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Dedicated to Professor Ionel Haiduc
on the occasion of his 75th anniversary

PODANDS WITH 10-ETHYL-3,7-DITHIENYL-10*H*-PHENOTHIAZINE CORE: SYNTHESIS AND STRUCTURAL ANALYSIS

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New podands showing substituted thiophene-2-yl groups connected to positions 3 and 7 of a central 10-ethyl-10*H*-phenothiazine unit were obtained in good yields by cross-coupling reaction strategies. The thiophene rings are substituted either with formyl or hydroxymethyl groups, either at position 4' or at position 5'. These podands can participate by various reactions to the enclosure of macrocycles, and the reported compounds are versatile precursors for host molecules embedding thiophene and phenothiazine moieties. The structure of the podands was investigated by NMR and MS spectra.

INTRODUCTION

Phenothiazines are relevant aromatic heterocycles with many pharmacological applications (as sedatives, tranquilizers, antituberculotics, antipyretics, antitumor agents, bactericides or parasiticides)[1] and they exhibit electrochemical properties showing good donor abilities and a low oxidation potential. The phenothiazine derivatives might be able to form radical-cations, they can display electron-donor properties and they can be used as chromophores for photoinduced electron transfer experiments or as fluorescent materials.[2] Regarding its stereochemistry, phenothiazine exhibits a "butterfly structure",[3] but upon oxidation to radical cation it can adopt a planar geometry. Phenothiazine derivatives can be light sensitive and they can be photochemically oxidized to the corresponding sulfoxide;[4] many phenothiazine derivatives are useful in material sciences [5] or in biochemical systems.[6]

Herein we report on the synthesis of some new podands (Chart 1) exhibiting substituted thiophene units connected in the positions 3 and 7 to a phenothiazine core. The thiophene units are connected to the phenothiazine at position 2' and bear the other substituents (-CHO or CH_2OH) either at positions 4' or 5'.

RESULTS AND DISCUSSION

The synthesis of the target compounds I and II (Chart 1) was carried out using different strategies. The access to these podands requests, as a preliminary step, the preparation of boronic esters **4** and **6** (Schemes 1 and 2). Compound **4** was obtained starting from phenothiazine **1** following synthetic steps reported in the literature (Scheme 1). The N-alkylated derivative **2** was transformed *via* the dibrominated phenothiazine **3**[7] into the pinacol diboronicdiester **4**.[8] The already reported[9]

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boronic ester **6** was prepared starting from 2-bromothiophene **5** by a similar procedure with that used for the obtaining of **4** (Scheme 2). In the synthetic itineraries towards podands I and II different strategies were approached for each case: (i) at first the 10-ethyl-3,7-dithienyl-10*H*-phenothiazine core is built by Suzuki cross coupling reaction and then the -CHO groups are introduced on the thiophene rings by specific reactions for the podands I; (ii) the synthetic pathway for II is based on the first connection of the -CHO groups to the thiophene rings, followed by the formation of the bonds between the phenothiazine and the thiophene units by cross coupling reactions.

The synthesis of dithienyl derivative **7** was carried out using four different procedures adapted from the literature[10] (Scheme 2). Two of them started from the brominated precursors (**3** or **5**) and were based on one-pot reactions (A and B), while the other two procedures used either the diboronic ester **4** (C) or the boronic ester **6** (D, Scheme 3). The recorded yields for the four methods are close and the advantages of the one-pot procedures are revealed.

