Development of Imidazole-Reactive Molecules Leading to a New Aggregation-Induced Emission Fluorophore Based on the Cinnamic Scaffold

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ABSTRACT: In order to obtain new fluorophores potentially useful in imidazole labeling and subsequent conjugation, a small series of Morita–Baylis–Hillman acetates (3a–c) was designed, synthesized, and reacted with imidazole. The optical properties of the corresponding imidazole derivatives 4a–c were analyzed both in solution and in the solid state. Although the solutions display a very weak emission, the powders show a blue emission, particularly enhanced in the case of compound 4c possessing two methoxy groups in the cinnamic scaffold. The photophysical study confirmed the hypothesis that the molecular rigidity of the solid state enhances the emission properties of these compounds by triggering the restriction of intramolecular motions, paving the way for their applications in fluorogenic labeling.

INTRODUCTION

Imidazole is an aromatic five-membered heterocyclic ring in which the nitrogen atoms are not adjacent and is considered as a fascinating tool in organic chemistry because of its features including high polarity, water solubility, and amphoteric character.1,2 Imidazole is contained in many synthetic compounds of pharmaceutical interest including some antifungal, antiprotozoal, antihypertensive, and antileukemic.3,4 Moreover, its structure is also frequent in natural compounds possessing two methoxy groups in the cinnamic scaffold. The photophysical study confirmed the hypothesis that the molecular rigidity of the solid state enhances the emission properties of these compounds by triggering the restriction of intramolecular motions, paving the way for their applications in fluorogenic labeling.

On the other hand, biochemists exploit fluorescence spectroscopy as an analytical technique in the study of protein interactions and functions. The most commonly used detection techniques are based on the use of fluorescent organic dyes, but recently, fluorogenic labeling methods emerged as more promising approaches owing to their higher signal-to-noise ratio, which is caused by the fluorescence activation in the...
probe after its reaction/attachment to the desired site.\textsuperscript{10,14–16} Particularly interesting are fluorogens showing emission intensities higher in the solid state than in solution, possessing aggregation-induced emission (AIE) properties.\textsuperscript{17,18} These fluorogens offer higher sensitivity, better accuracy, and improved photostability with respect to traditional fluorescence probes that are generally well-emissive in solution but undergo aggregation-caused quenching processes at high concentrations.\textsuperscript{19,20}

Alkylation of histidine residues in polyhistidine tags of engineered proteins could be a difficult task because imidazole rings usually show low reactivity in conventional alkylation reactions. Morita–Baylis–Hillman adducts (MBHAs) have been proposed to represent interesting reagents capable of alkylating imidazole in the presence of water,\textsuperscript{21} MBHA derivatives could find applications as reagents for imidazole modification. For example, a successful alkylation of N-acetylhexahistidine with MBHA derivatives was performed by means of the aid of transition-metal cations interacting with a nitrilotriacetate ligand linked to an MBHA leaving group.\textsuperscript{23}

In the present paper, MBHA derivatives 3a–c (Figure 1) were designed as imidazole-reactive molecules capable of producing imidazole-binding cinnamic derivatives (IBCDs) 4a–c.

![Scheme 1. Synthesis of MBHA Derivatives 3a–c and Their Reaction with Imidazole\textsuperscript{a}](image)

3a was prepared by a previously published procedure with the exception that the final esterification of 7a was performed with acetyl chloride.\textsuperscript{23} The MBHA derivative 3a was then made to react with 1.2 equiv of imidazole in tetrahydrofuran (THF)—water (5:1) under reflux to obtain the imidazole derivative 4a.

MBHA derivatives 3b,c bearing additional methoxy substituents were prepared by the same procedure starting from the appropriate aromatic aldehydes 5b,c, which were converted into the corresponding propargyloxy derivatives 6b,c.\textsuperscript{25,29} These compounds were then reacted with methyl acrylate in the presence of DABCO to provide MBHA alcohols 7b,c, which were in turn transformed into MBHA acetates 3b,c. Finally, compounds 3b,c were made to react with 1.2 equiv of imidazole in THF—water (5:1) under reflux to obtain the imidazole derivatives 4b,c in 82–78% yields.

