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Article

Thiosemicarbazone- and Thiourea-Functionalized Calix[4]arenes in *cone* and 1,3-*alternate* Conformations: Receptors for the Recognition of Ions

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Abstract: In this research we have synthesized and evaluated five calix[4]arene-based receptors functionalized with thiosemicarbazone or thiourea groups, incorporating pyridinyl naphthalene or triazolopyridine chromophores in 1,3-*alternate*, pinched *cone* and *cone* conformations. The ion recognition capabilities of these receptors were investigated using UV-visible and fluorescence spectroscopy. Receptor (**I**), which adopts a pinched *cone* conformation with thiosemicarbazone groups, demonstrated bifunctional sensing abilities by detecting both cations and anions. Receptors (**II**) and (**III**) showed remarkable selectivity and sensitivity for Cu^{2+} ions. Receptors (**IV**) and (**V**), in *cone* and 1,3-*alternate* conformations, respectively, where functionalized with a triazolo[1,5-a]pyridine fluorophore and exhibited highly sensitive ON-OFF fluorescence sensing for Co^{2+}, Cu^{2+} and Ni^{2+} ions, with significant fluorescence quenching upon binding and a low detection limit of 2.94 μg/L for the Co^{2+} ion in receptor (**IV**). Ion receptor (**I**) demonstrates a strong performance in broad-spectrum ion detection, whereas the structural conformations of receptors (IV) and (V) play a pivotal role in their remarkable selectivity and sensitivity for specific transition metals in fluorescence-based sensing.

Keywords: calix[4]arene; conformations; receptor; bifunctional

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1. Introduction

The development of molecular systems for the detection of anions [1,2], cations [3,4] or neutral molecules [5] is a fundamental area of research within supramolecular chemistry, due to its wide range of applications in fields such as medicine, biology, and environmental sciences. Molecular systems capable of selectively binding and detecting these species are essential tools for advancing analytical chemistry. Among these systems, chemosensors based on calixarenes have received significant attention due to their unique structural features and versatility in functionalization.

Calix[4]arenes, macrocyclic compounds composed of phenolic units linked by methylene bridges, are particularly valued for their ability to act as molecular scaffolds in the design of ion sensors. These structures can adopt multiple conformations such as *cone*, partial *cone*, 1,2-*alternate*, and 1,3-*alternate*, allowing for the design of tunable host–guest structures. These interactions were also influenced by factors like the cavity size and the type of solvent used in previous studies [6,7]. Functionalization at the upper or lower rims with groups such as amide, urea, and thiourea enables the introduction of specific binding sites for ions, enhancing the selectivity and efficiency of these sensors [8–14].

To achieve effective ion recognition, various functional groups are incorporated into calixarenes. For example, the thiosemicarbazone group, which includes hydrogen bond donors, thiocarbonyl groups and imine groups, offers multiple interaction sites (N, O and S atoms). This structural arrangement improves the binding efficiency and selectivity of the sensor towards various metal cations and anions [11–14]. The incorporation of fluorescent moieties further amplifies their utility, allowing for sensitive detection through spectroscopic methods [15–20].

Recent studies have focused on developing dual-function sensors capable of detecting both cations and anions within a single receptor molecule [21,22]. Various systems for ion detection have been studied in this area, the most important of which are (i) focused on the use of calixarenes in analytical chemistry, particularly for selective ion recognition [23], (ii) calixarenes as selective agents in ion-selective electrodes (ISE) [24] and (iii) calixarenes on nanoparticle surfaces which have a high sensitivity for environmental and biological analytes [25].

The most fundamental fluorescent groups employed in the design of chemosensors are polycyclic aromatic compounds such as anthracene, pyrene, phenanthrene and naphthalene. These groups were integrated into the calixarenes, either at the upper or lower rim, to enhance their ion detection [26–29]. Among the various groups attached to calixarenes, particular attention has been applied to heterocyclic rings in this study. Specifically, two pyridine-based chromophores incorporating naphthalene or triazolopyridine were investigated.

For the first chromophore, the synthesis method described in the literature for *N*-2-pyridinyl-2-naphthalenecarboxamide was employed. This technique, involving catalysis and microwave irradiation, yielded a compound with promising fluorescent properties [30–33]. For the second chromophore, 3-(2-pyridyl)-[1–3]triazolo[1,5-a]pyridine, obtained from the researcher Belen Abarca, was used. Its synthesis has been extensively described in previous publications [34–36], and its fluorescent properties have been exploited in cation detection studies in the presence of cyclodextrins [37].

