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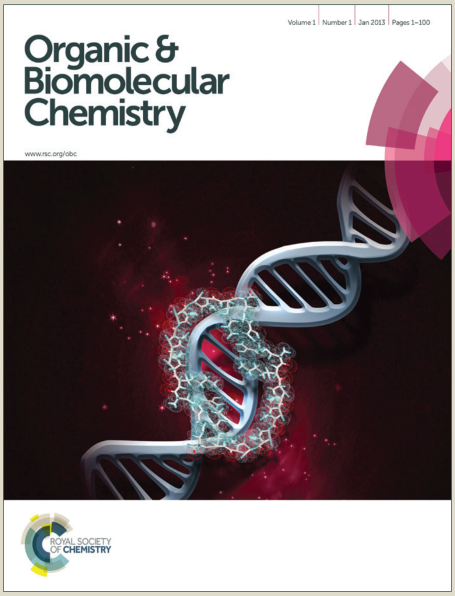

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ARTICLE TYPE

# Tris(triazole) tripodal receptors as selective probes for citrate anion recognition and multichannel transition and heavy metal cations sensing

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***Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX***

**DOI: 10.1039/b000000x**

The three-armed pyrenyl-triazole receptor **1** behaves as highly selective fluorescent molecular sensor for citrate anion over similar carboxylates such as malate or tartrate. In addition, this receptor senses $Cu^{2+}$ cations through absorption and emission channels even in the presence of $Hg^{2+}$ metal cations. The related three-armed ferrocenyl-triazole receptor **2** behaves as a high selective dual (redox and chromogenic) chemosensor molecule for $Pb^{2+}$ metal cations.

## Introduction

The design of receptors that contain two quite different binding sites for the complexation of cationic and anionic guest species is a new emerging and topical field of supramolecular chemistry.[1] Among different types of chemosensors, research on fluorescence-based chemosensors has received special attention because they generally offer a high sensitivity and selectivity, a lower detection limit for the desired analyte. As fluorogenic groups, photoactive pyrenyl substituents are very attractive because of long fluorescence lifetime, pure blue fluorescence, strong and well characterized emissions and their chemical stabilities.[2] Formation of the self-assembled complex results in a remarkable change in the fluorescence emission intensities of the pyrene excimer and monomer.[3]

Moreover, the 1,2,3-triazole motif has proved to be a versatile ion recognition unit for both cations and anions. Thus, several triazole derivatives recognize anions through cooperative triazole C-H···anion hydrogen bond.[4] In addition, as a nitrogen-containing Lewis base, triazole-based ligands have also been shown to coordinate transition-metal cations.[5] The advent of so-called “click” chemistry has been instrumental in exploiting the diverse functions provided by this single heterocyclic scaffold resulting in a large number of applications in supramolecular and coordination chemistry that have served to extend the traditional frontiers associated with the recognition chemistry.

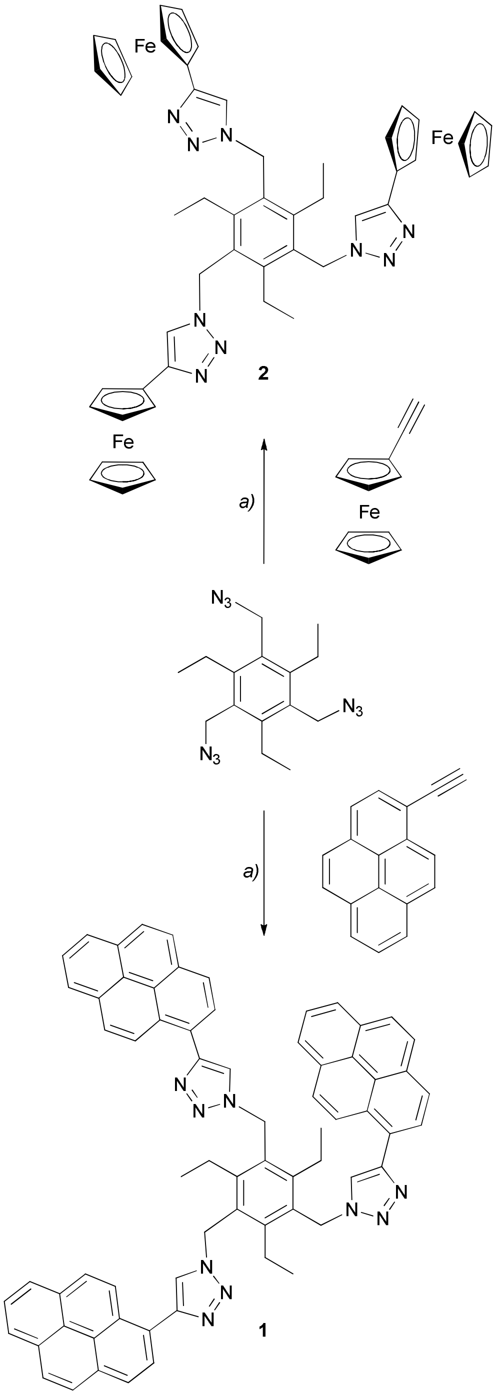
It is worth noting that among different anions having biological significance, citrate sensing has attracted considerable attention because of its crucial role in the Krebs cycle providing the vast majority of energy used by aerobic cells in human beings, In addition, diminished of citrate levels in urine have been linked to some pathological dysfunctions such as nephrolithiasis and nephrocalcinosis or glycogen storage disease.[6] Moreover, citrate levels are markedly reduced in malignant prostate cancer tissue and provide the most consistent characteristic change in the onset and progression of prostate cancer.[7] Consequently, the development of simple, fast and chemoselective methods for detecting this anion in biological fluids such as cell extracts, serum urine and especially in prostate or seminal fluid samples constitutes a challenging field of research. In this context it is interesting to highlight the contributions provided by Anslyn[8] and Wolfbeis[9] based on cationic guanidinium receptors and a weakly-emissive europium(III) tetracycline complex, respectively. Some other chemosensors for detecting citrate anion have also been reported, many of them based on metal complexes and supramolecular systems.[10] However, such recognition motifs are often structurally complicated and require an elaborate and sophisticated synthetic process.