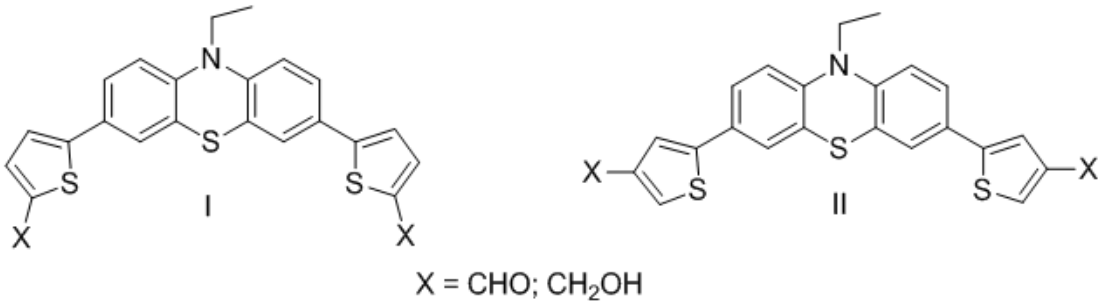
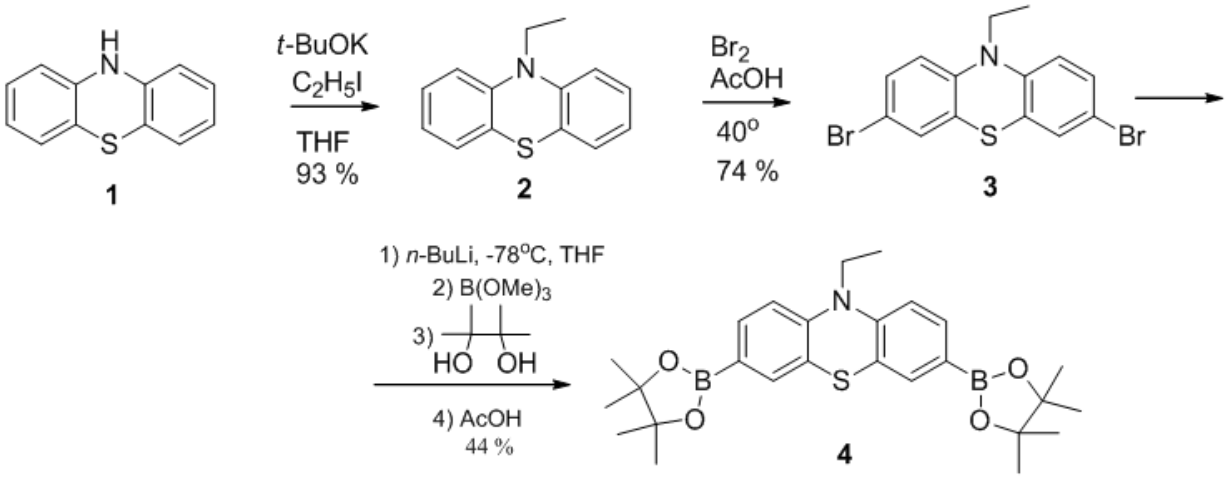
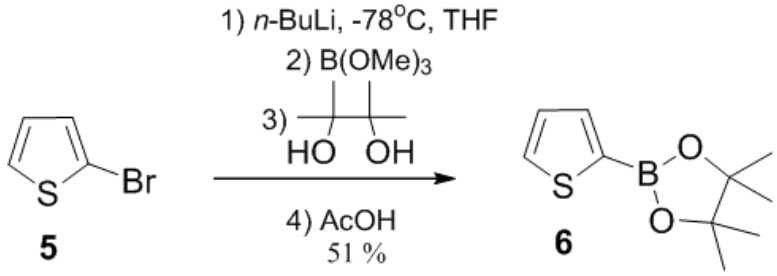


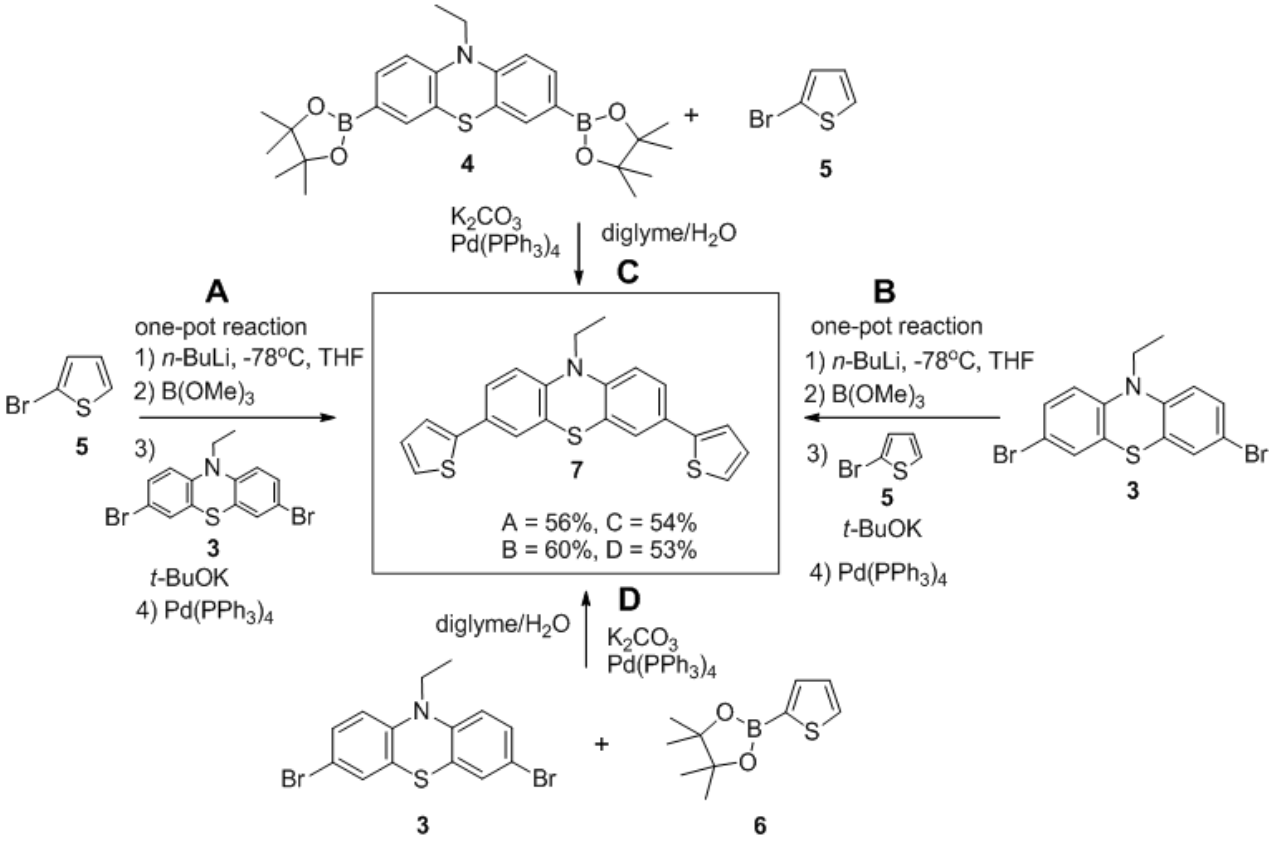
Chart 1 – Target podands with 3,7-dithienyl-phenothiazine core.



