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Hydrazone-Based Small-Molecule Chemosensors

Thiago Moreira Pereira and Arthur Eugen Kümmerle

Abstract

The hydrazone functional group is widely applied in several fields. The versatility and large use of this chemotype are attributed to its easy and straightforward synthesis and unique structural characteristics which is useful for different chemical and biological purposes. Recently hydrazone scaffold has been widely adopted in the design of small-molecule fluorescent and colorimetric chemosensors for detecting metals and anions because of its corresponding non-covalent interactions. This chapter provides an overview of hydrazone-based fluorescent and colorimetric chemosensors for anions and metals of biological interest, with their representative rational designs in the last 15 years. We hope this chapter inspires the development of novel and powerful fluorescent and colorimetric chemosensors for a broad range of applications.

1. Introduction

Hydrazone-based molecular structures are ubiquitous in many research fields, such as medicinal chemistry [1], organic synthesis [2], supramolecular chemistry [3], metal-organic coordination [4], dyes [5], fluorescent sensors, and molecular machines [6], besides others applications [7]. Over the last decades, the popularity of hydrazone group has increased due to its easy and direct-obtaining synthesis, stability toward hydrolysis in comparison with imines, modularity, and mainly, functional diversity of C=N—N useful in several fields (**Figure 1**). In terms of structure, hydrazones are considered as azomethine compounds; however they are distinguished from imines and oximes, for example, by the presence of additional linked nitrogen atom [8]. Hydrazone backbone has an imine carbon that has an
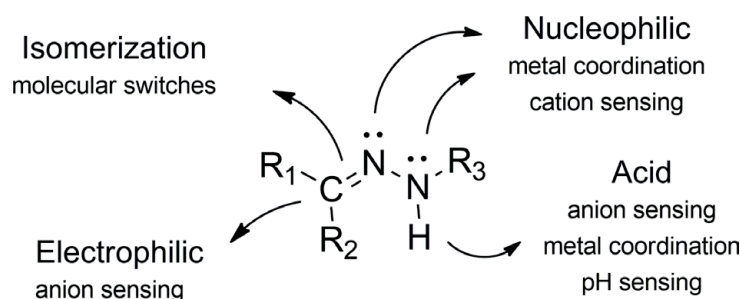

Figure 1.
General molecular structure of hydrazones.

electrophile character, two nucleophilic nitrogen in both imine and amine groups and a possible isomerization of C=N double bond typically from the conjugation of imine and the acid N–H. These structural properties play a crucial role to determine the specificity of applications which hydrazone group can be involved [6, 9].

The main synthesis of hydrazones is carried out from acid-catalyzed condensation between hydrazines (R_1NHNH_2) and activated carbonyl aldehydes or ketones, generally in alcoholic media. Other forms to obtain hydrazones are from Japp-Klingemann reaction (i.e., aryl diazonium salts coupling with β-keto esters or acids) and coupling between aryl halides and non-substituted hydrazones [9].

1.1 Hydrazone-based compounds as fluorescent chemosensors

Most hydrazone derivative fluorescent chemosensors were designed combining fluorophores or aromatic structures with this functional group. The wide range of chemical reactivity of hydrazones allows their application in the detection of anions, cations, and other species [10].

Some hydrazone-based chemosensors have weak fluorescence because of quenching effects such as E/Z double bond isomerization in the excited state; photoinduced electron transfer (PET) process (excited electron is transferred from donor to acceptor; generating a charge separation, i.e., redox reaction takes place in excited state); [11] excited state intramolecular proton transfer (ESIPT) process (photoexcited molecule relax their energy through tautomerization by transfer a proton); and others [12, 13]. The main objective for this class of chemosensors is inhibiting the quenching effects after interaction with some analytes promoting a fluorescence state. Other possible mechanisms are based on nucleophilic addition or induced N–H and O–H deprotonation. These mechanisms will be detailed after.

A quick literature survey using Scopus database has shown few reviews on the chemistry of hydrazones, most of them focusing on medicinal chemistry [14] or organic synthesis [15]. Only one review on hydrazone compounds describes some examples of hydrazone-based fluorescent chemosensor, which covered some results reported before 2014 [6].

This chapter book aims to present the progress of fluorescent and colorimetric chemosensor based on hydrazone scaffold, as reported in the literature in the period of 2006 until 2019. We hope that this chapter book helps in the design and development of new and selective fluorescent and colorimetric chemosensors for a broad range of applications.

2. Fluorescent chemosensors for anions

Anions, such as cyanide (CN^-), fluoride (F^-), chlorine (Cl^-), and acetate (AcO^-), play an important role in many environmental, clinical, chemical, and biological processes. Due to these important roles, anion recognition is an area with growing interest in supramolecular chemistry, and considerable efforts has been focused on the design of receptors (compounds) that are able to recognize anions. The detection and quantification of anions is a challenge, especially in biological systems. Some aspects as microenvironmental sensitivity, specificity, basicity, and nucleophilicity are among the main complicating factors in the detection of anions. One way to solve these problems is to develop chemosensors with high specificity for individual anions [16, 17]. Among different types of anions, fluoride and cyanide aroused great interest. The optimum concentration of F^- anions in the human body is a positive aspect to our health and can prevent dental caries and osteoporosis; however the excess of F^- may cause dental or osseous fluorosis, thyroid and liver

damage, and bone diseases [18–20]. Additionally, F⁻ is known as a test index for residues of some nerve agents, being also associated with certain drugs, Alzheimer disease, and drinking water. The level of F⁻ recommended in potable water by the US Environmental Protection Agency (EPA) is about 2 ppm [18–21].

Commonly involved in chemicals and industrial processes, cyanide is highly toxic and its exposure to live organisms and environment is extremely detrimental. Moreover, cyanide anion has a strong affinity with cytochrome a_3 which can lead to cell death because of respiratory arrest [22]. According to the World Health Organization (WHO), the permissible level of cyanide in drinking water is 1.9×10^{-6} M [18]. Therefore, considering the notorious toxicity of CN⁻ and F⁻, the development of sensitive sensors for the accurate detection and quantification of anions is of great importance.

2.1 Hydrazone derivatives as chemosensors for CN⁻

The main mechanisms of fluorescent sensing CN⁻ in hydrazone derivatives are based on nucleophilic addition to polarized C=N [23, 24] and C=O [25] bonds, which leads to disruption of C=N and C=O double bond to C−NH or C−OH forms, deprotonation of NH or OH by means of acid-base reactions [26–28], and the displacement of fluorescent hydrazones from hydrazone-copper complexes.

2.1.1 Nucleophilic addition of CN⁻

Two highly selective CN⁻ chemosensors **1**–**2** based on hydrazones functionalized with salicylaldehyde were described as capable of detecting this anion in aqueous solution at very low concentrations (**Figure 2A**). The ability of **1**–**2** complexing with several anions was tested by means of UV-vis absorption and fluorescence spectrometry. Among these anions, only CN⁻ caused spectral changes due to its nucleophilic attack to the imine group (**Figure 2B**), and spectroscopy analysis (H¹ NMR and MS studies) confirmed a 1:1 binding stoichiometry. In the presence of CN⁻ (0–120 equivalents), a new intramolecular hydrogen bond network is formed, resulting in a turn-on fluorescence response for probe **1** and colorimetric naked-eye
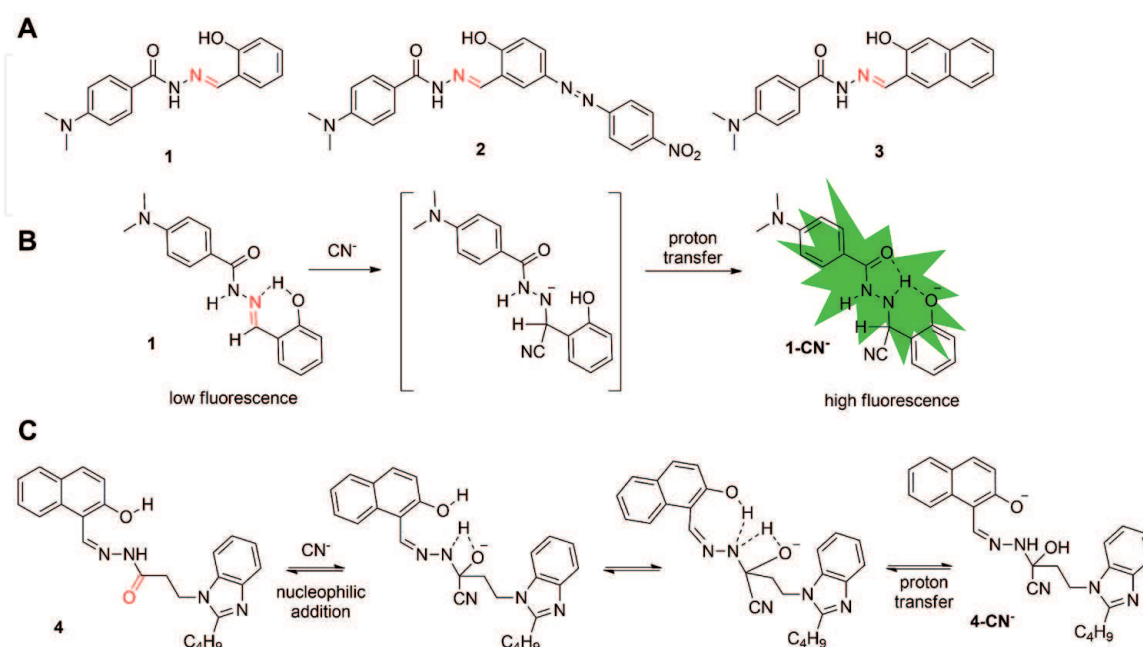
Figure 2.
*(A) Molecular structures of CN⁻ chemosensors **1**–**3** with polarized C=N bond as sensing sites. (B) Proposed cyanide sensing mechanism of **1**. (C) Proposed CN⁻ sensing mechanism for **4** based on polarized C=O bond.*

