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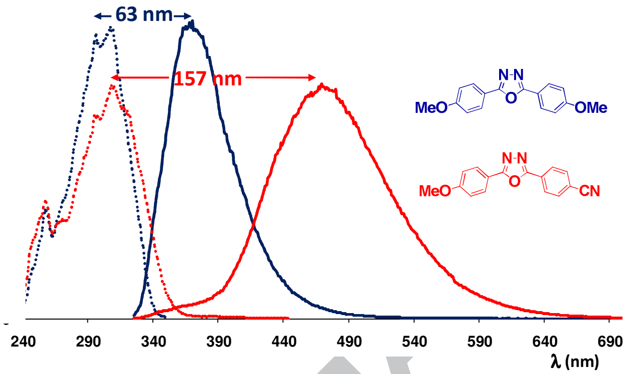

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Symmetrical and non-symmetrical 2,5-diaryl-1,3,4-oxadiazoles: synthesis and photophysical properties

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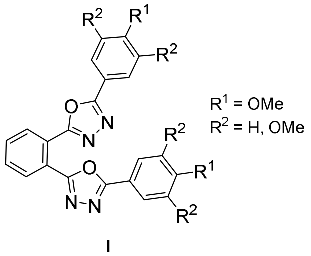
ABSTRACT

We report herein the synthesis of 2,5-diaryl-1,3,4-oxadiazoles containing both electron-donating and withdrawing substituents as well as bis- and tris-2,5-disubstituted-1,3,4-oxadiazoles containing electron-donating substituents. The photophysical properties of the synthesized compounds were studied using UV-Vis and fluorescence spectroscopy. The aryl substitution pattern was found to have a marked impact on both luminescence efficiency and other photophysical properties. An increase in the number of electron-donating groups and/or the number of heterocyclic rings provided a red shift of the emission maxima, as well as an increase of the Stokes shifts. The same effect was observed for mono-1,3,4-oxadiazoles containing push-pull substituents on the aryl rings.

In the search for new molecules with remarkable optoelectronic properties, the 1,3,4-oxadiazole core has found a central place, mainly due to its electron-deficient character.[1] In particular, the 2,5-diaryl-1,3,4-oxadiazole core has been largely exploited in order to access new materials for use as electron-transporting compounds for the preparation of Organic Light-Emitting Diodes (OLEDs).[1,2] Moreover, recent publications indicate useful applications of the 1,3,4-oxadiazole scaffolds as sensors for various cations[3] or anions.[4] In addition, metal complexes of 1,3,4-oxadiazoles have gained attention as gelators of organic solvents,[5] molecular logic gates and fluorescent switches[6] or simply due to displaying interesting photoluminescent properties.[7] Polymers or copolymers containing the 1,3,4-oxadiazole core have also been reported to exhibit good luminescence properties.[8]

The influence of the number of heterocyclic rings and the nature of their substituents[9,10] have been studied in order to provide structurally diversified molecules with improved photoelectronic properties. In this context, synthetic strategies to prepare such molecules have been investigated.[11,12] Essentially, 1,3,4-oxadiazoles can be obtained by the dehydration of *N,N*-diacylhydrazines,[13] oxidative cyclization of *N*-acyl-hydrazones[14] or the Huisgen reaction of tetrazoles and acid chlorides.[9] Due to the ready availability of *N*-acylhydrazones from aldehydes and carboxylic acid hydrazides and the mild conditions required for ~~the hetero~~cyclic ring closure, oxidative cyclisation is often the method of choice for their preparation. We recently reported a smooth, room temperature synthesis of 1,2-(bis-1,3,4-oxadiazol-2-yl)benzenes **I** (Figure 1) using PIFA (bis(trifluoroacetoxy)iodobenzene) as an oxidative cyclization agent.[15]



I

Figure 1. Structure of 1,2-bis(1,3,4-oxadiazol-2-yl)benzenes bearing 4-methoxyphenyl or 3,4,5-(trimethoxy)phenyl substituents

In a continuation of our work, we have examined in detail the fluorescent properties of 2,5-diaryl-1,3,4-oxadiazoles bearing one or three methoxy groups as substituents on the aryl rings and we describe herein these properties. In addition, other 2,5-disubstitued-1,3,4-oxadiazoles were synthesized for comparative purposes. Therefore, we set out to evaluate the influence of the substituents and the number of the heterocyclic rings on the absorption and emission properties with the aim of developing compounds with improved photophysical properties.

