Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Synthesis of novel scaffolds based on thiazole or triazolothiadiazine linked to benzofuran or benzo[*d*]thiazole moieties as new hybrid molecules

Mostafa E. Salem, Ahmed F. Darweesh & Ahmed H. M. Elwahy

To cite this article: Mostafa E. Salem, Ahmed F. Darweesh & Ahmed H. M. Elwahy (2019): Synthesis of novel scaffolds based on thiazole or triazolothiadiazine linked to benzofuran or benzo[*d*]thiazole moieties as new hybrid molecules, Synthetic Communications, DOI: 10.1080/00397911.2019.1694689

To link to this article: https://doi.org/10.1080/00397911.2019.1694689

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1694689

Taylor & Francis
Taylor & Francis Group

Synthesis of novel scaffolds based on thiazole or triazolothiadiazine linked to benzofuran or benzo[*d*]thiazole moieties as new hybrid molecules

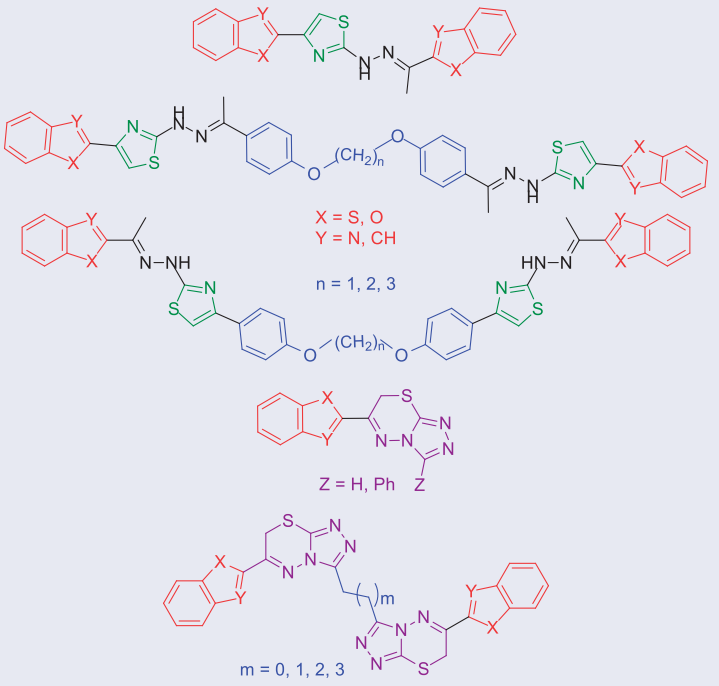
Mostafa E. Salem, Ahmed F. Darweesh, and Ahmed H. M. Elwahy

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

ABSTRACT

A synthesis of novel hybrid molecules containing thiazole or bis(thiazoles) each bearing benzofuran and/or benzo[*d*]thiazole moieties by the reaction of the appropriate thioamide derivatives with the corresponding bis-bromoacetyl derivatives is reported. Mono- and bis(triazolothiadiazine) derivatives based on benzofuran or benzo[*d*]thiazole moieties were also synthesized in good yields by the reaction of the appropriate bis(bromoacetyl) derivatives with each of 4-amino-5-mercapto-1,2,4-triazoles and their corresponding bis-derivatives.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 17 September 2019

KEYWORDS
Bis(benzo[d]thiazol-2-yl)thiazol; bis(benzofuran-2-yl)thiazol; bis(triazolothiadiazine); molecular hybridization; triazolothiadiazine

CONTACT Ahmed F. Darweesh darweesh@sci.cu.edu.eg; Ahmed H. M. Elwahy aelwahy@hotmail.com
Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article can be accessed on the publisher's website

Introduction

Thiazoles are promising scaffolds in the pharmaceutical chemistry and many of their derivatives were reported to exhibit a wide variety of biological properties including anti-HIV, anti-inflammatory, antimicrobial, antihypertensive, antifungal, anticonvulsant, antiviral, anticancer, antimalarial, and anti-hypolipidemic activities.[1–11]

Moreover, 1,2,4-triazoles and their heterocyclic fused analogs especially, triazolothiadiazines, have received considerable attention owing to their promising biological activities. They are reported to possess a widespread of medical applications such as antimicrobial, anti-inflammatory, hypoglycemic, anticancer, anti-HIV, CNS-stimulant, antifungal, antiviral, and analgesic properties.[12–20]