changes for probe **2** [23]. With the same sensing mechanism based on nucleophilic attack of CN^- on the imine group, a remarkably and selective fluorescent and colorimetric chemosensor **3** was reported (**Figure 2A**). Among various anions, sensor **3** responded to only CN^-, resulting in a color change from colorless to yellow. Moreover, a fluorescence analysis showed **3** has a weak fluorescence, and after addition of CN^- (0–120 equivalents), the fluorescence emission has increased to a bright green fluorescence [24].

Exploring the same principle of nucleophilic attack, a highly selective and sensitive naphthalene-acylhydrazone chemosensor for CN^- in aqueous media was designed. By this time, the mechanism proposed was the nucleophilic attack on the carbonyl group instead of the imine one, according to ^1H NMR, ^{13}C NMR, ESI-MS, and DFT calculations data (**Figure 2C**). Among several anions tested, only CN^- could induce a remarkable color change from colorless to yellow and increase of fluorescence emission in DMSO/H_2O solution. Moreover, the detection limits were 5.0×10^{-7} M and 2.0×10^{-9} M of CN^- for color and fluorescence changes respectively, far lower than the WHO guideline of 1.9×10^{-6} M [25].

2.1.2 Deprotonation mechanism

Cyanide anion is a Lewis base and can form hydrogen bonds with hydrogen bond donors as hydroxyl and amines usually followed by deprotonation.

The highly selective and sensitive chemosensor (**5**) based on acyl hydrazone could detect CN^- in aqueous solution with colorimetric and fluorimetric turn-on response (**Figure 3A**). The detection limit of CN^- was 1.2×10^{-9} M, which is lower than the maximum level of 1.9×10^{-6} M for cyanide in drinking water according to WHO guidelines. Additionally, test strips based on **5** were fabricated and demonstrated that it could be used as an efficient CN^- sensing in aqueous solution [26].

Another deprotonation mechanism was reported in the design of a two-dimensional carbazole-based chromophore **6** as chemosensor for the measurement of CN^-. In terms of structure, this compound possesses two types of donor-π-acceptor (D-π-A) chromophores, where carbazole moiety is a donor for the two branches, each one with an accepting group (**Figure 3B**). Addition of CN^- to the solution of **6** in DMSO/H_2O (95/5, v/v) redshifted from 440 nm to 500 nm its absorption, changing its naked-eye observed color from yellow to violet. The sensing mechanism proposed was based on proton abstraction of —NH— when this group reacts with CN^- resulting in the obvious color change [27].

Like compound **5**, a rhodamine B hydrazone derivative (**7**) was reported as highly selective chemosensor for CN^- by means of a phenol deprotonation.
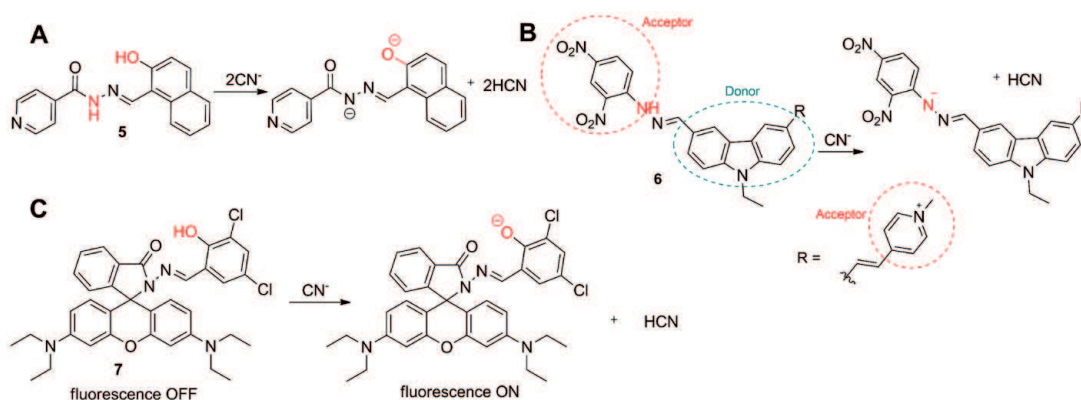

Figure 3.
*Molecular structures of CN^- chemosensors **5** (A), **6** (B), and **7** (C) and their proposed sensing mechanism.*

The complete sensing mechanism proposed was deprotonation followed by an intramolecular charge transfer (ICT), supported by ^{1}H NMR studies and DFT calculations (**Figure 3C**). This compound is a fluorescence and colorimetric sensor in DMSO/H$_2$O (1:9) medium with a significant color change after addition of CN$^-$ to a chemosensor solution from colorless to pale yellow visible to the naked eye, and the fluorescence increased to strong green fluorescence. The good detection limit observed of 5.81×10^{-8} is lower than the maximum level of 1.9×10^{-6} M for cyanide according to WHO guidelines, leading this compound to be applied in the detection of CN$^-$ in germinated potatoes and also in tests strips for CN$^-$ detection [28].

2.2 Hydrazone derivatives as chemosensors for F$^-$

2.2.1 Hydrogen bond interactions and deprotonation

Fluoride is a weak Lewis base and can form hydrogen bonds with hydrogen bond donors. This coordination usually promotes deprotonation.

A Ru-bpy-based quinone hydrazone was designed as chromo-fluorogenic hybrid chemosensor (**8**) for F$^-$ (**Figure 4A**). This compound contains a quinone-hydrazone group that can be converted to azophenol tautomer in **8-F$^-$** induced by the proton transfer from **8** to F$^-$ causing a color change from orange to blue-violet. Only F$^-$ was capable of inducing color change to **8** in MeCN, suggesting the high selectivity could be attributed to the strong intramolecular N—H—O hydrogen bond interaction in **8**, which means only the most electronegative anion could form an additional hydrogen bond. Generally, anion sensors based on hydrogen bond interactions cannot serve as good sensors in aqueous media due to hydrogen bond competition with water. To avoid this problem, a filter paper impregnated with acetonitrile solution of **8** and dried in air has been prepared. Immersing this paper into aqueous fluoride solution was successful, and fluoride solution exhibited color changes [29].