On the other hand, studies related to design and development of highly sensitive and specific probes for heavy- and transition-metal ions such as copper, lead and mercury ions remains of widespread interest because of their wide use in various fields of science and the subsequent effects of these metals on both human health and environment.[11]

Thus, here we report on the synthesis and sensing properties of the tripodal chemosensors **1** and **2**, constituted by a 1,3,5-trisubstituted-2,4,6-triethylbenzene framework,[12] containing three highly flexible arms composed by a 1,2,3-triazole ring, as a binding site, resulting from the Cu-catalyzed alkyne azide cycloaddition, end-capped either by a photoactive pyrene signalling unit or a redox active ferrocene moiety.

## Results and discussion

The tripodal receptors **1** and **2** have been synthesized in 88% and 89% yield, respectively, as depicted in Scheme 1, employing a click reaction between pyrenylacetylene or ferrocenylacetylene and 1,3,5-tris(azidomethyl)-2,4,6-triethylbenzene which was prepared from the 1,3,5-tris(chloromethyl)-2,4,6-triethylbenzene.[12]



**Scheme 1** Synthesis of receptors **1** and **2**. *a)* Reagents and conditions [$Cu(CH_3CN)PF_6$], TBTA, sodium ascorbate, DIPEA, anhydrous THF.

The structure of these receptors was fully characterized by using the standard spectroscopic techniques ($^1$H, $^{13}$C NMR, COSY, DEPT and HMQC) as well as electrospray mass spectra (ESI-MS) and elemental analysis. Their most remarkable $^1$H and $^{13}$C NMR features are the presence in these spectra of an only set of signals associated to the three pyrenyl- or ferrocenyltriazolomethylene arms present in these molecules, which were kept even when their $^1$H-NMR were carried out at -20 ºC (see Figure S3).

## Anion binding properties

The chemosensory ability of **1** and **2** towards a number of anions (Cl$^-$, Br$^-$,I$^-$, $H_2PO_4^-$, $HP_2O_7^{3-}$, $HSO_4^-$, CN$^-$, $NO_3^-$ AcO$^-$, BzO$^-$, oxalate, malonate, succinate, glutarate, adipate, picolinate, nicotinate, isonicotinate, dipicolinate, terephthalate, isophthalate, trimesate, citrate, malate, and tartrate)[13] of different topologies was investigated by UV-vis, fluorescence and $^1$H NMR spectroscopies.

It is worth mentioning that for the case of receptor **1** the results obtained in both the absorption and emission titration studies were almost identical when they were performed in pure acetonitrile (c = 1.5 x $10^{-5}$ M) or in acetonitrile/water (1:1) (c = 2 x $10^{-6}$ M). Thus, its absorption spectrum shows in both media the typical pyrene absorption bands[14] in the region 270-346 nm. However, no obvious changes were observed in this spectrum upon addition of the set of anions tested. On the other hand, the electronic absorption spectra of **2** (c = 3 x $10^{-5}$ M in $CH_3CN/CH_2Cl_2$, 1:1) is consistent with most ferrocenyl derivatives, which exhibit charge transfer bands in the UV-vis region which are ascribed to a high-energy ligand-centered $\pi$–$\pi^*$ and L-$\pi^*$ electronic transitions. [15] However, all these bands are overlapped giving rise an only broad band centred at $\lambda$ = 350 nm. In addition to this, another absorption band appeared at $\lambda$ = 446 nm which is assigned to another localized excitation with a lower energy produced either by two nearly degenerate transitions, a Fe(II) d-d transition[16] or by a metal-ligand charge transfer (MLCT) process ($d_\pi$-$\pi^*$) (LE band). This assignment is in accordance with the latest theoretical treatment (model III) reported by Barlow et al.[17] Such spectral characteristics confer a yellow colour to this species. However, in this case no notable changes in its UV-vis spectra were either observed when the set of anions tested were added.

The anion biniding properties of **1** were also studied by monitoring the emission spectral changes caused by the addition of the above mentioned set of anions to a $CH_3CN/H_2O$ (1:1, v/v) solution of this receptor (c = 2 x $10^{-6}$ M). When excited at $\lambda$ = 345 nm, **1** displayed two distinct emission bands at 386 and 405 nm which are attributed to the pyrene monomeric emission and a red-shifted structureless maximum at 486 nm, typical of pyrene excimer fluorescence. The titration experiments carried out in the presence of anions demonstrated that only the citrate anion is able to promote significant fluorescence changes which can visually be discernible using a standard UV- lamp, as can be seen in Figure 1. Thus, upon addition of this anion, a slight decrease in the intensity of the pyrene excimer emission band along with pronounced intensity enhancement of the pyrene monomer emission was observed. An intensity maximum was reached at upon addition of 80 equiv of anion, where the $\lambda_{monomer}$ shifts from 386 and 405 nm to 400 and 417 nm, respectively, the ratio of the fluorescence intensity ($I_{400}/I_{484}$) monomer/excimer being higher (1.90) than in the free receptor ($I_{386}/I_{486}$ = 0.090), and the quantum yield ($\Phi$ = 7.74x$10^{-2}$) resulting 1.87 fold compared to that of **1** ($\Phi$ = 4.15x$10^{-2}$). A clear isoemissive point at 476 nm supported only one type of complexation involved. The stoichiometry of the complex system was also determined by the changes in the fluorogenic response of **1** in the presence of varying concentrations of citrate anion and the results obtained indicate the formation of a 1:1 complex giving an association constant of 8.2x10$^3$ M$^{-1}$.[18] Moreover, receptor **1** was found to have a detection limit[19] of 3.7x10$^{-6}$ M as fluorogenic sensor for the analysis of citrate anions (see Figure S6). It is worth mentioning the remarkable selectivity shown by receptor **1** for citrate anions even when compared to other structurally very similar carboxylate anions such as malate or tartrate.

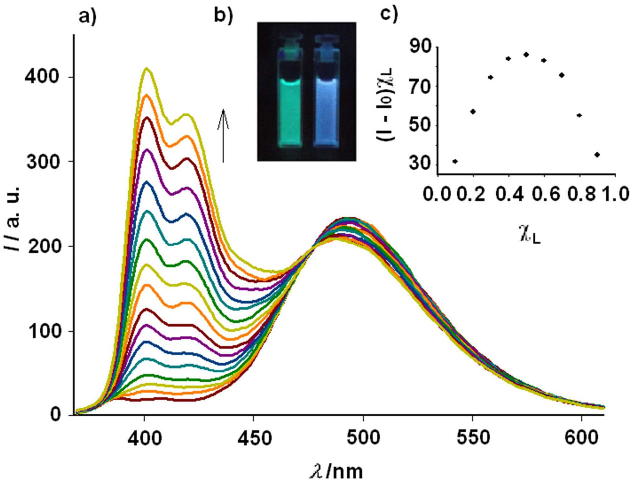


**Fig. 1** (a) Changes in the emission spectrum of **1** (c = 2 x 10$^{-6}$ M in $CH_3CN/H_2O$ (1:1, v/v) upon addition of increasing amounts of citrate anions up to 80 equiv; the arrow indicate the emissions that increase during the titration process; (b) Visual changes observed in the fluorescence of **1** (left) upon addition of citrate anion (right); (c) Job's plot indicating the formation of a 1:1 complex.

