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Tuning fluorescence properties of imidazole derivatives with thiophene and thiazole

Ke Feng [a], Fu-Lian Hsu [b], Donald Van DerVeer [c,1], Kofi Bota [a], Xiu R. Bu [a,*]

[a] *Department of Chemistry and Laboratory for Electro-Optical Materials, Clark Atlanta University, 223 James P. Brawley Dr., Atlanta, GA 30314, USA*
[b] *US Army Edgewood Chemical and Biological Center, Aberdeen Proving Ground, MD 21010, USA*
[c] *School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, USA*

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Abstract

The steric effect from aromatic species at the 2-position has been evaluated in 2,4,5-trisubstituted imidazole system. The steric interaction from the 2-position has a direct impact on the fluorescent properties. There is a correlation between the twist and fluorescence quantum yield. The larger the twist is, and the more reduction of quantum yield it will have. The use of thiazole at the 2-position almost eliminates the interaction and retains the coplanarity. As a result, the substitution at the 1-position does not compromise the quantum yield.

Keywords: Imidazole; Lophine; Thiazole; Thiophene; Fluorescence; Crystal structure

1. Introduction

Stability and high emission efficiency are two desirable properties of fluorophores which are indispensable components in molecular sensors [1–3]. Often, a parent fluorophore has to be modified for the sake of stability and other needs. At the same time, it is imperative to maintain emission efficiency at the highest possible. Heterocyclic imidazole derivatives have attracted considerable attention lately because of the unique optical properties of both linear and nonlinear optical nature [4–6]. 2,4,5-Triphenylimidazole (lophine, **1**, Fig. 1) possesses a well-known chemiluminescence property which has been examined for the potential determination of metal ions and organic halogen compounds [7–10]. Its fluorescent property has been evaluated in HPLC assay for human serum analysis [11], and in photochromic materials as fluorescent tags [12].

The presence of the active proton (N–H) at the 1-position is the source of concern since it will potentially lead to undesirable reactivity. The unprotected imidazole ring is known to be photochemically instable, leading to various inter- or intra-molecular couplings (C–C or N–N, or C–N) [13–16]. One approach to reduce the chemical reactivity is to derive the parent imidazole. Various functional groups are readily placed at the 1-position through the substitution of active N–H [17]. The modification of this site through substitution blocks undesirable reactivity, and most importantly, introduces functional groups for the unit attachment [17]. However, it often leads to significant fluorescence reduction.

The focus of this work is on one of the three aromatic species attached to the central imidazole ring. The aim is to minimize the distortion of conjugation between imidazole ring and the aromatic ring at the 2-position, and to gain detailed understanding of the relationship between the structure and the fluorescence properties.

2. Experimental

All the compounds are prepared according to the published procedures [4,5,18] and purity is verified by ^{1}H NMR, TLC and GC–MS. UV-Vis absorption spectra were recorded on a Beckman DU 650 spectrophotometer. Fluorescence spectra were obtained on PTI fluorometer. Solvents used for spectral measurement are spectroscopic grade, and used as received commercially. Quinine (in 0.1N H_2SO_4, Φ_f = 0.53) was used as a reference for the determination of quantum yields. The values are calculated based on the equation $\Phi_f = (I/I')(A'/A)(n/n')^2\Phi'$, where I', A', and Φ' are

* Corresponding author. Tel.: +1-404-880-6897; fax: +1-404-880-6890.
E-mail address: xbu@cau.edu (X.R. Bu).
[1] Present address: Department of Chemistry, Clemson University, Clemson, SC 29634, USA.

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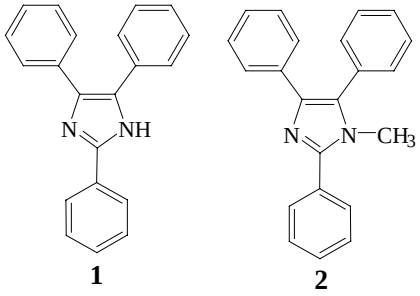


1 **2**

Fig. 1.

the integrated emission, absorbance (at the excitation wavelength), and quantum yield of the reference sample, respectively. n' is the refractive index of the solvent used for the reference sample. I, A, n, and Φ are related to the sample with the same definitions applied to the reference sample.

