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Reinvestigation of the synthesis of "covalent-assembly" type probes for fluoride ion detection. Identification of novel 7-(diethylamino)coumarins with aggregation-induced emission properties

Valentin Quesneau [a], Benoît Roubinet [b], Pierre-Yves Renard [b], Anthony Romieu [a,*]

[a] ICMUB, UMR 6302, CNRS, Univ. Bourgogne Franche-Comté, 9, Avenue Alain Savary, 21078 Dijon Cedex, France
[b] Normandie Univ, UNIROUEN, INSA Rouen, CNRS, COBRA (UMR 6014), IRCOF, 1 Rue Tesnières, 76821 Mont-Saint-Aignan Cedex, France

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ABSTRACT

An unprecedented C-3 functionalization of 4-(diethylamino)salicylaldehyde through a Friedel-Crafts type alkylation reaction has been discovered during the synthesis of "covalent-assembly"-based fluorescent probes for detection of fluoride ions. The resulting Friedel-Crafts adduct was successfully used for the preparation of two novel 8-substituted 7-(diethylamino)coumarin dyes. The photophysical study of these fluorophores has enabled us to highlight their remarkable aggregation-induced emission (AIE) properties characterized by a yellow-orange emission of aggregates in water. Therefore, 4-(*tert*-butyldimethylsilyloxy)benzyl substituent was identified as a novel AIE-active moiety which could be seen as a possible alternative to popular tetraphenylethylene (TPE).

Introduction

Among the various classes of organic-based fluorophores currently used for the construction of small molecule fluorescent chemosensors/chemodosimeters, coumarin derivatives figure prominently because of several valuable features including: (1) convenient synthetic accessibility, (2) good structural flexibility, (3) valuable spectral features (large Stokes shift and high fluorescence quantum yield), (4) easy modulation of their fluorescence properties through the implementation of different photophysical processes (*e.g.*, PeT, ICT, FRET, ...) and/or protection-deprotection of an optically tunable amino or hydroxyl group introduced at the C-7 position and (5) low toxicity [1]. Consistently seeking to optimize the fluorogenic response (mainly, intensometric detection mode) arising from selective interaction/reaction of the coumarin-based probe with its supposed target (bio)analyte, a new probe design principle namely the "covalent-assembly" approach has recently emerged [2,3]. This cutting-edge strategy is based on *in situ* formation of a fluorophore from a non-fluorescent compound (also known as caged precursor) and through an effective intramolecular reaction triggered/catalyzed by the species to be detected. The fundamental feature of this approach is that it guarantees, in theory at least, a "turn-on" fluorimetric signal from a zero background, hence an optimal detection sensitivity. In this area, pioneering works of the Swager (2003) [4] and Anslyn (2005) groups [2a], on the fluorescent detection of fluoride anions and divalent heavy metal cations respectively, are based on *in situ* formation of 7-(diethylamino)coumarin (DEAC) derivatives through lactonisation or Heck-type cyclization reactions. Since these early remarkable achievements, more than 50 examples of "covalent-assembly" type probes for the detection of a wide range of analytes including biothiols, enzymes, metal cations and ROS/RNS, have already been published [5]. In all these cases, creation of blue-green emitting 7-dialkylamino/7-hydroxy-(2-imino)-coumarins or related fluorophores through lactonisation or Pinner cyclization reactions, is the keystone of the sensing mechanism (Fig. 1).

In the specific case of such reaction-based chemodosimeters devised for the selective sensing of fluoride ions whose detection/quantification in drinking or surface water is very important for public health, the analyte-responsive caged precursor is a *O*-protected 2-(dialkylamino)-4-hydroxycinnamonitrile (or cinnamate ester) derivative and the phenol is masked as a *tert*-butyldimethylsilyl (TBDMS) or *tert*-butyldiphenylsilyl (TBDPS) ether (Fig. 1). The direct linkage of this triggering unit to the phenol moiety may negatively affect probe properties such as poor stability and slow response time. By analogy with some colorimetric, fluorescent or chemiluminescent probes recently published in the literature [6], a self-immolative spacer can be used to circumvent these possible issues. In this context, we wished to explore the synthesis and fluorogenic reactivity (towards fluoride ions) of

* Corresponding author.
E-mail address: anthony.romieu@u-bourgogne.fr (A. Romieu).

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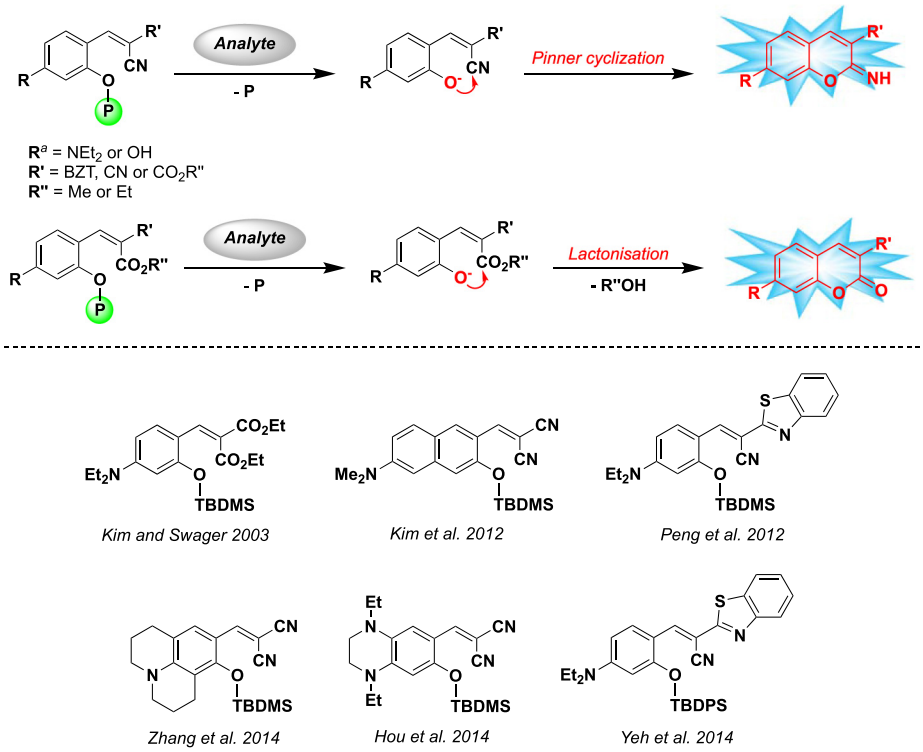

