Some new symmetric rigidified triheterocyclic heptamethinecyanine dyes absorbing in the near infrared

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Abstract

Several new rigidified heptamethinecyanine dyes bearing different *N*-alkyl chains were readily prepared by a novel semi-catalyzed method, envisioning their potential usefulness for photodynamic therapy. All dyes displayed absorption within the so-called "phototherapeutic window". In order to improve the structural versatility of the dyes, it was incorporated in the exocyclic conjugated bridge present in the polimethine chain a chlorine atom. In some cases the later underwent an unexpected *in situ* substitution by a third oxygenated heterocyclic group, depending on the solubility of the chloro dye in the reaction solvent. Two possible mechanisms for the formation of these triheterocyclic dyes are proposed. The full spectroscopic characterisation of all the cyanines synthesised is described. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Cyanine dyes have been extensively studied over the past century, mainly as photosensitisers for photography [1–3]. In recent decades, other applications such as visible and near-infrared laser dyes [4–6], optical recording and storage media [3,4], biological fluorescent stains and probes [7], among others, have added renewed interest to the study and development of this family of dyes, especially heptamethinecyanines, owing to their absorption in the infrared region.

Since the end of the 1980's, cationic dyes have been regarded as potential agents for Photodynamic Therapy (PDT) [8,9], being an alternative to the classical porphyrins and porphyrins-based photosensitisers [10–12]. In this context, cyanine dyes are considered to be very promising candidates for PDT and the possibility to use them for this purpose critically depends on their photophysical and photochemical properties. These include strong absorption ($> 10^5$ M^{-1} cm^{-1}) within the so-called "phototherapeutic window" (600–1100 nm), in which tissue light scattering is low and light penetration in tissues increases, and an

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inherent ability to generate cytotoxic singlet oxygen from ground-state triplet oxygen [13,14].

One important structural aspect related to cyanine dyes, while potential PDT sensitisers, is the length of the *N*-alkyl chains. Studies carried out with thiacarbocyanines showed that the lipophilic properties of the dye could be gradually increased, extending the number of carbons of the *N*-alkyl groups, without compromising the photophysical properties of the dye [14,15]. Furthermore, it was observed that dyes with short *N*-alkyl substituents were already cytotoxic in the dark, while longer chain cyanines exhibited antineoplastic activity only after exposure to light [16].

Herein we report the synthesis of some new rigidified meso hepthamethine-, oxa-, selena- and thiacyanines **4** and **5** (Scheme 1), displaying absorption near 800 nm, in which some structural variations as the nature of the heteroaromatic ring and the length of the *N,N'*-dialkyl groups were made, envisioning their potential usefulness as PDT sensitisers. For long polymethine chains, as those of heptamethinecyanines, the replacement of an ethylene unit by a cyclic conjugated bridge is well known to improve the stability of the dye [17]. The chlorine atom in the exocyclic conjugated bridge of the dye is thought to undergo substitution by different nucleophiles, as it happens with similar indolenine cyanines [18–24], potentially extending its structural versatility.

Chlorocyanine dyes **4** have traditionally been synthesised by condensation between *N*-alkyl heterocyclic bases, containing an activated methyl group in the 2- or 4-position in relation to the quaternary ammonium salt, and an unsaturated bisaldehyde or its equivalent, usually as Schiff base. In such cases, the process is usually catalysed by sodium acetate [22,23,25–27] or triethylamine [26–28], using a mixture of acetic acid and acetic anhydride [25,27] or ethanol [22,23,26] as solvents. More recently, an uncatalysed synthesis of several symmetric and asymmetric chloroindocyanine dyes analogous to **4** (Z = CMe$_2$), achieved heating under reflux a solution of an *N*-alkyl substituted quaternary salt derived from 2,3,3-trimethylindole or 2,3,3-trimethylbenzoindole and a bisaldehyde, 2-chloro-1-formyl-3-(hydroxymethylene)cyclohex-1-ene (**2**), in butan-1-ol/benzene (7/3), with continuous

azeotropic removal of the water formed, was described and claimed to be advantageous over the traditional method by avoiding complex mixtures [20,21].

Nevertheless a number of chloro- and chloro-substituted indoheptamethinecyanines similar to **4** are now commercially available [29] and increasingly used for such different purposes as near infrared laser dyes [30], silver halide emulsions [3], optical recording media [31], spectrophotometric determination of trace water in organic solvents [32,33], determination of hydrophobicity of proteins [34] and micelles [35], fluorescent labelling agents for proteins and their ultra-trace determination [18–22,24,36–38], fluorescent tags in DNA sequencing [18–21,39,40], immunoassay [37,38] and flow cytometry [41], non-indolenine dyes of the type mentioned, namely those incorporating a benzoxazole, benzoselenazole, benzothiazole or quinoline nucleus, are far from being so extensively studied. Their poorer thermal and photostability as well as an increased difficulty of their synthesis probably accounts for it. Morever, chlorobenzothiazole dyes alike **4** lack structural versatility, when compared to indolenine ones, owing to a generally less efficient nucleophilic substitution of the chlorine atom [18].

2. Results and discussion

Our efforts to synthesise symmetric chloroheptamethinecyanines **4** bearing different heterocyclic nucleus (Z = CH = CH, O, S and Se) by the usual basic catalysed condensation between a suitable quaternarium ammonium salt (**1**) and a bisaldehyde (**2**), always produced complex mixtures. In our hands, the presumably more advantageous method of heating under reflux a solution of both reagents in butan-1-ol/benzene (7/3), in the absence of a catalyst, with azeotropic removal of water, lead to incomplete reaction providing, chiefly, the intermediate red dye **3** and only traces of the desired **4**.

Therefore, we used a new synthetic approach involving, firstly, an uncatalysed condensation between the quaternary salt **1** and bisaldehyde **2**, in butan-1-ol/benzene (7/3), accomplished heating

the solution under reflux. The resulting inter-mediate **3** was then treated, in situ, with a second molar equivalent of **1**, in the presence of pyridine, to produce the chlorocyanine dye **4** (Scheme 1). In some cases the later easily precipitated from the

cooled reaction mixture, allowing its isolation by a simple filtration.