A thiocarbonohydrazone anion chemosensor **9** was described and rationally designed based on previously reported anion chemosensors, where the presence of strong electron withdrawing —NO$_2$ group enhanced the acidity of the thioamide protons and stabilized the negative deprotonated species (**Figure 4B**). After successive addition of F$^-$, the UV-vis absorption band with maximum at 360 nm has decreased, whereas new peaks at 407 and 495 appeared. The absorption at 360 nm is attributed to the Ar—CH=N—NH conjugation moiety, and its bathochromic shift clearly indicated an interaction/reaction of fluoride with this portion. After addition of more than four equivalents of F$^-$, a new absorption band at 600 nm appeared with a new isosbestic point at 535 nm. The significant changes in UV-vis spectra of chemosensor **9** was attributed to the deprotonation of thioamide protons in a three-step process (**Figure 4B**) confirmed by ^{1}H NMR titration analysis from the observed peak of the FHF— at δ = 16.13 ppm [30].
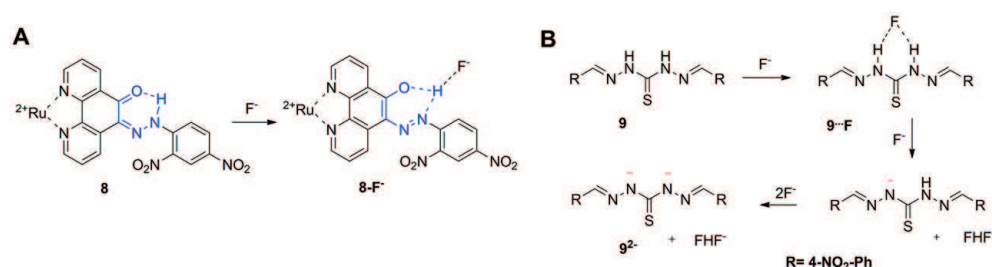

Figure 4.
*Molecular structure of F$^-$ chemosensor **8** (A) and **9** (B) and their proposed sensing mechanism.*

Still exploring the N—H acidity of hydrazones, a new series of diketopyrrolo-pyrrole (DPP) derivatives **10–14** bearing phenylhydrazone group was described presenting a ESIPT-PET fluoride sensing mechanism. The authors aimed to study the effect of nitro substituent of phenylhydrazone on their photophysical property and optical fluoride sensing. The anion sensing capabilities of **10–14** were evaluated in DMSO by the addition of several anions. The presence of nitro substituent at *ortho*-position of phenylhydrazone in **11** and **14** significantly altered the electronic properties through intramolecular hydrogen bonding and furnished an excited state intramolecular proton transfer (**Figure 5**). So, *o*-NO$_2$-DPPH (**11**) has a weak fluorescence, partly attributed to the photoinduced electron transfer from the imine and similar situation was found in *o, p*-NO$_2$-DPPH (**14**) (**Figure 5**).

The visual naked-eye color change was observed under natural light for DPPPH (**10**), *m*-NO$_2$-DPPPH (**12**), *p*-NO$_2$-DPPPH (**13**), and *o, p*-NO$_2$-DPPPH (**14**) in the presence of F$^-$. Among these designed chemoreceptors, *p*-NO$_2$-DPPPH demonstrated selectivity for F$^-$ in UV-vis and fluorescence evaluations in DMSO solution. Additionally, experimental results of ^{1}H NMR and ^{19}F NMR revealed that the spectral changes occur due to deprotonation of the hydrazone N—H moiety by fluoride ion [31].

2.3 Hydrazone derivatives as chemosensor for AcO$^-$

Acetate (AcO$^-$) and dicarboxylate are essential components in several metabolic processes in living organisms. Without them, many enzymes and antibodies are unable to function properly. In this sense, the synthesis of chemosensors that can recognize AcO$^-$, mainly via hydrogen bond interaction, is of great importance for biological systems [32].

An interesting naked-eye selective colorimetric sensor for AcO$^-$ based on 1,10-phenanthroline-2,9-dicarboxyaldehyde-di-(p-nitrophenylhydrazone) (**15**) was described by Lin's group. The UV-vis absorption in DMSO showed a dramatic color change from yellow to green in the presence of AcO$^-$ with no changes for other anions. The presence of electron withdrawing groups increasing the hydrogen bond donor ability of N—H framework was favorable for AcO$^-$ sensing. In addition, ^{1}H NMR studies showed that after interaction, AcO$^-$ lead to deprotonation of **15** [33].

Similarly a fluorescent and naked-eye colorimetric chemosensor (**16**) for AcO$^-$ based on thiosemicarbazone was evaluated by UV–vis spectroscopic titrations in dry DMSO solution, presenting high selectivity and affinity for AcO$^-$. After addition of this anion, the absorption band at 373 nm decreased gradually, whereas a new band appeared at 457 nm, followed by color change in the solution from light yellow to orange. The complex formed between AcO$^-$ and **16**, through hydrogen bond interactions, caused intramolecular charge transfer between the electron-rich urea unit and the electron-deficient benzene moiety (**Figure 6**). In addition, the fluorescence spectroscopic titrations were carried out, and the **16** also displayed a switch-on reaction toward AcO$^-$, which was attributed to the binding-induced
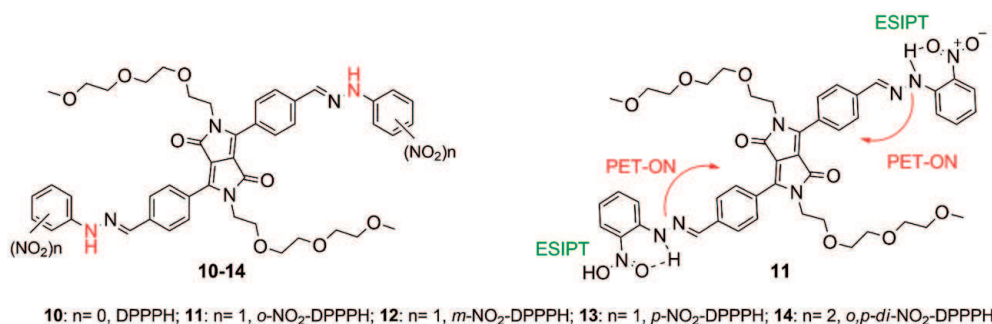

10: n= 0, DPPPH; 11: n= 1, *o*-NO$_2$-DPPPH; 12: n= 1, *m*-NO$_2$-DPPPH; 13: n= 1, *p*-NO$_2$-DPPPH; 14: n= 2, *o,p-di*-NO$_2$-DPPPH

Figure 5.
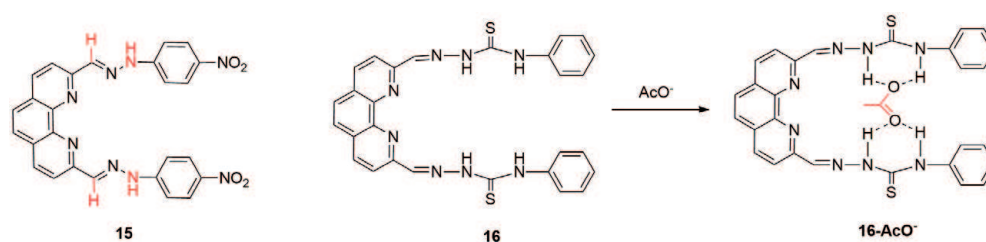*Molecular structures of F$^-$ chemosensors 10–14.*

Figure 6.
Molecular structures of acetate chemosensors 15–16 and the proposed sensing mechanism.

rigidity of the host molecule. The free receptor (**16**) had a flexible configuration and could rotate freely; however, after complexation with AcO⁻, the host molecule was rigidified, and the fluorescence emission has increased [32].

2.4 Hydrazone derivatives as chemosensors for multiple anions

In contrast to previously described, where receptors had a certain degree of selectivity toward single anion, several hydrazone-based chemosensors have been published exhibiting a response to more than one anion species, and some interesting examples will be described below [34–36].

A tripodal benzaldehyde-phenylhydrazone (**17**) was developed as a colorimetric naked-eye chemosensor for AcO⁻, F⁻, and $H_2PO_4^-$ by Lin and colleagues, and UV-vis spectroscopic studies in DMSO were used to determine the binding mode of **17**. After addition of these anions, a naked-eye color change from yellow to purple and a significant bathochromic shift of 124 nm were observed. However, both the color and spectral changes were reverted by the addition of protic solvent such as H_2O into the mentioned host-guest system, indicating that protic solvents could compete with anion binding sites. Considering these results, the authors proposed that a strong hydrogen bonding interaction was taking place between receptor **17** and AcO⁻ as well as F⁻, OH⁻, and $H_2PO_4^-$. The complete interaction mode described in **Figure 7** was only attributed after assays indicating that stoichiometry of the host and specific guests was different depending on the anion. The receptor formed 1:1 complex with F⁻ ion and 1:3 complexes with AcO⁻, OH⁻, and $H_2PO_4^-$. This was attributed to the smaller ionic radius of F⁻ than that of other larger ones. A further ^{1}H NMR investigation showed that resonance peak at 11.77 ppm, attributed to NH protons, exhibited a downfield to 12.27 ppm upon addition of 2 equivalents of F⁻ ion confirming the formation of NH···F⁻ hydrogen bonding [34].

