Inorganic Chemistry Communications 70 (2016) 71–74

Contents lists available at ScienceDirect

Inorganic Chemistry Communications

journal homepage: www.elsevier.com/locate/inoche

Short Communication

Ascorbic acid-based quinoxaline derivative as a chromogenic chemosensor for Cu^{2+}

Lilian C. da Silva [a], Erivaldo P. da Costa [a], Gutto R.S. Freitas [a], Miguel A.F. de Souza [a], Renata M. Araújo [a], Vanderlei G. Machado [b], Fabrício G. Menezes [a,*]

[a] Química Biológica e Quimiometria, Instituto de Química, Universidade Federal do Rio Grande do Norte, Natal, RN 59072-970, Brazil
[b] Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC 88040-900, Brazil

ARTICLE INFO

Article history:
Received 26 February 2016
Accepted 16 May 2016
Available online 20 May 2016

Keywords:
Quinoxaline
Naked-eye detection
Chromogenic chemosensor
Copper detection

ABSTRACT

Detection of cationic species represents an important field due to its importance in biological and environmental processes. This communication shows the synthesis and application of an ascorbic acid-based quinoxaline derivative (**1**) in the colorimetric detection of Cu^{2+} against several other cationic species, including Sr^{2+}, Fe^{2+}, Pb^{2+}, Mn^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Sn^{2+}, Hg^{2+}, Ca^{2+}, Ba^{2+}, Co^{2+}, Cr^{3+}, Al^{3+}, and Fe^{3+}. Based on experimental and theoretical results, a 1:2 binding model involving **1** and Cu^{2+} is proposed.

The development of molecular and supramolecular strategies for the recognition and detection of cationic species represents a field of increasing importance in recent years [1]. In this context, the study of chromogenic chemosensors for these analytes is attractive due to the fact that the analysis procedures are simple and require low cost, with naked-eye detection also being possible [2–4]. Copper (II) ions are one of the main target analytes with relevance to be detected, since the referred metal is highly abundant in nature and essential to many biological processes; on the other hand, its abnormal levels may lead to several pathologies [5–8].

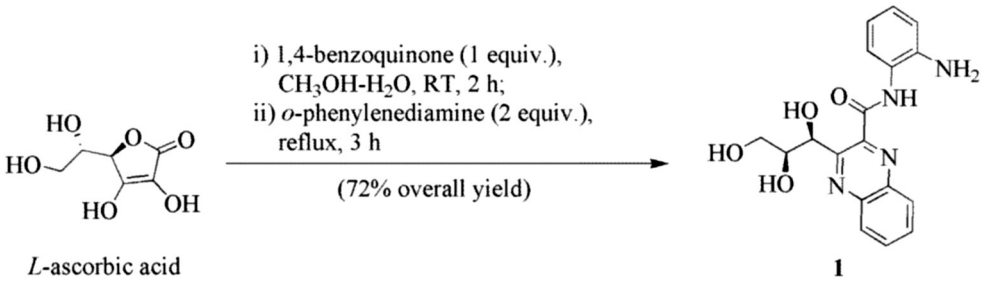
A wide range of quinoxaline derivatives has been reported in the literature due to their relevant biological activity [9] and applications in technological fields [10]. In addition, quinoxalines are found as interesting nitrogenated ligands for coordination chemistry [11,12]. Traditionally, the synthesis of 2,3-disubstituted quinoxalines proceeds through Brønsted or Lewis acid-catalyzed condensation of aromatic *o*-diamines and *α*-diketones [13]. Based on this synthetic strategy, there are several investigations reported in the literature concerned with reactions of dehydro-L-ascorbic acid and *o*-phenylenediamine, and an interesting aspect in these processes is related with the possibility of different products mainly depending on the ratio of the reactant and of the experimental conditions [14–21]. For instance, *one pot* procedure involving mixing an equimolar amount of L-ascorbic acid and 1,4-benzoquinone, followed by the addition of two equivalents of *o*-phenylenediamine, leads to the formation of *N*-(2-aminophenyl)-3-[(1*S*,2*S*)-1,2,3-trihydroxy-propyl]quinoxaline-2-carboxamide (**1**), as presented in Scheme 1 [14,15].

