

Synthesis and structure of new 3,7,10-substituted-phenothiazine derivatives

Research Article

Raluca Turdean¹, Elena Bogdan¹, Anamaria Terec¹, Anca Petran¹,
Laurian Vlase², Ioan Turcu³, Ion Grosu^{1*}

¹"Babes-Bolyai" University, Organic Chemistry Department and CCOCCAN,
RO-400028, Cluj-Napoca, Romania

²Faculty of Pharmacy, University of Medicine and Pharmacy "Iuliu Hațieganu",
RO-400023, Cluj-Napoca, Romania,

³National Institute of Research and Development for Isotopic and Molecular Technologies,
RO-400293 Cluj-Napoca, Romania

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Abstract: The synthesis of new 3,7-dibromophenothiazine derivatives bearing bromoalkyl, mercaptoalkyl and alkylthioacetate groups on the N atom at position 10 is reported. The Suzuki coupling reaction of one of these derivatives via the bromine atoms at positions 3 and 7 with bromothiophene derivatives is also discussed.

Keywords: *N*-Bromoalkyl • *N*-alkylthioacetate and *N*-Mercaptoalkyl 3,7-dibromophenothiazines • Podands • Suzuki coupling

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1. Introduction

Phenothiazine and its derivatives exhibit many applications as pharmaceuticals, in material sciences and biochemistry [1-5]. Many phenothiazine derivatives are fluorescent, show a low oxidation potential having the ability to form stable radical-cations, and are used as chromophores for photoinduced electron transfer experiments [2,6]. The oxidation of phenothiazine derivatives leads to the corresponding sulfoxide, which (in non-symmetrically substituted compounds) can be used to determine the chirality of the molecules [7]. Due to their properties, phenothiazine derivatives are interesting candidates for obtaining new materials (e.g. mercapto or thioacetate derivatives) by deposition as self assembled monolayers (SAMs) on gold (1.1.1) surface. Some recent publications revealed special properties for the aggregates obtained by the deposition of phenothiazine units on GNP (gold nanoparticles) via mercapto derivatives [8], or for aggregates that exhibit phenothiazine units at their surface and are built up by ester or ether group formation reactions [9-10]. The phenothiazine units are connected to different materials or substrates using as linkers alkyl or (poly) ethyleneoxid chains attached to the N atom at position 10 (Fig. 1, I: X = H, Y = SH, COOH, OH). In the majority

of the cases the key compounds are the brominated precursors (X = H, Y = Br; n = 2, 5, 9).

The synthesis of 10-bromoalkylphenothiazines was carried out using unsubstituted phenothiazine with dibromoalkanes (A), chlorobromoalkanes (B) or bromoalcohols (C) and a base, either NaH, BuLi (A), NaNH₂ (B), or K₂CO₃ and I₂ (C). The access to 10-bromoalkylphenothiazines exhibited different problems:

- the formation of important amounts of side products (A, 10-alkenylphenothiazines),
- requested several steps (C)
- the reagents are commercially available in a limited variety (B, C).

We considered of interest to develop new strategies for the synthesis of 10-bromoalkylphenothiazines (X = H, Y = Br, Fig. 1), for their mercapto analogs (X = H, Y = SH, Fig. 1) and for the obtaining of similar derivatives with bromine atoms at the positions 3 and 7 of the phenothiazine skeleton (X = Br; Y = Br, SH; n = 2, 5, 7; Fig. 1). 3,7-Dibrominated phenothiazine derivatives can be important intermediates for the synthesis of large varieties of 3,7-substituted derivatives of this heterocyclic substrate [11]. Some of them can be used as podands for the synthesis of macrocycles with phenothiazine motif [12].

* E-mail: igrosu@chem.ubbcluj.ro

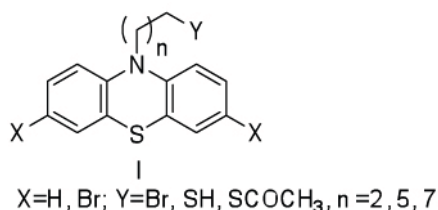


Figure 1. 10-Substituted-phenothiazines as possible starting compounds or precursors for SAMs

2. Results and Discussion

New phenothiazine derivatives, substituted at position 10 with alkyl chains bearing thioacetate (8-10) or mercapto (11-13) groups, were obtained starting from phenothiazine 1 (Scheme 1, Table 1)

In the first step the starting compound was alkylated to 10-bromoalkyl phenothiazine compounds using dibromoalkanes [Br-(CH₂)_{n+1}-Br; n = 2, 5, 7]. After several experiments carried out to obtain the compound 2 we concluded that the best results are obtained using Cu / K₂CO₃ in an alkylation procedure adapted from the literature [13]. In this procedure the conversion of phenothiazine in 10-bromoalkylphenothiazine is running in fair to good yields and no side products are obtained. The method described for obtaining the bromodecyl derivative (n = 9), based on the deprotonation of phenothiazine with BuLi followed by reaction with the dibrominated alkane, gives poor yields of the monobrominated derivative 2 [14]. The reaction could not be controlled and the alkylation process was followed by dehydrobromination to yield the terminal 10-alkenyl-phenothiazine derivative as the main product. Similar results were obtained when BuLi was replaced with NaH or t-BuOK following other alkylation procedures described in the literature [15-17].

