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Synthesis and fluorescence properties of 2-aryl-3-hydroxyquinolones, a new class of dyes displaying dual fluorescence

Dmytro A. Yushchenko,[a,b,*] Mykhailo D. Bilokin',[a] Oleksandr V. Pyvovarenko,[a] Guy Duportail,[b] Yves Mély[b] and Vasyl G. Pivovarenko[a,b]

[a]*Department of Chemistry, Kyiv National Taras Shevchenko University, 01033 Kyiv, Ukraine*
[b]*Photophysique des Interactions Biomoléculaires, UMR 7175-LC1 du CNRS, Institut Gilbert Laustriat, Faculté de Pharmacie, Université Louis Pasteur, 67401 Illkirch, France*

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Abstract—A series of 2-aryl-3-hydroxyquinolones (3HQs) with different electron donating aryl substituents at the position 2 were synthesized. Their absorption and fluorescence properties were studied in solvents of medium and high polarity. Almost all the synthesized 3HQs display dual fluorescence in the tested solvents, in line with an excited state intramolecular proton transfer reaction. For *N*-methyl substituted compounds, the intensity ratio of the two emission bands was found to be exquisitely sensitive to solvent polarity, with a two orders of magnitude change from toluene to dimethylsulfoxide. Consequently, these compounds appear as prospective polarity fluorescent labels for proteins and nucleic acids.

1. Introduction

Due to its exquisite sensitivity, fluorescence is one of the most important techniques for investigating molecular events in biological systems. However, this technique strongly relies on the availability of fluorescent probes with optimal properties. Of particular interest are the dual fluorescence probes that exhibit two well separated emission bands.[1] In this case, the ratio of the intensities of the two bands can be used as a signal. This ratiometric response constitutes a strong advantage of the dual fluorescent dyes over the intensiometric response of the common single-band fluorescent probes, since the ratiometric response does not depend on the probe concentration. This advantage is especially of interest in cellular and tissular studies where the local concentrations of the dyes cannot be controlled. Excited state intramolecular proton transfer (ESIPT) reaction[2,3] is one of the most effective principles used in the design of probes with dual fluorescence.[4–7] ESIPT results in the formation of two tautomeric forms in the excited state of the probe. Due to their different photophysical properties, these tautomeric forms exhibit largely separated emission bands on the wavelength scale. Moreover, these two forms also show different sensitivities to their environment, so that the ratio of the intensities of the two emission bands can be used as a sensitive mean to characterize the probe environment.[8] The most interesting and characterized representatives of this class of probes are the 3-hydroxyflavone derivatives (3HFs) that have been shown to be highly effective tools for investigating the polarity,[4–9] hydration,[10] electronic polarization[8] and electrostatic effects in different media[11–14] including microheterogeneous systems and proteins.[15–18]

However, despite their significant advantages compared to common single-band probes, 3HFs present some drawbacks notably in respect with their limited photostability and quantum yield that limit their applications. As a consequence, the development of new dual fluorescence probes with improved fluorescent properties is strongly required. In this respect, 2-aryl-3-hydroxyquinolones (3HQs), which are structural analogs of 3HFs may constitute potential interesting candidates.

Keywords: 3-Hydroxyquinolones; Absorption; Fluorescence probes; Polarity sensors.
* Corresponding author. Tel.: +33 390 244262; fax: +33 390 244313; e-mail: ydmytro@yahoo.com

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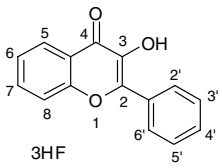
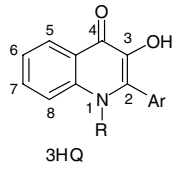




Indeed, substitution of the oxygen atom of the 3HF moiety by a nitrogen atom in 3HQs will permit additional modifications, which may further improve the dye properties. However, only very limited spectroscopic data are actually available on 3HQs[19] and no attempts have been done to adjust their spectroscopic properties. In the present work, we describe the synthesis and spectroscopic characterization of a series of 3HQs with different substituents in two key positions of the molecule, namely on the heterocyclic nitrogen atom and the aromatic ring at position 2.

