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Current State of Art of Diaminomalenonitrile Based Synthetic Receptors for Ion Sensing With Bio Applications: Mechanistic, Sensing and Photophysical Aspects

Masood Ayoub Kaloo[1]* and Bilal A Bhat[2]

Abstract

To the best of our knowledge, only a few number of single molecule based receptors synthesized from Diaminomalenonitrile (DAMN) have been explored and developed as highly selective and sensitive recognition motifs for cations and anions in a organic, aqueous or mixed solvent system. The interaction between such receptors and ions has been reported with remarkable alteration in absorption and fluorescence properties of the molecule. The signal transduction is prompt, and attributed to the modulation of Internal Charge Transfer (ICT) and/or Photo Induced Electron Transfer (PET) processes within the molecule. In this review, we have compiled whole literature about recognition of ions via DAMN based molecular receptors possessing biological applications including live cell imaging. Emphasis has been diverted to summarize and briefly discuss signal response, operation of solvent, selectivity, binding affinity and detection limit. In addition to this, some of the crucial design considerations, such as choice of fluorophore, tuning of electronic effects and mechanism of operation are momentarily discussed.

Keywords: Diaminomalenonitrile; Receptor; Sensing; Photophysical; Colour; Fluorescence

Introduction

Owing to critical role of ions (cations and anions) in myriad of process of biological, chemical and environmental significance, considerable attention has been paid towards the development of single molecule based detection methods [1,2]. In this direction, a library of cation and anion sensing molecules "receptors" have been proposed [3,4], and continues to be a key theme in modern chemistry and biochemistry [5-7]. This can be attributed to the fact that molecular receptors are highly valuable tools to perform *in situ* monitoring in real time, amid high selectivity and sensitivity. Most importantly, synthetic receptors are usually reusable, easy to operate and realize high sample through output [8]. A number of interactions, such as hydrogen bonding, electrostatic force, metal-ligand coordination, hydrophobic and vander Waals forces have been employed to develop novel and effective receptors [9-11].

Nowadays the field of molecular recognition has reached a stage where one can confidently design and synthesize a specialized receptor with a good degree of predictability and selectivity for many kinds of small or medium-sized ions [12]. In this direction, use of a wide variety of N-H polarization based molecular functionalities in the form of amides, ureas, thioureas, ammonium, imidazole, and Imidazolium based systems have been proposed [13-18]. Besides, chemical reaction based chemodosimetric and/or coordination approaches utilizing functional materials with rhodamine, coumarin, BODIPY, hemicyanine, calixpyrrole, oxazine, naphthalimide, hemicyanine, azo zincon and benzofuran based molecular units have also been reported [19,20].

However, in recent times, receptors constructed from DAMN backbone have emerged to be of significant importance in chemical, biological, and environmental assays. These molecules besides being robust, exhibit selective response to specific ions or neutral species. Some of the excellent examples of receptors from DAMN for various analytes (ions) have been prepared and studied for application in physiology, medical diagnostics and in imaging. To the best of our knowledge, no such work has been

Affiliation:
[1]*Department of chemistry, Islamic University of Science and Technology Awantipora, Pulwama, India*
[2]*Department of chemistry, Govt. Degree College, Shopian, India*

***Corresponding author:**
Masood Ayoub Kaloo,
Department of chemistry, Islamic University of Science and Technology Awantipora, Pulwama, India. Tel: +91-8491857406
E-mail: masood.kaloo@islamicuniversity.edu.in

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reported wherein current state of art of DAMN based receptor platform has been reviewed along with its biological applications. Thus herein, we have tried to compile such class of synthetic receptors with biological and live cell imaging applications. These receptors include Phenothiazine-DAMN, Rhodamine-DAMN, Azo-azomethine-DAMN, Phenanthroimidazole-DAMN, Triphenyl Schif base-DAMN.