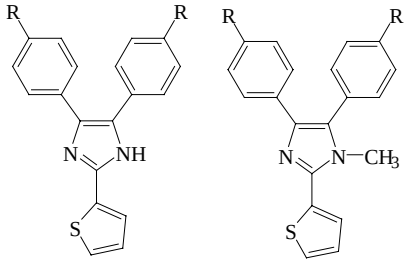
Data for X-ray crystallographic determination were collected on a Bruker 1K CCD platform diffractometer. Absorptions were corrected using SADABS [19]. The structure was solved by direct methods and subsequent Fourier difference techniques, and refined anisotropically, by full-matrix least squares, on F^2 using SHELXTL 5.1 [20]. Hydrogen atoms were calculated from ideal geometry with coordinates fixed and temperature factors varied. Crystal data and conditions for data collections are listed.[2] Molecular geometry is optimized with 6-31 G* in Spartan 02.

3. Results and discussion

Fluorescence of lophine (**1**) and *N*-substituted lophine was evaluated first and established as reference. Lophine has a Φ of 0.48 in hexane. The fluorescence is dramatically reduced upon the *N*-substitution. The quantum yield of 1-methyl lophine (**2**), obtained from the substitution of lophine at the 1-position, decreases to 0.29. This reduction is also found in 1,4-dioxane solvent. The quantum yield decreases from 0.45 to 0.27 upon the Me substitution. In both solvents, the reductions are up to 40% over the original emission of lophine.

The use of thiophene to replace phenyl at the 2-position was followed (Fig. 2). Imidazole derivatives **3**–**5** are prepared from condensation of benzils with 2-thiophenecarboxaldehyde and ammonium acetate. *N*-methylation using iodomethane/potassium carbonate in DMAC produces **6**–**8** [4,5,18]. The five-membered heterocyclic thiophene is

[2] Crystal and experimental data formula: $C_{21}H_{19}N_3O_2S$; formula weight: 377.45; crystal system: monoclinic; space group: $P2(1)/n$; unit cell dimensions: $a = 32.130(2)$ Å, $b = 19.613(1)$ Å, $c = 23.741(1)$ Å, $\beta = 115.141(10)^\circ$. Volume = 4874.7(6) Å^3, $Z = 4$. Density = 1.339 g/cm^3; $F_{000} = 792$; absorption coefficient = 0.189 mm^{-1}; crystal size = 0.58 mm × 0.41 mm × 0.10 mm; θ range (°) for data collection: 2.20–25.05; limiting indices: $-7 \le h \le 6$, $-34 \le k \le 36$, $-11 \le l \le 11$; reflection collected/unique: 9829/3410 [$R_{int} = 0.0480$]; $T = 298(2)$ K; wavelength = 0.71073 Å; data/restraints/parameters: 3410/0/261; goodness of fit: 1.028; final R indices [$I > 2\theta(I)$]: $R_1 = 0.0516$, $wR_2 = 0.1319$; $(\Delta/\sigma)_{max} = 0.002$; $(\Delta\rho)_{max} = 0.283$ eÅ^3; $(\Delta\rho)_{min} = -0.334$ eÅ^3.



3: R = H
4: R = Me
5: R = OMe

6: R = H
7: R = Me
8: R = OMe

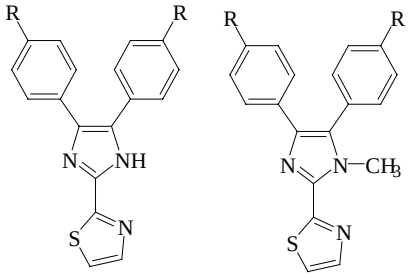
Fig. 2.

Table 1
Absorption and fluorescence data of **3**–**8**

	λ_{max} (nm) (ε, M^{-1} cm^{-1})	$\lambda(ex)_{max}$ (nm)	$\lambda(em)_{max}$ (nm)	Φ_f
3	317 (10,500)	324	388	0.86
4	321 (15,200)	326	393	0.59
5	313 (20,500)	331	402	0.61
6	309 (17,600)	319	383	0.62
7	298 (15,000)	321	388	0.45
8	300 (18,800)	322	395	0.47

smaller than phenyl, the introduction of methyl group at the *N*-position in the imidazole ring may effectively reduce the deviation between the thiophene and imidazole. Imidazoles **3**–**8** have quantum yields ranging from 0.45 to 0.86 in 1,4-dioxane (Table 1). Comparison of **3**–**5** with **6**–**8** indicates that the substitution at the 2-position still compromised fluorescence, as evident by the fact that the quantum yield of **6** is 0.72 times that of **3**. Also **7** and **8** have quantum yields 0.76 and 0.77 times those of **4** and **5**, respectively. However, the fluorescence decrease is noticeably much smaller than that from **1** to **2**.

