

Synthesis of novel bis- and poly(hydrazinylthiazole) linked to benzofuran or benzothiazole as new hybrid molecules

Mostafa E. Salem, Ahmed F. Darweesh, Mohamed R. Shaaban, and Ahmed H. M. Elwahy*

Chemistry Department, Faculty of Science, Cairo University, Giza-Egypt

E-mail: aelwahy@hotmail.com

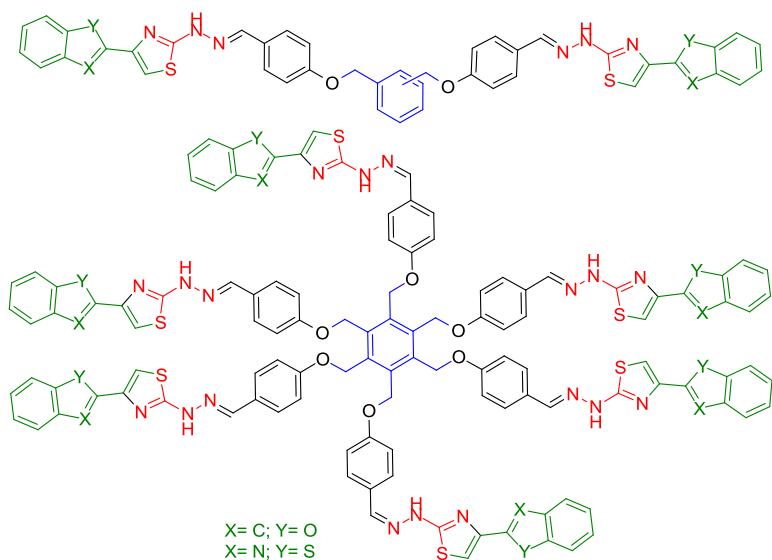
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Abstract

A novel series of bis- and poly(thiazoles) substituted with benzofuran and benzothiazole moieties were prepared in good yields by the reaction of the appropriate bis(α -bromoketones) with the corresponding bis- and poly(hydrazinecarbothioamide) in refluxing EtOH in the presence of TEA. The structures of the new compounds were confirmed based on elemental analyses as well as spectral data.



Keywords: Bisaldehydes, poly(aldehydes), bis(thiazoles), poly(thiazoles), bromoacetylbenzofuran, bromoacetylbenzothiazole, hybrid molecules

Introduction

Thiazoles are promising scaffolds in the area of medicinal and pharmaceutical chemistry and have accounted to show different biological activities, such as anti-HIV, anti-inflammatory, antimicrobial, antihypertensive, antifungal, anticonvulsant, antiviral, anticancer, antimalarial, and anti-hyperlipidemic activities.^{1–10} Some thiazole containing compounds are well established as medicines (Figure 1).^{11–16}

Moreover, among different heterocyclic compounds, benzofuran constitutes the most important class of fused ring heterocyclic. They are considered the core of several interesting pharmacologically active natural products.^{17–20} Recently, benzofuran derivatives attracted natural product researchers due to their valuable biological activities including antifungal,^{21,22} antiprotozoal,²¹ antitubercular,^{23,24} antiinflammatory,²⁵ anticonvulsant,²⁶ anticancer,²⁷ antiHIV,²⁸ analgesic,²⁹ antiparasitic,³⁰ antihyperlipidemic,³¹ antioxidant,³² antiplasmodial³³ and anti-Alzheimer's.³⁴ Several clinically approved drugs based on benzofuran moiety are outlined in Figure 1.^{35–38}

Furthermore, benzothiazole core is an important scaffold for drug development, because it has demonstrated a wide spectrum of pharmacological activities and therapeutic functions including antitumor,^{39,40} antimicrobial,^{41,42} anti-tubercular,^{43,44} anti-HIV,⁴⁵ anti-malarial,⁴⁶ anti-convulsant,⁴⁷ anthelmintic,^{48,49} anti-oxidant⁵⁰ and analgesic. Synthesis and biological activities of benzothiazoles have been recently reviewed.^{51–55} Some important and clinically used drugs having benzothiazole ring in their structures including; Riluzole, Pramipexole, Dimazole and Ethoxzolamide are shown in Figure 1.

