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Delocalized cationic azo dyes containing a thiazole moiety

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Abstract

Several new delocalized cationic azo dyes incorporating a bathochromic thiazole moiety have been prepared in moderate to good yields. The synthesis involved the Knoevenagel condensation of an intermediate azo compound, bearing a terminal formyl group, with methylenic bases generated in situ from benzoazolium and quinolinium salts. All dyes display strong absorption around 700 nm and have shown negative solvatochromic behaviour.

Keywords: Cationic azo dyes; Thiazole; PDT; Solvatochromism

1. Introduction

Photodynamic therapy (PDT) is an increasingly attractive treatment for cancer and for a variety of diseases.[1] It is based on the use of photosensitizing drugs that acquire the desired activity only when excited by light of the appropriate wavelength. The activation of the sensitizer gives rise to lethal reactive species, amongst which singlet oxygen is considered to be main one,[2] that destroy the cells circumscribed to the region illuminated.

Hematoporphyrin derivatives have been the most widely used drugs for clinical PDT. They present, however, several limitations, which have led, in the last years, to a considerable research effort directed towards other classes of photosensitizers with improved characteristics.[3] Any new photosensitizer for PDT must fulfill several multidisciplinary requirements, such as high quantum yield of the compound's triplet state and long triplet lifetime, because photochemical reactions predominantly occur in the excited state; efficient conversion of ground-state triplet oxygen to cytotoxic singlet oxygen; and strong absorption ($\varepsilon > 10^5\ M^{-1}\ cm^{-1}$) within the phototherapeutic window (600–1000 nm).[4]

Despite the enormous synthetic versatility of azo dyes, which has turned them into the most widely used dye class, they have scarcely been modified to display absorption in the near-infrared[5] and their aptitude as sensitizers for PDT was rarely explored.[6] So far, no delocalized cationic azo dyes appear to have been studied with regard to their use for PDT. Nevertheless cationic dyes have attracted great attention as a new family of promising sensitizers since it was found that cancer cells take up and retain them in a greater extent than most normal cells.[7]

Following our interest in the development of alternative sensitizers for PDT,[8] we addressed the synthesis of novel delocalized cationic azo dyes displaying absorption in the long-wavelength region.

2. Results and discussion

The bathochromic nature of the thiazole ring in azo dyes was long established[9] and it was used by Griffiths and co-workers[5a,b] in one of the few successful approaches to near-infrared absorbing azo dyes, mainly of the neutral type, through the incorporation of a 4-chlorothiazole unit into the chromophoric system. The bathochromism of chlorothiazolylazo dyes, however, is somewhat hampered by a certain lack of chemical stability.[10]

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The synthetic strategy pursued herein involved the formation of an intermediate azo dye incorporating a bathochromic thiazole ring and a terminal formyl group to allow the extension of conjugation through condensation with an active methylene benzoazolium or quinolinium quaternary salt (Scheme 1). Thus, 2-aminothiazole-5-carbaldehyde[11] (**1**) was diazotized in nitrosylsulphuric acid to afford the diazonium salt **2**, which was subsequently coupled with *N*,*N*-diethylaniline to afford 2-(4-diethylaminophenylazo)thiazole-5-carbaldehyde (**3**). Knoevenagel condensation of the latter with the methylenic bases generated in situ from benzoazolium and quinolinium salts **4a**–**h** in EtOH/pyridine gave the corresponding dyes **5a**–**h** in moderate to good yields. All delocalized cationic azo dyes display intense absorption (log ε>5.6) above ca. 650 nm (Table 1). Generally, a weak secondary band is apparent around 430 nm.

The red shift promoted by the thiazole moiety is perceivable when comparing the absorption of the intermediate azo dye **3**, having λ_{max} (CH_2Cl_2) 549 nm, with that of 4-(4-diethylaminophenylazo)benzaldehyde, for which has been reported λ_{max} 472 nm in the same solvent.[5a]

Since delocalized cationic azo dyes are a border case of polymethine dyes[12] it is noteworthy that the maximum wavelength of absorption of dyes **5** does not show the same order of dependence neither from the basicity of the heteroaromatic nuclei nor from the length of the π-conjugated system observed for polymethine dyes, i.e., indole<benzothiazole< benzoselenazole<quinoline<lepidine.[13] The lepidine-derived dye **5h**, despite possessing a more extended conjugation than the parent quinoline-based dye **5g**, displays a value of λ_{max} inferior to that of **5g** regardless of the solvent.

