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By Jia Li Zhao

Faculty mentor: Dr. Robert M. Strongin

Abstract

The synthesis and characterization of a new series of long wavelength and NIR-active dyes for use as diagnostic indicators in biological fluids has been carried out. The dyes are synthesized by a one-pot acid promoted condensation and isolated by flash column chromatography. Their structures are assigned by NMR and mass spectrometry. The spectral properties are evaluated by UV-vis and fluorescence spectroscopy. Preliminary spectroscopic data reveal these dyes exhibit anticipated characteristics that apparently meet the current requirements as NIR-active dye candidates for bioimaging and medical applications.

Introduction

Among the absorbing and emitting near infrared (NIR) dyes, there is only one that is FDA approved. Strongin¹ has recently reviewed the current literatures on the synthesis and evaluation of new NIR dyes including phthalocyanines, cyanines, and squaraines. These exhibit many outstanding properties, but their use in biomedical research may be restricted by aqueous insolubility, aggregation, small Stoke's shifts, and/or relatively larger molecular weight. Thus, there is a general need for simple innovative NIR-active dyes.² Xanthene dyes such as fluorescein are relatively non-toxic to humans; however, they are typically not NIR active. To help meet criteria for medical purposes, fluorophores in the xanthene series that are being developed in the Strongin group reveal a combination of desirable traits including 1) comparatively low molecular weight, 2) aqueous solubility, 3) dual excitation and emission in the forms of neutral and anionic species, 4) readily attainable changes in the regiochemistry of benzannulation and the ionizable groups resulting in tunable deep-red to NIR emission, and 5) large Stoke's shifts. The structures of SNAFR-5 (seminaphthofluorone) derivatives investigated in my research are depicted in Fig.1. Herein I describe studies of **2**.

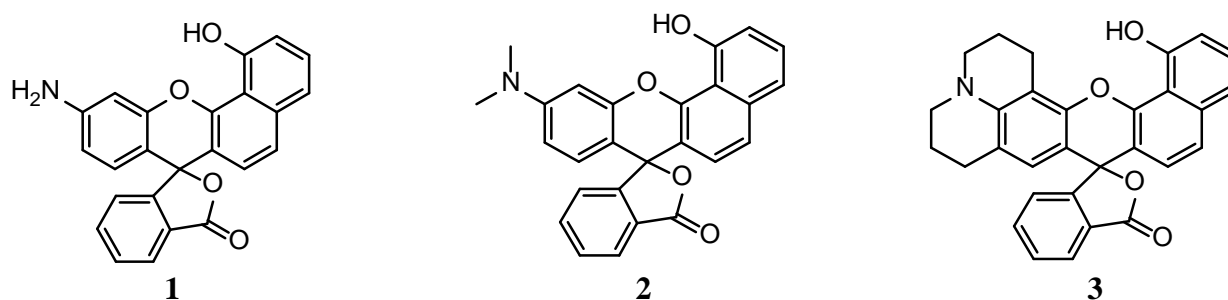
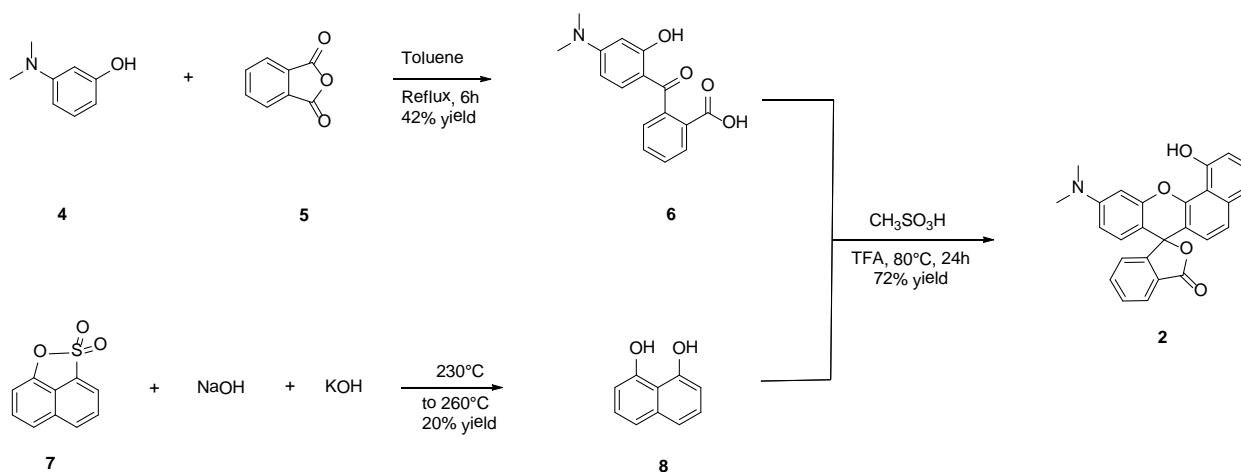