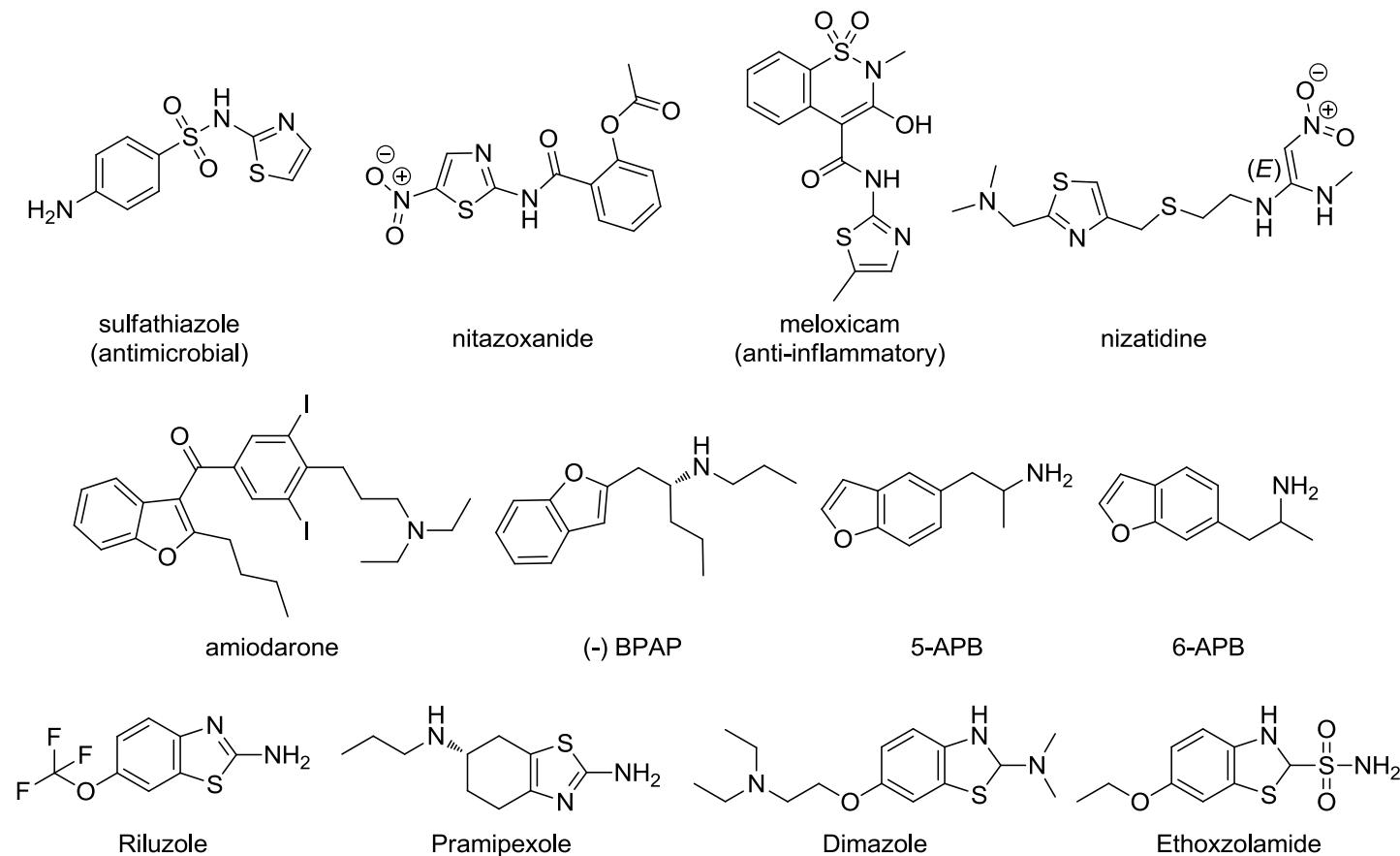


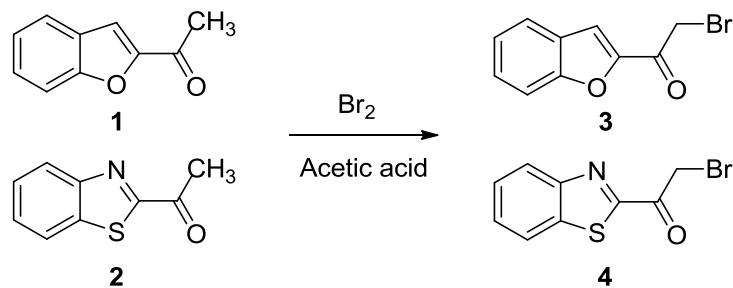
Figure 1

In addition, molecular hybridization have attracted much attention in the last decades in drug design and development as it can lead to compounds with superior efficacy *via* integration of pharmacophoric moieties from different bioactive substances.⁵⁶⁻⁶³

Motivated by these findings and in conjunction with our ongoing research work on bis- as well as poly(heterocycles)⁶⁴⁻⁷¹ we report herein on the synthesis of novel scaffolds based on thiazole linked with benzofuran or benzothiazole moieties as new hybrid molecules with enhanced biological potentials.

Results and Discussion

The desired starting building blocks; bromoacetylbenzofuran (**3**) and bromoacetylbenzothiazole (**4**) were obtained in good yields by bromination of the corresponding acetyl derivatives **1** and **2** with bromine in acetic acid (Scheme 1).⁷²⁻⁷⁵

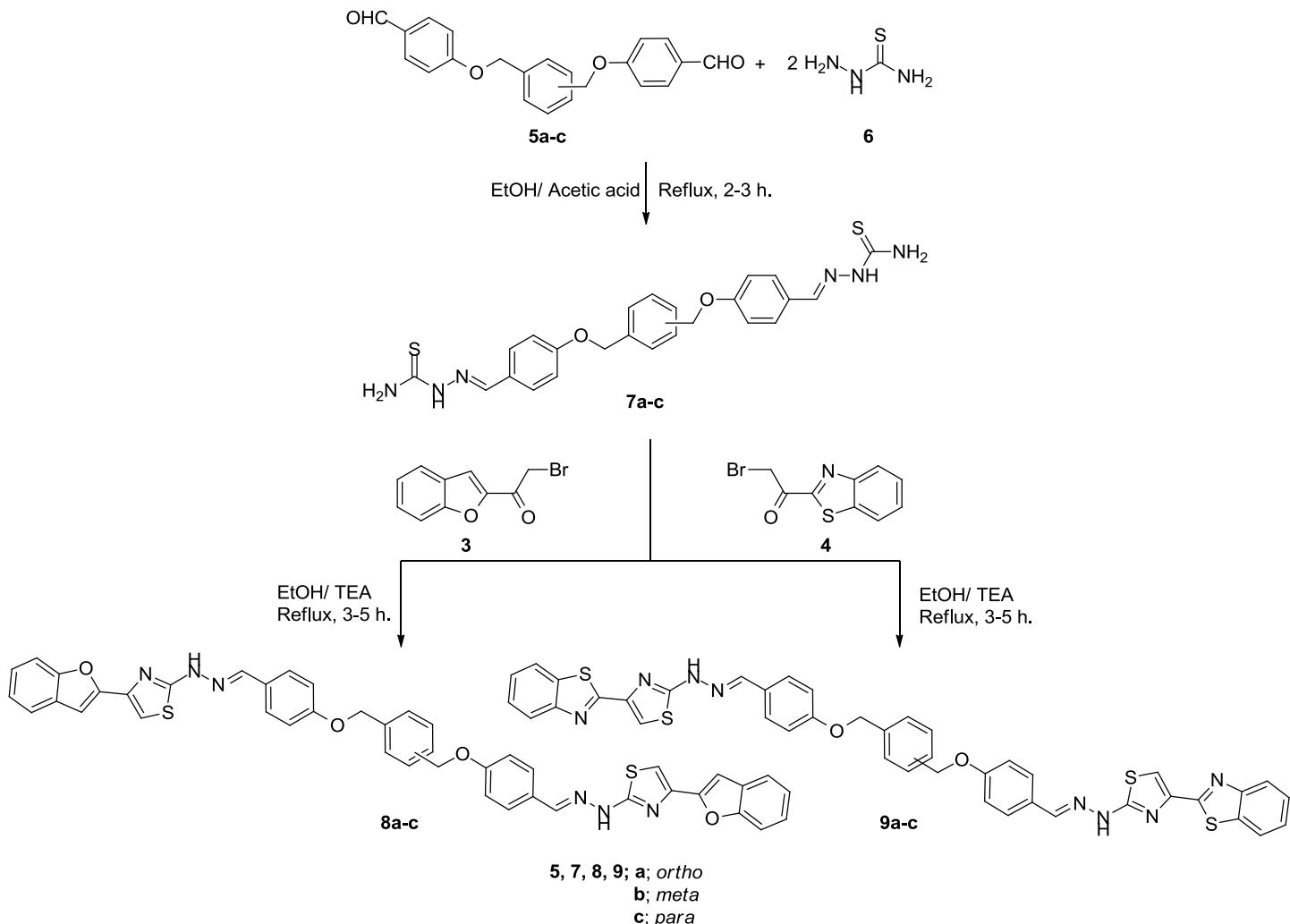


Scheme 1

The preparation of bis(thiazole) **8a-c**, in which the (benzofuran-2-yl)-hydrazinylthiazole is linked to benzene core *via* phenoxyethyl group, is depicted in Scheme 2. Thus, reaction of the appropriate bis(aldehydes) **5a-c** with thiosemicarbazide (**6**) in refluxing EtOH containing few drops of AcOH, gave the corresponding alkylenebis(oxy)bis(2,1-phenylene)bis(methan-1-yl-1-ylidene))bis-(hydrazinecarbothioamide) **7a-c**.⁶⁵ Reaction of the latter compounds with 1-(benzofuran-2-yl)-2-bromoethanone (**3**) in refluxing ethanol in the presence of TEA, gave **8a-c** in 75–85% yields (Scheme 2).

