

A Novel Imidazole Derivative: Synthesis, Characterization and Chemosensory Ability for Ions [†]

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Abstract: Imidazoles have been explored over the years as optical chemosensors for their ability to coordinate with analytes, through specific binding sites, especially for ions, provided by the nitrogen heteroatom. Consequently, a novel 2,4,5-triheteroarylimidazole was synthesized bearing indolyl and furyl moieties. The compound was characterized by the usual spectroscopic techniques, and the preliminary chemosensory ability was carried out in acetonitrile and acetonitrile/water (25:75) in the presence of ions with biological, medicinal, and environmental relevance. In aqueous medium, the new compound showed a slight enhancement of fluorescence in the presence of HSO_4^- . As for cations, an enhancement of the fluorescence was observed upon interaction with Fe^{2+} , Sn^{2+} , Fe^{3+} and Al^{3+} . On the other hand, a quenching of fluorescence was observed in the presence of Cu^{2+} .

Keywords: imidazole; heterocycles; synthesis; fluorescent probe

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1. Introduction

Imidazole derivatives can be applied in varied scientific areas, such as in supramolecular chemistry, in medicinal chemistry and in the production of fuel cells and artificial materials, among other applications. At a supramolecular level, the imidazole ring has the ability to coordinate with a variety of inorganic metal ions or to interact with organic molecules through intermolecular forces, functioning as a recognition moiety. [1,2]

The detection of analytes, especially ions, can be made through optical chemosensors, which are abiotic molecules that bind selectively and irreversibly with an analyte, resulting in a change in the optical properties of the chemical system. The development of colorimetric and fluorimetric chemosensors for ionic species has been widely investigated, as these species take part in several biological processes and can act as environmental pollutants. [3–5]

The interaction of an organic compound with ions can be improved by the inclusion of tailored functional groups or heterocyclic rings in its structure, providing specific binding sites. The versatile imidazole ring is a heterocyclic donor unit that has the ability to establish hydrogen bonds with anions. The introduction of groups of different electronic nature can tune the NH proton acidity. Simultaneously, the sp^2 nitrogen atom with a non-bonding electron pair is able to selectively bind with cations, making imidazole an exceptional receptor for metal ions. Additionally, functionalization of imidazole structure with heterocyclic moieties (e.g., thiophene, pyrrole or furan) will introduce additional binding sites in the receptor molecule. [6–12]

Bearing in mind the above considerations, in this work is reported the synthesis and characterization of a new imidazole derivative, bearing indole heterocycle at position 2 and furyl moieties at positions 4 and 5 of the imidazole ring. The chemosensory ability of

the new compound was studied in acetonitrile and acetonitrile/water (25:75) in the presence of ions.

2. Material and Methods

The commercial reagents were supplied by Sigma-Aldrich (St. Louis, MO, USA), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland) and were used as received. The ion salts used (in the form of tetrabutylammonium salts for anions and perchlorate for cations, except for Li^+ , Cu^+ , and Pd^{2+} in the form of tetrafluoroborate and Sn^{2+} 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 0.20 mm thick Macherey-Nagel silica gel plates (DC-Fertigfolien 60F254) and plates were visualized under ultraviolet light (λ_{max} 254 and 365 nm) in a CN-15LC light chamber (Vilber Lourmat). Melting points were measured on a Stuart Scientific Melting Point SMP1 apparatus.

The ^1H and ^{13}C nuclear magnetic resonance spectra were recorded using a Bruker Avance III device at 400 MHz and 100.6 MHz, respectively, using the solvent peak as an internal reference. The assignment of the ^1H and ^{13}C signals was performed using two-dimensional heteronuclear correlation techniques, in $\text{DMSO-}d_6$ with a 99.9% deuteration degree, containing 0.1% v/v tetramethylsilane from Sigma-Aldrich. The UV-Vis absorption spectra were made on a Shimadzu UV/2501PC spectrophotometer and the fluorescence spectra were collected in a FluoroMax-4 (HORIBA) spectrophotometer in quartz cells. The infrared spectra were obtained on a Spectrum Two—PerkinElmer FTIR apparatus with ATR accessory.

2.1. Synthesis and Spectroscopic Characterization of Imidazole Derivative 3

5-Methylindole-3-carboxaldehyde **1** (1 mmol), furil **2** (1 mmol), NH_4OAc (20 mmol) and I_2 (5 mol %) were dissolved in ethanol (5 mL), followed by stirring and heating at reflux for 8 h. The reaction was monitored by TLC, using a mixture of dichloromethane/methanol (9:1) as eluent. Then, the reaction mixture was diluted with water (15 mL) having a small amount of $\text{Na}_2\text{S}_2\text{O}_3$ and was cooled in an ice bath. The mixture was kept in cold and the pure imidazole derivative **3** (Figure 1), precipitated as a dark brown solid in 45% yield, m. p. = 200–202 °C.

