



5,5'-Bis-vanillin derivatives as discriminating sensors for trivalent cations



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ABSTRACT

Several bis-vanillin derivatives containing semicarbazone moieties have been prepared and used in discriminating trivalent cations. The prepared probes are readily obtained and they are usually highly crystalline. Depending on the ligand and the studied cations, quenching, enhancement or no changes in the fluorescence spectrum were observed. Using a series of the prepared ligands allows distinguishing between Fe^{3+} , Cr^{3+} and Al^{3+} . Detection limits and selectivity in front of divalent cations have been evaluated.

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Introduction

The design and synthesis of chemosensors for transition and p-block metal cations is an important subject in the field of supramolecular chemistry because of their impact in the environment and in human health.¹ Due to these facts the interest for developing chemical sensors, able to detect the presence of trivalent cation ions in environmental and biological systems, has increased in the last years. Among the different chemosensors, those based on ion-induced changes in fluorescence are especially suitable as they are easy to use and usually give an instantaneous response with high sensitivity.² Even though lately a large number of publications related to trivalent cations recognition have appeared in the literature³ only few of them indicate some selective discrimination between Cr^{3+} , Fe^{3+} and Al^{3+} .⁴

The hydrazone functional group has been extensively studied and used in the context of supramolecular chemistry. These compounds are readily obtained, they are usually highly crystalline and crash out of the reaction mixture, which simplifies their

purification process and adds to the appeal of these systems. Among the different applications of hydrazones, they have been widely used in cation sensing through different approaches.⁵ On the other hand, the semicarbazone group also has been used as a complexing moiety.⁶ This group presents an additional carbonyl group that can be involved in complexation giving rise to more stable complexes. Among the different dialdehydes that could be used in the synthesis of dihydrazones or disemicarbazones we decided to explore the utility of 5,5'-bis-vanillin. 5,5'-Bis-vanillin is a bisphenol that can be easily prepared from the monomeric compound in good yields and that can be functionalized at the carbonyl groups giving rise to a large number of compounds.⁷ Even though it has been reported that some of these compounds are able to complex Fe^{3+} and Cu^{2+} ,^{7,8} the applicability of these derivatives in sensing experiments has not been yet evaluated. However, the simplicity of the synthetic procedures in addition to the low cost of its preparation^{8,9} makes these types of compounds appropriate candidates to evaluate their behaviour as chemosensors for different cations. So we here report the synthesis and evaluation of a library of 5,5'-bis-vanillin (1) derivatives (Chart 1) that are cheaply and easily prepared in one step¹⁰ from commercially available compounds and that are able to act as selective chemosensors for Cr^{3+} , Fe^{3+} and Al^{3+} .

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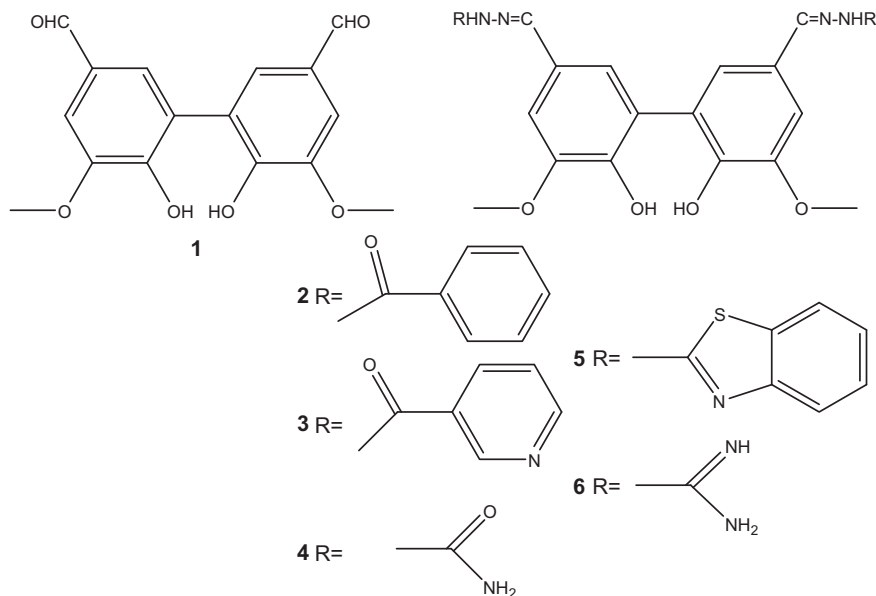


Chart 1. Structures of the synthesized sensors.