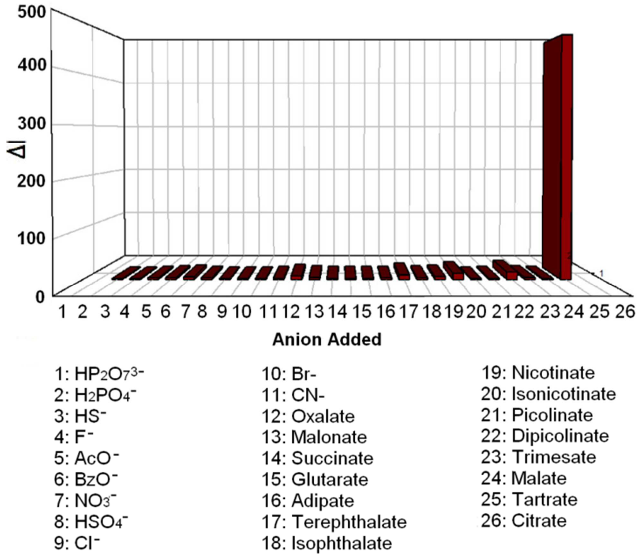


**Fig. 2** Bar profiles of fluorescence intensity of **1** (c = 2 x 10$^{-6}$ M in $CH_3CN/H_2O$ (1:1, v/v) measured at λ = 400 nm upon addition of 80 equiv of the set of anions tested, when excited at λ = 345 nm .

The presence of a ferrocene moiety in receptor **2**, which can act as electrochemical antenna, allowed us to explore its ability for anion sensing. However, the receptor did not exhibited any selectivity towards the set of anions tested the $\Delta E_{1/2}$ being around 60 mV for the cases of carboxylate derivatives, including the citrate anion (Figure 3, Table S1and Figure S7).

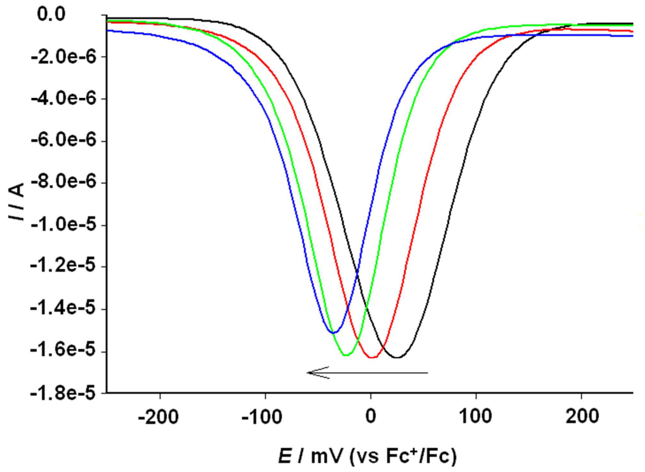


**Fig. 3** Evolution of the OSWV of **2** (black) (c = 5 x 10$^{-4}$ M) in $CH_3CN/CH_2Cl$ (4:1, v/v) in the presence of $n$-$Bu_4NPF_6$ and scanned at 0.1 V s$^{-1}$, upon addition of increasing amounts of citrate anion up to 10 equiv (blue)

To look into the anion binding properties of receptor **1** and **2** $^1$H NMR experiments were carried out both in the absence and presence of citrate anions. It is worth noting that, in both cases, appropriate concentrations for carrying out these experiments at room temperature were only achieved using $CDCl_3$ as a solvent. Thus, Figure 4 and Figure S8 show the changes promoted in the $^1$H NMR spectrum of a solution of **1** or **2** (c = 2x10$^{-3}$ M in $CDCl_3$), respectively, when increasing amounts of citrate anions were added. The spectra obtained during the titration process of **1** are characterized by the presence of only one set of signals in which that of the triazole CH proton, which appears at δ = 7.62 ppm (red), is progressively deshielded with reference to the free receptor (Δδ = 0.10 ppm), while those associated to the pyrene unit (black) and methylene group (blue, Δδ = - 0.14 ppm) are shielded. Similarly, in receptor **2** the triazole CH-proton also experienced a similar deshielding while the protons within the ferrocene unit underwent a slight shielding (see Figure S8). These results gave support to the participation of the CH-triazole protons in hydrogen bonding with this anion. Once again, the pattern of signals corresponding to the $^1$H NMR of the complex formed by **1** and **2** did not experience either any change even when it was carried out at -20 ºC.

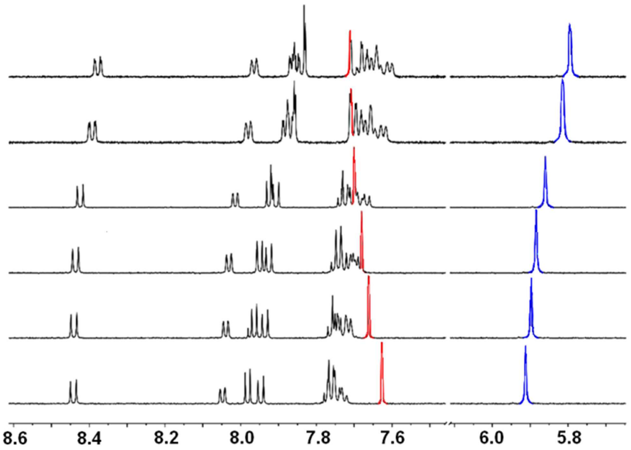


**Fig. 4** Changes in the $^1$H NMR (in $CDCl_3$) spectrum of **1** upon addition of citrate anions from 0 (bottom) to 20 equiv (top)