Although quinoxaline derivative **1** has been known since 1964 [16], this compound is surprisingly marginally reported in literature. A quick look at the molecular structure of compound **1** reveals the presence of eight Lewis basic sites from primary aniline, amide, quinoxaline and hydroxyl groups, suggesting an attractive design to be applied in coordination chemistry. In this context, we report herein the use of ascorbic acid-based quinoxaline **1** as a cationic chromogenic chemosensor. More specifically, we demonstrate that compound **1** in methanol is very selective for naked-eye and quantitative detection of Cu^{2+} between several utilized cations.

Compound **1** was easily obtained according to the literature (Scheme 1) [14,15], from low cost reactants starting from L-ascorbic acid in 72% yield, and spectroscopic data were in full agreement to the proposed structure [22]. NMR characterization of compound **1** was reported only in 2014, but not properly detailed [15], such as for data obtained from bidimensional analysis, which is found to be very relevant due to the complexity of the structural nature of the referred ligand, including chirality aspects. All NMR spectra related to compound **1** are presented here in the Supplementary Material (Figs. S1–S4). Fig. S4 (Supplementary Material) shows the experimental $^{1}J_{H,C}$–HSQC spectrum of compound **1**. Quinoxaline hydrogens are downfield in relation to a substituted phenyl ring. This is a consequence of the combination of the electron deficient nature of the heterocyclic unit, which is even increased due to its direct connectivity to the carbonyl group, with the

* Corresponding author.
E-mail address: fabricio@quimica.ufrn.br (F.G. Menezes).

http://dx.doi.org/10.1016/j.inoche.2016.05.019
1387-7003/



Scheme 1. *One pot* synthesis of compound **1**.

electron donation ability of both nitrogen atoms of the amine and amide groups attached to the phenyl ring. In the aliphatic moiety of the molecular structure, the diastereotopic hydrogens of the methylene group appear as two multiplets at the higher field region of the spectrum, as a consequence of the two stereogenic centers in the ligand.

Quinoxaline **1** (1×10^{-4} mol L^{-1}) was added to solutions containing 5 equivalents of several cationic species (Cu^{2+}, Sr^{2+}, Fe^{2+}, Pb^{2+}, Mn^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Sn^{2+}, Hg^{2+}, Ca^{2+}, Ba^{2+}, Co^{2+}, Cr^{3+}, Al^{3+}, and Fe^{3+}) in methanol. Only the solution containing Cu^{2+} changes its color immediately after the addition of **1** (Fig. 1a), and this behavior is consistent with the results obtained from UV–vis analysis (Fig. 1b–c). All data in Fig. 1 were acquired 5 min after the mixture of the reagents. A new band emerges in the visible region with maximum absorbance at 416 nm, suggesting a formation of a coordination complex between **1** and Cu^{2+} (Fig. 1b–c).