Furthermore, benzofuran constitutes one of the most important class of fused ring heterocyclic due to their valuable biological activities including antifungal, antiprotozoal, antitubercular, anti-inflammatory, anticonvulsant, anticancer, anti-HIV, analgesic, antiparasitic, antihyperlipidemic, antioxidant, antiplasmodial, and anti-Alzheimer's.[21–31]

Likewise, benzothiazole is an important core of drug development. Their derivatives demonstrated a wide spectrum of therapeutic functions including antitumor, antimicrobial, anti-tubercular, anti-HIV, anti-malarial, anti-convulsant, anthelmintic, antioxidant, and analgesic properties.[32–44]

The incorporation of thiazole, 1,2,4-triazole, benzothiazole as well as benzofuran into a wide variety of therapeutically interesting drugs are well established (Fig. 1).

Additionally, molecular hybridization concept has attracted much attention in the last decades in the area of drug design. This tool involves the combination of two pharmacophoric moieties of different bioactive substances in new hybrid molecules aiming at improving their biological efficacy and overcoming drug resistance.[14,44–49]

Motivated by these findings and in conjunction with our ongoing research work on bis(heterocycles) as well as the new concept in drug design, we report herein on the synthesis of novel hybrid molecules containing benzofuran and/or benzothiazole linked to thiazole or triazolothiadiazine and their corresponding bis-derivatives.[50–78]

Results and discussion

The starting materials needed in the synthesis of our target compounds are prepared as outlined in Scheme 1. Thus, bromoacetylbenzothiazole **2a** and bromoacetylbenzofuran **2b** were, respectively, obtained in good yields by the reaction of the corresponding acetyl derivatives **1a** and **1b** with bromine in acetic acid.[70] 2-(1-(Benzo[*d*]thiazol-2-yl)ethylidene)hydrazinecarbothioamide **4a** and 2-(1-(benzofuran-2-yl)ethylidene)-hydrazinecarbothioamide **4b** were prepared by condensation of thiosemicarbazide (**3**) with the corresponding acetyl derivatives **1a** and **1b**, respectively, in acetic acid at reflux (Scheme 1).

The novel 2-(2-(2-(1-(benzo[*d*]thiazol-2-yl)ethylidene)hydrazinyl)thiazol-4-yl)benzo[*d*]thiazole (**5**) in which (ethylidenehydrazinyl)thiazole is located between two benzothiazole rings were prepared in 76% yield by the reaction of **2a** with **4a** in refluxing EtOH in the presence of TEA (Scheme 2). Similarly, 4-(benzofuran-2-yl)-2-(2-(1-(benzofuran-2-yl)ethylidene)-hydrazinyl)thiazole (**6**) in which (ethylidenehydrazinyl)-thiazole

