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Tautomeric enhancement of the hyperpolarizability in new acridine-benzothiazolylamine based NLO chromophores

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Abstract—The second order NLO response of a new family of acridine-based chromophores is greatly enhanced due to the presence of a tautomeric minor form with high charge-transfer capabilities.

1. Introduction

Within the field of photonics and opto-electronics[1] non-linear optics stands out due to its important technological applications. In the past few years, major advances in organic materials have led to compounds with high and fast nonlinearities. Push–pull organic chromophores, in which a conjugated π-system contains asymmetrically positioned electron-donor and electron-acceptor substituents, were the first and have been the most widely studied of these molecules.[2] The charge transfer between the functional groups imparts a high degree of polarity to push–pull systems. Nonlinearity in organic chromophores can be synthetically modulated by varying the composition or length of conjugated π-systems, and by evaluating the effects of various electron-donor and -acceptor groups. The literature contains numerous examples of these systems, for which high values of hyperpolarizabilities have been reported.[3] Optimized chromophores have generally been obtained via arduous synthetic pathways,[4] usually based on condensation reactions plagued by low regio- and stereo-selective control.

2. Results and discussion

The aim of the present study was to apply our experience in the synthesis of heterocyclic systems[5] to obtain and evaluate novel push–pull chromophores based on 2-nitroacridine as a π-conjugated system and on benzothiazol-2-yl-amino as an electron-donor group. We made this choice both are well-known systems with well-established synthetic methods, however, their nonlinear properties are rarely studied. From structural standpoint, the influence of the benzothiazol-2-yl amino moiety was expected to present some advantages, for instance, Marder[6] and others have shown that for push–pull systems, less-aromatic heterocycles correlate with high nonlinearities. In addition, the high thermal stability of these heterocycles is desirable for practical applications.

Secondary 2-aminobenzothiazoles have commonly been obtained by the reaction of the corresponding 2-halobenzothiazoles with the primary amines.[7] However, our syntheses comprised the reaction of 2-aminobenzothiazole and 6-fluoro-2-nitroacridine via aromatic nucleophilic substitution as described by Rosevear[7] because of the easy preparation of the 6-fluoro-2-nitroacridine, owing the strongly electron-withdrawing group, nitro group in position 2, useful for our purposes to prepare push–pull systems, and the previously reported method for the synthesis of 2-aminobenzothiazole-6-substituted,[8] a substitution pattern useful to enable polymer linkage of these molecules in later works. The major drawback of the Rosevear method for obtaining the target chromophores was the low nucleophilicity of 2-aminobenzothiazoles, which had to be made more reactive by employing an auxiliary base and a polar aprotic solvent. The best yields for the products **2**, **3**, and **4** were obtained when an equimolar ratio of reactants was used and the reaction was run at approximately 130 °C.

Keywords: Synthesis of nonlinear optical chromophores; Tautomeric equilibria; Surface determination of hyperpolarizabilities.
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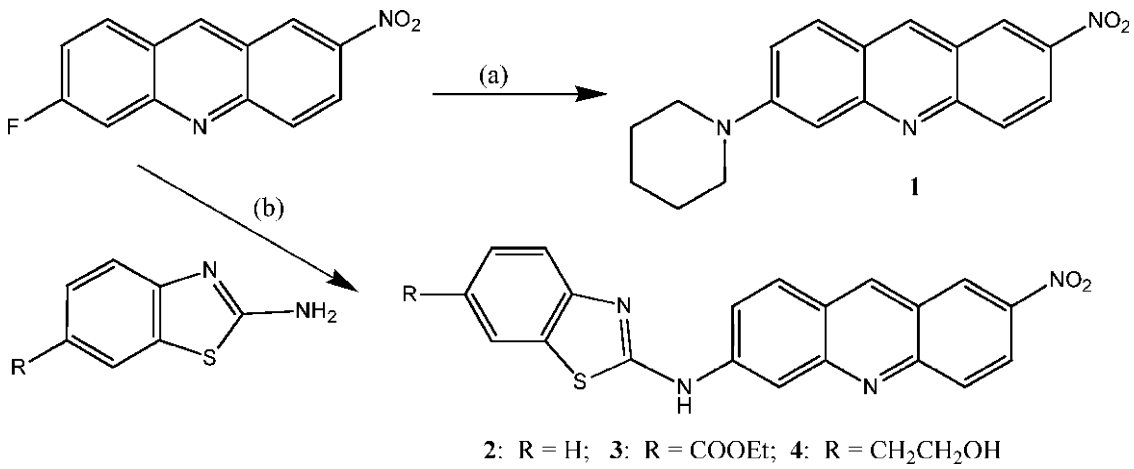

Scheme 1. (a) Refluxing piperidine, 1 h, (95%); (b) K_2CO_3, DMA or NMP, 130 °C, 4 h (55–65) %.