A Schiff-base thiophene-based hydrazone (**18**) was described as visual anion chemosensor in aqueous media exhibiting sensing properties for F⁻, AcO⁻, and $H_2PO_4^-$, among several anions tested with colorimetric response changes from
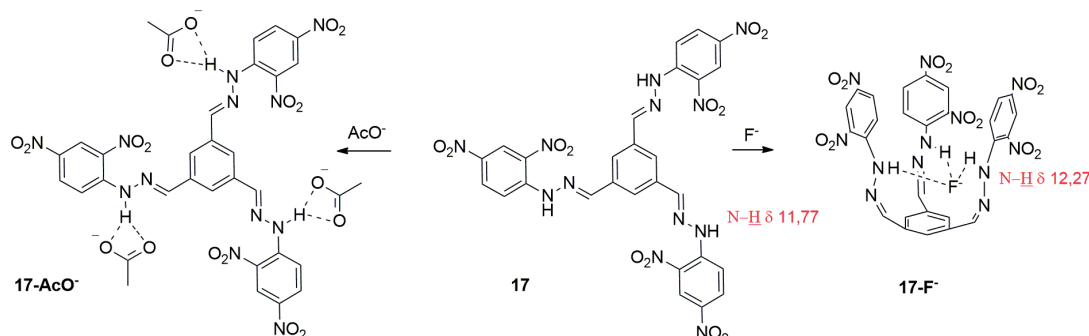

Figure 7.
Molecular structures of multianalyte chemosensor 17 and their proposed sensing mechanism.

Figure 8.
*Molecular structure of multianalyte chemosensor **18** (A) and **19**–**22** (B) and mechanism of acetate detection for **18** (A).*

orange to violet at a micromolar level. The UV-vis analysis confirmed the naked-eye colorimetric changes and showed a decrease in band centered at 420 nm and increase in intensity of the band at 590 nm with the clear isosbestic point at 520 nm after addition of F^-, AcO^-, and $H_2PO_4^-$ to **18** solution. The chemosensor **18** works by means of a N—H deprotonation mechanism. ^{1}H NMR analysis confirmed this mechanism, showing that **18** presented signals at δ 11.79 and 8.91 corresponding to N—H and imine protons, respectively. After addition of AcO^- and F^- ion, N—H signal disappeared (deprotonation), while the signal corresponding to the imine and phenyl rings shifted to the upfield at the region of δ 8.59 and 8.54 (**Figure 8**). Additionally, a real sample qualitative estimation analysis of F^- and AcO^- in commercially available toothpaste and vinegar was successfully achieved by this simple and easy colorimetric method [35].

Four furan/thiophene-based fluorescent hydrazones **19**–**22** were described as CN^- and F^- sensors (**Figure 8**) and could detect these ions with naked-eye color changes from yellow to blue, while their fluorescence emission intensities were completely quenched. The presence of electron donating/withdrawing groups attached to furan ring as in **21** (—NO_2) and **22** (—CH_3) curiously resulted in increased selectivity for CN^- ions compared to F^- ones. ^{1}H NMR confirmed that the sensing mechanism goes through hydrogen bonding interaction between sensors and F^-/CN^-, followed by deprotonation, leading to elicited ICT. Job's plot afforded a stoichiometry of 2:1 binding ratio between **19** and **20** and F^- ions. However, curiously **21** and **22** exhibited a 1:1 ratio with F^- and CN^- due to steric constraint. The limit of detection (LOD) analysis revealed that the four sensors displayed the LOD below 0.3 ppm for CN^- and F^- and a good selectivity. Competitive experiments revealed a negligible perturbation in the optical response which confirms a higher selectivity for F^- and CN^- than other competitor anions [36].

3. Fluorescent chemosensors for metal ions

Metal ions such as Cu^{2+}, Zn^{2+}, Fe^{3+}, Al^{3+}, Hg^{2+}, Mg^{2+}, etc. play an important role in many biological and environmental processes, and excessive or insufficient amounts may lead to diseases [37]. As an example, copper (Cu^{2+}) is the third most abundant transition metal in the human body and plays essential roles in several environmental, chemical, and physiological systems. In living organisms, Cu^{2+} acts as a key catalytic center in many enzymes and as cofactor in a variety of metalloproteins [38]. Its insufficient concentration may affect the development of bone and brain tissues as well as the nervous and immune system, whereas excessive intake may lead to serious problems including cirrhosis and neurological diseases such as Alzheimer's and Wilson's diseases and prion disorders [39]. The extreme toxicity of heavy metal ions such as Pb^{2+} and Hg^{2+}, even in small amounts, remains a danger to

human health and the environment, but they have been widely used in industrial processes [40]. Therefore, the development of sensitive sensors for the accurate detection and quantification of these ions is of great importance.

3.1 Hydrazone derivatives as chemosensors for Cu^{2+}

Fluorescent and colorimetric hydrazone-based chemosensors for Cu^{2+} attract interest and are mainly based on coordination mechanism, often quenching the fluorescence emission due to PET mechanism [41].

Coumarins are widely associated with hydrazones for sensing Cu^{2+} and the on–off fluorescent chemosensor (23) was described for Cu^{2+} detection in aqueous media. This chemosensor showed very strong luminescence in H_2O/DMSO (9:1, v/v) with quantum yield of 0.289, which was almost completely quenched after addition of copper (1 equivalent), decreasing the quantum yield to 0.024. This process was associated with the complexation of Cu^{2+} to the tautomeric enol-like form of 23 leading to 23-Cu^{2+} and the PET mechanism (**Figure 9**). Compound 20 showed detection limit of 0.1 μM for Cu^{2+}, which is useful to sense Cu^{2+} in blood system, a 1:1 binding mode supported by a Job's plot, an association constant estimated to be 6.4×10^5 M^{-1}, and a response time of 2 min upon addition of 1 equivalent of this cation. Only Cu^{2+} causes a significant fluorescence decrease, while other metals such as K^+, Ag^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Fe^{2+}, Fe^{3+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+} and Zn^{2+} did not cause any significant change. In addition, living cell experiments were successfully applied, and confocal image changes were observed, demonstrating its value in practical applications and biological systems [42].

Differently from turn-off PET mechanism, off-on (turn-on) chemosensors for detecting Cu^{2+} often present a FRET mechanism (described by energy transfer between two light-sensitive molecules or chromophores, where a donor chromophore in its electronic excited state may transfer energy to an acceptor chromophore through nonradiative dipole-dipole coupling). An example is the hybrid coumarin-rhodamine hydrazone chemosensor 24 based on metal ion-induced FRET. In this mechanism, coumarin nucleus acts as donor and rhodamine acts as acceptor of energy. Free ligand coumarin-rhodamine hydrazone (24) absorbs around 460 nm, which is attributed to coumarin chromophore. The absorbance remained unchanged upon addition of various metal ions except Cu^{2+}. Upon addition of Cu^{2+}, the solution color changes from yellow to bright red indicating metal complexation. It was confirmed analyzing the decrease in absorption band centered at 460 nm with a slowly redshifts to 475 nm, while a new peak at 556 nm arise from the rhodamine chromophore in the visible region.
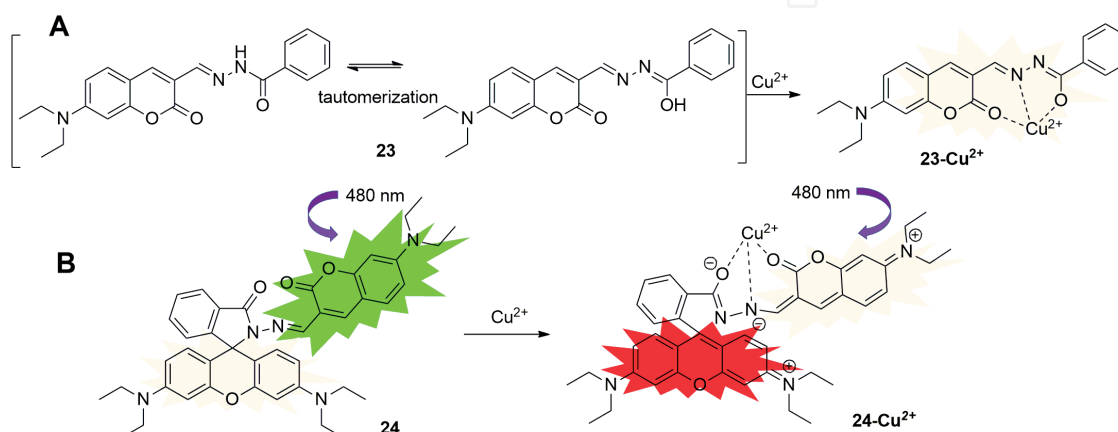

Figure 9.
Molecular structures of Cu^{2+} chemosensors 23 (A) and 24 (B) and their proposed sensing mechanism.