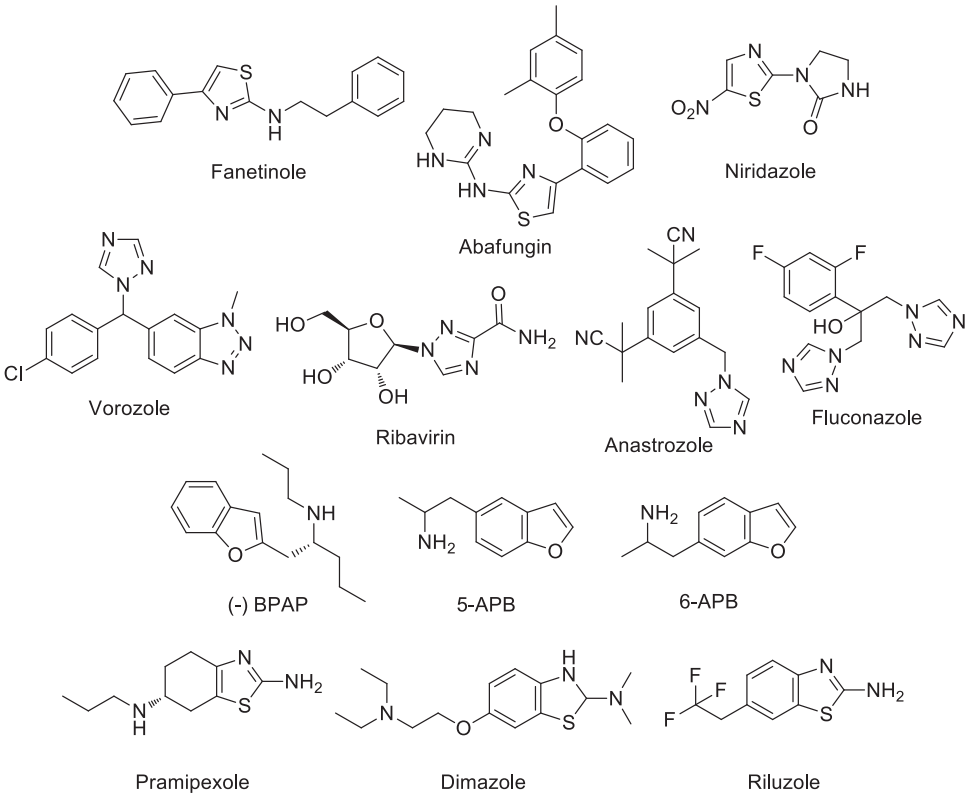
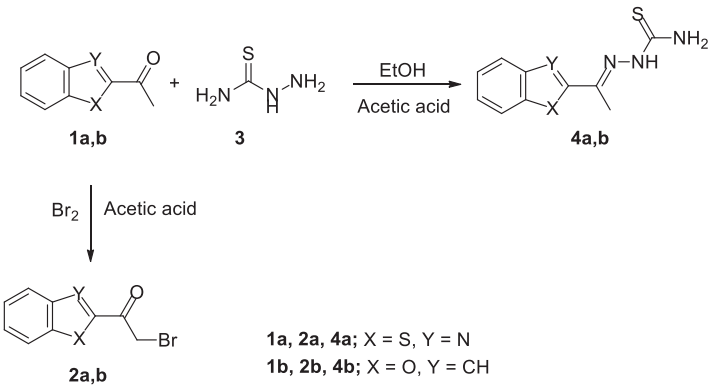


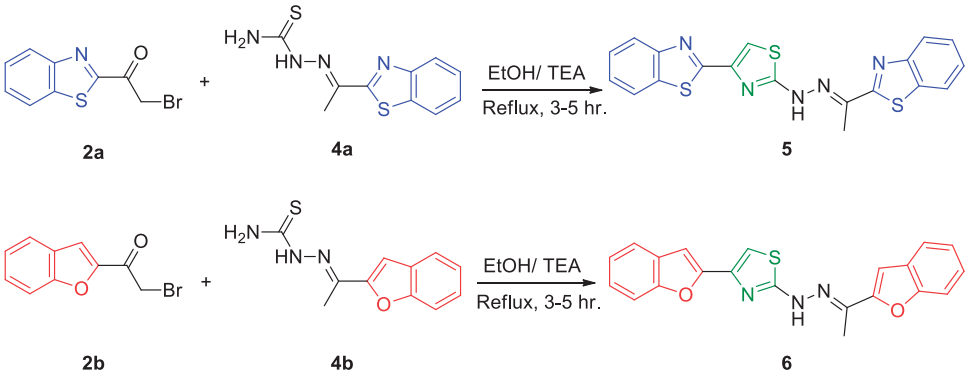
Figure 1. Some therapeutically interesting drugs incorporated thiazole, 1,2,4-triazole, benzothiazole as well as benzofuran.



Scheme 1. Synthesis of bromoacetyl derivatives **2a,b** and thiosemicarbazone derivatives **4a,b.**

is located between two benzofuran rings was obtained in 71% yield by the reaction of **2b** with **4b** under the same reaction conditions.

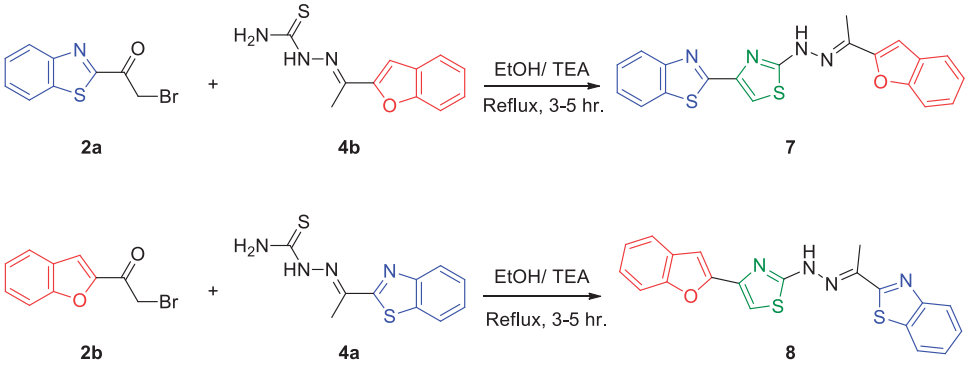
Our study also included the synthesis of the new isomeric compounds, 2-(2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)thiazol-4-yl)benzo[*d*]thiazole (**7**) and 2-(1-(2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazono)ethyl)benzo[*d*]thiazole (**8**) in which