Next, we extend to use another five-membered heterocyclic species-thiazole at the 2-position (Fig. 3). A class of fluorophores **9**–**11** is then developed from direct



9: R = H
10: R = Me
11: R = OMe

12: R = H
13: R = Me
14: R = OMe

Fig. 3.

Table 2
Absorption data of **9**–**14**

Fluorophores	λ_{max} (nm) ($\varepsilon \times 10^{-4}$, $M^{-1}\,cm^{-1}$)	
	DMSO	1,4-Dioxane
9	339 (2.10)	337 (1.75)
10	344 (1.85)	341 (1.75)
11	350 (1.94)	348 (1.78)
12	335 (2.33)	334 (1.87)
13	339 (2.24)	337 (1.95)
14	344 (2.05)	345 (1.78)

condensation of ammonium acetate, α-dione, and 2-carboxaldehyde thiazole. Their derivatives **12**–**14** are obtained by *N*-methylation of **9**–**11** using iodomethane in the presence of potassium carbonate [4,5,18].

UV-Vis spectra have been examined in two solvents which have significantly different polarity: DMSO and 1,4-dioxane (Table 2). Comparison of absorption maxima in both solvents revealed that absorption intensity of **12**–**14** increased over that of their counterparts **9**–**11**. For example, **12** has the molar absorptivity of $2.33 \times 10^4\,M^{-1}\,cm^{-1}$ and **9** has $2.10 \times 10^4\,M^{-1}\,cm^{-1}$. Each of these compounds has very minimal absorption maxima shift in both solvents, indicative of the lack of dramatic response to solvent polarity. On the other hand, the substituent group effect in both solvents exists, consistently leading to bathchromic shift in the order from H, to Me, and to OMe. The trend is found in both **9**–**11** and **12**–**14**.

Emission properties of fluorophores **9**–**14** are examined in hexane first. They possess strong fluorescence property with quantum yields ranging from 0.45 to 0.59 (Table 3). Unlike in lophine and thiophene-based imidazoles **3**–**5**, the *N*-methylation in this series does not appear to compromise the emission property. For example, the quantum yield of **12** (0.59) is comparable to that of **9** (0.57). Likewise, the data for **13** and **14** match well with those for **10** and **11**, respectively. 1,4-Dioxane, acetonitrile, and DMSO have been used for further study to validate this trend. Again, for **12**–**14** in 1,4-dioxane, quantum yields ranging from 0.50 to 0.65 are comparable to those of their counterparts **9**–**11** (from 0.47 to 0.63). Actually, a noticeably small increase in quantum yields was realized in **12**–**14**. Moreover, a significant enhancement in DMSO was obtained for **12**, which has the Φ of 0.67 while the value is 0.56 for **9**.

Representative Figs. 4 and 5 illustrate two observations discussed above. One is nonpolar nature of the ground state of the fluorophores, as evident from absorption spectra of **12** in various solvents with no dramatic shift of the absorption maxima as shown in Fig. 4 (dotted line). The emission maxima, however, not only shift significantly, but also do so corresponding to the polarity of the solvents, suggesting the polar nature of the excited state. A total shift by 15 nm is observed from nonpolar hexane to polar DMSO. The other one is the size effect of the aromatic rings at the 2-position. Fig. 5 shows that the red-shift of both absorption and

Table 3
Fluorescence property of fluorophores **9**–**14**

Solvent	Fluorophore	Φ_f [a]	λ_{max}(ex) (nm)	λ_{max}(ex) (nm)
DMSO	**9**	0.56	340	408
	10	0.54	344	415
	11	0.51	352	431
	12	0.67	335	399
	13	0.58	339	406
	14	0.56	343	424
Acetonitrile	**9**	0.54	333	404
	10	0.50	337	413
	11	0.46	344	432
	12	0.59	330	397
	13	0.54	333	405
	14	0.50	340	421
1,4-Dioxane	**9**	0.63	336	398
	10	0.53	341	405
	11	0.47	348	418
	12	0.65	333	392
	13	0.56	338	398
	14	0.50	343	408
Hexane	**9**	0.57	334	391
	10	0.51	342	398
	11	0.45	349	408
	12	0.59	332	384
	13	0.55	337	390
	14	0.48	342	397

[a] Excitation wavelength: 366 nm and quinine in 0.1N H_2SO_4 as reference.

emission bands takes place in thiazole-based imidazoles (**9** and **12**) compared to those in thiophene-based ones (**3** and **6**).