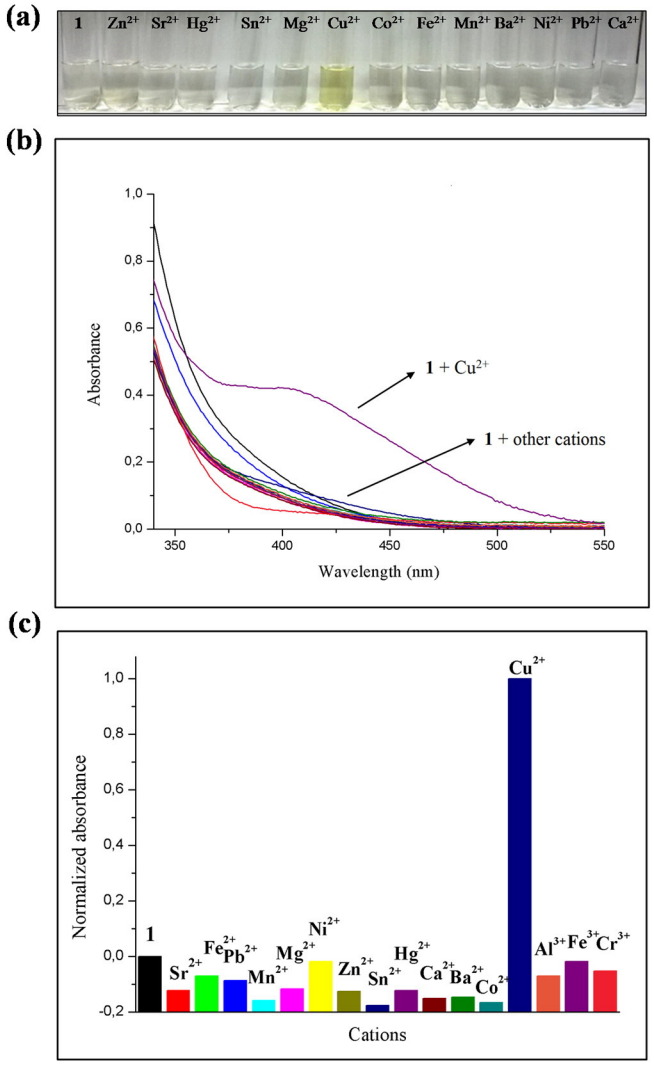


Fig. 1. Methanolic solutions of compound **1** (1.0×10^{-4} mol L^{-1}) in absence and in presence of Cu^{2+}, Sr^{2+}, Fe^{2+}, Pb^{2+}, Mn^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Sn^{2+}, Hg^{2+}, Ca^{2+}, Ba^{2+}, Co^{2+}, Fe^{3+}, Cr^{3+} and Al^{3+} (5.0×10^{-4} mol L^{-1}): (a) naked-eye detection of Cu^{2+}; (b) UV–vis spectra of resulting solutions; (c) changes in the absorbances at 416 nm. All spectra were obtained 5 min after the addition of the reagents.

Spectrophotometric titration was performed in order to investigate the stoichiometry of this interaction and it was found that absorbance of the complex between ligand **1** (1×10^{-4} mol L^{-1}) and Cu^{2+} was enhanced as the concentration of Cu^{2+} ion increased until saturation at approximately 2×10^{-4} mol L^{-1}, suggesting a 1:2 **1**:Cu^{2+} stoichiometry (Fig. 2). In attempt to verify sensibility aspects, another experiment using 0.5 μmol L^{-1} of chemosensor **1** toward 10 equivalents of each metal was performed and Cu^{2+} selectivity could be demonstrated by UV–vis spectroscopy, through with an increase in the absorbance at 416 nm. The selectivity of compound **1** for Cu^{2+} in the presence of different metal ions was investigated using UV–vis analysis of solutions containing compound **1** together with one equivalent of Cu^{2+} and an equimolecular amount of another cation (Fig. 3). A small increase in the absorbance at 416 nm was found when Mg^{2+} and Pb^{2+} compete with Cu^{2+}. On the other hand, Al^{3+} and Sn^{2+} lead to a substantial decrease in the absorbance at 416 nm. This is not an unexpected result since there are several electronic donor sites in compound **1** able to complex cationic species. Data suggest that those metal ions are complexing with **1** in a different binding site than the site responsible for the complexation of Cu^{2+}. Those metal ions would be responsible for reinforcing or weakening the interaction of Cu^{2+} with **1**, leading to the observed results.

The infrared spectra of compound **1** and its coordination complex were compared in an attempt to understand the chemical nature of

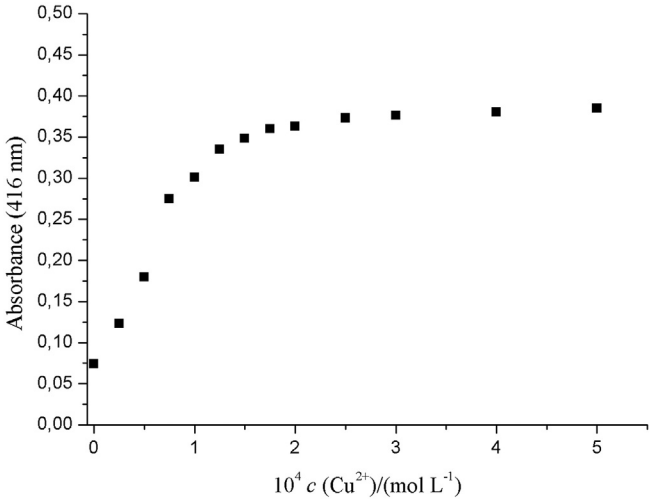


Fig. 2. Corresponding titration curve based on addition of Cu^{2+} (0 to 5 equivalents) to solutions of compound **1** (1.0×10^{-4} mol L^{-1}). All spectra were obtained 5 min after the addition of the reagents.