It was observed, however, that when dye **4** was sufficiently soluble in the reaction solvent it was obtained, instead, a mixture consisting of the
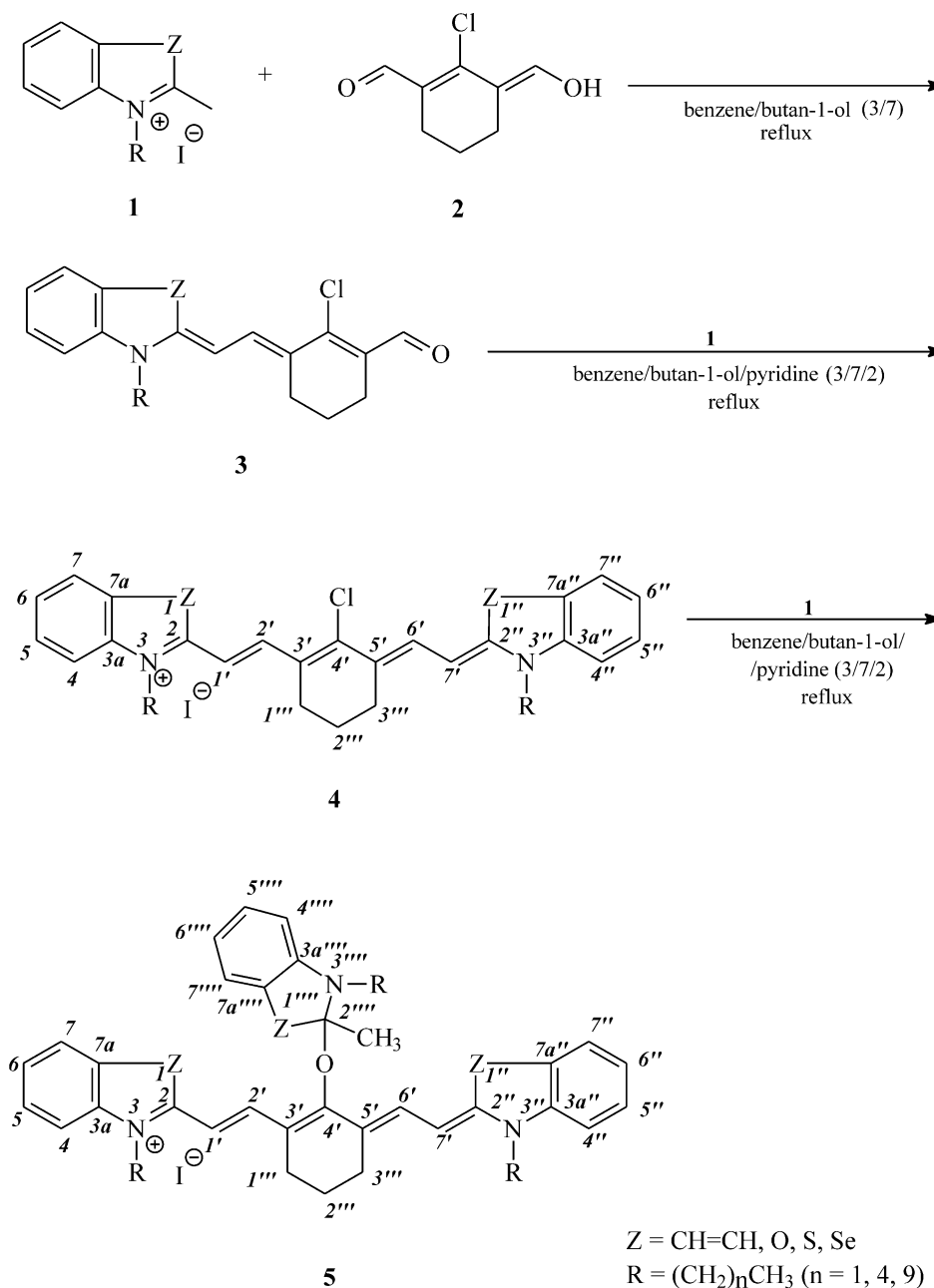
Scheme 1. Synthesis of substituted heptamethinecyanine dyes **4** and **5**.

unexpected derivative **5**, possessing a third oxygenated heterocyclic moiety substituting the central chlorine atom trough an ether linkage, together with an appreciable amount of intermediate **3** and

Table 1
Yields for the synthesis of heptamethinecyanine dyes **4** and **5**

Dye	Z	R	Yield (%)
4a	CH=CH	CH_2CH_3	47
4b	O	CH_2CH_3	25
4c	S	CH_2CH_3	75
5a	S	CH_2CH_3	85[a]
5b	S	$(CH_2)_4CH_3$	40
5c	S	$(CH_2)_9CH_3$	53
5d	Se	CH_2CH_3	97
5e	Se	$(CH_2)_4CH_3$	58
5f	Se	$(CH_2)_9CH_3$	41

[a] Starting from the isolated chloro dye **4c**.
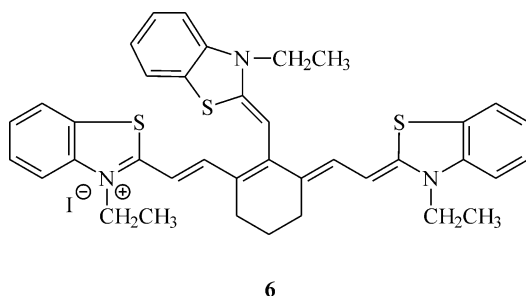
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Fig. 1. Structure of the tricyclic heptamethinecyanine dye previous proposed by Slominskii et al. [26].

only vestiges of **4**. In such cases the addition of 2 molar equivalents of the quaternarium ammonium salt **1** all at one go in the second reaction step readily increased the yield of the substituted dye **5**, which thus became the main reaction product.

By the aforementioned procedure several new symmetric rigidified heptamethinecyanine dyes have been prepared in rather good yields (Table 1).

The importance of the solubility of chloro dye **4** to the course of the reaction, determining which dye **4** or **5** could be isolated, was illustrated by the conversion of **4c** into **5a** in 85% yield heating under reflux a mixture of the former and 1 molar equivalent of the respective ammonium quaternary salt in pyridine, where were both completely soluble. Slominskii et al. [26] have previously briefly mentioned this same reaction, although they have ascribed to the isolated dye structure **6**, resulting from the direct nucleophilic substitution of the chlorine atom by the methylenic base, followed by elimination (Fig. 1). However, no analytical or spectroscopic data to corroborate this structure was given by those authors.