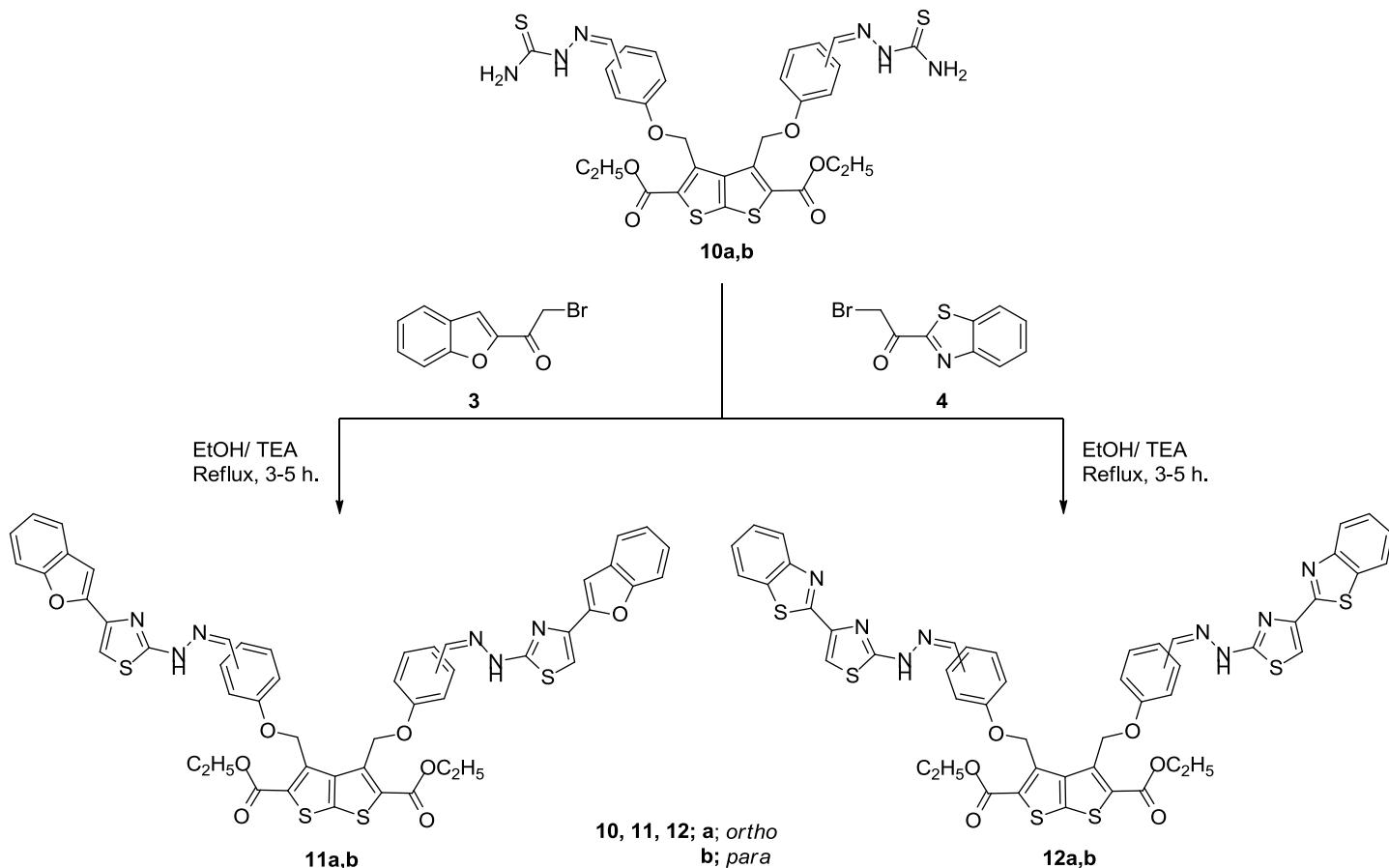
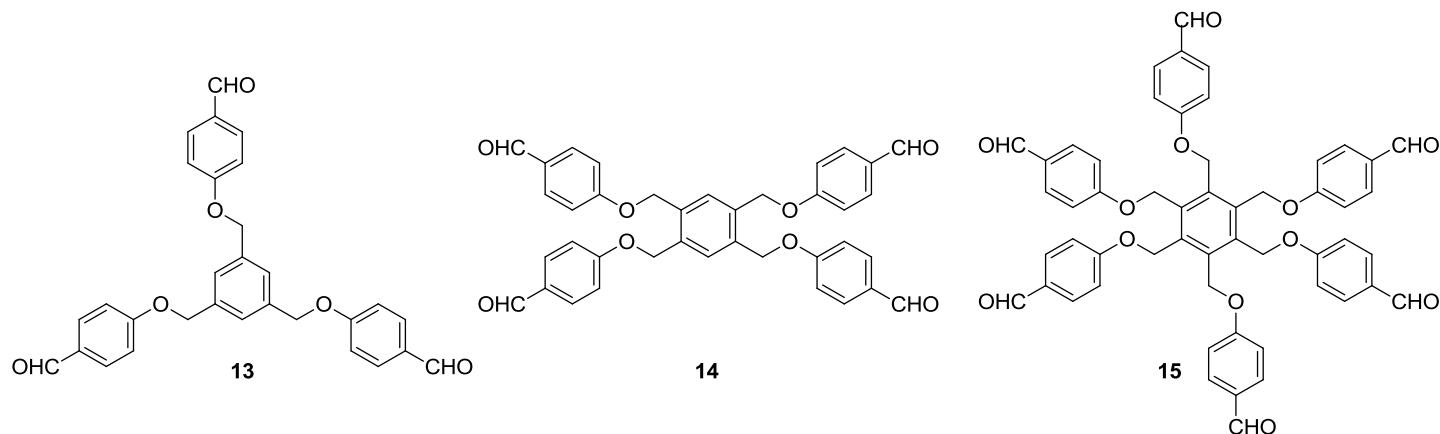
The same methodology was extended to the preparation of bis(thiazole) **9a-c** in which hydrazinylthiazol-4-yl)benzo[d]thiazole is linked to benzene core *via* phenoxyethyl group. Thus, reaction of **7a-c** with 1-(benzo[d]thiazol-2-yl)-2-bromoethanone (**4**) in refluxing ethanol in the presence of TEA, gave **9a-c** in 71–82% yields (Scheme 2).