Building on this foundation, the present study expands on previous research into the development of innovative sensors based on calix[4]arenes [21,38–43]. Pyridinyl chromophore moieties were introduced into a calix[4]arene framework through thiosemicarbazone or thiourea bridges, positioned either at the lower or upper rim. These receptors, designed in *cone*, pinched *cone* and 1,3-*alternate* conformations, are intended for the dual detection of cations and anions. Detection was carried out using both UV–visible and fluorescence spectroscopy, highlighting the versatility and potential of these systems in chemical sensing applications.

2. Materials and Methods

2.1. General Procedures

The synthetic chemicals, including perchlorate salts, tetrabutylammonium salts, and other reactants, were procured from Sigma-Aldrich. All reagents and solvents were of analytical grade and used without further purification. Appropriate safety measures and handling guidelines were strictly followed throughout the experimental work, particularly for the storage and use of potentially hazardous reagents. The UV-Vis absorption spectra of the samples were recorded on an Agilent 8453 spectrophotometer using standard 1.00 cm quartz cells in accordance with standard operating procedures. Melting points (uncorrected) were obtained using a Kofler hot-stage microscope. Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AVANCE III HD (300 MHz) spectrometer with tetramethyl silane as the internal reference at room temperature. Infrared spectra were obtained using a FT-IR spectrometer (Thermo iS50) with a germanium attenuated total reflection (ATR) accessory. The range was 4000–600 cm^{-1}, with an average of 20 scans per analysis. Prior to taking any measurements, a blank analysis was conducted to account for any air signals. The mass spectra (LC/MSD-TOF) were obtained at the University of Valencia in Spain. The carbon, hydrogen, and nitrogen contents were determined using an Elemental LECO TRUSPEC CHNS Micro analyzer at the University of Seville in Spain. All experiments were conducted in triplicate.

2.2. Spectrophotometric Measurements

The receptors were dissolved in DMSO (stock solution 1.5 mmol L^{-1}) and stock solutions (15 mmol L^{-1}) of cations and anions were prepared in CH_3CN. All anions were countered with tetrabutylammonium, and all cations were countered with perchlorate. UV absorption measurements were conducted on an Agilent 8453 spectrophotometer using standard 1.00 cm quartz cells. The titrations were conducted by varying the equivalents of the ion between 0 and 40 depending on the receptor under investigation, using stock solutions, with the receptor concentration fixed at 11.5 µmol L^{-1}. All solutions were diluted to 2.6 mL. The screening studies were conducted with the receptor concentration fixed at 11.5 µmol L^{-1}, and 10 equivalents of the stock solutions of ions were added accordingly. Job plot experiments were conducted with the total concentration (receptor + ion) maintained at 11.5 µmol L^{-1}, in accordance with the methodology described in reference [44].

Fluorescence spectra were measured on a Perkin Elmer LS55, with excitation at 350 nm and bandwidths of 5 and 10 nm, respectively, for both excitation and emission. The emission spectrum was recorded within the 380–560 nm range. All measurements were conducted in a 1 cm quartz cell with a final receptor concentration of 0.158 µmol L^{-1}. During the titration, the concentration of cations varied from 0 to 3 equivalents. The appropriate amounts of ion stock solutions were added to prepare the screening response experiments. All experiments were carried out under standard conditions of pressure, temperature and humidity, in accordance with established laboratory procedures.

2.3. Determination of Association Constants

The association constant (K_a) for a 1:1 receptor–ion complex or the binding constant (β) for a 1:2 receptor–ion complex was obtained by nonlinear least-squares fitting of these plots using the BindFit programme (http://supramolecular.org accessed on 7 January 2025) from Thordarson's group [45,46]. Please refer to the Supplementary Information for all results and data obtained from the fits. This includes the values of fit data points, parameters, root mean square (RMS) and covariance to confirm the fits, which are highlighted for both stoichiometries.

2.4. Determination of Limit of Detections

The limit of detection (LOD) was calculated using Equation (1) [39]

$$\mathbf{LOD} = \frac{\mathbf{K} \cdot \boldsymbol{Sb}}{\mathbf{m}} \tag{1}$$

where *Sb* corresponds to standard deviation of the blank, m corresponds to the calibration sensitivity from the plot of the difference in absorbance ($A - A_o$) or fluorescence ($I - I_o$) as function of the concentration of ions and K corresponds to the method detection limit of 3.