Results and discussion

Synthesis and characterization

Compounds **3**, **5** and **6** had been previously reported⁸ whereas **2** and **4** are firstly described here. 5,5'-Bis-vanillin was synthesized by oxidant coupling of vanillin in the presence of sodium persulfate and iron sulfate with 95% yield after precipitation.⁷ Reaction of 5,5'-bis-vanillin with the corresponding hydrazine or semicarbazide produces compounds **1–6** that were isolated by filtration and purified by recrystallization.⁹ All the new compounds were characterized by ¹H NMR, ¹³C NMR and MS.^{11,12}

Compounds **1** and **2** do not present any absorption band at wavelengths higher than 200 nm, compounds **4** and **5** show absorption bands in the zone of 220–250 nm and, finally, compounds **3** and **6** in addition to the band at 220–250 nm show a shoulder at 350 and 330 nm respectively. On the other hand, whereas **4** is fluorescent ($\Phi = 0.21$ measured at $\lambda_{exc} = 278$ nm) the other compounds are scarcely fluorescent ($\Phi < 0.001$, $\lambda_{exc} = 278$ nm).

Sensing experiments

Examination of the recognition capabilities of **1–6** were carried out in a series of UV and fluorescence spectroscopy studies in DMSO solutions. After addition of 1 equiv of the cation ($AlCl_3$, $Cr(NO_3)_3$ and $FeCl_3$)¹³ only a small bathochromic shift of the band was observed in the absorption band. However some compounds showed clear changes in their fluorescent properties in the presence of the studied cations. Thus, the fluorescence spectrum of compound **6** showed a strong enhancement in the presence of Fe^{3+} whereas no changes were observed for Al^{3+} and Cr^{3+} . In addition, the emission corresponding to ligand **4** experiments an appreciable enhancement in the presence of Fe^{3+} and Cr^{3+} whereas it was quenched in the presence of Al^{3+} . What is more, the emission band of this ligand was **6** nm hypsochromically shifted in the presence of Cr^{3+} (Fig. 1).

Taking into account not only the fluorescence enhancement but also the wavelength shift observed, ligand **4** was able to discriminate the three trivalent cations Fe^{3+} , Cr^{3+} and Al^{3+} as can be seen in Figure 2.

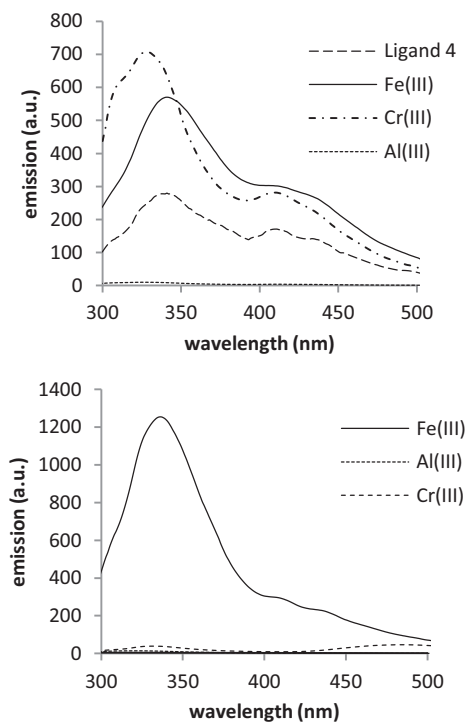


Figure 1. (up) Fluorescence spectra of ligand **4** (10^{-5} M in DMSO) free and in the presence of 1 equiv of Fe^{3+} , Cr^{3+} and Al^{3+} ($\lambda_{exc} = 279$ nm). (bottom) Fluorescence spectra of ligand **6** (10^{-5} M in DMSO) in the presence of 1 equiv of Fe^{3+} , Cr^{3+} and Al^{3+} ($\lambda_{exc} = 278$ nm). Free ligand **6** has not been represented because it is not fluorescent in this range.

These results indicated that the substitution of the carbonyl group of compound **4** by the imino group in compound **6** gives rise to an important change in the sensing properties in front of Cr^{3+} . Thus, whereas in compound **6** only small changes in the fluorescence of the ligand was observed, in the case of **4** a strong enhancement of the fluorescence was induced. By contrast the observed response with both ligands for Fe^{3+} and Al^{3+} was similar (enhancement of the fluorescence for Fe^{3+} and no emission for Al^{3+}) (Fig. 3).