2-Nitro-6-(piperid-1-yl)acridine (**1**) was prepared and studied as a matter of comparison. Scheme 1 shows synthetic routes followed to obtain the chromophores.

The second order optical behavior of **2**, **3**, and **4**, exhibited marked differences as compared to that of **1**, for which the second harmonic generation was clearly inferior. Considering that in all cases the electron-donor group directly linked to the 2-nitroacridine moiety is an amine, the variation in response must be attributed to the presence or absence of the benzothiazole. As the benzothiazole system is slightly π-deficient, the 2-aminobenzothiazole group of chromophores **2**, **3**, and **4** was expected to have a lower electron-donating character than the piperidine present in **1** and, consequently, a lower NLO response. Surprisingly, the experimental results were the opposite. This contradiction may be explained by the existence of tautomeric forms of the 2-aminobenzothiazole moiety (Fig. 1).

Tautomeric equilibria in molecules that contain 2-amino-benzothiazole moiety have typically been described to be predominantly displaced to the aromatic form (Fig. 1a).[9] However, the minor tautomer, benzothiazolin-2-imine (Fig. 1b), could contribute to the hyperpolarizability in the cases of our molecules by increasing the donor strength of the benzothiazole system, because charge transfer increases stability by restoring aromaticity in the benzothiazole ring. This gain in aromaticity could imply an increase in the polarization of the ground-state, another important factor for reaching high hyperpolarizabilities.[10] Nonetheless, the spectroscopic data for our chromophores indicate a very fast tautomeric equilibrium that strongly favors the aromatic tautomer. Charge-transfer bands in the UV-absorption spectra of **2**, **3**, and **4** exhibit a hypsochromic displacement, whereas those of the spectra of **1** do not. This phenomenon suggested the presence of major aromatic tautomers, in which the slightly electron-deficient benzothiazole ring reduces the charge-transfer strength of the amino group. This conclusion was refined and completed by comparing ^{13}C NMR spectra of **2**, **3**, and **4** and their benzothiazole containing precursors with literature data.[9] Unfortunately the low solubility of our compounds in practically all

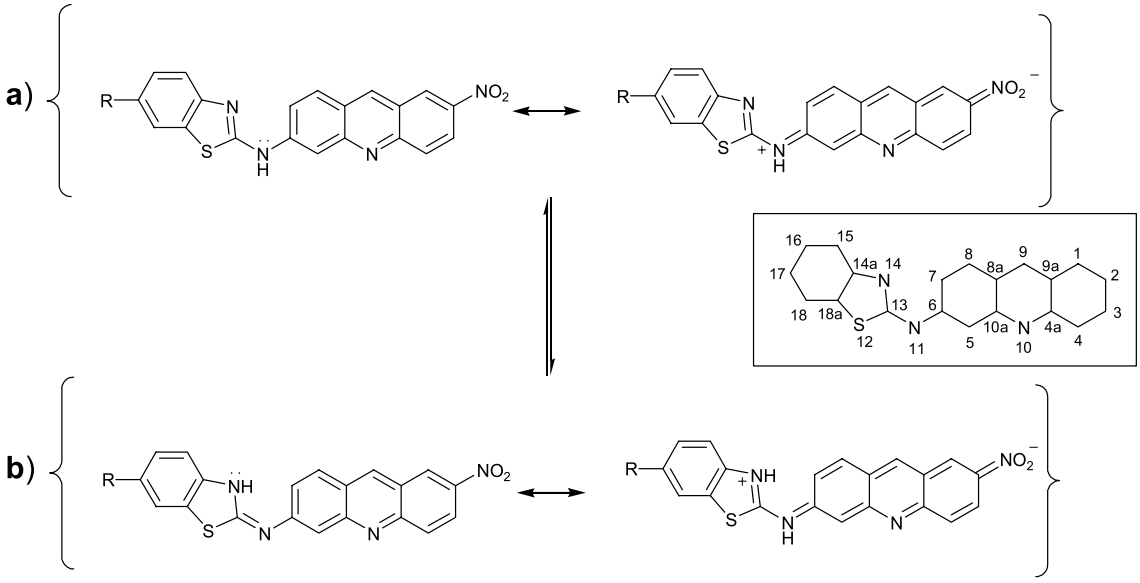

Figure 1. Tautomeric benzothiazol-2-yl-(7-nitroacridin-3-yl)amine (a) and (3*H*-benzothiazol-2-ylidene)-(7-nitroacridin-3-yl)amine (b) and their respective mesomeric forms.