Not surprisingly, the length of the *N*-alkyl chain seems to have a negligible influence on the λ_{max} of the dyes, as illustrated for dyes **5a** and **5b** possessing, respectively, an *N*-ethyl and *N*-hexyl pendent group.

Azo dyes **5** showed negative solvatochromism on passing from CH_2Cl_2 to DMSO and from this to the even more polar MeOH. The observed hypsochromic displacement of λ_{max} from CH_2Cl_2 to MeOH ranged from 48 to 69 nm, being more pronounced for the 6-iodobenzothiazolium dye **5d** (Fig. 1). Azo dyes chiefly reveal positive solvatochromic behaviour;[14] negative solvatochromism has been seldom referred.[14,15]

Table 1
Yield and vis spectral data of dyes **5a**–**h**

Compound	Yield (%)	λ_{max} (nm) (log ε) CH_2Cl_2	λ_{max} (nm) DMSO	λ_{max} (nm) MeOH
5a	82	690 (5.73)	639	630
5b	58	693 (5.82)	639	633
5c	32	708 (5.70)	645	642
5d	99	711 (5.78)	648	642
5e	40	693 (5.61)	642	636
5f	59	729 (5.90)	672	669
5g	48	657 (5.71)	621	609
5h	53	648 (5.75)	612	597

This synthetic methodology constitutes an interesting alternative to that traditionally employed in the synthesis of

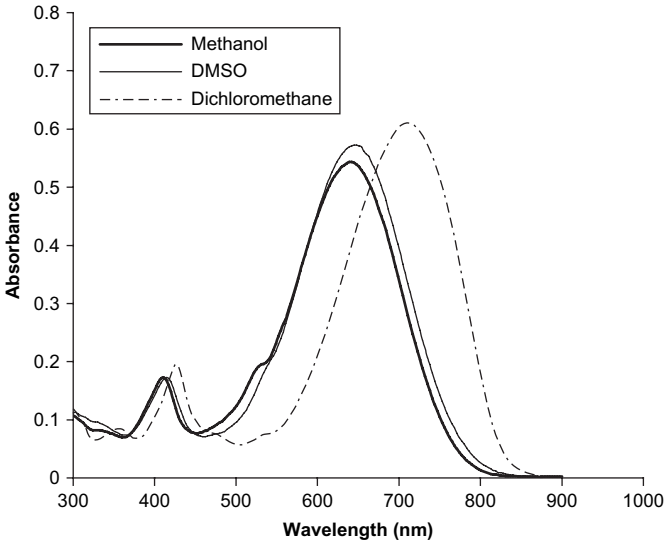
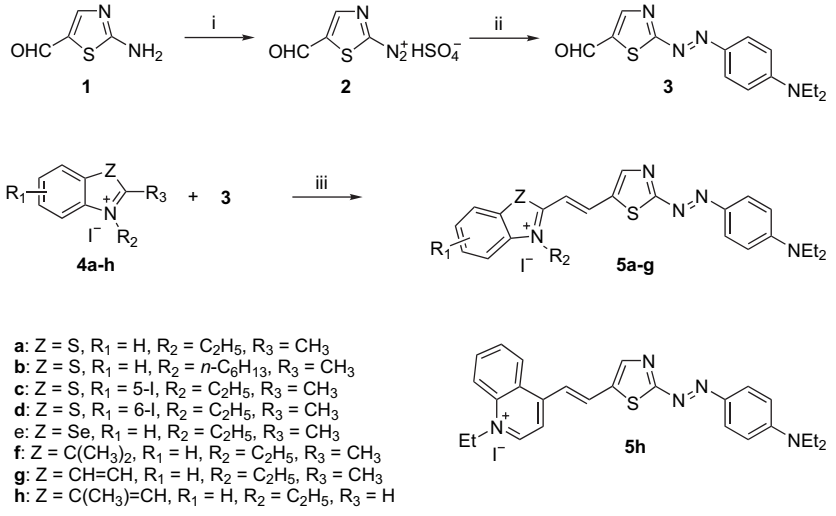


Figure 1. Absorption spectra of dye **5d** in various solvents.



