Synthesis and characterization of novel 4*H*-pyran-4-ylidene indole-based heterocyclic systems for several optical applications

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Abstract: Two new quadrupolar 4*H*-pyran-4-ylidene fluorophores (**3**) derived from indole were prepared in good yields through condensation of 5-methyl-1*H*-indole-3-carbaldehyde with the acceptor precursors 2-(2,6-dimethyl-4*H*-pyran-4-ylidene)malononitrile (**1**) and 1,3-diethyl-dihydro-5-(2,6-dimethyl-4*H*-pyran-4-ylidene)-2-thiobarbituric (**2**), in the presence of a catalytic amount of piperidine. These building blocks were prepared by Knoevenagel condensation of the corresponding ketone precursor with malononitrile or 1,3-diethyl-dihydro-2-thiobarbituric acid. The new compounds were completely characterized by the usual spectroscopic techniques (UV-vis., FT-IR and multinuclear NMR - ^{1}H, ^{13}C).

Keywords: Indole, 4*H*-Pyran-4-ylidene; π-conjugated systems, Two-Photon Absorbing (TPA) chromophores.

1. Introduction

The development of organic materials displaying high two-photon absorption (TPA)[1] has attracted much attention in recent years due to a variety of potential applications in photonics and optoelectronics, such as three-dimensional optical data storage, fluorescence imaging, two-photon microscopy, optical limiting, microfabrication, photodynamic therapy, upconverted lasing, etc.[1b, 2] In view of biological applications, such as *in vivo* imaging, the advantages of a two-photon process play an important role as it leads to finer resolution and better in-depth tissue penetration, combined with reduced cell damage. As a consequence, two-photon microscopy experiences as an increasing popularity.[2c, 2d] The most frequently employed structural motifs for TPA materials are donor–π bridge–acceptor (D–π–A) dipoles, donor–π bridge–donor (D–π–D)

and acceptor–π bridge–acceptor (A–π–A) quadrupoles, octupoles, etc.[2a, 3] In particular, extended π-conjugated systems symmetrically substituted with electron-donating (D) and/or electron-accepting (A) functionalities have been revealed as efficient TPA dyes. On the basis of this general setting, many factors are relevant in increasing delta TPA, such as the efficiency of intramolecular charge transfer (ICT), the conjugation length, the molecular planarity, the dimensionality of the charge-transfer network, and the donating and withdrawing abilities of the electron donor and acceptor.[4]

In this work we present the synthesis and photophysical characterization of quadrupolar heterocyclic systems with potential application in materials and biological sciences as TPA chromophores. Indole is a versatile building block for the synthesis of heterocyclic systems for several optoelectronic applications (chemosensors, nonlinear optical, OLEDs) due to its photophysical properties and donor electron ability[5] and 4*H*-pyran-4-ylidene fragment is frequently used for the synthesis of red light-emitting materials.[6] On the other hand, 2-(2,6-dimethyl-4*H*-pyran-4-ylidene)malononitrile (**1**) and 1,3-diethyl-dihydro-5-(2,6-dimethyl-4*H*-pyran-4-ylidene)-2-thiobarbituric (**2**) units are usually used as strong acceptor moieties for the preparation of π-conjugated systems of the push-pull type.

Recently our research group has reported experimental and theoretical results concerning the synthesis and characterization of the optical properties of a large variety of functionalized heterocyclic systems with different optoelectronic applications such as OLEDs, second-order nonlinear optical chromophores, photochromic materials, etc.[7] Accordingly and as part of our continuing interest in developing chromophores for several optical applications, we report here the synthesis and characterization of two new derivatives of pyran-containing fluorophores **3a-b** of the type D–π–A–π–D bearing an indole donor system and two different acceptor moieties.

2. Experimental

2.1 Instruments

NMR spectra were obtained on a Varian Unity Plus Spectrometer at an operating frequency of 300 MHz for ^{1}H and 75.4 MHz for ^{13}C or a Brucker Avance III 400 at an operating frequency of 400 MHz for ^{1}H and 100.6 MHz for ^{13}C using the solvent peak as internal reference at 25 ºC (δ relative to TMS). All chemical shifts are given in Hz. Assignments were made by comparison of chemical shift, peak multiplicities and *J* values and were supported by spin decoupling-double resonance and bidimensional

heteronuclear HMBC and HMQC correlation techniques. IR spectra were determined on a BOMEM MB 104 spectrophotometer. UV-Visible absorption spectra (200-800 nm) were obtained using a Shimadzu UV/2501PC spectrophotometer. All melting points were measured on a Gallenkamp melting point apparatus. 2,6-(Dimethyl-4*H*-pyran-4-ylidene)malononitrile (**1**) was synthesized through the procedure described elsewhere.[6c] Other chemicals were common commercial grade and were used as received.