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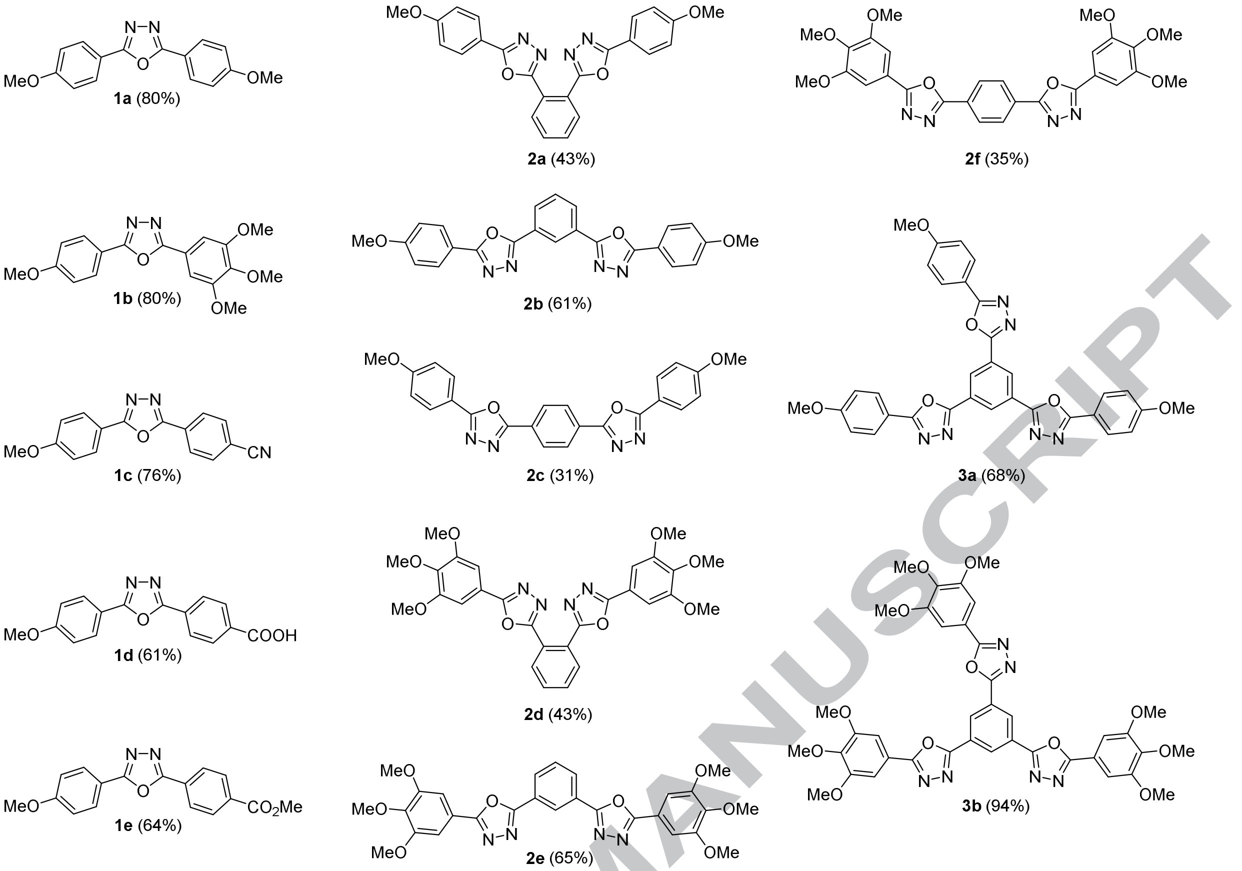
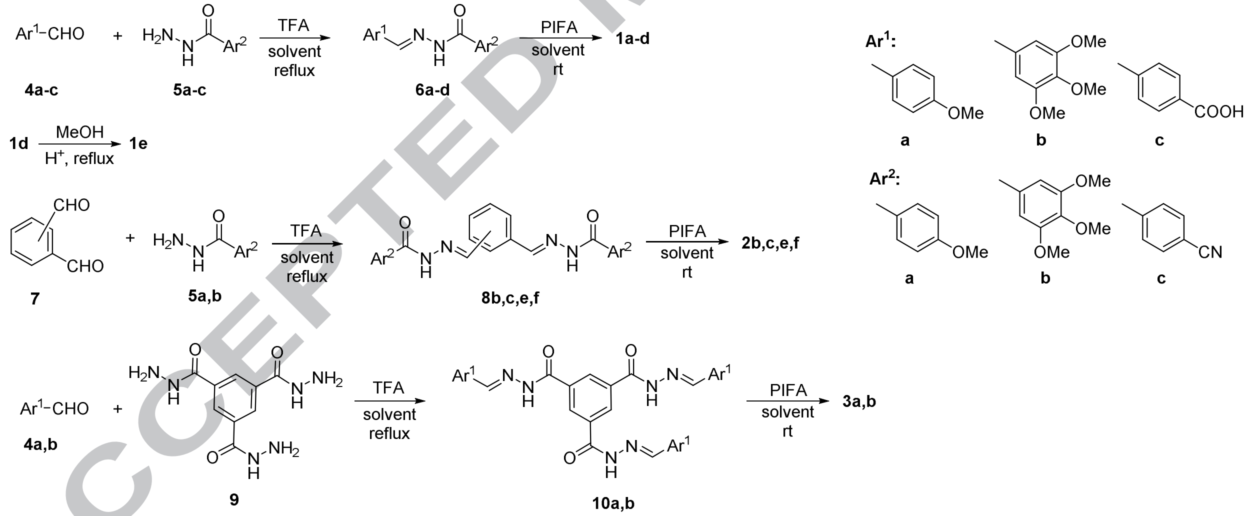