Scheme 1. Reagents and conditions: (i) H_2SO_4, $NaNO_2$, AcOH, −5 to 0 °C; (ii) *N*,*N*-diethylaniline, H_2SO_4, H_2O, 0 °C to rt; (iii) EtOH, pyridine, 35 °C to reflux.

delocalized cationic azo dyes, which generally involves the regioselective alkylation of disperse azo dyes.[12]

The photochemical evaluation of the dyes synthesized, with prominence for the determination of the singlet oxygen generation ability, as well as the assessment of their potential phototoxicity against selected cancer cells is currently the subject of a separate study, the results of which shall be published elsewhere.

3. Conclusions

The Knoevenagel condensation of 2-(4-diethylaminophenylazo)thiazole-5-carbaldehyde (**3**) with methylenic bases generated in situ from benzoazolium and quinolinium salts was used to prepare several new delocalized cationic azo dyes in moderate to good yields. The synthesized dyes display strong absorption around 700 nm and have shown negative solvatochromic behaviour.

4. Experimental

4.1. General

All reagents were of the highest purity available, obtained from commercial suppliers and used as received. Solvents were of analytical grade. 6-Iodo-2-methylbenzothiazole (**6b**)[8a] and 2-aminothiazole-5-carbaldehyde (**1**)[11] were prepared as described in the literature. Reactions were monitored by TLC using 0.25 mm aluminium-backed silica gel plates (Merck 60 F_{254}). Melting points were measured in open capillary tubes in a Büchi 530 melting point apparatus and are uncorrected. FTIR spectra were recorded on a Mattson 5000 FT IR spectrophotometer. UV/vis spectra were performed on a Perkin–Elmer Lambda 6 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Brücker ARX 400 spectrometer. Chemical shifts are reported with respect to the solvent or TMS as internal standard. Mass spectra were determined on a Micromass AutoSpec M spectrometer, operating at 70 eV. A matrix of 3-nitrobenzyl alcohol (3-NBA) was used for Fast Atom Bombardment High Resolution mass spectra.

4.2. 2-(4-Diethylaminophenylazo)thiazole-5-carbaldehyde (*3*)

To stirred H_2SO_4 (7 mL) at 30 °C was added $NaNO_2$ (0.647 g, 9.38 mmol) and the mixture was heated at 65 °C until complete dissolution. The solution was then cooled in an ice bath, CH_3CO_2H (4 mL) was added and the mixture was left for 10 min. Following cooling to −5 °C, 2-aminothiazole-5-carbaldehyde (**1**)[11] (1.00 g, 7.81 mmol) was added portionwise and the mixture stirred for 2 h 30 min at 5 °C. The resulting diazonium salt solution was added slowly to a stirred suspension of *N*,*N*-diethylaniline (1.3 mL, 8.17 mmol) in water (62 mL) and H_2SO_4 (1.2 mL). Once the addition was completed, the reaction mixture was left at rt for 30 min and then extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to afford chromatographically pure **3**. Yield: 55%. Dark-green crystals. Mp 140–143 °C. Vis (CH_2Cl_2) λ_{max} (log ε) 549 nm (5.65). IR (KBr) ν_{max} 2967 (w), 1661 (s), 1597 (s), 1543 (w), 1525 (w), 1509 (w), 1413 (w), 1382 (w), 1328 (s), 1306 (s), 1259 (s), 1228 (s), 1130 (s), 1074 (s), 1007 (m), 826 (w), 700 (w) cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.27 (t, 6H, J=7.1 Hz, C*H*$_3$), 3.51 (q, 4H, J=7.1 Hz, C*H*$_2$), 6.73 (d, 2H, J=9.1 Hz, Ar*H*), 7.94 (d, 2H, J=9.1 Hz, Ar*H*), 8.43 (s, 1H, =C*H*N), 9.97 (s, 1H, C*H*O). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 12.7 (*C*H$_3$), 45.3 (*C*H$_2$), 111.8, 136.8, 142.8, 151.9, 153.2, 182.9, 184.4. FABHRMS (3-NBA) calcd for $C_{14}H_{17}N_4OS$ $[M+H]^+$: 289.1123; found 289.1126.

