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Synthesis, optical properties, and cellular imaging of novel quinazolin-2-amine nopinone derivatives

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ABSTRACT

Quinazolin-2-amine derivatives (**4**–**6**) were successfully synthesized from β-pinene derivative nopinone and characterized by Fourier transform infrared spectroscope (FT-IR), nuclear magnetic resonance (NMR), mass spectrometry, and X-ray single crystal diffraction. Then, their optical and thermal properties were characterized with ultraviolet–visible spectroscopy, photoluminescence (PL) spectroscopy, thermogravimetric analysis, and confocal fluorescent microscopic imaging. Three target compounds had enhanced fluorescence in solid and solution states and fluorescent quenching occurred when acid or base was added to the solution. Thermal decomposition temperatures of compounds **4**–**6** were 138, 290, and 291 °C, respectively and no compound was cytotoxic to normal L02 hepatocyte cells, and confocal fluorescent microscopic imaging in human lung A549 adenocarcinoma cells was realized using these compounds. These new fluorescent compounds may be candidates for future fluorescent bio-imaging agents.

1. Introduction

Recently, organic fluorescent probes and organic light-emitting materials have received attention due to their potential applications. Many synthesized fluorescent compounds no longer are limited by emission quenching in a solid state and luminescent properties and thermal stability have been greatly improved [1,2]. Many fluorescent materials have been used for bio-imaging. For example, triphenylamine isophorone derivatives [3] and glycosylated cross-linked red fluorescent amphiphilic polymer [4] and multi-charged AuNP-block copolymer chromophores conjugates [5] have been synthesized for fluorescent visualization of Hela, A549 and B16-F10 cells, respectively.

Sensors are also important to bio-imaging [6]. After a cell-permeable derivative based on the structure of 7-hydroxyquinoline was synthesized and used to image Zn^{2+} in living cells [7], a similar Ir(III) based sensor ($ZIrdCF_3$) was applied for life time-based imaging of intracellular Zn^{2+} in HeLa cells [8].

Many natural products have good fluorescent properties: chalcone, coumarin, eumelanin biopolymer [9], and indicaxanthin natural dyes [10]. Thus, derivatives of these compounds have utility for optical materials. A chalcone derivative, dimethylaminochalcone, is a sensitive and selective fluorescent sensor for Fe^{3+} in DMF solution [11]. In addition, coumarin derivatives of 7-diethylamino-coumarin-3-carboxamide have been successfully synthesized, and they help to resolve emission quenching problems [12]. A TREN-type ligand probe incorporating a coumarin chromophore for Zn^{2+} has been reported [13]. 7-*N*,*N*-Diethylamino-3-(benzotriazol-1-yl)coumarins and triarylamines based on dehydroabietic acid methyl ester moieties may also be excellent candidates for applications in OLED devices [14,15].

β-Pinene is a natural compound with constituents that are used for medicine and perfume [16–18]. Nopinone is a derivative synthesized from β-pinene, and many nopinone derivatives have been synthesized such as chiral annulated indenes [19], nopinone-based triazole ketones [20], chiral 1,3-aminoalcohols and 1,3-diols [21]. However, luminescent materials synthesized from nopinone attract little attention but this is an unfortunate oversight: fluorescent materials can be made from nopinone which is renewable and these derivatives have applications in optical devices.

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2. Results and discussion

2.1. Synthesis

Quinazolin-2-amine derivatives (**4**–**6**) were synthesized directly from nopinone (Scheme 1). These novel compounds were characterized by MS, FT-IR, ^{1}H NMR, ^{13}C NMR. In addition, compound **5** was characterized by X-ray single crystal diffraction (Table S1, Supplementary data, and Fig. 1). These analyses confirmed **5** to be 5,6,7,8-tetrahydro-4-(3′-hydroxyphenyl)-7,7-dimethyl-6,8-methano-2-quinazolinamnie.

2.2. Optical properties

2.2.1. Solid state fluorescent properties

Some fluorescent compounds enhance fluorescence in a solution state, but quench fluorescence in a solid state, so fluorescent properties of solids should be studied. Fluorescent images of compounds **4**–**6** appear in Figs. 2a and S1 (Supplementary data). To study fluorescent intensity, a KBr pellet was obtained with a mixture of 1.0×10^{-6} mol compound **4** (**5** or **6**) and 1.0 g KBr. Photoluminescent (PL) emission spectra of compounds **4**–**6** are shown in Fig. 2b and c.

Fig. 2a depicts compounds **4**–**6** with enhanced fluorescence in a solid state. Compound **4** had strong fluorescent enhancement and emitted Kelly light. Meanwhile, compound **5** provided good fluorescence, was light-emitting and emitted blue light. Compound **6** weakly enhanced fluorescence, and emitted a blue light. Fig. 2b and c shows that compound **4** offered the best intensity (528 nm), and compound **5** had good intensity (371 nm), but compound **6** had little intensity (388 nm). A maximal emission peak of compound **4** was at longer wavelength, but the other two compounds peaked at shorter wavelengths which may explain compound **4**'s emission of Kelly light and the other two emitting blue light. Comparing fluorescent properties and all three structures the fluorescent intensity and colors were greatly affected by the position of –OH. A 2′-OH or 3′-OH substituent of the quinazolin-2-amine derivatives increased fluorescent intensity in the solid state.