The novel isomeric bis(thiazoles) **11a,b** and **12a,b** in which the thiazoles are linked to thieno[2,3-*b*]thiophene core could also prepared using a similar approach. Thus, reaction of bis(thiosemicarbazones) **10a,b** with 1-(benzofuran-2-yl)-2-bromoethanone (**3**) and 1-(benzo[d]thiazol-2-yl)-2-bromoethanone (**4**), respectively, in refluxing ethanol in the presence of TEA afforded **11a,b** and **12a,b** in 69–83% and 73–78% yields, respectively (Scheme 3). Compounds **10a,b** was obtained by the reaction of the appropriate bis(aldehyde) with thiosemicarbazide (**6**) in refluxing EtOH containing few drops of AcOH.⁷⁶

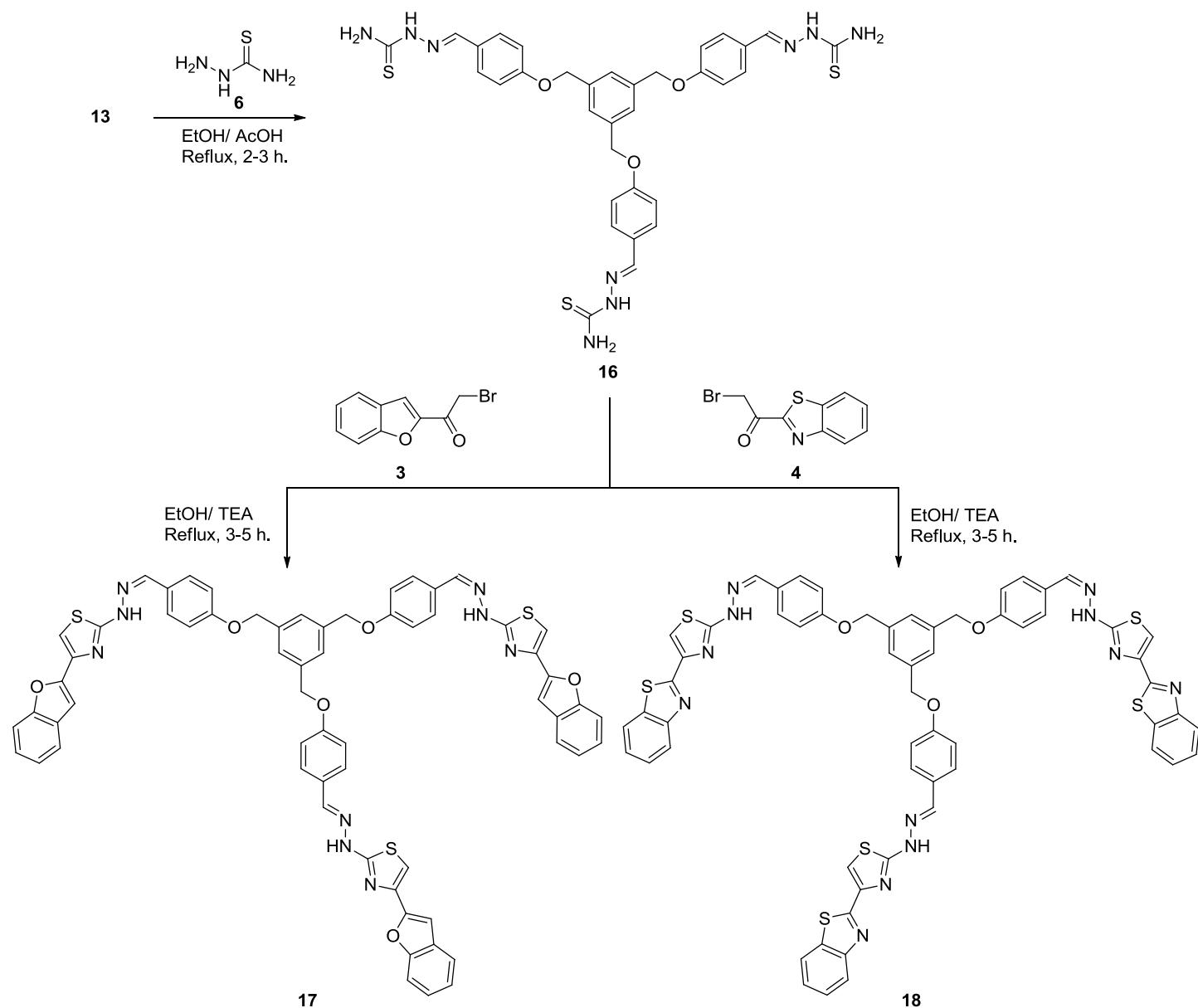
**Scheme 2**

All of the isolated compounds were characterized by elemental analyses, as well as their spectral data which agree with the proposed structures. The structure of bis(thiazole) **8a** as a representative example was confirmed by IR, ¹H-NMR and mass spectra. Thus, the IR spectrum of **8a** showed absorption bands at 3428 cm⁻¹ because of NH group. Moreover, the ¹H NMR spectra of compound **8a** showed a D₂O-exchangeable signal at δ 12.26 because of NH protons and sharp singlet signals at δ 5.24 and 7.35 attributed to OCH₂ group and C-5 proton of the thiazole ring, respectively. All other protons appeared at the expected chemical shifts and integral values. Mass spectrum of compound **8a** showed an intense molecular ion peak at m/z 772 in agreement with its respective molecular formula.

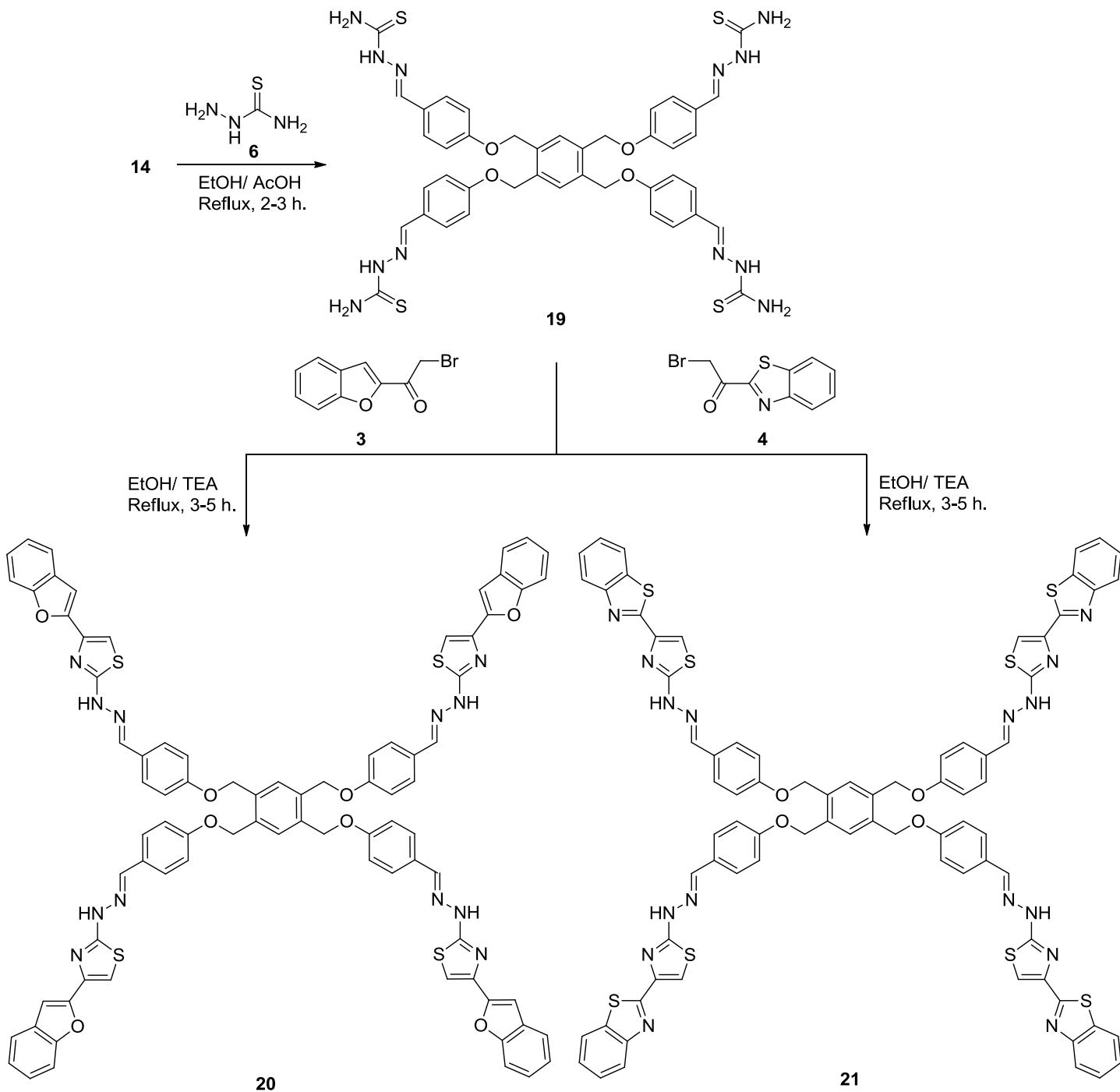
Our study was extended to include the synthesis of novel tris-, tetrakis-, and hexakis(thiazoles), in which the thiazolylhydrazone is linked to benzene core *via* phenoxyethyl group. For this purpose the required aldehydes, tris(formylphenoxyethyl)benzenes (**13**), tetrakis(formylphenoxyethyl)benzenes (**14**) and hexakis(formylphenoxyethyl)benzenes (**15**) were firstly synthesized as recently described by our group *via* the reaction of 4-hydroxybenzaldehyde with the appropriate poly(bromomethyl)benzene in basic medium (Figure 2).⁷⁷