2a **4a** **5**

2b **4b** **6**

Scheme 2. Reaction of the appropriate bromoacetyl derivatives **2a,b** with the corresponding thiosemicarbazone derivatives **4a** and **4b**, respectively.



2a **4b** **7**

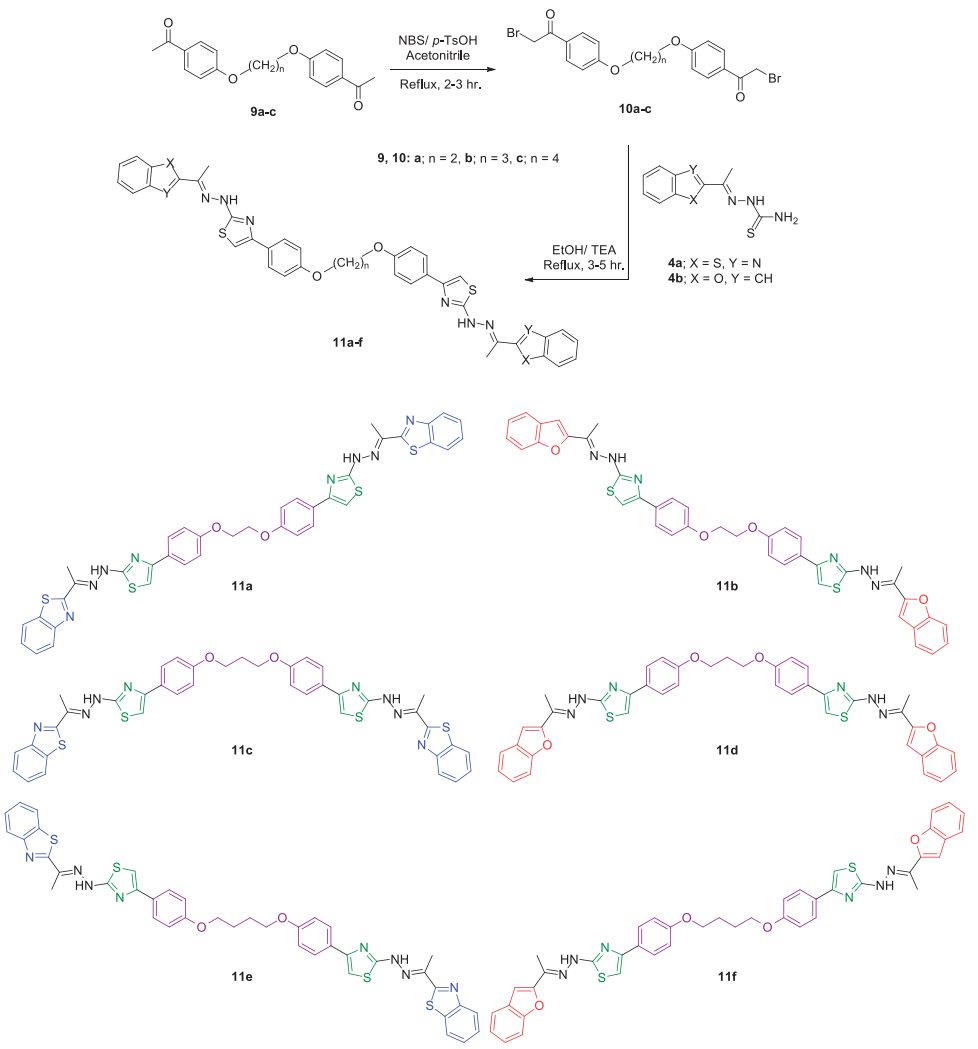
2b **4a** **8**

Scheme 3. Reaction of the appropriate bromoacetyl derivatives **2a,b** with the corresponding thiosemicarbazone derivatives **4b** and **4a**, respectively.

(ethylidene-hydrazinyl)thiazole is located between benzothiazole and benzofuran rings. These isomers were prepared in 70 and 73% yields by the reaction of **2a** and **2b,** respectively, with **4b** and **4a** in refluxing EtOH in the presence of TEA (Scheme 3).