4.3. Synthesis of quaternary ammonium salts *4*

A solution of appropriate methylbenzoazole or methylquinoline (1.0 mmol) and 1-iodoethane or 1-iodohexane (3.0–5.0 mmol) in CH_3CN (25 mL) was heated at reflux for 5 days. After cooling, Et_2O was added, the precipitated quaternary salt collected by filtration under reduced pressure, washed several times with Et_2O and dried under reduced pressure to afford spectroscopically pure salts **4**. The combined filtrates were evaporated at reduced pressure and the remaining residue, consisting mainly of unreacted starting materials, was heated at reflux for another 5 days and worked up as described above. The process was repeated until a suitable yield was achieved (usually 2–3 times). The spectroscopic characterization of salts **4a**,**b**,**e**–**h** has been previously reported.[16]

4.3.1. 3-Ethyl-5-iodo-2-methylbenzothiazol-3-ium iodide (*4c*)

Yield: 61%. Yellowish solid. Mp 240–243 °C (dec). IR (KBr) ν_{max} 3041 (w), 2975 (m), 2931 (w), 2905 (w), 1578 (m), 1561 (m), 1442 (s), 1414 (m), 1367 (m), 1330 (m), 1200 (m), 1098 (w), 872 (w), 817 (s), 801 (w) cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.42 (t, 3H, J=7.3 Hz, C*H*$_3$), 3.19 (s, 3H, C*H*$_3$), 4.74 (q, 2H, J=7.3 Hz, C*H*$_2$), 8.12 (dd, 1H, J=1.3, 8.6 Hz, 6-C*H*), 8.20 (d, 1H, J=8.6 Hz, 7-C*H*), 8.77 (d, 1H, J=1.3 Hz, 4-C*H*). FABHRMS (3-NBA) calcd for $C_{10}H_{11}NSI$ $[M]^+$: 303.9657; found 303.9659.

4.3.2. 3-Ethyl-6-iodo-2-methylbenzothiazol-3-ium iodide (*4d*)

Yield: 78%. Dark-yellowish solid. Mp 269–272 °C (dec). IR (KBr) ν_{max} 3044 (m), 2974 (w), 2937 (w), 1567 (m), 1511 (m), 1451 (s), 1384 (s), 1330 (s), 1266 (m), 1204 (w), 1098 (w), 802 (m) cm^{-1}. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.42 (t, 3H, J=7.3 Hz, C*H*$_3$), 3.18 (s, 3H, C*H*$_3$), 4.72 (q, 2H, J=7.3 Hz, C*H*$_2$), 8.13 (d, 1H, J=8.6 Hz, 4-C*H*), 8.20 (d, 1H, J=1.6, 8.9 Hz, 5-C*H*), 8.85 (d, 1H, J=1.6 Hz, 7-C*H*). FABHRMS (3-NBA) calcd for $C_{10}H_{11}NSI$ $[M]^+$: 303.9657; found 303.9659.

4.4. Synthesis of dyes *5*: general procedure

A solution of the quaternary ammonium salt **4** (1.0 mmol) and the intermediary azo dye **3** (1.0 mmol) in EtOH (13.5 mL) containing pyridine (1.5 mL) was heated from

35 °C to reflux until complete consumption of the starting azo dye (6–52 h). The heating rate was carefully controlled to avoid the decomposition of **3**. The reaction mixture was then cooled in an ice bath and Et_2O was added. The resulting dark-blue solid was collected by filtration under reduced pressure, washed several times with Et_2O, redissolved in $CHCl_3$ and washed with water. The organic layer, after being separated by decantation, was dried over anhydrous $NaSO_4$ and the solvent evaporated to dryness. The resulting residue was recrystallized from $CHCl_3/Et_2O$ until a chromatographically pure material was obtained (1–3 times).