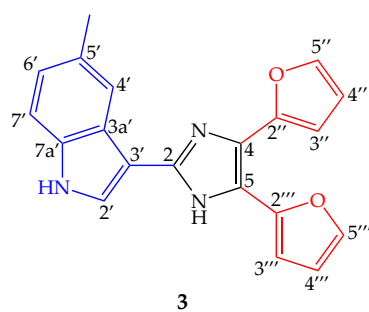


Figure 1. Structure of imidazole derivative **3**.

^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ = 2.43 (s, 3H, CH_3), 6.62 (s, 2H, $\text{H4''}+\text{H4'''}$), 6.83 (s large, 2H, $\text{H3''}+\text{H3'''}$), 7.00 (dd, J = 1.2 and 6.8 Hz, 1H, H6'), 7.31 (d, J = 8.0 Hz, 1H, H7'), 7.76 (s, 2H, $\text{H5''}+\text{H5'''}$), 8.03 (d, J = 2.8 Hz, 1H, H2'), 8.18 (s, 1H, H4'), 11.30 (s, 1H, NH_{imid}) and 12.42 (s, 1H, NH_{ind}) ppm.

^{13}C NMR (100.6 MHz, $\text{DMSO-}d_6$): δ = 21.47 (CH_3), 105.62 (C3'), 107.15 ($\text{C3''}+\text{C3'''}$), 111.36 (C7'), 111.68 ($\text{C4''}+\text{C4'''}$), 120.95 (C4'), 123.61 (C6'), 124.74 (C2'), 125.25 (C3a'), 128.43 (C5'), 134.65 (C7a'), 141.77 ($\text{C5''}+\text{C5'''}$) and 144.59 (C2) ppm.

FTIR-ATR (solid): ν 3305, 3243, 1604, 1580, 1433, 1375, 1302, 1212, 1146, 1107, 1023, 1006, 986, 907, 883, 793, 737, 669, 591, 520 cm^{-1} .

2.2. Preliminary Chemosensory Studies of Imidazole Derivative 3

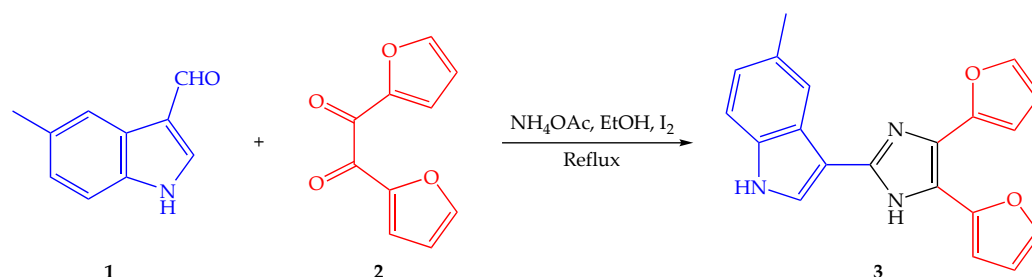
The solution of the synthesized compound **3** and the ions (anions: H_2PO_4^- , AcO^- , NO_3^- , ClO_4^- , HSO_4^- , BzO^- , Br^- , CN^- , I^- and F^- ; cations: Ag^+ , K^+ , Na^+ , TBT^+ , Hg^{2+} , Ca^{2+} , Co^{2+} , Pb^{2+} , Mn^{2+} , Fe^{2+} , Zn^{2+} , Ni^{2+} , Cd^{2+} , Cu^{2+} , Cs^{2+} , Fe^{3+} , Al^{3+} , Li^+ , Cu^+ , Pd^{2+} and Sn^{2+}) were prepared with concentrations of 1×10^{-5} and 1×10^{-2} M, respectively, in UV-grade ACN. Then, 50 equivalents of each ion were added to 1 mL of solution of compound **3**, at room temperature to check for variations in color and fluorescence of the imidazole derivative 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. Taking into account the results obtained from this preliminary test, it was decided to carry out a new preliminary test in aqueous solution that consisted of preparing the solutions of the compound and the ions, with equal concentrations, using a mixture of ACN/water (75:25) as solvent.

3. Results and Discussion

3.1. Synthesis and Spectroscopic Characterization of Imidazole Derivative 3

The synthesis of imidazole derivative **3** was performed in ethanol, using 5-methylindole-3-carboxaldehyde **1**, furil **2**, ammonium acetate (as nitrogen source) and iodine, as catalyst (Scheme 1). Iodine is recurrently used as a catalyst in different organic reactions, as it will act as a mild Lewis acid and is capable of bonding with the carbonyl oxygen, increasing the reactivity of the parent carbonyl compound. [9,13]

After work-up, the pure imidazole **3** was obtained as a dark brown solid in 45% yield.