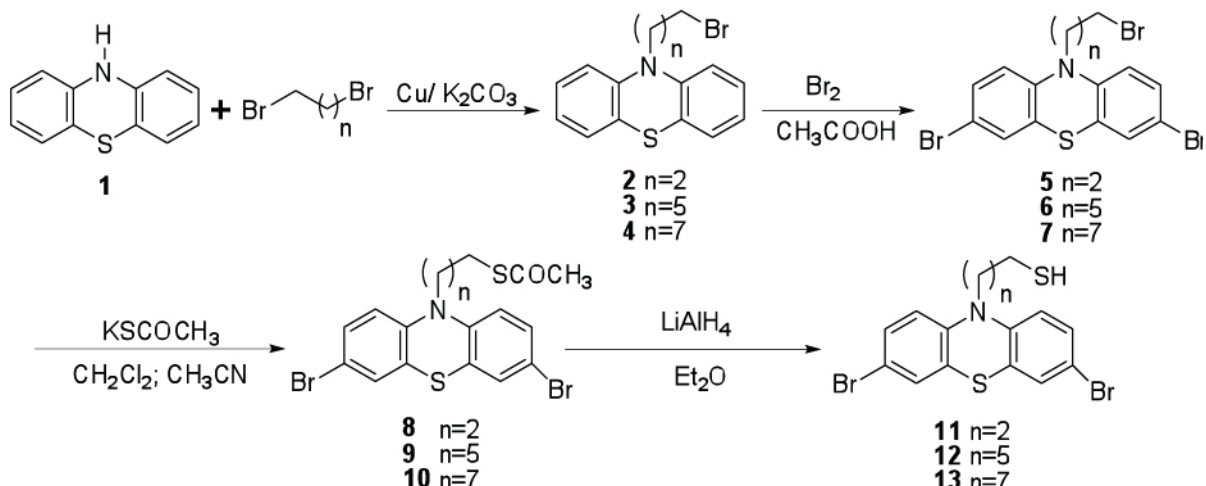
The second step was carried out using CH₃COSK [14] and the yields were very good, while the reduction of thioacetate to the mercapto group was carried out using a procedure described in the literature for the synthesis of other thiol substrates [18]. The yields varied in this case from fair to good.

Table 1. Results obtained in the synthesis of compounds 2-13.

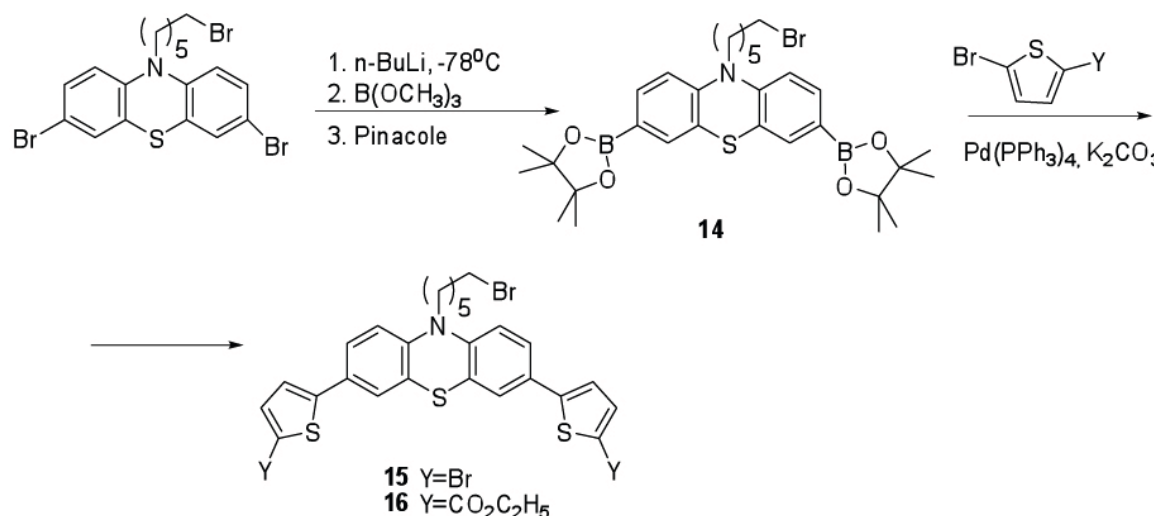
Compd.	Yields (%)	Compd.	Yields (%)	Compd.	Yields (%)
2	33	6	68	10	74
3	36	7	68	11	59
4	40	8	62	12	59
5	60	9	77	13	21