*4.4.1. 3-Ethyl-2-{2-[2-(4-diethylaminophenylazo)thiazol-5-yl]vinyl}benzothiazol-3-ium iodide (**5a**)*

Yield: 82%. Dark solid. Mp 215 °C (dec). IR (KBr) ν_{max} 2975 (w), 1594 (s), 1580 (s), 1541 (w), 1444 (w), 1418 (w), 1293 (w), 1253 (s), 1235 (s), 1207 (w), 1131 (s), 1119 (s), 1075 (m), 1036 (w), 1007 (w), 792 (w) cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (t, 6H, J=6.9 Hz, CH_3), 1.45 (t, 3H, J=6.9 Hz, CH_3), 3.57 (q, 4H, J=6.9 Hz, CH_2), 4.92 (q, 2H, J=6.9 Hz, CH_2), 6.93 (d, 2H, J=9.3 Hz, Ar*H*), 7.70 (d, 1H, J=15.4 Hz, =C*H*C), 7.76–7.80 (m, 3H, Ar*H*), 7.86 (t, 1H, J=7.8 Hz, Ar*H*), 8.26 (d, 1H, J=8.5 Hz, Ar*H*), 8.42–8.47 (m, 2H, Ar*H*+=C*H*C), 8.55 (s, H, =C*H*N). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 12.5 (*C*H_3), 14.1 (*C*H_3), 44.3 (*C*H_2), 44.8 (*C*H_2), 112.6, 113.4, 116.4, 124.4, 128.2, 128.3, 129.5, 133.4, 139.1, 140.8, 142.1, 151.7, 153.1, 170.2, 181.5. FABHRMS (3-NBA) calcd for $C_{24}H_{26}N_5S_2$ $[M]^+$: 448.1630; found 448.1623.

*4.4.2. 2-{2-[2-(4-Diethylaminophenylazo)thiazol-5-yl]-vinyl}-3-hexylbenzothiazol-3-ium iodide (**5b**)*

Yield: 58%. Dark solid. Mp 136 °C (dec). IR (KBr) ν_{max} 2925 (w), 2857 (w), 1593 (s), 1580 (s), 1538 (w), 1441 (w), 1416 (w), 1298 (w), 1253 (s), 1235 (s), 1127 (s), 1069 (s), 1005 (m), 882 (w), 793 (w) cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ 0.86 (t, 3H, J=6.9 Hz, CH_3), 1.21 (t, 6H, J=6.9 Hz, CH_3), 1.25–1.36 (m, 4H, CH_2), 1.40–1.46 (m, 2H, CH_2), 1.80–1.88 (m, 2H, CH_2), 3.59 (q, 4H, J=6.9 Hz, CH_2), 4.89 (t, 2H, J=7.3 Hz, CH_2), 6.95 (d, 2H, J=9.0 Hz, Ar*H*), 7.69 (d, 1H, J=15.3 Hz, =C*H*C), 7.77–7.89 (m, 4H, Ar*H*), 8.26 (d, 1H, J=8.5 Hz, Ar*H*), 8.43–8.47 (m, 2H, Ar*H*+=C*H*C), 8.55 (s, 1H, =C*H*N). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 12.4 (*C*H_3), 13.6 (*C*H_3), 21.7 (*C*H_2), 25.2 (*C*H_2), 28.5 (*C*H_2), 30.5 (*C*H_2), 44.7 (*C*H_2), 48.6 (*C*H_2), 112.5, 113.4, 116.5, 124.2, 128.0, 128.2, 129.4, 133.3, 139.0, 141.0, 142.2, 151.5, 153.1, 170.4, 181.4. FABHRMS (3-NBA) calcd for $C_{28}H_{34}N_5S_2$ $[M]^+$: 504.2256; found 504.2259.