Fig. 1. (Top) "Covalent-assembly" probe design principle applied to fluorogenic detection of (bio)analytes through *in situ* synthesis of 7-dialkylamino/7-hydroxy-2-iminocoumarins or 7-dialkylamino/7-hydroxycoumarins; (bottom) examples of "covalent-assembly" type probes for F^- detection reported in the literature (BZT = 2-benzothiazolyl, TBDMS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl) [4,5f,i,k,n]. [a]*Please note: fused julolidine, 4-dimethylaminophenyl and 1,4-diethylpiperazine fragments are also frequently used in the design of such "caged" precursors, to red-shift spectral features of in situ formed coumarin.*

next-generation "covalent-assembly" type probes that incorporate a self-immolative *para*-hydroxybenzyl alcohol (PHBA) linker [5j,7]. During the course of this work, we have highlighted an unexpected S_EAr reaction leading to regioselective C-3 benzylation of 4-(diethylamino)salicylaldehyde. Since this type of building blocks is frequently used as starting material for the synthesis of coumarins, we next considered the Knoevenagel condensation between this 2-hydroxybenzaldehyde derivative and C-nucleophiles (*i.e.*, malononitrile and benzothiazole-2-acetonitrile) to produce novel DEAC-based fluorophores.

In this Letter, in the course of our research on self-immolative linker based second generation "covalent-assembly" probes for fluoride ions, we report our findings on the unusual reactivity of 4-(diethylamino)salicylaldehyde towards 4-(*tert*-butyldimethylsilyloxy)benzyl bromide. This unprecedented reaction led us to consider the preparation and photophysical characterization of novel DEAC-based fluorophores. A comparative study of their spectral features with those of parent DEAC derivatives lacking a C-8 substituent, and conducted in different solvents (aq. buffers, DMSO and EtOH), has put in evidence an expected added value for these coumarin-based fluorophores, namely aggregation-induced emission properties.

Results and discussion

The vast majority of coumarin-based "covalent-assembly" type probes reported in the literature (see Fig. 1 for the general structure), are readily prepared *via* a well-established two-step process: (1) protection of the phenol group of salicylaldehyde derivative (mostly, 2-OH of 4-(diethylamino)salicylaldehyde or 2,4-dihydroxybenzaldehyde) with the selected trigger-recognition unit and subsequent (2) Knoevenagel condensation with malononitrile or related C-nucleophiles. In cases where a self-immolative spacer is used to connect salicylaldehyde and recognition moiety, step (1) is often a 2-*O*-alkylation reaction performed with a benzyl bromide derived from PHBA. To the best of our knowledge, this latter strategy was never applied to the design of fluoride-sensitive caged precursors of coumarins and TBDMS or TBDPS moiety is always directly attached to the phenol oxygen atom of salicylaldehyde derivative (Fig. 1) [4,5f,i,k,n]. In order to fill this gap and to assess the performances of "covalent-assembly" type probes bearing a fluoride-sensitive self-immolative linker, we planned the synthesis of fluorescent chemodosimeters **1** and **2** (Fig. 2). This entailed us, first, to revisit the synthesis of alkylating agent namely 4-(*tert*-butyldimethylsilyloxy)benzyl bromide (4-*O*TBDMS benzyl bromide) **3**, because the published procedures are tedious and time-consuming.

*Revisited synthesis of 4-OTBDMS benzyl bromide **3***

Published synthetic procedures towards 4-*O*TBDMS benzyl bromide **3** are based on a four-step reaction sequence (Scheme 1, top)

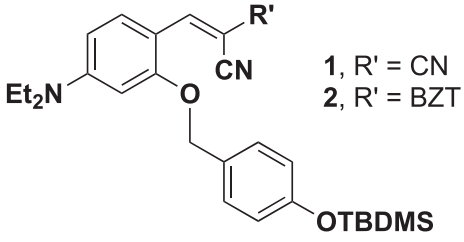

Fig. 2. Self-immolative "covalent-assembly" type probes for F^- detection and based on the use of PHBA linker (BZT = 2-benzothiazolyl, TBDMS = *tert*-butyldimethylsilyl), targeted in our project.

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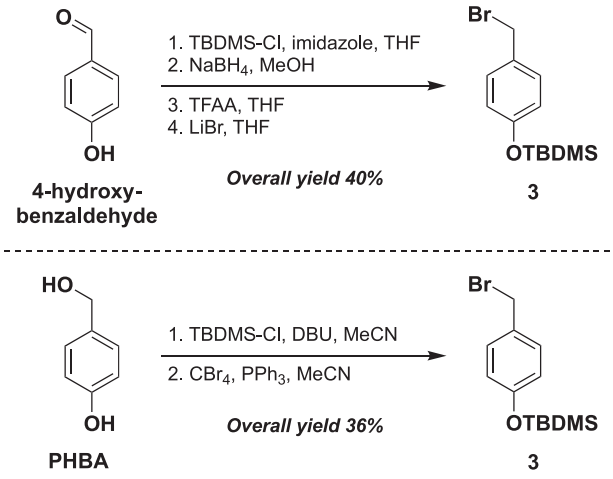

Scheme 1. (Top) Published synthesis of 4-*O*TBDMS benzyl bromide **3** [8]; (bottom) shortened synthesis of 4-*O*TBDMS benzyl bromide **3** devised by us (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBDMS-Cl = *tert*-butyldimethylsilyl chloride, TFAA = trifluoroacetic anhydride).

[8]. First, selective protection of the phenol of 4-hydroxybenzaldehyde with TBDMS-Cl, followed by $NaBH_4$-mediated reduction of the formyl moiety provided 4-*O*TBDMS benzylic alcohol. Next, in order to provide a good leaving group, this alcohol was esterified with trifluoroacetic anhydride (TFAA), and finally this trifluoroacetate underwent nucleophilic reaction with LiBr. This procedure enables obtaining 4-*O*TBDMS benzyl bromide **3** with a satisfactory 40% yield, yet requires tedious purification steps. To shorten the overall number of steps, we have explored direct and selective silylation of PHBA (phenol *vs.* primary alcohol) with TBDMS-Cl in the presence of a base (Scheme 1, bottom). Several organic and inorganic bases (*i.e.*, DBU, DIEA, Cs_2CO_3 and K_2CO_3) were tested and DBU appeared to be the best one providing a satisfying 65% isolated yield. Thereafter, the implementation of Appel reaction (*i.e.*, treatment of alcohol with CBr_4 and PPh_3 in MeCN) enabled the quantitative conversion of 4-*O*TBDMS benzylic alcohol into the targeted benzyl bromide derivative **3**. However, the poor stability of this latter compound over silica gel prevents its chromatographic isolation in a pure form and with a good yield (only 39% was obtained). To overcome this issue, we used liquid-liquid extractions with heptane to recover pure **3** and with an acceptable yield of 55%. Its structure was unambiguously confirmed by NMR analyses and comparison with published spectroscopic data (see Supplementary data and Figs. S1 and S2). If the overall yield is slightly lower than the published procedure (36% *vs.* 40%), this new procedure competes thanks to a lower number of steps and easier purification processes.