Synthetic receptors

Phenothiazine-DAMN: Sekar *et al.* studied fluorescent properties of phenothiazine-DAMN synthetic receptor in the presence of various metal ions in solution (ethanol–water, 6:4, V/V) [21]. The designed receptor displayed intense emission signal at 550 nm upon excitation at 425 nm. Upon the addition of Hg^{2+}, quenching of emission band at 550 nm was observed. The results were ascribed due to an ICT (internal charge transfer) process. Complexation of Hg^{2+} results in the inhibition of original ICT process from N-Hexyl Phenothiazine group to the diaminomalenonitrile moiety (Figure 1). The detection limit (DL) for Hg^{2+} was found to be 17.8×10^{-9} M. The binding constant of receptor with Hg^{2+} was found to be 4.18×10^{4} M^{-1}**.** Furthermore the probe was also utilized for fluorescence imaging of Hg^{2+} in living cells. To test the capability of **1** and explore its imaging application in living cells, cancer cells were incubated with receptor **1** for 30 min at room temperate, and then it was treated with $HgCl_2$ for 10 min. The fluorescence image became dim and quenches, implying that the intracellular uptake of Hg^{2+} ions complexed with **1** and a yielded non-fluorescent ensemble. Upon further incubation of cells with S^{2-} (20 μM) for 10 min, green fluorescence image was recovered, indicating that the uptake of S^{2-} resulted in the decomplexation of intracellular [receptor + Hg^{2+}] ensemble to fluorescent receptor. Therefore, the '*on–off–on*' fluorescence imaging of receptor was accomplished in cancer cells. These findings showed that the designed receptor **1** is biocompatible in nature and can be used for detecting Hg^{2+} and S^{2-} ions in cells.

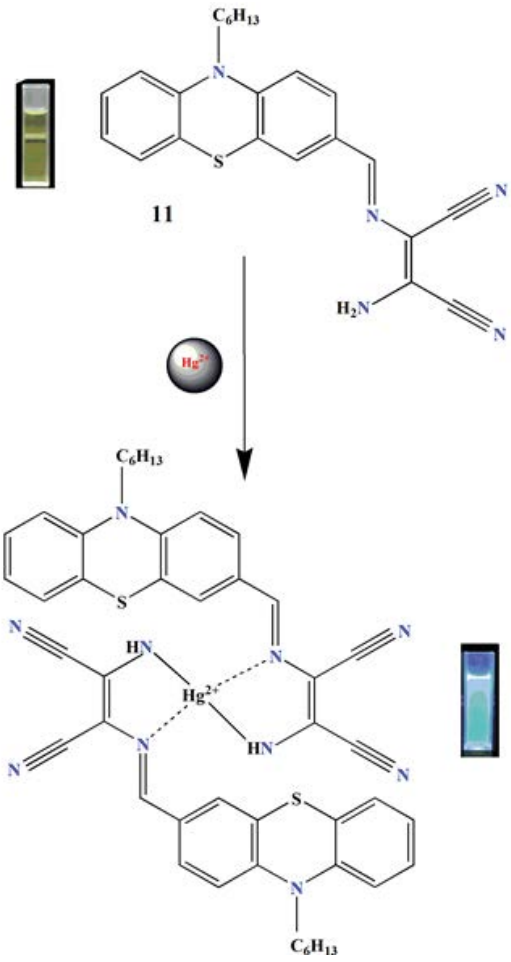

Figure 1: Structure of receptor 1 and its complexation with Hg^{2+} with Fluorescence response shown.

Rhodamine-DAMN

Singaravadivel *et al.* reported a novel receptor from Rhodamine dye, conjugated with diaminomalenonitrile moiety (Molecule **2** in Figure 2). The receptor shows highly sensitive and selective turn-on fluorescent response to Cd^{2+} over other metal ions [22]. Receptor **2** displayed weak fluorescence response at 553 nm upon excitation at 530 nm. Aft gradual addition of Cd^{2+}, a significantly strong emission band at 553 nm appeared. The enhancement in fluorescence intensity was likely due to the Cd^{2+}-triggered rhodamine spiroring opening reaction mechanism. The detection limit of Cd^{2+} is 18.5 nm in acetonitrile-water (7:3, V/V). The association constant between receptor and Cd^{2+} was calculated 2.33×10^{5} M^{-1}. For the live cell imaging *via* confocal microscopy, HeLa cells (cervical cancer cells) were used. Receptor **2** possesses low cytotoxicity with good membrane permeable property and hence is successfully applied to fluorescence microscopic imaging, for the detection of Cd^{2+} ions. For live cell imaging, cells were incubated with a 10 μM solution of receptor **2** for 30 min at 37°C in growth medium, and a very weak fluorescence was observed.