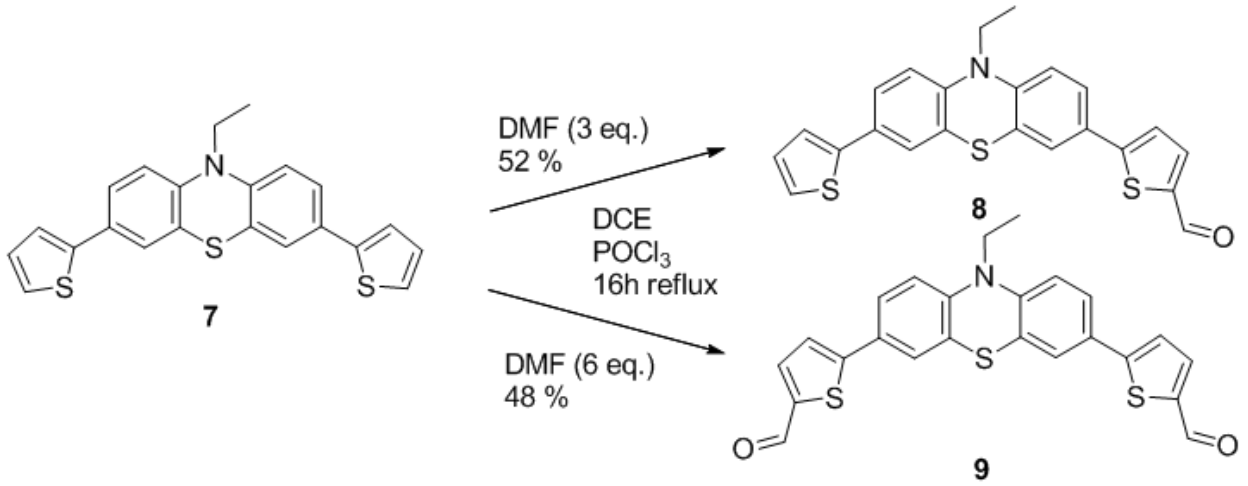
Scheme 1



Scheme 2



Scheme 3



Scheme 4

Derivative **7** was then submitted to a Vilsmeier-Haack formylation reaction [dichloroethane (DCE) as solvent].[11] Depending on the dithienyl derivative **7** / DMF (N,N-dimethylformamide) ratio, the reaction underwent with the formation of monoaldehyde **8** or of target dialdehyde **9** as main product (Scheme 4).

Compounds **8** and **9** exhibit different polarities and can be isolated by column chromatography (DCM as eluent). They can also easily be distinguished by their ^{1}H NMR spectra (Fig. 1) with a reduced number of signals for the symmetrically substituted **9** and with a doubled number of signals for the monoaldehyde **8**.

The corresponding dialdehyde **12** belonging to podands II (Chart 1) was obtained by the Suzuki cross-coupling reaction (Scheme 5) of diboronic ester **4** with 5-bromothiophene-3-carbaldehyde **11**

(obtained by the bromination of the commercially available aldehyde **10**, Scheme 5) using a similar procedure with that of route C (Scheme 3). The bromination of **10** is delicate due to the competition of positions 2 and 5 in the substitution reaction. The ratio between the two products is very sensitive to the conditions of the bromination reaction and the best yield (30 %) was obtained in the conditions shown in Scheme 5.