Scheme 1. Synthesis of imidazole derivative **3**.

The photophysical characterization of the synthesized imidazole derivative was carried out using ACN as solvent (Figure 2). Compound **3** showed an intense absorption band ($\log \epsilon = 4.5$) at 319 nm and an emission band at 374 nm. The Stokes' shift was 55 nm and the relative fluorescence quantum yield, determined by using 9,10-diphenylanthracene in ethanol as fluorescence standard [14], was found to be 0.29.

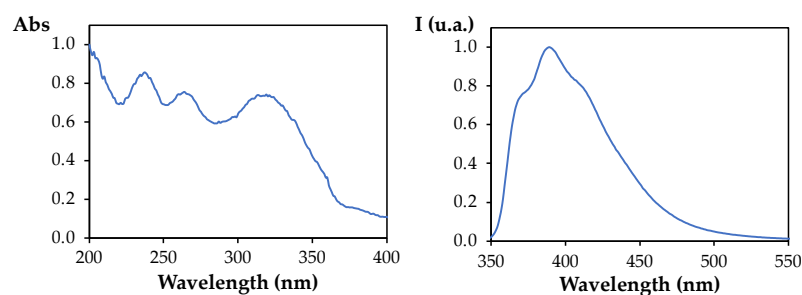


Figure 2. Normalized absorption and emission spectra of compound **3**, in ACN.

3.2. Preliminary Chemosensory Studies of Imidazole Derivative 3

The solutions of compound **3** for the chemosensory study were analyzed after the addition of 50 equivalents of the studied anions and cations, in ACN and ACN/water

(75:25), under the incidence of natural light and of ultraviolet radiation. From these preliminary tests, changes in color and fluorescence were observed, depending on the ion that was added.

3.2.1. Chemosensory Capacity of Imidazole Derivative **3**, in ACN

Considering the interaction of imidazole derivative **3** with anions, in ACN, (Figure 3), no color changes were observed (Figure 3A) and this compound cannot be considered as a colorimetric chemosensor for anions. Regarding fluorescence changes (Figure 3B), it was observed that this compound exhibited interaction with CN^- and F^- ions, resulting in a slight increase in fluorescence as well as a change from blue to green emission.

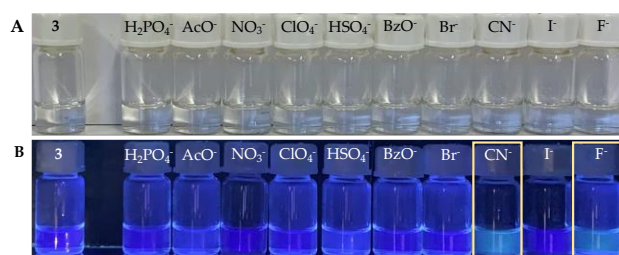


Figure 3. Solutions of compound **3**, in ACN (1×10^{-5} M), after adding 50 equivalents of anions, under natural light (A) and UV radiation at 365 nm (B).

Regarding the interactions of compound **3** with cations in ACN (Figure 4), it was possible to observe a color change of the solutions of the compound from colorless to light blue and orange, in the presence of Cu^{2+} and Fe^{3+} , respectively (Figure 4A). In case of fluorimetric response (Figure 4B), compound **3** showed noticeable enhancement of fluorescence in the presence of Li^+ , Pb^{2+} , Mn^{2+} , Fe^{2+} , Zn^{2+} , Pd^{2+} , and Sn^{2+} , being the interaction with Fe^{2+} the most pronounced. In addition, a marked quenching of fluorescence was observed upon interaction with Hg^{2+} , Cu^{2+} and Fe^{3+} .

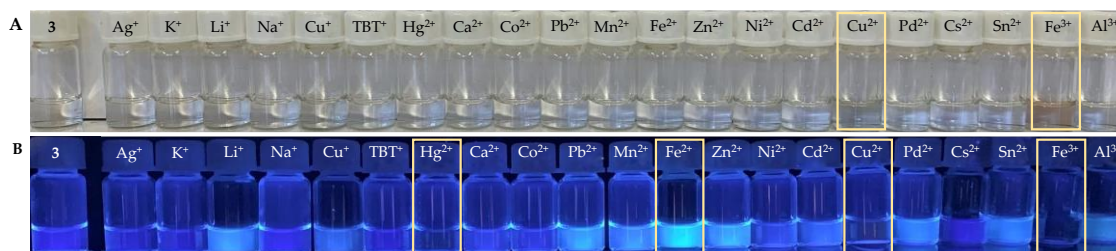


Figure 4. Solutions of compound **3**, in ACN (1×10^{-5} M), after adding 50 equivalents of cations, under natural light (A) and UV radiation at 365 nm (B).