Figure 2. Structures of the compounds studied



Scheme 1. Synthesis of the 2,5-disubstituted 1,3,4-oxadiazoles **1a-e, 2a-d** and **3a,b**

We prepared three series of compounds possessing various numbers of 2,5-disubstituted-1,3,4-oxadiazole rings and/or substituents with different electronic properties as depicted in Figure 2. The synthesis of the compounds was performed as described in Scheme 1. Firstly, condensation of benzaldehydes **4a-c** with the corresponding hydrazides **5a-c** afforded, after filtration, the expected acylhydrazines **6a-d**.

Treatment of compounds **6a-d** with 1.1 equivalents of PIFA at room temperature triggered the ring closure and provided the oxadiazoles **1a-d** in very good yields. Compound **1e** was synthesized by esterification of **1d** (see ESI). Besides the symmetrical 2,5-disubstituted-1,3,4-oxadiazole **1a**, this procedure allowed the synthesis of non-symmetrical structures containing on one side an electron rich and on the other side an electron-donating or electron-withdrawing substituent grafted on the aryl rings. In a similar manner, condensation of *meta*- and *para*-phthalaldehyde **7** with the hydrazides **5a,b** yielded the corresponding acylhydrazines **8b,c,e,f** which were further converted into the oxadiazoles **2b,c,e,f** by oxidation. Compounds **2a** and **2d** were synthesized as previously described.[15] Compounds **3a,b** were obtained by following the same two step strategy starting from 1,3,5-benzene trihydrazide **9** and *p*-methoxybenzaldehyde or 3,4,5-trimethoxybenzaldehyde to afford hydrazones **10a,b** and their subsequent oxidative cyclisation (see ESI for general procedures).

All compounds were characterized by NMR and HRMS analysis (see ESI for the NMR and MS spectra of the compounds). Notably, an increase of the number of the heterocyclic moieties leads to a decrease of the solubility in organic solvents.

The fluorescence spectra were each collected under identical conditions for all compounds (20% DMSO-phosphate buffer 10^{-2} mol L^{-1}, pH=7.4, Figures 3 and 4) and the fluorescence quantum yields (± 10%) were determined using quinine sulfate in 0.5 M H_2SO_4, $\Phi = 0.55$).[16] Our choice to perform the measurements in aqueous medium is based on our intent for further use of the oxadiazoles as fluorescent tags under biological conditions.[17] The photophysical properties of all compounds are summarized in Tables 1-3 and Figures 3-4.