Diols **13** and **14** were obtained by the reduction reaction of corresponding dialdehydes using sodium borohydride and a typical procedure for the transformation of aldehydes into alcohols (Scheme 6).[12] The reactions underwent at two groups connected to the same substrate and the overall yields (75-80 %) can be considered good for this type of reactions.

The diols were purified by column chromatography.

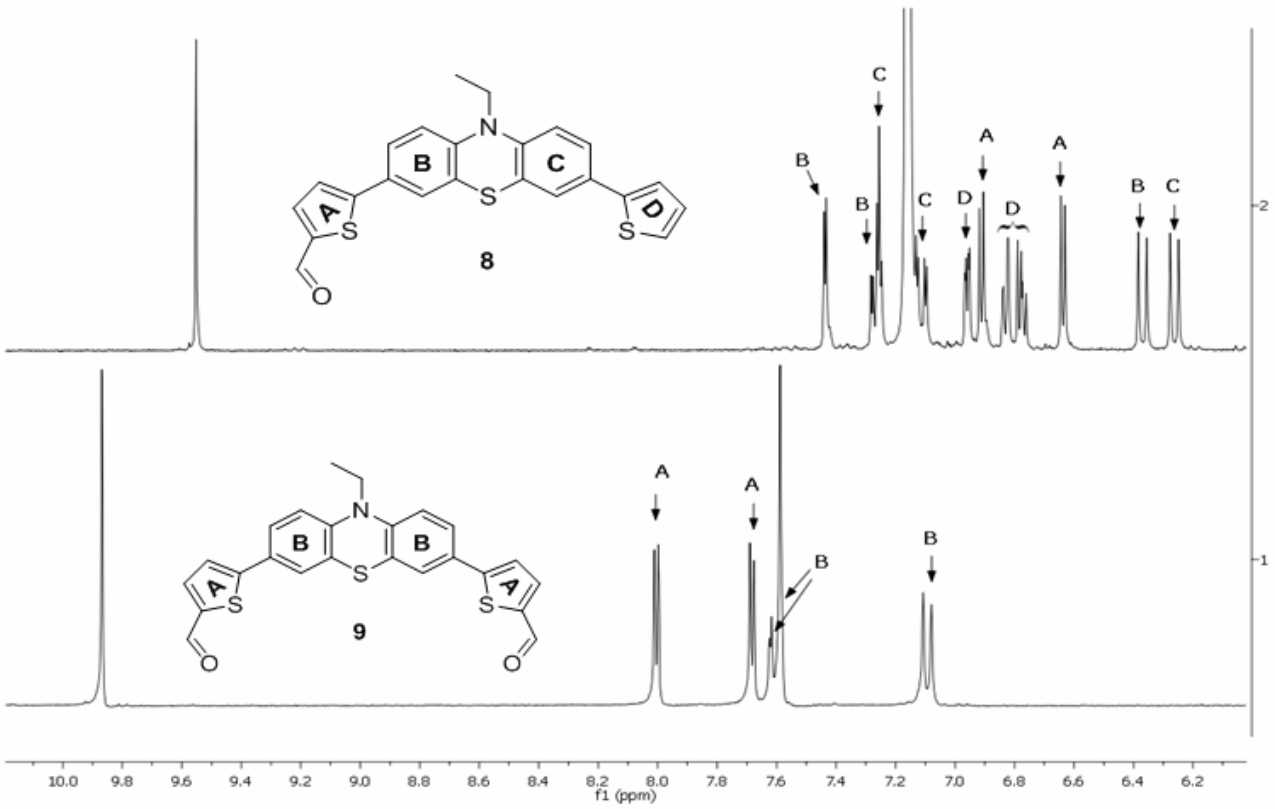
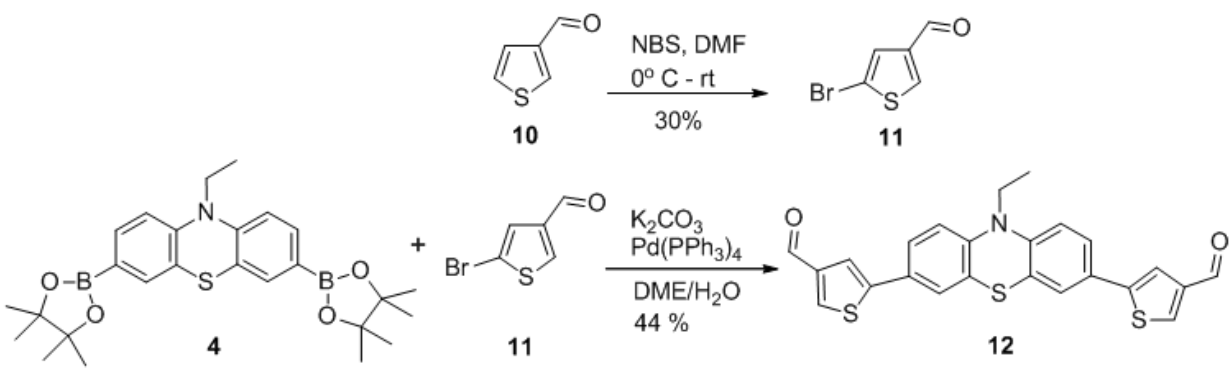
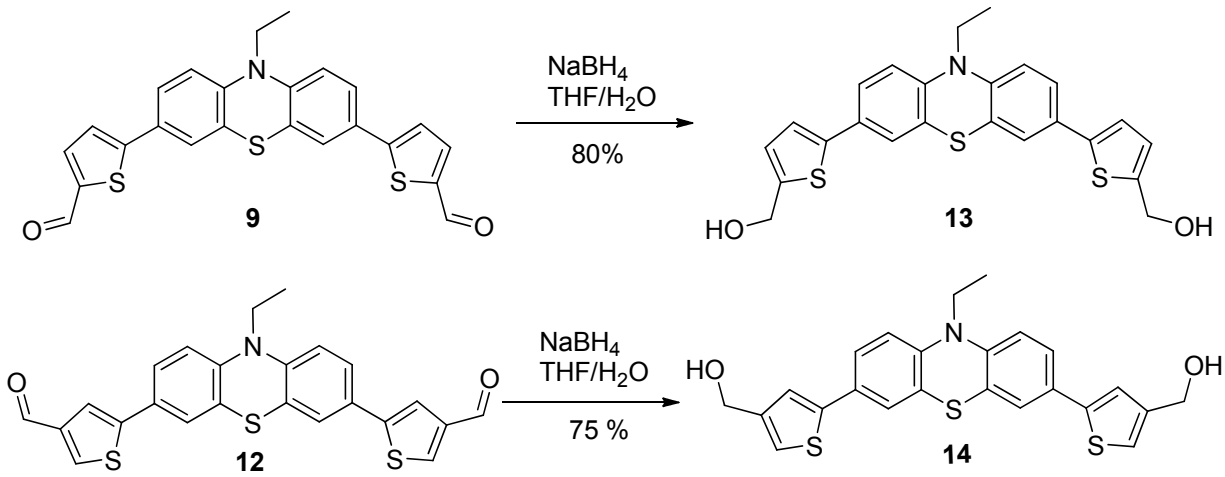