Two possible mechanisms for the formation of **5** are outlined in Scheme 2, both involving the water produced in the first uncatalysed condensation step and/or eventually present in the reaction solvents. In one way, the addition of a hydroxyl group to the quaternary salt **1** originates the 2-hydroxybenzoazole **8** which, under the basic
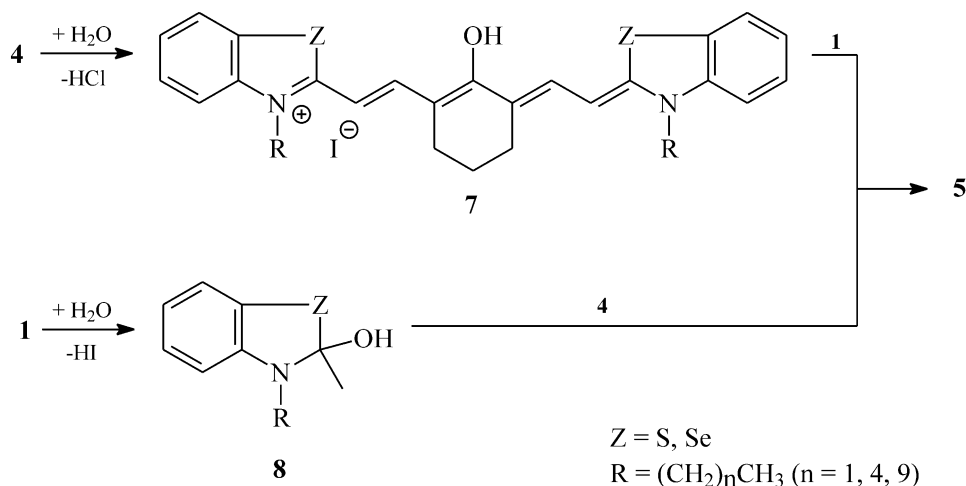
Scheme 2. Proposed mechanisms for the formation of the substituted heptamethinecyanine dyes **5**.

conditions of the second reaction step, substitutes the chlorine atom in the preformed dye **4**. Alternatively, the chlorine atom can undergo direct nucleophilic substitution by a hydroxyl group and the resulting dye **7** affords **5** by addition to salt **1**.

The in situ substitution of the chloro atom of rigidified heptamethinecyanines **4** by a third molecule of salt, providing a way for their expeditious functionalization, seems to be an interesting alternative to the usual process employing arylthiolates, phenolates or anilines [18–24].

The full spectroscopic characterisation of all dyes, including ¹H and ¹³C NMR shift assignments, which were established with the aid of HMQC (Heteronuclear Multiple Quantum Coherence), HMBQ (Heteronuclear Multiple Bond Correlation) and COSY (Correlated Spectroscopy) experiments, is reported. The numbering system (Scheme 1 and Fig. 2) used for that purpose is based on that of benzoazole dyes, being in agreement with previously published literature [32,34].

Mechanistic studies concerning the formation of **5** as well as the photochemical evaluation of dyes **4** and **5**, with prominence to the singlet oxygen production ability, are currently been undertaken.

3. Experimental

3.1. General

The ammonium quaternary salts **1** were prepared heating under reflux a solution of quinaldine or 2-methylbenzoazole and the appropriate alkyl iodide, in acetonitrile, as described elsewhere [42]. 2-Chloro-1-formyl-3-(hydroxymethylene)cyclohex-1-ene (**2**) was prepared according to the literature procedure [43]. All other reagents were purchased from Sigma-

Aldrich and used without further purification. Solvents were of analytical grade.

Reactions were monitored by thin-layer chromatography (tlc) using 0.25 mm aluminium-backed silica-gel plates (Merck 60 F_{254}). The tlc plates were eluted with CH_2Cl_2 or CH_2Cl_2/MeOH (9/1), the spots examined under 254, 312 and 365 nm UV light and developed upon exposure to iodine.

Melting points were measured in open capillary tubes in a Büchi 530 melting point apparatus and are uncorrected.

IR spectra were recorded on a Mattson 5000 FT-IR spectrophotometer. All samples were prepared by mixing FT-IR-grade KBr (Sigma-Aldrich) with 1% (w/w) dye, and grinding to a fine powder. Spectra were recorded over the 400–4000 cm^{-1} range without baseline corrections. Characteristic absorptions are given in cm^{-1}.

UV/Vis spectra were performed on a Perkin-Elmer Lambda 6 spectrophotometer using EtOH/MeCN (0.10 or 0.20%) as solvent. Wavelength of maximum absorption is reported in nm.

¹H and ¹³C NMR spectra were recorded in DMSO-d_6/CDCl$_3$ (1/1) solutions on a Brücker ACP 250 (250.13 and 62.90 MHz), a Brücker ARX 400 (400.13 and 100.62 MHz) and a Brücker ARX 500 Avance spectrometer (500.13 and 125.76 MHz). Chemical shifts are reported in ppm using TMS as an internal standard. Coupling constants (*J*) are given in Hz. HMQC, HMBC and COSY spectra were acquired on the Brücker ARX 400 spectrometer.

High Resolution Fast Atom Bombardment Mass Spectra (HR FAB-MS) were recorded in a Micromass AutoSpec M, operating at 70 eV, using a matrix of 3-nitrobenzyl alcohol (3-NBA).

3.2. General procedure for the synthesis of heptamethinecyanines 4 and 5

A solution of the quaternary ammonium salt **1** (1.0 mmol) and bisaldehyde **2** (1.0 mmol) in 75 mL of butan-1-ol/benzene (7/3) was heated under reflux. After complete consume of the salt (2–5 h), more **1** (1.0 mmol for the synthesis of **4** or 2.0 mmol for the synthesis of **5**) and 15 mL of pyridine were added and the resulting mixture heated under reflux for further 1–3 h.
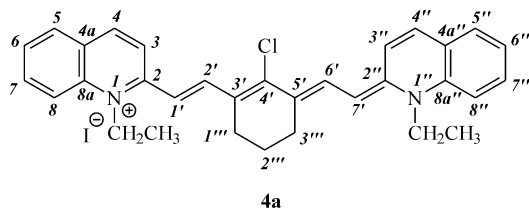

Fig. 2. Numbering system for NMR shift assignments of dye **4a**.

The chloro dyes **4** were collected by filtration of the cooled reaction mixture at reduced pressure (isolation method A).

For the isolation of the substituted chloro dyes **5** the solvent was evaporated to ca. 1/3 and the precipitated crystals collected by filtration at reduced pressure after cooling the concentrated reaction mixture (isolation method B). Alternatively, the solvent was removed at reduced pressure, the resulting residue redissolved in methanol and diethyl ether added. The precipitated dye was collected by filtration at reduced pressure and washed several times with water and diethyl ether (isolation method C).