3. Results

3.1. Synthetic Procedures

The synthesis of the receptors (**I–V**) was based on experimental procedures that involved a convergent synthesis, whereby the calixarene in the upper or lower rim in different conformations (*cone* and 1,3-*alternate*) was modified with terminal functional groups: amino or isothiocyanates. Finally, a condensation reaction was performed with N-(6-isothiocyanatopyridin-2-yl)-2-naphthamide (**6**) or 3-(6-(6-(N-diethylamino)- 2-pyridinyl)-1,2,3-triazolo[1,5-a]pyridine (**10**) as appropriate. The structures are shown in Figure 1 and a description of the scheme, synthesis and spectra of the characterisations is given in the Supplementary Information.

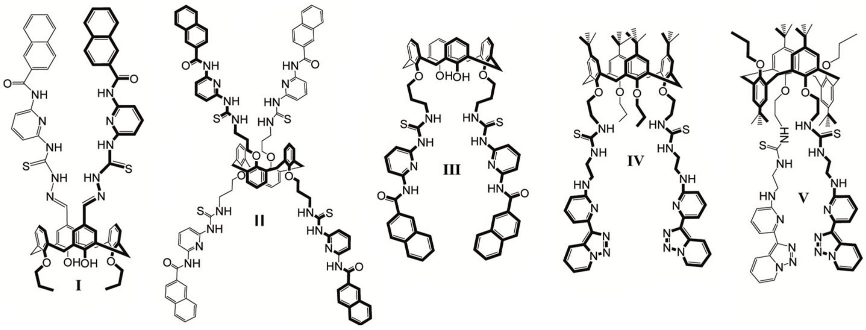

Figure 1. Structures of receptors **I**, **III** and **IV** in *cone* conformations and receptors **II** and **V** in *alternate* conformations.

In order to obtain the precursor dimethylhydrazine (**5**), a retro Friedel–Crafts reaction was carried out on the p-tert-butylcalix[4]arene [47]. Two hydroxyl groups of calix[4]arene (**2**) were transformed into an di-alkylation with propyl bromide and potassium carbonate (K_2CO_3) [48]. A Duff reaction, the compound (**3**) was conducted using hexamethylenetetramine (HMTA) as a source of formyl groups on the upper rim. [49] Thus, the distally di-formylated calix[4]arene (**4**) was obtained. Subsequently, the aldehyde groups of the molecule were nucleophilically attacked by an excess of hydrazine monohydrate, resulting in the formation of Schiff bases such as di-methylhydrazine calix[4]arene (**5**). Subsequently, N-(6-isothiocyanatopyridin-2-yl)-2-naphthamide (**6**) was synthesized from 2,6-diaminopyridine. The synthesis was conducted using a controlled route in tetrahydrofuran at 0 °C. The reaction was carried out with an excess of 2,6-diaminopyridine [50,51]. The formation of the isothiocyanate group was subsequently achieved by reacting the aromatic primary amine with thiophosgene ($CSCl_2$) in a 1:1 molar ratio. Finally, the synthesis of receptor (**I**), through a coupling reaction based on the nucleophilic attack of the amino group on the isothiocyanate in chloroform, was employed to obtain the thiosemicarbazone group [52].

The syntheses of receptors (**II**) and (**III**) starts with derivative 2, which is modified by dialkylation at the distal 1,3-positions with N-(3-bromopropyl)phthalimide using potassium carbonate to obtain compound (**7**) [53]. In the presence of cesium carbonate, the 1,3-*alternated* conformation with N-(3-bromopropyl)phthalimide groups is obtained, producing precursor (**8**) [54]. The two routes share a common reaction for the formation of the amino calix[4]arenes (**9**) and (**10**), where deprotection of the phthalimide groups leads to the primary amines via the Gabriel reaction [55]. In route 1, the final reaction consists of the condensation of the amine groups of the calix[4]arene with the isothiocyanate groups of the chromophore to give, in this case, the thiourea bridges of the (**II**) and (**III**) receptors.

Calix[4]arene-based thiourea receptors (**IV**) and (**V**) were synthesized from precursors (**14**) and (**19**). The first step was the dialkylation of (**1**) with N-bromoethylphthalimide in the presence of a weak base to obtain derivative (**11**) [56]. The reaction of diphthalimide calixarene (**11**) with 1-bromopropane in the presence of cesium carbonate resulted in the formation of 1,3- *alternate* derivative (**17**) [54]. Through the same method used to prepare (**17**), when a change in the base from cesium carbonate to sodium hydride was made, the *cone* conformation derivative (12) was obtained. Hydrazinolysis of diphtalimide (**12**) or (**17**) gave the derivative diamine (**13**) or (**18**) in a *cone* or 1,3-*alternate* conformation as required [55]. Then, (**13**) and (**18**) were transformed into the corresponding diisothiocyanate precursors (**14**) and (**19**) by a modified procedure described by Santoyo-Gonzalez [57]. Finally, the reaction of the triazolopyridine derivatives with terminal amino groups obtained by Belén et al. [34–36] with calixarene isothiocyanate in conical and 1,3-*alternate* conformations in methanol, catalyzed by triethylamine, gave receptors (**IV**) and (**V**) based on calix[4]arene.