2.2 Synthesis of 1,3-diethyl-dihydro-5-(2,6-dimethyl-4*H*-pyran-4-ylidene)-2-thiobarbituric acid (2)

2,6-Dimethyl-γ-pyrone (8 mmol, 1.00 g) and 1,3-diethyl-2-thiobarbituric acid (12 mmol, 1.68 g) were dissolved in 10 mL of acetic anhydride and stirred for 2 h under heating at reflux. After cooling, the reaction mixture was poured into ice water. The precipitate was filtered and recrystallized from ethanol. Compound **2** was obtained as orange needles in 83% yield (8 mmol, 2.00 g). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.30–1.34 (t, 6H, 2× CH_3), 2.47 (s, 6H, 2× CH_3), 4.56–4.61 (s, 6H, 2× CH_3), 8.83 (s, 2H, 2x CH).

2.3 General procedure for the synthesis of 4*H*-pyran-4-ylidene derivatives (3a-b)

5-Methyl-1*H*-indole-3-carbaldehyde (0.16 mmol), 4*H*-pyran-4-ylidene precursors (**1-2**) (2 equiv, 0.32 mmol), and 2 drops of piperidine in 5 mL of dry acetonitrile were heated at reflux under nitrogen for 24 h with a Dean-Stark apparatus. The reaction mixture was cooled to room temperature. The yellow precipitate was filtered and washed with 10 mL of acetonitrile. The crude products were purified by recrystallization from methanol.

2-(2,6-Bis(2-(5'-methyl-1'H-indol-3'-yl)vinyl)-4H-pyran-4-ylidene)malononitrile (**3a**). Compound **3a** was obtained as a dark red solid (53 mg, 58 %). Mp > 300 ºC. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.48 (s, 6H, 2× CH_3), 6.85 (s, 2H, 2× H-3), 7.06 (dd, 2H, *J*= 8.4 and 1.2 Hz, 2× H-6'), 7.12 (d, 2H, *J*= 16 Hz, 2× Hβ), 7.37 (d, 2H, *J*= 8.4 Hz, 2× H-7'), 1.94–8.00 (m, 6H, 2× (H-2', Hα and H-4')), 11.75 (s, 2H, 2× N*H*). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ 21.3, 52.3, 104.1, 112.0, 112.2, 112.9, 116.8, 120.5, 124.2, 124.8, 129.9, 132.8, 132.9, 135.9, 156.3, 160.5. λ_{max} (THF) 450 nm. IR (nujol): υ 3277 (NH), 2205 (CN), 1629, 1298, 1198, 1187, 1132, 947 cm^{-1}.