Free coumarin-rhodamine hydrazone (**24**) emits in the green fluorescence region with a fluorescence band centered at 524 nm which is attributed to *N,N*-diethyl-coumarin moiety upon excitation at 480 nm. Upon sequential addition of Cu^{2+}, coumarin emission band was observed at 524 nm, while an emission signal corresponding to ring-opened rhodamine appeared at 582 nm (**Figure 9**). This chromo-fluorogenic probe can detect concentrations below 20 µM of Cu^{2+} in aqueous buffer medium. The FRET mechanism is possible due to integral overlap between emission band of *N,N*-diethyl coumarin moiety and absorption band of ring-opened zwitterionic rhodamine unit in buffer medium. Additionally, probe **24** undergoes a 1:1 stoichiometric complexation with Cu^{2+} with the calculated association constants of 8.81 M^{-1} and was successfully employed as ratiometric biosensor for living cell imaging of Cu^{2+} [43].

A highly selective and sensitive naked-eye colorimetric chemosensor for Cu^{2+} in aqueous solution was designed and developed based on hydrazone framework. In the UV-vis spectroscopic studies, compound **25** exhibited a broad band at 336 nm, and after addition of copper, a new absorption band at 502 nm appeared, whereas the absorption band at 336 nm was gradually reduced. This gradually increasing absorption peak at 502 nm (after sequential addition of Cu^{2+}) was attributed to the coordination of **25** with Cu^{2+}.

Trying to understand its sensing mechanism, the stoichiometry of the **25-Cu2+** complexation was determined by the Job's plot analysis which indicates a 2:1 stoichiometric between **25** and Cu^{2+} and after confirmed by ESI/MS analysis. With stoichiometry on hands, complementary infrared (IR) and ^1H NMR spectroscopy were employed, and even Cu^{2+} which is a paramagnetic ion helped to describe the coordination mode. The ^1H NMR revealed that N—H (**a**) proton almost completely disappeared upon addition of Cu^{2+} and proton **b** became broader after binding, indicating that Cu^{2+} binds with nitrogen of pyridine after an initial tautomerization with a deprotonation of O—H.

The selectivity of **25** over other metals was investigated by adding several metal cations to the solution of **25** in THF/H_2O (9:1, v/v), and there was no obvious change with any other metal. The colorless solution of the compound **25** became pink after addition of Cu^{2+} with the detection limit by the naked eye around 2 µM which is lower than the limit of copper in drinking water (~20 µM). Additionally, to evaluate the practical application of chemosensor **25**, competition experiments of Cu^{2+} mixed with other metal ions were carried out from UV-vis absorption spectra. The treatment of **25** solution with Cu^{2+} in the presence of the same concentration of other metal cations did not show any significant changes [44].

Using a strategy of intraligand charge transfer transition (ILCT) turn-on mechanism, a small chromo-fluorogenic chemosensor (**26**) for Cu^{2+}, based on hydrazones, was described. This chemosensor exhibited a weak fluorescence in DMSO with a 44-fold increase in fluorescence emission intensity upon addition of Cu^{2+}, being attributed to ILCT. This receptor showed a prominent colorimetric change from yellow to brown in the presence of Cu^{2+} with a detection limit in the order of 10^{-8} M. In the presence of other environmentally significant metal cations such as Hg^{2+}, Pb^{2+}, Cd^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Fe^{3+}, Mn^{2+}, Zn^{2+}, Al^{3+}, and Cr^{3+}, no significant spectral changes were observed. Interesting, this chemosensor was capable of extracting Cu^{2+} selectively from aqueous mixture of metal ions using dichloromethane as solvent with an efficiency of 94% at 6.5–11 pH range.

The binding sense mechanism was explained by ^1H NMR titration in DMSO, in which the peak attributed to acid O—H proton of **26** gradually decreased upon addition of Cu^{2+}, also indicating a 2:1 (**26-Cu^{2+}**) stoichiometric binding (**Figure 10**). During the extraction process, the stoichiometry of ligand and Cu^{2+} was confirmed to be 2:1, and, in addition, the color changes and concentration of Cu^{2+} were
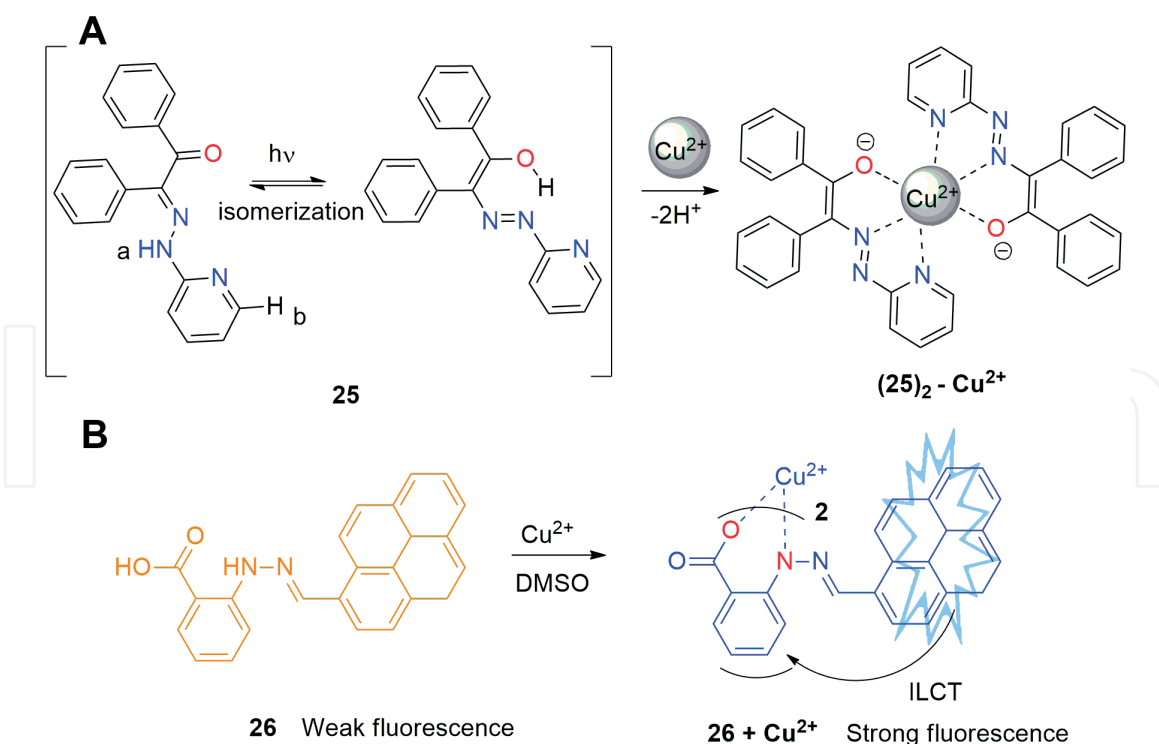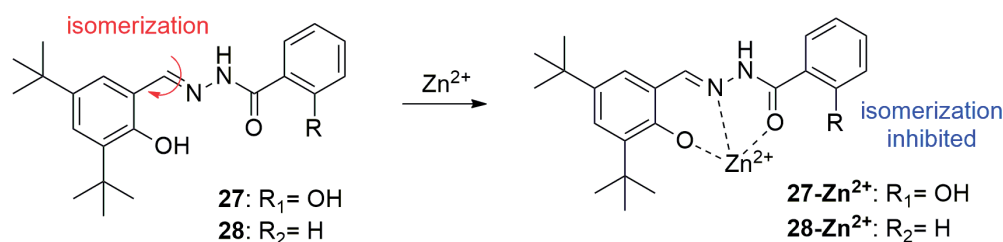
Figure 10.
Molecular structures of Cu²⁺ chemosensor 25 and its coordination mode (A) and structure of chemosensor 26 and its sensing mechanism (B).

monitored by a readily usable smartphone as an analysis tool. Interesting, this receptor showed a good recyclability and reusability in Cu^{2+} extraction, being very useful for the detection and selective extraction of Cu^{2+} from aqueous media in chemical and biological systems [45].