Fig.1. Structures of SNAFR-5 dyes

Materials and Methods

Shown in Scheme 1 is the synthesis of a new NIR-active derivative **2**. This method involved a one-pot condensation under acidic conditions of a hydroxyl benzophenone **6** with the corresponding dihydroxynaphthalene **8**. The corresponding hydroxyl benzophenone **6** is obtained by reaction of 3-dimethylaminophenol **4** with phthalic anhydride in toluene under reflux conditions. 1, 8-Dihydroxynaphthalene **8** is obtained by basic fusion of 1, 8-naphthosultone **7**. Compound **2** was isolated and purified by flash chromatography and characterized by ^1H NMR, ^{13}C NMR, and MS.

Absorption measurements and titrations were performed with a Cary 50 UV-Vis spectrophotometer. Absorption maxima were obtained for dye concentrations of 40, 20, 10, 5 and 2.5 μM . Titration samples were prepared with dye concentrations of 8 μM in 200 mM phosphate buffers of pH from 5 to 9. Extinction coefficients (ϵ) were determined by Beer's Law calculations; pK_a values were determined by linear regression analysis of the absorbance data obtained.



Scheme 1. Synthesis of new type [c] derivative

Result and Discussion

Synthesis

Shown in Figs. 2 and 3, ^1H NMR and ^{13}C NMR (Fig 2) data reveal the correlated structure of compound **2**. Shown in Fig. 4 is the MS data, the observed m/z is 410.1392, within 1.25 ppm mass accuracy, and there is a 72% yield.