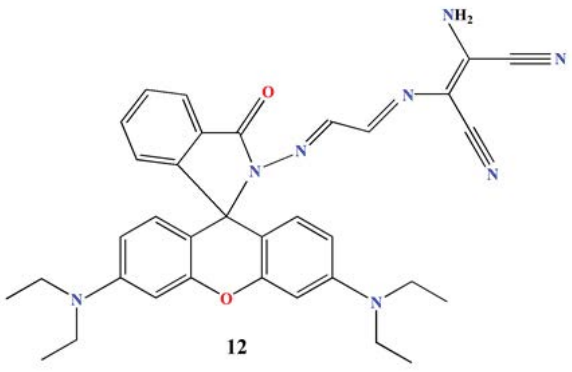

Figure 2: Molecular structure of receptor **2**.

In succession, the cells were added with $Cd(NO_3)_2$ (10 μM) for 10 min at 37°C. After the cells were washed with 3 × 1 mL of PBS three times, an obvious fluorescence response from the intracellular region was observed. The bright field image confirmed that the cells were viable throughout the imaging experiments and

the receptor **2** had good cell-membrane permeability, and hence useful for detecting intracellular Cd^{2+}.

Phenanthroimidazole-DMAN

In another study, Zhao *et al.* reported sensing properties of receptor **3** (Figure 3) with sodium hypochlorite (NaOCl), and were investigated by means of fluorescence readout in EtOH/H_2O solution (3:1, V/V, 10 mM PBS buffer, pH 7.4) [23]. The receptor exhibited very weak fluorescence emission upon excitation wavelength of 340 nm. This is attributed to an efficient ICT from NH_2 of DAMN moiety to phenanthroimidazole (Figure 3). Upon the addition of NaOCl, a significant enhancement of the emission intensity at 410 nm was observed. The detection limit for **OCl^-** was found to be 1.4×10^{-2} M. The imaging experiment showed good cell-membrane permeability of receptor 3, and was to image exogenous HOCl. The optical window at the blue channel (400–500 nm) was choosen to be a signal output. The HeLa cells (cervical cancer cells) incubated with receptor (5 M) for 30 min did not display any fluorescence at 400–500 nm. However after addition of OCl^- (60 M) and then incubating for another 30 min, strong fluorescence was clearly observed. In addition to this, during the experimental process, no obvious cytotoxicity was noticed.

Triphynyl Schiff base-DAMN

Zhou *et al.* reported the sensing ability of receptor **4** (**Figure 4**), a Schiff base derivative based on diaminomalenonitrile, and was tested by mixing it with a range of metal ions Ag^+, Al^{3+}, Ba^{2+}, Ca^{2+}, Ce^{3+}, Co^{2+}, Cr^{3+}, K^+, La^{3+}, Li^+, Mg^{2+}, Na^+, Ni^{2+}, Pb^{2+}, Zn^{2+}, Fe^{3+}, Hg^{2+} and Cu^{2+} in acetonitrile solvent [24]. Fluorescence spectra showed that only Cu^{2+} results in a pronounced fluorescence enhancement at 501 nm. In the absorption spectroscopy, signal at 420 nm decreases and a new band centred at 350 nm with blue shift 70 nm emerged. The phenomenon was attributed to the fact that the magnitude of the energy difference between the ground and excited states of a dipolar compound is significantly influenced by intermolecular solute-solvent interactions. Increased dipole-dipole interactions between the receptor and polar solvents lead to the lowering of energy levels. The color of the solution changes from pale yellow to colourless (**Figure 4**) which can be attributed to the Metal-Ligand (ML) type electronic transition. The detection limit of Cu^{2+} in molar fraction is 0.5. To evaluate the performance of receptor with Cu^{2+} and receptor alone in living cells, the fluorescence microscopy imaging was performed. HepG2 cells (carcinoma cells derived from liver), testing candidates were cultured and stained with the sample for 2h. The excess substances were washed away by buffer solution and the fluorescent signal was collected by using confocal laser scanning microscopy. The mixture of Cu^{2+} with receptor **4** show good cell imaging ability. This could be attributed to the fact that addition of Cu^{2+} ions not only result in enhancement of the fluorescence intensity of the solution, but also increased the aqueous solubility of the mixtures. The fluorescent and the merged images showed that the mixtures go through the membrane and just localize uniformly in the cytoplasm. The intense fluorescence is mainly because the mixture internalizes in the HepG2 cell cytoplasm and the distribution in the nucleolus is significantly lower, suggesting that only the cell cytoplasm can be labelled by the mixture. The results demonstrate the bioimaging application of receptor **4** for Cu^{2+} ions.