**Scheme 3****Figure 2**

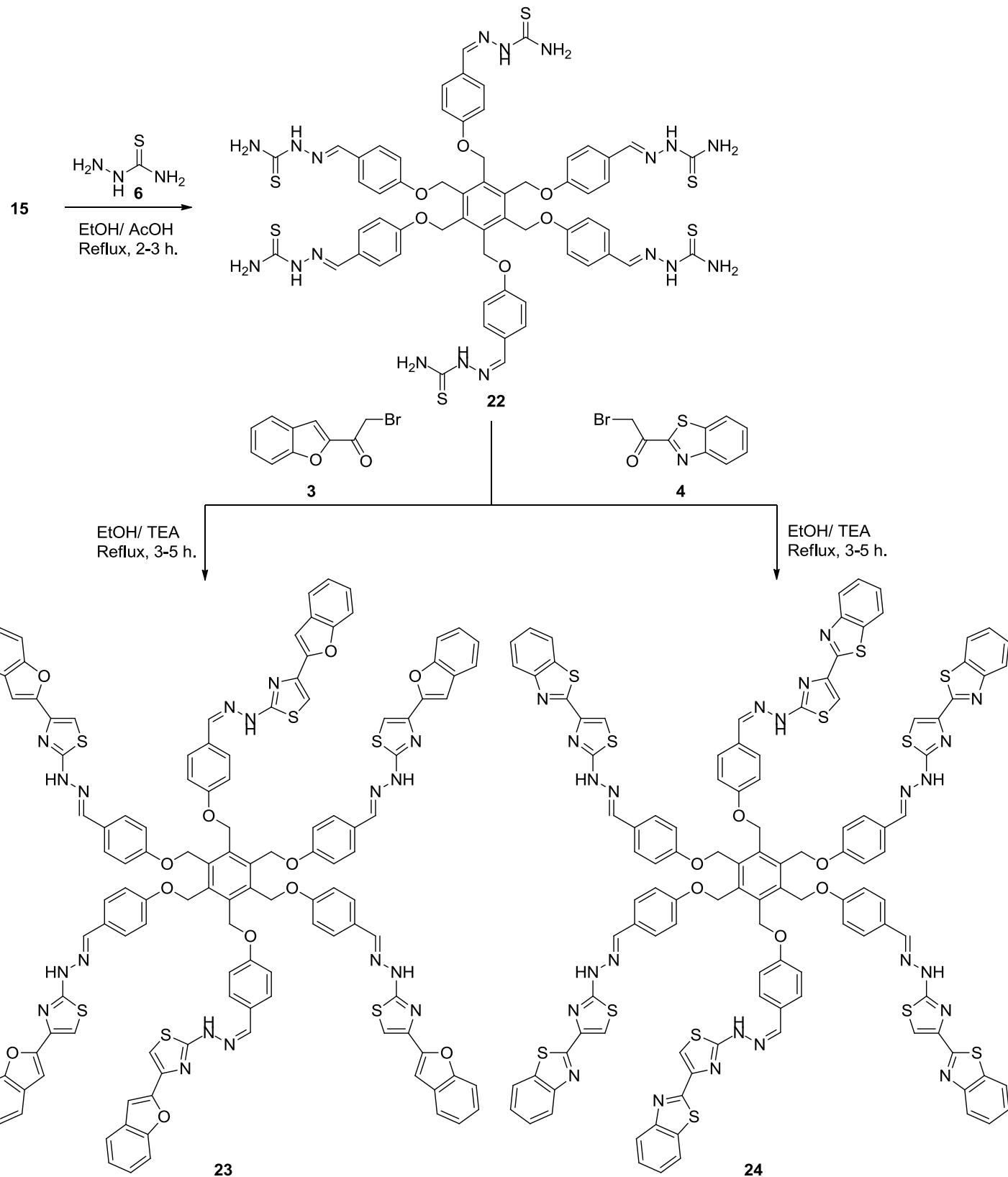
Acid catalyzed condensation of tris(aldehyde) **13** with thiosemicarbazide (**6**) afforded the corresponding tris(aldehyde thiosemicarbazones) **16**⁶⁶. Reaction of the latter compound with each of 1-(benzofuran-2-yl)-2-bromoethanone (**3**) and 1-(benzo[d]thiazol-2-yl)-2-bromoethanone (**4**), respectively, in refluxing ethanol in the presence of TEA afforded **17** and **18** in 70% and 67% yields, respectively (Scheme 4).

**Scheme 4**

The same methodology was extended to the preparation of tetrakis(thiazoles) **20** and **21**. Thus, reaction of **14** with thiosemicarbazide (**6**) in refluxing EtOH containing few drops of AcOH gave tetrakis(aldehyde thiosemicarbazone) **19**⁶⁶ in good yield. Reaction of the latter compound with the appropriate bromoacetyl compounds **3** and **4** in refluxing ethanol in the presence of TEA afforded the corresponding tetrakis(thiazoles) **20** and **21** in 68 and 64% yields, respectively (Scheme 5).

**Scheme 5**

The hexakis(thiazoles) **23** and **24** were similarly prepared, starting from **15** by firstly reaction with thiosemicarbazide (**6**) in refluxing EtOH containing few drops of AcOH to give hexakis(aldehyde thiosemicarbazones) **22**⁶⁶ followed by reaction with the appropriate bromoacetyl derivatives **3** and **4** under similar conditions (Scheme 6).