solvents avoid us to perform low temperature and change of solvent NMR experiments to determine the tautomeric population. However, in the paper of Faure et al.,[9a] on prototropic tautomerism in benzothiazoles, the authors reported that the displacement to lower values of ^{13}C shifts for C4[11] upon passing from the aromatic to the non-aromatic tautomer enables the detection and relative quantification of non-aromatic tautomers of the heterocycles. For example, for 2-aminobenzothiazole, in which the aromatic tautomer dominates over the non-aromatic tautomer, C4-δ= 118.4 ppm. In 2-cyanamidebenzothiazole, in which the non-aromatic tautomer is favored but not exclusive, C4-δ=113.9 ppm. Lastly, in 3-methyl-3*H*-benzothiazol-2-yl-ideneamine, which exists in its purely non-aromatic form because tautomerism is blocked by the methyl group in N3, C4-δ=109.3 ppm. Thus, lower δ values translate to higher proportions of non-aromatic tautomers. Upon applying this rule to **2**, **3**, and **4**, a displacement to lower C15-δ values is observed: C15-δ=123.3, 121.8, and 116.6 ppm for **2**, **3**, and **4**, respectively. If we observe now the displacement of C4-δ from 2-aminobenzothiazole to ethyl 2-aminobenzothiazol-6-carboxylate and 2-amino-6-(2-hydroxyethyl)benzothiazole the values are 118.4, 120.0, and 117.9 ppm, respectively. Thus, when the 6-substituent is ethyl carboxylate, a downfield shift in C4 is observed with respect to that of 6-unsubstituted 2-aminobenzothiazole. In contrast, the 2-hydroxyethyl group as a 6-substituent has little or no influence on the C4 chemical shift, contrariwise to the observed in **2**, **3**, and **4**. As the 2-nitroacridine moiety is the same in all cases, the decrease in δ values observed in moving from **2** to **3**, and again from **3** to **4**, only can be explained by the increase in the population of non-aromatic tautomers.

Furthermore, the experimental values for NLO parameters conclusively agreed with the existence of a significant proportion of non-aromatic, imine-type tautomer. This form should present a much higher second-order NLO response than that of the more abundant amino-like tautomer. Spectroscopic data reveal that, under the conditions used, an equilibrium exists in, which the aromatic form dominates. However, if the amount of the non-aromatic tautomer is significant, it must contribute to a higher NLO response; hence higher proportions of the non-aromatic tautomer must yield higher NLO responses. Combining this reasoning with the ^{13}C NMR experimental data led us to the conclusion that lower C15-δ values correspond with higher NLO responses.

The nonlinear optical properties of the chromophores were measured via surface second harmonic generation (SHG).[12] The noncentrosymmetry at the interface between a glass surface and a monolayer of adsorbed molecules, whereby the molecules are uniformly distributed and free of interactions between them, can be used to obtain a considerable second harmonic output.[13] The adsorption of the monolayers of chromophores **1**–**4** and the reference compound 4-dimethylamino-4′-nitrostilbene (DANS) onto glass surfaces was performed by slow (1 mm s^{-1}) withdrawal of a glass plate from a solution of the corresponding molecule in 1-propanol.[14] If we assume that DπA chromophores **1**–**4** have an average rod-like geometry, the molecular nonlinear polarizability tensor would be dominated by the nonlinear axial coefficient along the molecular axis, and then the values for the dominant component of their corresponding microscopic hyperpolarizabilities can be determined.[15]

Briefly, the methodology used consists in measuring the TE and TM second harmonic intensities generated as a function of polarizations of the fundamental field.[16] The exact average orientation of each of the chromophores in the monolayer can be calculated from such measurements. By comparing these values with the measurements obtained for DANS under the same conditions, while taking into account its known hyperpolarizability $\beta(0)$, the values for the second-order nonlinear parameters of the new chromophores were obtained. For each case, the fraction of hyperpolarizability due to the absorption resonance had to be determined for the each chromophore and for DANS.[17] The results are summarized in Table 1.

Chromophores **1**, **2**, and **3** actually exhibited the rod-like nonlinear behavior necessary for the method used to determine static hyperpolarizability. However, a large deviation from said behavior was observed for **4**. The size and conformational freedom of the 2-hydroxyethyl chain enables interaction of the hydroxyl groups with the glass plate surface. The interaction of both hydroxyl and nitro groups with the glass surface confers an angular shape to the adsorbed molecules, whereby the amino group rests at the vertex of the resulting angle that effectively divides each molecule into two sections. Each half-molecule gives an independent NLO response, and the superposition of both vectorial responses leads to non-standard behavior. Hence, neither an average angle of orientation for the adsorbed molecules nor a representative hyperpolarizability value could be obtained in this case. Therefore, only the non-vanishing nonlinear second-order tensor components d_{15}, d_{24}, and d_{33} were possible to determine. The values are given in Table 1. However, the 6-(hydroxyethyl) group in **4** were expected to have a minimal effect on the electronic structure of the π system of the molecule and, consequently, on its NLO properties, and we can legitimately expect an optical behavior similar to **2** and **3**, as, in fact, is observed in

Table 1. NLO parameters of new acridine-benzothiazolylamine chromophores, including DANS as term of comparison