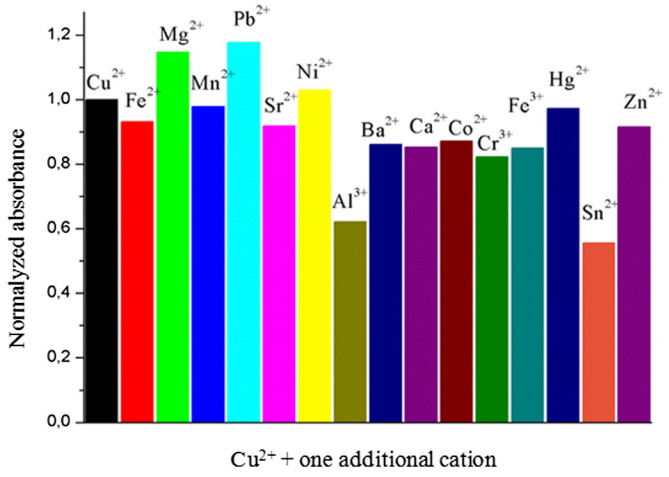


Fig. 3. Normalized absorbances at 416 nm for equimolar mixtures of ligand **1**, Cu^{2+} and one more metal ion, both 1.0×10^{-4} mol L^{-1} in methanol. Normalization was based on absorbance of the solution containing only compound **1** and Cu^{2+} (black bar).

the interactions between quinoxaline derivative **1** and Cu^{2+} ion (Fig. 4). Data strongly suggest coordination through carbonyl oxygen, since the band attributed to C═O bond stretching shifts from 1650 cm^{-1} in the free ligand to 1627 cm^{-1} in the coordination complex, and this shift to red is coherent with previous data in the literature [23,24]. In addition, a change in the position of the band relative to C═N bond, from 1532 cm^{-1} to 1485 cm^{-1}, suggests a quinoxaline nitrogen also participating in coordination to the metal ion.

The M06-L/6-31G(d)//PM6 (DFT//semi-empirical combined method [25,26], see details in Supplementary Material) calculations have been performed to support the evidence obtained from spectrophotometric titration, which suggests a complex formed by ligand **1** and two equivalents of $CuCl_2$. Firstly, a scanning of several conformations was performed to indicate the more favorable structure of compound **1** (see Fig. S5 in Supplementary Material). Afterwards, optimization calculations were performed to find a minimum structure for the bi-metallic complex. Fig. 5 shows the more thermodynamically favorable complexation structure obtained. The equilibrium of this reaction was

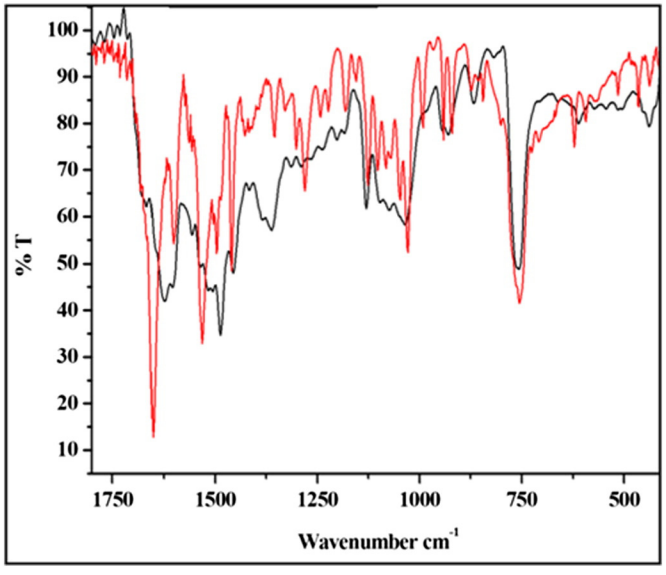


Fig. 4. Infrared spectra (1750 to 500 cm^{-1}) of compound **1** (red line) and its copper coordination complex (black line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