The UV–visible (UV–vis) absorption and emission spectra of imidazole derivatives 4a–c are shown in Figure 2 for the compounds in diluted solution (i.e., 10\textsuperscript{−5} M in methanol) and in the solid state (i.e., powders). Their main properties are compared in Table 1 in which the photoluminescence quantum

\textsuperscript{a}Reagents: (i) propargyl bromide, K\textsubscript{2}CO\textsubscript{3}, and acetonitrile; (ii) methyl acrylate, 1,4-diazabicyclo[2.2.2]octane (DABCO), CH\textsubscript{3}OH, and THF; (iii) CH\textsubscript{3}COCl, triethylamine (TEA), and CH\textsubscript{2}Cl\textsubscript{2}; and (iv) imidazole, THF, and H\textsubscript{2}O.

Interestingly, we envisioned that the important structural elements (i.e., the push–pull structure in blue in Figure 1) of IBCD cinnamic scaffold are contained into the green fluorescent protein (GFP) fluorophore (1), leading to the assumption that compounds 4a–c could enhance their emissive features by the RIM (restriction of intramolecular motions) phenomenon, thus showing fluorogenic properties.

Moreover, the introduction of the electron donor methoxy groups in the cinnamic scaffold should increase the push–pull character of the scaffold, altering the emission features of the compounds.\textsuperscript{24–27} Thus, a small series of Morita–Baylis–Hillman acetates (3a–c) was synthesized and made to react with imidazole to obtain the corresponding imidazole derivatives 4a–c, which were characterized from the point of view of their optical properties.
yield (PL QY)\textsuperscript{30} is also reported. The three compounds show a very similar optical absorption, with a band peaked at about 300 nm in solution. The solutions are only weakly emissive, with PL QYs below 1% and lifetimes below the experimental resolution (about 300 ps). In the solid state, all of them display blue emissions, rather weak for compound 4a, increasing for compound 4b, and becoming quite bright for compound 4c. The weakly emissive compound 4a shows a broad PL spectrum peaked at 474 nm with about 0.5 ns lifetime. A deeper photophysical analysis reveals that this broad emission is associated with the presence of a longer lived component (average lifetime of about 260 μs) with a red-shifted (500–600 nm) spectrum (see Figure S1 in the Supporting Information). The methoxy 4b and dimethoxy 4c derivatives show narrow emission spectra peaked at 411 nm (0.6 ns lifetime) and 436 nm (15 ns lifetime), respectively, with the 4c derivative characterized by a PL QY as high as 14% (see Table 1 and Figure 2).

In order to understand the nature of the weak emission of the compounds in solution and to assess the mechanism responsible for the increase of their emission intensity in the solid state, we have performed a deeper analysis of the emission properties of compound 4c because its powders display the strongest emission intensity. The PL intensities of the compound dissolved in solvents with increasing polarities (THF or methanol) do not reveal any clear dependence on the solvent polarity, whereas an increase in the PL QY is observed by using a viscous solvent (PEG 400, QY = 1.3%, see Figure S2 in the Supporting Information). This observation suggests that the origin of the weak emission in solution is ascribed to the intramolecular motions that are slowed down by increasing the solvent viscosity.\textsuperscript{26,31} We have then performed a PL analysis of 4c dissolved in methanol (good solvent) by adding a nonsolvent (water) while keeping constant its concentration (about 3.5 $\times$ 10\textsuperscript{−5} M) in order to monitor the emission of the compound upon microaggregation in solution. The results, reported in Figure 3, show that the PL spectra progressively red-shift from 415 to 450 nm by the addition of water while the PL intensity (see the inset of Figure 3) displays a clear increase at a water fraction of 60% and then decreases for higher water fractions. These results demonstrate that (i) the emission intensity of the compound is influenced by the environment rigidity rather than by its polarity and that (ii) a particular type of aggregation (occurring at about 60% of water fraction in methanol) is necessary to enhance the emission. Other organic compounds possessing a similar molecular structure have shown fluorescence strongly dependent on the nature of the aggregated particles and hence on the preparation meth-

| compd | $\lambda_{ab}^a$ (nm) | $\lambda_{em}^b$ (nm) | PL QY\textsuperscript{c} (%) | $\lambda_{em}^c$ (nm) | PL QY\textsuperscript{d} (%) | $\tau$\textsuperscript{d} (ns) |
|-------|----------------------|----------------------|-----------------------------|----------------------|-----------------------------|-----------------------------|
| 4a    | 298                  | 420                  | 0.07                        | 474                  | <0.1                        | 0.51                        |
| 4b    | 300                  | 395                  | 0.10                        | 411                  | 1                           | 0.63                        |
| 4c    | 300                  | 400                  | 0.11                        | 436                  | 14                          | 14.86                       |

\textsuperscript{a}Methanol. \textsuperscript{b}THF. \textsuperscript{c}PL QY = 0.6 ns. \textsuperscript{d}PL QY = 300 nm. \textsuperscript{e}77 K.