Molecule	λ_{max} (nm)	d_{15} ($\times 10^{-29}$ esu)	d_{24} ($\times 10^{-29}$ esu)	d_{33} ($\times 10^{-29}$ esu)	$(L\cdot\beta)/(L\cdot\beta)_{DANS}$	DπA length, L (Å)[a]	$\beta(0)$ ($\times 10^{-30}$ esu)
1	476	3.92	3.92	6.02	1.18	10.815	43
2	437	3.98	3.98	5.37	1.26	10.795 (12.791)	78
3	430	3.87	3.87	6.40	1.41	10.761 (12.421)	93
4	437	7.83	4.49	4.74	—	10.765 (12.726)	—
DANS	432	3.53	3.53	8.46	1	12.920	55

[a] Values in brackets are the lengths of non-aromatic tautomers.

the calculated values of the hyperpolarizability tensor components (Table 1).

The dipole length of each chromophore was determined using a semi-empiric (AM1) calculation of the geometry of the appropriate charge-separated resonance form. The most widely accepted value for the static hyperpolarizability $\beta(0)$ of DANS is 55×10^{-30} esu.[18] The ratio $(L\cdot\beta)/(L\cdot\beta)_{\mathrm{DANS}}$, in which the hyperpolarizabilities β are wavelength-dependent, can be calculated from the experimental results. In order to determine the static hyperpolarizability $\beta(0)$ of the new chromophores from this ratio, the absorption correction factor derived from the two-state model for the hyperpolarizability must be included.[16] These calculations were far less challenging for the case of **1** than for **2**, **3**, and **4**, all of which contain the benzothiazol-2-yl-amino moiety and are therefore complicated by the presence of two possible tautomers. In addition to unique electronic distributions, each of these tautomeric forms has a corresponding SH that generates a dipole of particular length. Both tautomers must be present in the working mixture, and determining the relative tautomeric populations, as well as the length of the charge-transfer system necessary to calculate the value of β, is not trivial. As previously explained, the position of the tautomeric equilibria could not be established, and was most likely different in solution than in the adsorbed sample, as well as being related to the length of the push–pull system. Fortunately, the second-harmonic generation only depends on the length of dipolar electronic distributions, as shown by Shen,[19] with little or no influence of atoms that do not contribute to resonance. In other words, the dipole 'starts' in the first atom contributing to the resonance of the conjugated system and 'finishes' in the last, functioning independently of atoms that do not contribute to the resonance.

When we combined the aforementioned considerations with the assumption that the aromatic tautomer (i.e., benzothiazol-2-yl-amino) is the predominant form, we established that for all cases, the dipole length is the distance from the nitrogen atom that bridges the acridine and benzothiazole to the oxygen atoms of the nitro group, and is not influenced by the benzothiazole system. In fact, Moylan[20] prepared a broad group of push–pull chromophores, in which the dialkylamino electron-donor groups were substituted by diarylamino groups, obtaining similar SHG values, or in some cases, slightly lower NLO responses due to the lower electron-donating character of the diarylamino groups. We calculated the dipole distances and used them to determine the NLO parameters of our chromophores.

Chromophores **2**, **3**, and **4** should behave similarly to **1** because the electronic distributions of the push–pull systems should themselves be similar. Alternatively, slightly lower intensities could be observed for **2**, **3**, and **4** as compared to **1**, which would be consistent with the findings of Moylan for dialkyl-diarylamino derivatives. Surprisingly the NLO responses of **2**, **3**, and **4** were all greater than that of **1** by nearly 20%. This difference becomes even greater if the relatively higher absorbance at 532 nm for **1** is taken to contribute positively to the final SHG observed. These SHG enhancements can only be caused by the existence of minor tautomeric forms capable of acquiring a stabilized, highly polarized charge-transfer state. Taking into account that spectral characterization did not allow quantification of tautomeric forms, the calculations were performed under the assumption that the dipole length, as previously defined, is approximately the same in all cases (see, Table 1). It is should be noted that the calculated lengths of non-aromatic tautomer dipoles are approximately 2 Å (i.e., ca. 20%) longer than aromatic ones. Hence, in using the ratio $(L\cdot\beta)/(L\cdot\beta)_{\mathrm{DANS}}$ to calculate $\beta(0)$ from the observed SHG, the values obtained for $L_{\mathrm{chromophore}}$ should be inversely proportional to those for $\beta(0)_{\mathrm{chromophore}}$ if all other data are held constant. As the experimental β values were clearly higher than expected, it can be deduced that the β of the longer, minor non-aromatic tautomers are larger than the aromatic ones by at least one order of magnitude.