**Scheme 6**

The structures of the new synthesized compounds were confirmed by IR, NMR, and mass spectra as well as elementary analyses. The IR spectrum of tris (thiazolylhydrazone) **17** as a representative example of this class of compounds revealed an absorption band at 3427 cm^{-1} because of (NH). Its ^1H NMR spectra showed the presence of singlet signals at δ 5.20 and δ 8.00 ppm characteristic for the OCH_2 group and the methine proton ($-\text{N}=\text{CH}-$), respectively. The presence of a single set of signals characteristic of the equivalent groups in the $^1\text{H-NMR}$ spectra of these compounds demonstrated their symmetry. The spectra of the poly(thiazoles) **18**, **20**, **21**, **23** and **24** showed similar spectral data which are listed in the experimental part.

Conclusions

We have developed an efficient approach for the synthesis of bis(thiazoles) which are linked to arene or heteroarene core *via* phenoxy methyl group. We used a similar strategy for the synthesis of novel poly(thiazoles) which are linked to a benzene core *via* phenoxy methyl spacers. Full characterization of these compounds is reported. The mild reaction conditions, good yields and easily accessible starting material are the advantages of this methodology. The successful synthesis of these compounds opens a new access to novel hybrid molecules with interesting inclusion properties as well as broad range biological activities.

Experimental Section

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded using a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (^1H NMR) and at 75 MHz (^{13}C NMR) using $\text{DMSO}-d_6$ as solvent. Capillary GC analyses were performed with a Shimadzu GC-14A or GC-14B, a Shimadzu C-R6A Integrator, and a HP 5 column (25 m length, 0.25 mm i.d., 0.25 μm film) or recorded with an Agilent GC 6890N. Mass spectra (EI) were obtained at 70 eV using a type Shimadzu GCMQP 1000 EX Spectrometer. Compounds **3**,⁷⁴ **4**,⁷⁵ **7a-c**,⁶⁵ **10a,b**,⁷⁶ **16**,⁶⁶ **19**⁶⁶ and **22**⁶⁶ were prepared according to literature.

Synthesis of bis((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzenes (**8a-c**) and bis((4-((2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzenes (**9a-c**).

General Procedure. To a solution of alkylenebis(oxy)bis(2,1-phenylene)bis(methan-1-yl-1-ylidene))bis(hydrazinecarbothioamide) **7a-c** (1 mmol) in ethanol (15 mL) containing TEA (0.1 ml, 1 mmol), a solution of 1-(benzofuran-2-yl)-2-bromoethanone (**3**) (2 mmol) or 1-(benzo[d]thiazol-2-yl)-2-bromoethanone (**4**) (2 mmol) in ethanol (10 mL) was added. The reaction mixture was heated at reflux for 5 h. The solvent was then evaporated in *vacuo* and the solid residue was collected and recrystallized from ethanol/DMF to give the corresponding bis((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzenes **8a-c** and bis((4-((2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzenes **9a-c**, respectively.

1,2-Bis((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (8a**).** Brown crystals (75%); mp 232-234 °C; IR (KBr) ν 3428, 3298, 1602, 1557, 1245, 1048 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 5.24 (s, 4H, CH_2O), 7.01-7.22 (m, 6H, ArH), 7.35 (s, 2H, thiazole-5-H), 7.37-7.56 (m, 14H, ArH), 7.80 (s, 2H, benzofuran-3-H), 8.50 (s, 2H, $\text{CH}=\text{N}$), 12.26 (br. s, 2H, NH); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 69.3, 101.7, 106.9,

112.8, 113.1, 115.4, 121.0, 122.6, 123.5, 125.0, 126.9, 127.6, 130.7, 136.4, 137.5, 141.4, 152.8, 153.1, 156.1, 168.8; MS m/z (%) 772 (M^+). Anal. Calcd for $C_{44}H_{32}N_6O_4S_2$: C, 68.38; H, 4.17; N, 10.87; S, 8.30. Found: C, 68.51; H, 4.48; N, 10.95; S, 8.60%.

1,3-Bis((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (8b). Brown crystals (82%); mp 260–262 °C; IR (KBr) ν 3423, 3294, 1602, 1568, 1245, 1047 cm^{-1} ; 1H NMR (300 MHz, DMSO- d_6) δ 5.18 (s, 4H, CH_2O), 7.03–7.10 (m, 6H, ArH), 7.35 (s, 2H, thiazole-5-H), 7.43–7.62 (m, 14H, ArH), 7.86 (s, 2H, benzofuran-3-H), 7.99 (s, 2H, $CH=N$), 12.13 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO- d_6) δ 69.1, 101.6, 106.8, 112.9, 115.2, 115.4, 123.6, 125.0, 127.0, 127.3, 127.8, 130.7, 131.8, 137.0, 141.1, 141.8, 153.2, 154.1, 159.3, 169.0; MS m/z (%) 772 (M^+). Anal. Calcd for $C_{44}H_{32}N_6O_4S_2$: C, 68.38; H, 4.17; N, 10.87; S, 8.30. Found: C, 68.65; H, 4.32; N, 10.55; S, 8.60%.

1,4-Bis((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (8c). Brown crystals (85%); mp > 300 °C; IR (KBr) ν 3415, 3289, 1602, 1569, 1245, 1046 cm^{-1} ; 1H NMR (300 MHz, DMSO- d_6) δ 5.16 (s, 4H, CH_2O), 7.02–7.09 (m, 6H, ArH), 7.36 (s, 2H, thiazole-5-H), 7.42–7.62 (m, 14H, ArH), 7.85 (s, 2H, benzofuran-3-H), 7.99 (s, 2H, $CH=N$), 12.13 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO- d_6) δ 69.0, 101.7, 106.8, 112.8, 115.1, 115.4, 116.6, 123.6, 127.0, 127.7, 127.8, 128.8, 130.7, 131.7, 136.4, 141.3, 141.8, 152.8, 159.3, 169.0; MS m/z (%) 772 (M^+). Anal. Calcd for $C_{44}H_{32}N_6O_4S_2$: C, 68.38; H, 4.17; N, 10.87; S, 8.30. Found: C, 68.55; H, 4.34; N, 10.60; S, 8.41%.

1,2-Bis((4-((2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (9a). Brown crystals (71%); mp 205–207 °C; IR (KBr) ν 3416, 1564, 1240, 1092 cm^{-1} ; 1H NMR (300 MHz, DMSO- d_6) δ 5.25 (s, 4H, CH_2O), 7.05 (t, 2H, J 7.5 Hz, ArH), 7.21 (d, 2H, J 8.4 Hz, ArH), 7.36–7.57 (m, 12H, ArH), 7.75 (s, 2H, thiazole-5-H), 7.83 (d, 2H, J 6.9 Hz, ArH), 8.00 (t, 2H, J 8.7 Hz, ArH), 8.52 (s, 2H, $CH=N$), 12.43 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO- d_6) δ 69.2, 109.0, 113.1, 121.0, 122.1, 122.3, 122.5, 124.9, 126.3, 127.4, 130.7, 134.3, 136.3, 137.8, 144.5, 153.4, 156.1, 162.4, 168.5; MS m/z (%) 807 (M^+). Anal. Calcd for $C_{42}H_{30}N_8O_2S_4$: C, 62.51; H, 3.75; N, 13.89; S, 15.89. Found: C, 62.86; H, 3.94; N, 14.03; S, 16.01%.