*4.4.3. 3-Ethyl-2-{2-[2-(4-diethylaminophenylazo)thiazol-5-yl]vinyl}-5-iodobenzothiazol-3-ium iodide (**5c**)*

Yield: 32%. Dark solid. Mp 208 °C (dec). IR (KBr) ν_{max} 2973 (w), 1588 (s), 1569 (m), 1523 (w), 1438 (w), 1411 (w), 1331 (w), 1296 (w), 1247 (s), 1125 (s), 1075 (m), 1008 (w), 793 (w) cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (t, 6H, J=6.9 Hz, CH_3), 1.41 (t, 3H, J=7.0 Hz, CH_3), 3.59 (br q, 4H, CH_2), 4.88 (br q, 2H, CH_2), 6.96 (d, 2H, J=8.6 Hz, Ar*H*), 7.67 (d, 1H, J=14.6 Hz, =C*H*C), 7.81 (d, 2H, J=8.6 Hz, Ar*H*), 8.08 (d, 1H, J=8.3 Hz, Ar*H*), 8.19 (d, 1H, J=8.3 Hz, Ar*H*), 8.48 (d, 1H, J=14.6 Hz, =C*H*C), 8.56 (s, 1H, =C*H*N), 8.69 (s, 1H, Ar*H*). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 12.4 (*C*H_3), 13.9 (*C*H_3), 44.2 (*C*H_2), 44.7 (*C*H_2), 95.3, 112.5, 113.0, 124.4, 125.6, 127.9, 133.3, 136.6, 139.6, 141.9, 142.2, 151.8, 153.1, 170.7, 181.6. FABHRMS (3-NBA) calcd for $C_{24}H_{25}N_5S_2I$ $[M]^+$: 574.0596; found 574.0599.

*4.4.4. 3-Ethyl-2-{2-[2-(4-diethylaminophenylazo)thiazol-5-yl]vinyl}-6-iodobenzothiazol-3-ium iodide (**5d**)*

Yield: 99%. Dark-green solid. Mp 220 °C (dec). IR (KBr) ν_{max} 2976 (w), 1585 (s), 1566 (m), 1541 (w), 1450 (w), 1286 (w), 1249 (s), 1235 (m), 1207 (w), 1124 (s), 1074 (m), 1030 (w), 1008 (w), 806 (w) cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (t, 6H, J=7.1 Hz, CH_3), 1.42 (t, 3H, J=7.1 Hz, CH_3), 3.60 (br q, 4H, CH_2), 4.88 (br q, 2H, CH_2), 6.97 (d, 2H, J=9.2 Hz, Ar*H*), 7.70 (d, 1H, J=15.4 Hz, =C*H*C), 7.82 (d, 2H, J=9.2 Hz, Ar*H*), 8.06 (d, 1H, J=8.8 Hz, Ar*H*), 8.17 (d, 1H, J=8.8 Hz, Ar*H*), 8.51 (d, 1H, J=15.4 Hz, =C*H*C), 8.56 (s, 1H, =C*H*N), 8.86 (d, 1H, J=1.4 Hz, Ar*H*). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 12.6 (*C*H_3), 14.1 (*C*H_3), 44.4 (*C*H_2), 44.8 (*C*H_2), 94.0, 112.7, 113.1, 118.0, 130.1, 132.4, 133.4, 137.8, 139.6, 140.5, 142.2, 152.0, 153.2, 170.3, 181.8. FABHRMS (3-NBA) calcd for $C_{24}H_{25}N_5S_2I$ $[M]^+$: 574.0596; found 574.0594.

*4.4.5. 3-Ethyl-2-{2-[2-(4-diethylaminophenylazo)selenazol-5-yl]vinyl}benzothiazol-3-ium iodide (**5e**)*

