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Graphical Abstract

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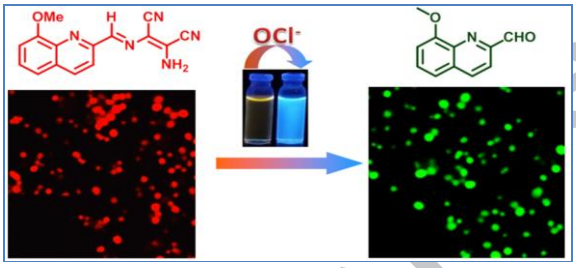
Sangita Das,[a] Krishnendu Aich,[a] Lakshman Patra,[a] Kakali Ghoshal,[b] Saswati Gharami,[a] Maitree Bhattacharyya[b] and Tapan Kumar Mondal [a]*



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ABSTRACT

Increased oxidative stress in metabolic complications like type 2 diabetes, dyslipidemia and cardiovascular disorders exerts potential health hazards in many facets. Enhanced production of reactive oxygen species (ROS) due to increased oxidative stress promotes the damage of many biologically important macromolecules. Hypochlorous acid (HOCl), a microbicidal agent is also known to be an important ROS sub-species. An enhanced generation of endogenous HOCl due to diseased condition therefore can be detrimental to health. In present work, a new quinoline-diaminomaleonitrile based probe (HQMN) has been designed for the selective detection of hypochlorite. The probe in hand shows a selective ratiometric emission change towards OCl^-. The probe behaves as a highly selective and sensitive tool for the detection of OCl^- over other analytes with a fast response time (within 100 sec). Bioimaging study revealed that HQMN can detect endogenous OCl^- in human monocytes and an increase in endogenous HOCl concentration has been witnessed in diabetic condition compared to healthy control. Thus HQMN can be used as an excellent fluorescent probe for dynamic tracking of hypochorite in living biological cells especially to identify diabetic conditions.

Introduction

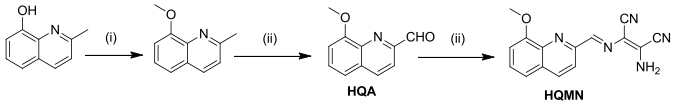
Hypochlorous acid (HOCl) acts as one of the most powerful microbicidal agent in the innate immune system,[1] which is slightly acidic and under physiological pH solutions it partially dissociates to give the hypochlorite ion (OCl^-).[2] In living organisms, the endogenous hypochlorite is produced predominantly from the peroxidation of chloride ions catalyzed by the heme enzyme myeloperoxidase (MPO)[3]. The produced hypochlorite is generally localized in activated macrophages, neutrophils and monocytes.[4] Hypochlorite plays crucial roles in human immune defence system by demolition of invading bacteria and pathogens.[5] Therefore, an enhanced endogenous HOCl can indicate a variety of diseases including type 2 diabetes mellitus[6], dyslipidemia[6], cardiovascular diseases,[7] neuron degeneration,[8] arthritis,[9] and cancer.[10] Type 2 diabetes mellitus, a metabolic complication is increasing rapidly across the globe causing death worldwide[11]. It is believed that type 2 diabetes increases endogenous HOCl by increased MPO as well as H_2O_2 generation in both monocytes and neutrophils, two predominant white blood cells[10]. Therefore, significant effort has recently been focused on the fabrication of switches which can selectively detect HOCl in biological systems. A number of sensitive and selective analytical methods have been proposed for conducting such research.[12] Recently, a few fluorescence probes for OCl^- have been reported based on the strong oxidation property of it.[13] Motivated by the above mentioned pioneering works, herein, we report the synthesis, photophysical characterization and cellular imaging experiments of the quinoline-diaminomaleonitrile based chemodosimeter system (HQMN) which can selectively detects hypochlorite ion in a unique ratiometric manner. This is an in-situ approach where the target molecule (HQMN) reacted with the ROS (OCl^-) to form the adduct (HQMN-OCl^-), which on further hydrolysis liberated the dye (diaminomaleonitrile). The signalling approach was accomplished by a unique inorganic ion-induced dye releases method. We investigated that the probe in hand (HQMN) can detect not only hypochlorite selectively in presence of other ROS and guests but can also detect intracellular hypochlorite released in living blood cells. Bioimaging study also revealed that HQMN can effectively detect endogenous hypochlorite in living monocytes isolated from normoglycemic healthy control and type 2 diabetic subjects. We propose that novel probe HQMN is an excellent fluorescent marker to detect endogenous HOCl and can be used extensively in disease detection especially diabetes. These results suggest that the probe (HQMN) is an efficient one which can distinguish diabetic cells from normal cells by hypochlorite-induced dye releases method.