Table 1. Photophysical properties of oxadiazoles **1a-e**

Cmpn.	λ_{ex} (nm)	$\varepsilon@\lambda_{ex}$[a] (L mol^{-1} $cm^{-1} \times 10^{-4}$)	λ_{em} (nm)	Stokes shift (nm; $cm^{-1} \times 10^{-3}$)	Φ
1a	307	2.48	370	63; 5.55	0.23
1b	308	2.98	415	107; 8.37	0.085
1c	308	2.20	465	157;10.96	0.11
1d	307	2.97	415	108; 8.48	0.085
1e	307	ND[b]	478	171; 1.55	<0.01

[a]The molar extinction coefficient was calculated from the UV-Vis spectra at the indicated excitation wavelength;[18] [b]not determined

Superimposition of the spectra of compounds **1a-e** and quinine shows that compounds **1a-d** are easily detected in highly diluted solutions. Interestingly, **1a** is a more brilliant (ε×Q) fluorophore than quinine (even though its quantum yield is only 0.23) due to a higher molar absorptivity at the excitation maximum.

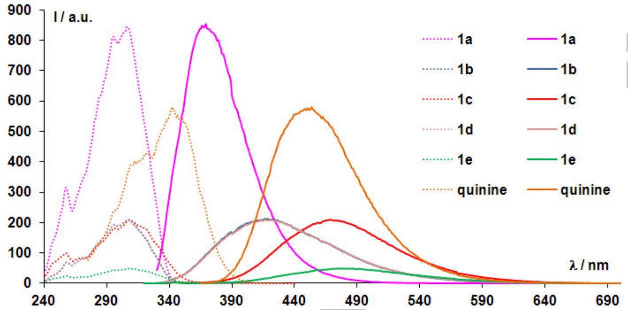


Figure 3. Excitation (dotted lines) and emission (plain lines) spectra of compounds **1a-e** as well as quinine. (5×10^{-7} mol L^{-1}) [19]

The excitation maxima of compounds **1a-e** are very similar: $\lambda_{ex,max}$~308 nm (Figure 3, Table 1) which indicate that the substituents grafted on the oxadiazole core have no significant influence on the absorption properties. On the contrary, the emission maxima of compounds **1a-e** (Figure 3) – hence their Stokes shifts – are different and are dependent on the electronic polarization due to the aromatic ring substituent(s). Indeed, an increase in the number of the methoxy substituents (**1a** vs. **1b**) resulted in a bathochromic shift of 45 nm. The same pattern was observed, in an even larger extent, when a methoxy group from compound **1a** was replaced by an electron-withdrawing substituent: **1a** vs. **1c** (MeO vs. CN, shift: 95 nm), **1a** vs. **1d** (MeO vs. CO_2^-, shift: 55 nm) and **1a** vs. **1e** (MeO vs. CO_2Me, shift: 105 nm). Intriguingly, compound **1a** displayed the highest quantum yield obtained for all compounds tested. Compounds **1b**, **1d** and particularly **1c** have reasonable luminescence intensities and quantum yields combined with large Stokes shifts, a desirable property in fluorescence assays.

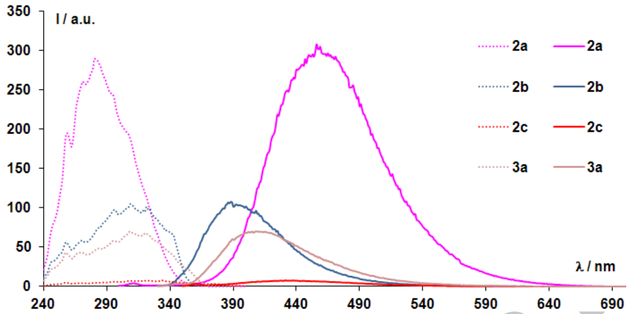


Figure 4. Excitation (dotted lines) and emission (plain lines) spectra of compounds **2a-c** and **3a** (5×10^{-7} mol L^{-1}).[19]