2. Results and discussion

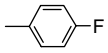
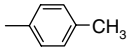
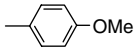
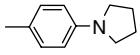
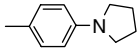
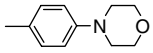
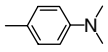
2.1. Synthesis

Since some alkaloids are based on the structure of 3HQs, several methods of 3HQs synthesis have been developed.[19–23] We have selected two of these methods to synthesize our 3HQ derivatives. First, we used the Algar–Flynn–Oyamada reaction, which is largely used in 3HF synthesis. Treatment of 2′-aminochalcones by hydrogen peroxide in basic conditions leads to 3HQs.[19]

However, as previously shown,[24] we found that the synthesis of 3HQ derivatives by this method requires a more complex procedure than for 3HFs (Scheme 1, pathway 1).

The second used method consists in the synthesis and subsequent conversion of phenacyl anthranilates to 3HQ derivatives in polyphosphoric acid (PPA)[22,24] or in the presence of a base.[24] This method proved to be simple and effective for the synthesis of most of our 3HQ derivatives and was thus preferred (Scheme 1, pathway 2, Table 1).

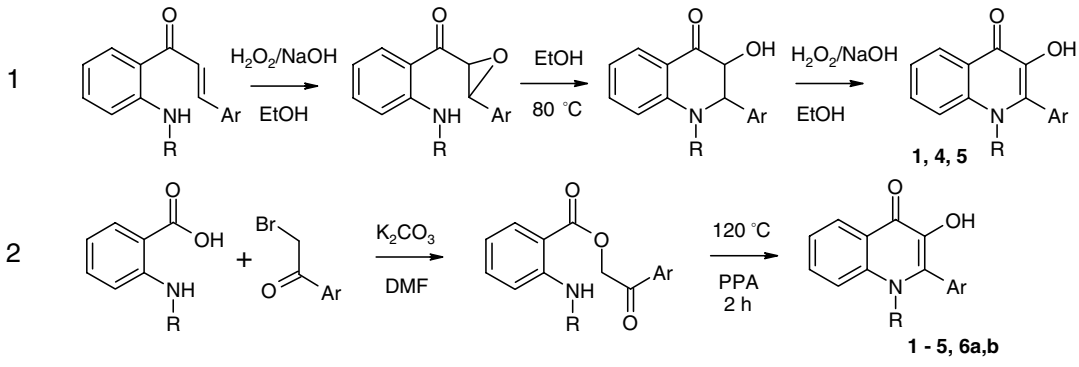
Table 1. Synthesized 3HQs and their characteristics[26]

Compd. no.	Ar	R	Total yield (%)	Mp (°C)
1		H	61[a]/24[b]	276
2		Me	60[a]	238
3		Me	71[a]	257
4		Me	60[a]/32[b]	224
5		Me	59[a]/27[b]	259
6a		H	55[a]	293
6b		Me	57[a]	301
7		Me	49[c]	316
8		Me	52[c,d]	294

[a] Prepared by pathway 2 (Scheme 1).
[b] Prepared by pathway 1 (Scheme 1).
[c] Obtained by nucleophilic substitution of fluorine (Scheme 2).
[d] DMF as a source of dimethylamine was used instead of the corresponding amine.

Since substitution of the 4′ position of the aryl group by the strong electron donor dialkylamino group has been shown to increase the sensitivity of the fluorescence properties of 3HF to its environment,[5,6,8] 4′-dialkylamino substituted 3HQ compounds (**6a**,**b**, **7**, **8**) have been synthesized. Since the starting 4′-(*N*,*N*-dialkylamino)phenyl-2-bromoketones cannot be prepared by the common procedure of bromination, we prepared them through their 2,2-dibromide intermediates as recently described.[25] Alternatively, we found that the 4′-dialkylamino substituted 3HQs could also be prepared by substituting the halogen atom in a corresponding fluorine derivative (Scheme 2). We successfully applied this procedure to the synthesis of quinolones **7** and **8**.

Taken together, our data indicate that pathway 2 through phenacylanthranilates is the most appropriate one for 3HQ synthesis. Even dialkylamino derivatives can be easily obtained with substitution of the fluorine



Scheme 1.