Fig. 1 – ^{1}H NMR spectra (fragments) for monoaldehyde **8** (top) and dialdehyde **9** (bottom).



Scheme 5



Scheme 6

EXPERIMENTAL PART

General experimental data

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in C_6D_6, DMSO-d_6 and $CDCl_3$ at *rt* on a Bruker 300 MHz spectrometer using the solvent line as reference.

Melting points were measured with a Kleinfeld melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was conducted on silica gel 60 F254 TLC plates purchased from Merck. Preparative column chromatography was performed using PharmPrep 60 CC (40–63 μm) silica gel purchased from Merck. Solvents were dried and distilled under argon using standard procedures. Chemicals of commercial grade were used without further purification. MS were recorded using an Esquire 3000 ion-trap MS (Bruker Daltonic GmbH, Bremen, Germany) equipped with a standard ESI/APCI source.

Procedures for the one-pot Suzuki coupling reaction

Route A: A solution of *n*-BuLi (8.77 mmol) in hexane was added dropwise to a stirred solution of 2-bromothiophene **5** (6.74 mmol) in dry THF (50 mL) at -78^{0}C. The stirring was continued at -78^{0}C for 30 minutes, then trimethylborate (8.08 mmol) was added and the temperature was raised slowly. When the temperature reached the *rt* value, 3,7-dibromophenothiazine **3** (2.69 mmol), *t*-BuOK (47.18 mmol) and 0.34 mmol of $Pd(PPh_3)_4$ (5%) were added. The reaction mixture was heated to 60^{0}C and the stirring was continued for 16 hours. After removing the solvents in vacuum, the raw product was poured into dichloromethane (DCM) (50 mL) and the organic phase was separated and washed several times with water (3x30 mL). The organic phase was dried on anhydrous magnesium sulphate, then the solvents were removed in vacuum. The crude product was purified by column chromatography (using pentane as mobile phase) in order to get the pure compound as a yellow solid, 56% yield.