It is noteworthy that the characterization of these sensors revealed the formation of thiosemicarbazone or thiourea bridges, clearly identified by the thiocarbonyl signal in infrared spectroscopy, which occurs at around 1200 cm^{-1}. It is noteworthy that the receptors adopt different conformations, with calix[4]arenes (**II**) and (**V**) exhibiting a *cone* conformation. This is evidenced by the separation of the geminal hydrogens of the calixarene bridge, which range from 1 to 0.8 ppm. In the case of compounds (**III**) and (**IV**) in the 1,3-*alternate* conformation, only one signal was observed for these hydrogens, which are characteristic of this conformation.

Finally, the receptor (**I**) is in the pinched *cone* conformation, probably due to the hydrogen bridge-type interaction between the thiourea groups of the spacers, which causes these fragments to approach the aromatic units of the calix[4]arene that are not substituted and rotates them outwards. This results in a separation of the signals from the hydrogens of the calixarene bridge by 0.6 ppm.

3.2. Screening with Ions

The UV–visible responses of calixarenes towards different cations were investigated in acetonitrile, with the addition of 10 equivalents of Ag^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, K^+, Li^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Zn^{2+} and Fe^{2+} and 10 equivalents of F^-, HSO_4^-, I^-, N_3^-, NO_3^-, NO_2^-, SCN^-, ClO_4^-, Br^-, Cl^-, CH_3COO^-, $CF_3SO_3^-$ and CN^- to the solutions of (**I**)–(**V**). Figure 2 summarizes only the changes in the absorbance or fluorescence (as appropriate) of the spectra of the receptors with the ions with which they may interact. All observed changes within the ions of each receptor are given in the Supplementary Information.

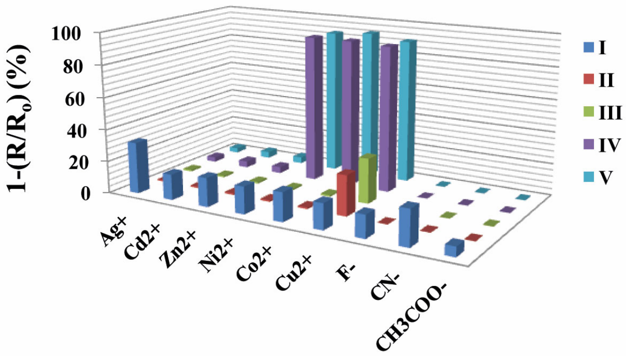

Figure 2. UV–visible or fluorescent ratiometric (R) behaviour of receptors (**I**)–(**V**) after addition of 10 equivalent of different cations and anions in acetonitrile solution.

Figure 2 shows that the behaviour of (**I**) in the presence of cations can detect a wide range of cations, including nickel (**II**), copper (**II**), cobalt (**II**), zinc (**II**) and silver (**I**). The absorbance band shows a significant decrease, ranging from 16% to 32%. Compared to receptors (**II**) and (**III**), these receptors show a higher degree of selectivity, only recognizing copper (**II**). Receptors (**IV**) and (**V**) were studied by fluorescence spectroscopy, which showed a significant decrease in fluorescence intensity (about 90%) in the presence of copper (**II**), nickel (**II**) and cobalt (**II**) ions.

In the figure showing receptors (**II**)–(**V**), the observed behaviour is practically identical and there is no interaction with anions. When analyzed with an excess of anions in acetonitrile, the absorption spectra of receptor (**I**) showed a decrease in the band between 22 and 6% when interacting with fluoride, cyanide and acetate anions.

*3.3. UV-Visible Studies of Receptor (**I**) with Ions*

Following the results of the receptor screening in the presence of the ions, corresponding titration and Job plot studies were carried out, the results of which are presented below. See the graphs and data obtained from Figure S4 in the Supplementary Information for a more detailed report.

