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Synthesis of novel Tröger's bases analogues. The first ones fluorescent by excited state intramolecular proton transfer (ESIPT)

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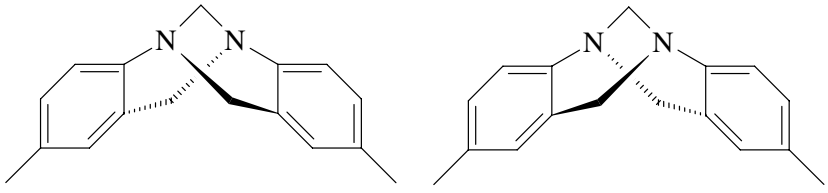
Abstract—Three new Tröger's bases, fluorescent by an ESIPT mechanism and with large Stokes shift has been synthesized from 2-(4′-amine-2′-hydroxyphenyl)benzazoles using urotropine and trifluoroacetic acid.

Tröger's base 2,8-bis(methyl)-6*H*,12*H*-(5,11)-methanodibenzo[*b*,*f*][1,5]diazocine, as presented in Figure 1, was firstly described by Julius Tröger[1] and was the first amine to be resolved.[2] Thus Tröger's base is a chiral molecule, with a C_2 axis, which exists in two enantiomeric forms (5*S*,11*S*)-(+) and (5*R*,11*R*)-(−).

Due to its relatively rigid chiral frameworks, the study of V-shaped Tröger's base in the construction of molecular receptors has become a very attractive research field.[3] The essential characteristic of a small molecule receptor is the concavity.[4] The great majority of synthetic receptors have used macrocyclic rings to enforce the formation of concave surfaces.[5] The rigid chiral concavity in Tröger's bases is maintained by intrinsic conformational constraints, produced without structural elements from these macrocyclic rings. The angle formed by the least-squares planes containing the two aryl rings depends on the ring substituents, varying from 92° to 104°.[6] So far, Tröger's base has been used for several interesting applications such as, synthetic receptors,[7] chiral solvating agent,[8] interaction with DNA,[9] biological,[10] and catalytic activity.[11]

Tröger's bases are well known to interact with DNA as well as benzazoles,[12] interesting compounds with many applications.[13] In this way, it was decided to synthesize Tröger's bases based on 2-(4′-amino-2′-hydroxyphenyl)benzazoles to be used as potential fluorescent molecular probes for DNA intercalators. 2-(2′-hydroxyphenyl)benzazoles are fluorescent compounds through an ESIPT phenomena with large Stokes shift ($\Delta\lambda$). In the ESIPT mechanism (Fig. 2), the UV light absorption by the enol ($\mathbf{E_0}$) produce the excited enol



(5S,11S)-(+) (5R,11R)-(-)

Figure 1. Tröger's base structure.

Keywords: Benzazoles; DNA intercalators; ESIPT; Proton transfer; Fluorescent probes.
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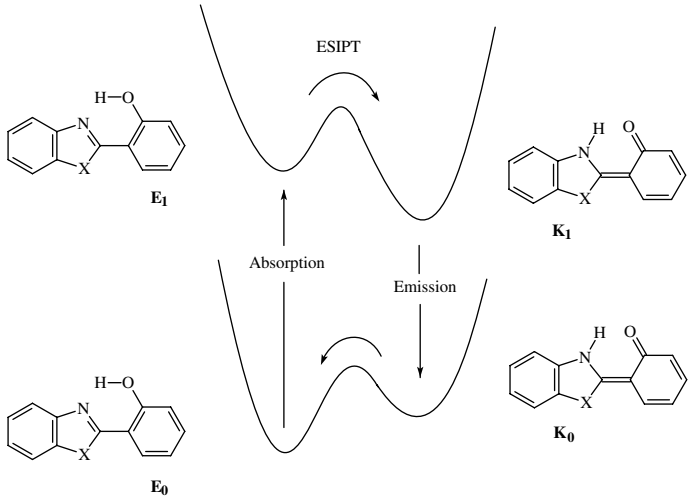


Figure 2. ESIPT mechanism for 2-(2′-hydroxyphenyl)benzazoles.