Regarding bis- and tris-oxadiazoles bearing methoxyphenyl (**2a-c**, **3a**, Figure 4) or trimethoxyphenyl (**2d-f**, **3b**, see ESI), one can note the following features. *ortho*-Substituted compound **2a** is an interesting brilliant fluorophore with a large Stokes shift. The blue shift observed in the case of the excitation of **2a** vs. **1a** (26 nm) as compared to **2b** vs. **1a** (1 nm) is consistent with the lack of planarity for the *ortho* substituted **2a**.[9] On the other hand, *meta*-substituted **2b** shows a smaller Stokes shift and a reduced quantum yield, which may be correlated with inefficient communication between the oxadiazole moieties. The tris-oxadiazole **3a** presents a spectral signature quite similar to **2b**, as the oxadiazole moieties are likewise unable to interact. This “isolated oxadiazole” behaviour is also consistent with the similar excitation wavelengths for **1a**, **2b** and **3a**. The *para*-substitution in **2c** results in a very weak emission. Compounds **2d-f** and **3b**, bearing trimethoxyphenyl substituent(s) are generally less emissive than their methoxyphenyl counterparts. Compound **2e** displays a spectral signature quite similar to that of **2b** albeit with a larger Stokes shift (see ESI).

Table 2. Photophysical properties of oxadiazoles **2a-f**

Cmpn.	λ_{ex} (nm)	$\varepsilon@\lambda_{ex}$[a] (L mol^{-1} $cm^{-1} \times 10^{-4}$)	λ_{em} (nm)	Stokes shift (nm; $cm^{-1} \times 10^{-3}$)	Φ
2a	281	4.18	456	175; 13.66	0.082
2b	308	1.86	388	80; 6.69	0.03
2c	~320	ND[b]	434	114; 8.21	<0.01
2d	294	ND[b]	402	108; 9.14	<0.01
2e	308	2.40	430	122; 9.21	0.026
2f	294	ND[b]	418	124; 10.09	<0.01

[a]The molar extinction coefficient was calculated from the UV-Vis spectra at the indicated excitation wavelength[18]; [b] not determined

Table 3. Photophysical properties of oxadiazoles **3a-b**

Cmpn.	λ_{ex}, (nm)	$\varepsilon@\lambda_{ex}$[a] (L mol^{-1} $cm^{-1} \times 10^{-4}$)	λ_{em} (nm)	Stokes shift (nm; $cm^{-1} \times 10^{-3}$)	Φ
3a	309	5.83	425	116; 8.83	0.012
3b	334	1.91	515	181;10.52	0.018

[a]The molar extinction coefficient was calculated from the UV-Vis spectra at the indicated excitation wavelength[18]

A comparison of the whole set of compounds discussed herein is difficult due to the variation of several structural and electronic parameters. However, for each subset of compounds containing a given aromatic substituent motif (methoxy: **1a**, **2b**, **3a**; trimethoxy: **1b**, **2e**, **3b**), a regular trend in terms of the bathocromic emission shift (and an increase in the Stokes shift) may be observed, although at the expense of the luminescence intensity.

In conclusion, we have synthesized and studied the fluorescent properties in aqueous medium of three series of compounds containing one, two or three 1,3,4-oxadiazole rings and substituents with various electronic properties. The compounds bearing only electron-donating substituents on the aryl ring displayed an increase of the emission wavelength which was also observed with an increase of the number of heterocyclic rings and the number of methoxy groups. The same behaviour is observed for the Stokes shifts. Importantly, the same results are obtained for compounds containing only one heterocyclic ring by the introduction of push-pull substituents on the aryl rings. In addition, the small size of the oxadiazole ring, an amide isostere,[20] as well as their good photophysical properties may mean these are candidates for use in protein fluorescent tagging. It might be interesting to study the behaviour of bis- and tris-oxadiazoles containing compounds bearing push-pull groups system for such applications.

Acknowledgments

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18. Measurements were performed on a minimum of eight different dilutions using 20% DMSO-phosphate buffer 0.01 mol L^{-1} from stock solutions of compounds dissolved in DMSO with concentrations varying between 2 x10^{-5} mol L^{-1} and 6.5 x10^{-5} mol L^{-1} and the extinction coefficients were calculated as an average of the individual values resulted for each sample.
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Supplementary Material

Details of the experimental procedures for the synthesis of the *N*-acylhydrazones, 2,5-disubstituted-1,3,4-oxadiazoles, NMR and HR-MS spectra as well as the experimental procedures for the study of the absorption and emission properties are described.