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Dedicated to Professor Valer Farcasan on the occasion of his 95th anniversary

PAPERS

PODANDS WITH 3,7,10-TRISUBSTITUTED PHENOTHIAZINE UNITS: SYNTHESIS AND STRUCTURAL ANALYSIS

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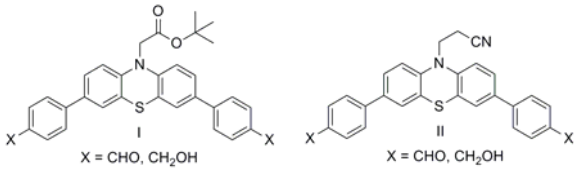
The synthesis of 10*H*-phenothiazine dipodands exhibiting -CH_2-OH or -CHO reactive groups at positions 3 and 7, suitable for macrocyclization reactions, as well as -CH_2COOtBu or -CH_2CH_2CN groups at position 10, which allow further functionalization, was achieved using a multistep approach. The structure of the compounds was deduced from NMR spectra and HRMS measurements.



INTRODUCTION

10*H*-Phenothiazine is an intriguing heterocycle, both in terms of structure and properties.[1] Phenothiazine or dibenzo-1,4-thiazine exhibits a flexible boat conformation of the central six-membered heterocycle which is involved in a conformational equilibrium suggesting the flapping of butterfly's wings.[2] 10*H*-Phenothiazine derivatives revealed important applications in medicine,[3] biology and biochemistry as marker for proteins or DNA,[4] and in material sciences as molecular wires,[5] dyads and triads,[6] as well as fluorophores.[7]

10*H*-Phenothiazine derivatives show a low oxidation potential and form a relatively stable radical-cation with planar structure. They have high stacking abilities and interesting absorption and emission properties.[8] Compounds with two or more (up to seven) phenothiazine units connected to each other *via* triple bonds or aryl groups reveal peculiar redox properties and are recommended for applications in electrochemically active materials.[9]

Macrocycles and cyclophanes embedding phenothiazine units were also reported. The majority of the published macrocycles and cyclophanes are rigid,[10] but flexible ones showing oligoethyleneoxide bridges were also reported.[11] These macrocycles and cyclophanes revealed spectacular electronic properties, as well as important applications in recognition processes. Therefore, phenothiazine based host molecules witnessed an increasing interest. In this context we considered important to develop new synthetic pathways to access phenothiazine based podands decorated with various functional groups. Our target compounds (Fig. 1) display reactive groups allowing macrocyclisation reactions (-CHO or

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CH_2OH) at positions 3 and 7, and functional groups, at position 10, which can be further used (after deprotection) to connect other relevant entities to the macrocycles or to link to each other several such macrocycles containing phenothiazine moieties ($CH_2COOtBu$ in I and CH_2CH_2CN in II).

RESULTS AND DISCUSSIONS

New phenothiazine derivatives substituted with reactive groups at positions 3, 7 and 10 were obtained starting from phenothiazine core in a multistep procedure. The first two steps are the bromination of the phenothiazine unit at positions 3 and 7 and the functionalization at the position 10, respectively (Scheme 1). Bromination (Br_2 in acetic acid) of phenothiazine **1** or of the *N*-protected phenothiazine **4** was carried out in good yields using a method described in the literature for the bromination of **1**[12] and *N*-ethyl-10*H*-phenothiazine[13] and also successfully applied for other substrates,[14] while the protection of phenothiazine with the *t*-butylacetate or β-cyanoethyl moieties was performed adapting procedures of the literature.[15] In both cases, the H atom at position 10 was removed by NaH and then the protecting group was introduced *via* nucleophilic substitution with an appropriate brominated derivative. These two steps are inverted for series I and II, respectively (Scheme 1). For compounds of type II, bromination of the compound already exhibiting the β-cyanoethyl group led to the failure of the reaction (decomposition of the products) and the protection of the *N* atom was postponed after the bromination reaction. The next steps are similar for both series I and II and consist in the Suzuki-Miyaura cross coupling reaction of the dibrominated derivatives **3** and **5** with *p*-formylphenyl-boronic acid with the obtaining of the dialdehydes **6** and **7**, followed by the reduction of the formyl groups with $NaBH_4$ to the corresponding diols **8** and **9**.