With this alkylating reagent in hand, we next examined its reactivity towards 4-(diethylamino)salicylaldehyde with the aim of rapidly synthesizing self-immolative "covalent-assembly" type probes **1** and **2**.

*2-O-Alkylation of 4-(diethylamino)salicylaldehyde with 4-OTBDMS benzyl bromide **3***

By analogy with the self-immolative caged precursors of 7-(dialkylamino)-(2-imino)coumarins already published, especially those bearing either a 4-(pinacolboronate)benzyl [5p] or a 4-nitrobenzyl moiety [5am], reactive towards RNS/ROS and nitroreductase (NTR) enzymes respectively, phenol alkylation of 4-(diethylamino)salicylaldehyde was achieved with 1 equiv. of **3**, in the presence of K_2CO_3 (2 equiv.) as base, in MeCN and at room temperature (Scheme 2). Surprisingly, this reaction was found to be not univocal with the formation, in addition to the desired benzyl ether **4**, of an unknown product which was isolated by column chromatography over silica gel in a 10% to 25% yield (depending on the reaction attempt and age of benzylation reagent **3**). The same mixture of these two compounds was obtained when K_2CO_3 was replaced by NaH (60% dispersion in mineral oil). The unknown compound is less polar than **4** but has the same molecular mass as revealed by the HPLC-MS analyses (see Figs. S6, S7, S13 and S14). Thus, two hypothetical structures **5** and **6** resulting either from quaternarization of the *N*,*N*-diethylanilino moiety (S_N reaction) or from Friedel-Crafts type alkylation of the electron-rich benzene ring (S_EAr reaction) can be theoretically put forward. Gratifyingly, a comprehensive NMR study based on 1D and 2D experiments (*i.e.*, COSY and NOESY, see Figs. S11 and S12) confirmed both the lack of aromatic proton H-3, the *ortho* coupling between protons H-5 and H-6 (J = 8.5 Hz) and the spatial proximity between benzylic methylene protons of 4-*O*TBDMS benzyl moiety and CH_2-protons of diethylamino substituent. We may thus conclude that unknown product formed during the *O*-alkylation process is the Friedel-Crafts adduct **6**. Such C-3-alkyl-substituted 4-(diethylamino)salicylaldehyde derivatives have never been described and their formation under mild conditions as these presented here, is somewhat surprising even if the corresponding benzene ring is electronically enriched by phenolic hydroxyl (deprotonated form in the reaction mixture containing K_2CO_3) and diethylamino donating groups. Indeed, the sole example of Fridel-Crafts type C-2 benzylation of a 1,3-diheterosubstitued benzene was reported by Kumar et al. and it was the reaction between resorcinol (1,3-dihydroxybenzene) and benzyl chloride performed under refluxing xylene (140 °C) for 8 h. In this case, a mixture of mono- (C-2), di- (C-2/C-4) and tri-benzyl (C-2/C-4/C-6) adducts in the ratio 6:3:1 was obtained (combined yield 82%) [9]. The regioselectivity of Friedel-Crafts type alkylation leading to **6**, is in agreement with the Holleman rules since diethylamino and phenol groups are *ortho*/*para* directing and formyl is known to be *meta* directing group [10]. To gain further information about the possible scope of this reaction, we implemented this synthetic procedure with other alkylating agents including 4-nitrobenzyl bromide and 4-(2,4-dinitrophenyloxy)benzyl bromide but *O*-alkylation of 4-(diethylamino) salicylaldehyde was overwhelmingly observed and only traces of Friedel-Crafts product was detected. This result is consistent with the synthesis of "covalent-assembly" type probes presented above and for which this latter undesired reaction was never mentioned. One possible interpretation of this peculiar reactivity is that the formation of benzyl-type carbocation (the reactive intermediate required for S_EAr reactions on salicylaldehyde derivative) is favored only in the case 4-*O*TBDMS benzyl bromide due to the electron-donating ability of its *para*-substituent (*i.e.*, +M effect of the silyloxy group *vs.* -M effect of nitro and 2,4-dinitrophenyloxy moieties). Also noteworthy and in agreement with our hypotheses, is that when we assayed the reaction of 4-(diethylamino)salicylaldehyde with 4-*O*TBDMS benzyl alcohol under Mitsunobu conditions (*i.e.*, treatment with PPh_3 and DIAD in Et_2O) [11] the sole observed product was *O*-alkylated product **4**.

To check the reactivity of the salicylaldehyde part of the molecule **6** and to access to novel 7-(diethylamino)coumarins, we have then explored its condensation with malononitrile and benzothiazole-2-acetonitrile.

*Synthesis of 8-substituted-7-(diethylamino)coumarins **7** and **8***

The synthesis of both coumarins **7** and **8**, through Knoevenagel condensation reaction, was achieved under conventional conditions: treatment with C-nucleophile (1 equiv.), in the presence of piperidine (1 equiv.) and anhydrous Na_2SO_4 (2 equiv.), in EtOH at room temperature (Scheme 3). Purification by column chromatog-

