colorless, an event that allows naked eye sensing of this ion. None of the other metal ions examined gives rise to detectable color sensitivity even at 10 times higher concentration than Cu^{2+}.

Fluorescence spectral studies in the presence of metal ions

Excitation of Anthrox at 330 nm produced a structured fluorescence spectrum showing emission maxima at 396, 416 and 439 nm, which could be ascribed to the anthracene fluorophore. The quantum yield, Φ_f of the probe was determined to be 0.054 with reference to coumarin 151 in cyclohexane ($\Phi_f = 0.28$) [47]. The weakly emissive nature of Anthrox is presumably due to the PET quenching operating via electron transfer from the saturated nitrogen to the excited state of the anthracene fluorophore. On this ground, we expected that strong binding interaction with the diamagnetic metal ions should induce chelation enhanced fluorescence (CHEF), while the paramagnetic metal ions might lead to fluorescence quenching effects.

Accordingly, we also investigated the fluorescence modulation of the probe in the presence of different metal ions. Addition of Li^+, Na^+, K^+, Ca^{2+}, Ba^{2+}, Cd^{2+}, Pb^{2+} and up to 1000 equiv did not noticeably perturb the excited state behavior of the probe, whereas Mg^{2+}, Co^{2+}, Ni^{2+}, Ag^+ and Zn^{2+} induced insignificant emission intensity

enhancement by ca. 3–12%. These emission enhancements, probably caused by blocking of the PET process are too weak to have any sensing implications. For the case of Hg^{2+}, the quenching effect though by a small margin of ca. 5% is observed at a 1000 equiv with respect to that of the probe. The insignificant fluorescence perturbations clearly imply negligible binding affinity of the above studied metal ions towards the probe.

On the other hand, addition of Cu^{2+} at 100 equiv caused remarkably high emission quenching of ca, 95%. Fluorimetric titration of an ACN solution of Anthrox with $Cu(ClO_4)_2$ is shown in Figs. 2, 3. A steady decline in emission intensities at 396, 416 and 439 nm maxima is observed on incremental (0 to 100 equiv) addition of Cu^{2+} ions. A plateau is reached at a limiting concentration of ca. 100 equiv of Cu^{2+} and under this condition with the
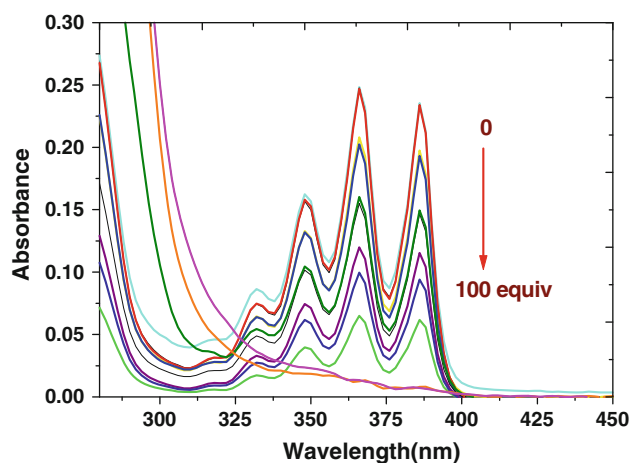

Fig. 2 Spectrophotometric titration of Anthrox (2.83×10^{-5} M) on incremental addition of $Cu(ClO_4)_2$ (0–2.83×10^{-3} M) in CH_3CN
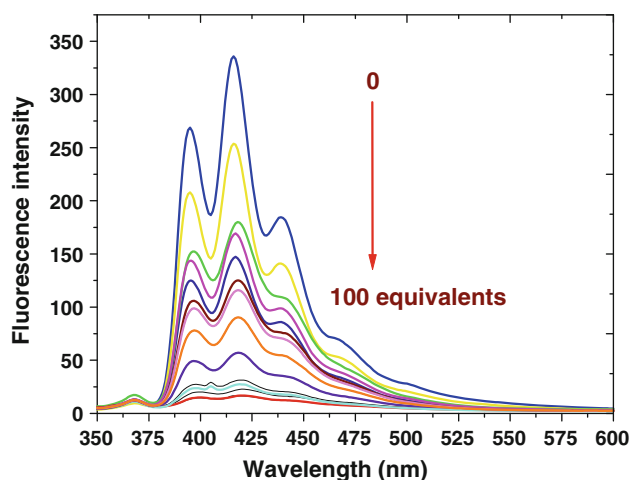
Fig. 3 Fluorimetric titration of Anthrox (2.83×10^{-5} M) on incremental addition of $Cu(ClO_4)_2$ (0–2.83×10^{-3} M) in CH_3CN ($\lambda_{ex} = 330$ nm)