3.2.1. 2-(2-{2-Chloro-3-[2-(1-ethyl-1H-quinolin-2-ylidene)ethylidene]cyclohex-1-enyl}vinyl)-1-ethyl-quinolinium iodide (4a)

Obtained from 1-ethyl-2-methylquinolinium iodide (isolation method A) in 47% overall yield, as ochre crystals; m.p. 257–258 °C (253–254 °C [27]); IR (KBr): 1534, 1478, 1434, 1356, 1239, 1217, 1192, 1146, 1119, 1080, 1051; UV/Vis (EtOH/CH$_3$CN 0.20%): 850; ^{1}H NMR [400.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 1.77 (6H, t, $J = 7.0$ MHz, NCH$_2$**CH$_3$**), 2.18 (2H, qt, $J = 6.0$ Hz, **H2$'''$**), 2.94 (4H, t, $J = 6.0$ Hz, **H1$'''$**, **H3$'''$**), 4.47 (4H, q, $J = 7.0$ Hz, N**CH$_2$**CH$_3$), 6.15 (2H, d, $J = 13.5$ Hz, **H1$'$**, **H7$'$**), 7.39 (2H, t, $J = 7.5$ Hz, **H6**, **H6$''$**), 7.69–7.73 (6H, m, **H5**, **H5$''$**, **H7**, **H7$''$**, **H8**, **H8$''$**), 7.78 (2H, d, $J = 9.5$ Hz, **H3**, **H3$''$**), 7.88 (2H, d, $J = 9.5$ Hz, **H4**, **H4$''$**), 8.14 (2H, d, $J = 13.5$ Hz, **H2$'$**, **H6$'$**); ^{13}C NMR [100.62 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 11.8 (NCH$_2$**CH$_3$**), 20.5 (**C2$'''$**), 26.4 (**C1$'''$**, **C3$'''$**), 43.1 (N**CH$_2$**CH$_3$), 103.7 (**C1$'$**, **C7$'$**), 115.2 (**C8**, **C8$''$**), 119.4 (**C3**, **C3$''$**), 124.8 (**C6**, **C6$''$**), 124.9 (**C3$'$**, **C5$'$**), 125.0 (**C4a**, **C4a$''$**), 128.9 (**C5**, **C5$''$**), 132.4 (**C7**, **C7$''$**), 136.1 (**C4**, **C4$''$**), 138.7 (**C8a**, **C8a$''$**), 140.0 (**C2$'$**, **C6$'$**), 145.8 (**C4$'$**), 150.1 (**C2**, **C2$''$**); HR FAB-MS (3-NBA): C$_{32}$H$_{32}$^{35}ClN$_2$: calc. 479.225402; found 479.224482; C$_{32}$H$_{32}$^{37}ClN$_2$: calc. 481.222452; found 481.223613.

3.2.2. 2-(2-{2-Chloro-3-[2-(3-ethyl-3H-benzoxazol-2-ylidene)ethylidene]cyclohex-1-enyl}vinyl)-3-ethylbenzoxazol-3-ium iodide (4b)

Obtained from 3-ethyl-2-methylbenzoxazol-3-ium iodide (isolation method A) in 25% overall yield, as green crystals; m.p. 255 °C; IR (KBr): 2943, 1576, 1515, 1435, 1419, 1393, 1272, 1233, 1180, 1115, 1083; UV/Vis (EtOH/CH$_3$CN 0.20%): 722; ^{1}H NMR [500.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 1.36 (6H, t, $J = 7.0$ Hz, NCH$_2$**CH$_3$**), 1.84 (2H, qt, $J = 5.5$ Hz, **H2$'''$**), 2.65 (4H, brs, **H1$'''$**, **H3$'''$**), 4.35 (4H, q, $J = 7.0$ Hz, N**CH$_2$**CH$_3$), 6.07 (2H, d, $J = 13.5$ Hz, **H1$'$**, **H7$'$**), 7.38 (2H, t, $J = 8.0$ Hz, **H6**, **H6$''$**), 7.44 (2H, t, $J = 8.0$ Hz, **H5**, **H5$''$**), 7.68 (2H, d, $J = 8.0$ Hz, **H4**, **H4$''$**), 7.78 (2H, d, $J = 8.0$ Hz, **H7**, **H7$''$**), 8.12 (2H, d, $J = 13.5$ Hz, **H2$'$**, **H6$'$**); ^{13}C NMR [62.90 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 12.5 (NCH$_2$**CH$_3$**), 20.4 (**C2$'''$**), 26.3 (**C1$'''$**, **C3$'''$**), 40.0 (N**CH$_2$**CH$_3$), 86.5 (**C1$'$**, **C7$'$**), 110.6 (**C4**, **C4$''$**, **C7**, **C7$''$**), 122.8 (**C3$'$**, **C5$'$**), 125.0 (**C6**, **C6$''$**), 125.8 (**C5**, **C5$''$**), 130.8 (**C3a**, **C3a$''$**), 141.7 (**C2$'$**, **C6$'$**), 146.6 (**C7a**, **C7a$''$**), 147.5 (**C4$'$**), 160.3 (**C2**, **C2$''$**); HR FAB-MS (3-NBA): C$_{28}$H$_{28}$^{35}ClN$_2$O$_2$: calc. 459.183931; found 459.185579; C$_{28}$H$_{28}$^{37}ClN$_2$O$_2$: calc. 461.180981; found 461.183132.

3.2.3. 2-(2-{2-Chloro-3-[2-(3-ethyl-3H-benzothiazol-2-ylidene)ethylidene]cyclohex-1-enyl}vinyl)-3-ethylbenzothiazol-3-ium iodide (4c)

Obtained from 3-ethyl-2-methylbenzothiazol-3-ium iodide (isolation method A) in 75% overall yield, as green shining crystals; m.p. 267 °C (248–249 °C [26]; 246–247 °C [27]; 263–265 °C [28]); IR (KBr): 2994, 2938, 1534, 1505, 1457, 1430, 1401, 1230, 1184, 1158, 1127, 1080, 1063, 1035, 1022; UV/Vis (EtOH/CH$_3$CN 0.10%): 799; ^{1}H NMR [400.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 1.38 (6H, t, $J = 7.0$ Hz, NCH$_2$**CH$_3$**), 1.89 (2H, qt, $J = 5.0$ Hz, **H2$'''$**), 2.69 (4H, t, $J = 5.0$ Hz, **H1$'''$**, **H3$'''$**), 4.48 (4H, q, $J = 7.0$ Hz, N**CH$_2$**CH$_3$), 6.46 (2H, d, $J = 13.5$ Hz, **H1$'$**, **H7$'$**), 7.37 (2H, t, $J = 7.5$ Hz, **H6**, **H6$''$**), 7.55 (2H, t, $J = 7.5$ Hz, **H5**, **H5$''$**), 7.71 (2H, d, $J = 8.0$ Hz, **H4**, **H4$''$**), 7.85 (2H, d, $J = 13.5$ Hz, **H2$'$**, **H6$'$**), 7.96 (2H, d, $J = 8.0$ Hz, **H7**, **H7$''$**); ^{13}C NMR [100.62 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 12.7 (NCH$_2$**CH$_3$**), 20.7 (**C2$'''$**), 26.7 (**C1$'''$**, **C3$'''$**), 41.7 (N**CH$_2$**CH$_3$), 99.3 (**C1$'$**, **C7$'$**), 113.0 (**C4**, **C4$''$**), 122.9 (**C7**, **C7$''$**), 124.5 (**C3$'$**, **C5$'$**), 125.2 (**C6**, **C6$''$**), 125.6 (**C7a**, **C7a$''$**), 128.1 (**C5**, **C5$''$**), 141.2 (**C3a**, **C3a$''$**), 141.6 (**C2$'$**, **C6$'$**), 145.7 (**C4$'$**), 163.2 (**C2**, **C2$''$**); HR FAB-MS (3-NBA): C$_{28}$H$_{28}$^{35}ClN$_2$S$_2$: calc. 491.138245; found 491.137408; C$_{28}$H$_{28}$^{37}ClN$_2$O$_2$: calc. 493.135295; found 493.136293.