Static hyperpolarizability [$\beta(0)$] results are shown in the last column of the Table 1. In molecule **1**, a considerable decrease in comparison with β at 1064 nm is observed, in which the $\beta(0)$ was 20% lower than that of the reference compound DANS. Similar decreases were not observed for the other chromophores, in which the enhancement due to the absorption resonance effect is much lower. Chromophores **2** and **3** had $\beta(0)$ values of ca. 142 and 169%, respectively, in relation to DANS and, more importantly, 181 and 216%, respectively, in relation to **1**. The larger value observed for **3** is probably due to an additional favorable effect on the tautomeric equilibrium stemming from the carboxylate group at the position 6. Similar tensor components values were obtained for **2**, **3**, and **4**, indicating that, most likely, the nonlinear polarizabilities of all of them are similar. It should be noted that in the majority of light polarization combinations, the nonlinear performance of **4** would be better or equivalent to that of chromophores **1**–**3**, since the d_{15} and d_{24} values for **4** are larger than the those corresponding to **1**–**3**, and only the d_{33} of chromophore **4** was 25% lower than that of **3**, the best chromophore between **1**, **2**, and **3**.

3. Conclusions

Several new NLO push–pull chromophores have been synthesized via a facile, two-step procedure and their second-order optical behavior was evaluated. The SHG capability of molecules with the benzothiazol-2-yl-amino electron-donating group is considerably enhanced in relation to the analogous piperidyl compound. This phenomena is due to the contribution of a minor non-aromatic tautomer. These tautomers, previously described in the literature, have a less aromatic ground state that enables an aromatic, stabilized and highly polarized charge-transfer state. The $\beta(0)$ of such chromophores are considerably higher than those of similar organic molecules. The surface method used to determine the hyperpolarizability of test compounds was validated and shown to be facile as well as rapid for common DπA rod-like type molecules. Chromophore **4**, with a 2-hydroxyethyl side group, exhibited abnormal optical behavior due to its comb-shaped, non-rod-like geometry in the monolayer due to the simultaneous interaction of nitro and hydroxyl groups with

the glass slide used to perform the measurements. However, **4** has hyperpolarizability tensor component values equal to, or even larger than, those of chromophores **2** and **3**.

4. Experimental

4.1. General

Melting points were determined using a Köfler apparatus equipped with a Reichert Thermovar microscope and are uncorrected. TLC was carried out on SiO_2 (Alugram SIL G/UV_{254} Macherey–Nagel 0.25 mm) and visualized with UV light. Flash chromatography was carried out on SiO_2 (Silica Gel 60 A CC, Merck). Organic extracts were dried over anhydrous $MgSO_4$, and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. NMR spectra were measured with Varian Gemini-200 (200 MHz) and Varian Unity-300 (300 MHz) spectrometers, data are given in δ/ppm and referenced to TMS for ^{1}H NMR and to $CDCl_3$ (77.0 ppm) for ^{13}C NMR, and J values are given in Hz. Mass spectra were measured in chemical ionization (CI, NH_3) mode with a Hewlett-Packard 5988A spectrometer, or with a Fisons VG-Quattro spectrometer. The samples were then introduced into a matrix of 2-nitrobenzyl alcohol for FAB analysis.

4.1.1. Synthesis of 6-fluoro-2-nitroacridine.[7] 6-Fluoro-2-nitroacridine was synthesized following the method described in the reference 7 with slightly modifications. 2-Fluoro-5-nitrobenzaldehyde (1.185 g, 7 mmol), 3-fluoroaniline (1.556 g, 14 mmol) and 2 ml of triethylamine were dissolved in 20 ml DMSO and heated to 100 °C under nitrogen atmosphere for 4 h, at which point the reaction mixture was poured into 100 ml of water. The precipitate was filtered off and thoroughly washed with water. The solid was then dissolved in 25 ml of ethanol and 5 ml of dichloromethane, and 5 ml of concentrated hydrochloric acid were subsequently added to the solution. The reaction mixture was refluxed for 30 min, and then poured into 150 ml of a 15% solution of ammonium hydroxide, which precipitated out a pale yellow solid. The solid was filtered off, washed with water and vacuum pump dried. The low solubility of the desired product in ethyl acetate was exploited for the purification. Hence, the solid was solved in a mixture of dichloromethane and ethyl acetate, and the solution was vacuum distilled until the pure title product precipitated. The precipitation was completed by maintaining the solution at 5 °C for a few hours. After several precipitations, 1.215 g (72% yield) of the product was collected; mp 237–238 °C (lit. 237–239 °C). TLC (SiO_2, CH_2Cl_2) R_f=0.48; ^{1}H NMR ($CDCl_3$, TMS_{int}): δ_H (ppm)= 9.02 (s, H8 and H9, 2H), 8.53 (dd, H3, J^{3-4}=10 Hz, J^{3-1}= 3 Hz, 1H), 8.31 (d, H4, J^{4-3}=10 Hz, 1H), 8.11 (dd, H8, J^{8-7}=10 Hz, $J^{8\text{-}F}$=6 Hz, 1H), 7.87 (dd, H5, $J^{5\text{-}F}$=10 Hz, J^{5-7}=2 Hz, 1H), 7.48 (ddd, H7, J^{7-8}=$J^{7\text{-}F}$=10 Hz, J^{7-5}= 2 Hz, 1H); ^{13}C NMR (CD_3OD, TMS_{int}): δ_C (ppm)=165.22 (C6, J^{C-F}=245 Hz), 151.47 (C4a), 149.80 (C2), 144.93 (C10a, J^{C-F}=10 Hz), 142.33 (C9), 133.15 (C8, J^{C-F}= 11 Hz), 130.71 (C4), 127.59 (C1), 124.87 (C9a), 124.81 (C3). 124.41 (C8a), 119.72 (C7, J^{C-F}=28 Hz). 111.66 (C5, J^{C-F}=21 Hz); FTIR (film): ν=1620, 1508, 1341, 1168, 822 cm^{-1}; MS (CI, NH_3): m/z=243.0 ($[M-H]^+$, 100%); HRMS (FAB+): m/z observed 243.056592, calculated for $C_{13}H_8N_2O_2F$ 243.056981.