The initial structural information was acquired from the solid state structure of **14**, determined by the X-ray crystallography (Fig. 6), see Footnote 2. Bond distance and selected bond angles are listed in Table 4. Several important dihedral angles have been determined as follows: (1) the two phenyl groups at the 4,5-positions of the imidazole ring are

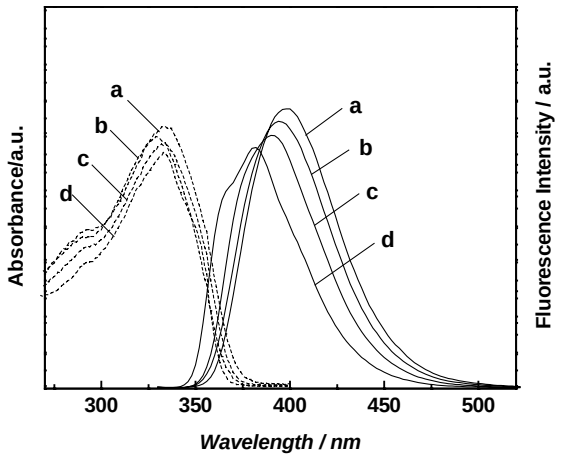


Fig. 4. Absorption (dotted line) and emission spectra (solid line) of **12** in various solvents: (a) DMSO; (b) MeCN; (c) dioxane; (d) hexane. Excitation wavelength: 300 nm.

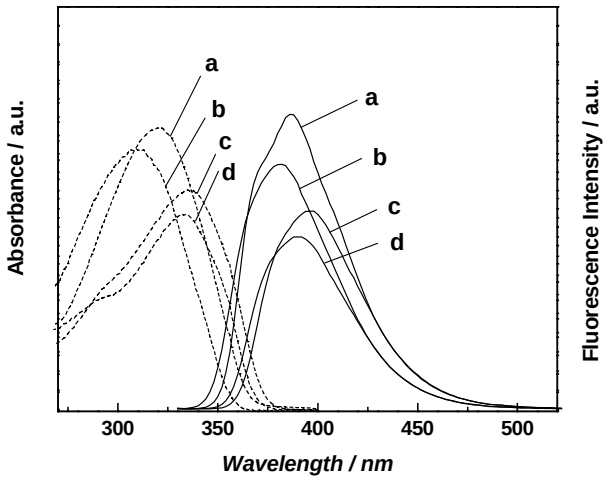


Fig. 5. Absorption (dotted line) and fluorescence emission spectra of **3** (a), **6** (b), **9** (c), and **12** (d) in 1,4-dioxane (c = 5–10 μM). Excitation wavelength: 300 nm.

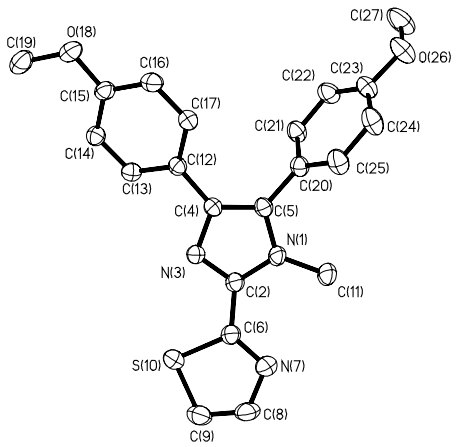


Fig. 6. The crystal structure of **14**.

twisted from each other by 63.14°; (2) the individual twist from the imidazole is 26.27° (for phenyl at the 4-position) and 59.22° (for phenyl at the 5-position), respectively; (3) the thiazole ring is deviated by 3.74° from the imidazole.