3.2.4. 2-(2-{2-(2-Methyl-3-pentyl-2,3-dihydrobenzo-thiazol-2-yloxy)-3-[2-(3-pentyl-3H-benzothiazol-2-ylidene)ethylidene]cyclohex-1-enyl}vinyl)-3-pentyl-benzothiazol-3-ium iodide (5b)

Obtained from 2-methyl-3-pentylbenzothiazol-3-ium iodide (isolation method B), in 40% overall yield, as green shining crystals; m.p. 209–210 °C; IR (KBr): 2981, 2935, 1651, 1515, 1454, 1394, 1223, 1173, 1152, 1117, 1108, 1062; UV/Vis (EtOH/CH$_3$CN 0.20%): 817; ^{1}H NMR [400.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 0.87 [9H, t, $J = 7.0$ Hz, N(CH$_2$)$_4$CH$_3$], 1.36 [12H, brs, N(CH$_2$)$_2$(CH$_2$)$_2$-CH$_3$], 1.60 [2H, brs, N3$''''$CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$], 1.74 [4H, brs, NCH$_2$CH$_2$(CH$_2$)$_2$CH$_3$], 1.94 (3H, s, C2$''''$CH$_3$), 2.00 (2H, qt, $J = 5.5$ Hz, H2$'''$), 2.71 (4H, brs, H1$'''$, H3$'''$), 3.29 [partially overlapped by the signal of H$_2$O, N3$''''$CH$_2$(CH$_2$)$_3$CH$_3$], 4.28 [partially overlapped by the signal of NCH$_2$(CH$_2$)$_3$-CH$_3$, N3$''''$CH$_2$(CH$_2$)$_3$CH$_3$], 4.30 [4H, t, $J = 7.0$ Hz, NCH$_2$(CH$_2$)$_3$CH$_3$), 6.37 (2H, d, $J = 13.5$ Hz, H1$'$, H7$'$), 6.93 (1H, d, $J = 7.0$ Hz, H$''''$), 7.13–7.21 (3H, m, H$''''$), 7.31 (2H, t, $J = 7.5$ Hz, H6, H6$''$), 7.46 (2H, t, $J = 7.5$ Hz, H5, H5$''$), 7.52 (2H, d, $J = 8.5$ Hz, H4, H4$''$), 7.66 (2H, d, $J = 7.5$ Hz, H7, H7$''$), 8.08 (2H, d, $J = 13.5$ Hz, H2$'$, H6$'$); ^{13}C NMR [62.90 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 13.4 [N(CH$_2$)$_4$CH$_3$], 13.6 [N3$''''$(CH$_2$)$_4$CH$_3$], 20.3 (C2$'''$), 21.6 [N(CH$_2$)$_3$CH$_2$CH$_3$], 21.8 [N3$''''$(CH$_2$)$_3$CH$_2$-CH$_3$], 22.2 (C2$''''$CH$_3$), 26.4 (C1$'''$, C3$'''$), 26.8 [N(CH$_2$)$_2$CH$_2$CH$_2$CH$_3$], 27.1 [N3$''''$(CH$_2$)$_2$CH$_2$CH$_2$-CH$_3$], 28.0 [NCH$_2$CH$_2$(CH$_2$)$_2$CH$_3$], 28.7 [N3$''''$CH$_2$-CH$_2$(CH$_2$)$_2$CH$_3$], 46.1 [NCH$_2$(CH$_2$)$_3$CH$_3$], 46.7 [N3$''''$CH$_2$(CH$_2$)$_3$CH$_3$], 99.6 (C1$'$, C7$'$), 112.8 (C4, C4$''$), 122.1 (C7, C7$''$), 124.8 (C6, C6$''$, C7a, C7a$''$), 125.7 and 125.9 (CH$''''$), 127.8 (C5, C5$''$), 128.8 and 129.3 (CH$''''$), 131.4 (C3$'$, C5$'$), 136.6 and 138.1 (C3a$''''$, C7a$''''$), 141.1 (C3a, C3a$''$), 142.0 (C2$'$, C6$'$), 143.5 (C4$'$), 162.7 (C2, C2$''$), 169.1 (C2$''''$); HR FAB-MS (3-NBA): C$_{47}$H$_{58}$N$_3$OS$_3$: calc. 776.374204; found 776.371587.

3.2.5. 3-Decyl-2-(2-{3-[2-(3-decyl-3H-benzothi-azol-2-ylidene)ethylidene]-2-(3-decyl-2-methyl-2,3-dihydrobenzothiazol-2-yloxy)cyclohex-1-enyl}-vinyl)benzothiazol-3-ium iodide (5c)

Obtained from 3-decyl-2-methylbenzothiazol-3-ium iodide (isolation method C) in 53% overall yield, as dark copper crystals; m.p. 186 °C; IR (KBr):