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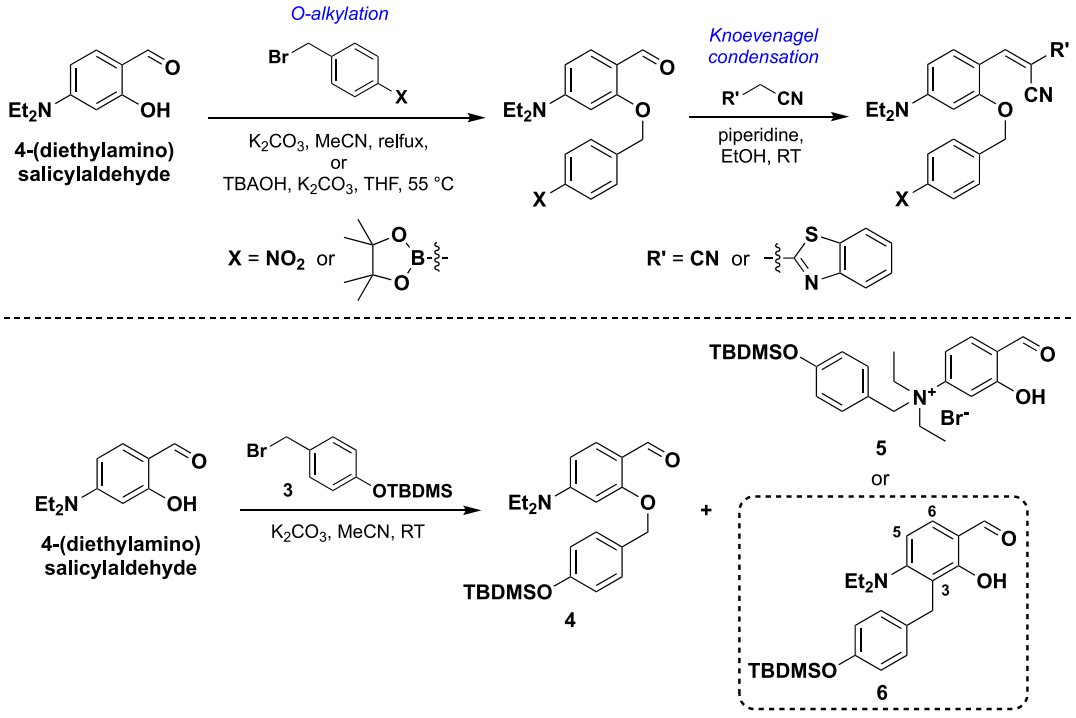
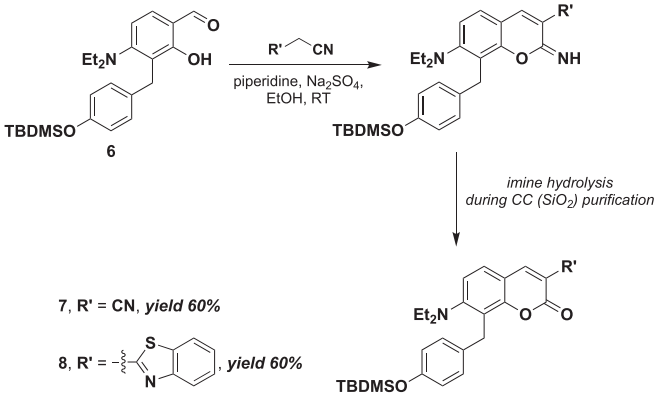


Scheme 2. (Top) Published syntheses of NTR- and peroxynitrite-responsive self-immolative "covalent-assembly" type probes based on *O*-alkylation of 4-(diethylamino) salicylaldehyde with 4-nitrobenzyl bromide or 4-(pinacolboronate)benzyl bromide and subsequent Knoevenagel condensation reaction (TBAOH = tetrabutylammonium hydroxide) [5p,am]; (bottom) alkylation of 4-(diethylamino)salicylaldehyde with 4-*O*TBDMS benzyl bromide **3** leading to unexpected Friedel-Crafts alkylation product **6**.



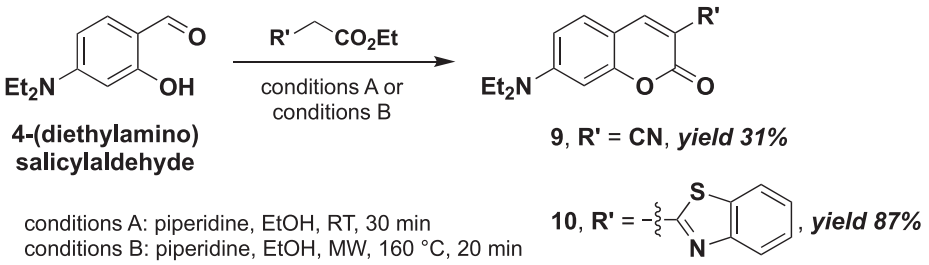
Scheme 3. Synthesis of 8-substituted 7-(diethylamino)coumarin dyes **7** and **8** (CC (SiO_2) = column chromatography over silica gel).

raphy over silica gel provided the 7-(diethylamino)coumarins **7** and **8** in a satisfying 60% yield even if an additional purification by trituration with MeOH was required to recover **7** in a pure form. It is important to note that the hydrolysis of imine moiety (this two-step Knoevenagel-cyclization sequence actually leads to 2-iminocoumarin derivatives) occurred during the purification process.

In order to assess the effect of 4-*O*TBDMS benzyl moiety on photophysical properties of theses novel 7-(diethylamino)coumarin derivatives, we have also prepared the parent compounds **9** and **10** lacking this C-8 substituent (Scheme 4). 3-Cyano-7-(diethylamino)coumarin **9** was prepared from 4-(diethylamino)salicylaldehyde and ethyl cyanoacetate, according to a literature procedure [12]. As for the Knoevenagel condensation with 2-(2-benzothiazolyl)acetic acid ethyl ester, reaction time was dramatically shortened using microwave irradiation (20 min at 160 °C *vs.* 6 h under refluxing MeOH [13]), and purification by column chromatography provided **10** with a good 87% yield. For these four compounds, all spectroscopic data, especially IR, NMR and mass spectrometry, were in agreement with the structures assigned (see Supplementary data).

Photophysical characterization of DEAC-based fluorophores

The photophysical properties of synthesized 7-(diethylamino)-coumarins **7**–**10** were evaluated in DMSO (solvent in which these



Scheme 4. Synthesis of 7-(diethylamino)coumarin dyes **9** and **10** (MW = microwave irradiation).

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compounds are perfectly soluble and used for the preparation of their stock solutions), in EtOH and in phosphate-buffered saline (PBS, pH 7.5) which mimics physiological conditions. Fluorophores **7**–**10** were found to be perfectly soluble in PBS only at low concentrations (less than 5 μM). At higher concentrations, light scattering by suspension was clearly observed on UV–vis absorption spectra (Fig. 3C and Figs. S21, S22, S32, S33, S36 and S39). All results are compiled in Table 1 (see Fig. 3 for the absorption/fluorescence spectra of **8** and Supplementary data for the absorption/fluorescence spectra of compounds **7**, **9** and **10**). In polar organic solvents (DMSO and EtOH), the C-8 substitution of DEAC scaffold caused the broadening and dramatic blue-shift of the absorption band, quite probably because the formation of aggregates especially in the case of derivative **8** which bears the hydrophobic benzothiazolyl C-3 substituent (*e.g.*, $\Delta\lambda_{1/2max}$ values: 89–93 nm for **8** *vs.* 64–65 nm for its C-8 unsubstituted counterpart **10**). The lack of a significant blue-green fluorescence emission upon excitation at 410 nm (Φ_F = 1–2%), confirms the preponderance of non-emissive species in solution and a possible radiation less de-excitation pathway caused by rotational motions of 4-*O*TBDMS benzyl moiety. The spectral signature in aq. buffer (PBS) is somewhat different because **7** and **8** exhibit a wide emission band ranging from 500 to 700 nm (centered at ca. 560 nm) which is consistent with the behavior described by an aggregation-induced emission (AIE) effect [14].