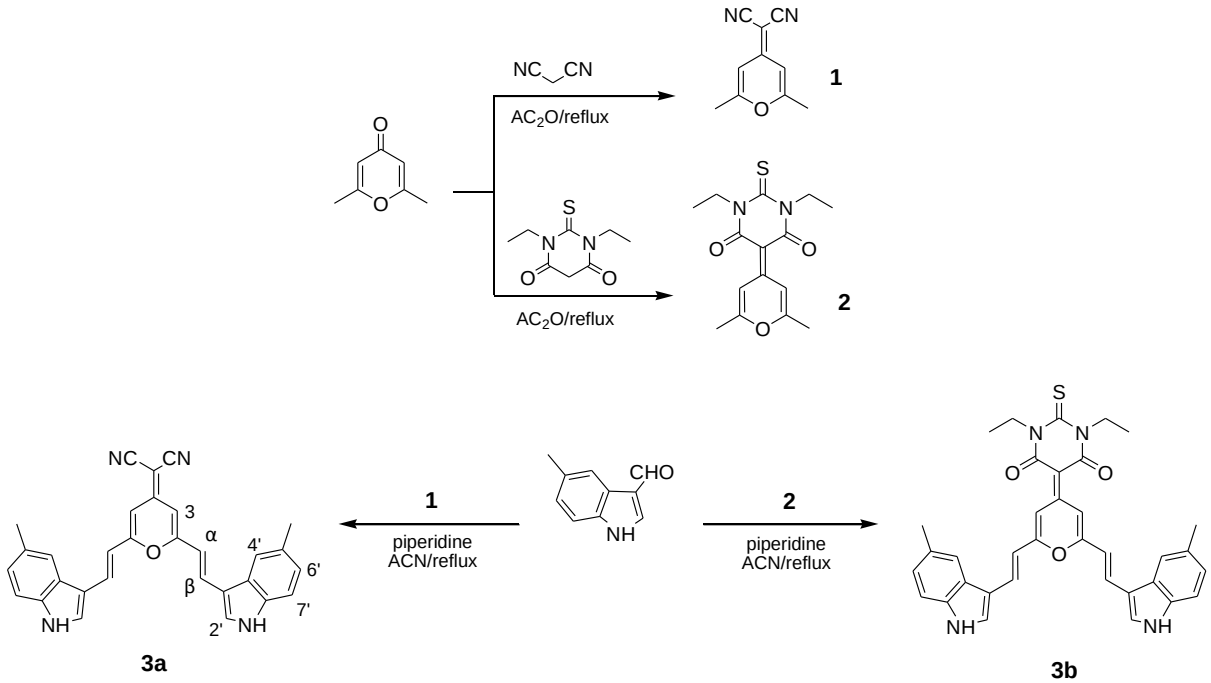
5-(2,6-Bis(2-(5'-methyl-1'H-indol-3'-yl)vinyl)-4H-pyran-4-ylidene)-1,3-diethyl-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (**3b**).

Compound **3b** was obtained as a dark purple solid (60 mg, 64 %). %). Mp > 300 ºC. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.20–1.24 (t, 6H, 2× CH_3), 2.49 (s, 6H, 2× CH_3), 4.46–4.51 (q, 4H, 2× CH_2), 7.06–7.12 (m, 4H, 2× (Hβ and H-6')), 7.37 (d, 2H, *J*= 8.4 Hz, 2× H-7'), 8.00 (s, 2H, 2× H-2'), 8.05–8.09 (m, 4H, 2× (Hα and H-4')), 8.76 (s, 2H, 2× H-3), 11.82 (s, 2H, 2× N*H*). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ 12.4, 21.3, 42.4, 94.1, 110.6, 112.1, 112.9, 113.1, 120.3, 124.4, 125.0, 130.2, 133.0, 133.6, 135.9, 156.6, 160.6, 162.7, 176.4. λ_{max} (THF) 497 nm. IR (nujol): υ 3283 (NH), 1661, 1612 (C=O), 1589, 1517, 1291, 1253, 1208, 1109, 956, 874, 796 cm^{-1}.

3. Results and discussion

3.1. Synthesis

The synthesis of 4*H*-pyran-4-ylidene D–π–A–π–D type fluorophores (**3a**-**b**) with two electron donor fragments was achieved in two steps: (*i*) addition of an electron acceptor fragment to the backbone by condensation reaction of 4*H*-pyran-4-one derivative with the active methylene group followed by (*ii*) condensation of the (hetero)aromatic aldehyde (donor part) with the acceptor moiety previously prepared (Scheme 1, Table 1).



Scheme 1. Synthesis of 4*H*-pyran-4-ylidene derivatives (**3a**-**b**).

Therefore, 2-(2,6-dimethyl-4*H*-pyran-4-ylidene)malononitrile (**1**) and 1,3-diethyl-dihydro-5-(2,6-dimethyl-4*H*-pyran-4-ylidene)-2-thiobarbituric acid (**2**) were synthesized by Knoevenagel condensation reaction of the corresponding ketone precursors with malononitrile or with 1,3-diethyl-dihydro-2-thiobarbituric acid. Then, 4*H*-pyran-4-ylidene fluorophores (**3a-b**) bearing indole as donor segment were prepared in moderate to good yields (58–64%) through condensation of 5-methyl-1*H*-indole-3-carbaldehyde with (**1**-**2**) in the presence of a catalytic amount of piperidine.

Table 1. Yields, UV-visible (in THF) and IR data for compounds (**3a-b**).