Figure 2. Optical properties of imidazole derivatives 4a–c. Absorption and emission spectra of the diluted methanol solutions (blue solid and dotted lines, respectively) and emission spectra of the powders (dashed black line).

Table 1. Optical Properties of Compounds 4a–c

Figure 3. Optical absorption and PL of the imidazole derivative 4c in diluted methanol–water solutions for different methanol–water volume ratios. In the inset, the PL QY measured by exciting at 313 nm is plotted as a function of the water fraction.
This behavior is typical of systems possessing crystallization-induced emission (CIE) properties. In these systems, the free intramolecular motions (vibrations and rotations) responsible for the solution emission quenching are active also in the aggregated state unless a strongly rigid solid-state packing is obtained. Only a very rigid environment, such as that of a tight crystal packing or a very rigid matrix, is capable of inhibiting the molecular motions responsible for the nonradiative deactivation of the excitations. For this reason, such compounds often display polymorphism-dependent emissive properties and have recently shown interesting mechanofluorescence and thermoluminescence properties.

In order to verify if this mechanism is at the origin of the PL properties of the compounds 4a–c, we have studied their behavior in a good solvent when the diluted solution is frozen so that the molecular motions are blocked in the solutions. In Figure 4, we report the PL spectra of 4c in THF solution as measured at room temperature and at 77 K (see Figures S3 and S4 in the Supporting Information for the PL spectra of 4a and b, respectively), and the PL emission maxima positions are reported in Table 1. For all compounds, a strong increase of the PL intensity (more than 2 orders of magnitude) is observed, in agreement with the presence of a quenching induced by the intramolecular motions in the solution at room temperature.

Interestingly, by comparing the PL spectra of the glassy solutions with those of the powders, we note that for compound 4a, a large spectral broadening and red shift are observed in the powder emission. In particular, the presence of a long lived component in the PL emission of 4a powders might be associated to excimeric states formed by strong intermolecular interactions. From the comparison of the photophysical properties of the three compounds, we can therefore suggest that compound 4c displays the highest tendency to aggregate in a rigid packing where weak intermolecular interactions favors the emission, whereas a tight molecular packing in compound 4a introduces weakly emissive excimeric states accounting for the observed reduced emission efficiency. A combined structural and spectroscopic analysis of the three compounds in the solid state will further shed light on their complex photophysical behaviors.

### CONCLUSIONS

With the aim of obtaining new fluorophores potentially useful in imidazole labeling and subsequent conjugation, a small series of Morita–Baylis–Hillman acetates (3a–c) was designed, synthesized, and made to react with imidazole to obtain the corresponding imidazole derivatives 4a–c, which were characterized from the point of view of their photophysical properties.

The analysis of the photophysical features showed that the three compounds display a very weak emission in solution. The starting imidazole derivative 4a failed in showing a significant emission in the solid state, which was instead observed in its methoxy and dimethoxy derivatives 4b and 4c. These latter compounds featured the AIE, and in particular, the bright blue emission of compound 4c suggests the presence of CIE phenomenon, with PL QYs in the powders increased by 2 orders of magnitude with respect to the corresponding values measured in solution. The photophysical study confirmed the hypothesis that the molecular rigidity of the solid state enhances the emission properties of these compounds by triggering the RIM as it occurs for GFP fluorophores inside the protein. Moreover, the results emphasized 3c as an imidazole-reactive molecule capable of forming a new AIE fluorophore bearing a “clickable” propargyl group potentially useful in the labeling of imidazole derivatives and subsequent conjugation.

### EXPERIMENTAL SECTION

#### Chemistry

All chemicals used were of reagent grade. The yields refer to the purified products and are not optimized. The melting points were determined in open capillaries on a Gallenkamp apparatus and were uncorrected. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Merck thin-layer chromatography (TLC) plates (silica gel 60 F254) were used for TLC. NMR spectra were recorded by means of either a DRX 400 AVANCE or a Bruker DRX 500 AVANCE spectrometer in the indicated solvents (tetramethylsilane as internal standard); the values of the chemical shifts (δ) were expressed in ppm, and the coupling constants (J) were expressed in Hz. Mass spectra were recorded on an Agilent 1100 LC/MSD.