In order to elaborate procedures for the synthesis of other intermediates we transformed compound 6 into its diboronic ester 14 (by a procedure taken from the literature [19]) and then by a palladium catalyzed Suzuki coupling reaction [20-25] we obtained 3,7-bis(5'-bromothiophene-2'-yl)phenothiazines 15 and 16 (Scheme 2).

Compound 14 was obtained in fair yields (28%), it could be isolated by flash chromatography and after that it was submitted to the Suzuki coupling reaction. Compound 15 was obtained in good yield (63%), while the synthesis of 16 was isolated in 23% yield. The use of pinacole for the synthesis of the intermediate boronic ester is crucial. The resulting cyclic hindered ester, in comparison with the similar methyl or ethyl esters, is considerably more stable and makes the column purification of the boronic derivative possible. The use of crude boronic methyl or ethyl esters in the Suzuki coupling reactions (obtaining of 15 and 16) resulted into poor yields. Compounds 15 and 16 are potential candidates as substrate for the synthesis



Scheme 1. Scheme of synthesis of the new phenothiazine derivatives



Scheme 2. Scheme of synthesis of 3,7-bis(5'-bromothiophene-2'-yl)phenothiazines 15 and 16

of macrocycles, which after similar modifications with those shown for 2-4 could be transformed into the mercapto derivatives and then deposited on gold 1.1.1 surface.

The structure of the compounds was deduced by ^1H and ^{13}C NMR spectra using monodimensional and bidimensional experiments. The patterns of ^1H NMR spectra belonging to the proton signals of the phenothiazine moieties are complicated (spectra of second order) and the direct determination of the δ and J values is not possible in all cases. For some of the compounds (5, 7 and 10), we could simulate the spectra (using the MestReC Plus program), and from the simulated spectra similar with the experimental ones, the values of the coupling constants and the chemical shifts could be obtained. For the compounds with longer chains (6 or 8 carbon atoms), the signals belonging to the protons of the CH_2 groups that are not located at the extremities of the chains are also overlapped, and their assignment is not possible.

3. Experimental Procedures

^1H and ^{13}C -NMR spectra were recorded at room temperature using CDCl_3 or $\text{DMSO}-d_6$ as solvent in 5 mm tubes on Bruker AM 300 spectrometer operating at 300 MHz for protons and 75 MHz for carbon atoms. Melting points were determined with a Kleinfeld apparatus and are uncorrected. Thin-layer chromatography was performed on Merck 60F 254 silica gel sheets. Merck silica gel (40 - 63 μm) was used for flash chromatography. Phenothiazine, dibromoalkanes, 2,5-dibromothiophene, 2-ethyloxycarbonylthiophene, as well as usual reagents ($n\text{-BuLi}$, Br_2 , $\text{B}(\text{OCH}_3)_3$, pinacol, K_2CO_3) were purchased from Merck. 5-bromo-2-ethyloxycarbonylthiophene was obtained by

the direct bromination of 2-ethyloxycarbonylthiophene using a procedure described in the literature [26].

General procedure for synthesis of compounds 2-4

A mixture of phenothiazine 1 (30 mmol, 5.97 g), dibromoalkane (30 mmol) [1,3-dibromopropane (6.05 g) for 2, 1,6-dibromohexane (7.31 g) for 3, and 1,8-dibromooctane (8.16 g) for 4], potassium carbonate (15 mmol, 2.07 g) and copper powder (10 mmol, 0.635 g) were heated on an oil bath for 5 hours at 150 - 170°C. After cooling at rt the reaction mixture was stirred for 30 minutes with dichloromethane (50 mL) then filtered in order to obtain the solution of the target compound. The solvent was removed in vacuum and the crude product was subjected to column chromatography on silica gel. Compound 4 is new but 2 and 3 were previously described in the literature [3,15-17].