The Suzuki-Miyaura cross-coupling reaction was performed in good yields (Table 1) in a mixture of solvents (toluene/methanol/H_2O = 5/10/3), with Cs_2CO_3 as base and $Pd(PPh_3)_4$ as catalyst by a classic procedure adapted from the literature.[16]

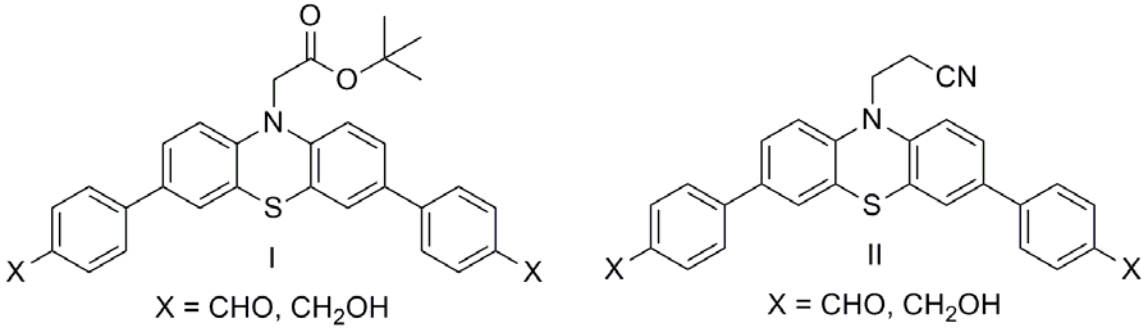
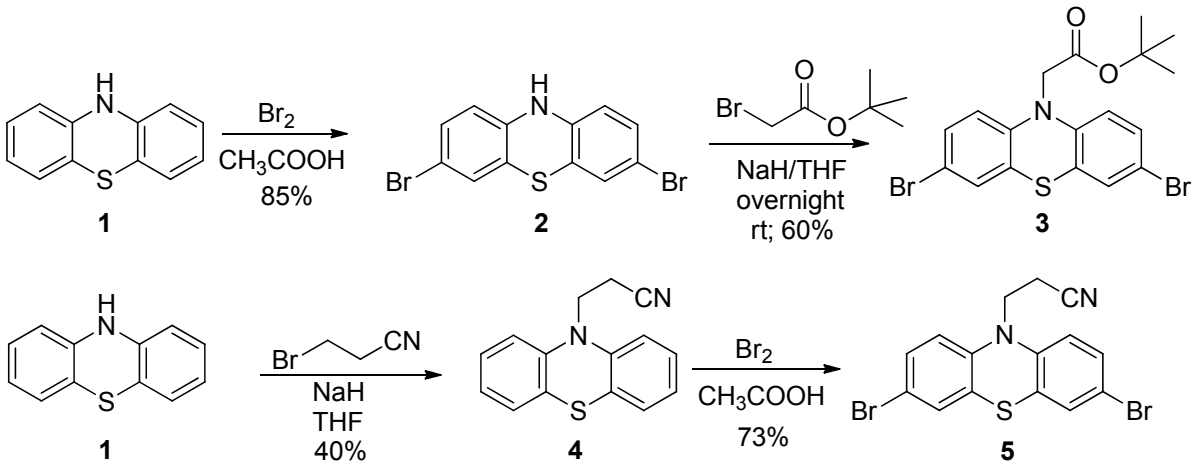
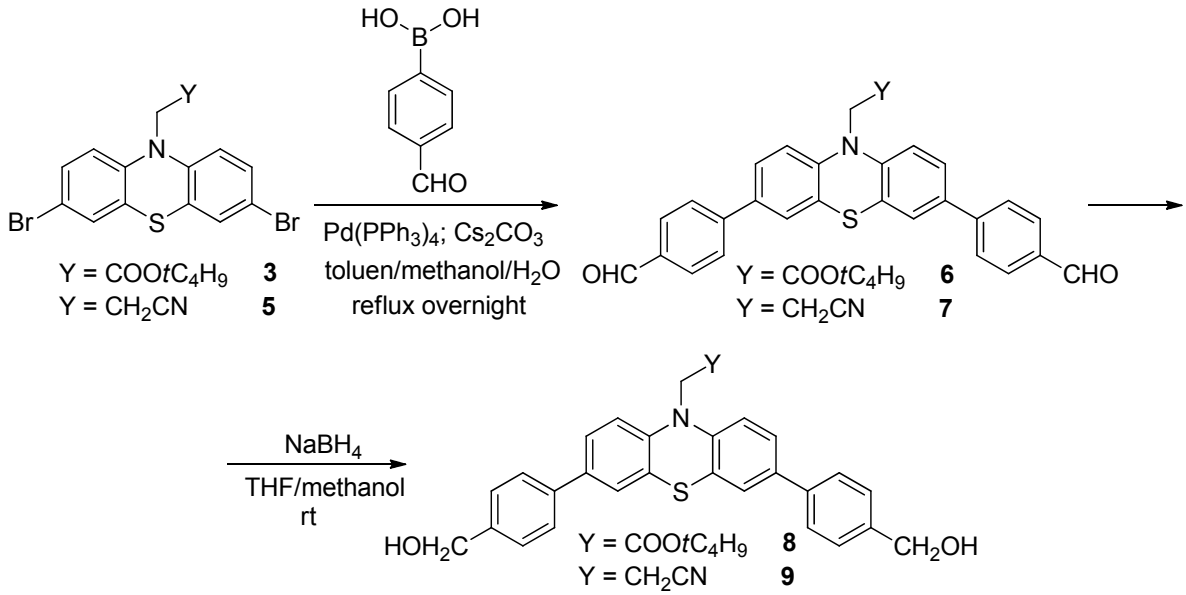