#### General Procedure for the Preparation of Compounds 6a–c

A mixture of the suitable aldehyde derivative (5a–c, 1 equiv), potassium carbonate (3 equiv), and propargyl bromide (80 wt %, 3 equiv) in acetonitrile was heated under reflux for 3 h and then concentrated under reduced pressure. The resulting residue was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography with the suitable eluent afforded the expected propargyloxy derivative (6a–c).

**4-(Prop-2-ynyloxy)benzaldehyde (6a).** The title compound was prepared from 5a (1.0 g, 8.2 mmol), K₂CO₃ (3.4 g, 24.6 mmol), and propargyl bromide (2.7 mL, 24.6 mmol) by following the above general procedure and purified by flash chromatography with petroleum ether–ethyl acetate (85:15) as the eluent to obtain compound 6a (1.2 g, yield 91%).

**1H NMR (400 MHz, CDCl₃):** 2.56 (t, J = 2.4 Hz, 1H), 4.78 (d, J = 2.4 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H).
The title compound was prepared from $5b$ (1.0 g, 6.6 mmol), K$_2$CO$_3$ (2.0 g, 15.0 mmol), and propargyl bromide (2.0 mL, 15.6 mmol) by following the above general procedure and purified by flash chromatography with petroleum ether—ethyl acetate (85:15) as the eluent to obtain compound $6c$ (1.1 g, yield 91%) as a white solid melting at 112−113 °C. $^1$H NMR (400 MHz, CDCl$_3$): 2.55 (t, $J$ = 2.4 Hz, 1H), 3.93 (s, 3H), 4.83 (d, $J$ = 5.4 Hz, 1H), 6.38 (s, 1H), 6.93 (d, $J$ = 8.2 Hz, 2H), 7.13 (s, 2H). 13C NMR (125 MHz, CDCl$_3$): 21.2, 52.1, 56.2, 60.0, 73.1, 75.8, 78.4, 104.8, 125.2, 133.9, 139.6, 146.9, 149.4, 165.5, 169.5. MS (ESI) $m/z$: [M + Na]$^+$ calcd for C$_{14}$H$_{15}$O$_{2}$Na, 291.1; found, 291.1.

**General Procedure for the Preparation of Compounds 7a−c.** To a solution of the suitable alcohol (7a−c) in dry dichloromethane containing TEA (2.0 equiv), acetyl chloride (2.0 equiv) was added dropwise. After stirring at room temperature for 1 h, the reaction mixture was washed with water. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography with petroleum ether—ethyl acetate (8:2) as the eluent to obtain the corresponding acetate (7a−c).

**Methyl 2-[(3,5-Dimethoxy-4-(prop-2-ynyl)phenyl)(hydroxy)methyl]acrylate (7c).** The title compound was prepared from $6c$ (0.20 g, 0.26 mmol), methanol (10 mL), THF (5.0 mL), methyl acrylate (10 mL), and DABCO (0.35 g, 3.1 mmol) by following the above general procedure and purified by flash chromatography with petroleum ether—ethyl acetate (8:2) as the eluent to obtain compound $7c$ (0.18 g, yield 79%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): 2.54 (t, $J$ = 2.4 Hz, 1H), 3.69 (s, 3H), 4.67 (d, $J$ = 2.4 Hz, 2H), 5.53 (d, $J$ = 5.4 Hz, 1H), 5.83 (s, 1H), 6.32 (s, 1H), 6.91−6.99 (m, 2H), 7.27−7.34 (m, 2H). MS (ESI) $m/z$: [M + Na]$^+$ calcd for C$_{14}$H$_{15}$O$_{2}$Na, 291.1; found, 291.1.
General Procedure for the Preparation of Imidazole Derivatives 4a–c. A mixture of the appropriate acetate (3a–c) in THF–water (5:1) containing imidazole (1.2 equiv) was heated under reflux overnight. After cooling to room temperature, the reaction mixture was diluted with brine and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography with ethyl acetate as the eluent gave the corresponding imidazole derivative (4a–c).