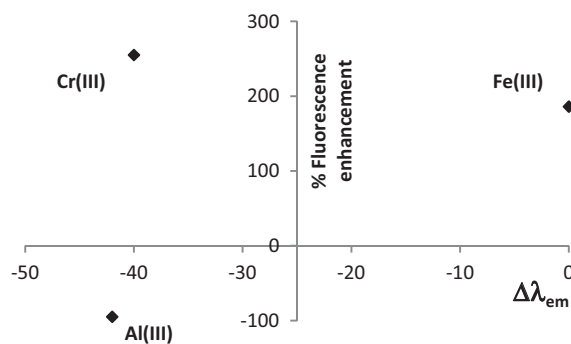


Figure 2. 2D representation of significant changes in the fluorescent properties of **4** in the presence of Fe^{3+} , Cr^{3+} and Al^{3+} .

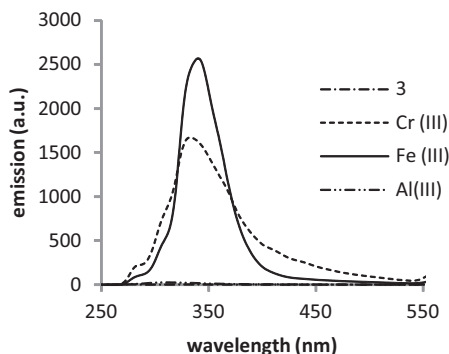


Figure 3. Fluorescence spectra of ligand **3** (10^{-5} M in DMSO) free and in the presence of 1 equiv of Fe^{3+} , Cr^{3+} and Al^{3+} ($\lambda_{\text{exc}} = 278$ nm).

From a qualitative point of view, ligand **6** was able to distinguish Fe^{3+} from Cr^{3+} and Al^{3+} whereas ligand **4** could be used to discriminate between the three studied cations. On the other hand, complexation with ligand **3** gave rise to higher fluorescence enhancement. Thus whereas the fluorescence of ligand **4** showed an enhancement around 400–500 times on complexation, that of ligand, ligand **3** showed an enhancement higher than 1500 for Cr^{3+} and 2500 and Fe^{3+} .

Due to the stronger effect observed with ligand **3** the complexation characteristics of this ligand were studied. Thus, titration experiments developed with this ligand showed that the stoichiometry of the formed complexes was 1:1 being the corresponding complexation constants $\log K = 4.5 \pm 0.4$, 5.2 ± 0.4 and 4.4 ± 0.5 for Fe^{3+} , Cr^{3+} and Al^{3+} , respectively¹⁴ (Fig. 4). In order to know the functional groups involved in the complexation process ^1H NMR experiments were undergone.

The changes observed in the ^1H NMR spectrum of ligand **3** in the presence of Al^{3+} (important upfield shift of the NH signal and downfield shift of the azomethine hydrogen) suggest that both the carbonyl and the imine nitrogen atom are involved in complexation (Fig. 5). In addition, the sharper signals in the ^{13}C NMR spectrum of the complex indicate a conformational restriction when compared with the free ligand. On the other hand, the observed downfield shifts of the azomethine and carbonyl carbon signals are compatible with the suggested structure. Finally, a conformational change in the ligand could explain the shifts of the bis-vanillin aromatic signals.

The sensing response of different divalent cations (especially Fe^{2+}) was studied to have additional information about the probes selectivity. These cations did not induce any change in the fluorescent response of the studied ligands. Finally the limits of detection with this ligand were evaluated from the equation:

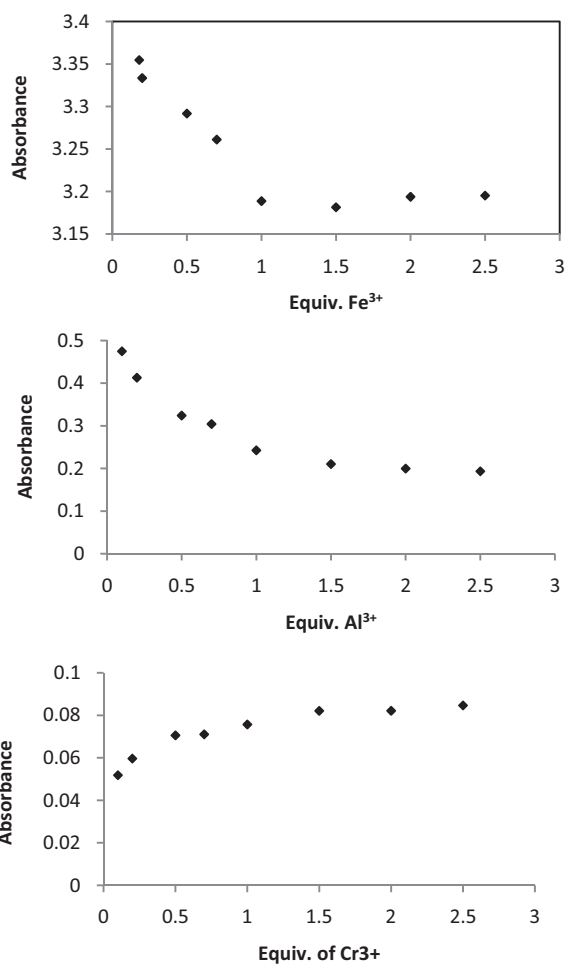


Figure 4. Stoichiometry determination of the complexes formed between ligand **3** and the studied trivalent cations.

