

Proceeding Paper

Synthesis, Characterization and Preliminary Chemosensory Ability of a Novel 2,4,5-Tri(Hetero)Arylimidazole Based on an 8-Hydroxy-Quinoline Group [†]

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Abstract: 2,4,5-Trisubstituted imidazole derivatives with heteroaromatic groups are versatile heterocyclic compounds exhibiting a wide range of biological activities, as well as very interesting thermal, optical, electronic and redox properties. In the past years, this type of imidazole derivatives has been explored as optical colorimetric and fluorimetric chemosensors due to their ability to coordinate with ions with biological and environmental relevance. In order to continue the work developed by the research group, we report the synthesis and characterization using usual spectroscopic techniques (NMR, absorption and emission spectroscopies) of a new imidazole derivative, substituted at position 2 of the imidazole with an 8-hydroxy-quinoline group. Furthermore, to complement the characterization of the synthesized imidazole compound, a preliminary study as an optical chemosensor was carried out in acetonitrile in the presence of ions with biological, medicinal and environmental relevance.

Keywords: Imidazole; Quinoline; Optical chemosensor; Synthesis

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1. Introduction

Many heterocyclic compounds substituted by electron donor and/or acceptor groups have played an important role in several areas, including environmental, biological, medicinal, industrial and waste management, due to their optical properties, high thermal and chemical stability, good transparency, easy synthetic methodology, etc. These derivatives are used in the most varied applications, such as nonlinear optics, optical chemosensors, fluorescent probes for bioimaging, organic light-emitting diodes (OLEDs), and Photodynamic Therapy (PDT), among others [1–7].

The recognition and selective detection of biologically and environmentally important anions and cations leads to the development of organic compounds containing functional groups with heterocyclic rings that have binding sites and that can behave as selective and effective ion receptor systems. In this context, imidazoles and their derivatives, due to their structure and easily tune optical properties, become versatile systems for multiple applications, such as optical chemosensors of ions and neutral molecules, as well as fluorescent probes for the detection of cells *in vivo* [1,4–5,7].

The imidazole ring is present in several bioactive compounds that have antiviral, anticancer, antihypertensive, antifungal, antibacterial properties, among others [8]. This heterocycle is an excellent hydrogen bond donor fraction in anion receiving systems and the acidity of the NH proton can be modulated by modifying the electronic properties of the imidazole derivatives. Also, due to the presence of a pyridine-type nitrogen, imidazole derivatives are able to selectively bind to cationic species [2–5,7].

This work reports the synthesis and spectroscopic characterization, as well as the evaluation of the chemosensory capacity of an imidazole derivative substituted at positions 2, 4 and 5 by heterocyclic moieties.

2. Material and Methods

Commercial reagents were supplied by Sigma-Aldrich, Acros, Fluka, Panreac, Li-ofilchem and used as received. The ion salts used (in the form of tetrabutylammonium salts for anions and perchlorate for cations, except for Cu(I), Pd(II) and Li(II), in the form of tetrafluoroborate and Sn(II) in the form of chloride) and the solvents are from Sigma-Aldrich, Acros and Fluka and were used as received.

Thin layer chromatography (TLC) was performed on silica gel 60 plates with fluorescence indicator F254 (Macherey-Nagel). The ^1H nuclear magnetic resonance spectra were recorded using a Bruker Avance III device at 400 MHz, using the solvent peak as an internal reference. The solvent was $\text{DMSO-}d_6$ with a 99.9% deuteration degree, containing 0.1% *v/v* tetramethylsilane from Sigma-Aldrich.

The UV-visible absorption spectra were made using a Shimadzu UV/2501PC spectrophotometer and the fluorescence emission spectra using a FluoroMax-4 (HORIBA) spectrofluorometer.

2.1. Synthesis and Spectroscopic Characterization of Imidazole Derivative 1

8-Hydroxy-quinoline-2-carbaldehyde (1 mmol), furil (1 mmol), ammonium acetate (20 mmol) and iodine (5 mol%) were dissolved in ethanol (5 mL), followed by stirring and heating at reflux for 4 h. The reaction was monitored by performing a TLC, using DCM/methanol (9:1) as eluent. The reaction mixture was cooled to room temperature, a small amount of solid sodium thiosulfate dissolved in 15 mL of water was added, causing the formation of a precipitate, which was then filtered under vacuum. The crude product was purified by SiO_2 column chromatography using DCM/methanol (10:1) to obtain compound **1** (Figure 1).