Route B: A solution of *n*-BuLi (6.3 mmol) in hexane was added dropwise to a stirred solution of 3,7-dibromophenothiazine **3** (2.59 mmol) in dry THF (50 mL) at -78^{0}C. The stirring was continued at -78^{0}C for 30 minutes, then trimethylborate (5.70 mmole) was added and the temperature was raised slowly. When the temperature reached *rt*, 2-bromothiophene **5** (5.18 mmol), *t*-BuOK (18.13 mmol) and 0.26 mmol of $Pd(PPh_3)_4$ (5%) were added. The reaction mixture was heated to 60^{0}C and the stirring was continued for 16 hours. After removing the solvents in vacuum, the raw product was poured into DCM (100 mL) and the organic phase was separated and washed several times with water (3x50 mL). The organic phase was dried on anhydrous magnesium sulfate, then the solvents were removed in vacuum and the crude product was purified by column chromatography (using pentane as mobile phase) to get the pure compound as a yellow solid, 60% yield.

Procedures for the two-steps Suzuki coupling reactions

Route C: Pinacol diboronic diester of phenothiazine **4** (1 mmol), and the bromo thiophene derivative (2 mmol) [2-bromothiophene (for **7**) or 5-bromothiophene-3-carbaldehyde **11** (for **12**)], K_2CO_3 (7 mmol) were solved in a mixture of diglyme:water = 4/1 (20 mL). The reaction mixture was well degased (15 min) with argon, then 0.05 mmol $Pd(PPh_3)_4$ (5%) was added and the reaction mixture was stirred over night, under argon, to reflux. The solvent was partially removed in vacuum, and then water (30 mL) was added and the aqua's phase was extracted three times with DCM (3x30 mL). The combined organic phases were dried on anhydrous magnesium sulfate, then the solvents were removed and the crude product was purified by column chromatography (using pentane as mobile phase) to get the pure compound as a colored solid (yields 54 % for **7** and 44 % for **12**).

Route D: Pinacol boronic ester of thiophene **6** (2 mmol), 3,7-dibromophenothiazine **3** (1 mmol), K_2CO_3 (7 mmol) were solved in a mixture of diglyme:water = 4:1 (20 mL). The reaction mixture was well degased (15 min) with argon, then 0.1 mmol $Pd(PPh_3)_4$ (5%) was added and the reaction mixture was stirred over night, under argon, to reflux. The reaction solvent was partially removed in vacuum, and then water (30 mL) was added, the water phase was extracted three times with DCM (30 mL). The combined organic phases were dried on anhydrous magnesium sulfate, then the solvents were removed and the crude product was purified by column chromatography (using pentane as mobile phase) to get the pure compound as a yellow solid, 53% yield.

10-Ethyl-3,7-bis(thiophen-2'-yl)-10H-phenothiazine (**7**)

Yellow solid, Rf = 0.32 (pentane) m.p. = 139-140^{o}C. Calculated for $C_{22}H_{17}NS_3$; C, 67.48; H, 4.38; N, 3.58; S, 24.57. Found: C, 67.63; H, 4.49; N, 3.37; S, 24.31

^{1}H-NMR (300 MHz, C_6D_6): δ (ppm) 0.95 (t, CH_3, 3H, *J* = 6.9 Hz), 3.27 (q, CH_2, 2H, *J* = 6.9 Hz), 6.38 (d, 2H, *J* = 8.4 Hz), 6.74-6.82 (overlapped peaks, 4H), 6.93 (d, 2H, *J* = 3.6 Hz), 7.26 (dd, 2H, *J* = 8.7 Hz, *J*= 2.1 Hz), 7.43 (d, 2H, *J* = 2.1 Hz). ^{13}C (75MHz, C_6D_6) 12.3 (CH_3), 41.8 (CH_2), 115.2, 122.56, 124.1, 124.8, 125.06 (tertiary aromatic C atoms), 122.58, 129.3, 129.4, 143.9 (quaternary aromatic C atoms).
MS (ESI) *m/z* = 392.7 $[M+H]^+$.

10-Ethyl-3,7-bis(4'-formyl-thiophen-2'-yl)-10H-phenothiazine) (**12**)

Yellow solid, yields 44%. Rf = 0.76 (pentane / EtOAc = 4:3) m.p.= 123 ^{o}C. Calculated for $C_{24}H_{17}NO_2S_3$; C, 64.40; H, 3.83; N, 3.13; S, 21.49. Found: C, 64.61; H, 4.02; N, 3.15; S, 21.30.