Figure 3 illustrates the titration of compound (**I**) with copper (**II**) and fluoride ions. As the cation concentration increases from 0 to 5 equivalents, a decrease in the maximum at 300 nm and the appearance of an isosbestic point at 360 nm are observed. The appearance of an isosbestic point in the titrations indicates equilibrium between the free receptor and the complex formed. In this case, it allows for the confirmation of the formation of the complex between the Cu^{2+} ion and (**I**). Furthermore, in the specific case of copper (**II**), the band at 300 nm is broadened and coupled with the band at 310 nm into a single large band, as shown in Figure 3a. This behaviour was observed to be similar for the interaction with other cations, except for the cadmium (**II**) ion, which only shows absorbance changes at high concentrations of the ion (3–5 eq). All presented a decrease in the maximum at 300 nm, an increase in the band around 380 nm, and the appearance of an isosbestic point at 360 nm (Figure S4), which is consistent with the observed behaviour. In the specific cases of silver (I), copper (II) and zinc (II), an isobestic point is observed at 290 nm. This suggests a potential 1:2 stoichiometry in the formation of their complexes.

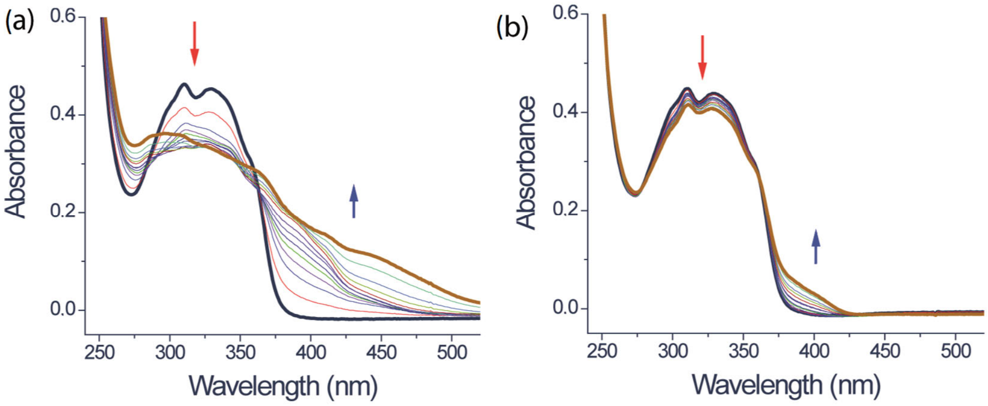

Figure 3. Titrations of receptor (**I**). (**a**) Change in absorbance spectrum of receptor (**I**) after titration of 0–5 equivalents of copper (II) ion. (**b**) Change in absorbance spectrum of receptor (**I**) after titration of 0–5 equivalents of fluoride ion. (red arrow: decrease in absorbance maximum and blue arrow: appearance and increase of a band).

As the concentration of the fluoride ion increases, the band around 335 nm gradually decreases, and in turn, a band at a lower energy appears at 390 nm, with a clear isosbestic point at 360 nm (Figure 3b). Identical behaviour is presented by the cyanide anion (S4), while no change in absorbance could be detected in the presence of the acetate ion. This behaviour can be explained by the fact that these ions may produce a strong interaction with the N-H of the thiosemicarbazone groups, resulting in the deprotonation of the latter due to the basic character of both ions in acetonitrile [58–60].

The association constants and binding constants were determined by utilizing data from UV–visible titrations through fitting in BindFit v0.5. The stoichiometry was identified using the continuous variation method (Figure S5), where a 1:1 stoichiometric complex was determined for the interaction of the ion (Co^{2+}, Ni^{2+}, F^-, CN^-) with the receptor (**I**). We observed that the maximum is shifted but does not correspond to a 1:2 complex in the stoichiometry with the Job plot obtained with the silver (I), copper (II) and zinc (II) ions. However, an excellent fit with the 1:2 complex models was observed in the fit of the experimental data.

The values of all constants determined by BindFit are presented in Table 1. It is evident that the complex formation constants for 1:2 complexes are higher than those for 1:1 complexes. This is due to the fact that the cumulative formation constant (β) for a 1:2 complex is the product of the successive formation constants. This indicates that the 1:2 complexes are more stable than the 1:1 complexes. The values observed for both anions are practically identical, which is clearly due to the similar behaviour of these ions in acetonitrile and their possible interaction with the thiosemicarbazone group. It should be noted that receptor (**I**) has a limit of detection for nearly all cations, except zinc (**II**), which are similar to each other, indicating that they can be recognized in solution. The best values observed correspond to close to 0.60 mg/L, allowing them to detect silver (**I**), nickel (**II**), cobalt (**II**) and copper (**II**) at low concentrations (Figure S6).

Table 1. Binding constant and limit of detection of receptor (**I**) determined in UV–visible spectroscopy in acetonitrile.