3.2.2. Chemosensory Capacity of Imidazole Derivative **3**, in ACN/Water (75:25)

In the presence of anions, under natural light, compound **3** didn't reveal any change of color, in ACN/water (75:25) (Figure 5A). Under UV radiation, it was observed a selective enhancement of fluorescence in the presence of HSO_4^- (Figure 5B).

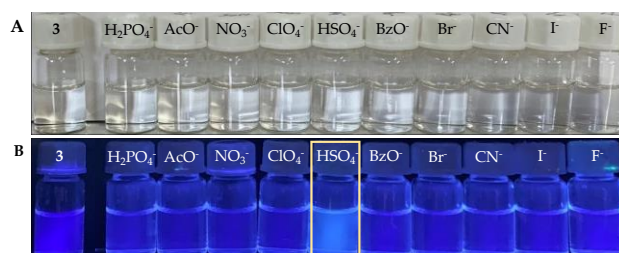


Figure 5. Solutions of compound **3**, in ACN/water (75:25) (1×10^{-5} M), after adding 50 equivalents of anions, under natural light (A) and UV radiation at 365 nm (B).

Regarding the interaction of imidazole derivative **3** with cations, it was observed a color change of the solution of the compound from colorless to orange and yellow after the addition of Cu^{2+} and Fe^{3+} , respectively (Figure 6A). Considering the fluorimetric behavior, compound **3** exhibited an enhancement of fluorescence with the addition of Fe^{2+} , Sn^{2+} , Fe^{3+} e Al^{3+} . Furthermore, it was observed a quenching of fluorescence in the presence of Cu^{2+} , Pd^{2+} e Cs^{2+} , being the response with Cu^{2+} the most marked with a complete quenching (Figure 6B).

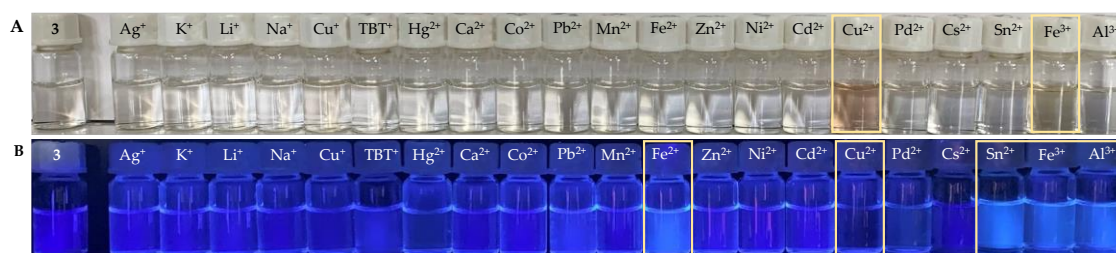


Figure 6. Solutions of compound **3**, in ACN/water (75:25) (1×10^{-5} M), after adding 50 equivalents of cations, under natural light (A) and UV radiation at 365 nm (B).

It is noteworthy the different chromo/fluometric response of compound **3** in the presence of iron in different oxidation states, as it allows discrimination between the two forms: the interaction with Fe^{2+} results in higher fluorescence intensity whereas the interaction with Fe^{3+} results in a noticeable change in color.

4. Conclusions

Compound **3** was easily synthesized, in 45% yield, through a modification of the Radziszewski reaction, in which ethanol was used as solvent and iodine as catalyst. The new synthesized imidazole derivative was successfully characterized by NMR, FTIR, absorption and emission spectroscopies. Finally, the preliminary tests of the chemosensory capacity showed some interactions that in the future will be studied with more detail, through spectrofluorimetric titrations. Regarding the interaction with anions, compound **3** revealed an enhancement of fluorescence in the presence of CN^- and F^- , in ACN, and in the presence of HSO_4^- , in ACN/water (75:25). Bearing in mind the interaction with cations in ACN, compound **3** showed an enhancement of fluorescence in the presence of several cations, being the interaction with Fe^{2+} the most pronounced, exhibiting an accentuated quenching of fluorescence upon the interaction with Cu^{2+} . In ACN/water (75:25) the ions that caused an enhancement of fluorescence were Fe^{2+} , Sn^{2+} , Fe^{3+} and Al^{3+} and the presence of Cu^{2+} revealed an intense quenching.

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