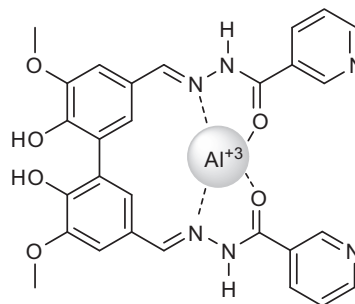


Figure 5. Model of complex proposed for $3 \cdot \text{Al}^{3+}$ in DMSO based on the ^1H NMR observations.

$\text{LOD} = K \times \text{Sb}_1 / S$, where $K = 3$, Sb_1 is the standard deviation of the blank solution and S is the slope of the calibration curve.¹⁵ The obtained value was around 10^{-5} M for the three studied cations.¹⁶

Conclusions

Five bis-vanillin derivatives containing hydrazine or semicarbazone moieties have been studied as sensors for trivalent cations (Fe^{3+} , Cr^{3+} and Al^{3+}). Two of these compounds have been reported in this Letter for the first time. All the studied compounds are easily prepared in one step from cheap commercial compounds and they are isolated by precipitation and purified by

recrystallization. The structural differences between the prepared compounds have strong influence of their response in front of trivalent cations. Thus, whereas compound **4** shows an appreciable enhancement of fluorescence in the presence of Cr^{3+} , the fluorescence of compound **6** does not experiment any change in the presence of this cation. On the other hand, chemosensor **3** was the most sensible among all the prepared compounds. In conclusion, either compound **4** alone or, even better an array containing several of the prepared sensors can be used to discriminate between Fe^{3+} , Cr^{3+} and Al^{3+} .

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.04.120>.