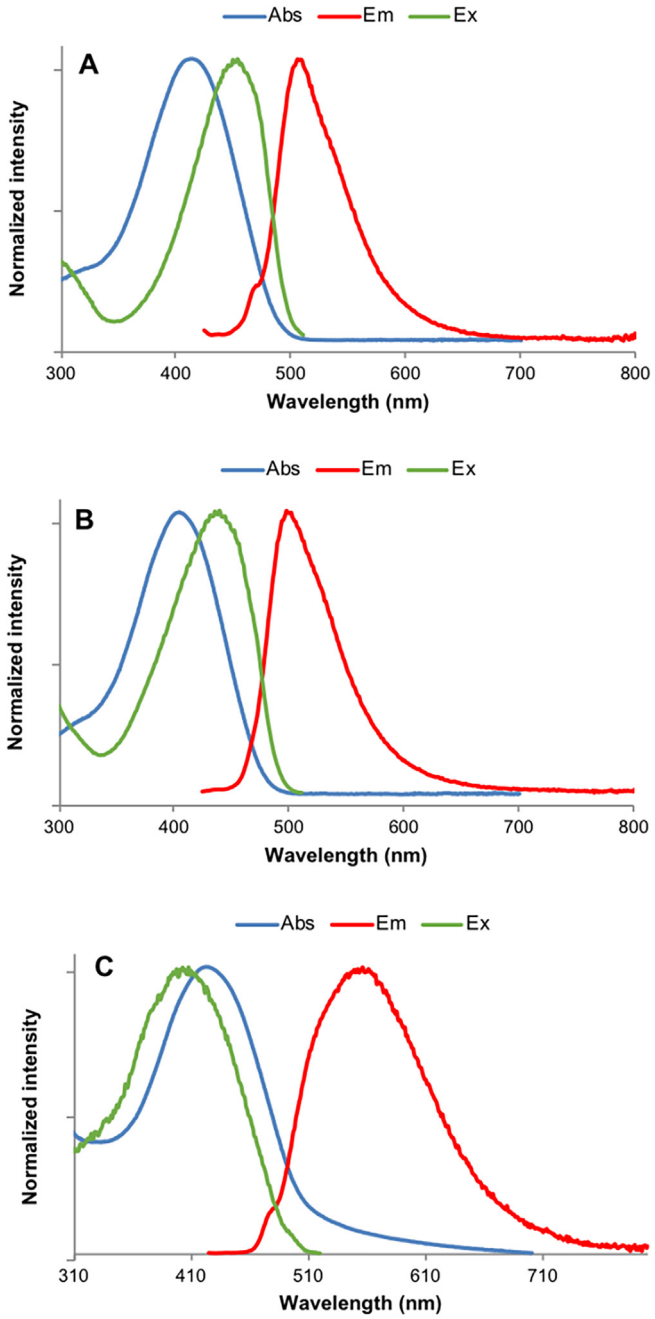

Fig. 3. Normalized absorption (blue), excitation (Em. 525 or 600 nm, slit 5 nm, green) and emission (Ex. 410 nm, slit 5 nm, red) spectra of coumarin **8** in DMSO (A), EtOH (B) and PBS (C) at 25 °C. *Please note: the recorded absorption spectrum of **8** in PBS is due both to light scattering (by aggregates) and absorption.*

To confirm this property, the fluorescence behavior of **7** and **8** in water/EtOH mixtures was studied. As displayed in Fig. 4, in pure EtOH, **8** shows weak fluorescence centered at 500 nm. When water fraction varies from 10% to 50%, the emission marginally decreases but without alterations in the shape of emission curve. This is probably related to the aggregation-caused quenching (ACQ) effect. When the fraction of water is greater than 50%, the emission maximum peak red shifts to 560 nm along with a fluorescence intensity increase evidently.

As water is a poor solvent of **8**, the addition of water would induce the formation of aggregates, that hinders the intramolecular rotational motions of 4-*O*TBDMS benzyl moiety, thus blocking the non-radiative relaxation pathways and boosting the yellow-orange emission (*i.e.*, restriction of intramolecular rotations (RIR) mechanism) [14]. Moreover, the fluorescence quantum yield of **8** in the solid state was measured to be 7% for an emission maximum centered at 534 nm (see Supplementary data for experimental details related to the determination of solid state absolute fluorescence quantum yields and Figs. S41–S44). The same behavior was observed with the less hydrophobic 3-cyano derivative **7** but the formation of strongly emissive aggregates was occurred at a higher fraction of water in EtOH (>70%) (Fig. S45). As expected, this AIE effect was found to be negligible in the case of parent C-8 unsubstituted 7-(diethylamino)coumarins **9** and **10** (Figs. 4 and S45). Indeed, the shape and position of the fluorescence emission spectrum of 3-cyano derivative **9** are similar whatever the solvent used for the spectral measurements. The fluorescence quantum yield is also in the same order of magnitude. For its part, the 3-(2-benzothiazolyl) derivative **10** emits intense green light both in DMSO and in EtOH (Φ_F = 67% and 75% respectively), but its dissolution in PBS causes a large bathochromic shift in the emission color with an almost complete quenching of its fluorescence (Φ_F = 2.5%). These features are consistent with an ACQ effect instead of AIE characteristics displayed by this more hydrophobic derivative. To clarify which rotors of 4-*O*TBDMS benzyl moiety are responsible for the AIE effect, we have finally synthesized (*i.e.*, aq. TFA deprotection of TBDMS ether of **8**) and studied photophysical properties of the 8-(4-hydroxybenzyl) derivative **11**. This compound displays the same spectral features and AIE behavior than that for **8** (Figs. 4 and S39 and S40), even if the fluorescence emission efficiency of aggregates in water is lower (Φ_F 2% *vs.* 7% for **8**). These results may indicate that the AIE activity of **7** and **8** is mainly ascribed to rotational motions of the benzyl moiety and not those of silyl group.

To the best of our knowledge, few works have already described the facile functionalization of 2*H*-chromen-2-one scaffold with AIE-active moieties to generate coumarin-based AIE fluorophores with long-wavelength emission. Worth mentioning in this context are 7-(diethylamino)coumarin or 4-methylumbelliferone Schiff base derivatives bearing an AIE-active substituent connected to C-3 or C-8 position *via* an imine linkage [16]. Some of them have been used as fluorescent probes for effective detection of biothiols (cysteine) or heavy metal cations such as Hg(II) [16a,b].