Titration isotherm, generated from the change in chemical shift of the triazole CH-signals upon addition of the citrate anions, in the pure deuterated organic solvent $CDCl_3$, was nicely fitted to a 1:1 binding model, using the computer program WinEQNMR[20] (see Fig. S9). Under these conditions, the calculated association constant was 162 $M^{-1}$ (error 0.001). It is not surprising that the calculated value for the association constant through the $^1$H NMR titration data, differs from that obtained from the fluorescent titration data because it is very well known that the $K_{as}$ values showed considerable variations as function of the solvent identity.[21]

To explore the coordination mechanism of **1** toward citrate anion, quantum chemical calculations at the DFT level (see ESI) were also carried out. A simplified model of **1** bearing methyl groups at the central benzene ring instead of ethyl substituents, **1'**, was chosen for all calculations. The most stable conformation found for receptor **1'** displays two parallel side-arms stabilized by $\pi$-stacking, whereas the third pending arm locates the pyrenyl ring system almost perpendicular to the other two thus enabling the formation of additional stabilizing T-stacking interactions (Figure 5a). The two first parallel pyrenyl moieties account for the excimer fluorescence emission, whilst most likely the T-stacking quenches the fluorescence of the third unit. Assuming the preference for a 1:1 complex receptor/anion stoichiometry found from the fluorescence studies with citrate (*vide supra*), the most stable geometry for the nesting-type $[\mathbf{1'}\cdot\text{citrate}]^{3-}$ complex features all three 1-pyrenyl moieties in an almost perfectly parallel arrangement and the triazole H atoms oriented towards the inner part of the receptor. This conformation defines a central cleft where one of the citrate $CH_2CO_2^-$ fragments is docked and the strongest host-guest interactions are taking place, involving all three triazole CH units ($d_{H\text{-}O}$ = 1.965, 2.009 and 2.216 Å; WBI = 0.027, 0.024 and 0.009; $\rho(r)$ = $2.71\times10^{-2}$, $2.47\times10^{-2}$ and $1.41\times10^{-2}$ $e/a_o^3$) as well as secondary interactions with the central pyrenyl H2 and H3 atoms ($d_{H\text{-}O}$ = 2.029 and 2.514 Å; WBI = 0.023 and 0.003; $\rho(r)$ = $2.46\times10^{-2}$ and $0.92\times10^{-2}$ $e/a_o^3$) (Figure 5b).

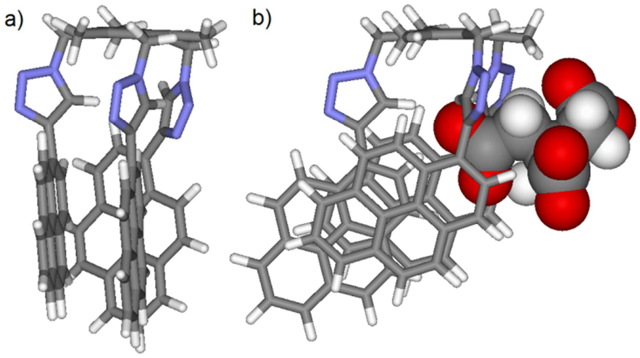


**Fig. 5** Calculated ($COSMO_{H2O}$/B3LYP-D3/def2-TZVP) most stable geometries for a) model receptor **1'** and b) $[\mathbf{1'}\cdot\text{citrate}]^{3-}$ complex. The guest citrate ion highlighted in spacefill representation.

Among several other relative minima in the potential energy surface of the $[\mathbf{1'}\cdot\text{citrate}]^{3-}$ complex system, worth is to mention the second most stable minimum that features only two $\pi$-stacked side-arms, whereas the third unit moves to the other free $CH_2CO_2^-$ fragment of the citrate substrate in order to wrap it (see Figure 6). This could account for a fast dynamic equilibrium in which $\pi$-stacked and isolated pyrenyl units coexist, thus explaining the appearance of both excimer and monomer florescence emissions.

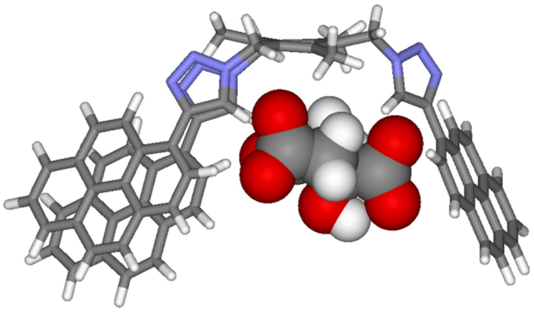


**Fig. 6** Calculated ($COSMO_{H2O}$/B3LYP-D3/def2-TZVP) second most stable geometry for the $[\mathbf{1'}\cdot\text{citrate}]^{3-}$ complex. The guest citrate ion highlighted in spacefill representation.

## Cation binding properties

As it has been already mentioned, triazole-based ligands have been shown to coordinate metal cations.[5] Consequently, the chemosensor behaviour of receptors **1** and **2** towards a variety of cations ($Li^+$, $Na^+$, $K^+$, $Ca^{2+}$, $Mg^{2+}$, $Cu^{2+}$, $Ni^{2+}$, $Zn^{2+}$, $Cd^{2+}$, $Hg^{2+}$, and $Pb^{2+}$)[22] of both biological and environmental relevance, has also been investigated through electrochemistry, UV-vis, fluorescent and $^1$H NMR spectroscopic techniques.

Among the metal ions tested only significant spectral changes were observed both in the UV-vis and fluorescence titration experiments only when $Cu^{2+}$ and $Hg^{2+}$ were added to a solution of **1**. Thus, although the change in absorbance was minor upon the stepwise addition of $Hg^{2+}$ cation, until 5 equiv were added, the appearance of three clear isosbestic points at 288, 311 and 370 nm indicated that only one spectrally distinct $[\mathbf{1}\cdot Hg^{2+}]$ complex was formed. Its stoichiometry was evaluated to be 1:1 by using the method of continuous variation (Job plot) (see Figure S10). By contrast, the changes observed in the UV-vis absorbance spectra of the free receptor **1** upon the gradual addition of $Cu^{2+}$

cation, until 20 equiv were added, were more pronounced (see Figure S11) giving rise to a concomitant change in the colour of the solution from colourless to pale green which can be used for the naked-eye detection of this metal cation. The calculated detection limits were 6.8 x $10^{-6}$ M and 5.6 x $10^{-6}$ M for the cases of $Hg^{2+}$ and $Cu^{2+}$ respectively.