In order to eliminate crystal packing effect in the solid state, the molecular geometry of **1**, **2**, **5**, **8**, **11** and **14** is further examined by 6-31 G* ab initio calculations [21] to make necessary comparison on an equal state basis. Three key twists, designated as α, β, and γ have been examined. α is used to indicate the twist of imidazole ring from the aromatic six-membered or heterocyclic five-membered ring at the 2-position. β and γ are used for twists of imidazole ring from phenyls at the 5-, and the 4-positions, respectively (Fig. 7).

The optimized geometry revealed that the α twist in **2** is much bigger than that in **1**. The α twist in lophine derivatives is normally around 6–7° [22]. In **1**, it is 6.86°, which dramatically increases to 33.82° in **2**, indicating that the α twist is highly sterically sensitive to the presence of a group at the 1-position, and it increases as the size of the group does. The nonzero α twist in **1** is ascribed to N–H interaction with phenyl at the 2-position. The substitution from N–H to N–Me increases the twist accordingly because of the larger size of Me group.

When the five-membered ring at the 2-position is thiophene as in **5**, the α twist becomes smaller compared to that in **1**. This is ascribed to the weaker interaction of N in the 3-position of imidazole with the adjacent H from thiophene ring. Once the N–H is substituted by methyl group, the α twist increases to 22.87°. However, it is still ca. 10° less twisted than that in **2**, due to the smaller ring of thiophene.

Table 4
Bond distances (Å) and selected angles (°) of **14**

N(1)–C(2)	1.362(3)	C(4)–C(5)	1.377(3)	C(23)–O(26)	1.362(3)
N(1)–C(5)	1.383(3)	C(4)–C(12)	1.470(3)	C(23)–C(24)	1.374(4)
N(1)–C(11)	1.468(3)	C(5)–C(20)	1.476(3)	C(24)–C(25)	1.383(4)
C(2)–N(3)	1.316(3)	C(6)–N(7)	1.298(3)	O(26)–C(27)	1.418(4)
C(2)–C(6)	1.454(4)	C(6)–S(10)	1.725(3)	C(2)–N(1)–C(11)	127.1(2)
N(3)–C(4)	1.381(3)	N(7)–C(8)	1.375(4)	C(5)–N(1)–C(11)	126.2(2)
C(4)–C(5)	1.377(3)	C(8)–C(9)	1.329(5)	N(3)–C(2)–N(1)	112.1(2)
C(4)–C(12)	1.470(3)	C(9)–S(10)	1.705(3)	N(3)–C(2)–C(6)	121.3(2)
C(5)–C(20)	1.476(3)	C(12)–C(13)	1.389(3)	N(1)–C(2)–C(6)	126.7(2)
C(6)–N(7)	1.298(3)	C(12)–C(17)	1.395(3)	C(2)–N(3)–C(4)	105.7(2)
C(6)–S(10)	1.725(3)	C(13)–C(14)	1.383(3)	C(5)–C(4)–N(3)	109.7(2)
N(7)–C(8)	1.375(4)	C(14)–C(15)	1.382(4)	C(5)–C(4)–C(12)	130.9(2)
C(8)–C(9)	1.329(5)	C(15)–O(18)	1.366(3)	N(3)–C(4)–C(12)	119.4(2)
C(9)–S(10)	1.705(3)	C(15)–C(16)	1.386(4)	C(4)–C(5)–N(1)	105.8(2)
N(1)–C(2)	1.362(3)	C(16)–C(17)	1.373(4)	C(4)–C(5)–C(20)	131.0(2)
N(1)–C(5)	1.383(3)	O(18)–C(19)	1.412(4)	N(1)–C(5)–C(20)	123.2(2)
N(1)–C(11)	1.468(3)	C(20)–C(21)	1.374(4)	N(7)–C(6)–C(2)	127.0(3)
C(2)–N(3)	1.316(3)	C(20)–C(25)	1.384(4)	C(2)–C(6)–S(10)	118.46(19)
C(2)–C(6)	1.454(4)	C(21)–C(22)	1.386(4)	C(13)–C(12)–C(4)	119.6(2)
N(3)–C(4)	1.381(3)	C(22)–C(23)	1.374(4)	C(17)–C(12)–C(4)	123.1(2)