Fig. 1 – Target phenothiazine based dipodands exhibiting -$CH_2COOtBu$ (I) and -CH_2CH_2CN (II) groups at position 10.



Scheme 1



Scheme 2

Table 1

Results (yields) of the Suzuki-Miyaura cross-coupling and $NaBH_4$ reduction reactions

Reactions	Suzuki-Miyaura cross-coupling		Reduction with $NaBH_4$	
Products	**6**	**7**	**8**	**9**
Yields (%)	72	57	83	71

The classic reduction of -CHO groups to alcohols with $NaBH_4$ in THF/methanol[17] underwent selectively and in very good yields (Table 1), without the loss of protecting ester or cyano groups.

The structural analysis made by NMR and HRMS measurements confirmed the structures of the new compounds. As an example, the ^{1}H NMR spectrum of **6** (Fig. 2) reveals three singlets for the protons of the *t*Bu (δ = 1.55 ppm), CH_2 (δ = 4.68 ppm) and CHO (δ = 10.08 ppm) groups, two doublets for the *p*-phenylene units (δ = 7.90 and 7.98 ppm) and the characteristic group of three multiplets (δ = 6.92, 7.56 and 7.61 ppm) for the pattern of a symmetrically 3,7-disubstituted-10*H*-phenothiazine moiety.

The ^{13}C NMR spectrum of **6** (Fig. 2) exhibits the 5 signals belonging to the aliphatic substituents [(CHO; δ = 192.60 ppm; $-CH_2COOC(CH_3)_3$; δ = 28.33, 51.96, 82.90 and 169.29 ppm], 5 signals for tertiary (δ = 116.56, 126.15, 127.44, 127.77 and 131.08 ppm) and 5 signals for quaternary (δ = 124.05, 135.23, 136.49, 145.25 and 146.11 ppm) aromatic carbon atoms.