4.1.2. Synthesis of 2-nitro-6-(piperid-1-yl)-acridine (1). 6-Fluoro-2-nitroacridine (242 mg, 1 mmol) was suspended in 5 ml of piperidine, and the mixture was heated to reflux for 1 h. The resulting red solution was cooled to room temperature and poured into 100 ml of water. The crude product was extracted with dichloromethane (3×100 ml), the organic layer was dried over anhydrous sodium sulfate and evaporated, and the resulting residue was flashed through a short pad of silica gel using dichloromethane as eluent. A major fraction was collected and concentrated by evaporation to afford 291 mg of an intense-red solid; mp 199–200 °C. TLC (SiO_2, DCM) R_f=0.21; ^{1}H NMR ($CDCl_3$, TMS_{int}): δ_H (ppm)=8.83 (d, H1, J^{8-6}=3 Hz, 1H), 8.60 (s, H9, 1H), 8.38 (dd, H3, J^{3-4}=10 Hz, J^{3-1}= 3 Hz, 1H), 8.06 (d, H4, J^{4-3}=10 Hz, 1H), 7.80 (d, H8, J^{8-7}=9 Hz, 1H), 7.40 (dd, H7, J^{7-8}=9 Hz, J^{7-5}=2 Hz, 1H), 7.27 (d, H5, J^{5-7}=2 Hz, 1H), 3.54 (m, –N(CH_2)$_2$–, 4H), 1.75 (m, –(CH_2)$_3$–, 6H); ^{13}C NMR ($CDCl_3$, TMS_{int}): δ_C (ppm)=154.00 (C3), 153.51 (C4a), 150.73 (C10a), 143.14 (C7), 138.12 (C8), 129.75 (C5), 129.59 (C1), 126.34 (C9), 123.28 (C6), 122.70 (C8a), 122.66 (C9a), 121.04 (C2), 106.30 (C4), 49.27 (–N(CH_2)$_2$–), 25.68 (–CH_2–), 24.66 (–CH_2–); UV vis (CH_2Cl_2) λ_{max} (nm)=476 (ε=19,500), 312 (ε=25,100), 270+(ε=41,500); MS (CI, NH_3): m/z= 308.1 ($[M-H]^+$, 100%); HRMS (FAB+): m/z observed 308.139926, calculated for $C_{18}H_{18}N_3O_2$ 308.139902.

4.1.3. Synthesis of ethyl 2-aminobenzothiazole-6-carboxylate.[21] Ethyl *p*-aminobenzoate (5.000 g, 30 mmol) was dissolved in 40 ml of acetic acid, and to the resulting solution was suspended sodium thiocyanate (9.720 g, 120 mmol). A solution of 1.50 ml of bromine in 20 ml of acetic acid was slowly added, and the reaction mixture was stirred at room temperature overnight. A mixture of 100 ml of 30% aqueous ammonium hydroxide and 200 ml of water was then added, and the crude product was extracted by ethyl acetate (5×100 ml). The organic layer was dried over sodium sulfate and concentrated by evaporation, and the resulting solid was purified by flash chromatography (silica gel, 1:4 CH_2Cl_2/ethyl acetate) to obtain 5.970 g of the desired 2-aminobenzothiazole-6-carboxylate; mp 242–243 °C (lit. 243 °C). TLC (SiO_2, AcOEt/CH_2Cl_2 4:1) R_f= 0.58; ^{1}H NMR ($CDCl_3$, TMS_{int}): δ_H (ppm)=8.15 (s, H7, 1H), 7.86 (d, H5, J^{5-4}=8 Hz, 1H), 7.32 (d, H4, J^{4-5}=8 Hz, 1H), 4.38 (q, H8, J^{8-9}=7 Hz, 2H), 1.41 (t, H9, J^{9-8}=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS_{int}): δ_C (ppm)=169.87 (C2), 164.90 (C=O), 156.32 (C3a), 132.01 (C7a), 130.41 (C5), 129.80 (C6), 125.42 (C7), 120.02 (C4), 63.82 (–OCH_2–), 16.82 (–CH_3); FTIR (KBr): 3407, 3332, 1679, 1542, 1458, 1045 cm^{-1}; MS (CI, NH_3): 223.1 ($[M+1]^+$, 100%); HRMS (FAB+): m/z observed 223.054662, calculated for $C_{10}H_{11}N_2O_2S$ 223.054125.