Results and discussion

Synthesis of the probe (HQMN)

The synthetic procedure for the synthesis of the probe (HQMN) is outlined in Scheme 1. 8-methoxyquinoline-2-carbaldehyde (HQA) is prepared by following literature procedure.[14] Condensation of HQA with 1,2-diaminomaleonitrile affords the probe (HQMN) as yellow crystalline solid. Detailed

synthetic procedure is given in experimental section. The chemical structure of the probe is characterised through ^{1}H NMR, ^{13}C NMR and HRMS (Fig. S7- Fig. S9, Supporting Information).



Scheme 1: Reagents and conditions: (i) CH_3I, K_2CO_3, TBAB, acetone, reflux, 8 h. (ii) SeO_2, 1,4-dioxane, reflux, 4 h. (iii) 1,2-diaminomaleonitrile, ethanol, reflux, 4 h.

Photophysical Study

UV-vis study

We first investigated the spectroscopic properties of the probe (HQMN) in mixed aqueous solvent (H_2O/MeOH, 1/1, v/v, 1 mM PBS, pH=7.1). In order to test the selectivity of HQMN (10 μM), UV-vis and fluorescence titration experiments were performed by using various interfering analytes (S^{2-}, N_3^-, NO_2^-, NO_3^-, H_2O_2, I^-, Cl^-, F^-, OCl^-, SO_4^{2-}, $ONOO^-$, $O_2^{\cdot-}$, and ^{t}BuOOH).

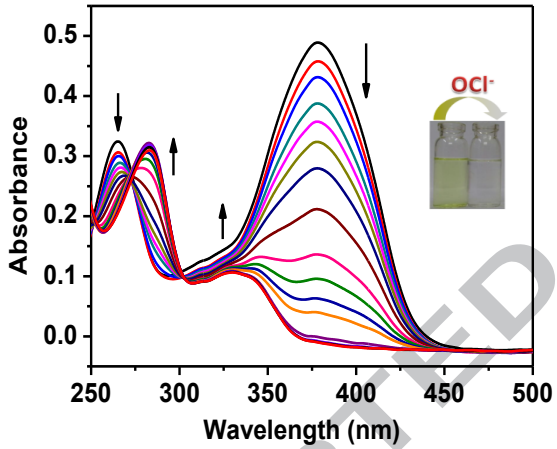


Figure 1: (a) Absorption spectra of HQMN (10 μM) upon gradual addition of OCl^- (0-25 μM) in Methanol/H_2O (1/1, v/v) solution.

In absence of any guest analyte, the probe (HQMN) itself showed two absorption bands at 263 nm and 378 nm in mixed aqueous media (10 μM, H_2O/MeOH, 1/1, v/v, 1 mM PBS, pH=7.1). We found that a prominent change in color from yellow to colourless was observed only after addition of OCl^-. Deep investigation of the probe towards hypochlorite was done by incremental addition of OCl^- to a light yellow solution of HQMN (10 μM). Consequently, the peak at 378 nm and 263 nm gradually decreased whereas two new peaks centred at 282 nm and 330 nm were formed with two well defined isosbestic points at 272 nm and 300 nm (Fig. 1). Colorimetric change of HQMN was investigated in the presence of several ROS and other guest analytes of interest, but OCl^- was the only reactive species that caused significant change in the UV-vis profile (Fig. 2). Subsequently, the yellow colored solution of HQMN was drastically changed to colourless. We presumed that the color change could be attributed to the oxidation of imine bond followed by hydrolysis into its corresponding aldehyde derivative, HQA (Scheme 2). A good linear relationship was observed of HQMN at absorbance 378 nm with the concentrations of OCl^- (0–14.3 μM) added with a very good R^2 value = 0.99 (Fig. S2, Supporting Information).