The interaction properties of **1** towards $Cu^{2+}$ and $Hg^{2+}$ studied by emission spectroscopy demonstrate that in both cases the gradual addition of these metal cations, up to 2 equiv, promoted a quenching effect of the fluorescence of the free receptor. However, while further addition of $Hg^{2+}$ metal cation did not give rise to any change in the emission spectrum, it was significantly perturbed upon addition of increasing amounts of $Cu^{2+}$. Nevertheless, such remarkable changes took place in two successive steps. Firstly, the stepwise addition of $Cu^{2+}$ resulted in a clear progressive quenching of the fluorescence, which was almost complete when 2 equiv were added. However, on progression of the titration process, by adding increasing amounts of $Cu^{2+}$, a new excimer emission band at $\lambda_{em}$ = 530 nm ($\Delta\lambda_{em}$ = 44 nm) appeared which intensity reached a plateau after addition of 15 equiv of $Cu^{2+}$ (Figure 7).

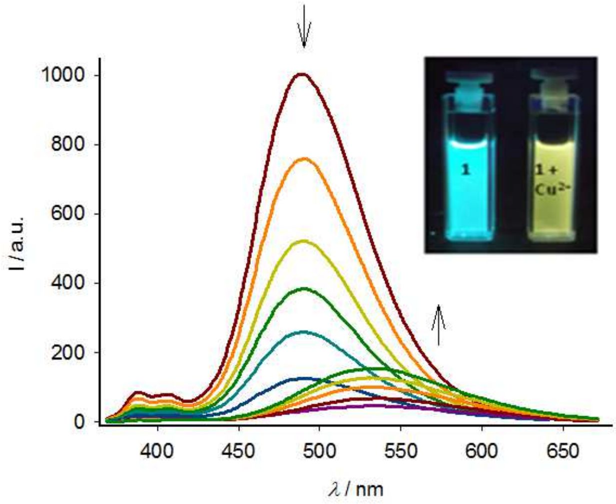


**Fig. 7** Changes in the emission spectrum of **1** (c = 2 x $10^{-6}$ M in $CH_3CN/H_2O$ (1:1, v/v) upon addition of increasing amounts of $Cu^{2+}$ from 0 to 15 equiv.; arrows indicate the emissions that decrease (when 0-2 equiv were) or increase (when 2-15 equiv were added); Inset: Visual changes observed in the fluorescence of **1** (left) upon addition of 15 equiv of $Cu^{2+}$ cations (right).

Fluorescent competition experiments were carried out to check the selectivity of the $Cu^{2+}$ ion over $Hg^{2+}$ and to confirm the potential applicability of **1** for the selective discrimination of $Cu^{2+}$ in the presence of $Hg^{2+}$ in $CH_3CN$. Thus, addition of $Cu^{2+}$ to a solution of the complex [**1**·$Hg^{2+}$] ($\lambda_{em}$ of the excimer = 486 nm) promoted the progressive disruption of this complex with concomitant formation of the corresponding [**1**·$Cu^{2+}$] complex ($\lambda_{em}$ = of the excimer 530 nm) (Figure 8). However, when we performed the reverse experiment, that is, by adding $Hg^{2+}$ to the previously formed [**1**·$Cu^{2+}$] complex no significant changes in the corresponding emission spectrum were observed (Figure 8, inset)

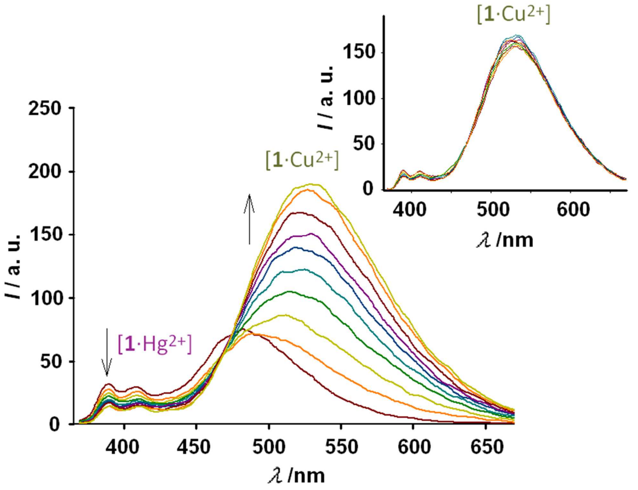


**Fig. 8** Evolution of the emission spectrum of [**1**·$Hg^{2+}$] (a) to [**1**·$Cu^{2+}$] (b) in $CH_3CN$ upon addition of increasing amounts of $Cu^{2+}$, up, to [**1**·$Hg^{2+}$] ; arrows indicate the emissions that decrease; Inset: Changes promoted in the emission spectrum of [**1**·$Cu^{2+}$]. Inset: in $CH_3CN$ upon addition of increasing amounts of $Hg^{2+}$ up to 30 equiv.

In order to assess more clearly the identity of the complex species formed in solution by **1** and $Cu^{2+}$, as well as to determine the complete binding thermodynamics of the recognition event and to obtain a more accurate explanation about such complexation process, isothermal titration calorimetry (ITC)[23] studies were also carried out. ITC experiments were performed by adding aliquots of $Cu^{2+}$ (c = 7 x $10^{-3}$ M) to a solution of **1** (c = 3 x $10^{-4}$ M) at 298 K in $CH_3CN/CH_2Cl_2$ (1:1). The titration curve obtained showed two inflection points around 1 and 2 equivalents of metal cation added, which confirms the formation of complexes with 1:1 and 1:2 (receptor: cation) stoichiometries (Figure 9). The titration data were fitted to a 1:1 or 1:2 binding model using a nonlinear least-squares fitting procedure the corresponding association constants being: $K_1$ = 2.77 x $10^7$ $M^{-1}$ (± 3.09 x $10^6$) and $K_2$ = 4.93 x $10^4$ $M^{-2}$ (± 3.16 x $10^3$).