(E)-Methyl 2-[[1Himidazol-1-yl]methyl]-3-(prop-2-ynloxy)phenylacrylate (4a). The title compound was prepared from 3a (50 mg, 0.173 mmol), imidazole (14 mg, 0.208 mmol), THF (5.0 mL), and water (1.0 mL) to obtain compound 4a (42 mg, yield 82%) as an off-white solid melting at 103–104 °C. 1H NMR (500 MHz, CDCl3): 2.54 (t, J = 2.4 Hz, 1H), 3.80 (s, 3H), 4.72 (d, J = 2.4 Hz, 2H), 4.99 (s, 2H), 6.89 (s, 1H), 6.96–7.06 (m, 3H), 7.26–7.36 (m, 2H), 7.49 (s, 1H), 7.98 (s, 1H). 13C NMR (125 MHz, CDCl3): 43.2, 52.5, 55.8, 76.2, 77.9, 115.4, 118.7, 124.8, 127.1, 129.3, 130.9, 136.9, 144.6, 158.8, 167.2. MS (ESI) m/z: [M + H]+ calcld for C18H19N2O4, 327.1; found, 327.0.

(E)-Methyl 2-[[1Himidazol-1-yl]methyl]-3-(3-methoxy-4-prop-2-ynloxy)phenylacrylate (4b). The title compound was prepared from 3b (50 mg, 0.157 mmol), imidazole (13 mg, 0.188 mmol), THF (5.0 mL), and water (1.0 mL) to obtain compound 4b (42 mg, yield 82%) as a pale yellow oil which crystallized on standing (mp 101–104 °C). 1H NMR (500 MHz, CDCl3): 2.53 (t, J = 2.4 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.79 (d, J = 2.4 Hz, 2H), 5.02 (s, 2H), 6.80 (d, J = 1.9 Hz, 1H), 6.89–6.96 (m, 2H), 7.02–7.08 (m, 2H), 7.56 (br s, 1H), 8.00 (s, 1H). 13C NMR (125 MHz, CDCl3): 43.5, 52.6, 55.9, 56.6, 76.4, 77.8, 112.5, 113.8, 118.8, 122.4, 124.7, 127.6, 129.1, 136.7, 145.2, 148.2, 149.7, 167.2. MS (ESI) m/z: [M + H]+ calcld for C19H21N2O5, 357.1; found, 357.1.

(E)-Methyl 2-[(1Himidazol-1-yl)methyl]-3-(4-(prop-2-ynyloxy)phenyl)acrylate (4c). The title compound was prepared from 3c (50 mg, 0.144 mmol), imidazole (12 mg, 0.173 mmol), THF (5.0 mL), and water (1.0 mL) to obtain compound 4c (42 mg, yield 82%) as a white solid melting at 103–104 °C. 1H NMR (500 MHz, CDCl3): 2.44 (t, J = 2.4 Hz, 1H), 3.72 (s, 6H), 3.82 (s, 3H), 4.75 (d, J = 2.4 Hz, 2H), 5.00 (s, 2H), 6.48 (s, 2H), 6.91 (s, 1H), 7.06 (s, 1H), 7.52 (s, 1H), 8.00 (s, 1H). 13C NMR (125 MHz, CDCl3): 43.4, 52.6, 56.2, 60.0, 75.2, 79.0, 106.1, 118.6, 125.9, 129.4, 129.9, 136.8, 145.4, 153.8, 167.0. MS (ESI) m/z: [M + H]+ calcld for C19H19N2O5, 375.1; found, 375.1.

Optical Properties and PL. UV–vis absorption spectra were obtained with a PerkinElmer Lambda 900 spectrometer. PL spectra were obtained with a SPEX 2700 monochromator equipped with a N2-cooled charge-coupled device exciting with a monochromated 450 W Xe lamp. The spectra were corrected for the instrument response. PL QY values of the solutions were obtained by using quinine sulfate as the reference, with an experimental error of about 5% for values below 0.1%. PL QY values of the solid powders were measured with a homemade integrating sphere, with an experimental error of 10% and a sensitivity of about 0.1%, according to the procedure reported elsewhere.50 Time-resolved studies of the emission were performed with a Nanolog spectrofluorometer with a DeltaTime TCSPC (time-correlated single-photon counting) equipped with a single-photon detection module PPD-850 by exciting with a DeltaDiode source at 300 nm or a pulsed Xe lamp.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00789.

Prompt PL and delayed emission of 4a powders; absorption and PL spectra of 4c in PEG; PL spectra of 4a and 4b in diluted THF solution at room temperature and at 77 K; and 1H and 13C NMR of compounds 4a–c and of their intermediates (PDF).

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Author Contributions

The manuscript was written through the contributions of all authors.

Notes

The authors declare no competing financial interest.

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