10-(8'-bromo-octyl)-10H-phenothiazine 4

Yellow oil, Yield 40%, $R_f=0.57$ (hexane:dichloromethane = 5:1), Found: C 61.72, H 6.33, Br 20.69, N 3.41, S 8.19%. Calc. for $\text{C}_{20}\text{H}_{24}\text{BrNS}$: C 61.53, H 6.20, Br 20.47, N 3.59, S 8.21%. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ_{H} ppm: 1.23-1.36 (overlapped peaks, 8H, CH_2), 1.61-1.76 (overlapped peaks, 4H, CH_2), 3.46 (t, 2H, 8'- CH_2 , $J=6.9$ Hz), 3.84 (t, 2H, 10- CH_2 , $J=6.9$ Hz), 6.92 (t, 2H, $J=7.5$ Hz, aromatic), 7.00 (d, 2H, $J=8.1$ Hz, aromatic), 7.13 (dd, 2H, $J=1.2$ Hz, $J=7.5$ Hz, aromatic), 7.18 (dd, 2H, $J=1.2$ Hz, $J=8.1$ Hz, aromatic).

^{13}C -NMR (75 MHz, $\text{DMSO}-d_6$): 25.8 (CH_2), 26.0 (CH_2), 27.2 (CH_2), 27.8 (CH_2), 28.2 (CH_2), 32.0 (CH_2), 35.0 (8'- CH_2), 46.2 (10- CH_2), 115.7, 122.2 (tertiary aromatic carbon atoms), 123.5 (quaternary aromatic carbon atom), 126.9, 127.4 (tertiary aromatic carbon atoms), 144.6 (quaternary aromatic carbon atom).

General procedure for synthesis of new compounds 5-7:
 Bromine (3.9 mmol, 0.62 g) in glacial acetic acid (20 mL) was added dropwise to a stirred solution of 10-bromoalkylphenothiazine (2-4) (1.8 mmol) in glacial acetic acid (50 mL). After stirring overnight (at rt), dichloromethane (50 mL) and sodium sulfite oversaturated solution (50 mL) were added and the reaction mixture was stirred for two more hours. The organic layer was separated and the aqueous layer was washed twice with dichloromethane (30 mL). The united organic layers were washed with a solution of sodium bicarbonate and dried over sodium sulfate, the solvent was removed in vacuum and the crude product was subjected to column chromatography on silica gel.

3,7-dibromo-10-(3'-bromopropyl)-10H-phenothiazine 5
 Red oil, yield 60%, $R_f=0.17$ (hexane), Found: C 37.42, H 2.69, Br 50.40, N 3.02, S 6.65%. Calc. for $C_{15}H_{12}Br_3NS$: C 37.69, H 2.53, Br 50.14, N 2.93, S 6.71%

1H -NMR (300 MHz, DMSO- d_6) δ_H ppm: 2.14 [quintuplet (overlapped tt), 2H, 2'-CH₂, J=5.7 Hz], 3.57 (t, 2H, 3'-CH₂, J=5.7 Hz), 3.98 (t, 2H, 10-CH₂, J=5.7 Hz), 7.017 (m, 2H, J=9.0 Hz, J=0.5 Hz, 1-H, 9-H), 7.377 (m, 2H, J=9.0 Hz, J=2.0 Hz, 2-H, 8-H), 7.380 (m, 2H, J=0.5 Hz, J=2.0 Hz, 4-H, 6-H).

^{13}C -NMR (75 MHz, DMSO- d_6): 28.9 (CH₂), 31.7 (3'-CH₂), 44.6 (10-CH₂), 114.2 (quaternary aromatic carbon atom), 117.6 (tertiary aromatic carbon atom), 125.7 (quaternary aromatic carbon atom), 129.1, 130.3 (tertiary aromatic carbon atoms), 143.5 (quaternary aromatic carbon atom)

3,7-dibromo-10-(6'-bromohexyl)-10H-phenothiazine 6
 Pale green solid, melting point 85°C, yield 68%, $R_f=0.54$ (petroleum ether:dichloromethane=5:1), Found: C 41.42, H 3.64, Br 45.83, N 2.44, S 6.03%. Calc. for $C_{18}H_{18}Br_2NS$: C 41.57, H 3.49, Br 46.09, N 2.69, S 6.16%.

1H -NMR (300 MHz, DMSO- d_6) δ_H ppm: 1.35 (overlapped peaks, 4H, CH₂), 1.62-1.75 (overlapped peaks, 4H, CH₂), 3.46 (t, 2H, 6'-CH₂, J=6.6 Hz), 3.80 (t, 2H, 10-CH₂, J=6.6 Hz), 6.94 (overlapped peaks, 2H, aromatic), 7.33-7.38 (overlapped peaks, 4H, aromatic)

^{13}C -NMR (75 MHz, DMSO- d_6) δ_C ppm: 25.0 (CH₂), 25.6 (CH₂), 26.9 (CH₂), 32.0 (CH₂), 34.9 (6'-CH₂), 46.4 (10-CH₂), 113.9 (quaternary aromatic carbon atom), 117.5 (tertiary aromatic carbon atom), 125.4 (quaternary aromatic carbon atom), 129.0, 130.2 (tertiary aromatic carbon atoms), 143.7 (quaternary aromatic carbon atom)