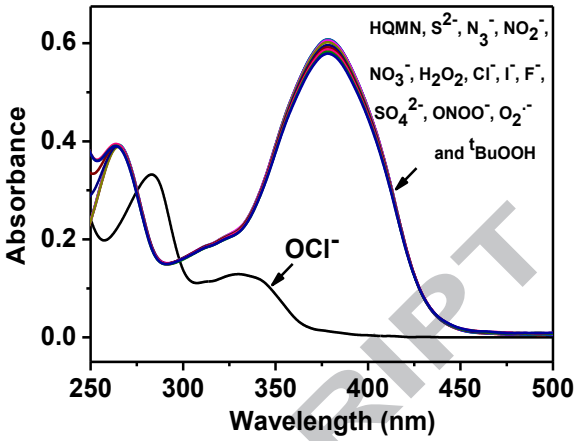


Figure 2: Absorption spectra of HQMN (10 μM) upon addition of different guest analytes (30 μM) in Methanol/H_2O (1/1, v/v) solution.

Fluorescence study

The fluorescent response of HQMN towards hypochlorite was investigated in the same condition as that of maintained in UV-vis study. The free sensor only exhibited a strong emission peak at 572 nm upon excited at 370 nm (Fig. 3). There was no typical emission at around 468 nm, indicates no dye have been released yet and the diaminomaleonitrile, the acceptor portion in the imine funtionalised form was stable in the assay condition.

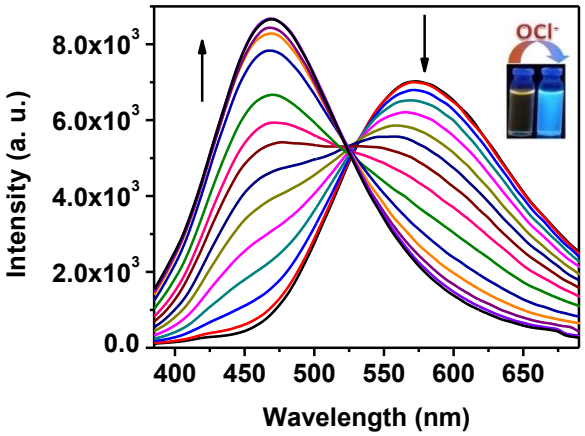


Figure 3: Emission spectra of HQMN (10 μM) upon gradual addition of OCl^- (0-20 μM) in methanol/H_2O (1/1, v/v) solution. λ_{ex} = 370 nm.

After exposure of hypochlorite a sharp contrast was observed, which was shown in Fig. 3. On addition of OCl^-, the fluorescence intensity at around 572 nm diminished significantly whereas a new blue-shifted emission band was appeared at around 468 nm. Consequently, a change in emission colour was observed from light orange to cyan which is observable through naked eyes after irradiation under UV light (Fig. 3, Inset). A ratiometric spectrum was obtained with increasing concentration of hypochlorite, the peak at 572 nm gradually decreases and the peak at 468 nm progressively increases with a well-defined isoemissive point appeared at 526 nm. There is a remarkable difference in the two emission wavelengths is observed (shift of emission wavelength: ΔF = 104 nm). This high ΔF value contributes to the accurate measurement of the intensities of the two emission peaks.

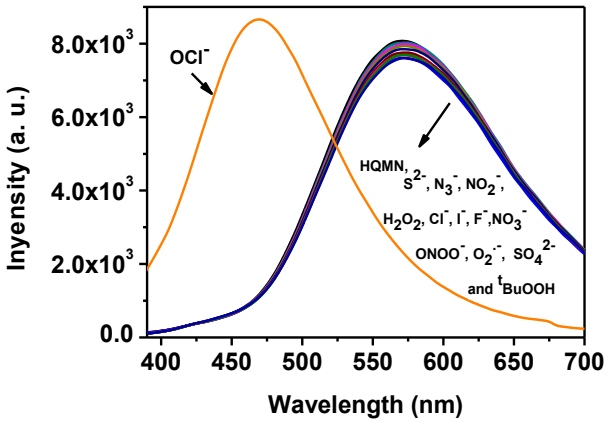


Figure 4: Emission spectra of HQMN (10 μM) upon addition of different guest analytes (20 μM) in methanol/H_2O (1/1, v/v) solution. λ_{ex} = 370 nm.