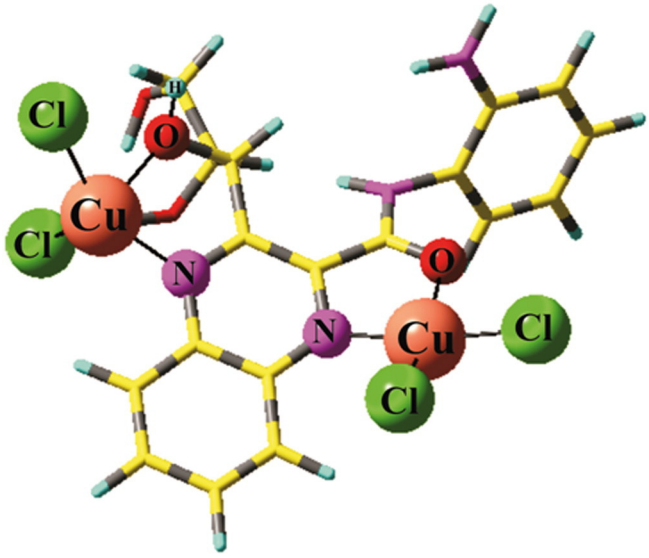


Fig. 5. Proposed structure for the bi-metallic complex obtained from interaction of ligand **1** and two equivalents of $CuCl_2$.

found to be slightly thermodynamically unfavorable (+6.0 kcal mol^{-1}). The following coordination sites were found for the interaction of ligand **1** with two copper ions: (1) copper to a nitrogen of the quinoxaline unit and the oxygen of the carbonyl group, leading to distorted planar square geometry; (2) copper to the another quinoxaline nitrogen and an oxygen of the hydroxyl group, resulting in distorted tetrahedral geometry. In both cases, the complexation led to five-membered metallocyclic structures. Experimental infrared data and theoretical results were found to be in good agreement, particularly with respect to the bands attributed to C═O bond stretching of the bi-metallic complex, which were centered at 1627 cm^{-1} and 1617 cm^{-1} in the experimental and theoretical spectra, respectively.

To summarize, compound **1** was easily obtained from ascorbic acid and *o*-phenylenediamine. This compound is an efficient chromogenic chemosensor in methanol for the detection of Cu^{2+} between several other cationic species studied. Experimental data, in combination with theoretical calculations, allowed for an evaluation of the selective binding of quinoxaline **1** to Cu^{2+}, suggesting the formation of a complex exhibiting 1:2 ligand:metal stoichiometry. Due to the high relevance of the development of selective chemosensors for ionic species [2,3,27], we are currently working on additional studies involving interactions of ligand **1** with cationic species, including synthetic transformations on compound **1** in attempt to improve the recognition and sensing ability of this system.

Acknowledgments

The authors give thanks for the financial support from the Brazilian Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação de Apoio à Pesquisa do Rio Grande do Norte (FAPERN, grant 005/2012), as well as UFRN and UFSC.

Appendix A. Supplementary data

Supplementary data associated with this article include experimental and theoretical procedures, NMR spectra and scanning of the more stable energetic conformer of compound **1**. These data can be found in the online version at: http://dx.doi.org/10.1016/j.inoche. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.inoche.2016.05.019.

References

[1] D.T. Quang, J.S. Kim, Fluore- and chromogenic chemodosimeters for heavy metal ion detection in solution and biospecimens, Chem. Rev. 110 (2010) 6280–6301, http://dx.doi.org/10.1021/cr100154p.

[2] Y. Jeong, J. Yoon, Recent progress on fluorescent chemosensors for metal ions, Inorg. Chim. Acta 381 (2012) 2–14, http://dx.doi.org/10.1016/j.ica.2011.09.011.