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Table 1
Photophysical properties of DEAC-based fluorophores studied in this work, determined at 25 °C.

Cmpd[a]	Solvent	λ_{max} Abs (nm)	λ_{max} Em (nm)	$\Delta\lambda_{1/2max}$ (nm)	$\varepsilon(M^{-1}\ cm^{-1})$	Φ_F (%)[b]
7	PBS, pH 7.5	419	561	90	17 700	2
7	DMSO	411	468	88	16 300	–[c]
7	EtOH	405	467	76	16 400	–[c]
8	PBS, pH 7.5	423	556	112	20 550	7
8	DMSO	414	506	93	23 800	1.5
8	EtOH	405	502	89	22 900	2
9	PBS, pH 7.5	352, 431	479	–[d]	12 200, 6 000	–[c]
9	PBS + 5% EtOH, pH 7.5	352, 431	479	–[d]	10 700, 7 100	1.5
9	DMSO	430	478	49	46 600	3.5
9	EtOH	423	467	49	46 900	3
10	PBS, pH 7.5	463, 498	557	–[d]	17 200, 18 000	2.5
10	DMSO	468	516	65	56 400	67
10	EtOH	459	503	64	54 100	75

[a] Stock solutions (1.0 mg/mL) of fluorophores were prepared in DMSO.
[b] Determined using coumarin 153 as a standard (Φ_F = 38% in EtOH, Ex. at 410 nm) except for **7** in PBS, $Ru(bpy)_3Cl_2$ was used in this case (Φ_F = 2.8% in water saturated with air, Ex. at 410 nm) [15].
[c] Very low or no fluorescence.
[d] Not determined due to the presence of two maxima.

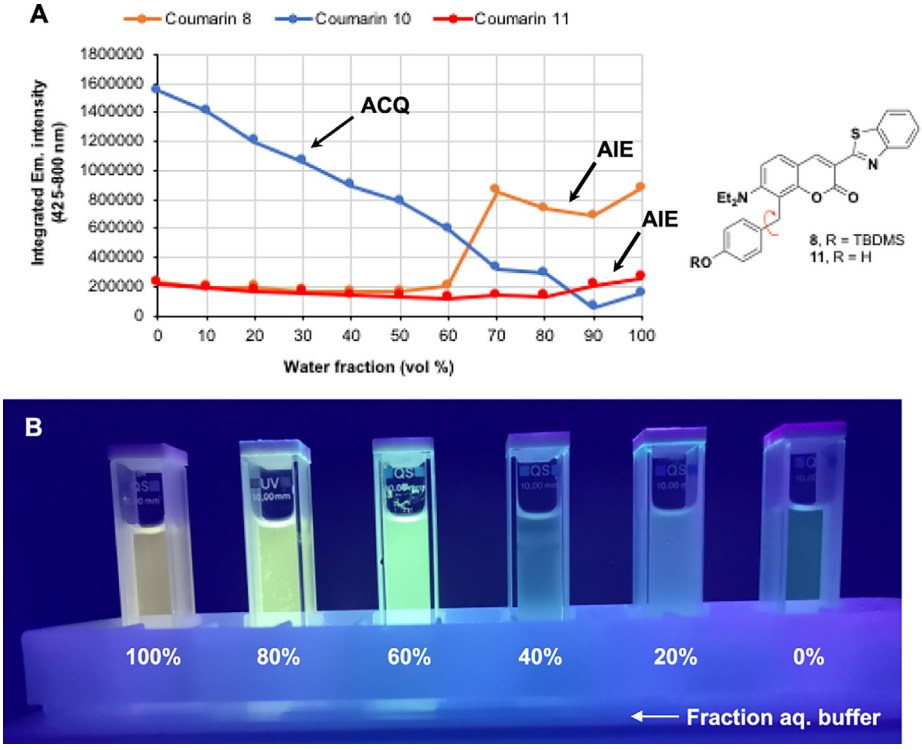

Fig. 4. Demonstration of AIE properties of 8-substituted 3-(2-benzothiazolyl)-7-(diethylamino)coumarin **8**. (A, left) Fluorescence emission (integrated between 425 and 800 nm) of **8**, **10** and **11** *vs.* water fraction in EtOH/water mixtures (concentration = 1.0 μM, Ex. at 410 nm, Em. 425–800 nm, Ex./Em. slit = 5 nm for **8** and **11** and 2 nm for **10**); (A, right) schematic representation of intramolecular rotations in coumarins **8** and **11**; (B) Photographs of **8** (15 μM) in PB/EtOH (fraction aq. buffer vol%) mixtures taken under 365 nm UV illumination (PB = phosphate buffer, 100 mM, pH 7.6). *Please note: for the recording of Em. spectra, water was used instead of PB to avoid interferences causing by partial precipitation of phosphate salts in EtOH as observed in Fig. 4B. Suspension observed in quartz cells (Fig. 4B) was due to phosphate salts precipitation at low fractions of aq. buffer, and to partial precipitation of coumarin **8** at high fractions of aq. buffer.*

Conclusion

In summary, we have reported our findings related to the unprecedented C-3 functionalization of 4-(diethylamino)salicylaldehyde through a Friedel-Crafts alkylation reaction conducted under mild conditions and with electron-rich 4-*O*TBDMS benzyl bromide **3**. This unusual reaction is not applicable to a wide range of *para*-substituted benzyl bromide derivatives, especially those currently employed for the synthesis of self-immolative fluorescent probes for (bio)sensing purposes. However, the availability of unusual salicylaldehyde derivative **6** has enabled us to prepare two novel 7-(diethylamino)coumarins through conventional Knoevenagel reaction. A comprehensive photophysical study of these fluorophores led both to the discovery of their AIE properties and the identification of 4-*O*TBDMS benzyl as a novel AIE-active moiety. The conversion of conventional 7-(diethylamino)coumarin dyes to AIE fluorophores is thus realized by a simple transformation (Friedel-Crafts alkylation), avoiding laborious and more complex synthetic operations sometimes associated with the incorporation of popular AIE-active moieties (*e.g.*, tetraphenylethylene, TPE) onto fluorescent scaffolds [14,17]. We are confident that this strategy and others related could be applied to the introduc-

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tion of benzyl-type rotors onto fluorophores for which some positions reactive towards electrophiles are clearly identified (*e.g.*, C-4/C-5 and possibly C-2/C-7 positions of xanthene dyes including fluoresceins, pyronins and rhodamines). Lastly, the identification of some 8-substituted 7-hydroxycoumarin derivatives as potent α-amylase inhibitors [9], could maybe lead medicinal chemists to assess the potential of the reported Friedel-Crafts type reaction for facile preparation of coumarin-based antidiabetic agents [18].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151279.