3.2 Hydrazone derivatives as chemosensors for Zn^{2+}

Zinc (Zn^{2+}) is the second most abundant transition metal (after Fe^{3+}) in the human body and is considered essential for living organisms. Zn^{2+} exerts influence on many cellular processes, including proliferation, differentiation, apoptosis, transcription, neural signal transmission, and microtubule polymerization. Therefore, significant changes in Zn^{2+} concentration may be related to many diseases, including Alzheimer's and Parkinson's diseases, diabetes, and prostate cancer [46, 47]. Chemosensors for Zn^{2+} are mainly based on the coordination mechanism; however, these probes often still lack specificity.

Aroylhydrazone derivatives (**27–28**) were described as fluorescent chemosensors for Zn^{2+} recognition. These ligands and their metal complexes (**27** (Zn^{2+}, Cu^{2+}), **28** (Zn^{2+}, Co^{2+}, Fe^{3+})) have been synthesized and characterized in terms of their crystal structures, elemental analysis, and spectroscopic properties. First, chemosensor **27** displayed high selectivity for Zn^{2+} over other transition metals compared to **28** in aqueous ethanol solution, which indicate that hydroxyl group exerts effect on the selectivity of the fluorescent chemosensor. The possible reason is that the presence of hydroxyl group gives the carbonyl a better binding ability for Zn^{2+} to form a 1:1 complex. The fluorescence response of **27** in solution increased approximately 25-fold upon addition of 10 equivalents of Zn^{2+} probably due to rigidity imposed by the complex formed, inhibiting isomerization (**Figure 11**). Otherwise, **28** exhibited only small increase in fluorescence (5-fold) when Zn^{2+} was introduced to the solution, indicating also the importance of *ortho*-hydroxyl group for fluorescence [48].
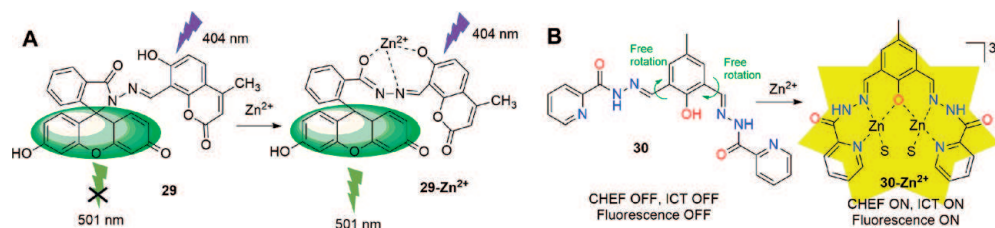
Figure 11.
Molecular structures of Zn²⁺ chemosensors 27–28 and their sensing mechanism.

A fluorescein-coumarin conjugate (**29**) was reported as turn-on fluorescent sensor for Zn^{2+} in aqueous medium. The mechanism involved in this chemosensor is related to spirolactam ring opening mediated selectively by Zn^{2+} over other earth and transition metal ions. The free chemosensor **29** showed almost no absorption characteristic of the fluorescein moiety which indicate the existence of the spiro-lactam form. However, upon Zn^{2+} addition in the sensing system, a new absorption band corresponding to fluorescein moiety increased indicating the generation of a ring-opening amide form (**29-Zn²⁺**). The absorbance ascended linearly as a function of Zn^{2+} concentration with a saturation at the ratio of 1:1 (**Figure 12**). The fluorescence emission intensity was increased 33-fold at 501 nm upon zinc addition, which is characteristic of fluorescein, confirming the spirocycle opening of **29** after coordination. In addition, this chemosensor was highly selective toward several metals such as Na^+, K^+, Ca^{2+}, Mg^{2+}, Cu^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Hg^{2+}, Cd^{2+}, and Cr^{3+} that showed none or little fluorescence intensity changes. The ability of chemosensor **29** works in aqueous medium and shows potential applications in environmental, biological, and medicinal areas [49].

The hydrazone-based fluorescent chemosensor **30** was reported as an interesting and selective sensor for Zn^{2+} over other biologically important metal ions (Na^+, K^+, Mg^{2+}, Ca^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Cd^{2+}, Ag^+, Pb^{2+}, Hg^{2+}, Al^{3+}, Cr^{3+}, Fe^{3+}, and Zn^{2+}) under completely physiological conditions (HEPES buffer medium (1 mM, pH = 7.4) containing 0.33% of DMSO), also demonstrating detection of zinc in live Hela cells by fluorescence imaging. The recognition of Zn^{2+} was investigated by absorption and emission spectroscopy, DFT calculations, ESI-MS experiment, and ¹H NMR titration.

The free ligand (**30**) exhibited two absorption peaks at 305 nm and 367 nm attributed to the π-π* transitions, in which zinc addition (10 equivalents) promoted a prominent change where the absorption band at 305 nm decreased, whereas a new peak at 450 nm emerged. This absorption spectra change became minimum upon the addition of two equivalents of metal ions, which suggested a 1:2 ratio between **30** and Zn^{2+}. Free receptor (**30**) has weak fluorescence with visible light excitability; however zinc caused drastic enhancement in the fluorescence emission with a prominent peak at 555 nm. The Zn^{2+} sensing mechanism was attributed to

Figure 12.
Molecular structures of Zn²⁺ chemosensors 29 (A) and 30 (B) and their sensing mechanism.

the chelation-enhanced fluorescence (CHEF) and ICT processes. The low fluorescence state of **30** (Φ = 0.009) is may be due to free rotation of imine (−C=N) bond (**Figure 12**). Upon Zn^{2+} addition, the coordination of this metal with imine nitrogen and the hydroxyl group inhibited the free rotation around the imine bond, leaving the system more rigid. Thus, the chelation of Zn^{2+} leads to the formation of binuclear zinc complex with drastic increase in conjugation, resulting in a CHEF effect. Furthermore, due to the binding of Zn^{2+}, the ICT is facilitated over the π-system. These conjugated effects caused the improvement in the fluorescence emission (Φ = 0.16, 18-fold) of **30** (**Figure 12**) [50].

3.3 Hydrazone derivatives as chemosensors for Hg^{2+}

Mercuric ion (Hg^{2+}) is considered highly dangerous, because it is known as one of the most toxic metal ions and is generated by many sources such as mercury lamps, gold production, electronic equipment, paints, and batteries [51]. Mercuric ion can cause serious detrimental effects to living organisms, resulting in hepatitis, uremia, digestive diseases, and fatal damage to the central nervous system, and its accumulation can lead to various cognitive and motor disorders, such as Minamata disease [52]. Due to its high toxicity, considerable attention has been devoted to the development of new sensors for Hg^{2+} detection. Hydrazone-based fluorescence chemosensors for Hg^{2+} are mainly based on coordination mechanism.

One example is the 3,4-ethylenedioxythiophene (EDOT) rhodamine-hydrazine-based compound **31** which acts as colorimetric and turn-on fluorescent chemosensor for Hg^{2+} detection. Between several metals, only Hg^{2+} coordination promoted the turn-on effect. The sensing mechanism is quite similar to that observed to compound **29**, in which free receptor has a spirolactam moiety, which inhibits the intramolecular charge transfer between electron-acceptor moiety of xanthene and the electron donor of EDOT. Once Hg^{2+} complexation occurs, a ring opening takes place delivering the rhodamine B moiety, which is a well-known fluorophore. The spirolactam moiety of the rhodamine acts as a signal switcher, which is envisioned to turn on upon complexation with the cation. The spectroscopic parameters of Hg^{2+} in mixed ethanol and HEPES (10 mM, 1:1, v/v, pH = 7.2) solution demonstrated that only Hg^{2+} was capable to change the color of the sensing solution from colorless to red (570 nm) and to increase fluorescence emission (593 nm), also indicating a 2:1 complex formation (**Figure 13**) [53].