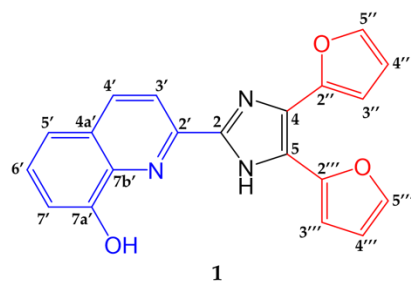


Figure 1. Structure of imidazole derivative **1**.

^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ = 6.6.2–6.2.3 (m, 1H, $\text{H4}''''$), 6.72–6.73 (m, 1H, $\text{H4}''$), 6.82 (d, J = 2.8 Hz, 1H, $\text{H3}''''$), 7.08 (d, J = 3.6 Hz, 1H, $\text{H3}''$), 7.13 (d, J = 6.4 Hz, 1H, $\text{H7}'$), 7.40–7.47 (m, 2H, $\text{H3}' + \text{H6}'$), 7.77 (s, 1H, $\text{H5}''''$), 7.90 (s, 1H, $\text{H5}''$), 8.19 (d, J = 8.8 Hz, 1H, $\text{H5}'$), 8.42 (d, J = 8.4 Hz, 1H, $\text{H4}'$), 13.35 (s, 1H, NH_{imid}). The signal of OH was not visualized.

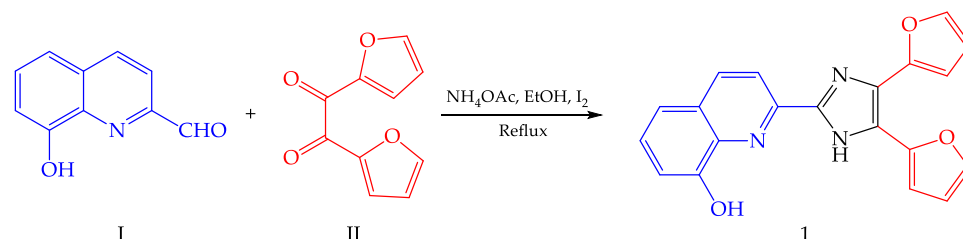
2.2. Preliminary Chemosensing Studies of Imidazole Derivative 1

The solutions of compound **1** and ions were prepared with concentrations of 1×10^{-5} and 1×10^{-2} mol/ dm^3 , respectively, in ACN. Then, 50 equivalents of each ion were added to 1 mL of solution of compound **1**. Taking into account these results, it was decided to carry out a new preliminary test in some cases. This consisted of preparing the same solutions of the compound and the ions, with equal concentrations, but in a mixture of ACN/water (75:25) was used as a solvent. Similarly, 50 equivalents of each ion were added to the imidazole **1** solution.

3. Results and Discussion

3.1. Synthesis and Spectroscopic Characterization of Imidazole Derivative 1

The synthesis of imidazole derivative **1** was performed in ethanol, using 8-hydroxyquinoline-2-carbaldehyde (I), furil (II), ammonium acetate and iodine, as catalyst (Scheme 1). After purifying the product by chromatography, using DCM/methanol (10:1) as eluent, the pure derivative **1** was obtained in the form of a dark green solid in 25% yield.



Scheme 1. Synthesis of imidazole derivative **1**.

The photophysical properties of imidazole derivative **1** were studied in ACN solutions. The compound showed an intense absorption band ($\log \epsilon = 3.9$) at 376 nm and an emission band at 499 nm. The Stoke's Shift was 123. The relative fluorescence quantum yield, determined by using 9,10-diphenyl anthracene in ethanol as fluorescence standard [3], was found to be 0.26.

3.2. Preliminary Studies of the Sensing Capacity of the Imidazole Derivative 1

A preliminary sensing study was carried out at room temperature, in order to check if there were variations in color and fluorescence of the imidazole derivative **1** solution in the presence of selected ions. Thus, the visualization of the solutions, after addition of 50 equivalents of the studied ions, was performed through "naked eye" detection and in a UV-Vis chamber, under ultraviolet light at 365 nm.

3.2.1. Sensing Capacity of Imidazole Derivative 1, in ACN

Regarding the interaction of compound **1** with anions (Figure 2), no color changes were observed (Figure 2A). In case of fluorescence response (Figure 2B), the imidazole derivative showed a partial quenching of fluorescence in the presence of AcO^- and changes in λ_{em} of fluorescence (from green to orange), upon the interaction with CN^- and F^- .