Yield: 40%. Dark solid. Mp 193 °C (dec). IR (KBr) ν_{max} 2971 (w), 2927 (w), 1590 (s), 1541 (w), 1526 (w), 1441 (w), 1416 (w), 1296 (w), 1248 (s), 1231 (m), 1123 (s), 1071 (m), 1007 (w), 758 (w) cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (t, 6H, J=7.0 Hz, CH_3), 1.44 (t, 3H, J=6.9 Hz, CH_3), 3.59 (q, 4H, J=7.0 Hz, CH_2), 4.91 (q, 2H, J=6.9 Hz, CH_2), 6.97 (d, 2H, J=9.4 Hz, Ar*H*), 7.69–7.74 (m, 2H, Ar*H*+=C*H*C), 7.80–7.84 (m, 3H, Ar*H*), 8.25 (d, 1H, J=8.7 Hz, Ar*H*), 8.45 (d, 1H, J=7.4 Hz, Ar*H*), 8.54–8.58 (m, 2H, =C*H*C+=C*H*N). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 12.6 (*C*H_3), 14.1 (*C*H_3), 44.9 (*C*H_2), 45.3 (*C*H_2), 112.7, 116.4, 118.1, 127.4, 128.0, 129.1, 130.3, 133.9, 140.9, 142.1, 142.3, 151.7, 153.2, 179.5, 181.5. FABHRMS (3-NBA) calcd for $C_{24}H_{26}N_5S^{78}Se$ $[M]^+$: 494.1082; found 494.1089; calcd for $C_{24}H_{26}N_5S^{80}Se$ $[M]^+$: 496.1074; found 496.1082.

*4.4.6. 1-Ethyl-2-{2-[2-(4-diethylaminophenylazo)thiazol-5-yl]vinyl}-3,3-dimethyl-3H-indolium iodide (**5f**)*

Yield: 59%. Dark solid. Mp 221 °C (dec). IR (KBr) ν_{max} 2971 (w), 1604 (m), 1577 (s), 1536 (w), 1466 (w), 1302 (w), 1252 (s), 1229 (w), 1209 (w), 1147 (s), 1119 (s), 1089 (m), 1072 (m), 1042 (w), 1006 (w), 765 (w) cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (t, 6H, J=7.0 Hz, CH_3), 1.43 (t, 3H, J=7.1 Hz, CH_3), 1.79 (s, 6H, CH_3), 3.62 (q, 4H, J=7.0 Hz, CH_2), 4.65 (q, 2H, J=7.1 Hz, CH_2), 7.00 (d, 2H, J=9.3 Hz, Ar*H*), 7.30 (d, 1H, J=15.8 Hz, =C*H*C), 7.61–7.62 (m, 2H, Ar*H*), 7.83–7.92 (m, 4H, Ar*H*), 8.70 (d, 1H, J=15.8 Hz, =C*H*C), 8.76 (s, 1H, =C*H*N). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 13.2 (*C*H_3), 14.2 (*C*H_3), 26.1

(CH_3), 42.4 (CMe_2), 45.6 (CH_2), 52.5 (CH_2), 112.7, 113.6, 115.4, 123.6, 129.6, 129.7, 134.8, 141.0, 143.2, 144.3, 144.6, 154.1, 155.0, 180.5, 183.5. FABHRMS (3-NBA) calcd for $C_{27}H_{32}N_5S$ $[M]^+$: 458.2378; found 458.2376.

*4.4.7. 1-Ethyl-2-{2-[2-(4-diethylaminophenylazo)thiazol-5-yl]vinyl}quinolinium iodide (**5g**)*

Yield: 48%. Dark solid. Mp 207 °C (dec). IR (KBr) ν_{max} 2969 (w), 2929 (w), 1591 (s), 1521 (w), 1412 (w), 1347 (w), 1303 (w), 1254 (m), 1227 (m), 1130 (s), 1073 (m), 1008 (w), 968 (w) cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (t, 6H, J=7.0 Hz, CH_3), 1.56 (t, 3H, J=7.1 Hz, CH_3), 3.56 (q, 4H, J=7.0 Hz, CH_2), 5.11 (q, 2H, J=7.1 Hz, CH_2), 6.89 (d, 2H, J=9.3 Hz, Ar*H*), 7.51 (d, 1H, J=15.4 Hz, =C*H*C), 7.77 (d, 2H, J=9.3 Hz, Ar*H*), 7.94 (t, 1H, J=7.5 Hz, Ar*H*), 8.17 (dt, 1H, J=1.2, 8.1 Hz, Ar*H*), 8.34 (dd, 1H, J=1.2, 8.1 Hz, Ar*H*), 8.41 (s, 1H, =C*H*N), 8.48–8.55 (m, 3H, Ar*H*+=C*H*C), 9.03 (d, 1H, J=9.0 Hz, =C*H*C). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 12.5 (CH_3), 14.1 (CH_3), 44.7 (CH_2), 46.5 (CH_2), 112.3, 118.8, 118.9, 120.8, 128.1, 128.9, 130.3, 134.3, 135.1, 137.9, 138.0, 141.9, 143.9, 149.7, 152.8, 154.1, 180.3. FABHRMS (3-NBA) calcd for $C_{26}H_{28}N_5S$ $[M]^+$: 442.2065; found 442.2062.