4.1.4. Synthesis of 2-amino-6-(2-hydroxyethyl)-benzothiazole.[22] 4-Aminophenethyl alcohol (4.770 g, 35 mmol), potassium thiocyanate (13.200 g, 140 mmol) and bromine (1.70 ml) were reacted according to a literature procedure to obtain 4.085 g (73% yield) of 2-amino-6-(2-hydroxyethyl)-benzothiazole; mp 176–178 °C (lit.

175–177 °C). TLC (SiO_2, AcOEt/CH_2Cl_2 4:1) R_f=0.47; ^{1}H NMR (DMSO-d_6,TMS_{int}): δ_H (ppm)=7.45 (s, H7, 1H), 7.33 (s, –NH_2, 2H), 7.21 (d, H5, J^{5-4}=8 Hz, 1H), 7.02 (d, H4, J^{4-5}=8 Hz, 1H), 4.61 (t, –OH, J^{OH-9}=4 Hz, 1H), 3.56 (m, H9, 2H), 2.70 (t, H8, J^{8-9}=7 Hz, 3H); ^{13}C NMR (DMSO-d_6 TMS_{int}): δ_C (ppm)=166.34 (C2), 151.59 (C3a), 132.72 (C6), 131.42 (C7a), 126.96 (C5), 121.44 (C7), 117.91 (C4), 63.14 (–CH_2CH_2OH), 39.45 (–CH_2CH_2OH); FTIR (KBr): ν=3427, 3268, 3200–2900 (broad band), 1615, 1532, 1451, 1046 cm^{-1}; MS (FAB+): m/z=195.0 ($[M-H]^+$).

4.1.5. Synthesis of 6-(benzothiazol-2-yl-amino)-2-nitroacridine (2). 6-Fluoro-2-nitroacridine (121 mg, 0.5 mmol) was reacted with 2-aminobenzothiazole (78 mg, 0.6 mmol) and 71 mg of anhydrous potassium carbonate (83 mg, 0.6 mmol, 1.2 equiv) in 10 ml of DMA at 130–140 °C for 4 h. The crude reaction mixture was concentrated under vacuum, then purified by column chromatography (silica gel, 20:1 CH_2Cl_2/MeOH) to afford 92 mg of the title product (yield: 57%); mp >300 °C. TLC (SiO_2, hexane/AcOEt 1:3) R_f=0.47; ^{1}H NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_H (ppm)=9.74 (s, H9, 1H), 9.31 (d, H1, J^{1-3}=2 Hz, 1H), 8.97 (dd, H3, J^{3-4}=9 Hz, J^{3-1}=2 Hz, 1H), 8.56 (s, H5, 1H), 8.54 (d, H4, J^{4-3}=9 Hz, 1H), 8.52 (d, H8, J^{8-7}=9 Hz, 1H), 8.03 (dd, H7, J^{7-8}=9 Hz, J^{7-5}=2 Hz, 1H), 7.98 (d, H14, J^{14-15}=8 Hz), 7.87 (d, H17, J^{17-16}=8 Hz, 1H), 7.77 (dd, H16, J^{16-15}=8 Hz, J^{16-17}=8 Hz, 1H), 7.66 (dd, H15, J^{15-14}=8 Hz, J^{15-16}=8 Hz, 1H); ^{13}C NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_C (ppm)=165.27 (C13), 149.96 (C9), 147.15 (C6), 146.33 (C2), 143.42 (C18a), 141.49 (C4a), 136.60 (C10a), 132.98 (C8), 131.25 (C3), 130.41 (C17), 128.00 (C16), 126.52 (C1), 125.27 (C14a), 124.91 (C7), 124.30 (C8a), 123.35 (C15), 123.17 (C9a), 122.23 (C4), 116.32 (C18), 104.26 (C5); FTIR (KBr): ν=3365 (broad band), 1637, 1609, 1543, 1439, 1339, 1331, 1197 cm^{-1}; MS (MALDI-TOF+): m/z=373.1 ($[M]^+$, 100%); HRMS (FAB+): m/z observed 373.076187, calculated for $C_{20}H_{13}N_4O_2S$ 373.075923; UV vis (MeOH) λ_{max} (nm)= 437 (ε=2.4×10^4), 331 (ε=3.7×10^4).