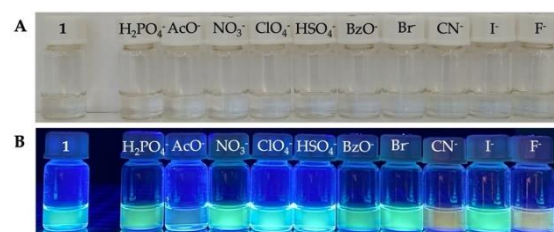


Figure 2. Solutions of compound **1**, in ACN, after adding 50 equivalents of anions, under natural light (A) and UV radiation at 365 nm (B).

In case of the interaction of compound **1** with cations (Figure 3), upon the addition of Fe^{3+} , a slight change in color was observed from colorless to light orange (Figure 3A). With incidence of ultraviolet radiation (Figure 3B), it was observed a quenching of fluorescence for Hg^{2+} , Co^{2+} , Pb^{2+} , Mn^{2+} , Fe^{2+} , Ni^{2+} , Cu^{2+} , Pd^{2+} , Sn^{2+} , Fe^{3+} and Al^{3+} ions. There was also a change in λ_{em} in the presence of TBT^+ , Zn^{2+} and Cd^{2+} accompanied by a change from green to red color (for TBT^+ and Zn^{2+}) and orange (for Cd^{2+}). Finally, it was possible to visualize an enhancement of fluorescence upon the interaction with Ca^{2+} .

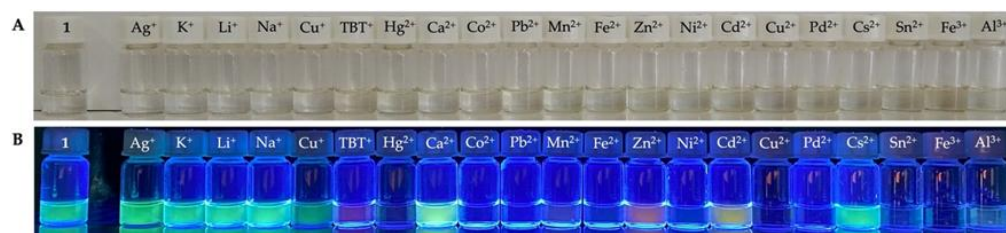


Figure 3. Solutions of compound **1**, in ACN, after adding 50 equivalents of cations, under natural light (A) and UV radiation at 365 nm (B).

3.2.2. Sensing Capacity of Imidazole Derivative **1**, in ACN/Water (75:25)

In order to see the potential biological and environmental application of this heterocyclic receptor, the chemosensory studies were also performed in ACN/water (75:25) solutions. Regarding the interaction of compound **1** with anions (Figure 4), no color changes were observed (Figure 4A). In case of fluorescence response (Figure 4B), the imidazole derivative showed a quenching of fluorescence in the presence of ClO_4^- .

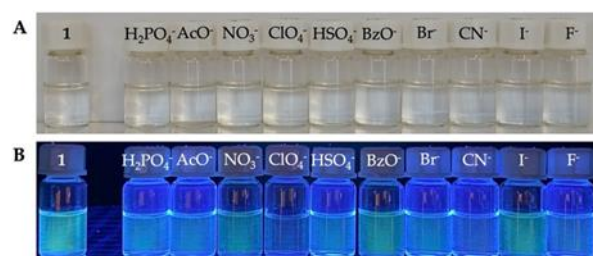


Figure 4. Solutions of compound **1**, in ACN/water (75:25), after adding 50 equivalents of anions, under natural light (A) and UV radiation at 365 nm (B).

In case of the interaction of compound **1** with cations (Figure 5), no color changes were observed (Figure 5A). With incidence of ultraviolet radiation (Figure 5B), it was observed a quenching of fluorescence of **1** in the presence of Na^+ , Cu^+ , Hg^{2+} , Co^{2+} , Pb^{2+} , Ni^{2+} , Cd^{2+} , Cu^{2+} and Pd^{2+} ions. There was also a change in λ_{em} accompanied by a change from green to red color in the presence of TBT^+ .