The beauty of such type of ratiometric spectrum is that it minimise the background signal with high ratiometric value. It was observed that the ratio of the emission intensities at the two wavelengths (I_{468}/I_{572}) exhibits a good linearity with the concentration of OCl^- from 0–8 μM (Fig S4b, ESI). Essentially, these changes became constant when the amount of OCl^- added reached to 8 μM, after that a plateau was reached, indicating the occurrence of saturation. Even excess amount of hypochlorite did not change the emission profile of the probe (Fig. 4). The detection limit of the probe for OCl^- was determined from the fluorescence spectral changes and was found to be 7.87×10^{-7} M indicating that the probe is highly sensitive to hypochlorite. The detection limit was calculated by using the equation DL = K × Sb_1/S, where K = 3, Sb_1 is the standard deviation of the blank solution and S is the slope of the calibration curve.[15] Next, in order to examine the selectivity of HQMN, we have measured its fluorescence response upon treatment with various analytes. Especially, the addition of other co-existing analytes, even in excess amounts, caused insignificant changes in the emission intensity of the probe (Fig. 4). Quantum yield of HQMN before and after reaction with OCl^- are determined using anthracene (Φ = 0.27 in ethanol) as standard and found to be 0.12 and 0.34 respectively.

Selectivity study

In order to evaluate the specificity of the probe in hand (HQMN) towards hypochlorite anion, the influence of other co-existing anions and oxidants was investigated.

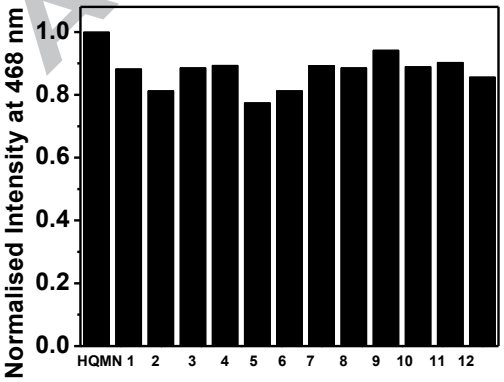


Figure 5: A comparative study of emission intensity after addition of different analytes (3 equivalents each, 1=S^{2-}, 2=NO_2^-, 3= NO_3^-, 4 = H_2O_2, 5 = N_3^-, 6 = I^-, 7 = SO_4^{2-}, 8 = F^-, 9 = $ONOO^-$, 10 = $O2^{\cdot-}$, 11 = ^{t}BuOOH and 12= Cl^-) in the solution of HQMN in presence of OCl^- (2 equivalents).

To examine this, competing experiment was performed by adding OCl^- (2.0 equiv.) in presence of other guest analytes (3.0 equiv.). As shown in Fig. 5 there was almost no change in the emission intensity at 468 nm upon addition of other above mentioned anions in presence of OCl^-. This observation suggests that HQMN specifically detects OCl^- in presence of other anions and oxidants. The studies clearly revealed the detection of OCl^- was not hampered even if other guest analytes are present in excess amounts.

Kinetics study

Reaction kinetic study is a very important parameter to evaluate the performance of any chemodosimeter. The time course of the fluorescence intensity ratio at I_{468}/I_{572} with time was studied by means of fluorescence experiment (Fig. 6). The reaction time required for the interaction between HQMN and OCl^- was monitored after the addition of 2 equivalents of OCl^-. Upon introduction of OCl^-, a significant enhancement in the emission intensity was noticed, and the intensity essentially reached maximum within 70 sec. (Fig. S4, Supporting Information). The entire reaction completed within 100 sec. This indicates that HQMN responds towards OCl^- very rapidly and the sensor may have potential for monitoring of OCl^- in real time.