		Ag^+	**Ni^{2+}**	**Co^{2+}**	**Zn^{2+}**	**Cu^{2+}**	**CN^-**	**F^-**
(**I**)	Log (K_a)	-	5.65	6.49	-	-	3.89	3.57
	Log (β)	13.13	-	-	10.87	11.11	-	-
	LOD (mg/L)	0.60	0.73	0.68	4.25	0.76	1.45	2.09

During the titrations, a colour change was observed in the solutions of receptor (**I**) in the presence of copper (**II**), associated with changes in the absorption spectra of the calix[4]arene-based compounds. As shown in Figure 4, the solution of receptor (**I**) at a concentration of 7.88 µM in acetonitrile is colourless. By adding aliquots of 0.4 mM copper (**II**) solution, the solution becomes increasingly yellow. These results indicate that a colorimetric sensor has been obtained that changes colour in the presence of anions and cations when complexes are formed [61].

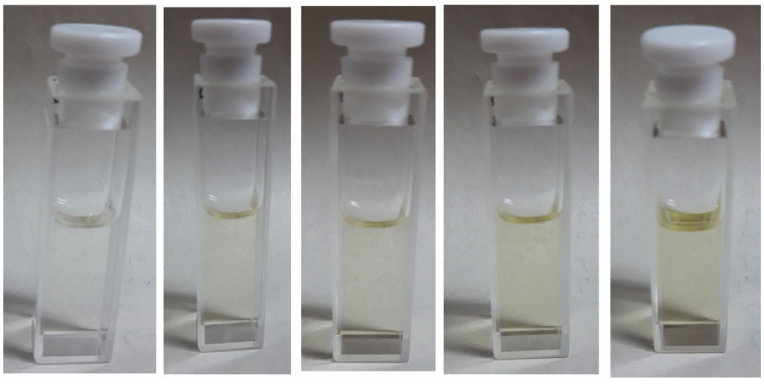

Figure 4. Colorimetric studies of receptors of (**I**) (7.88 mM) with aliquots 0.4 mM copper (II) ions.

For the absorbance spectra of the complexes with molecule (**I**) with copper (**II**), the appearance of a new band at a lower energy (around 400 nm) was observed, which was very pronounced compared to other cations, and can be related to the colour change observed in the cuvettes. Based on the above, it was concluded that this compound could be used as a naked-eye sensor for the detection of copper (**II**) cations.

*3.4. UV–Visible Studies of Receptors (**II**) and (**III**) with Copper (**II**) Ions*

Based on the results obtained in the screening, only the Cu^{2+} ion produces a change in the absorbance spectrum for both receptors. Figure 5 shows the absorbance spectra for calixarenes (**II**) and (**III**) in the presence of copper (**II**), where an increase in the absorption band at 270 and 320 nm is exhibited, transforming into a single band with a maximum at 270 nm and the appearance of a band between 350 and 400 nm. This observation is in accordance with Pearson's hard–soft acid–base (HSAB) theory, which postulates that sulphur and nitrogen atoms of the pyridine moiety exhibit an affinity for copper (**II**) ions [62,63].

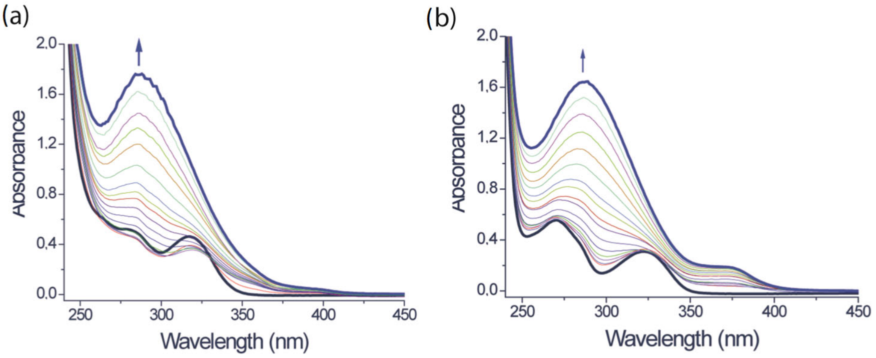

Figure 5. Titrations of receptors (**II**) and (**III**). (**a**) Change in absorbance spectrum of receptor (**II**) after titration of 0–40 equivalents of copper (II) ion. (**b**) Change in absorbance spectrum of receptor (**III**) after titration of 0–40 equivalents of copper (II) ions. (blue arrow: increase of a maximum).