The previous exposed FRET mechanism has been used in the design of selective turn-on fluorescent chemosensor for Hg^{2+} based on bis-hydrazone derivative from 2,5-furancarboxaldehyde. In this case, furan ring is the donor, and rhodamine B is the acceptor chromophore. Free ligand has the spirolactam moiety which in turn inhibits the charge transfer between these chromophores. When Hg^{2+} binds to **32**, a rapid naked-eye visual color change occurs from colorless to sharp pink, as well as a bright red fluorescent emission under UV lamp irradiation, which is attributed to the spirolactam ring opening (**Figure 13**). The FRET mechanism was confirmed by overlap of the emission band of 2,5-furan-dicarboxaldehyde (donor) and absorption spectra of rhodamine B (acceptor). After the binding of **32** to Hg^{2+}, leading to **32-Hg^{2+}**, furan moiety makes an energy transfer to induce the spirolactam opening which allowed the FRET process with increasing in the conjugation of the system (**Figure 13**). Additionally, the high increase in quantum yield of **32-Hg^{2+}** (0.23) when they compared **32** (0.015) and its limit of the detection at very low ppb level concentration (3.6×10^{-9} M) allowed applications for detecting Hg^{2+} in drinking water (LOD = 10 nM) [54].
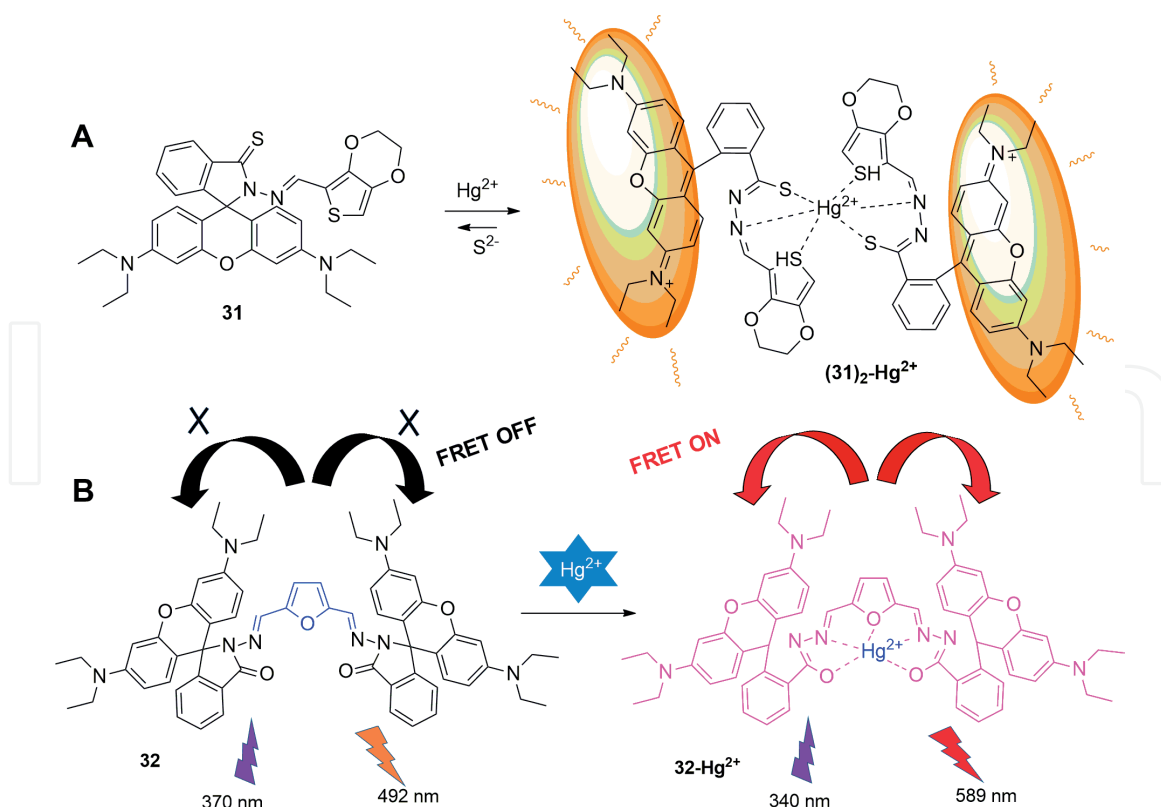
Figure 13.
Molecular structure of Zn²⁺ chemosensors 31 (A) and 32 (B) and their sensing mechanism.

3.4 Hydrazone derivatives as chemosensors for Al³⁺

Aluminum (Al³⁺) is the most abundant (8.3% by weight) metallic element and, after oxygen and silicon, is the third most abundant of all elements in the earth. Aluminum is widely used in the environment around us in modern society, such as in water treatment, food packing, medicines, etc. However, the excess of this metal can result in health problems such as Alzheimer's and Parkinson's diseases [55]. Moreover, it is believed that around 40% of the world's acid solid are caused by aluminum toxicity, which is harmful to plants' performance [56]. Thus, the detection of aluminum is essential in controlling its effects on environment and on human health. Hydrazone-based chemosensors for aluminum ion (Al³⁺) are mainly based on coordination with fluorescence turn-on response as a result of restricted molecular motion through inhibiting ESIPT or PET effects.

A Schiff-base 7-methoxychromone-3-carbaldehyde-(pyridylformyl) hydrazone was reported as turn-on fluorescent and colorimetric chemosensor for Al³⁺. This chemosensor (**33**) is colorless and nonfluorescent either in aqueous medium or organic solvents; however, in the presence of aluminum ions (Al³⁺), the development of a yellow-green color and yellow-green fluorescence occurred. The emission intensity of **33** is very low with low fluorescence quantum yield of 0.051 in ethanol, being attributed to a PET mechanism from the Schiff-base nitrogen free pair electrons. As exposed, PET process involves the deactivation of excited state of a fluorophore by the addition of an electron to one of its excited state frontier orbitals which leaves the fluorophore in a non-emissive state.

Metal complexation to Schiff base produces a less efficient electron donor character, interrupting the PET process and, in some cases, improving the fluorescence emission, which is known as CHEF effect [57]. The selective coordination between **33** and Al³⁺ on the carbonyl of chromone, nitrogen of imine (−C=N),

and carbonyl of pyridylformyl hydrazone moiety suppressed the PET effect, restoring the fluorescence of the system with an increase of more than 800-fold (**Figure 14**) [58].

The simple and selective fluorescent naphthalene-hydrazone chemosensor (**34**) for Al^{3+} is a good example of chemosensor based on the excited state intramolecular proton transfer mechanism, that is a process in which photoexcited molecules relax their energy through tautomerization by transfer of protons. Compound **34** has a characteristic UV-vis bands 325 nm and 366 nm which should be assigned to π-π^* transitions of the naphthalene. Only in the presence of Al^{3+} the spectra of **34** exhibited a peak at 432 nm, which remained constant even after more than 1 equivalent of aluminum addition, which indicates 1:1 binding stoichiometry between **34** and Al^{3+}. The free receptor (**34**) exhibited no fluorescence emission with low fluorescence quantum yield (0.5%), justified by the electron transfer from nitrogen atom of imine to the naphthalene ring (PET) and also transfer of the hydroxyl proton to a neighboring imine nitrogen along with the formation of intramolecular hydrogen bond (OH···N) (ESIPT). Upon addition of several metal ions, only Al^{3+} could cause a significant enhancement in the fluorescence emission at 475 nm with a high fluorescence quantum yield (0.26%), due to PET and ESIPT process inhibition (**Figure 14**). Chemosensor **34** showed an interesting fluorogenic response to Al^{3+} in fully aqueous medium which allows its application in biological assays and environmental systems [55].

3.5 Hydrazone derivatives as chemosensors for multiple metals

Although several chemosensors have relatively high degree of selectivity as previously exposed, some chemosensors have been reported to recognize more than one metal ion.