2921, 2852, 1659, 1517, 1394, 1224, 1152, 1119, 1060, 1034, 1012; UV/Vis (EtOH/CH$_3$CN 0.20%): 811; ^{1}H NMR [400.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 0.80 [3H, t, $J = 7.0$ Hz, N3$''''$(CH$_2$)$_9$CH$_3$], 0.83 [6H, t, $J = 7.0$ Hz, N(CH$_2$)$_9$CH$_3$], 1.14–1.39 [42H, m, N(CH$_2$)$_2$(CH$_2$)$_7$CH$_3$], 1.73 [6H, qt, $J = 7.0$ Hz, NCH$_2$CH$_2$(CH$_2$)$_7$CH$_3$], 1.94 (3H, s, C2$''''$CH$_3$), 1.97 (2H, qt, $J = 6.0$ Hz, H2$'''$), 2.73 (4H, brs, H1$'''$, H3$'''$), 3.30 [partially overlapped by the signal of H$_2$O, N3$''''$CH$_2$(CH$_2$)$_8$CH$_3$], 4.19–4.26 [1H, m, N3$''''$CH$_2$(CH$_2$)$_8$CH$_3$], 4.33 (4H, t, $J = 7.0$ Hz, NCH$_2$(CH$_2$)$_8$CH$_3$), 6.40 (2H, d, $J = 13.0$ Hz, H1$'$, H7$'$), 6.96 (1H, d, $J = 8.0$ Hz, H$''''$), 7.14–7.24 (3H, m, H$''''$), 7.31 (2H, t, $J = 7.5$ Hz, H6, H6$''$), 7.48 (2H, t, $J = 8.0$ Hz, H5, H5$''$), 7.57 (2H, d, $J = 8.5$ Hz, H4, H4$''$), 7.70 (2H, d, $J = 8.0$ Hz, H7, H7$''$), 8.08 (2H, d, $J = 13.0$ Hz, H2$'$, H6$'$); ^{13}C NMR [62.90 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 13.7 [N(CH$_2$)$_9$CH$_3$], 20.6 (C2$'''$), 22.4 (C2$''''$CH$_3$), 22.0 and 25.9 [NCH$_2$(CH$_2$)$_8$CH$_3$], 26.5, 26.7 and 27.2 [C1$'''$, C3$'''$, NCH$_2$(CH$_2$)$_8$CH$_3$], 27.6, 28.6, 28.8, 28.9, 29.1 and 31.2 [NCH$_2$(CH$_2$)$_8$CH$_3$], 46.2 [NCH$_2$(CH$_2$)$_8$CH$_3$], 47.0 [N3$''''$CH$_2$(CH$_2$)$_8$CH$_3$], 99.7 (C1$'$, C7$'$), 112.9 (C4, C4$''$), 122.2 (C7, C7$''$), 124.9 (C6, C6$''$, C7a, C7a$''$), 125.9 and 126.0 (CH$''''$), 127.9 (C5, C5$''$), 128.9 and 129.0 (CH$''''$), 131.4 (C3$'$, C5$'$), 136.7 and 138.3 (C3a$''''$, C7a$''''$), 141.2 (C3a, C3a$''$), 142.2 (C2$'$, C6$'$), 143.5 (C4$'$), 162.8 (C2, C2$''$), 169.3 (C2$''''$); HR FAB-MS (3-NBA): C$_{62}$H$_{88}$N$_3$OS$_3$: calc. 986.608956; found 986.609693.

3.2.6. 3-Ethyl-2-(2-{3-[2-(3-ethyl-3H-benzoselen-azol-2-ylidene)ethylidene]-2-(3-ethyl-2-methyl-2,3-dihydrobenzoselenazol-2-yloxy)cyclohex-1-enyl}-vinyl)benzoselenazol-3-ium iodide (5d)

Obtained from 3-ethyl-2-methylbenzoselenazol-3-ium iodide (isolation method B) in 97% overall yield, as copper crystals; m.p. 271 °C; IR (KBr): 2976, 2937, 1654, 1514, 1388, 1218, 1173, 1149, 1110, 1062, 1017; UV/Vis (EtOH/CH$_3$CN 0.20%): 819; ^{1}H NMR [400.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 1.29 (3H, t, $J = 7.0$ Hz, N3$''''$CH$_2$CH$_3$), 1.39 (6H, t, $J = 7.0$ Hz, NCH$_2$CH$_3$), 1.97 (3H, s, C2$''''$CH$_3$), 2.01 (2H, qt, $J = 5.5$ Hz, H2$'''$), 2.79 (4H, brs, H1$'''$, H3$'''$), 3.46 (1H, dq, $J = 13.5$, 7.0 Hz, N3$''''$CH$_2$CH$_3$), 4.28 (1H, (1H, dq, $J = 13.5$, 7.0 Hz, N3$''''$CH$_2$CH$_3$), 4.41 (4H, q, $J = 7.0$ Hz,

NCH$_2$CH$_3$), 6.55 (2H, *d*, *J* = 13.0 Hz, **H**1′, **H**7′), 7.11–7.14 (1H, *m*, **H**′′′′), 7.23–7.28 (3H, *m*, **H**′′′′), 7.29 (2H, *t*, *J* = 7.5 Hz, **H**6, **H**6′′), 7.50 (2H, *t*, *J* = 7.5 Hz, **H**5, **H**5′′), 7.54 (2H, *d*, *J* = 8.0 Hz, **H**4, **H**4′′), 7.93 (2H, *d*, *J* = 8.0 Hz, **H**7, **H**7′′), 8.11 (2H, *d*, *J* = 13.0 Hz, **H**2′, **H**6′); ^{13}C NMR [100.62 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 12.5 (NCH$_2$**C**H$_3$), 13.4 (N3′′′′CH$_2$**C**H$_3$), 20.9 (**C**2′′′), 22.9 (**C**2′′′′**C**H$_3$), 27.3 (**C**1′′′, **C**3′′′), 42.2 (N3′′′′**C**H$_2$CH$_3$), 42.5 (N**C**H$_2$CH$_3$), 103.3 (**C**1′, **C**7′), 114.3 (**C**4, **C**4′′), 125.0 (**C**6, **C**6′′), 125.3 (**C**7a, **C**7a′′), 126.2 (**C**7, **C**7′′), 127.1 (**C**H′′′′), 128.0 (**C**5, **C**5′′), 129.0, 129.4 and 129.8 (**C**H′′′′), 133.0 (**C**3′, **C**5′), 133.8 and 140.1 (**C**3a′′′′, **C**7a′′′′), 142.6 (**C**3a, **C**3a′′), 146.6 (**C**4′), 147.2 (**C**2′, **C**6′), 167.5 (**C**2, **C**2′′), 169.3 (**C**2′′′′); HR FAB-MS (3-NBA): C$_{38}$H$_{40}$N$_3$O^{78}Se$_3$: calc. 788.069050; found 788.071391; C$_{38}$H$_{40}$N$_3$-O^{78}Se$_2^{80}$Se: calc. 790.068267; found 790.066321; C$_{38}$H$_{40}$N$_3$O^{78}Se^{80}Se$_2$: calc. 792.067483; found 792.063864; C$_{38}$H$_{40}$N$_3$O^{80}Se$_3$: calc. 794.066922; found 794.066700.