3,7-dibromo-10-(8'-bromo-octyl)-10H-phenothiazine 7
 Green solid, melting point 69°C, yield 68%, $R_f=0.47$ (hexane:dichloromethane = 5:1), Found: C 44.05, H 4.22, Br 43.89, N 2.40, S 5.71%. Calc. for $C_{20}H_{22}Br_2NS$: C 43.82, H 4.05, Br 43.73, N 2.56, S 5.85%

1H -NMR (300 MHz, DMSO- d_6) δ_H ppm: 1.27-1.32 (overlapped peaks, 8H, CH₂), 1.59-1.76 (overlapped peaks, 4H, CH₂), 3.46 (t, 2H, 8'-CH₂, J=6.6 Hz), 3.80 (t, 2H, 10-CH₂, J=6.9 Hz), 6.939 (m, 2H, J=9.0 Hz, J=0.8 Hz, 1-H, 9-H), 7.338 (m, 2H, J=0.8 Hz, J=2.2 Hz, 4-H, 6-H), 7.347 (m, 2H, J=9.0 Hz, J=2.2 Hz, 2-H, 8-H).

^{13}C -NMR (75 MHz, DMSO- d_6) δ_C ppm: 25.7 (CH₂), 27.1 (CH₂), 26.9 (CH₂), 27.8 (CH₂), 28.1 (CH₂), 32.0 (CH₂), 34.9 (8'-CH₂), 46.4 (10-CH₂), 113.8 (quaternary aromatic carbon atom), 117.5 (tertiary aromatic carbon atom), 125.3 (quaternary aromatic carbon atom), 128.9, 130.2 (tertiary aromatic carbon atoms), 143.6 (quaternary aromatic carbon atom)

General procedure for synthesis of new compounds 8-10
 Potassium thioacetate (3.2 mmol, 0.36 g) was added to 3,7-dibromo-10-bromoalkylphenothiazine (5-7) [1.6 mmol, 0.76 (5), 0.83 (6), 0.87g (7)] in 1:1 acetonitrile / dichloromethane solution. The mixture was stirred at rt overnight, then the solvents were removed in vacuum and the residue was subjected to column chromatography on silica gel.

3-(3',7'-dibromo-10'H-phenothiazin-10'-yl)propylthioacetate 8

Yellow oil, yield 62%, $R_f=0.22$ (hexane), Found: C 43.01, H 3.44, Br 33.64, N 3.06, S 13.39%. Calc. for $C_{17}H_{15}Br_2NS_2$: C 43.15, H 3.19, Br 33.77, N 2.96, S 13.55%
 1H -NMR (300 MHz, DMSO- d_6) δ_H ppm: 1.86 [qv (overlapped tt), 2H, 2'-CH₂, J=6.9 Hz], 2.27 (s, 3H, SCOCH₃), 2.87 (t, 2H, 3'-CH₂, J=7.2 Hz), 3.86 (t, 2H, 10-CH₂, J=6.6 Hz), 6.94 (m, 2H, aromatic), 7.33-7.36 (overlapped peaks, 4H, aromatic).

^{13}C -NMR (75 MHz, DMSO- d_6) δ_C ppm: 25.6 (CH₂), 25.9 (3'-CH₂), 30.5 (CH₃), 45.3 (10-CH₂), 114.2 (quaternary aromatic carbon atom), 117.6 (tertiary aromatic carbon atom), 125.7 (quaternary aromatic carbon atom), 129.1, 130.3 (tertiary aromatic carbon atoms), 143.5 (quaternary aromatic carbon atom), 195.1 (CO)

6-(3',7'-dibromo-10'H-phenothiazin-10'-yl)hexylthioacetate 9

Yellow red oil, yield 77%, $R_f=0.12$ (petroleum ether:dichloromethane = 5:2), Found: C 46.53, H 3.89, Br 31.18, N 2.61, S 12.59%. Calc. for $C_{20}H_{21}Br_2NS_2$: C 46.61, H 4.11, Br 31.01, N 2.72, S 12.44%

1H -NMR (300 MHz, DMSO- d_6) δ_H ppm: 1.26-1.62 (overlapped peaks, 8H, CH₂), 2.28 (s, 3H, SCOCH₃), 2.76 (t, 2H, 6'-CH₂, J=7.2 Hz), 3.79 (t, 2H, 10-CH₂, J=6.6 Hz), 6.94 (m, 2H, aromatic), 7.33-7.35 (overlapped peaks, 4H, aromatic).