Compounds **5–8** were characterized by elemental analyses, as well as their spectral data which agree with the proposed structures. The structure of Compound **5** as a representative example was confirmed by IR, ^{1}H NMR, and mass spectra. Thus, Mass spectrum of compound **5** showed an intense molecular ion peak at *m/z* 407 in agreement with its respective molecular formula. IR spectrum of **5** showed absorption bands at 3525 cm^{-1} because of NH group. Moreover, the ^{1}H NMR spectra of compound **5** showed a D_2O-exchangeable signal at δ 12.26 because of NH proton, a sharp singlet signal at 2.48 attributed to methyl group, and a characteristic singlet signal at δ 7.91 attributed to C-5 proton of the thiazole ring. All other protons appeared at the expected chemical shifts and integral values.

Our study was extended to include the synthesis of novel bis(benzofuran-2-ylethylidenehydrazinylthiazoles) and bis(benzo[*d*]thiazol-2-ylethylidene-hydrazinylthiazoles) **11a–f**, which are linked to aliphatic spacer *via* phenoxy groups (Scheme 4). Thus, the reaction

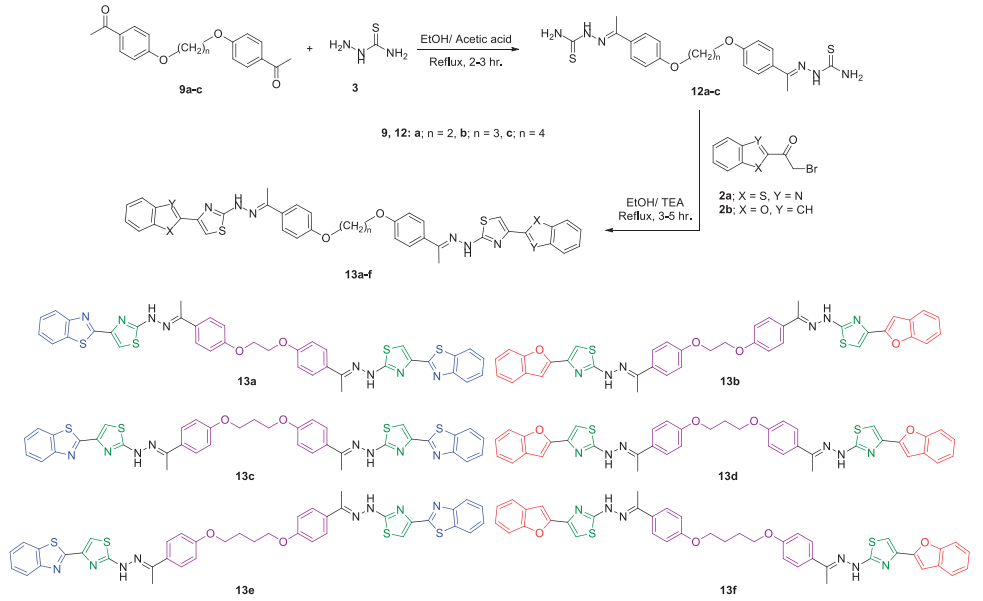


Scheme 4. Reaction of the appropriate bis(α-bromoketones) **10a–c** with the corresponding thiosemicarbazone derivatives **4a,b.**

of bis(α-bromoketones) **10a–c** with each of 2-(1-(benzo[*d*]thiazol-2-yl)ethylidene)hydrazinecarbothioamide (**4a**) and 2-(1-(benzofuran-2-yl)ethylidene)hydrazinecarbothioamide (**4b**) in refluxing EtOH in the presence of TEA afforded **11a–f** respectively, in 72–86% yields (Scheme 4).