3.2.7. 2-(2-{2-(2-Methyl-3-pentyl-2,3-dihydrobenzo-selenazol-2-yloxy)-3-[2-(3-pentyl-3H-benzoselenazol-2-ylidene)ethylidene]cyclohex-1-enyl}vinyl)-3-pentylbenzoselenazol-3-ium iodide (5e)

Obtained from 2-methyl-3-pentylbenzoselenazol-3-ium iodide (isolation method C) in 58% overall yield, as copper shining crystals; m.p. 212 °C; IR (KBr): 2953, 2934, 2869, 1653, 1509, 1392, 1221, 1172, 1153, 1112, 1062; UV/Vis (EtOH/CH$_3$CN 0.10%): 819; ^{1}H NMR [400.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 0.87 [3H, *t*, *J* = 6.5 Hz, N3′′′′(CH$_2$)$_4$**C**H$_3$], 0.92 [6H, *t*, *J* = 6.5 Hz, N(CH$_2$)$_4$**C**H$_3$], 1.36 [4H, *brs*, N3′′′′(CH$_2$)$_2$(**C**H$_2$)$_2$-CH$_3$], 1.42 [8H, *brs*, N(CH$_2$)$_2$(**C**H$_2$)$_2$CH$_3$], 1.64 [2H, *brs*, N3′′′′CH$_2$**C**H$_2$(CH$_2$)$_2$CH$_3$], 1.77 [4H, *brs*, NCH$_2$**C**H$_2$(CH$_2$)$_2$CH$_3$], 1.95 (3H, *s*, C2′′′′**C**H$_3$), 2.02 (2H, *qt*, *J* = 5.5 Hz, **H**2′′′), 2.78 (4H, *brs*, **H**1′′′, **H**3′′′), 3.26 [partially overlapped by the signal of H$_2$O, N3′′′′**C**H$_2$(CH$_2$)$_3$CH$_3$], 4.26 [partially overlapped by the signal of NCH$_2$(CH$_2$)$_3$CH$_3$, N3′′′′**C**H$_2$(CH$_2$)$_3$CH$_3$], 4.33 [4H, *t*, *J* = 7.0 Hz, N**C**H$_2$(CH$_2$)$_3$CH$_3$], 6.53 (2H, *d*, *J* = 13.0 Hz, **H**1′, **H**7′), 7.15–7.17 (1H, *m*, **H**′′′′), 7.24–7.28 (3H, *m*, **H**′′′′), 7.30 (2H, *t*, *J* = 7.5 Hz, **H**6, **H**6′′), 7.50 (2H, *t*, *J* = 7.5 Hz, **H**5, **H**5′′), 7.53 (2H, *d*, *J* = 7.5 Hz, **H**4, **H**4′′), 7.78 (2H, *d*, *J* = 8.0 Hz, **H**7, **H**7′′), 8.11

(2H, *d*, *J* = 13.0 Hz, **H**2′, **H**6′); ^{13}C NMR [62.90 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 13.5 [N(CH$_2$)$_4$**C**H$_3$], 13.8 [N3′′′′(CH$_2$)$_4$**C**H$_3$], 20.5 (**C**2′′′), 21.7 [N(CH$_2$)$_3$**C**H$_2$CH$_3$], 21.9 [N3′′′′(CH$_2$)$_3$**C**H$_2$CH$_3$], 22.6 (**C**2′′′′**C**H$_3$), 26.7 [N(CH$_2$)$_2$**C**H$_2$CH$_2$CH$_3$], 27.0 and 27.2 [**C**1′′′, **C**3′′′, N3′′′′(CH$_2$)$_2$**C**H$_2$CH$_2$CH$_3$], 28.1 [NCH$_2$**C**H$_2$(CH$_2$)$_2$CH$_3$], 28.7 [N3′′′′CH$_2$-**C**H$_2$(CH$_2$)$_2$CH$_3$], 46.8 [N3′′′′**C**H$_2$(CH$_2$)$_3$CH$_3$], 47.1 [N**C**H$_2$(CH$_2$)$_3$CH$_3$], 103.1 (**C**1′, **C**7′), 114.2 (**C**4, **C**4′′), 124.8 (**C**6, **C**6′′, **C**7a, **C**7a′′), 125.6 (**C**7, **C**7′′), 126.9 (**C**H′′′′), 127.7 (**C**5, **C**5′′), 129.0, 129.2 and 129.6 (**C**H′′′′), 132.6 (**C**3′, **C**5′), 133.2 and 140.0 (**C**3a′′′′, **C**7a′′′′), 142.6 (**C**3a, **C**3a′′), 146.7 (**C**4′), 147.1 (**C**2′, **C**6′), 167.4 (**C**2, **C**2′′), 169.2 (**C**2′′′′); HR FAB-MS (3-NBA): C$_{47}$H$_{58}$N$_3$O^{78}Se$_3$: calc. 914.205431; found 914.205977; C$_{47}$H$_{58}$N$_3$O ^{78}Se$_2^{80}$Se: calc. 916.209117; found 916.202894; C$_{47}$H$_{58}$N$_3$O^{78}Se^{80}Se$_2$: calc. 918.208334; found 918.203844; C$_{47}$H$_{58}$N$_3$O^{80}Se$_3$: calc. 920.207550; found 920.204857.

3.2.8. 3-Decyl-2-(2-{3-[2-(3-decyl-3H-benzoselena-zol-2-ylidene)ethylidene]-2-(3-decyl-2-methyl-2,3-dihydrobenzoselenazol - 2 - yloxy)cyclohex - 1 - enyl}-vinyl)benzoselenazol-3-ium iodide (5f)

Obtained from 3-decyl-2-methylbenzoselenazol-3-ium iodide (isolation method C) in 41% overall yield, as dark copper crystals; m.p. 185–186 °C; IR (KBr): 2924, 2853, 1660, 1513, 1390, 1218, 1152, 1102, 1061, 1001; UV/Vis (EtOH/CH$_3$CN 0.20%): 821; ^{1}H NMR [400.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 0.80 [3H, *t*, *J* = 7.0 Hz, N3′′′′(CH$_2$)$_9$**C**H$_3$], 0.83 [6H, *t*, *J* = 7.0 Hz, N(CH$_2$)$_9$**C**H$_3$], 1.12–1.39 [42H, *m*, N(CH$_2$)$_2$(**C**H$_2$)$_7$CH$_3$], 1.71 [6H, *qt*, *J* = 7.5 Hz, NCH$_2$**C**H$_2$(CH$_2$)$_7$CH$_3$], 1.89 (3H, *s*, C2′′′′**C**H$_3$), 1.95 (2H, *qt*, *J* = 6.5 Hz, **H**2′′′), 2.74 (4H, *brs*, **H**1′′′, **H**3′′′), 3.29 [partially overlapped by the signal of H$_2$O, N3′′′′**C**H$_2$(CH$_2$)$_8$CH$_3$], 4.15–4.25 [1H, *m*, N3′′′′**C**H$_2$(CH$_2$)$_8$CH$_3$], 4.33 [4H, *t*, *J* = 7.5 Hz, N**C**H$_2$(CH$_2$)$_8$CH$_3$], 6.53 (2H, *d*, *J* = 13.0 Hz, **H**1′, **H**7′), 7.13–7.16 (1H, *m*, **H**′′′′), 7.23–7.26 (3H, *m*, **H**′′′′), 7.26 (2H, *t*, *J* = 7.5 Hz, **H**6, **H**6′′), 7.47 (2H, *t*, *J* = 8.0 Hz, **H**5, **H**5′′), 7.57 (2H, *d*, *J* = 8.5 Hz, **H**4, **H**4′′), 7.89 (2H, *d*, *J* = 8.0 Hz, **H**7, **H**7′′), 8.05 (2H, *d*, *J* = 13.0 Hz, **H**2′, **H**6′); ^{13}C NMR [100.62 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 13.7 [N(CH$_2$)$_9$**C**H$_3$], 20.5 (**C**2′′′), 21.9 [NCH$_2$(CH$_2$)$_8$-CH$_3$], 22.5 (**C**2′′′′**C**H$_3$), 25.7, 25.9 [NCH$_2$(CH$_2$)$_8$-