^{13}C -RMN (75 MHz, DMSO- d_6) δ_C ppm: 25.3 (CH₂), 25.6 (CH₂), 27.5 (CH₂), 28.1 (CH₂), 28.9 (CH₂), 30.4 (CH₃),

46.4 (N-CH₂), 113.9 (quaternary aromatic carbon atom), 117.5 (tertiary aromatic carbon atom), 125.3 (quaternary aromatic carbon atom), 128.9, 130.2 (tertiary aromatic carbon atoms), 143.6 (quaternary aromatic carbon atom), 195.2 (CO)

8-(3',7'-dibromo-10'H-phenothiazin-10'-yl)

octylthioacetate 10

Yellow oil, yield 74%, $R_f=0.18$ (hexane:dichloromethane = 5:2). Found: C 48.79, H 4.82, Br 29.17, N 2.43, S 11.63%. Calc. for C₂₂H₂₅Br₂NS₂ C 48.63, H 4.64, Br 29.41, N 2.58, S 11.80%

¹H-NMR (300 MHz, DMSO-d₆) δ_H ppm: 1.19-1.44 (overlapped peaks, 10H, CH₂), 1.56-1.65 (overlapped peaks, 2H, CH₂), 2.30 (s, 3H, SC(=O)CH₃), 2.76 (t, 2H, 8'-CH₂, J=7.2 Hz), 3.79 (t, 2H, 10-CH₂, J=6.6 Hz), 6.944 (m, 2H, J=9.0 Hz, J=1.2 Hz, 1-H, 9-H), 7.341 (m, 4H, J=1.2 Hz, J=2.5 Hz, 4-H, 6-H), 7.347 (m, 2H, J=9.0 Hz, J=2.5 Hz, 2-H, 8-H).

¹³C-NMR (75 MHz, DMSO-d₆) δ_C ppm: 25.7 (CH₂), 27.8 (CH₂), 28.2 (CH₂), 28.9 (CH₂), 30.5 (CH₃), 32.4 (CH₂), 46.4 (N-CH₂), 113.9 (quaternary aromatic carbon atom), 117.5 (tertiary aromatic carbon atom), 125.4 (quaternary aromatic carbon atom), 128.9, 130.2 (tertiary aromatic carbon atoms), 143.7 (quaternary aromatic carbon atom), 195.2 (CO)

General procedure for the synthesis of new compounds 11-13

To a suspension of lithium aluminium hydride (1.34 mmol, 0.05 g) in dry diethyl ether (10 mL) cooled in an ice bath was added dropwise a solution of 3,7-dibromo-10-alkylthioacetate-phenothiazine (8-10) [0.67 mmol, 0.31 (8), 0.34 (9), 0.36 g (10)] in dry diethyl ether (20 mL). The mixture was stirred for two hours, then sodium hydroxide solution 20% (2 mL) was added and the reaction mixture was stirred for another half an hour then filtered. The crude product was subjected to column chromatography on silica gel.

3-(3',7'-dibromo-10'H-phenothiazin-10'-yl)-1-propanethiol 11

Yellow oil, yield 59%, $R_f=0.24$ (hexane). Found: C 41.52, H 2.82, Br 37.37, N 3.43, S 14.63%. Calc. for C₁₅H₁₃Br₂NS₂ C 41.78, H 3.04, Br 37.06, N 3.25, S 14.87%

¹H-NMR (300 MHz, CDCl₃-d₆) δ_H ppm: 1.32 (t, 1H, SH, J=8.1 Hz), 2.02 (overlapped peaks, 2H, 2'-CH₂), 2.62 (q, 2H, 3'-CH₂, J=6.9 Hz), 3.96 (t, 2H, 10-CH₂, J=6.6 Hz), 6.74 (m, 2H, aromatic), 7.24-7.27 (overlapped peaks, 4H, aromatic H.).

¹³C-NMR (75 MHz, CDCl₃-d₆) δ_C ppm: 21.6 (CH₂), 30.1 (3'-CH₂), 45.1 (10-CH₂), 115.0 (quaternary aromatic

carbon atom), 116.7 (tertiary aromatic carbon atom), 126.9 (quaternary aromatic carbon atom), 129.8, 130.1 (tertiary aromatic carbon atoms), 143.8 (quaternary aromatic carbon atom)

6-(3',7'-dibromo-10'H-phenothiazin-10'-yl)-1-hexanethiol 12

Yellow solid, melting point 81°C, yield 59%, $R_f=0.65$ (hexane). Found: C 45.83, H 4.31, Br 33.57, N 2.93, S 13.34%. Calc. for C₁₈H₁₉Br₂NS₂ C 45.68, H 4.05, Br 33.77, N 2.96, S 13.55%

¹H-NMR (300 MHz, CDCl₃-d₆) δ_H ppm: 1.29 (t, 1H, SH, J=7.8 Hz), 1.38-1.77 (overlapped peaks, 8H, CH₂), 2.48 (q, 2H, 6'-CH₂, J=7.5 Hz), 3.77 (t, 2H, 10-CH₂, J=6.9 Hz), 6.68 (m, 2H, aromatic), 7.22-7.26 (overlapped peaks, 4H, aromatic).