($\mathbf{E_1}$), which is quickly converted to an excited keto tautomer ($\mathbf{K_1}$) by an intramolecular proton transfer.[14] The excited keto tautomer ($\mathbf{K_1}$) decays emitting fluorescence to a keto tautomer in the ground state ($\mathbf{K_0}$). Since the enol conformer ($\mathbf{E_0}$) is more stable than the keto tautomer in the ground state, the initial enol form is regenerated without any photochemical change.[15]

The benzazoles **1a**–**c** were obtained using a methodology previously described.[16] The classical method involving formaldehyde in ethanol and HCl was initially tried for the preparation of Tröger's base derivatives. However, with this procedure, a complex mixture of products was obtained and only traces of Tröger's bases could be detected. Another methodology,[17,18] using urotropine and trifluoroacetic acid was then used to produce the products **2a**–**c** (Scheme 1), in three possible regioisomeric forms as presented in Figure 3.

With the benzazole **1a** only the regioisomer **A** was isolated as a product, since in the aromatic region of the ^{1}H NMR spectra of Tröger's base **2a**, a typical AB system can be seen in 7.44 and 6.76 ppm with a $J_{ortho} = 8.6$ Hz. Using the benzazole **1b**, the regioisomer **A** was also isolated as a product. The AB system can be seen at 7.80 and 6.83 ppm with also a $J_{ortho} = 8.6$ Hz. However, for **1c**, which involved longer reaction times, a mixture of regioisomers was observed. Despite our best efforts we have been unable to separate the regioisomers. The

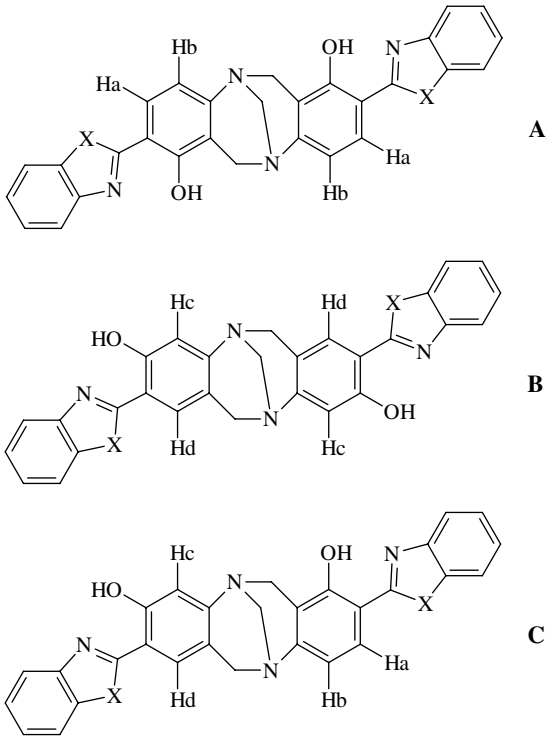
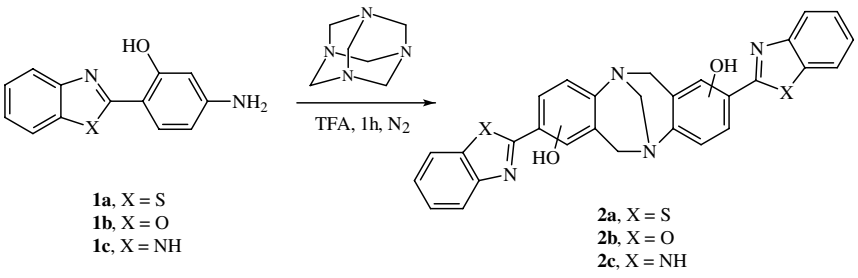


Figure 3. The three possible regioisomers that could be obtained.



Scheme 1. Tröger's bases synthesis.