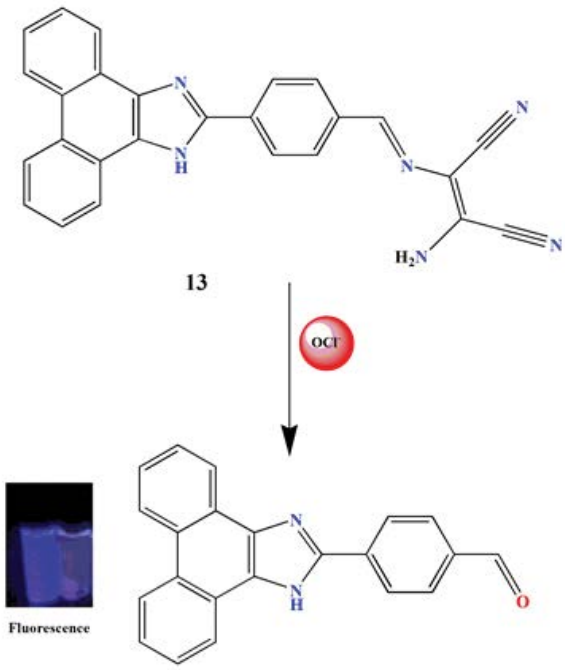

Figure 3: Structure of receptor **3**, interaction with OCl^- and Fluorescence response therein.

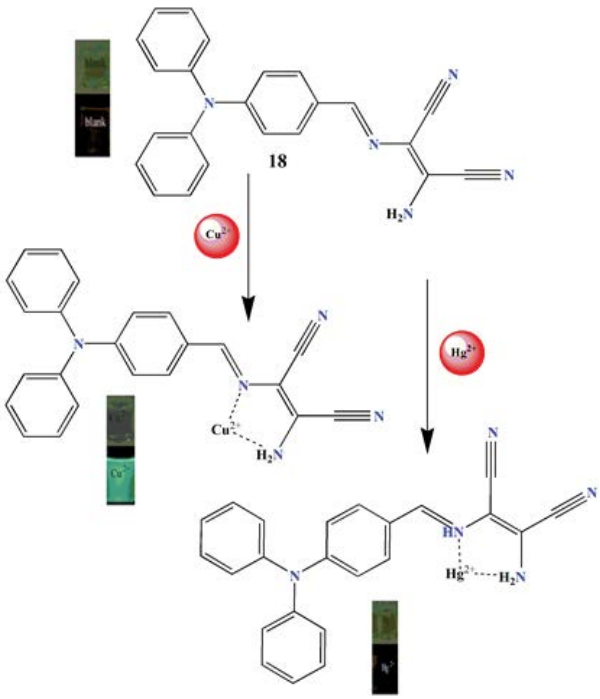

Figure 4: Structure of receptor **4**, interaction with Cu^{2+} and Hg^{2+} and Fluorescence changes displayed herein.