¹³C-NMR (75 MHz, CDCl₃-d₆) δ_C ppm: 24.4 (CH₂), 26.1 (CH₂), 26.4 (CH₂), 27.7 (CH₂), 33.7 (CH₂), 47.3 (N-CH₂), 114.8 (quaternary aromatic carbon atom), 116.6 (tertiary aromatic carbon atom), 126.6 (quaternary aromatic carbon atom), 129.7, 130.1 (tertiary aromatic carbon atoms), 144.0 (quaternary aromatic carbon atom)

8-(3',7'-dibromo-10'H-phenothiazin-10'-yl)1-octanethiol 13

Yellow oil, yield 21%, $R_f=0.67$ (hexane). Found: C 47.79, H 4.44, Br 31.61, N 2.53, S 12.66%. Calc. for C₂₀H₂₃Br₂NS₂ C 47.91, H 4.62, Br 31.88, N 2.79, S 12.79%

¹H-NMR (300 MHz, CDCl₃-d₆) δ_H ppm: 1.51-1.75 (overlapped peaks, 13H, CH₂, SH), 2.49 (q, 2H, 8'-CH₂, J=7.5 Hz), 3.73 (t, 2H, 10-CH₂, J=6.9 Hz), 6.67 (m, 2H, aromatic), 7.21-7.26 (overlapped peaks, 4H, aromatic).

¹³C-NMR (75 MHz, CDCl₃-d₆) δ_C ppm: 24.5 (CH₂), 26.5 (CH₂), 26.6 (CH₂), 28.1 (CH₂), 28.8 (CH₂), 28.9 (CH₂), 33.8 (CH₂), 47.4 (N-CH₂), 114.7 (quaternary aromatic carbon atom), 116.6 (tertiary aromatic carbon atom), 126.4 (quaternary aromatic carbon atom), 129.7, 130.0 (tertiary aromatic carbon atoms), 144.1 (quaternary aromatic carbon atom).

Procedure for synthesis of new compound 14

A solution of 3.67 g of 12 (10.1 mmol) in 40 mL of anhydrous tetrahydrofuran was cooled to -78°C under argon, then 12.6 mL of nBuLi 1.6 M in hexane (2 eq., 20.2 mmol) was added. After 30 minutes stirring at -78°C 2.82 mL (2.5 eq., 25.25 mmol, 2.62 g) trimethyl borate was added and the reaction mixture was stirred for 45 minutes at -78°C. After the cooling bath is removed and the reaction mixture was allowed to reach room temperature, 2.97 g (2.5 eq., 25.25 mmol) pinacol was added. After one hour 0.4 mL glacial acetic acid was added and the reaction mixture was stirred at

room temperature overnight. Then 50 mL diethyl ether and 50 mL water were added and the organic layer was separated and the aqueous layer was extracted twice with 20 mL diethyl ether. The reunited organic layers were dried over sodium sulfate, the solvents were removed in vacuum and the crude product was chromatographed on silica gel.

10-(6'-bromohexyl)-3,7-bis(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-10H-phenothiazine 14

White solid, melting point 143–146°C, yield 28%, R_f =0.46 (hexane)

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ_{H} ppm: 1.26 (s, 24H, CH_3), 1.36 (overlapped peaks, 4H, CH_2), 1.64–1.76 (overlapped peaks, 4H, CH_2), 3.46 (t, 2H, 6'- CH_2 , $J=6.9$ Hz), 3.89 (t, 2H, 10- CH_2 , $J=6.6$ Hz), 7.01 (d, 2H, aromatic, $J=8.1$ Hz), 7.31 (d, 2H, aromatic, $J=1.2$ Hz), 7.47 (dd, 2H, aromatic H, $J=9.6$ Hz, $J=1.2$ Hz).

$^{13}\text{C-NMR}$ (75 MHz, DMSO-d_6): 24.5 (CH_3), 24.9 (CH_2), 25.7 (CH_2), 26.9 (CH_2), 32.0 (CH_2), 34.8 (6'- CH_2), 46.3 (10- CH_2), 115.4 (tertiary aromatic carbon), 122.5 (quaternary aromatic carbon atom), 132.8, 134.1 (tertiary aromatic carbons), 146.6 (quaternary aromatic carbon).