Compounds **10a–c** were obtained from the corresponding bis(acetophenones) **9a–c** upon treatment with *N*-bromosuccinimide (NBS) in the presence of *p*-toluenesulfonic acid (*p*-TsOH).[53]

The novel isomeric bis(4-(2-(4-(benzo[*d*]thiazol-2-yl)thiazol-2-yl)hydrazono)-ethyl)-phenoxy)alkanes and bis(4-(2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazono)ethyl)-phenoxy)alkanes **13a–f** could also prepared using a similar approach. Thus, reaction of bis(thiosemicarbazones) **12a–c** with each of 1-(benzo[*d*]thiazol-2-yl)-2-bromoethanone



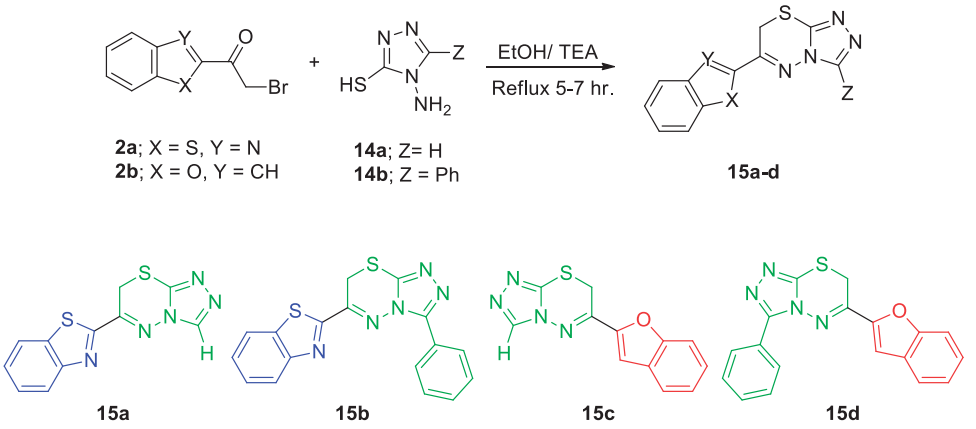
Scheme 5. Reaction of the appropriate bis(thiosemicarbazones) **12a–c** with the corresponding bromoacetyl derivatives **2a,b.**

(**2a**) and 1-(benzofuran-2-yl)-2-bromoethanone (**2 b**) in refluxing ethanol in the presence of TEA afforded **13a–f** in 69–83% yields, respectively (Scheme 5). Compounds **12a–c** were obtained by the reaction of the appropriate bis(ketones) **9a–c** with thiosemicarbazide (**3**) in refluxing EtOH containing few drops of AcOH.[62]

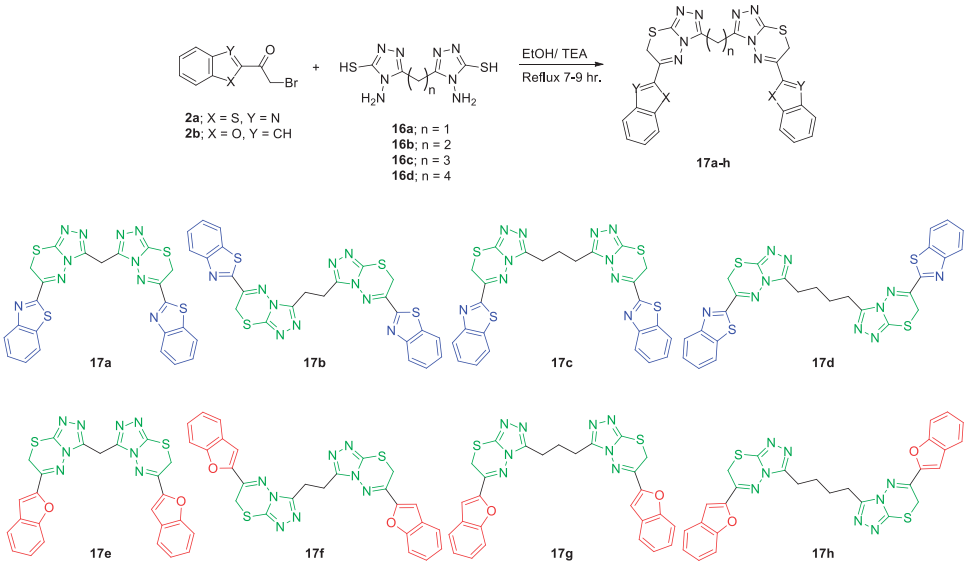
All of the isolated bis(compounds) **11a–f** and **13a–f** were characterized by elemental analyses, as well as their spectral data, which agree with the proposed structures. Thus, the IR spectrum of **11a**, as a representative example, showed absorption bands at 3425 cm^{-1} due to (NH) stretching frequency. The ^1H NMR spectra of compound **11a** showed a D_2O-exchangeable signal at δ 11.99 due to NH protons and a characteristic singlet signal at δ 7.44 attributed to C-5 proton of the thiazole ring. Moreover, they also featured the methylene ether linkage OCH_2 as a singlet signal at δ 4.36 ppm. All other protons were seen at the expected chemical shifts and integral values. Mass spectrum of compound **11a** showed the correct molecular ion peak at *m/z* 758.