Comp.	Yield (%)	Reaction time (h)	IR (cm^{-1})	UV-Vis	
				λ_{max} (nm)	log ε
3a	58	1	3277 (NH) 2205 (CN)	450	4.34
3b	64	6	3282 (NH) 1612 (C=O)	497	4.28

3.2. UV-vis study

The UV-visible spectra of derivatives (**3a-b**) were recorded in tetrahydrofuran (10^{-4} M). Both chromophores exhibited broad and intense CT absorptions in the visible region at 450 nm and 495 nm, respectively. The position of this band was strongly influenced by the electronic nature of different acceptor group linked to the 4*H*-pyran-4-ylidene moiety. Therefore, chromophore (**3b**), bearing the stronger thiobarbituric acceptor group linked to the 4*H*-pyran-4-ylidene fragment, showed a marked red shift in its charge transfer (CT) band (497 nm) compared with the corresponding malononitrile derivative (**3a**) (450 nm) (Table 1, Figure 1).

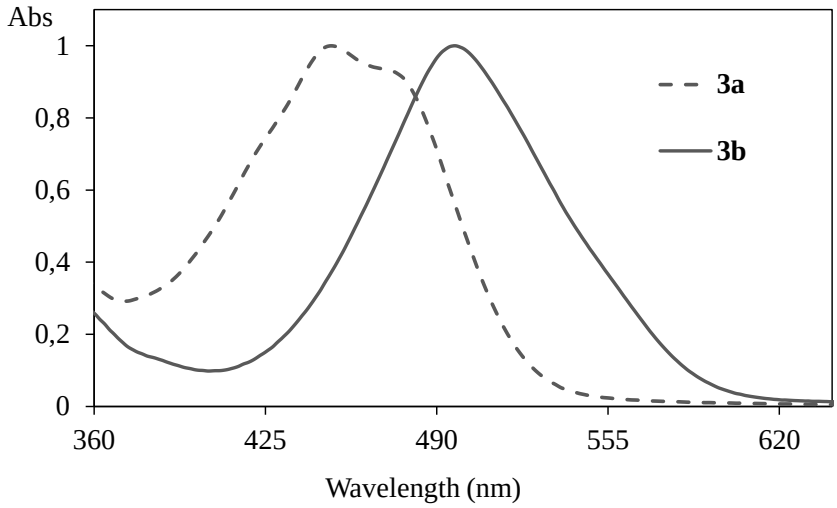


Fig. 1- Absorption spectra of 4*H*-pyran-4-ylidene derivatives (**3a-b**) in tetrahydrofuran at room temperature.

3.3. ^{1}H NMR analysis

The electronic nature of the acceptor groups has a clear influence on the ^{1}H NMR data of compounds (**3a-b**). For example, compound (**3a**) bearing a malononitrile acceptor moiety exhibited signals that are shifted upfield relative to the corresponding compound (**3b**) indicating the stronger acceptor ability of the thiobarbituric acceptor moiety when compared to the malononitrile group.

The most characteristic signals in the ^{1}H NMR spectra of 4*H*-pyran-4-ylidene derivatives (**3a-b**) are the singlets corresponding to the H-3 protons (6.86–8.76 ppm) and the signals of the indole NH, which were found between 11.75–11.82 ppm (Table 2).

The UV-Vis absorption data for compounds (**3a-b**) bearing malononitrile and thiobarbituric acid moieties reflected a charge separation in the ground state, confirming their push-pull character with a significant intramolecular charge transfer (ICT) from the donor indole heterocycle to the acceptor groups and a high polarizability of the whole donor-acceptor derivatives. This observation can be supported by the ^{1}H NMR chemical shifts data in these push-pull systems, as the chemical shifts of the protons in compound (**3b**) (bearing a stronger acceptor group linked to the 4*H*-pyran-4-ylidene spacer) exhibited signals that are downfield relative to compound (**3a**).

Table 2. Chemical shifts of protons of compounds (**3a-b**) in DMSO-d_6 at 400 MHz, in ppm.

Comp.	Hα	Hβ	NH	H-3	H-2’
3a	7.96	7.12	11.75	6.86	7.98
3b	8.07	7.10	11.82	8.76	8.00

4. Conclusions

New indole-based heterocyclic systems (**3a-b**) with a 4*H*-pyran-4-ylidene spacer functionalized with different acceptor moieties were synthesized in moderate to good yields using simple experimental procedures.

Modulation of the electronic and optical properties of compounds (**3a-b**) was achieved through the variation of the electronic acceptor ability of the 4*H*-pyran-4-ylidene precursor. Due to their push-pull character and marked acidity of NH protons, the new π-conjugated indole-based heterocyclic systems could have potential application in materials and biological sciences as TPA chromophores and/or as colorimetric chemosensors.

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