EXPERIMENTAL

^{1}H NMR (300, 400 or 600 MHz) and ^{13}C NMR (75, 100 or 150 MHz) spectra were recorded in acetone-d_6, DMSO-d_6 or methanol-d_4 at *rt* using the solvent line as reference. Thin layer chromatography (TLC) was conducted on silica gel 60 F254 TLC plates and preparative column chromatography was performed using 40–63 μm silica gel. Solvents were dried and distilled under argon using standard procedures. Chemicals of commercial grade were used without further purification. HRMSs were recorded using an LTQ XL OBITRAP mass spectrometer equipped with ESI/APCI sources.

Compounds **2**[12] and **4**[18] were already reported in the literature, compounds **3**, **5**-**9** are new. In the case of **4**, the reported preparation was based on the reaction of phenothiazine **1** with acrylonitril,[18] while we have obtained this compound via the alkylation of **1** with β-bromopropionitril by a procedure adapted from the literature.[15]

Procedure for the synthesis of **2** *and* **5**

To a solution of of 10*H*-phenothiazine compounds **1** or **4** (3 mmol) in glacial acetic acid (50 mL), a solution of bromine (6.4 mmol) in glacial acetic acid (20 ml) was dropped slowly. The reaction mixture was stirred at room temperature overnight. Diethylether (30 mL) and saturate solution of sodium sulfite (30 mL) were added and the new mixture was stirred for two more hours at room temperature (*rt*), then the organic layer was separated. The aqueous phase was extracted several times with diethylether (3 x 10 mL). The combined organic phases were washed with saturated solution (50 mL) of sodium bicarbonate and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the dibrominated compounds were obtained as solids and were purified by crystallization and/or column chromatography. Yields were 85% for **2** and 73% for **5**.