*4.4.8. 1-Ethyl-4-{2-[2-(4-diethylaminophenylazo)thiazol-5-yl]vinyl}quinolinium iodide (**5h**)*

Yield: 53%. Dark-purple crystals. Mp 223 °C (dec). IR (KBr) ν_{max} 2974 (w), 2924 (w), 1586 (s), 1562 (m), 1534 (w), 1398 (w), 1328 (w), 1302 (w), 1247 (s), 1219 (w), 1133 (s), 1074 (m), 1004 (w), 825 (w), 756 (w) cm^{-1}. ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (t, 6H, J=6.9 Hz, CH_3), 1.59 (t, 3H, J=7.1 Hz, CH_3), 3.56 (q, 4H, J=6.9 Hz, CH_2), 5.01 (q, 2H, J=7.1 Hz, CH_2), 6.93 (d, 2H, J=9.2 Hz, Ar*H*), 7.80 (d, 2H, J=9.2 Hz, Ar*H*), 7.99–8.04 (m, 2H, Ar*H*+=C*H*C), 8.24 (t, 1H, J=7.7 Hz, Ar*H*), 8.31 (s 1H, =C*H*N), 8.40 (d, 1H, J=15.6 Hz, =C*H*C), 8.45 (d, 1H, J=6.4 Hz, =C*H*C), 8.53 (d, 1H, J=9.0 Hz, Ar*H*), 8.98 (d, 1H, J=8.5 Hz, Ar*H*), 9.39 (d, 1H, J=6.4 Hz, =C*H*C). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 12.5 (CH_3), 15.0 (CH_3), 44.6 (CH_2), 52.1 (CH_2), 79.1, 112.2, 116.3, 118.9, 121.5, 126.4, 126.7, 129.1, 133.3, 135.0, 135.2, 137.5, 141.8, 147.0, 148.2, 151.6, 152.5, 179.3. FABHRMS (3-NBA) calcd for $C_{26}H_{28}N_5S$ $[M]^+$: 442.2065; found 442.2066.

*4.5. 5-Iodo-2-methylbenzothiazole (**6a**)*

To an ice-cooled mixture of 5-amino-2-methylbenzothiazole (1.00 g, 6.09 mmol), concd HCl (2.8 mL) and water (2.8 mL) was added dropwise a solution of $NaNO_2$ (0.772 g, 11.19 mmol) in water (3.6 mL) and, 30 min later, a solution of KI (1.75 g, 10.54 mmol) in the same solvent (2 mL). After stirring for 10 min, the reaction mixture was allowed to gradually reach rt and then heated at 30–40 °C for 15 min. The resulting dark cake was dissolved in CH_2Cl_2 and washed with 5% aqueous $NaHSO_3$ until a pale yellow colour was obtained. The organic layer was dried over anhydrous Na_2SO_4, the solvent removed under reduced pressure and the residue purified by column chromatography (silica, $CHCl_3$/*n*-hexane 1/1) to give **6a**. Yellowish solid. Yield: 46%. Mp 83–85 °C (lit.[17] 85.0–85.5 °C). IR (KBr) ν_{max} 3047 (w), 2960 (w), 1517 (m), 1433 (m), 1401 (m), 1379 (w), 1292 (w), 1168 (m), 1150 (m), 1065 (m), 882 (m), 794 (s) cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$) δ 2.83 (s, 3H, CH_3), 7.54 (d, 1H, J=8.4 Hz, 7-C*H*), 7.62 (dd, 1H, J=1.6, 8.4 Hz, 6-C*H*), 8.29 (d, 1H, J=1.6 Hz, 4-C*H*). TOFEIMS: 275 $[M]^+$.

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