References

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[1] (a) For comprehensive reviews, see: H.E. Katerinopoulos Curr. Pharm. Des. 10 (2004) 3835–3852;
(b) H. Li, L. Cai, Z. Chen, Advances in Chemical Sensors, InTech, 2011, pp. 121–150;
(c) D. Cao, Z. Liu, P. Verwilst, S. Koo, P. Jangjili, J.S. Kim, W. Lin, Chem. Rev. 119 (2019) 10403–10519.
[2] (a) Q. Wu, E.V. Anslyn, J. Mater. Chem. 15 (2005) 2815–2819;
(b) E.V. Anslyn, J. Am. Chem. Soc. 132 (2010) 15833–15835;
(c) Y. Yang, S.K. Seidlits, M.M. Adams, V.M. Lynch, C.E. Schmidt, E.V. Anslyn, J.B. Shear, J. Am. Chem. Soc. 132 (2010) 13114–13116.
[3] (a) For reviews on "covalent-assembly" type probes, see: A. Romieu Org. Biomol. Chem. 13 (2015) 1294–1306;
(b) T. He, H. He, X. Luo, Y. Yang, Y. Yang, Sci. Sinica Chim. 47 (2017) 945–954.
[4] T.-H. Kim, T.M. Swager, Angew. Chem. Int. Ed. 42 (2003) 4803–4806.
[5] (a) W. Jiang, W. Wang, Chem. Commun. (2009) 3913–3915;
(b) J.H. Do, H.N. Kim, J. Yoon, J.S. Kim, H.-J. Kim, Org. Lett. 12 (2010) 932–934;
(c) T.-I. Kim, M.S. Jeong, S.J. Chung, Y. Kim, Chem. - Eur. J. 16 (2010) 5297–5300;
(d) T.-I. Kim, H. Kim, Y. Choi, Y. Kim, Chem. Commun. 47 (2011) 9825–9827;
(e) D. Kim, S. Sambasivan, H. Nam, K. Hean Kim, J. Yong Kim, T. Joo, K.-H. Lee, K.-T. Kim, K. Han Ahn, Chem. Commun. 48 (2012) 6833–6835;
(f) D. Kim, S. Singha, T. Wang, E. Seo, J.H. Lee, S.-J. Lee, K.H. Kim, K.H. Ahn, Chem. Commun. 48 (2012) 10243–10245;
(g) I. Kim, D. Kim, S. Sambasivan, K.H. Ahn, Asian J. Org. Chem. 1 (2012) 60–64;
(h) H. Mohapatra, S.T. Phillips, Angew. Chem. Int. Ed. 51 (2012) 11145–11148;
(i) Y. Peng, Y.-M. Dong, M. Dong, Y.-W. Wang, J. Org. Chem. 77 (2012) 9072–9080;
(j) J. Park, Y. Kim, Bioorg. Med. Chem. Lett. 23 (2013) 2332–2335;
(k) P. Hou, S. Chen, H. Wang, J. Wang, K. Voitchovsky, X. Song, Chem. Commun. 50 (2014) 320–322;
(l) J. Kim, J. Park, H. Lee, Y. Choi, Y. Kim, Chem. Commun. 50 (2014) 9353–9356;
(m) C. Wang, S. Yang, M. Yi, C. Liu, Y. Wang, J. Li, Y. Li, R. Yang, ACS Appl. Mater. Interfaces 6 (2014) 9768–9775;
(n) J.-T. Yeh, P. Venkatesan, S.-P. Wu, New J. Chem. 38 (2014) 6198–6204;
(o) S. Zhang, J. Fan, S. Zhang, J. Wang, X. Wang, J. Du, X. Peng, Chem. Commun. 50 (2014) 14021–14024;
(p) J. Zhou, Y. Li, J. Shen, Q. Li, R. Wang, Y. Xu, X. Qian, RSC Adv. 4 (2014) 51589–51592;
(q) S. Debieu, A. Romieu, Org. Biomol. Chem. 13 (2015) 10348–10361;
(r) Q. Fang, Q. Liu, X. Song, J. Kang, Luminescence 30 (2015) 1280–1284;
(s) Y. Han, C. Yang, K. Wu, Y. Chen, B. Zhou, M. Xia, RSC Adv. 5 (2015) 16723–16726;
(t) P.K. Mishra, T. Saha, P. Talukdar, Org. Biomol. Chem. 13 (2015) 7430–7436;
(u) H. Mohapatra, H. Kim, S.T. Phillips, J. Am. Chem. Soc. 137 (2015) 12498–12501;
(v) G. Zhang, Y. Sun, X. He, W. Zhang, M. Tian, R. Feng, R. Zhang, X. Li, L. Guo, X. Yu, S. Zhang, Anal. Chem. 87 (2015) 12088–12095;
(w) H. Zhang, Y. Xie, P. Wang, G. Chen, R. Liu, Y.-W. Lam, Y. Hu, Q. Zhu, H. Sun, Talanta 135 (2015) 149–154;
(x) J. Zhang, Y. Li, W. Guo, Anal. Methods 7 (2015) 4885–4888;
(y) Y. Chen, B. Chen, D. Luo, Y. Cai, Y. Wei, Y. Han, Tetrahedron Lett. 57 (2016) 1192–1195;
(z) Y. Chen, M. Zhang, Y. Han, J. Wei, RSC Adv. 6 (2016) 8380–8383;
(aa) A.K. Das, S. Goswami, C.K. Quah, H.-K. Fun, RSC Adv. 6 (2016) 18711–18717;
(ab) Z. Hu, J. Hu, H. Wang, Q. Zhang, M. Zhao, C. Brommesson, Y. Tian, H. Gao, X. Zhang, K. Uvdal, Anal. Chim. Acta 933 (2016) 189–195;
(ac) D. Kim, S.-Y. Na, H.-J. Kim, Sens. Actuators B-Chem. 226 (2016) 227–231;
(ad) X. Liu, F. Qi, Y. Su, W. Chen, L. Yang, X. Song, J. Mater. Chem. C 4 (2016) 4320–4326;
(ae) X. Liu, D. Yang, W. Chen, L. Yang, F. Qi, X. Song, Sens. Actuators B-Chem. 234 (2016) 27–33;
(af) F. Qi, X. Liu, L. Yang, L. Yang, W. Chen, X. Song, Tetrahedron 72 (2016) 6909–6913;
(ag) J. Zhang, Y. Li, J. Zhao, W. Guo, Sens. Actuators B-Chem. 237 (2016) 67–74;
(ah) W. Chen, X. Yue, W. Li, Y. Hao, L. Zhang, L. Zhu, J. Sheng, X. Song, Sens. Actuators B-Chem. 245 (2017) 702–710;
(ai) M.A. Miller, B. Askevold, H. Mikula, R.H. Kohler, D. Pirovich, R. Weissleder, Nat. Commun. 8 (2017) 15906;
(aj) J. Hu, T. Liu, H.-W. Gao, S. Lu, K. Uvdal, Z. Hu, Sens. Actuators B-Chem. 269 (2018) 368–376;
(ak) B. Huo, M. Du, A. Gong, M. Li, L. Fang, A. Shen, Y. Lai, X. Bai, Y. Yang, Anal. Methods 10 (2018) 3475–3480;
(al) Y. Kim, M. Choi, S.V. Mulay, M. Jang, J.Y. Kim, W.-H. Lee, S. Jon, D.G. Churchill, Chem. - Eur. J. 24 (2018) 5623–5629;
(am) X. Liu, L. He, L. Yang, Y. Geng, L. Yang, X. Song, Sens. Actuators B-Chem. 259 (2018) 803–808;
(an) L. Xia, F. Hu, J. Huang, N. Li, Y. Gu, P. Wang, Sens. Actuators B-Chem. 268 (2018) 70–76;
(ao) L. Yang, Y. Su, Y. Geng, H. Xiong, J. Han, Q. Fang, X. Song, Org. Biomol. Chem. 16 (2018) 5036–5042;
(ap) L. Yang, Y. Su, Z. Sha, Y. Geng, F. Qi, X. Song, Org. Biomol. Chem. 16 (2018) 1150–1156;
(aq) W. Li, S. Zhou, L. Zhang, Z. Yang, H. Chen, W. Chen, J. Qin, X. Shen, S. Zhao, Sens. Actuators B-Chem. 284 (2019) 30–35;
(ar) Y. Liu, W. Yan, H. Li, H. Peng, X. Suo, Z. Li, H. Liu, J. Zhang, S. Wang, D. Liu, Anal. Methods 11 (2019) 421–426;
(as) H. Qin, L. Li, K. Li, Y. Xiaoqi, Chin. Chem. Lett. 30 (2019) 71–74;
(at) J. Wang, C. Li, Q. Chen, H. Li, L. Zhou, X. Jiang, M. Shi, P. Zhang, G. Jiang, B.Z. Tang, Anal. Chem. 91 (2019) 9388–9392;
(au) L. Yang, Y. Liu, Y. Li, H. Wang, H. Zhang, J. Xu, L. Ji, Q. Wang, G. He, Tetrahedron 75 (2019), 130538;
(av) L. Xia, Y. Tong, L. Li, M. Cui, Y. Gu, P. Wang, Talanta 204 (2019) 431–437.
[6] J. Yan, S. Lee, A. Zhang, J. Yoon, Chem. Soc. Rev. 47 (2018) 6900–6916.
[7] (a) E.K.Y. Chen, R.A. McBride, E.R. Gillies, Macromolecules 45 (2012) 7364–7374;
(b) H.-J. Jin, J. Lu, X. Wu, Bioorg. Med. Chem. 20 (2012) 3465–3469;
(c) S. Park, S.Y. Kim, J. Cho, D. Jung, D. Seo, J. Lee, S. Lee, S. Yun, H. Lee, O. Park, B. Seo, S. Kim, M. Seol, S.H. Woo, T.K. Park, Bioconjugate Chem. 30 (2019) 1969–1978.
[8] (a) K. Kopka, A. Faust, P. Keul, S. Wagner, H.-J. Breyholz, C. Höltke, O. Schober, M. Schäfers, B. Levkau, J. Med. Chem. 49 (2006) 6704–6715;
(b) J. Wu, R. Huang, T. Wang, X. Zhao, W. Zhang, X. Weng, T. Tian, X. Zhou, Org. Biomol. Chem. 11 (2013) 2365–2369.