[3] K.P. Carter, A.M. Young, A.E. Palmer, Fluorescent sensors for measuring metal ions in living systems, Chem. Rev. 114 (2014) 4564–4601, http://dx.doi.org/10.1021/cr400546e.

[4] M.C. Yeung, V.W. Yam, Luminescent cation sensors: from host-guest chemistry, supramolecular chemistry to reaction-based mechanisms, Chem. Soc. Rev. 44 (2015) 4192–4202, http://dx.doi.org/10.1039/c4cs00391h.

[5] Q. Hu, Y. Liu, R. Wen, Y. Gao, Y. Bei, Q. Zhu, A new rhodamine-based dual chemosensor for Al^{3+} and Cu^{2+}, Tetrahedron Lett. 55 (2014) 4912–4916, http://dx.doi.org/10.1016/j.tetlet.2014.07.040.

[6] H.S. Kumbhar, U.N. Yadav, B.L. Gadilohar, G.S. Shankarling, A highly selective fluorescent chemosensor based on thio-β-enaminone analog with a turn-on response for Cu(II) in aqueous media, Sensors Actuators B Chem. 203 (2014) 174–180, http://dx.doi.org/10.1016/j.snb.2014.06.100.

[7] A. Kumar, V. Kumar, U. Diwan, K.K. Upadhyay, Highly sensitive and selective naked-eye detection of Cu^{2+} in aqueous medium by a ninhydrin–quinoxaline derivative, Sensors Actuators B Chem. 176 (2013) 420–427, http://dx.doi.org/10.1016/j.snb.2012.09.089.

[8] M. Wang, K. Leung, S. Lin, D.S. Chan, D.W.J. Kwong, C. Leung, D. Ma, A colorimetric chemosensor for Cu^{2+} ion detection based on an iridium(III) complex, Sci. Rep. 4 (2014) 1–7, http://dx.doi.org/10.1038/srep06794.

[9] O.O. Ajani, Present status of quinoxaline motifs: excellent pathfinders in therapeutic medicine, Eur. J. Med. Chem. 85 (2014) 688–715, http://dx.doi.org/10.1016/j.ejmech.2014.08.034.

[10] S. Achelle, C. Baudequin, N. Plé, Luminescent materials incorporating pyrazine or quinoxaline moieties, Dyes Pigments 98 (2013) 575–600, http://dx.doi.org/10.1016/j.dyepig.2013.03.030.

[11] C.J. Dhanaraj, J. Johson, Metal complexes of quinoxaline derivatives: review (part-I), Research Journal of Chemical Sciences 4 (2014) 80–102 (http://www.isca.in/rjcs/Archives/v4/i11/14.ISCA-RJCS-2014-03.pdf).

[12] C.J. Dhanaraj, J. Johson, Metal complexes of quinoxaline derivatives: review (part-II), Research Journal of Chemical Sciences 5 (2015) 64–84 (http://www.isca.in/rjcs/Archives/v5/i4/13.ISCA-RJCS-2015-034.pdf).

[13] Y.V.D. Nageswar, H.V. Reddy, K. Ramesh, N. Murthy, Organic preparations and procedures international, The New Journal for Organic Synthesis 45 (2013) 1–27, http://dx.doi.org/10.1080/00304948.2013.743419.

[14] E.S.H.E. Ashry, K.F. Atta, S. Abouk-Ela, R. Beldi, MAOS of quinoxalines, conjugated pyrazolylquinoxalines and fused pyrazoloquinoxalines from L-ascorbic and D-isoascorbic acid, J. Carbohydr. Chem. 26 (2007) 1–16, http://dx.doi.org/10.1080/07328300701252359.

[15] C. Henning, K. Liehr, M. Girndt, C. Ulrich, M.A. Glomb, Extending the spectrum of α-dicarbonyl compounds in vivo, J. Biol. Chem. 289 (2014) 28676–28688, http://dx.doi.org/10.1074/jbc.M114.563593.

[16] H. Dahn, H. Moll, Über die reaktion von dehydro-ascorbinsäure und anderen 2,3-diketobutyrolactonen mit 2 mol. *o*-phenylendiamin. 21. Mitteilungüberreduktone und tricarbonylverbindungen, Helv. Chim. Acta 47 (1964) 1860–1870, http://dx.doi.org/10.1002/hlca.19640470724.