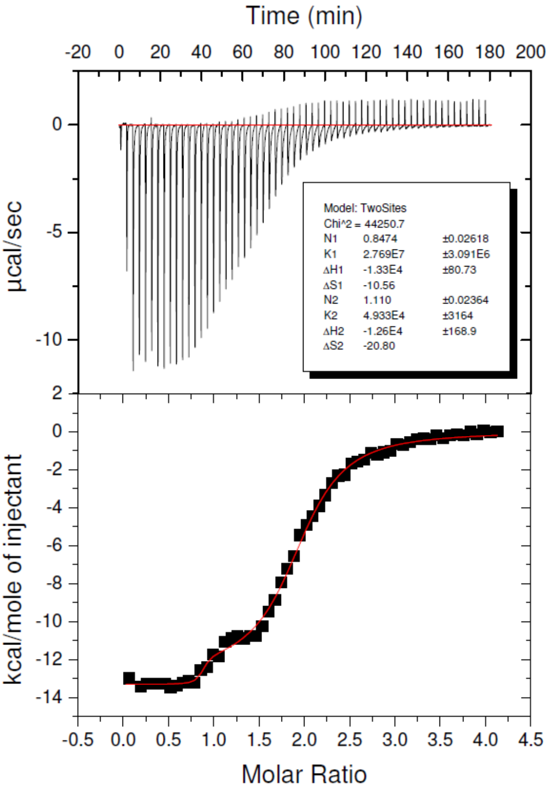


**Fig. 9** ITC enthalpogram and fitting curve of **1** ($CH_3CN/CH_2Cl_2$, c = $3 \times 10^{-4}$ M) upon addition of $Cu^{2+}$(c = $7 \times 10^{-3}$M)

The fluorescent behaviour of ligand **1** provides a good example for distinguishing between $Hg^{2+}$ and $Cu^{2+}$, notwithstanding the fact that both are intrinsically quenching ions and which is based on the absence of fluorescence in the presence of $Hg^{2+}$ and the existence of a green fluorescence in the presence of $Cu^{2+}$.

The chemosensor behaviour of **2** towards the above mentioned set of cations[22] was investigated by linear sweep voltammetry (LSV), cyclic voltammetry (CV), and Osteryoung square wave voltammetry (OSWV) as well as through UV-vis, and $^1$H NMR spectroscopic techniques.

The CV of the tris(ferrocene) receptor **2** (c = $5 \times 10^{-4}$ M in $CH_3CN/CH_2Cl_2$ 1:1, containing 0.1 M $[(n\text{-}Bu)_4N]PF_6$ (TBAHP) as supporting electrolyte) shows only a reversible oxidation wave at $E_{½}$ = 20 mV, *versus* ferrocenium/ferrocene ($Fc^+/Fc$) redox couple, indicating the electronically equivalence of the three metal centers. As expected, this potential value is also identical to that obtained from the corresponding OSWV peak. Titration studies upon the stepwise addition of the metal cations tested to the electrochemical solution of **2** demonstrated that only $Pb^{2+}$, $Cu^{2+}$ and $Hg^{2+}$ promoted electrochemical responses. However, while addition of $Pb^{2+}$ gave rise to the formation of the corresponding complex, showing an anodic shift of $\Delta E_{1/2}$ = 75 mV in its square wave voltammogram,[24] addition of $Cu^{2+}$ and $Hg^{2+}$ induced the oxidation of the ferrocene moiety present in the free receptor. This behaviour was corroborated by LSV studies carried out upon addition of $Cu^{2+}$ and $Hg^{2+}$ to the electrochemical solutions of receptor **2** which showed a significant shift of the sigmoidal voltammetric wave toward cathodic currents, confirming that these metal cations promote the oxidation of the free receptor (see Figure S16). By contrast, the same LSV experiments carried out upon addition of $Pb^{2+}$ metal cations to the receptor, revealed a shift of the linear sweep voltammogram toward more positive potentials, which is in agreement with the complexation process previously observed by CV and OSWV (see Figure S17).

The binding behaviour of **2** toward metal cations was also monitored using UV-vis spectroscopy. Significantly, among the metal cations tested, only the presence of $Pb^{2+}$ promoted a hyperchromic effect on the UV-vis spectrum of **2** without any new band being observed, giving rise to a concomitant change in the colour of the solution from pale to deep orange, which can be used for a "naked-eye" detection of this metal cation (Figure 10). Binding assays using the method of continuous variations (Job's plot) suggests a 1:1 binding model (metal:ligand) with a Ka = 1.8 x $10^5$ (± 1.23 ) $M^{-1}$ the calculated detection limit being $3.1 \times 10^{-6}$ M. This stoichiometry was also confirmed by electrospray mass spectrometry ESI-MS where a peak at *m/z* = 1264 $[\mathbf{2}\cdot Pb\cdot(ClO_4)]^+$ was observed (see Figure S18).

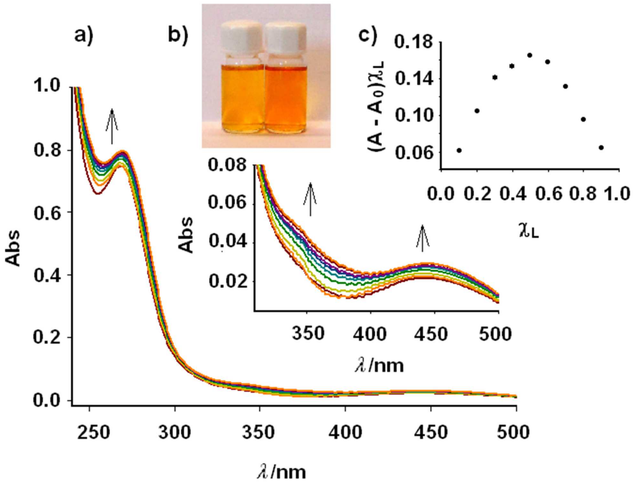


**Fig. 10** (a) Changes in the UV-vis spectrum of **2** (c = $3 \times 10^{-5}$ M in $CH_3CN/CH_2Cl_2$, 1:1) upon addition of increasing amounts of $Pb^{2+}$, from 0 to 2 equiv; arrows indicate the absorptions that increase during the titration process; (b) Visual changes observed in the colour of the solution of the free receptor **2** (left) upon addition of $Pb^{2+}$ cations (right); (c) Job's plot indicating the formation of a 1:1 complex.

To support the results obtained by electrochemical and UV-vis experiments, and in order to obtain additional information about the coordination of this metal cation by receptor **2**, we also performed a $^1$H NMR spectroscopic analysis (Figure 11). Significantly, during the titration experiments all the protons present in both the triazole recognition unit (red) and ferrocene signalling unit (blue) were downfield shifted, although in different magnitudes: $\Delta\delta$ = 0.76 ppm for the triazole proton, $\Delta\delta$ = 0.19 ppm for the singlet corresponding to the five protons within the unsubstituted Cp ring of the ferrocene moiety, and $\Delta\delta$ = 0.15 ppm and $\Delta\delta$ = 0.23 ppm for the $H_\alpha$ and $H_\beta$, present in the monosubstituted Cp ring of the ferrocene unit, respectively.