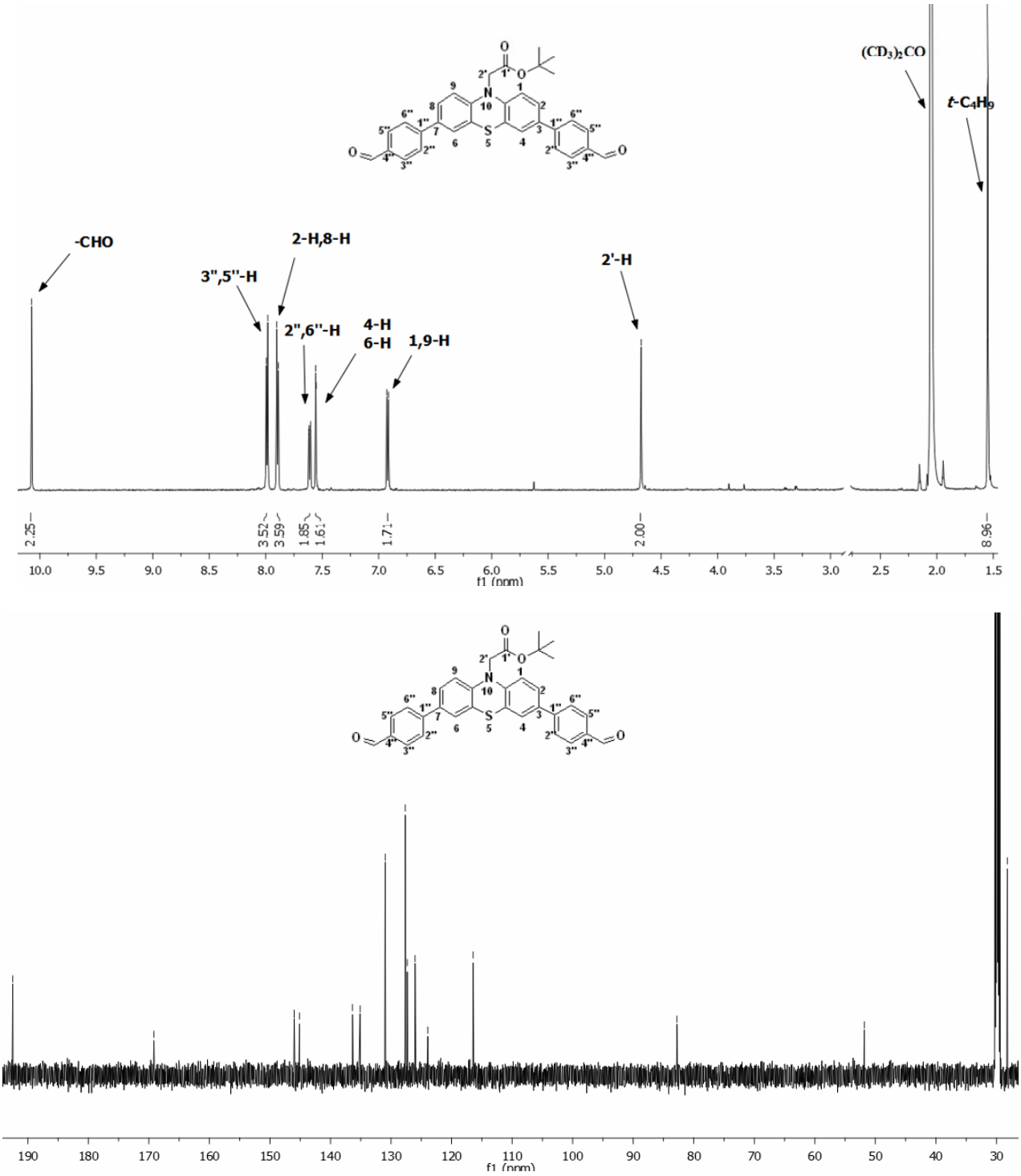


Fig. 2 – ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of compound **6** (600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR, acetone-d_6).

Procedure for the synthesis of **3** *and* **4**

To a solution of 10*H*-phenothiazine **1** or 3,7-dibromo-10*H*-phenothiazine **2** (4 mmol) in dry THF (100 mL), at 0°C and under argon, sodium hydride (10 mmol) was added and then the reaction mixture was stirred for two hours more at 0°C. Then, a solution containing 3-bromopropionitrile (for **1**) or *tert*-buthyl bromoacetate (for **2**) (5 mmol) in dry THF (15 mL) was added dropwise and the reaction mixture was stirred at *rt* for 48h. The reaction mixture was then filtered through a thin pad of celite and the celite was washed with 30 mL of diethylether. The solvents of the combined organic phases were removed *in vacuum* and the residue, in both cases, was chromatographed on silcagel. Yields were 60 % for **3** and 40 % for **4**.

Procedure for the synthesis of **6** *and* **7**

A mixture of **3** (1 mmol) or **5** (1 mmol) and (4-formylphenyl)boronic acid (2.4 mmol) and cesium

carbonate (6 mmol) in a mixture of methanol/toluen/water 10/5/3 v/v/v (20 mL) was degassed, then maintained under a flow of argon for one hour, then $Pd(PPh_3)_4$ (0.1 mmol) was added. The reaction mixture was refluxed overnight at 80˚C. After cooling at *rt*, toluene (20 mL) was added and the reaction mixture was filtered through a thin pad of celite. The organic phase of the filtrate was separated and the aqueous layer was washed several times with small portions of toluene (3x10 mL). The combined organic phases were washed with aqueous NaOH 5% and then with water. The combined organic layers were dried over anhydrous $MgSO_4$, the solvent was removed under vacuum and the crude products were chromatographed on silica.

Procedure for the synthesis of **8** *and* **9**

To a solution of 0.75 mmol of **6** or **7** in a mixture of THF/methanol = 5/12 v/v (17 mL), $NaBH_4$ (3 mmol) was added. The reaction mixture was stirred on a cooling bath for two hours at 0°C, and then it was allowed to warm to *rt*. The solvent was removed under *vacuum* and the residue was disolved in CH_2Cl_2 (40mL). The organic layer was separated and the aqueous phase was washed with CH_2Cl_2 (3x10mL). The combined organic layers were dried over anhydrous $MgSO_4$, the solvent was removed *in vacuo* and the crude products were chromatographed on silica gel.