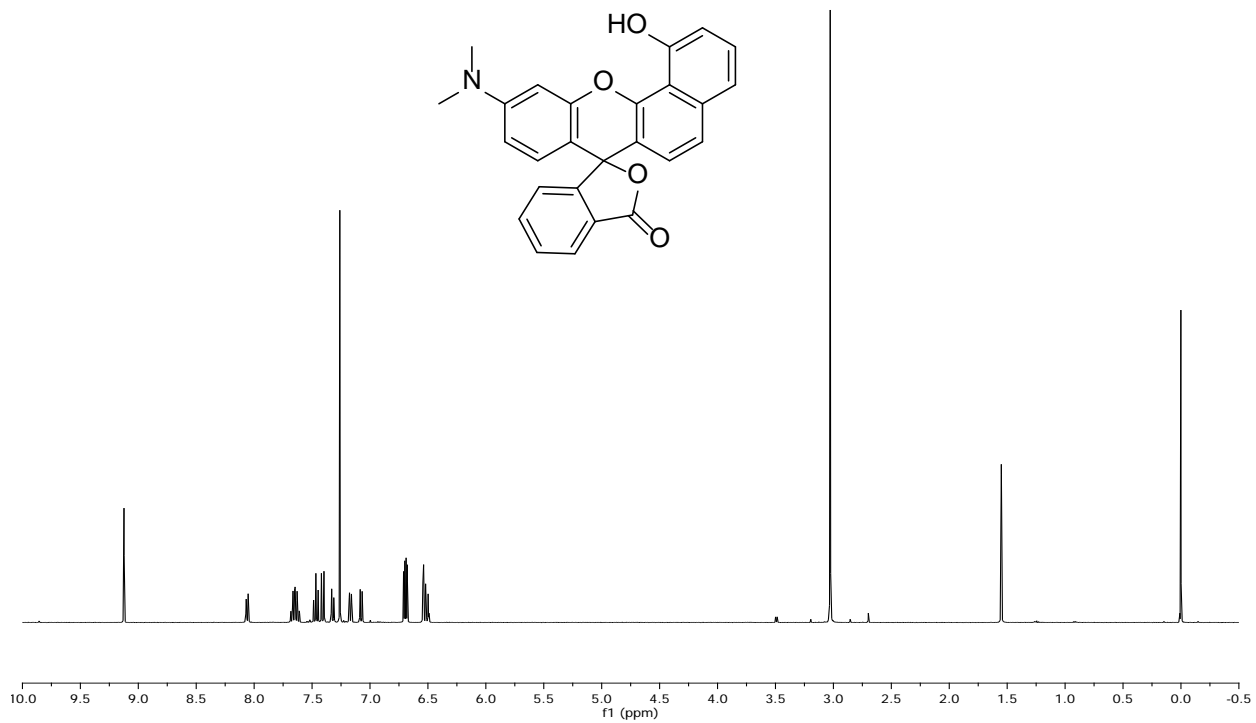


Fig. 2. ^1H NMR Spectrum of Compound 2

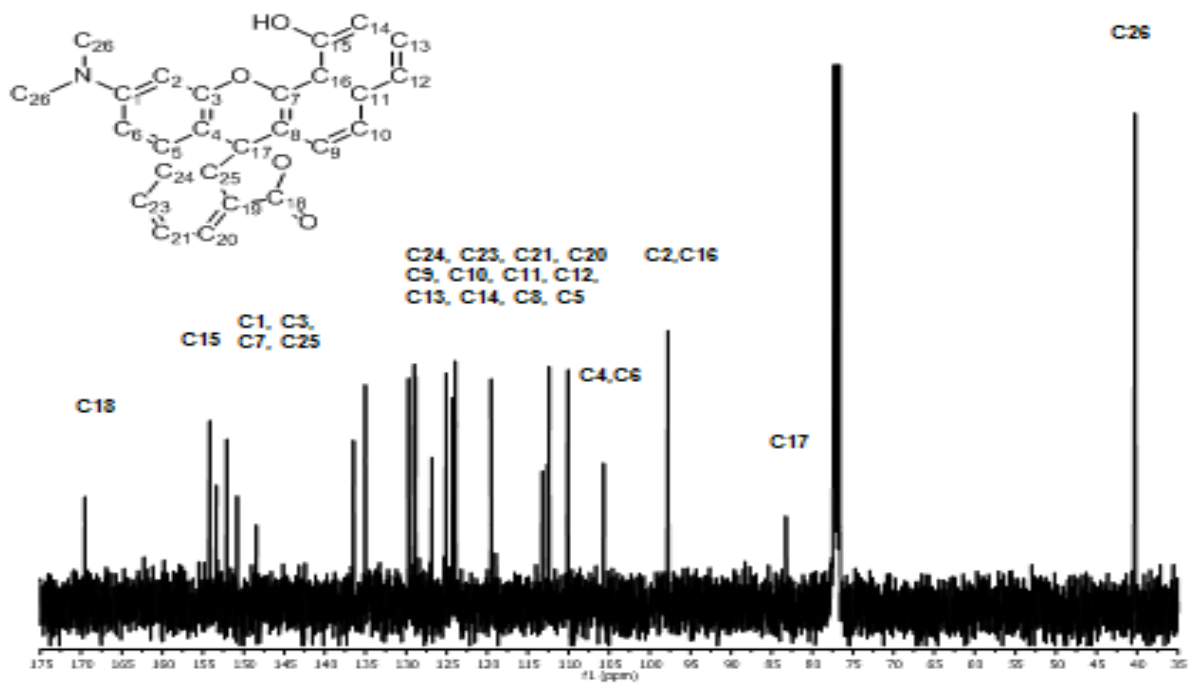


Fig. 3. ^{13}C NMR Spectrum of Compound 2

2010101106 #19-28 RT: 0.15-0.22 AV: 10 NL: 4.50E7
T: FTMS + p ESI Full ms [100.00-1207.87]