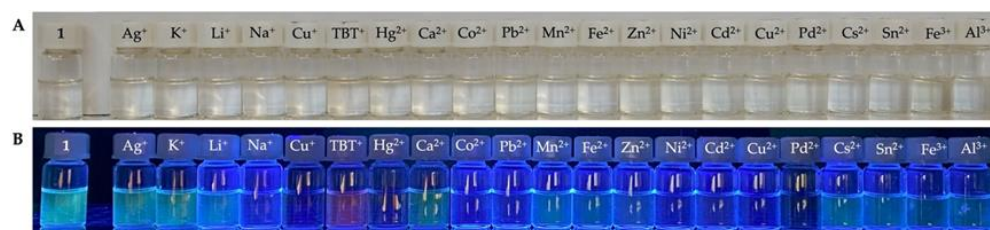


Figure 5. Solutions of compound **1**, in ACN/water (75:25), after adding 50 equivalents of cations, under natural light (A) and UV radiation at 365 nm (B).

4. Conclusions

A novel 2,4,5-trisubstituted imidazole derivative with heteroaromatic groups was synthesized, through a simple method. The new compound was characterized by ^1H NMR, UV-Vis absorption and fluorescence spectroscopies.

Considering the structure of imidazole **1** with various potential binding groups, a preliminary chemosensory study was undertaken in ACN solutions in the presence of relevant ions with biological, medicinal and environmental relevance showing that this receptor has a potential application as a colorimetric/fluorimetric chemosensor. A more detailed study concerning the interaction of imidazole **1** with the ions that gave the most

interesting results will be undertaken through spectrophotometric and spectrofluorimetric titrations.

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References

1. Pina, J.; Seixas de Melo, J.S.; Batista, R.M.F.; Costa, S.P.G.; Raposo, M.M.M. Synthesis and characterization of the ground and excited states of tripodal-like oligothieryl-imidazoles. *J. Phys. Chem. B* **2010**, *114*, 4964–4972. <https://doi.org/10.1021/jp9104954>.
2. Molina, P.; Tárraga, A.; Otón, F. Imidazole derivatives: A comprehensive survey of their recognition properties. *Org. Biomol. Chem.* **2012**, *10*, 1711–1724. <https://doi.org/10.1039/C2OB06808G>.
3. Ferreira, R.C.M.; Costa, S.P.G.; Gonçalves, H.; Belsley, M.; Raposo, M.M.M. Fluorescent phenanthroimidazoles functionalized with heterocyclic spacers: Synthesis, optical chemosensory ability and two-photon absorption (TPA) properties. *New J. Chem.* **2017**, *41*, 12866–12878. <https://doi.org/10.1039/C7NJ02113E>.
4. Okda, H.E.; El Sayed, S.; Ferreira, R.C.M.; Costa, S.P.G.; Raposo, M.M.M.; Martínez-Mañez, R.; Sancenón, F. 4-(4,5-Diphenyl-1H-imidazole-2-yl)-N,N-dimethylaniline-Cu(II) complex, a highly selective probe for glutathione sensing in water-acetonitrile mixtures. *Dyes Pigment.* **2018**, *159*, 45–48. <https://doi.org/10.1016/j.dyepig.2018.05.069>.
5. Okda, H.E.; Sayed, S.E.; Ferreira, R.C.M.; Otri, I.; Costa, S.P.G.; Raposo, M.M.M.; Martínez-Mañez, R.; Sancenón, F. A simple and easy-to-prepare imidazole-based probe for the selective chromofluorogenic recognition of biothiols and Cu(II) in aqueous environments. *Dyes Pigment.* **2019**, *162*, 303–308. <https://doi.org/10.1016/j.dyepig.2018.10.017>.
6. Moreira, X.; Santos, P.; Faustino, M.A.F.; Raposo, M.M.M.; Costa, S.P.G.; Moura, N.M.M.; Gomes, A.T.P.C.; Almeida, A.; Neves, M.G.P.M.S. An insight into the synthesis of cationic porphyrin-imidazole derivatives and their photodynamic inactivation efficiency against *Escherichia coli*. *Dyes Pigment.* **2020**, *178*, 108330. <https://doi.org/10.1016/j.dyepig.2020.108330>.
7. Sousa, R.P.C.L.; Figueira, R.B.; Gomes, B.; Costa, S.P.G.; Azenha, M.; Pereira, R.P.C.L.; Raposo, M.M.M. Organic-inorganic hybrid sol-gel materials doped with a fluorescent triarylimidazole derivative. *RSC Adv.* **2021**, *11*, 24613–24623. <https://doi.org/10.1039/D1RA03997K>.
8. Bellina, F.; Cauteruccio, S.; Rossi, R. Synthesis and biological activity of vicinal diaryl-substituted 1H-imidazoles. *Tetrahedron* **2007**, *63*, 4571–4624. <https://doi.org/10.1016/j.tet.2007.02.075>.