2.2.2. Optical properties in solution

The three quinazolin-2-amine derivatives (**4**–**6**) were readily soluble in methanol, ethanol, isopropanol, ethyl acetate, trichloromethane, dichloromethane, toluene, and cyclohexane. Fig. 3 shows that ethanol solutions of three compounds could enhance fluorescence under a 365 nm UV light, and compounds **5** and **6** enhanced fluorescence and emitted a blue light. UV–visible absorption and fluorescent spectra of compounds **4**–**6** (1.0×10^{-4} mol/L) in these solvents were also provided (Figs. S2–S4). Compound **4** had an absorption peak at 306 nm in methanol, ethanol and isopropanol, and a red-shift from 306 nm to 334 nm and the absorbance intensity increased when compound **4** was dissolved in ethyl acetate, trichloromethane, dichloromethane, toluene, or cyclohexane respectively (Fig. S2a). The fluorescent intensity of compound **4** was greatly affected by solvents, with better fluorescent intensity after dissolution in isopropanol or ethanol (Fig. S2b). However, the absorbance at 311 nm and 316 nm of compounds **5** and **6** had no red-shift in different solvents (Figs. S3a and S4a). The peak fluorescent intensity of compound **5** changed little (Fig. S3b), and it had a weak fluorescent intensity in methanol and a strong fluorescent intensity in trichloromethane (Fig. S4b).

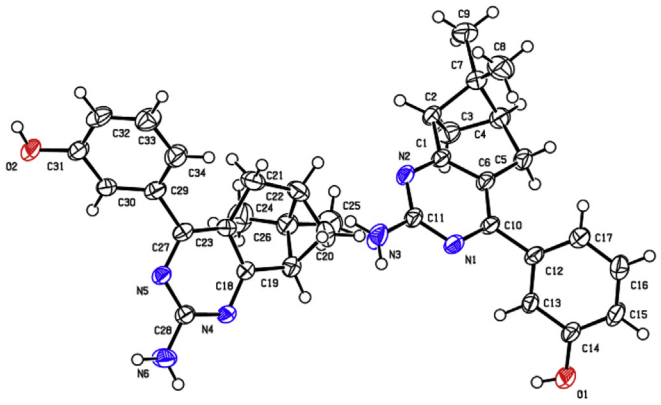
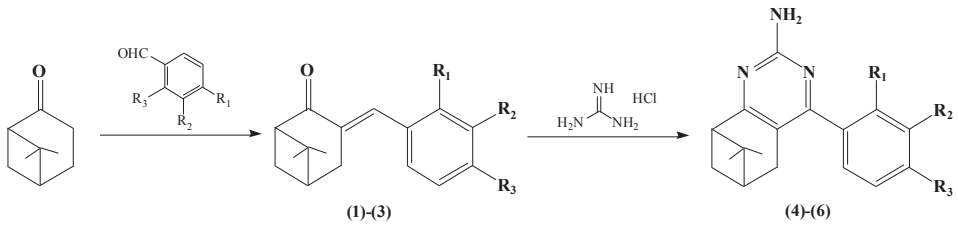


Fig. 1. X-ray crystal structure of compound **5**.

Water solubility is necessary for fluorescent probe applications, so we obtained UV–visible absorption and PL spectra for compounds **4**–**6** in ethanol/distilled water mixtures with different volume fractions of ethanol, keeping the final concentration constant at 1.0×10^{-4} mol/L (data appear in Figs. S5–S7).

Compound **4** had two absorption maximum peaks at 210 nm (greatest intensity) and 306 nm (Fig. S5a, b, Supplementary data). With the addition of ethanol, the 210 nm peak absorbance increased gradually and was maximal when the volume fraction of ethanol was 100%. However, the peak absorbance at 306 nm did not change. In comparison with compound **4**, compound **5** had two absorption maximum peaks at 210 nm and 311 nm (Fig. S6a, b, Supplementary data), and these peak changes were similar to those of compound **4**. Compared with compounds **4** and **5**, compound **6** had four absorption maximal peaks (207, 244, 270, and 316 nm; Fig. S7a, b). The 207 and 270 nm peaks increased consistently to a maximum, and the other peaks did not change as the volume fraction of ethanol increased. The –OH changed from 2′-OH to 4′-OH, and the absorption wavelength red-shifted from 306 nm to 311 nm, ending at 316 nm.

Shifts in fluorescent intensity were studied at a 300 nm excitation wavelength. Peak intensity of compound **4** decreased linearly



(1)-(3)

compound 1: R_1=OH, R_2=H, R_3=H
compound 2: R_1=H, R_2=OH, R_3=H
compound 3: R_1=H, R_2=H, R_3=OH

(4)-(6)

compound 4: R_1=OH, R_2=H, R_3=H
compound 5: R_1=H, R_2=OH, R_3=H
compound 6: R_1=H, R_2=H, R_3=OH

Scheme 1. Synthesis of quinazolin-2-amine derivatives (**4**–**6**).