Azo-azomethine-DAMN

Khanmohammadi *et al* reported receptor (**5** in Figure 5), a N-monosubstituted diaminomalenonitrile-based azo-azomethine dye for the anion-recognition with tetrabutylammonium (TBA) salts of F, AcO^- and $H_2PO_4^-$ in (9:1, V/V: DMSO-water) solvent system [25]. Here progressive addition of F^- resulted in the red shift of 94 nm accompanied by the dramatic color change from light green to greenish blue. The colour change could be attributed to the deprotonation of receptor at -NH_2 site. This phenomenon results in the concentration of negative charge on the nitrogen which results in the enhancement of the push–pull effect of the ICT transition. Here the introduction of electron-withdrawing group (NO_2) decreases the electron density on nitrogen atoms and hence increases the acidity of hydrogen-bind donors, so the deprotonation becomes easily. The detection limit of F^-, AcO^- and $H_2PO_4^-$ ions was found 1.50×10^{-6}, 1.21×10^{-6} and 2.25×10^{-6} M respectively. The association constants for receptor towards F^-, AcO^- and $H_2PO_4^-$ were calculated to be 1.59×10^5, 1.35×10^5 and 1.54×10^5 M^{-1} respectively. The designed receptor was used for qualitative and quantitative detection of inorganic fluoride in toothpaste and mouthwash. Due to the conspicuous color change from light green to greenish blue; the current receptor delivers immense potential to detect fluoride even by the naked eye in the above samples.

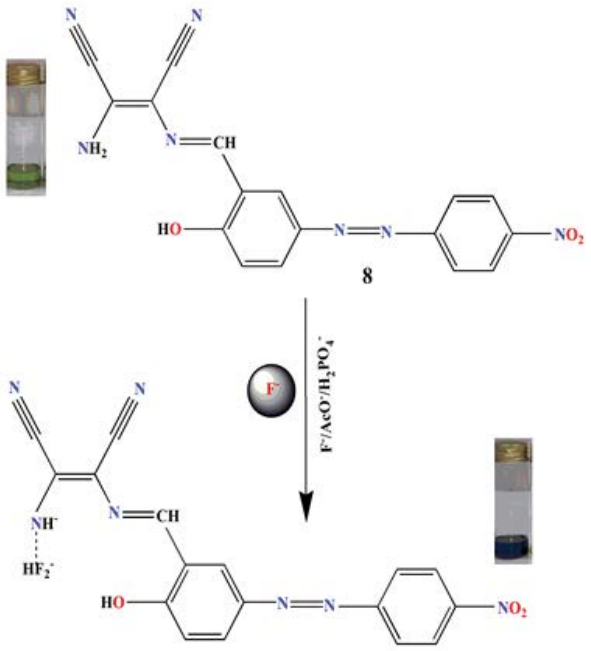

Figure 5: Structure of receptor **5**, interaction with anions and resulting Colorimetric changes.

Conclusions

This review summarizes the foremost progress made in the development of molecular receptors designed from DAMN backbone. On this functionality, large numbers of synthetic receptors have been described for the recognition of a range of anions and cations (F^-, Cu^{2+}, OCl^-, Cd^{2+}, S^-, Hg^{2+} and AcO^-) in both organic as well as mixed solvent system (organic/aqueous). The proposed receptor platform displayed pronounced colorimetric changes and/or fluorescence "turn on" response with the ions as a function of concentration. Besides these, the proposed receptor design is highly robust and displays sensing of ions in vitro as well as vivo. Because of such crucial characteristics, we have summarised here only those receptor which display applications for biological samples. Some of the crucial design considerations, such as choice of fluorophore/chromophore, selectivity, application in bio systems and mechanism of recognition are momentarily discussed. The detection limit as well as association/binding constant of the discussed receptors is also herewith. The recognition signal has been proposed to occur via the interaction between receptor with the ion, and hence resulting in the modulation of ICT and/or PET processes.

We hope this review inspires researchers with unique analytical, synthetic and physical chemistry tools, to delve into this newly explored area of chemical sensing, and also to those who have something to do with or interest in the environment and biology. Owing to the simplicity of molecular design, synthetic requirements, and sensitivity towards ions, described receptor approach is expected to display interesting and practical applications in biology besides environment.

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