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- General procedure to carboxamides*: 5,5'-Bis-vanillin (**1**) (0.66 mmol) was suspended in absolute ethanol (30 ml) and semicarbazide (1.32 mmol) was added to the suspension. The reaction mixture was refluxed for 24 h. At the beginning of the heating all product is dissolved and over time it begins to appear a new precipitate. The solid was filtered and dried to give a pure solid.
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- General methods*: The different materials were purchased and used as received. Silica gel 60 F254 (Merck) plates were used for TLC. ^1H and ^{13}C NMR spectra were recorded using a Bruker DRX-500 spectrometer (500 MHz for ^1H and 126 MHz for ^{13}C) and a Bruker Avance 400 MHz (400 MHz for ^1H and 100 MHz for ^{13}C) with the deuterated solvent as the lock and residual solvent as the internal reference. HRMS were recorded using a Shimadzu QP5050A. Absorption spectra were recorded with a Shimadzu UV-2101PC spectrophotometer. Fluorescence spectra were carried out in a Varian Cary Eclipse fluorimeter. 5,5'-Bis-vanillin was prepared following the procedure described in Ref. 7.
- Spectral data*: **2** ^1H NMR (DMSO- d_6 , 500 MHz): 8.88 (s, 2H, NH); 7.90 (s, 2H, CH=N); 7.65 (d, 4H, $J = 10$ Hz, H-2'); 7.52 (s, 2H, H-6); 7.29 (t, 4H, $J = 10$ Hz, H-3'); 7.13 (s, 2H, H-2); 7.01 (t, 2H, $J = 10$ Hz, H-4'); 3.95 (s, 6H, OCH_3). ^{13}C NMR (DMSO- d_6 , 125 MHz): 148.4 (CH=N); 146.2 (C-3), 142.1 (C-4); 139.7 (C-4'); 128.9 (C-3'); 125.7 (C-6); 125.3 (C-1'); 124.1 (C-5); 122.8 (C-1); 120.4 (C-2'); 108.7 (C-2); 56.6 (OCH_3). HRMS calcd for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_4$ 482.1954 found (M+1): 483.2013. **3** ^1H NMR (DMSO- d_6 , 500 MHz): 12.00 (s, 2H, NH); 9.01 (s, 2H, H-5'); 8.72 (d, 2H, $J = 5$ Hz, H-2'); 8.31 (s, 2H, CH=N); 8.22 (d, 2H, $J = 10$ Hz, H-4'); 7.55 (dd, 4H, $J = 10$ and 5 Hz, H-3'); 7.39 (s, 2H, H-6); 7.10 (s, 2H, H-2); 3.90 (s, 6H, OCH_3). ^{13}C NMR (DMSO- d_6 , 125 MHz): 161.8 (C=O); 152.5 (C-4'); 149.5 (C-3), 149.0 (CH=N); 148.7 (C-5'); 147.0 (C-4); 135.8 (C-2'); 129.9 (C-5); 125.6 (C-1'); 125.2 (C-6); 124.8 (C-1); 123.9 (C-3'); 108.4 (C-2); 56.5 (OCH_3). HRMS calcd for $\text{C}_{28}\text{H}_{24}\text{N}_6\text{O}_6$ 540.1757 found (M+1): 541.1863. **4** ^1H NMR (DMSO- d_6 , 300 MHz): 10.00 (s, 2H, NH); 8.74 (br. s, 2H, OH); 7.76 (s, 2H, CH=N); 7.39 (s, 2H, H-6); 6.97 (s, 2H, H-2); 6.45 (br. s, 4H, NH_2); 3.89 (s, 6H, OCH_3). ^{13}C NMR (DMSO- d_6 , 75 MHz): 155.7 (C=O); 150.4 (CH=N); 148.4 (C-3); 147.6 (C-4); 125.7 (C-5); 124.7 (C-6); 124.2 (C-1); 118.44 (C-2); 56.6 (OCH_3). HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{N}_6\text{O}_6$ 416.1444 found (M+1): 417.1732. **5** ^1H NMR (DMSO- d_6 , 400 MHz): 12.10 (s, 2H, NH); 9.00 (br. s, 2H, OH); 8.08 (s, 2H, CH=N); 7.72 (d, 2H, $J = 8$ Hz, H-6'); 7.40 (d, 2H, $J = 8$ Hz, H-3'); 7.31 (s, 2H, H-6); 7.29 (t, 2H, $J = 8$ Hz, H-4'); 7.13 (s, 2H, H-2); 7.09 (t, 2H, $J = 8$ Hz, H-5'); 3.93 (s, 6H, OCH_3). ^{13}C NMR (DMSO- d_6 , 125 MHz): 167.3 (C-1'); 150.4 (C-3); 148.4 (C-4); 146.3 (CH=N); 126.3 (C-2' and C-7'); 125.9 (C-1); 125.3 (C-5); 123.2 (C-3' and C-6'); 121.9 (C-6); 121.8 (C-2'); 108.5 (C-2); 56.3 (OCH_3). HRMS calcd for $\text{C}_{30}\text{H}_{24}\text{N}_6\text{O}_4\text{S}_2$ 596.1300 found (M+1): 597.1379. **6** ^1H NMR (DMSO- d_6 , 400 MHz): 11.93 (br. s, 4H, NH_2); 9.00 (br. s, 2H, NH); 8.08 (s, 2H, CH=N); 7.51 (s, 2H, H-6); 7.19 (s, 2H, H-2); 3.91 (s, 6H, OCH_3). ^{13}C NMR (DMSO- d_6 , 100 MHz): 155.3 (s, C-8); 147.8 (s, C-3); 147.0 (s, CH=N); 146.6 (s, C-4); 125.2 (s, C-5); 124.2 (s, C-6); 123.8 (s, C-1); 108.8 (s, C-2); 56.1 (s, OCH_3). HRMS calcd for $\text{C}_{18}\text{H}_{22}\text{N}_8\text{O}_4$ 414.1764 found (M+1): 415.1836.
- Spectroscopic measurements*: Metal cations (Fe^{3+} , Cr^{3+} , Al^{3+}) as nitrate or chloride salts were used to obtain solutions of concentration of 10^{-4} M in MeOH or acetonitrile. UV spectra were recorded using a Shimadzu UV-2600 spectrometer. Fluorescence spectra were recorded using a Varian Cary Eclipse fluorimeter. Titrations were performed by adding aliquots of M^{3+} (10^{-3} M in CH_3CN) in a solution of ligand (10^{-5} M) in DMSO.
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- General procedure for limit of detection determinations*. Increasing amounts of the corresponding simulant solutions (in MeOH) were added to ligand **6** in DMSO (10^{-5} M). The UV spectra were recorded in 1-cm path length cells at 25 °C (thermostatted). Representation of absorbance at the appropriate wavelength vs. concentration of simulant allowed the limit of detection to be calculated.