^{1}H-NMR (300 MHz, C_6D_6): δ (ppm) 0.90 (t, CH_3, 3H, *J* = 7.0 Hz), 3.20 (q, CH_2, 2H, *J* = 7.0 Hz), 6.23 (d, 2H, *J* = 6.0 Hz), 6.51 (dd, 2H, *J* = 8.0 Hz, *J* = 1.0 Hz), 6.83 (dd, 2H, *J* = 8.0 Hz, *J* = 1.0 Hz), 6.95 (d, 2H, *J* = 3.0 Hz), 7.52 (d, 2H, *J* = 6.0 Hz), 9.89 (s, -CHO, 2H). ^{13}C (75MHz, C_6D_6): 12.4 (CH_3), 41.9 (CH_2), 115.1 124.8 127.1, 128.6, 129.5 (tertiary aromatic carbon atoms), 124.6, 126.3, 127.0, 137.7, 145.2 (quaternary aromatic carbon atoms), 184.5 (CHO).
MS (ESI) *m/z* = 448.05 $[M+H]^+$.

General procedure for the formilation reaction of (7)

In a 25 mL round-bottomed flask, 3 mmol of dry DMF and 3 mmol of $POCl_3$ were added in dry dichloroethane, under nitrogen atmosphere, the reaction mixture was stirred until a pale yellow solution was obtained (Vilsmeier reagent). The Vilsmeier reagent was poured into a 100 mL round bottomed flask with three necks containing 1 mmol (for **8**) or 0.5 mmol (for **9**) of derivative **7** solved in 20 mL of dichloroethane and the reaction mixture was refluxed over night. After 16 h the reaction mixture was poured into 20 mL NaOH solution (1N) and washed with dichloromethane (3 x 30 mL). After drying and in vacuum evaporation of the organic solvent, the crude product was purified by column chromatography.

10-Ethyl-3-(5'-formylthiophen-2'-yl)-7-(thiophene-2-yl)-10H-phenothiazine (**8**)

Orange solid, yields 52%. Rf = 0.66 (DCM) m.p. = 120-122 ^{o}C. Calculated for $C_{23}H_{17}NOS_3$; C, 65.84; H, 4.08; N, 3.34; S, 22.93. Found: C, 65.67; H, 3.94; N, 3.49; S, 22.70.

^{1}H-NMR (300 MHz, C_6D_6): δ (ppm) 0.93 (t, CH_3, 3H, *J* = 6.9 Hz), 3.23 (q, CH_2, 2H, *J* = 6.9 Hz), 6.25 (d, 1H, *J* = 8.7 Hz), 6.35 (d, 1H, *J* = 8.7 Hz), 6.63 (d, 1H, *J* = 4.0 Hz), 6.77 (overlapped peaks, 1H), 6.82 (dd, 1H, *J* = 5.1 Hz, *J* = 1.2 Hz), 6.90 (d, 1H, *J* = 3.9 Hz), 6.95 (dd, 1H, *J* = 4.0 Hz, *J* = 1.2 Hz), 7.11 (dd, 2H, *J* = 8.4 Hz, *J* = 2.1 Hz), 7.26 (overlapped peaks, 2H), 7.43 (d, 1H, *J* = 2.1 Hz), 9.54 (s, -CHO, 1H). ^{13}C (75MHz, C_6D_6) 12.5 (CH_3), 41.9 (CH_2), 115.2, 115.5, 122.9, 123.2, 124.5, 125.05, 125.1, 125.4, 125.8, 136.9 (tertiary aromatic carbon atoms), 124.99, 127.19, 128.89, 130.0, 142.6, 143.5, 145.5, 152.8 (quaternary aromatic carbon atoms), 181.8 (CHO).
MS (ESI) *m/z* = 419.8 $[M+H]^+$.

10-Ethyl-3,7-bis(5'-formyl-thiophen-2'-yl)-10H-phenothiazine (**9**)

Red solid, yields 48%. Rf = 0.37 (DCM) m.p. = 168-170 ^{o}C. Calculated for $C_{24}H_{17}NO2S_3$; C, 64.40; H, 3.83; N, 3.13; S, 21.49. Found: C, 64.28; H, 3.76; N, 3.22; S, 22.31.