Tert-butyl-2'-(3,7-dibromo-10H-phenothiazin-10-yl)acetate **3**. Yield 60% (1.12g), white solid, R_f = 0.48 (pentane:ethylacetate = 70:1), m.p. = 103-104°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ(ppm): 1.44 (s, 9H, $C(CH_3)_3$), 4.55 (s, 2H, 2'-H), 6.60 (d, 2H, *J* = 9.3 Hz, 1-H, 9-H), 7.34 (dd, 2H, *J* = 9.3, 2.2 Hz, 2-H, 8-H), 7.35 (d, 2H, *J* = 2.2 Hz, 4-H, 6-H); ^{13}C NMR (150 MHz, DMSO-d_6), δ(ppm): 27.64, 50.38, 81.85, 114.41, 116.73, 123.59, 128.56, 130.24, 142.93, 167.98. HRMS (APCI+): calcd. for $C_{18}H_{17}Br_2NO_2S$ $[M]^+$: 468.9332, 470.9310, 472.9287; found: 468.9341, 470.9321, 472.9300.

3'-(3,7-Dibromo-10H-phenothiazin-10-yl)propionitril **5**. Yield 73% (0.93 g), pink-white solid (crystallized from 10 mL mixture of pentane/diethylether = 2/3), R_f = 0.36 (petroleum ether:ethylacetate = 3:1), m.p. = 147-148 °C. ^{1}H NMR (600 MHz, acetone-d_6), δ(ppm): 2.96 (t, 2H, *J* = 6.7 Hz, 3'-H), 4.32 (t, 2H, *J* = 6.7 Hz, 2'-H), 7.05 (d, 2H, *J* = 8.6 Hz, 1-H, 9-H), 7.33 (d, 2H, *J* = 2.4 Hz, 4-H, 6-H), 7.36 (dd, 2H, J = 8.6, 2.4 Hz, 2-H, 8-H); ^{13}C NMR (150 MHz, acetone-d_6), δ(ppm): 16.37, 43.69, 115.66, 118.16, 127.77, 130.11, 131.08, 144.05. HRMS (APCI+) calcd. for $C_{15}H_{11}Br_2N_2S$ $[M+H]^+$: 408.9031, 410.9002, 412.8976; found: 408.9004, 410.8984, 412.8963.

Tert-butyl-2'-[(3,7-bis(4''-formylphenyl)-10H-phenothiazin-10-yl]acetate **6**. Yield 66% (0.344 g), yellow solid (R_f = 0.25; dichloromethane:pentane = 10:1), m.p. = 205-206°C. ^{1}H NMR (600 MHz, acetone-d_6), δ(ppm): 1.55 [s, 9H, $-C(CH_3)_3$], 4.68 (s, 2H, 2'-H), 6.92 (d, 2H, *J* = 8.5 Hz, 1-H, 9-H), 7.56 (d, 2H, *J* = 2.2 Hz, 4-H, 6-H), 7.61 (dd, 2H, *J* = 8.5, 2.2 Hz, 2-H, 8-H), 7.90 (d, 4H, *J* = 8.3 Hz, 2''-H, 6''-H), 7.99 (d, 4H, *J* = 8.3 Hz, 3''-H, 5''-H), 10.08 (s, 2H, -CHO); ^{13}C NMR (150 MHz, acetone-d_6), δ(ppm): 28.20, 51.83, 82.77, 116.43, 123.92, 126.02, 127.32, 127.64, 130.95, 135.11, 136.36, 145.12, 145.99, 169.16, 192.47; HRMS (APCI+) : calcd. for $C_{32}H_{28}NO_4S$ $[M+H]^+$: 522.1720; found: 522.1734.