The utility of 1-(benzo[*d*]thiazol-2-yl)-2-bromoethanone (**2a**) and 1-(benzofuran-2-yl)-2-bromoethanone (**2b**) as building units for novel mono- and bis-(triazolothiadiazine) derivatives, each bearing benzo[*d*]thiazolyl or benzofuranyl moieties, were also investigated. Thus, reaction of **2a** and **2b** with 4-amino-3-mercapto-1,2,4-triazole derivatives[79,80] **14a** and **14b** in refluxing ethanol in the presence of triethylamine as a catalyst, afforded the novel 6-(benzo[*d*]thiazol-2-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **15a** and **15b** as well as 6-(benzofuran-2-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **15c** and **15d** in 76–79 and 74–76% yields, respectively (Scheme 6).

We also explored the reactivity of **2a** and **2b** towards bis(4-amino-5-mercapto-1,2,4-triazoles) **16a–d**.[81] Thus, the reaction of two equivalents of each of **2a** and **2b** with **16a–d** in ethanol at reflux in the presence of trimethylamine as a catalyst afforded the corresponding bis(6-(benzo[*d*]thiazol-2-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-



Scheme 6. Reaction of bromoacetyl derivatives **2a** and **2b** with 4-amino-3-mercapto-1,2,4-triazole derivatives **14a** and **14b.**



Scheme 7. Reaction of bromoacetyl derivatives **2a** and **2b** with bis(4-amino-5-mercapto-1,2,4-triazoles) **16a–d.**

yl)alkanes **17a–d** and bis(6-(benzofuran-2-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)alkanes **17e–h** in 69–77% and 69–76% yields, respectively (Scheme 7).

The structures of triazolothiadiazine compounds **15a–d** and their corresponding bis derivatives **17a–h** were characterized by elemental analysis and spectral data. Thus, the absence of NH_2 stretching bands in the IR spectra of triazolothiadiazines **15** together with the disappearance of the characteristic signals belonging to primary amine in their ^{1}H NMR spectra are evidences for the cyclocondensation reaction. In addition, the presence of SCH_2 protons, resonated at δ 4.48–4.71 as singlet signals integrating two protons, clearly indicated that ring closure reaction occurred. The aromatic and the

heteroaromatic protons appear as multiplets at δ 7.59–9.32. All other protons were seen at the expected chemical shifts and integral values.

Conclusions

We developed a simple approach for the synthesis of novel hybrid molecules containing thiazole or bis(thiazoles) each bearing benzofuran and/or benzothiazole moieties. Our study included also the synthesis of mono- and bis(triazolothiadiazine) derivatives based on benzofuran or benzo[*d*]thiazole moieties. The newly synthesized compounds are interesting as promising pharmacological molecules. The simple approach used in the synthesis of the target compounds from inexpensive starting materials is the main advantage of this strategy. Our current studies are directed to examine the biological activities of the new compounds and to extend the scope of the described tool to cover additional hybrid molecules with effective biological potency.

Experimental

Materials and methods

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The infrared spectra were recorded as potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer operating at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR), a Varian VXR spectrometer operating at 400 MHz (^{1}H NMR) and 101 MHz (^{13}C NMR) and a Varian VXR spectrometer operating at 500 MHz (^{1}H NMR) and 126 MHz (^{13}C NMR). Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography was performed using pre-coated silica gel 60,778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Acetyl derivatives **1a,b**,[70] bromoacetyl derivatives **2a,b,**[70] bis(acetophenones) **9a–c,**[53] bis(α-bromoketones) **10a–c**,[53] bis(thiosemicarbazones) **12a–c**,[62] 4-amino-3-mercapto-1,2,4-triazole **14a,b**[79,80] and bis(4-amino-5-mercapto-1,2,4-triazoles) **16a–d**[81] were prepared according to the literature procedures.