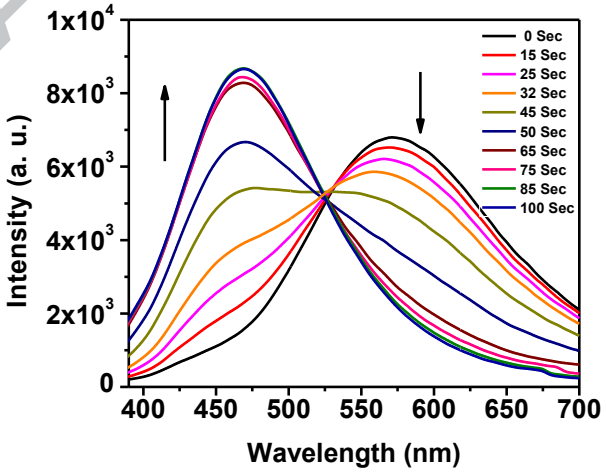
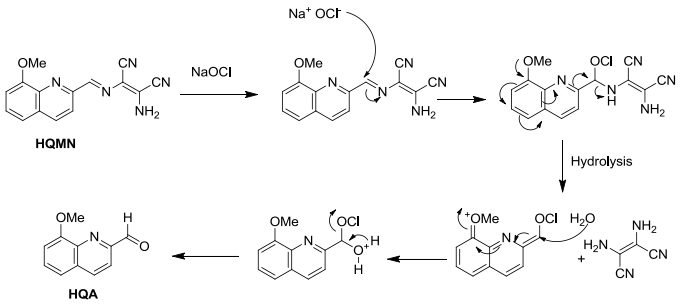


Figure 6: Emission spectra of HQMN (10 μM) after addition of OCl^- (20 μM) depending on time (0-100 sec) in Methanol/H_2O (1/1, v/v) solution. λ_{ex} = 370 nm.

Sensing mechanism

To examine the reaction mechanism of HQMN with OCl^-, the product was carefully analyzed by ^{1}H NMR (Figure S10, Supporting Information). The reaction of HQMN with OCl^- produced a new peak at about δ = 10 ppm, which may be assigned as oxidative decomposition products, the corresponding aldehyde (HQA). This result strongly indicates that HQMN experienced oxidative attacked by OCl^- to imine double bond to form corresponding aldehyde (HQA), which later may lose the diaminomeleonitrile unit. This reaction is further facilitated by the electron-donating effect of the lone pair on the O- atom (of methoxy group) through conjugation that accelerates the nucleophilic attack by H_2O with the elimination of 1,2-diaminomaleonitrile forming the HQA (HQMN-OCl^-) molecule (Scheme 2). The plausible mechanism of the interaction between HQMN and OCl^- is presented in Scheme 2.



Scheme 2: Possible mechanism of the response of HQMN towards hypochlorite (OCl^-)

Computational study

To understand the relationship between the structural changes of HQMN to HQMN-OCl^- (HQA) on addition of OCl^- and their electronic spectra, density functional theory (DFT) and time-dependent density functional theory (TDDFT) calculations were carried out using B3LYP/6-31+G(d) method in Gaussian 09W, Revision D.01 program and visualized using Gauss view program.

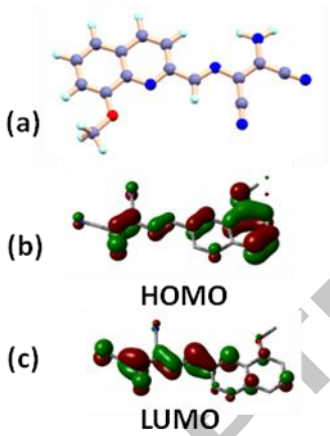


Figure 7: Optimized structure, HOMO and LUMO orbitals of HQMN calculated at the DFT level using the B3LYP/6-311G+(d,p) basis set.

The optimized geometry and the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of HQMN are shown in Figure 7. Contour plots of some selected molecular orbitals of HQMN and HQA are given in Fig. S5 & Fig. S6 (Supporting Information) respectively. For TDDFT calculation, solvent correction was incorporated by CPCM model and methanol was chosen as the solvent. The calculated absorption spectra show peaks at 447 nm (f = 0.3587) and 380 nm (f = 0.7929) for HQMN, which are due to HOMO-1 to LUMO+2 and HOMO to LUMO+2 transitions, respectively. However, for HQA, HOMO to LUMO transition is appeared at 379 nm (f = 0.0567) along with a strong transition at 253 nm (f = 0.5423) corresponds to HOMO-2 to LUMO transition (Table S1, Supporting Information).