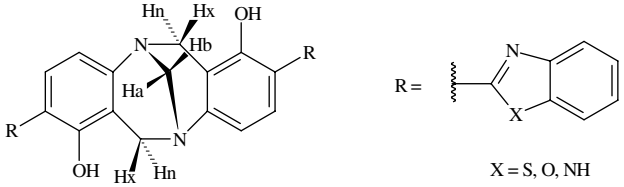


Figure 4. *exo* and *endo* Identification.

yields of the pure Tröger's bases were low, as expected [22% (**2a**), 18% (**2b**), and 20% (mixture of regioisomers **2c**)].

The stereochemistry of methylene protons in Tröger's bases **2a**–**b**, was determined by NOESY experiment. As previously observed the *exo* protons (H_x) (Fig. 4) resonate downfield from the *endo* protons (H_n).[19]

For all UV–vis and fluorescence measurements, spectroscopic grade solvents were used (Merck). The experiments were performed at room temperature in a dye concentration of 10^{-6} M. In Figures 5 and 6 are presented the normalized UV–vis absorption and fluorescence emission spectra of **2a** and **2b**, respectively. The compounds **1a** and **1b** are also depicted for comparison. Relevant data from photophysical characterization are showed in Table 1.

As can be seen in Figure 5, the observed UV–vis bands occur spectrally in agreement with the expected structure. All molar extinction coefficient values are in the order of 10^4 L mol^{-1} cm^{-1}, as expected of π–π^* transitions. The compound **2a** presented a bathochromic shift band (362 nm) with respect to the starting material **1a** (351 nm) in the UV–vis spectra. This is due to the more donating amino group in the benzazole moiety when compared to the hydrogens in the original compound.[20] A dual fluorescence can be seen in the fluorescence emission spectra for the dye **1a**, indicating the presence of another conformer in solution. An emission band at higher wavelengths can be detected with a maximum

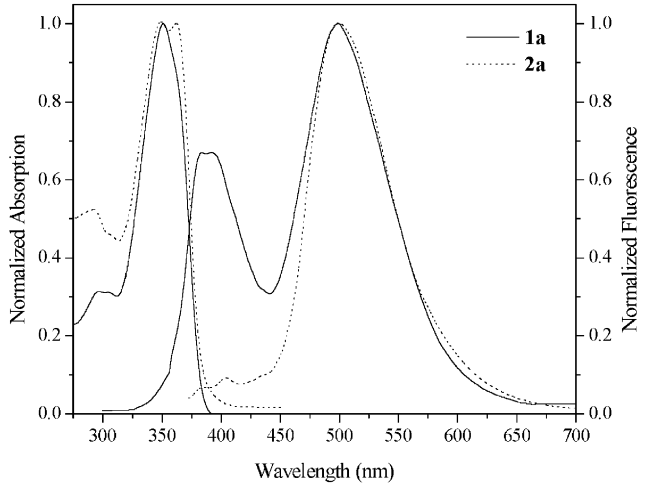


Figure 5. Normalized UV–vis absorption and fluorescence emission of **1a** and **2a**.

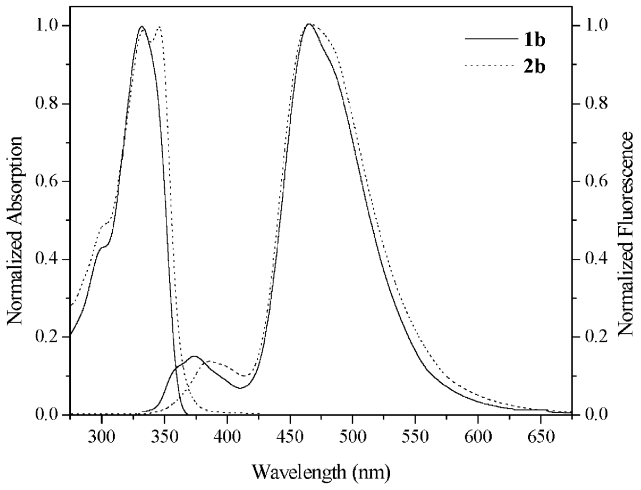


Figure 6. Normalized UV–vis absorption and fluorescence emission of **1b** and **2b**.