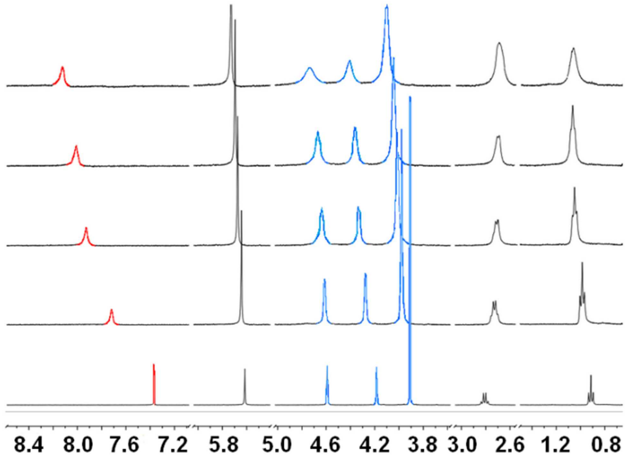


**Fig. 11** Changes in the $^1$H NMR (in $CDCl_3$) spectrum of **2** upon addition of $Pb^{2+}$ from 0 (bottom) to 2 equiv (top)

## Conclusions

Tripodal chemosensors based on a 1,3,5-trisubstituted-2,4,6-triethylbenzene, containing three highly flexible arms bearing a 1,2,3-triazole end-capped either by a photoactive pyrene unit or a redox active ferrocene moiety, have been prepared as potential molecular probes for anions and cations. The tris(pyrenyl) derivative **1**, displays a remarkable selectivity towards citrate anion, when compared to similar carboxylate anions such as malate or tartrate. The emission spectrum of **1** undergoes a slight decrease in the intensity of the pyrene excimer band along with a remarkable enhancement of the pyrene monomer emission band in the presence of citrate anion, and the quantum yield of the resulting complex was found to be 1.87 fold compared to that of the free receptor. Quantum chemical calculations at the DFT level indicates that its most stable conformation displays two parallel pyrenyl moieties stabilized by π-stacking, which account for the excimer fluorescence emission observed, whilst the third pirenyl unit, located almost perpendicular to the other, gives rise to a T-stacking effect which likely quenches the fluorescence of such unit. However, upon addition of citrate anions, a fast dynamic equilibrium between the two most stable complexes accounts for the coexistence of both the isolated and π-staked pyrene units thus explained the appearance in the spectrum of the monomer and excimer emissions.

As triazole-based receptors have been shown to coordinate metal cations, receptor **1** undergoes significant spectral changes in the absorption and emission spectra only in the presence of $Cu^{2+}$and $Hg^{2+}$. In particular, this receptor can be used for the naked-eye detection of $Cu^{2+}$ metal cation and for discrimination of this metal cation in the presence of $Hg^{2+}$ by using fluorometric measurements.

In the tris(ferrocenyl) receptor **2**, the oxidation wave of the ferrocene/ferrocenium couple only shows perturbation in the presence of $Pb^{2+}$cation ($\Delta E_{½}$ = 75 mV) whereas $Cu^{2+}$and $Hg^{2+}$ induced oxidation of the ferrocenyl groups. Moreover, the $Pb^{2+}$ cation promotes a hyperchromic effect in the absorption spectrum of **2** giving rise to a change in the colour of its solution from pale to deep orange, which can be used for a naked-eye detection of this metal cation.

## Experimental

### General

Melting points were determined on a hot-plate melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 600 MHz and 100 and 200 MHz, respectively**.** HMBC and HMQC spectra were recorded at 300 and 600 MHz. Chemical shifts refer to signals of tetramethylsilane in the case of $^1$H and $^{13}$C spectra.

UV-vis spectra were carried out in a UV-vis-NIR spectrophotometer using a dissolution cell of 10 mm path. For the case of receptor **1**, the samples were solved in $CH_3CN$ (c = 1.5 x $10^{-5}$ M) or in $CH_3CN$ /$H_2O$ (1:1) (c = 2 x $10^{-6}$ M) while for **2** they were dissolved in $CH_3CN/CH_2Cl_2$ (1:1) (c = 3 x $10^{-5}$ M). In both cases, the spectra were recorded with the spectra background corrected before and after of the sequential additions of aliquots of 0.1 equiv of cations or 0.5 equiv of anions in $CH_3CN$ (c = 2.5x $10^{-2}$ M).

Fluorescence spectra were carried out in a fluorescence spectrophotometer using a 10 mm fluorescence cell (c = 2 x $10^{-6}$ M in $CH_3CN/H_2O$ or c = 1.5 x $10^{-5}$ M in $CH_3CN$). Before recording the spectra, the samples were deoxygenated, to remove fluorescence quenching via oxygen, by bubbling nitrogen for at least 10 min. All the spectra were recorded before and after the sequential additions of aliquots of 0.1 equiv of a solution of cations or 0.5 equiv of anions in $CH_3CN$ (c = 2.5x $10^{-2}$ M). Quantum yield values were measured with respect to anthracene as standard ($\Phi = 0.27\pm0.01$),[25] using the equation $\Phi_x/\Phi_s = (S_x/S_s)$ $[(1-10^{-As})/(1-10^{-Ax})]^2(n_s^2/n_x^2)$ where x and s indicate the unknown and standard solution, respectively, Φ is the quantum yield, S is the area under the emission curve A is the absorbance at the excitation wavelength and n is the index of refraction.

Microcalorimetric titrations were carried out using an isothermal titration calorimeter (ITC) purchased from Microcal Inc., MA (USA). The ORIGIN software provided by Microcal Inc. was used to calculate the binding constants.