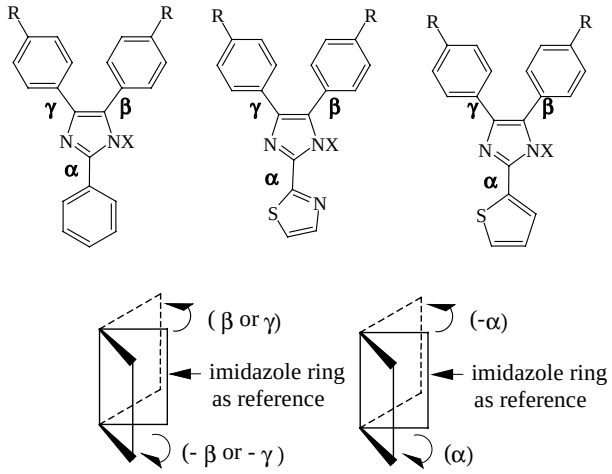


Fig. 7. Schematic presentation of α, β and γ. When imidazole is used as reference plane, the direction of the α twist is opposite to that of the β and γ twists.

When thiazole is used to replace thiophene, the twist is very minimal since there is no adjacent hydrogen available from thiazole to interact with the N (at the 3-position) of the imidazole. Indeed, the α twist for **11** is close to zero. Interestingly, even when methyl group is placed at the 1-position, the twist does not increase noticeably, suggesting that the substitution has a very little steric impact on the thiazole ring.

By comparison of results in Table 5, several additional interesting structural features can be concluded: (1) the γ twist is always smaller than the β twist. The difference is ca. 10° in the unsubstituted cases (**1**, **5**, and **11**). It becomes much larger (ca. 25–30°) in the substituted cases (**2**, **8**, and **14**); (2) while the β twist originates from the interaction of imidazole with the phenyl at the 5-position, the γ twist is a result of chain interaction event, triggered by the interaction of the phenyl at the 4-position with the other one at the 5-position; (3) the β twist always increases upon the substitution compared to the parent counterparts; (4) the substitution increases the β twist, but decreases the γ twist. This is explained by the chain event interaction as discussed above: more deviation of the phenyl at the 5-position from imidazole plane, the less steric effect is on the phenyl at the 4-position.

The present structural information allows us to further explore the correlation between structural features and fluorescent property. It reveals that one particular parameter, α, is correlated with fluorescent property: the larger α twist becomes from unsubstituted to substituted imidazole, the more drop the fluorescence quantum yield will take. This relationship can be seen from the followings. From **1** to **2**, the α twist increases by ca. 27° while the fluorescence drops by 40%. From **5** to **8**, the twist increases by ca. 19° and the drop is by 23%. From **11** to **14**, there is only a negligible change in the α value, well within the theoretically experimental error, the fluorescence does not drop at all. Such a clear correlation indicates the importance of coplanarity between imidazole and the aromatic ring at the 2-position.

Table 5
Deviation parameters (°) of imidazole from other rings

	α	β	γ
1	6.86	39.02	29.73
2	33.82	54.63	23.54
5	4.16	−39.03	−31.28
8	22.87	−52.42	−27.52
11	−0.20	−40.43	−28.89
14	1.90	−58.87	−26.20

The correlation can be ascribed to the conjugation rigidity. When the two adjacent aromatic species are in a coplanar geometry as in **11** and **14**, the p-orbitals from the C–C bond connecting the two species will have maximal overlapping and the two rings will have a rigid and delocalized conjugation. As the result, the bond is no longer a pure single bond, as evident from the X-ray data of **14**. The present bond distance of 1.454(4) Å (C2–C6, Table 4) is shorter than the regular single bond distance between two sp^2 carbon's (1.48 Å) [23], as a result from the delocalization. When the two rings are deviated from each other, as in **1**, **2**, **5**, and **8**, the p-orbital overlapping will be reduced. The partial conjugation will lead to less rigid structure, therefore, radiationless twist motion will deactivate the emitting state, leading to the low quantum yields.

In conclusion, a use of a five-membered thiazole at the 2-position of the imidazole ring has effectively reduced the steric interaction between each other. The dihedral angle in **11** indicates that these two rings are almost coplanar. Most importantly, the substitution at the 1-position does not cause any significant deviation of these two planes as evident in **14**. Accordingly, the fluorescence property of **14** remains comparably strong to that of the unsubstituted imidazoles **11**. Thus, it is suggested that fluorophores **9**–**11** can be used for the attachment via the substitution at the 2-position with a minimum loss of fluorescence property.

Acknowledgements

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