Table 1. UV–vis absorption and fluorescence emission data

Dye	λ_{max}^{abs} (nm)	$\varepsilon_{max} \times 10^{-4}$ (L mol^{-1} cm^{-1})	λ_{max}^{em} (nm)	$\Delta\lambda$ (nm)
1a	351	4.5	499	148
1b	332	2.8	467	135
2a	362	3.9	500	138
2b	346	3.2	467	121

located at 499 nm. This band is due to the excited keto tautomer ($\mathbf{K_1}$), which arises from the excited enol conformer ($\mathbf{E_1}$). It could also be seen another small band blue shifted at 389 nm, probably due to a conformer, which will emit fluorescence, by normal relaxation. A single fluorescence emission band can be seen in Tröger's bases **2a** at 500 nm. A Stokes shift ($\Delta\lambda$) of 148 and 138 nm could be observed for **1a** and **2a**, respectively.

In Figure 6, the same bathochromic shift can be seen, with Tröger's bases presenting a maximum wavelength of absorption at 346 nm and the original benzazole at 332 nm. The molar extinction coefficient values are also on the order of 10^{-4} L mol^{-1} cm^{-1}. Any difference in the maximum wavelength of the fluorescence emission between the benzazole and Tröger's bases could be detected (467 nm). Small blue shifted bands at 373 and 386 nm could be detected for **1a** and **2a**, respectively, with Stokes shift ($\Delta\lambda$) of 135 and 121 nm, respectively.

Quiral resolution and tests for interaction with DNA with Tröger's bases are in progress and will be reported elsewhere.

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18. *General procedure for the synthesis of Tröger's bases* (**2a**–**c**): A mixture of **1a** (or **1b**–**c**) (4.76 mmol), urotropine (4.76 mmol), and trifluoroacetic acid (10 mL) at 0 °C was then stirred for 1 h, under nitrogen, at room temperature. The mixture was poured into ice and neutralized with NH_4OH until alkaline pH (≈8). The precipitate was filtered, dried, and purified by column chromatography using dichloromethane and hexane (1:1) as the eluent. Compound **2a**: Yield: 22%. Melting point: >320 °C. IR (cm^{-1}): 3041 (ν_{arom} C–H), 2921 (ν_{as} CH_2), 2855 (ν_s CH_2), 1629 and 1475 (ν_{arom} C=C). ^1H NMR ($CDCl_3$) 300 MHz: δ (ppm) 7.44 (AB system, 2H, $J_o = 8.6$ Hz); 6.76 (AB system, 2H, $J_o = 8.6$ Hz); 4.74 (d, 2H, H_x $J = 17.1$ Hz); 4.56 (d, 2H, H_n $J = 17.1$ Hz); 4.31 (s, 2H, H_e and H_f). The exact molecular mass for $C_{29}H_{21}N_4O_2S_2$; $m/z = 521.11041 \pm 0.36383$ mD $[M+H^+]$ was confirmed by HRMS (MALDI). Compound **2b**: Yield: 18%. Melting point: >320 °C. IR (cm^{-1}) 3057 (ν_{arom} C–H), 2921 (ν_{as} CH_2), 2852 (ν_s CH_2), 1580 and 1549 (ν_{arom}C=C). ^1H NMR ($CDCl_3$) 300 MHz: δ (ppm) 7.80 (AB system, 2H, $J_o = 8.6$ Hz); 6.83 (AB system, 2H, $J_o = 8.6$ Hz); 4.67 (d, 2H, H_x $J = 17.1$ Hz); 4.51 (d, 2H, H_n $J = 17.1$ Hz); 4.35 (s, 2H, H_e and H_f). The exact molecular mass for $C_{29}H_{21}N_4O_4$; $m/z = 489.15573 \pm 1.34185$ mD $[M+H^+]$ was confirmed by HRMS (MALDI).
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