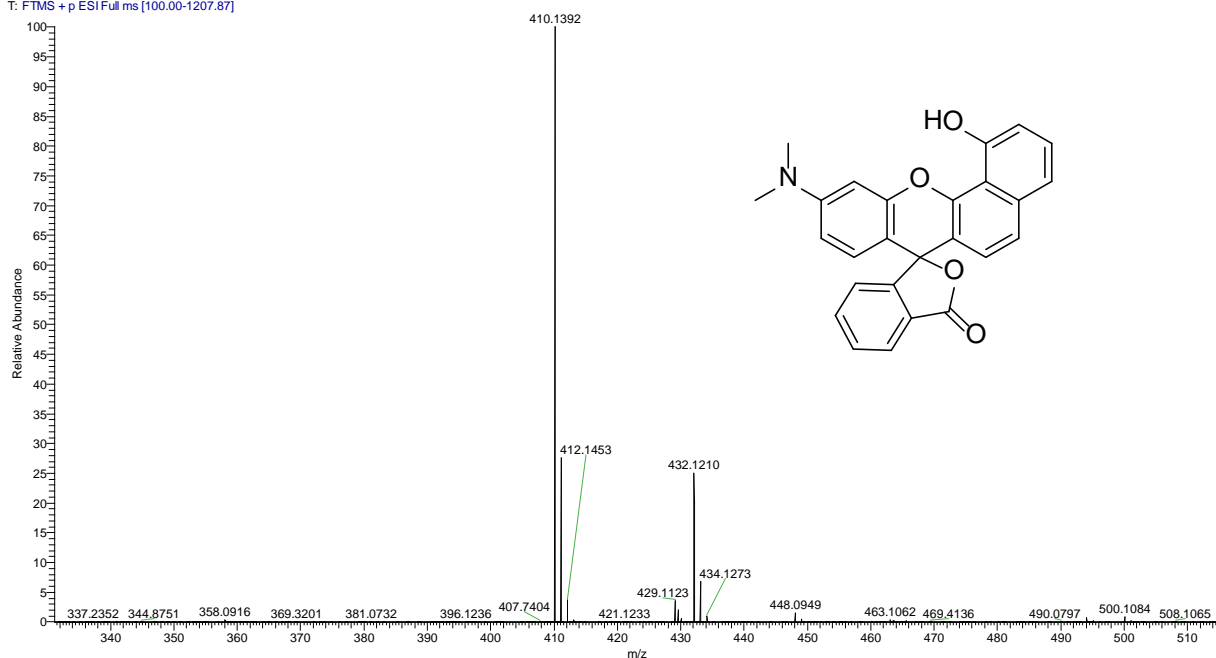
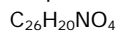


Fig. 4 HR ESI Mass Spectrum of Compound 2



m/z $[M+H^+]$ Calculated: 410.1386

m/z $[M+H^+]$ Observed: 410.1392

Mass accuracy: 1.25 ppm

Characterization

Extinction Coefficient

Standard calculation by Beer's Law, the extinction coefficient of compound **2** is obtained in 5%MeOH / 95%NaOH is $33048 \pm 591 \text{ cm}^{-1}\text{M}^{-1}$. This is a promising discovery. With this large extinction coefficient, absorbance of the dye in anionic form is extremely high, which will help for further characterization and analysis in biological fluid.

pKa Value

pKa values were obtained by linear regression analysis of the absorbance data. As shown in Fig. 5, compound **2** is pH sensitive in absorption intensity with good isosbestic points. The pKa value is calculated in anionic and cationic forms to be 7.0. Another promising finding, with this pKa value very close to neutral, it is could also be a very useful pH sensor in biological fluids.