General procedure for the synthesis of new compounds 15 and 16

Phenothiazine pinacolyl ester 14 (0.32 mmol, 0.19 g), 2,5-dibromothiophene for 15 (0.71 mmol, 0.17 g) or 5-bromo-2-carbethoxy-thiophene for 16 (0.71 mmol, 0.16 g) and potassium carbonate (3.20 mmol, 0.44 g) in a mixture of monoglym (20 mL) and water (10 mL) was degassed for ten minutes with argon. Then palladiumtriphenylphosphine (0.03 mmol, 0.03 g) was added and the reaction mixture was refluxed for 14 hours. After cooling to room temperature dichloromethane (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with small portions of dichloromethane and the reunited organic layers were dried over sodium sulphate, the solvent was removed in vacuum and the crude product was subjected to column chromatography on silica gel.

6-[3',7'-bis(5"-bromothiophen-2"-yl)-10'H-phenothiazin-10'-yl]-hexylbromide 15

Orange oil, yield 63%, R_f =0.42 (hexane:ethyl acetate = 6:1). Found: C 45.29, H 3.49, Br 35.30, N 2.29, S 14.21%. Calc. for $\text{C}_{26}\text{H}_{22}\text{Br}_3\text{NS}_3$ C 45.63, H 3.24, Br 35.03, N 2.05, S 14.06%

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ_{H} ppm: 1.37–1.38 (overlapped peaks, 4H, CH_2), 1.66–1.76 (overlapped peaks, 4H, CH_2), 3.46 (t, 2H, 6'- CH_2 , $J=6.0$ Hz), 3.85 (t, 2H, 10- CH_2 , $J=7.5$ Hz), 7.00 (m, 2H, aromatic), 7.20

(d, 2H, aromatic, $J=3.0$ Hz), 7.27 (d, 2H, aromatic, $J=6.0$ Hz), 7.37–7.39 (overlapped peaks, 4H, aromatic). $^{13}\text{C-NMR}$ (75 MHz, DMSO-d_6) δ_{C} ppm: 25.1 (CH_2), 25.8 (CH_2), 27.0 (CH_2), 32.0 (CH_2), 34.9 (CH_2), 46.4 (N- CH_2), 109.6 (quaternary aromatic carbon atom), 116.1, 123.4, 124.7 (tertiary aromatic carbon atoms), 127.4 (quaternary aromatic carbon atom), 131.5 (tertiary aromatic carbon atom), 143.6, 143.9 (quaternary aromatic carbon atoms)

6-[3',7'-bis(5"-carbethoxythien-2"-yl)-10'H-phenothiazin-10'-yl]-hexylbromide 16

Orange solid, melting point 125°C, yield 23%, R_f =0.19 (hexane). Found: C 57.62, H 4.54, Br 12.03, N 2.15, S 14.09%. Calc. for $\text{C}_{32}\text{H}_{32}\text{BrNO}_4\text{S}_3$ C 57.30, H 4.81, Br 11.91, N 2.09, S 14.34%

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ_{H} ppm: 1.29 (t, 6H, $\text{CH}_2\text{-CH}_3$, $J=6.9$ Hz), 1.40 (overlapped peaks, 4H, CH_2), 1.70–1.76 (overlapped peaks, 4H, CH_2), 3.49 (t, 2H, 6'- CH_2 , $J=6.6$ Hz), 3.92 (t, 2H, 10- CH_2 , $J=6.3$ Hz), 4.29 (q, 4H, $\text{CH}_2\text{-CH}_3$), 7.08 (d, 2H, aromatic, $J=8.7$ Hz), 7.50–7.58 (overlapped peaks, 6H, aromatic), 7.75–7.76 (overlapped peaks, 2H, aromatic).

$^{13}\text{C-NMR}$ (75 MHz, DMSO-d_6) δ_{C} ppm: 14.1 (CH_3), 25.0 (CH_2), 25.7 (CH_2), 26.9 (CH_2), 32.0 (CH_2), 34.8 (CH_2), 46.5 (N- CH_2), 60.8 (CH_2), 116.2 (tertiary aromatic carbon atom), 123.5 (quaternary aromatic carbon atom), 123.8, 124.1, 125.5 tertiary aromatic carbon atoms), 127.2, 130.6 (quaternary aromatic carbon atoms), 134.6 (tertiary aromatic carbon atom), 144.3, 149.1, 161.2 (quaternary aromatic carbon atoms)

4. Conclusions

The synthesis of new derivatives of 3,7-dibromophenothiazine bearing alkyl chains of different lengths, connected to the N atom of the heterocyclic system and exhibiting bromine atoms at the extremity of the chains, thioacetate or mercapto groups was carried out in fair or good yields by improving and adapting usual procedures described in the literature. The Suzuki coupling reaction was run successfully for one of the tribrominated compounds. The reported compounds are important candidates for obtaining of macrocyclic compounds and / or for the formation of SAMs by deposition on a gold 1.1.1 surface.

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