quantum yield dropping down to 0.0061 from a value of 0.054 for the unbound probe. This is one of the highest emission quenching observed among the known fluorescence chemosensors for Cu^{2+}. Moreover, the quenching, like the absorbance bleaching also occurs instantaneously upon mixing the ACN solution of Anthrox with Cu^{2+}. The interaction between Cu^{2+} and Anthrox is also found to be reversible, since the addition 1,4,7,10-tetraazatetradecane, a strong complexing ligand for Cu^{2+} caused the decomplexation of Anthrox-Cu^{2+} system and revived the fluorescence to the original level of the unbound probe. Apart from Cu^{2+}, Hg^{2+} is the only other metal ion for which quenching is detected at 1000 equiv, though by a small margin of ca. 5%.

Figure 4 shows the graphical representation of the steady changes in the emission profile of Anthrox giving an indication of stoichiometric complex formation between Anthrox and Cu^{2+}. The Job plot analysis performed on the basis of fluorimetric titration confirmed 1:1 binding stoichiometry. The stability constant, $\log K$, determined using the nonlinear square curve fitting using data both spectrophotometric and fluorimetric titrations gave the values of 4.36 and 4.76, respectively. This observation suggests that the binding interactions in both the ground and excited states are of similar magnitude. However, owing to insignificant absorbance and fluorescence perturbations, the stability constants for Li^+, Na^+, K^+, Ba^{2+}, Ca^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Ag^+, Pb^{2+} and Hg^{2+} are too small (<0.1) to be reliably determined. The significant perturbation in optical spectral properties of Anthrox with Cu^{2+} signifies its superior binding interaction and selectivity compared to several metal ions examined. Consequently, the probe allows for the selective detection of Cu^{2+} both by means of absorption bleaching and drastic fluorescence 'on–off' response.
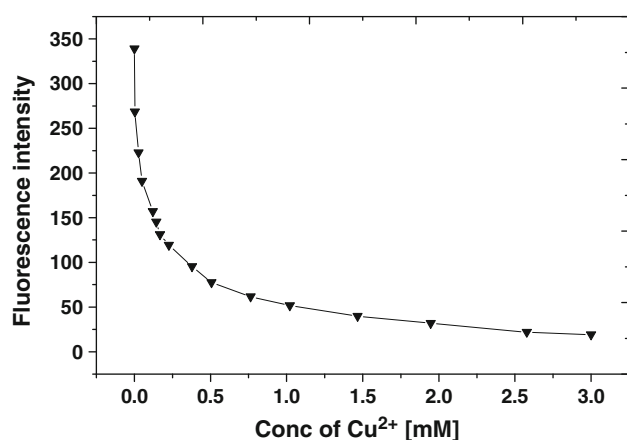
To check the interferences from other metal ions on the fluorescence signaling of Cu^{2+}, a competitive fluorescence experiment was performed by adding 100 equivalent of Cu^{2+} to the ACN solutions carrying 1000 equivalent of individual metal ions. As shown in Figs. 4, 5 prior to the addition of Cu^{2+}, the fluorescence intensity of the probe is only marginally affected. However, addition of Cu^{2+} causes a uniformly high fluorescence quenching in the range of 85–95%. This experiment clearly demonstrates that even in higher concentrations, the presently studied metal ions do not pose significant interferences in the fluorescent detection of Cu^{2+}. Inspite the high selectivity of Anthrox towards Cu^{2+}, a limitation of the probe is its inherent low sensitivity on account of the its very low quantum yield.

Comments on Cu^{2+} binding interaction

The probe, Anthrox has been found to serve as a highly selective chemosensor, offering naked eye detection by color bleaching as well as fluorescence 'turn-off' signaling in the presence of Cu^{2+}. Noteworthily, trace biological metal ions Zn^{2+}, Mg^{2+} and Co^{2+}, abundantly existing cellular ions, Na^+, K^+ and Ca^{2+}, as well as toxic, Cd^{2+}, Pb^{2+} and Hg^{2+} displayed none or negligible binding interactions. As far as fluorescence quenching alone is concerned, one can rationalize it by taking into account the paramagnetic nature of Cu^{2+}. However, in the present circumstance the fluorescence quenching cannot be considered in isolation, since it is also accompanied by the absorbance bleaching, a feature which is essentially rooted in the ground state interaction. Consequently, the observed quenching in the presence of Cu^{2+} may not be simply the result of either electron or energy transfer mechanism, operating only in the excited states [48]. Based on this
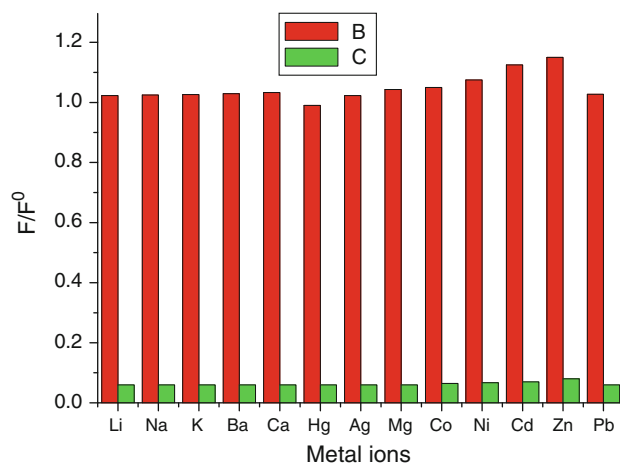