3'-[(3,7-Bis(4''-formylphenyl)-10H-phenothiazin-10-yl]propionitril **7**. Yields 57 % (0.262 g), yellow solid (R_f = 0.44; pentane:ethylacetate = 4:7), m.p. = 177-178 °C. ^{1}H NMR (600 MHz, acetone-d_6), δ(ppm): 3.07 (t, 2H, *J* = 6.7 Hz, 3'-H), 4.50 (t, 2H, *J* = 6.7 Hz, 2'-H), 7.29 (d, 2H, *J* = 8.5 Hz, 1-H, 9-H), 7.65 (s, 2H, 4-H, 6-H), 7.69 (dd, 2H, *J* = 8.5 Hz, 2.1 Hz, 2-H, 8-H); 7.91 (d, 4H, *J* = 8.5 Hz, 2''-H, 6''-H), 8.00 (d, 4H, *J* = 8.5 Hz, 3''-H, 5''-H), 10.08 (s, 2H, -CHO); ^{13}C NMR (150 MHz, acetone-d_6), δ(ppm): 16.44, 43.62, 116.79, 118.25, 126.14, 126.48, 127.20, 127.40, 130.57, 136.04, 144.72, 145.60, 192.06. HRMS (APCI+): calcd. for $C_{29}H_{21}N_2O_2S$ $[M+H]^+$: 461.1312; found: 461.1318.

Tert-butyl-2'-[(3,7-bis(4''-hydroxymethylphenyl)-10H-phenothiazin-10-yl]acetate **8**. Yields 78% (0.308 g), yellow solid (R_f = 0.26; dichloromethane:methanol=20:1), m.p. = 340-341°C. ^{1}H NMR (600 MHz, methanol-d_4), δ(ppm): 1.54 (s, 9H, $-C(CH_3)_3$); 4.56 (s, 2H, 2'-H); 4.62 (s, 4H, 4''-CH_2); 6.75 (d, 2H, *J* = 8.4 Hz, 1-H, 9-H), 7.34 (d, 2H, *J* = 2.1 Hz, 4-H, 6-H), 7.39-7.41 (overlapped peaks, 6H, 2-H, 8-H, 2''-H, 6''-H), 7.55 (d, 4H, *J* = 8.4 Hz, 3''-H, 5''-H); ^{13}C NMR (150 MHz, acetone-d_6), δ(ppm): 28.30, 64.93, 83.58, 116.12, 119.94, 124.52, 125.79, 126.85, 127.29, 128.64, 136.95, 140.02, 141.76, 144.62, 170.44. HRMS (orbitrap, APCI+) : calcd. for $C_{32}H_{32}NO_4S$ $[M+H]^+$: 526.2050; found: 525.2047.

3'-[(3,7-Bis(4''-hydroxymethylphenyl)-10H-phenothiazin-10-yl]propionitril **9**. Yields 71% (0.247 g), yellow-green solid (R_f = 0.54, dichloromethane:methanol = 30:1), m.p. = 120-121 °C. ^{1}H NMR (600 MHz, acetone-d_6), δ(ppm): 3.06 (t, 2H, *J* = 6.7 Hz, 3'-H), 4.25 (t, 2H, *J* = 6.0 Hz, -OH), 4.44 (t, 2H, *J* = 6.7 Hz, 2'-H), 4.66 (d, 4H, *J* =6.0 Hz , 4''-CH_2), 7.20 (d, 2H, *J* = 8.5 Hz, 1-H, 9-H), 7.42 (d, 4H, *J* = 8.0 Hz, 2''-H, 6''-H), 7.50 (d, 2H, *J* = 1.9 Hz, 4-H, 6-H), 7.53 (dd, 2H, *J* = 8.5, 1.9 Hz, 2-H, 8-H), 7.59 (d, 4H, *J* = 8.0 Hz, 3''-H, 5''-H); ^{13}C NMR (150 MHz, acetone-d_6), δ(ppm): 16.84, 43.95, 64.38, 116.90, 126.37, 126.50, 126.88, 127.02, 127.29, 136.87, 138.97, 142.56, 144.24. HRMS (APCI+): calcd. for $C_{29}H_{25}N_2O_2S$ $[M+H]^+$: 465.1636; found: 465.1631.

CONCLUSIONS

The procedures described in this work successfully led to dipodands with -CHO groups at positions 3 and 7 in three steps with overall yields of 37% (I) and 17% (II) and to dipodands with $-CH_2OH$ groups at positions 3 and 7 in four steps with overall yields of 30% (I) and 12% (II). The NMR and HRMS investigations fully confirmed the structure of the investigated dipodands.

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