1,3-Bis((4-((2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (9b). Green crystals (74%); mp 270–272 °C; IR (KBr) ν 3429, 1571, 1505, 1240, 1049 cm^{-1} ; 1H NMR (300 MHz, DMSO- d_6) δ 5.18 (s, 4H, CH_2O), 7.09 (d, 4H, J 8.7 Hz, ArH), 7.43–7.56 (m, 8H, ArH), 7.62 (d, 4H, J 8.4 Hz, ArH), 7.74 (s, 2H, thiazole-5-H), 7.99–8.01 (m, 4H, $CH=N$ & ArH), 8.09 (d, 2H, J 8.1 Hz, ArH), 12.30 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO- d_6) δ 69.1, 94.2, 108.9, 115.1, 122.2, 122.4, 125.0, 126.3, 126.9, 127.2, 127.9, 128.5, 134.5, 136.9, 142.1, 144.6, 153.5, 159.4, 162.6, 168.7; MS m/z (%) 807 (M^+). Anal. Calcd for $C_{42}H_{30}N_8O_2S_4$: C, 62.51; H, 3.75; N, 13.89; S, 15.89. Found: C, 62.69; H, 3.43; N, 13.57; S, 15.75%.

1,4-Bis((4-((2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (9c). Green crystals (82%); mp 265–267 °C; IR (KBr) ν 3423, 1569, 1508, 1245 cm^{-1} ; 1H NMR (300 MHz, DMSO- d_6) δ 5.17 (s, 4H, CH_2O), 7.09 (d, 4H, J 8.7 Hz, ArH), 7.43–7.53 (m, 8H, ArH), 7.62 (d, 4H, J 9.0 Hz, ArH), 7.74 (s, 2H, thiazole-5-H), 8.00–8.02 (m, 4H, $CH=N$ & ArH), 8.10 (d, 2H, J 8.1 Hz, ArH), 12.29 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO- d_6) δ 69.5, 109.5, 115.6, 122.7, 123.0, 125.6, 126.9, 127.4, 128.3, 128.4, 135.0, 136.9, 142.6, 145.1, 154.0, 159.9, 163.1, 169.2; MS m/z (%) 807 (M^+). Anal. Calcd for $C_{42}H_{30}N_8O_2S_4$: C, 62.51; H, 3.75; N, 13.89; S, 15.89. Found: C, 62.23; H, 3.47; N, 13.62; S, 15.60%.

Synthesis of diethyl 3,4-bis(((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methylphenoxy)-methyl)thieno[2,3-*b*]-thiophene-2,5-dicarboxylates (11a,b) and diethyl 3,4-bis(((2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazone)methylphenoxy)methyl)thieno[2,3-*b*]thiophene-2,5-dicarboxylates (12a,b).

General Procedure. To a solution of diethyl thieno[2,3-*b*]thiophene-2,5-dicarboxylate derivatives **10a** or **10b** (1 mmol) in ethanol (15 mL) containing TEA (0.1 ml, 1 mmol), a solution of 1-(benzofuran-2-yl)-2-

bromoethanone (**3**) (2 mmol) or 1-(benzo[*d*]thiazol-2-yl)-2-bromoethanone (**4**) (2 mmol) in ethanol (10 mL) was added. The reaction mixture was heated at reflux for 5 h. The solvent was then evaporated in *vacuo* and the solid residue was collected and recrystallized from ethanol/DMF to give the corresponding pure products **11a,b** and **12a,b**, respectively.

Diethyl 3,4-bis((2-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)thieno[2,3-*b*]-thiophene-2,5-dicarboxylate (11a). Brown crystals (69%); mp > 300 °C; IR (KBr) ν 3429, 1707, 1602, 1562, 1439, 1248, 1094 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.23 (t, 6H, CH₃CH₂-, *J* 7.2 Hz), 4.30 (q, 4H, CH₃CH₂-, *J* 7.2 Hz), 5.62 (s, 4H, CH₂O), 6.88-6.94 (m, 6H, ArH), 7.24 (s, 2H, thiazole-5-H), 7.39-7.51 (m, 10H, ArH), 7.73 (s, 2H, benzofuran-3-H), 8.17 (s, 2H, CH=N), 11.96 (s, 2H, NH); MS *m/z* (%) 979 (M⁺). Anal. Calcd for C₅₀H₃₈N₆O₈S₄: C, 61.33; H, 3.91; N, 8.58; S, 13.10. Found: C, 61.49; H, 3.69; N, 8.35; S, 13.30%.

Diethyl 3,4-bis((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)thieno[2,3-*b*]-thiophene-2,5-dicarboxylate (11b). Brown crystals (83%); mp > 300 °C; IR (KBr) ν 3423, 1708, 1604, 1565, 1439, 1246, 1101 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.28 (t, 6H, CH₃CH₂-, *J* 6.9 Hz), 4.33 (q, 4H, CH₃CH₂-, *J* 6.9 Hz), 5.59 (s, 4H, CH₂O), 6.84-6.88 (m, 6H, ArH), 7.19 (s, 2H, thiazole-5-H), 7.35-7.44 (m, 10H, ArH), 7.70 (s, 2H, benzofuran-3-H), 7.91 (s, 2H, CH=N), 12.04 (s, 2H, NH); MS *m/z* (%) 979 (M⁺). Anal. Calcd for C₅₀H₃₈N₆O₈S₄: C, 61.33; H, 3.91; N, 8.58; S, 13.10. Found: C, 61.30; H, 3.70; N, 8.79; S, 12.77%.

Diethyl 3,4-bis((2-((2-(4-(benzo[*d*]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)thieno[2,3-*b*]-thiophene-2,5-dicarboxylate (12a). Green crystals (73%); mp 270-272 °C; IR (KBr) ν 3430, 1708, 1564, 1438, 1244, 1091 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.23 (t, 6H, CH₃CH₂-, *J* 7.2 Hz), 4.30 (q, 4H, CH₃CH₂-, *J* 7.2 Hz), 5.64 (s, 4H, CH₂O), 6.89-6.96 (m, 4H, ArH), 7.19-7.47 (m, 6H, ArH), 7.64 (s, 2H, thiazole-5-H), 7.69-8.00 (m, 6H, ArH), 8.20 (s, 2H, CH=N), 12.17 (s, 2H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 13.8, 55.9, 61.6, 109.1, 112.5, 120.5, 121.2, 122.0, 122.4, 125.1, 126.2, 130.5, 134.4, 135.1, 135.6, 137.5, 144.5, 145.9, 153.4, 155.6, 161.1, 162.5, 168.4. Anal. Calcd for C₄₈H₃₆N₈O₆S₆: C, 56.90; H, 3.58; N, 11.06; S, 18.99. Found: C, 56.67; H, 3.43; N, 10.77; S, 18.70%.