Fig. 4 Variation in fluorescence intensity of a solution of Anthrox (2.83×10^{-5} M) in CH_3CN at 416 nm as a function of change in Cu^{2+} ion concentration

Fig. 5 Fluorescence response of Anthrox (2.83×10^{-5} M) in the presence of Li^+, Na^+, K^+, Ba^{2+}, Ca^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Ag^+, Pb^{2+} and Hg^{2+} (2.83×10^{-2} M) alone and after adding of $Cu(ClO_4)_2$ (2.83×10^{-3} M) in CH_3CN

reasoning, we propose that the fluorescence quenching may be a direct consequence of the absorbance bleaching.

Though, precedence for the absorbance bleaching has been earlier encountered by Kumar et al. in their study of certain anthracene based Cu^{2+} chemosensor [49], however no explanation was offered regarding the mechanism of the absorption bleaching. The cation-π interaction, a noncovalent electrostatic interaction between a cation and π-electron-rich systems is increasingly recognized as an important force influencing the structures and functions of molecules including proteins. Unlike other metal cations, up until recently Cu^{2+} was believed not to participate in a cation-π interaction because of its tendency to oxidize the π-electron rich systems. However, a recent report provides the first direct spectral evidence for the reversible cation-π interaction between Cu^{2+} and the electron rich indole ring of tryptophane [50]. In the present case, the interaction of Cu^{2+} with the probe is reversible, meaning the interaction does not lead to any chemical reaction. Thus, on grounds of the absorbance bleaching and the reversible nature of the Cu^{2+} binding interaction, the possibility of the involvement of noncovalent anthracene-Cu^{2+} interaction in this intriguing phenomenon can not be ruled out. Such an interaction might disrupt the electronic transition and cause the absorption due to the anthracene chromophore to vanish.

Conclusion

In conclusion, we have synthesized a new optical probe, Anthrox which offers highly selective and fast chromo- and fluorogenic 'turn-off' signaling responses in the presence of Cu^{2+}. Our work demonstrates that oxadiazole motif can be exploited as a binding motif to design Cu selective chemosensors. By contrast, the probe exhibits none or negligible optical sensitivity towards various metal ions of biological and or environmental significant such as Li^+, Na^+, K^+, Ba^{2+}, Ca^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Ag^+, Pb^{2+} and Hg^{2+}. Consequently, these metal ions pose no detectable interference in targeting Cu^{2+}. In spite the excellent selectivity, its organic working medium forms a limitation for biological studies, though potential is available for environmental sensing applications. Work is in progress to modify the present design by replacing the anthracene with other suitable fluorophores to render the probe compatible for aqueous measurements.

Experimental

Metal perchlorates were prepared as described in the literature and dried under vacuum prior to use. The chemicals and spectral grade solvents were purchased from S.D. fine Chemicals (India) and used as received. IR spectra were recorded on Shimadzu FTIR-420 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ solution on a Bruker 300 MHz spectrometer with TMS as an internal standard. Elemental analyses were performed on Carlo Erba instrument EA-1108 Elemental analyzer. UV–vis spectra were recorded on Jasco V-530 UV–vis spectrophotometer and fluorescence spectra were recorded on Hitachi F-4500 Fluorescence spectrophotometer. The slit width was set at 3 nm for both excitation and emission and the PMT detector voltage was 700 V.

Preparation of 2-(chloromethyl)-5-(4-t-butylphenyl)-1,3,4-oxadiazole (2)