The association constants of the UV–visible titration experiments were calculated using the results of the titrations. These were fitted to a 1:1 complex model, where the log (K_a) was 4.02 and 3.67 for receptors (II) and (III), respectively. It can be concluded that the behaviour of both receptors is similar in the presence of these ions. The binding stoichiometry is determined from the ratio of the mole fractions of the two components found at the maximum of the curve. Maximum complexation occurred at a molar fraction of 0.5 resulting in a 1:1 stoichiometry (Figures S10 and S16). Detection limit studies in the linear range from 6.0×10^{-5} to 1.5×10^{-4} were performed, resulting in limit of detection values for receptor (**II**) and (**III**) of 1.27 and 1.99 mg/L, respectively, for the detection of copper ion (**II**). Based on these results, it can be concluded that the copper ion complexes are similar to each other.

*3.5. Fluorescence Studies of Receptors (**IV**) and (**V**) with Nickel (**II**), Cobalt (**II**) and Copper (**II**) Ions*

Calix[4]arenes (**IV**) and (**V**) were be studied by fluorescence spectroscopy, where both receptors showed a strong fluorescence centred at 450 nm upon excitation at 350 nm, and based on the screening results, corresponding titration and Job plot studies were performed. (Figures S20–S26). The binding of copper, nickel and cobalt to photo physically active supramolecular sensors can lead to fluorescence enhancement, fluorescence quenching and/or other changes in the fluorescence emission spectrum of the host, depending on the host structure and the mechanism of the electronic interaction between the host and the cation analyte [64,65].

Figure 6 shows the titrations with the cobalt (**II**) ion, where the strong fluorescence intensity of receptors decreases after the gradual addition of cobalt ion, the interaction of thiourea bridge and triazolopyridine with the cation avoids the fluorescence process and a decrease in emission can be observed. This observation clearly indicates that the triazolopyridine nitrogen interacts with cobalt to form the complex. Similar behaviour can be observed for the other nickel and copper ions (Figures S20 and S25).

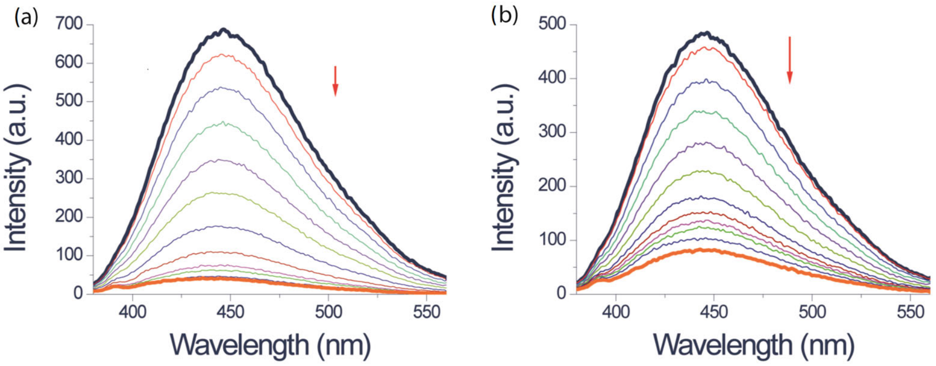

Figure 6. Titration of receptor (**IV**) and (**V**). (**a**) Change in fluorescence spectrum of receptor (**IV**) after titration of 0–3 equivalents of cobalt (**II**) ion. (**b**) Change in fluorescence spectrum of receptor (**V**) after titration of 0–3 equivalents of cobalt (**II**) ion. (red arrow: decrease of maximum emission).

The binding stoichiometry is determined from the ratio of the mole fractions of the two components found at the maximum of the curve; in the graphs of these receptors, the maximum is 0.66 resulting in a 1:2 stoichiometry (Figures S21 and S26). The two binding sites probably correspond to the fluorophore and the nearby thiourea bridge, since they contain S and N atoms known to interact with transition metals.

As a result of the observed decrease in fluorescence, the binding constant, β, was determined using the complex model for a 1:2 stoichiometry. The results of these constants are tabulated in Table 2. These were determined by considering the gradual changes in fluorescence intensity at 350 nm after the stepwise addition of cations to the solution.

Table 2. Binding constant and limit of detection of receptor (**IV**) and (**V**) determined in fluorescence spectroscopy in acetonitrile.