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 1.32 (t, CH_3, 3H, *J* = 6.7 Hz), 3.97 (q, CH_2, 2H, *J* = 6.7 Hz), 7.09 (d, 2H, *J* = 8.1 Hz), 7.60 (overlapped peaks, 4H), 7.68 (d, 2H, *J* = 3.9 Hz), 7.99 (d, 2H, *J* = 3.9 Hz), 9.86 (s, -CHO, 2H). ^{13}C (75MHz, DMSO-d_6): 12.8 (CH_3), 42.1 (CH_2), 116.3, 124.8, 125.0, 126.5, 139.9 (tertiary aromatic carbon atoms), 123.1, 127.5, 141.6, 144.6, 152.1 (quaternary aromatic carbon atoms), 184.3(CHO).
MS (ESI) *m/z* = 447.9 $[M+H]^+$.

General procedure for the reduction of dialdehydes 9 and 12

Dialdehydes **9** or **12** (1 mmol) were solved in 30 mL mixture THF: water = 4:1 in a round bottomed flask. The mixture was cooled down to 0^{o}C on an ice bath then a solution of 10 mmol $NaBH_4$ solved in 10 mL solvent (mixture, THF: water) was added dropwise for 30 min at this temperature. The reaction was left to warm at *rt* and stirred for another 2h and then the reaction mixture was extracted with DCM (3 x 20 mL). After removing the solvents the crude solid was purified on chromatographic column using pentane / ethyl acetate = 4:3 as eluent.

10-Ethyl-3,7-bis(5'-hydroxymethyl-thiophen-2'-yl)-10H-phenothiazine (**13**)

Yellow solid, yields 80%. Rf = 0.86 (pentane: ethyl acetate = 4:3), m.p. = 172- 174 ^{o}C. Calculated for $C_{24}H_{21}NO_2S_3$; C, 63.83; H, 4.69; N, 3.10; S, 21.30. Found: C, 64.02; H, 4.81; N, 3.25; S, 22.44.

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 1.30 (t, CH_3, 3H, *J* = 6.7 Hz), 3.94 (q, CH_2, 2H, *J* = 6.7 Hz), 4.61 (d, -CH_2-OH, 4H, *J* = 5.1 Hz), 6.91 (d, 2H, *J* = 3.6 Hz), 7.02 (d, 2H, *J* = 8.4 Hz), 7.26 (d, 2H, *J* = 3.6 Hz), 7.42-7.34 (overlapped peaks, 4H). ^{13}C-NMR (75 MHz, DMSO-d_6): 12.4 (CH_3), 41.2 (CH_2), 58.3 (CH_2-OH), 115.6, 122.2, 123.1, 124.5, 125.2 (tertiary aromatic carbon atoms), 122.7, 128.5, 140.9, 142.8, 145.2 (quaternary aromatic carbon atoms).
MS (ESI) *m/z* = 452.08 $[M+H]^+$.

10-Ethyl-3,7-bis(4'-hydroxymethyl-thiophen-2'-yl)-10H-phenothiazine (**14**)

Yellow solid, yields 85%. Rf = 0.15 (pentane: ethyl acetate = 4:3), m.p. = 144-146 ^{o}C. Calculated for $C_{24}H_{21}NO_2S_3$; C, 63.83; H, 4.69; N, 3.10; S, 21.30. Found: C, 63.92; H, 4.57; N, 3.19; S, 22.16.

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 1.33 (t, CH_3, 3H, *J* = 6.9 Hz), 3.96 (q, CH_2, 2H, *J* = 6.9 Hz), 4.41 (d, -CH_2-OH, 4H, *J* = 5.1 Hz), 7.08 (d, 2H, *J* = 8.4 Hz), 7.14 (d, 2H, *J* = 5.1 Hz), 7.28 (d, 2H, *J* = 2.1 Hz), 7.32 (dd, 2H, *J* = 8.4 Hz, *J* = 2.1 Hz), 7.43 (d, 2H, *J* = 5.1 Hz). ^{13}C-NMR (75 MHz, DMSO): δ (ppm) 12.2 (CH_3), 40.9 (CH_2), 56.7 (CH_2-OH), 115.2, 123.5, 126.3, 127.7, 129.9 (tertiary aromatic carbon atoms), 122.2, 127.6, 137.4, 137.9, 142.9 (quaternary aromatic carbon atoms).
MS (ESI) *m/z* = 452.3 $[M+H]^+$.

CONCLUSIONS

The good yields synthesis of some diol and dialdehyde podands (**7**, **12-14**) exhibiting a terheterocyclic core formed by two thiophene units connected to a central phenothiazine moiety is

reported. The linkage between the two types heterocycles is carried out by cross coupling Suzuki reactions. For the synthesis of **7** the one-pot procedures are proved to be the most efficient. Due to the different reactivities at positions 2 and 3 of the thiophene ring, for **7** the insertion of the formyl groups on the thiophene units could be carried out after the cross-coupling step, while for the obtaining of **12** the formylated thiophene derivative was used directly in the cross coupling reaction.

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