4.1.6. Synthesis of 6-(6-ethylcarboxylate-benzothiazol-2-yl-amino)-2-nitroacridine (3). Following the method described above, 6-fluoro-2-nitroacridine (242 mg, 1 mmol) was reacted with 2-aminobenzothiazole-6-carboxylate (225 mg, 1.1 mmol) and anhydrous potassium carbonate (165 mg, 1.2 mmol) in 15 ml of DMA to obtain 288 mg (65% yield) of the title product; mp 293–295 °C. TLC (SiO_2, CH_2Cl_2/MeOH 20:1) R_f=0.57; ^{1}H NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_H (ppm)=9.72 (s, H9, 1H), 9.31 (d, H1, J^{1-3}=2 Hz, 1H), 9.29 (dd, H3, J^{3-4}= 10 Hz, J^{3-1}=2 Hz, 1H), 8.99 (d, H18, J^{18-17}=10 Hz, 1H), 8.69 (s, H15, 1H), 8.55 (d, H4, J^{4-3}=10 Hz, 1H), 8.40 (d, H17, J^{17-18}=10 Hz, 1H), 8.35 (s, H5, 1H), 8.05 (d, H8, J^{8-7}=8 Hz, 1H), 7.95 (d, H7, J^{7-8}=8 Hz, 1H), 4.54 (q, CH_3CH_2O, J=6 Hz, 2H), 1.51 (t, CH_3CH_2O, J=6 Hz, 3H); ^{13}C NMR (DMSO-d_6,TMS_{int}): δ_C (ppm)=164.10 (C=O), 160.70 (C13), 152.91 (C9), 150.73 (C18a), 150.47 (C16), 144.38 (C4a), 144.38 (C2), 139.96 (C6), 135.68 (C10a), 135.55 (C9a), 130.72 (C3), 128.03 (C4), 127.97 (C7), 127.85 (C17), 124.46 (C1), 123.94 (14a), 123.68 (C18), 122.52 (C8), 121.81 (C15), 121.05 (C8a), 111.58 (C5), 62.33 (CH_2), 31.27 (CH_3); FTIR (KBr): ν=3268, 1675, 1532, 1451, 1046 cm^{-1}; MS (MALDI-TOF+): m/z=445.1 ($[M+1]^+$, 100%); HRMS (MALDI-TOF+): m/z observed 445.096738, calculated for $C_{24}H_{17}N_4O_4S$ 445.097050. UV vis (MeOH): 430 (ε=2.4×10^4), 331 (ε=3.8×10^4).

4.1.7. Synthesis of the 6-[6-(β-hydroxyethyl)-benzothiazol-2-yl-amino]-2-nitroacridine (4). 6-Fluoro-2-nitroacridine (242 mg, 1 mmol) was reacted with 2-amino-6-(2-hydroxyethyl)-benzothiazole (217 mg, 1.1 mmol) and anhydrous potassium carbonate (165 mg, 1.2 mmol), in 15 ml of DMA to obtain 249 mg (60% yield) of the title product; mp 297–298 °C. TLC (SiO_2, DCM/MeOH 20:1) R_f=0.27;. ^{1}H NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_H (ppm)=9.72 (s, H9, 1H), 9.31 (d, H1, J^{1-3}=2 Hz, 1H), 8.96 (dd, H3, J^{3-4}=10 Hz, J^{3-1}=2 Hz, 1H), 8.54 (d, H18, J^{18-17}=10 Hz, 1H), 8.53 (s, H5, 1H), 8.50 (d, H4, J^{4-3}= 10 Hz, 1H), 8.02 (d, H17, J^{17-18}=10 Hz, 1H), 7.86 (s, H15, 1H), 7.82 (d, H8, J^{8-7}=8 Hz, 1H), 7.60 (d, H7, J^{7-8}=8 Hz, 1H), 4.65 (t, –CH_2CH_2OH, J=6 Hz, 2H), 3.27 (t, –CH_2CH_2OH, J=6 Hz, 2H); ^{13}C NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_C (ppm)=165.14 (C13), 149.80 (C9), 147.19 (C18a), 146.26 (C4a), 143.52 (C2), 141.50 (C6), 137.19 (C10a), 136.09 (C16), 132.92 (C4), 131.27 (C3), 131.15 (C7), 126.52 (C17), 125.24 (C1), 124.92 (C8a), 124.24 (C8), 124.19 (C9a), 123.22 (14a), 122.22 (C18), 116.61 (C15), 103.95 (C5), 67.95 (–CH_2CH_2OH), 34.23 (–CH_2CH_2OH); FTIR (KBr): ν=3427, 3268, 3200–2900 (broad band), 1615, 1532, 1451, 1046 cm^{-1}; MS (MALDI-TOF+): m/z=416.0 ($[M]^+$, 100%); HRMS (MALDI-TOF+): m/z observed 417.10064, calculated for $C_{22}H_{17}N_4O_3S$ 417.10214. UV vis (MeOH) λ_{max} (nm)= 437 (ε=2.5×10^4), 329 (ε=3.8×10^4).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.07.045

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