Fluorescence life time

A nano second time-resolved fluorescence technique has been adapted in order to examine the excited state behaviour of our probe HQMN sensor and its reaction based product with hydrazine in CH_3OH solvent (Fig. 8). The radiative rate constant (k_r) and the total non-radiative rate constant (k_{nr}) of HQMN and HQMN-OCl^- species were calculated according to the equations[16] $\tau^{-1} = k_r + k_{nr}$, where $kr = \Phi_f/\tau$. For HQMN, τ = 0.606 ns ($\varkappa^2$ = 1.012) and HQMN- OCl^-, τ = 5.815 ns ($\varkappa^2$ = 1.094). The fluorescence decay curves of HQMN and the HQMN-OCl^- compounds were fitted by utilizing the mono and bi-exponential functions respectively with the acceptable $\varkappa^2$ values. The change in emission life time is attributed to the reaction of OCl^- with HQMN to form a new fluorescent compound HQMN-OCl^- (HQA) (Table S2, Supporting Information).

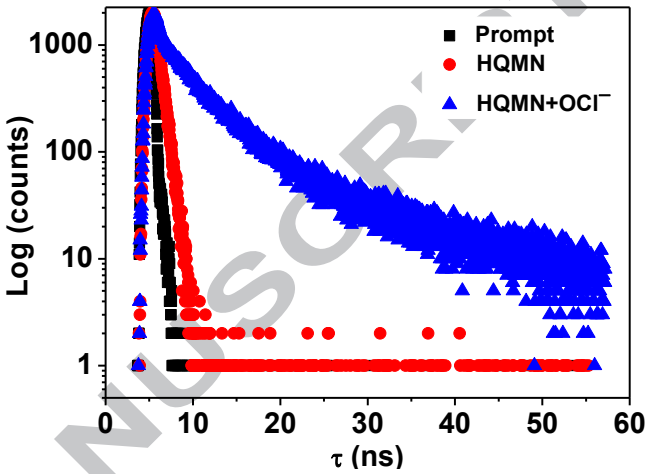


Figure 8: Time-resolved fluorescence decay of HQMN (Red), HQMN-OCl^- (blue), and prompt (black). λ_{ex} = 370 nm.

Bioimaging study

HQMN is an excellent endogenous probe for imaging of biological samples for its permeability, stability and non-toxic nature. Figure 9 depicts the bio-imaging of human monocytes by HQMN in diabetic and control conditions. Our previous study suggests that diabetic condition enhances the generation of endogenous HOCl.[6] In this present research, monocytes of healthy control subjects shows lower endogenous HOCl concentration as shifting of fluorescence intensity from red to green is poor. But in diabetic condition there is a significant enhancement of green fluorescence intensity indicating higher hypochlorous stress.Herein, we are interested to distinguish between normal and diabetic blood cells through their different behaviour towards the probe HQMN.

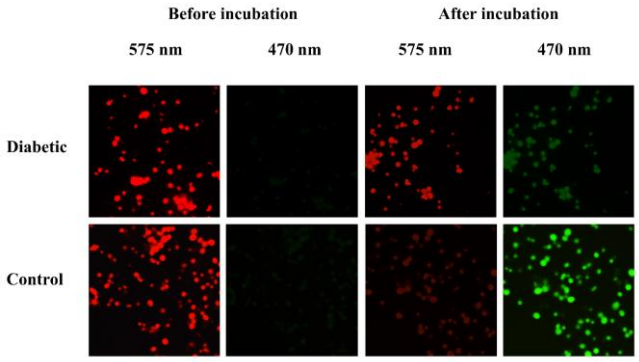


Figure 9: Human monocytes (40X) from diabetic and control subjects treated with 20 μM HQMN under fluorescence emissions of 575 nm and 470 nm respectively. Images were captured before and after 50 minutes of incubation at dark showing significant enhancement of endogenous HOCl in diabetic condition.

To explore the average fluorescence intensity, we have used Olympus Fluoview FV 1000 software. The data is provided in table S3 (Supporting Information). From the experimental value we can easily observe that the green/red ratio is significantly lower in samples containing normal blood cells (0.187) where its value is much higher (3.048) in case of diabetic cells (after incubation of 50 minutes). This green/red florescence ratio strongly suggests that hypochlorite production takes place much higher concentration in diabetic blood cells compared to normal blood cells. Thus, the probe in hand (HQMN**)** is an extremely innovative fluorescence tool which may be employed to detect diabetic cells over normal blood cells in term of HOCl production.