Following a previous described strategy, probes based on the opening of spirolactam ring upon metal coordination were designed as single molecule multianalyte (Cu^{2+} and Hg^{2+}) chemosensors. Compound **35** was reported as colorless and nonfluorescent in aqueous or organic medium (**Figure 15**). The UV-vis spectroscopy indicated that this chemosensor is a good chromogenic probe for Cu^{2+} in ethanol-water (1:99, v/v), whereas other competitive cations failed. Upon the addition of Cu^{2+} to the solution of **35**, a strong absorption band centered at 530 nm appeared, with changes from colorless to pink, because of spirolactam opening (**35-Cu^{2+}**). A significant increase in the fluorescence emission in ethanol was also observed in the presence of Hg^{2+} (ϕ = 0.335) and Cr^{3+} (ϕ = 0.445). However, small addition of water to the ethanol quenched the fluorescence produced by Cr^{3+}, whereas the fluorescence intensity of **35-Hg^{2+}** declined just a little. The rapid quenching of the **35-Cr^{3+}** is justified due to strong coordination between Cr^{3+} and water which may lead to
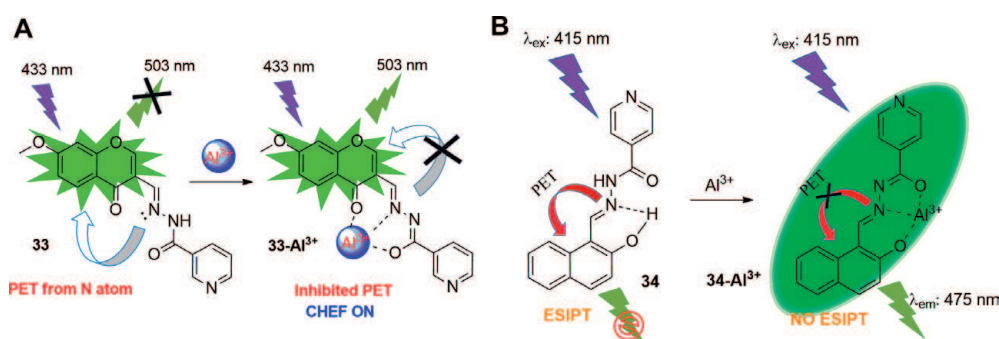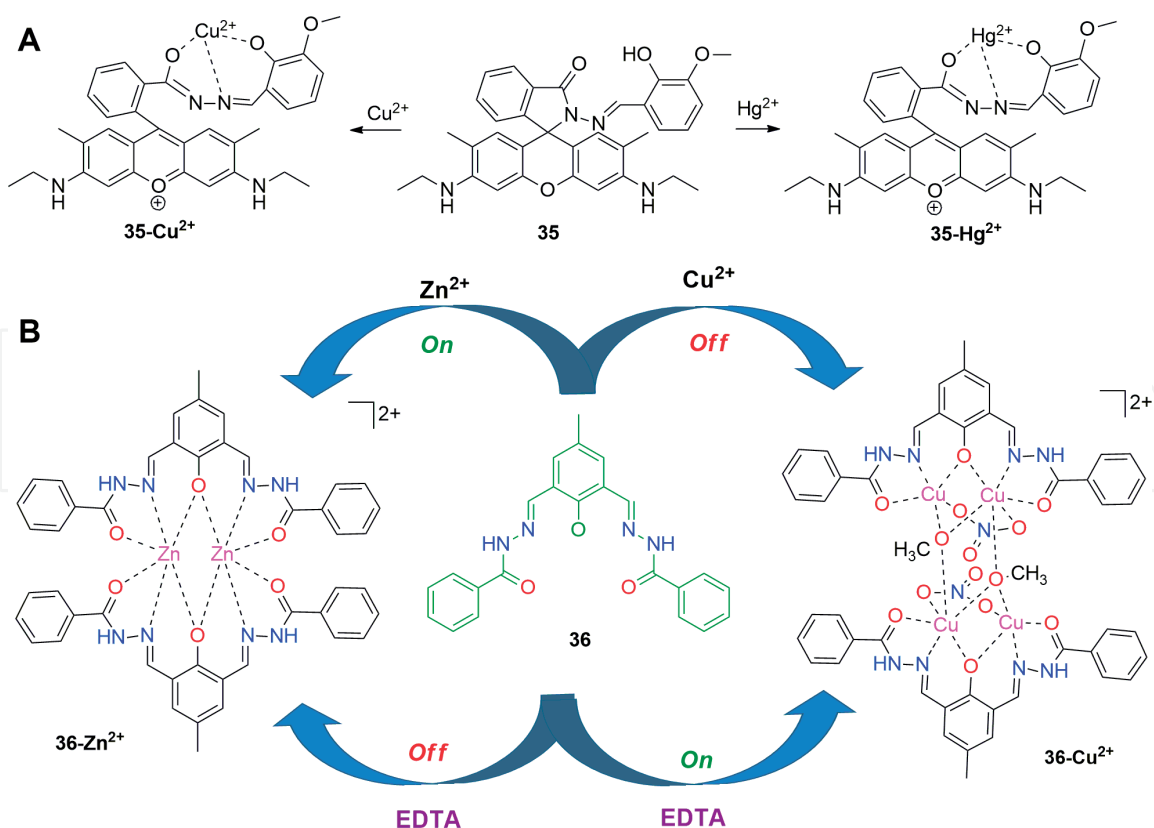

Figure 14.
Molecular structures of Al^{3+} chemosensors 33 (A) and 34 (B) and their sensing mechanism.

Figure 15.
Molecular structures of Cu²⁺ and Hg²⁺ multianalyte chemosensor 35 (A) and of Cu²⁺ and Zn²⁺ multianalyte chemosensor 36 (B).

hydrolysis of **35-Cr³⁺**, resulting in Cr(OH)₃. In addition, the open ring form of **35** after binding with Cu²⁺ has no fluorescence, which is attributed to the quenching of the fluorescence by Cu²⁺, due to paramagnetic properties of the d⁹ Cu²⁺ system [59].

With a similar structure to compound **30**, a hydrazone-based chemosensor (**36**) with *off-on* fluorescence response to Cu²⁺ and Zn²⁺ ion in aqueous media was reported. The reaction of **36** with Cu²⁺ and Zn²⁺ formed their corresponding dimeric complexes, which were characterized by single X-ray analysis (**Figure 15**).

The UV-vis absorption and fluorescence spectroscopy (CH₃CN/0.02 M HEPES buffer at pH 7.3) indicated the binding behavior of chemosensor **36** toward Zn²⁺ and Cu²⁺. The electronic spectra of **36** exhibit two sharp bands at 300 and 363 nm, and upon gradual addition of Cu²⁺ and Zn²⁺, new absorption bands appeared at 423 and 415 nm, attributed to charge transfer in complexes **36-Cu²⁺** and **36-Zn²⁺**. The occurrence of three well-defined isosbestic points demonstrated an equilibrium between **36** and **36-M²⁺**. The little fluorescence presented by **36** (at 493 nm) was almost quenched upon sequential addition of Cu²⁺, being ascribed to the reverse PET from the 4-methylphenyl moiety to the phenolic hydroxyl, and carbohydrazide nitrogen and oxygen atoms, arising from the decrease in electron density after copper ion binding (**Figure 15**). In contrast, Zn²⁺ ion caused the enhancement in the fluorescence emission (~4.1-fold) of **36** due to the filled d¹⁰ electronic configuration of the Zn²⁺ ion, which does not usually involve energy or electron transfer mechanisms for the deactivation of the excited state (**Figure 15**).

Finally, the sensing mechanism of **36-Cu²⁺** and **36-Zn²⁺** has been shown to be reversible in the presence of EDTA, in which the fluorescence of **36** was almost recovered immediately from both complexes, which suggests the high reversibility of the chemosensor and the potential application in real-time monitoring [60].

4. Conclusion

As exposed in this chapter, hydrazone derivatives have been extensively employed as fluorescent and colorimetric chemosensors targeting important biological analytes such as inorganic anions and metal cations. Thus, it is clear that hydrazone scaffold is of great importance in the design of optical sensors. Here we have demonstrated just some representative examples of hydrazone and their ability as chemosensor for CN^-, F^-, AcO^-, multiple anions, Cu^{2+}, Zn^{2+}, Hg^{2+}, Al^{3+}, and multiple metals. Furthermore, we hope that this book chapter with discussions about the sensing mechanisms (PET, FRET, ESIPT, etc.) could be an important tool and contribute to the development of new rational research projects with the hydrazine scaffold for biological and environmental monitoring of metals and anions.

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Conflict of interest

The authors declare no conflict of interest.

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