Diethyl 3,4-bis((4-((2-(4-(benzo[*d*]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)thieno[2,3-*b*]-thiophene-2,5-dicarboxylate (12b). Green crystals (78%); mp 267-269 °C; IR (KBr) ν 3433, 1701, 1570, 1503, 1242, 1105 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.27 (t, 6H, CH₃CH₂-, *J* 6.9 Hz), 4.32 (q, 4H, CH₃CH₂-, *J* 6.9 Hz), 5.60 (s, 4H, CH₂O), 6.87 (d, 4H, *J* 8.4 Hz, ArH), 7.33-7.40 (m, 4H, ArH), 7.43 (d, 4H, *J* 8.4 Hz, ArH), 7.62 (s, 2H, thiazole-5-H), 7.81-7.92 (m, 4H, ArH), 7.94 (s, 2H, CH=N), 12.21 (s, 2H, NH). Anal. Calcd for C₄₈H₃₆N₈O₆S₆: C, 56.90; H, 3.58; N, 11.06; S, 18.99. Found: C, 56.60; H, 3.66; N, 11.37; S, 19.29%.

Synthesis of poly(hydrazinylthiazole) derivatives **17, 18, 20, 21, 23** and **24**.

General Procedure. To a solution of poly(thiosemicarbazones) **16** or **19** or **22** (1 mmol) in absolute ethanol (25 mL) containing TEA (0.1 ml, 1 mmol), a solution of 1-(benzofuran-2-yl)-2-bromoethanone (**3**) or 1-(benzo[*d*]thiazol-2-yl)-2-bromoethanone (**4**) (3 or 4 or 6 mmol) in ethanol (10 mL) was added. The reaction mixture was heated at reflux for 3-5 h. The solid product formed upon cooling was collected and recrystallized from ethanol/DMF to give the corresponding poly(hydrazinylthiazoles) **17, 18, 20, 21, 23** and **24**.

1,3,5-Tris((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (17). Brown crystals (70%); mp > 300 °C; IR (KBr) ν 3427, 2916, 1604, 1568, 1439, 1240, 1050 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ 5.20 (s, 6H, CH₂O), 7.02-7.10 (m, 9H, ArH), 7.34 (s, 3H, thiazole-5-H), 7.42-7.62 (m, 18H, ArH), 7.85 (s, 3H, benzofuran-3-H), 8.00 (s, 3H, CH=N), 12.13 (br. s, 3H, NH). Anal. Calcd for C₆₃H₄₅N₉O₆S₃: C, 67.54; H, 4.05; N, 11.25; S, 8.59. Found: C, 67.68; H, 4.33; N, 11.52; S, 8.84%.

1,3,5-Tris((4-((2-(4-(benzo[*d*]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (18). Green crystals (67%); mp > 300 °C; IR (KBr) ν 3419, 1568, 1506, 1235, 1017 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆)

δ 5.21 (s, 6H, CH_2O), 7.10 (d, 6H, J 9.0 Hz, ArH), 7.43-7.55 (m, 9H, ArH), 7.63 (d, 6H, J 8.7 Hz, ArH), 7.74 (s, 3H δ , thiazole-5-H), 7.98-8.10 (m, 9H, $\text{CH}=\text{N}$ & ArH), 12.30 (s, 3H, NH). Anal. Calcd for $\text{C}_{60}\text{H}_{42}\text{N}_{12}\text{O}_3\text{S}_6$: C, 61.52; H, 3.61; N, 14.35; S, 16.42. Found: C, 61.77; H, 3.44; N, 14.70; S, 16.38%.

1,2,4,5-Tetrakis((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (20). Brown crystals (68%); mp > 300 °C; IR (KBr) ν 3425, 2922, 1602, 1507, 1437, 1239, 1046 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 5.32 (s, 8H, CH_2O), 6.99-7.09 (m, 12H, ArH), 7.30 (s, 4H, thiazole-5-H), 7.34-7.81 (m, 22H, ArH), 7.82 (s, 4H, benzofuran-3-H), 7.98 (s, 4H, $\text{CH}=\text{N}$), 12.11 (br. s, 4H, NH). Anal. Calcd for $\text{C}_{82}\text{H}_{58}\text{N}_{12}\text{O}_8\text{S}_4$: C, 67.10; H, 3.98; N, 11.45; S, 8.74. Found: C, 67.32; H, 3.61; N, 11.22; S, 8.53%.

1,2,4,5-Tetrakis((4-((2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (21). Brown crystals (64%); mp 270-273 °C; IR (KBr) ν 3408, 1570, 1507, 1231, 1021 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 5.32 (s, 8H, CH_2O), 7.09 (d, 8H, J 8.4 Hz, ArH), 7.41-7.50 (m, 8H, ArH), 7.61 (d, 8H, J 8.4 Hz, ArH), 7.72 (s, 4H, thiazole-5-H), 7.73 (s, 2H, ArH), 7.96 (d, 4H, J 7.8 Hz, ArH), 8.00 (s, 4H, $\text{CH}=\text{N}$), 8.06 (d, 4H, J 7.8 Hz, ArH), 12.29 (s, 4H, NH). Anal. Calcd for $\text{C}_{78}\text{H}_{54}\text{N}_{16}\text{O}_4\text{S}_8$: C, 61.00; H, 3.54; N, 14.59; S, 16.70. Found: C, 61.33; H, 3.65; N, 14.86; S, 16.93%.

1,2,3,4,5,6-Hexakis((4-((2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (23). Brown crystals (65%); mp > 300 °C; IR (KBr) ν 3427, 2921, 1600, 1566, 1506, 1436, 1230, 1162 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 5.32 (s, 12H, CH_2O), 6.96-7.09 (m, 18H, ArH), 7.25 (s, 6H, thiazole-5-H), 7.37-7.71 (m, 30H, ArH), 7.78 (s, 6H, benzofuran-3-H), 7.94 (s, 6H, $\text{CH}=\text{N}$), 12.08 (br. s, 6H, NH). Anal. Calcd for $\text{C}_{120}\text{H}_{84}\text{N}_{18}\text{O}_{12}\text{S}_6$: C, 66.65; H, 3.92; N, 11.66; S, 8.90. Found: C, 66.50; H, 3.78; N, 11.52; S, 8.63%.

1,2,3,4,5,6-Hexakis((4-((2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazone)methyl)phenoxy)methyl)benzene (24). Green crystals (61%); mp > 300 °C; IR (KBr) ν 3411, 1571, 1503, 1227, 1004 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 5.35 (s, 12H, CH_2O), 6.99-7.01 (m, 12H, ArH), 7.39-7.51 (m, 24H, ArH), 7.67 (s, 6H, thiazole-5-H), 7.89-7.95 (m, 12H, $\text{CH}=\text{N}$ & ArH), 8.02 (d, 6H, J 7.5 Hz, ArH), 12.26 (s, 6H, NH). Anal. Calcd for $\text{C}_{114}\text{H}_{78}\text{N}_{24}\text{O}_6\text{S}_{12}$: C, 60.46; H, 3.47; N, 14.84; S, 16.99. Found: C, 60.24; H, 3.19; N, 14.77; S, 16.69%.

Supplementary Material

Supplementary material related to this article, including Nuclear Magnetic Resonance (^1H and ^{13}C NMR) figures for compounds **8a-c**; **9a-c**; **11a,b**; **12a,b**; **17**; **18**; **20**; **21** and **23** are available in the online version of the text.

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