CH$_3$], 26.5, 27.0 and 27.4 [**C**1$'''$, **C**3$'''$, NCH$_2$(**CH$_2$**)$_8$CH$_3$], 28.4, 28.5, 28.7, 28.8, 29.0 and 31.1 [NCH$_2$(**CH$_2$**)$_8$CH$_3$], 46.9 [N**CH$_2$**(CH$_2$)$_8$CH$_3$], 103.5 (**C**1$'$, **C**7$'$), 114.5 (**C**4, **C**4$''$), 124.7 (**C**7a, **C**7a$''$), 124.9 (**C**6, **C**6$''$), 125.8 (**C**7, **C**7$''$), 127.0 (**CH**$''''$), 127.8 (**C**5, **C**5$''$), 129.0, 129.2 and 129.8 (**CH**$''''$), 132.5 (**C**3$'$, **C**5$'$), 133.2 and 140.2 (**C**3a$'''$, **C**7a$''''$), 142.7 (**C**3a, **C**3a$''$), 146.7 (**C**2$'$, **C**6$'$), 146.0 (**C**4$'$), 167.5 (**C**2, **C**2$''$), 169.0 (**C**2$''''$); HR FAB-MS (3-NBA): C$_{62}$H$_{88}$N$_3$O^{78}Se$_3$: calc. 1124.440182; found 1124.441085; C$_{62}$H$_{88}$N$_3$O^{78}Se$_2$^{80}Se: calc. 1126.443869; found 1126.447036; C$_{62}$H$_{88}$N$_3$O ^{78}Se^{80}Se$_2$: calc. 1128.443085; found 1128.445326; C$_{62}$H$_{88}$N$_3$O^{80}Se$_3$: calc. 1130.442302; found 1130.444122.

3.2.9. 3-Ethyl-2-(2-{3-[2-(3-ethyl-3H-benzothiazol-2-ylidene)ethylidene]-2-(3-ethyl-2-methyl-2,3-di-hydrobenzothiazol-2-yloxy)cyclohex-1-enyl}vinyl)-benzothiazol-3-ium iodide (5a)

A solution of **4c** (1.0 mmol) and 3-ethyl-2-methylbenzothiazolium iodide (1.0 mmol) in 25 mL of pyridine was heated under reflux for 3 h. The resulting cyanine dye **5a** was isolated by the method A previously described in 85% yield, as golden crystals, m.p. 264 °C; IR (KBr): 2925, 1656, 1513, 1390, 1218, 1173, 1147, 1113, 1079, 1060, 1033, 1017; UV/Vis (EtOH/CH$_3$CN 0.20%): 814; ^{1}H NMR [400.13 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 1.32 (3H, t, J = 7.0 Hz, N3$''''$**CH$_2$CH$_3$**), 1.41 (6H, t, J = 7.0 Hz, NCH$_2$**CH$_3$**), 1.93 (2H, qt, J = 6.0 Hz, **H**2$'''$), 2.00 (3H, s, C2$''''$**CH$_3$**), 2.68 (4H, brs, **H**1$'''$, **H**3$'''$), 3.51 (1H, dq, J = 13.5, 7.0 Hz, N3$''''$**CH$_2$**CH$_3$), 4.32 (1H, dq, J = 13.5, 7.0 Hz, N3$''''$**CH$_2$**CH$_3$), 4.45 (4H, q, J = 7.0 Hz, N**CH$_2$**CH$_3$), 6.40 (2H, d, J = 13.5 Hz, **H**1$'$, **H**7$'$), 6.96 (1H, d, J = 7.5 Hz, **H**$''''$), 7.19–7.28 (3H, m, **H**$''''$), 7.28 (2H, t, J = 7.5 Hz, **H**6, **H**6$''$), 7.42 (2H, t, J = 7.5 Hz, **H**5, **H**5$''$), 7.49 (2H, d, J = 8.0 Hz, **H**4, **H**4$''$), 7.75 (2H, d, J = 8.0 Hz, **H**7, **H**7$''$), 8.07 (2H, d, J = 13.5 Hz, **H**2$'$, **H**6$'$); ^{13}C NMR [62.90 MHz, DMSO-d_6/CDCl$_3$ (1/1)]: 12.5 (N**CH$_2$CH$_3$**), 13.2 (N3$''''$**CH$_2$CH$_3$**), 20.4 (**C**2$''$), 22.5 (C2$''''$**CH$_3$**), 26.6 (**C**1$'''$, **C**3$'''$), 41.4 (N**CH$_2$**CH$_3$), 41.5 (N3$''''$**CH$_2$**CH$_3$), 99.8 (**C**1$'$, **C**7$'$), 112.7 (**C**4, **C**4$''$), 122.6 (**C**7, **C**7$''$), 124.9 (**C**6, **C**6$''$), 125.1 (**C**7a, **C**7a$''$), 125.8 (**CH**$''''$), 127.9 (**C**5, **C**5$''$), 129.0 and 129.6 (**CH**$''''$), 131.7 (**C**3$'$, **C**5$'$), 137.1 and 137.9

(**C**3a$'''$, **C**7a$''''$), 140.8 (**C**3a, **C**3a$''$), 141.9 (**C**2$'$, **C**6$'$), 143.2 (**C**4$'$), 162.4 (**C**2, **C**2$''$), 169.1 (**C**2$''''$); HR FAB-MS (3-NBA): C$_{38}$H$_{40}$N$_3$OS$_3$: calc. 650.233354; found: 650.232079.

4. Conclusions

A novel semi-catalyzed method for the synthesis of symmetric rigidified chloroheptamethine-cyanine dyes displaying absorption in the near infrared was developed. This approach can, in principle, be extended to the synthesis of asymmetric dyes, both in the N-alkyl and heterocyclic nature.

The chlorine atom incorporated in the conjugated exocyclic ring of the polimethine chain of the dyes easily undergoes an in situ nucleophilic substitution by a third oxygenated heterocyclic group, with formation of an ether connection, depending on the solubility of the chloro dye in the reaction solvent. This process constitutes an expeditious alternative to the traditional functionalization methodology of chloroheptamethine-cyanine dyes.

Acknowledgements

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