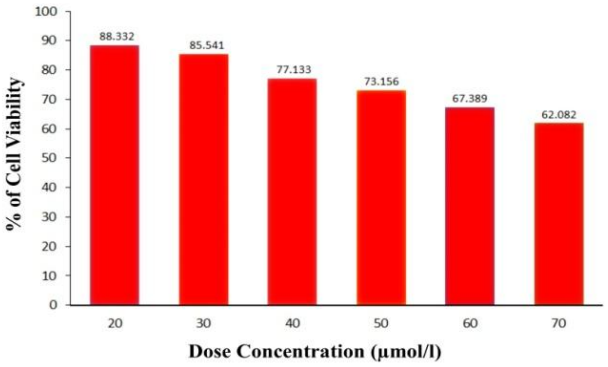


Figure 10: Percentage of viable cells over HQMN concentration range (20-70 µM).

Cell viability is represented in Figure 10, where up to 70 µM concentrations of HQMN shows around 62.082% of viable cells predicting it is a safe probe to use in a biological system. We have used 40 µM HQMN solutions for imaging which shows fairly high number of viable cells (77.133%) concluding its nontoxic nature. Cell viability is represented in Figure 8, where up to 70 µM concentrations of HQMN shows around 62.082% of viable cells predicting it is a safe probe to use in a biological system. We have used 40 µM HQMN solutions for imaging which shows fairly high number of viable cells (77.133%) concluding its nontoxic nature.

Application of the probe as a portable kit

Inspiring by the prompt response ability of HQMN towards OCl^-, we are interested to establish its potential application by using HQMN (absorbed in a solid surface) as a portable kit for sensing OCl^-. So as to execute this application, we have prepared HQMN solution in methanol. To perform this reaction we have dipped TLC plate into the HQMN solution (5×10^{-5} M) and let the TLC plates dry in air.

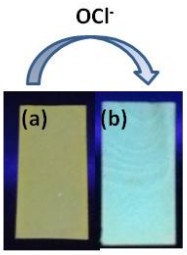


Figure 11: Emission color changes of HQMN on TLC plate in (a) absence and (b) presence of OCl^- under UV light.

Now in order to examine the sensitivity towards OCl^-, we immersed that TLC plate into the solution of OCl^- (5×10^{-5} M) and again the plate dried in air. Now a clear change in the color of the TLC plate was observed before and after interation with OCl^-. The color of the TLC plates thus changes from dull yellowish-green to deep cyan under hand-held UV-light (Figure 11). Thus this experiment strongly suggests HQMN can be employed as a real time monitoring device which sufficiently marks OCl^- qualitatively.

Conclusions

In this study, a new quinoline-diaminomaleonitrile based fluorescence probe HQMN was synthesized and characterized. The chemodosimeter HQMN displayed a high selectivity and sensitivity for hypochlorite ion. The chemodosimetric attack from the oxygen atom of OCl^- to the imine carbon forms HQMN-OCl^- complex, which was further hydrolysed to give the corresponding aldehyde (HQA). This chemodosimeter exposed a light orange fluorescence, which was blue shifted to cyan after addition of OCl^- ion with a LOD in 10^{-7} M range. Furthermore, we carried out live-cell imaging, by using human white blood cells (monocytes). We have witnessed an enhanced generation of endogenous HOCl in diabetic condition compared to healthy control. Therefore, probe HQMN can be utilized as an excellent novel fluorescence probe to identify endogenous HOCl concentration in living cells.

Acknowledgments

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Highlights:

- A new quinoline based probe has been designed for selective detection of OCl^-.
- The probe (HQMN) can detect OCl^- with a fast response time (within 100 sec).
- HQMN can detect endogenous OCl^- in human monocytes.
- HQMN can be used to track OCl^- in living cells to identify the diabetic conditions.

Graphical Abstract:

A new new quinoline-diaminomaleonitrile based probe was synthesised for the selective and ratiometric endogenous screening of OCl^- in living diabetic blood cells.