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[9] J.A. Kumar, A.K. Tiwari, G. Saidachary, D.A. Kumar, Z. Ali, B. Sridhar, B.C. Raju, Med. Chem. 9 (2013) 806–811.
[10] A.F. Holleman, Chem. Rev. 1 (1924) 187–230.
[11] D. Liu, L.P. Sanow, C. Zhang, Tetrahedron Lett. 55 (2014) 3090–3092.
[12] J. Volmajer, R. Toplak, I. Leban, A.M.L. Marechal, Tetrahedron 61 (2005) 7012–7021.
[13] J.-A. Cheng, C.-P. Chang, C.-H. Chen, M.-S. Lin, J. Polym. Res. 12 (2005) 53–59.
[14] (a) J. Mei, N.L.C. Leung, R.T.K. Kwok, J.W.Y. Lam, B.Z. Tang, Chem. Rev. 115 (2015) 11718–11940;
(b) Y. Hong, Methods Appl. Fluoresc. 4 (2016) 022003;
(c) L. Mao, Y. Liu, S. Yang, Y. Li, X. Zhang, Y. Wei, Dyes Pigm. 162 (2019) 611–623.
[15] A.M. Brouwer, Pure Appl. Chem. 83 (2011) 2213–2228.
[16] (a) G. Zhang, X. Zhang, Y. Zhang, H. Wang, L. Kong, Y. Tian, X. Tao, H. Bi, J. Yang, Sens. Actuators B-Chem. 221 (2015) 730–739;
(b) L. Yan, Z. Kong, W. Shen, W. Du, Y. Zhou, Z. Qi, RSC Adv. 6 (2016) 5636–5640;
(c) L.Q. Yan, Z.N. Kong, Y. Xia, Z.J. Qi, New J. Chem. 40 (2016) 7061–7067;
(d) L. Yan, R. Li, W. Shen, Z. Qi, J. Lumin. 194 (2018) 151–155.
[17] (a) J. Wang, S. Xia, J. Bi, M. Fang, W. Mazi, Y. Zhang, N. Conner, F.-T. Luo, H.P. Lu, H. Liu, Bioconjugate Chem. 29 (2018) 1406–1418;
(b) X. Zhao, Y. Chen, G. Niu, D. Gu, J. Wang, Y. Cao, Y. Yin, X. Li, D. Ding, R. Xi, M. Meng, ACS Appl. Mater. Interfaces 11 (2019) 13134–13139.
[18] H. Li, Y. Yao, L. Li, J. Pharm. Pharmacol. 69 (2017) 1253–1264.

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