		Ni^{2+}	Co^{2+}	Cu^{2+}
(**IV**)	Log (β)	11.06	11.25	11.11
	LOD (µg/L)	3.78	2.94	5.35
(**V**)	Log (β)	10.95	11.26	14.08
	LOD (µg/L)	10.89	6.57	10.89

The binding constants of both receptors are similar, but there is a key difference in the complex between the copper (II) and receptor (**V**). It is important to note that, independently of the conformers, the presence of a bridge between the thiourea and triazole-pyridine groups is clearly evident in the interaction with both ions. Their behaviour is consistent at all the titration points that fit the 1:2 complex models, but the data used to determine the limit of detection show differences between the two receptors. This is because the linear range corresponds to concentrations between 1×10^{-7} and 6×10^{-7}, and the receptor (**IV**) shows the best results. Furthermore, this is reflected in the detection limit results, where the behaviour discussed above is also reflected, with receptor (**IV**) showing the best results. Likewise, these receptors are the most sensitive of those studied (Figures S22 and S27), detecting concentrations in the μg/L range, with the cobalt (**II**) ion with receptor (**IV**) having the lowest value of 2.94 μg/L.

4. Discussion

The results demonstrate that receptor (**I**) functions as a novel bifunctional receptor for the identification of both ions, like the receptors currently described in the literature [41,43,66,67]. Furthermore, the receptor exhibits a distinct colour change from colourless to yellow upon interacting with Cu(**II**), highlighting its potential as an effective colorimetric sensor. Receptors (**II**) and (**III**) exhibit structural similarities and comparable behaviour despite the significant structural differences between them. The transition from two to four arms in these structures provides a potential explanation for this behaviour. Calixarene (**II**) has two possible binding sites, but according to the Job plot results only, one of these sites is responsible for the interaction with the copper (**II**) ion. The fluorescent compounds (**IV**) and (**V**) are particularly useful as receptors due to the advantages of the fluorescent technique, including their high sensitivity. They are capable of facilitating ON–OFF fluorescence sensing of first-row transition metal ions (Co^{2+}, Cu^{2+} and Ni^{2+}), indicating that the functional groups thiourea and triazolopyridine are involved in the interaction.

As mentioned above, the idea of adding this fluorophore to the calixarene structure was due to the results obtained with nickel in the presence of cyclodextrin, where this complex was able to detect at 65 μg/L in aqueous media [37], while our receptors have better detection limits (Table 2), but are only applicable in organic media. Expanding on the results of our experiments obtained with these receivers, they showed a low detection limit in the range between 1×10^{-7} M at 6×10^{-7} M and the results are given in Table 3. Therefore, it can be concluded that these fluorescent receptors are quite sensitive compared to the reported methods based on calixarenes. In a comparison between fluorescent receptors, our calixarene (**IV**) has a detection limit almost identical to the reported benzothiazin-functionalised calix[4]arene [68], indicating that this result is acceptable for the detection of cobalt (**II**) in solution.

Table 3. Comparison of the receptor, (**I**), (**IV**) and (**V**) with previously reported chemosensors for the detection of Co^{2+} ion.

Receptor	Method and Medium	LOD (μM)	Ref.
Calix[4]arene functionalized gold nanoparticles	Electrochemical—THF/H_2O	0.001	[69]
Anthracenyl-appended calix[4]arene- 1,3-diconjugate	Fluorescence—Ethanol/$CHCl_3$	0.920	[70]
Benzothiazin-functionalized Calix[4]arene	Fluorescence—DMSO	0.046	[68]
(**I**)	UV-Visible—CH_3CN	12.035	-
(**IV**)	Fluorescence—CH_3CN	0.050	-
(**V**)	Fluorescence—CH_3CN	0.110	-

5. Conclusions

In the present research, five derivatives of calix[4]arene were synthesized in 1,3-*alternate*, pinched *cone* and *cone* conformations. These derivatives were functionalized at the lower or upper rim with a thiosemicarbazone or thiourea group bearing pyridinylnaphtalene or triazolopyridine moieties. The synthesized receptors were evaluated for their ability to sense ions using UV–visible and fluorescence techniques. Of these, the synthesis of receptor (**I**), which behaves as a bifunctional sensor allowing for the detection of cations and anions, is noteworthy. Moreover, the most interesting receptors correspond to receptors (**IV**) and (**V**), where it is observed that the conformation gives better results than its analogue in the 1,3-*alternate* conformation. In these molecules, a strong fluorophore such as triazolo[1,5-a]pyridine was used to generate these ON–OFF receptors in the presence of cobalt (**II**), copper (**II**) and nickel (**II**) ions. The detection capacity with a value of 2.94 µg/L for the cobalt ion in this medium could lead us to use it as a sensor for the detection of low concentrations of the cobalt (**II**) ion.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemosensors13020048/s1, Characterization of molecules, determination of the association constant by absorbance or fluorescent titration and determination of the stoichiometry de each receptor ((**I**)–(**V**)) studied with respective ions.

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