To a solution of chloroacetyl chloride (0.626 mL, 7.8 mmol) in dry $CHCl_3$ (20 mL) was added 4-t-butyl benzoic acid hydrazide (1.5 g, 7.8 mmol) and the reaction was heated on water-bath for about 2 h till evolution of HCl gas ceased. At this time, freshly distilled $POCl_3$ (1 mL, 9.5 mmol) was added all at once and the reaction continued to be refluxed for further 3 h to effect the cyclization of the intermediate dihydrazide. After cooling to room-temperature, the reaction mixture was poured carefully over crushed ice and the mixture was treated with gradual addition of solid Na_2CO_3 till basic. The basified reaction mixture was refrigerated to deposit a brown solid, which was collected by filtration. The filtered solid was thoroughly washed with water and air dried. Crystallization from $CHCl_3$- petroleum ether (1:3) afforded chloromethyl oxadiazole (2) as a colorless solid in 62% yield (1.08 g) mp 152–155 °C; IR (KBr)/cm^{-1} : 3033, 2966, 1616, 1586, 1569, 1495, 1416, 1362, 1251, 1112, 1083, 1011, 841, 758, 708, 647 and 554; ^{1}H-NMR ($CDCl_3$) δ : 7.92 (d, 2H, $J = 7.2$ Hz Ar–H), 7.49 (d, 2H, $J = 7.2$ Hz Ar–H), 4.67 (s, 2H, Ar–CH_2–Cl), 1.38 (s, 9H, Ar–$C(CH_3)_3$). Anal. Calcd for $C_{13}H_{15}ClN_2O$: C, 62.27; H, 5.98; N, 11.17; Cl, 14.17. Found: C, 62.35; H, 6.05; N, 11.23; Cl, 14.24%.

Preparation of N-benzyl aminomethyl anthracene (3)

9-anthraldehyde (515 mg, 2.5 mmol) was condensed with benzyl amine (0. 28 mL, 2.5 mmol) in absolute ethanol (10 mL) by heating the mixture on water-bath for 1 h. On cooling the reaction mixture, the crude Schiff base precipitated out as a light yellow solid. Without further purification, the crude Schiff base was reduced in dry THF by portion-wise addition of $NaBH_4$ (114 mg, 3 mmol) during 30 min at room temperature. The reaction, after stirring for 5 h was poured in water and the precipitated solid filtered, washed with water and air dried. Crystallization from alcohol gave the product 3 in 81% yield (480 mg) mp 262–

265 °C; IR (KBr)/cm^{-1}: 3057, 2905, 2779, 1583, 1438, 1412, 1262, 1210, 1006, 968, 952, 890, 785 and 732; ^{1}H-NMR (CDCl$_3$) δ: 8.3 (s, 1H, Ar–H), 8.06–7.3 (m, 13H, Ar–H), 4.88 (s, 2H, Ar–CH$_2$–N–), 4.16 (s, 2H, Ar–CH$_2$–N–). ^{13}C-NMR (DMSO-d$_6$) 40.77, 41.73, 51.13, 123.55, 124.67, 125.88, 127.35, 129.15, 129.47, 129.56, 130.16, 131.06, 131.10, 131.26, 132.37. Anal. Calcd for C$_{22}$H$_{19}$N: C, 88.88; H, 6.39; N, 4.71. Found: C, 89.06; H, 6.42; N, 4.83%.

Synthesis of chemosensor, Anthrox

N-benzyl aminomethyl anthracene **3** (445 mg, 1.5 mmol), chloromethyl oxadiazole derivative **2** (376 mg, 1.5 mmol), K$_2$CO$_3$ (150 mg) and KI (250 mg) were refluxed in dry acetone for 48 h. After cooling to room temperature, the reaction mixture was filtered to remove insoluble inorganic salts and the filtrate was concentrated. The crude solid product was subjected to purification by SiO$_2$ column chromatography using CHCl$_3$: methanol (98:2) as eluant. The target product, Anthrox was obtained as a yellow solid in 58% yield (446 g), mp 174–176 °C; IR (KBr)/cm^{-1}: 3050, 2958, 1615, 1583, 1559, 1496, 1445, 1366, 1252, 1208, 1110, 1011, 957, 889, 857, 730; ^{1}H-NMR (CDCl$_3$) δ: 8.45 (m, 3H, Ar–H) 8.0 (d, 2H, 5.7 Hz, Ar–H), 7.92 (d, 2H, 6.3 Hz, Ar–H), 7.54 (d, 2H, $J = 6.3$ Hz, Ar–H), 7.46 (m, 4H, Ar–H), 7.30 (m, 5H, Ar–H), 4.88 (s, 2H), 3.99 (s, 2H), 3.92 (s, 2H), 1.38 (s, 9H, Ar–C(CH$_3$)$_3$). Anal. Calcd for C$_{35}$H$_{33}$N$_3$O: C, 82.19; H, 6.45; N, 8.21. Found: C, 82.25; H, 6.55; N, 8.24%. ^{13}C-NMR (DMSO-d$_6$) 31.27, 35.27, 46.71, 50.12, 57.01, 121.16, 125.25, 125.50, 126.34, 126.68, 126.74, 127.58, 128.13, 128.60, 129.14, 129.33, 129.67, 131.35, 131.40, 138.81, 155.28, 164.22, 164.52.

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