[17] X. Wu, Y. Diao, C. Sun, J. Yang, Y. Wang, S. Sun, Fluorimetric determination of ascorbic acid with o-phenylenediamine, Talanta 59 (2003) 95–99, http://dx.doi.org/10.1016/S0039-9140(02)00475-7.

[18] W. Kim, R.L. Dahlgren, L.L. Moroz, J.V. Sweedler, Ascorbic acid assays of individual neurons and neuronal tissues using capillary electrophoresis with laser-induced fluorescence detection, Anal. Chem. 74 (2002) 5614–5620, http://dx.doi.org/10.1021/ac025917q.

[19] G. Burini, Development of a quantitative method for the analysis of total L-ascorbic acid in foods by high-performance liquid chromatography, J. Chromatogr. A 1154 (2007) 97–102, http://dx.doi.org/10.1016/j.chroma.2007.03.013.

[20] I. Nemet, V.M. Monnier, Vitamin C degradation products and pathways in the human lens, J. Biol. Chem. 286 (2011) 37128–37136, http://dx.doi.org/10.1074/jbc.M111.245100.

[21] M.A.E. Sekly, S. Mancy, K. Fahmy, Some quinoxaline derivatives from dehydro-D-arabinoascorbic acid, Carbohydr. Res. 133 (1984) 324–328, http://dx.doi.org/10.1016/0008-6215(84)85209-X.

[22] Characterization data for compound **1**: Mp. 180 °C; IR (KBr) υ_{max} (cm^{-1}): 3453, 3302, 2873, 1670, 1517, 1456, 1047, 752. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.10 (s, 1H, CONH), 8.23 (d, 1H, J = 7.8 Hz, ArH), 8.18 (d, 1H, J = 8.0 Hz, ArH), 7.99–7.90 (m, 2H, ArH), 7.37 (d, 1H, J = 7.8 Hz, ArH), 7.00 (t, 1H, J = 7.7 and 7.5 Hz, ArH), 6.81 (d, 1H, J = 8.0 Hz, ArH), 6.64 (t, 1H, J = 7.6 and 7.4 Hz, ArH), 5.48–5.41 (br, 2H, CH and OH), 5.00 (br, 2H, NH_2) 4.79 (d, 1H, J = 9.8 Hz, CH), 4.61 (t, 1H, J = 5.3 and 5.5 Hz, CH), 4.05 (br, 1H, CH), 3.61–3.53 (m, 1H, CH), 3.49–3.42 (m, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.7, 155.6, 147.0, 142.7, 140.7, 139.1, 131.5, 130.5, 129.0, 128.5, 126.7, 125.9, 122.4, 116.2, 115.9, 74.0, 71.5, 62.8. *Elemental analysis for* $C_{18}H_{18}N_4O_4$: calculated: C, 61.01; H, 5.12; N, 15.81; found: C, 60.93; H, 5.20; N, 15.91.

[23] B.S. Garg, N. Bhojak, P. Dwivedi, V. Kumar, Copper(II) complexes of acid amide derivatives of 2-aminopyridine and an exogenous ligand, Transit. Met. Chem. 24 (1999) 463–466, http://dx.doi.org/10.1023/A:1006951109468.

[24] S. Kawaguchi, K. Araki, Mild, rapid and selective alcoholysis of terpyridine-appended amide substrates by Cu^{2+}-catalysis: protonation state and reactivity of the complex, Inorg. Chim. Acta 358 (2005) 947–956, http://dx.doi.org/10.1016/j.ica.2004.10.008.

[25] J.J.P. Stewart, Optimization of parameters for semiempirical methods. V. Modification of NDDO approximations and application to 70 elements, J. Mol. Model. 13 (2007) 1173–1213, http://dx.doi.org/10.1007/s00894-007-0233-4.

[26] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2009.

[27] R. Martínez-Mañez, F. Sancenón, Fluorogenic and chromogenic chemosensors and reagents for anions, Chem. Rev. 103 (2003) 4419–4476, http://dx.doi.org/10.1021/cr010421e.