The recognition properties were investigated in the presence of several metal cations ($Li^+$, $Na^+$, $K^+$, $Ca^{2+}$, $Mg^{2+}$, $Cd^{2+}$, $Cu^{2+}$, $Ni^{2+}$, $Zn^{2+}$, $Pb^{2+}$, and $Hg^{2+}$)[22]and anions.[13]

**General Procedure for the Preparation of tris[4-substituted] 1,1',1''-[(2,4,6-triethylbenzene-1,3,5-triyl)tris(methylene)]-1H-1,2,3-triazole**: To a solution of 1,3,5-tris(azidomethyl)-2,4,6-trietylbenzene (0.05 g 0.153 mmol) in anhydrous THF (20 mL), the appropriate acetylene derivative (0.534 mmol), tetrakis(acetonitrile)copper(I) hexafluorophosphate ($[Cu(CH_3CN)PF_6]$) (0.057 g, 0.153 mmol), tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) (0.196 g, 0.595 mmol) and sodium ascorbate (0.01g, 0.052 mmol) were added at room temperature and under nitrogen atmosphere. Thus, N,N-diisopropyletylamine (DIPEA) (400 µL, 2.3 mol) was also added. The resulting solution was stirred at room temperature for 12 hours and the solvent was removed under vacuum. The residue was extracted with $CH_2Cl_2/H_2O$ (100 mL), the organic solvent removed under reduced pressure and the crude product chromatographed using a silica gel column and the appropriate eluent.

**1,1',1''-[(2,4,6-triethylbenzene-1,3,5-**

**triyl)tris(methylene)]tris[4-(pyren-1-yl)]-1H-1,2,3-triazole, 1.** Eluent $CH_2Cl_2$/AcOEt (9:1), ($R_f$: 0.4). Yield, 88 %. Mp (from $CH_2Cl_2/Et_2O$, 1:5) > 310 °C (decomp). $\delta_H$ (600 MHz; $CD_2Cl_2$; $Me_4Si$) 8.54 (d, 3H, $^3J$ = 9 Hz), 8.12 (dd, 3H, $^3J$ = 6.6 Hz, $^4J$ = 2.4 Hz), 8.02 (d, 3H, $^3J$ = 7.8 Hz), 8.01 (d, 3H, $^3J$ = 9 Hz), 7.85 (t, 3H, $^3J$ = 6.6 Hz), 7.84 (d, 3H, $^3J$ = 9 Hz), 7.83 (d, 3H, $^3J$ = 7.8 Hz), 7.82 (dd, 3H, $^3J$ = 6.4 Hz, $^4J$ = 2.4 Hz), 7.81 (d, 3H, $^3J$ = 9 Hz), 7.71 (s, 3H), 5.94 (s, 6H), 3.08 (c, 6H, $^3J$ = 7.32 Hz), 1.26 (t, 9H, $^3J$ = 7.32 Hz); $\delta_C$ (151 MHz; $CD_2Cl_2$; $Me_4Si$) 148.4 ($C_q$), 147.7 ($C_q$), 132.1 ($C_q$), 132.0 ($C_q$), 131.5 ($C_q$), 131.0 ($C_q$), 129.2 ($C_q$), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 126.8 (CH), 126.1 (CH), 125.9 (CH), 125.8 ($C_q$), 125.5 (CH), 125.3 ($C_q$), 125.2 (CH), 123 (CH), 49.1 ($CH_2$), 24.6 ($CH_2$), 16.3 ($CH_3$); HR-MS m/z: Calcd ($C_{69}H_{52}N_9$ [M + 1]): 1006.4340, Found: 1006.4361

**1,1',1''-[(2,4,6-triethylbenzene-1,3,5-triyl)tris(methylene)]tris[4-(ferrocenyl)]-1H-1,2,3-triazole, 2.** Eluent $CH_2Cl_2$/MeOH (97:3), ($R_f$: 0.5).Yield, 89 % Mp (from $CH_2Cl_2/Et_2O$, 1:5) 245-7 °C (decomp). $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 7.12 (s, 3H), 5.65 (s, 6H), 4.69 (pt, 6H), 4.29 (pt, 6H), 4.04 (s, 15H), 2.82 (c, 6H, $^3J$ = 7.1 Hz), 1.00 (t, 9H, $^3J$ = 7.1 Hz); $\delta_C$ (101 MHz; $CDCl_3$; $Me_4Si$) 147.1 ($C_q$), 146.3 ($C_q$), 129.8 ($C_q$), 118.1 (CH), 69.5 (CH), 68.7 (CH), 66.7 (CH), 47.9 ($CH_2$), 23.6 ($CH_2$), 15.4 ($CH_3$); HR-MS m/z: Calcd ($C_{51}H_{52}Fe_3N_9$ [M + 1]): 958.2398, Found: 958.2451.

**Computational Details.** DFT calculations were performed with the ORCA program.[26] All geometry optimizations were run in redundant internal coordinates using the B3LYP functional[27] together with the def2-TZVP basis set[28] and the new efficient RIJCOSX algorithm.[29] Solvent effects (water) were taken into account via the COSMO solvation method.[30] From these optimized geometries all reported data were obtained by means of single-point (SP) calculations using the more flexible and polarized def2-TZVPP[31] basis set. Reported energies were not corrected for the zero-point vibrational term. In all optimizations and SP calculations the latest Grimme's semiempirical atom-pair-wise correction (DFT-D3 methods) accounting for the major part of the contribution of dispersion forces to the energy[32] was used. Wiberg bond indices (WBI) were obtained from the natural bond orbital (NBO)[33] population analysis. Bader's AIM-derived topological analysis of the electron density[34] was conducted with AIMAll.[35]

## Acknowledgements

We gratefully acknowledge the financial support from MICINN-Spain, Project CTQ2011-27175, Fondo Europeo de Desarrollo Regional (FEDER).

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† Electronic Supplementary Information (ESI) available: NMR spectra, titration experimental data for anions and cations, and computational data. See DOI: 10.1039/b000000x/

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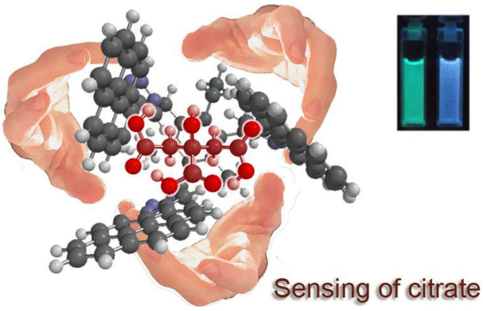
ARTICLE TYPE

# Table of contents entry

## Tris(triazole) tripodal receptors as selective probes for citrate anion recognition and multichannel transition and heavy metal cations sensing.

**María del Carmen González, Francisco Otón, Arturo Espinosa, Alberto Tárraga* and Pedro Molina***



The preparation and binding properties towards citrate anions and cations of two three-armed triazole based receptors are described.