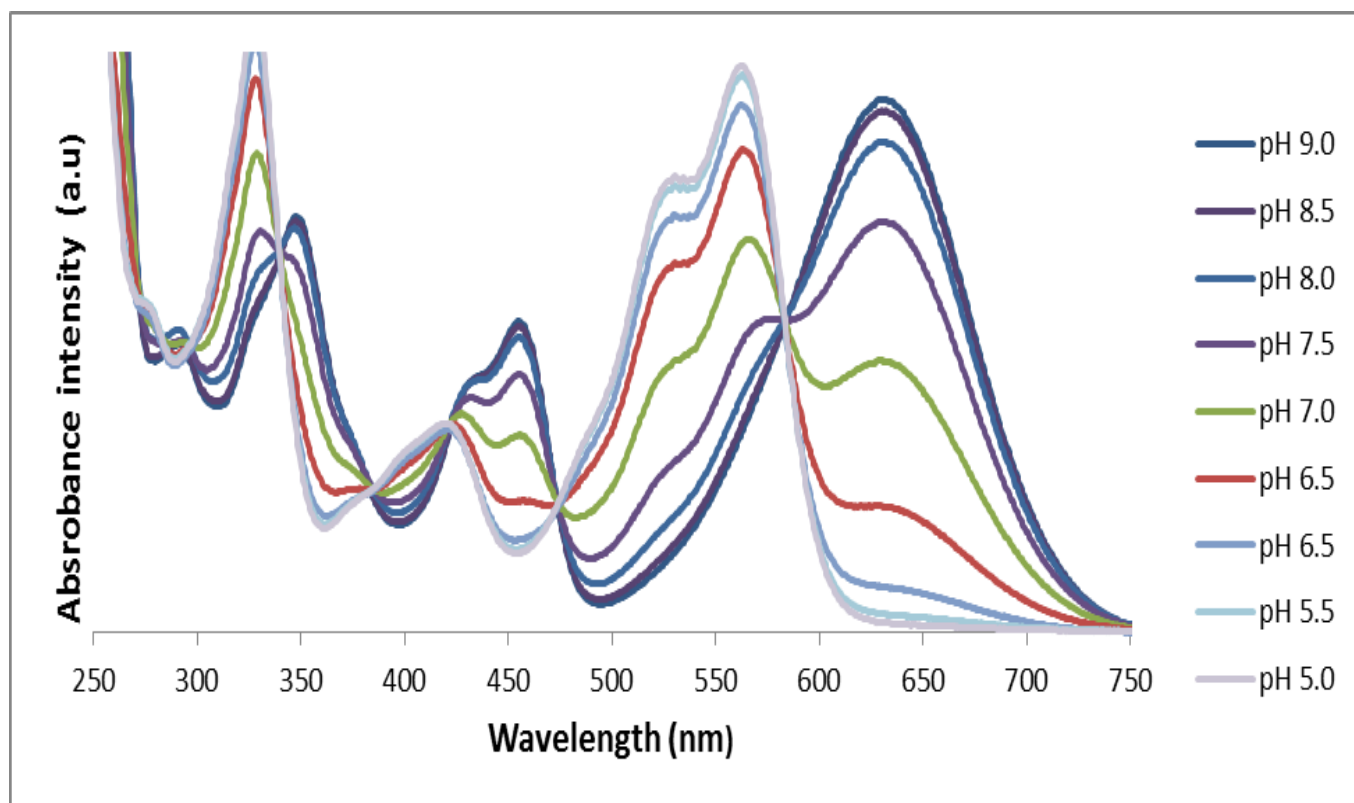


Fig. 5. Absorption spectra of 8 μ M compound 2 in 200 mM phosphate buffer solution of various pH

Additional characterization such as wavelength of maximum excitation and maximum emission, Stokes shift, quantum yields and Excitation-Emission Matrix (EEM) will be done on this series of seminaphthofluones before application studies in biological fluids.

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