Synthesis and characterization data for selected compounds

Synthesis of 2-(2-(2-(1-(benzo[d]thiazol-2-yl)ethylidene)hydrazinyl)thiazol-4-yl)benzo[d]thiazole (5)

A mixture of 1-(benzo[*d*]thiazol-2-yl)-2-bromoethanone **(2a)** (1 mmol) and 2-(1-(benzo[*d*]thiazol-2-yl)ethylidene)hydrazinecarbothioamide **(4a)** (1 mmol) was dissolved in ethanol (20 mL) containing TEA (1 mL). The reaction mixture was heated at reflux for 3 h. The solid obtained upon cooling was filtered off and recrystallized from DMF/EtOH to afford the title compounds **5** as green powder (76% yield), mp. 268–270 °C; IR: (potassium bromide) 3525 (NH), 1566 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ

2.48 (s, 3H, CH_3), 7.43–7.55 (m, 4H, ArH), 7.91 (s, 1H, thiazole-5-H), 8.00–8.13 (m, 4H, ArH), 12.26 (s, 1H, NH); ^{13}C NMR (101 MHz, DMSO) δ 13.85, 111.57, 122.62, 122.79, 123.06, 123.50, 125.70, 126.49, 126.77, 127.00, 135.00, 135.35, 143.73, 145.48, 153.56, 154.00, 162.83, 168.03, 169.53; ms: *m/z* (%) 407 (M^+). Anal. Calcd. for $C_{19}H_{13}N_5S_3$: C, 56.00; H, 3.22; N, 17.18; S, 23.60. Found: C, 55.76; H, 3.14; N, 17.09; S, 23.70%.

Synthesis of 4-(benzofuran-2-yl)-2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-thiazole (6)

A mixture of 1-(benzofuran-2-yl)-2-bromoethanone **(2b)** (1 mmol) and 2-(1-(benzofuran-2-yl)ethylidene)hydrazinecarbothioamide **(4b)** (1 mmol) was dissolved in ethanol (20 mL) containing TEA (1 mL). The reaction mixture was heated at reflux for 3 h. The obtained solid product was filtered off and recrystallized from DMF/EtOH to afford the title compounds **6** as brown powder (71% yield), mp. 249–251 °C; IR: (potassium bromide) 3325 (NH), 1543 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 2.34 (s, 3H, CH_3), 7.07 (s, 2H, benzofuran-3-H), 7.26 (s, 1H, thiazole-5-H), 7.43–7.49 (m, 4H, ArH), 7.57–7.88 (m, 4H, ArH),11.70 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO) δ 14.21, 102.22, 105.80, 108.62, 113.44, 113.72, 115.96, 116.01, 124.22, 124.28, 127.57, 128.33, 130.88, 131.27, 153.37, 153.77, 155.33, 170.22; ms: *m/z* (%) 373 (M^+). Anal. Calcd. for $C_{21}H_{15}N_3O_2S$: C, 67.54; H, 4.05; N, 11.25; S, 8.59. Found: C, 67.27; H, 3.89; N, 11.06; S, 8.33%.

Synthesis of 2-(2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)thiazol-4-yl)benzo-[d]thiazole (7)

A mixture of 1-(benzo[*d*]thiazol-2-yl)-2-bromoethanone **(2a)** (1 mmol) and 2-(1-(benzofuran-2-yl)ethylidene)hydrazinecarbothioamide **(4b)** (1 mmol) was dissolved in ethanol (20 mL) containing TEA (1 mL). The reaction mixture was heated at refluxed for 3 h. The solid product which formed was filtered off and recrystallized from DMF/EtOH to afford the title compounds **7** as dark Green powder (73% yield), mp. 228–230 °C; IR: (potassium bromide) 3433 (NH), 1558 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 2.36 (s, 3H, CH_3), 7.27 (s, 1H, thiazole-5-H), 7.45–7.62 (m, 5 H, ArH & benzofuran-3-H), 7.84 (d, 2H, ArH, $J = 7.5$), 8.01 (d, 1H, ArH, $J = 8.1$), 8.10 (d, 1H, ArH, $J = 7.8$), 11.79 (s, 1H, NH); 13C NMR (101 MHz, DMSO) δ 14.30, 105.96, 110.92, 113.73, 116.03, 122.77, 123.03, 124.30, 125.65, 126.97, 128.38, 130.85, 135.00, 139.15, 145.32, 153.79, 154.02, 155.24, 163.00, 170.06; ms: *m/z* (%) 390 (M^+). Anal. Calcd. for $C_{20}H_{14}N_4OS_2$: C, 61.52; H, 3.61; N, 14.35; S, 16.42. Found: C, 61.25; H, 3.53; N, 13.76; S, 16.30%.

Synthesis of 2-(1-(2-(4-(benzofuran-2-yl)thiazol-2-yl)hydrazono)ethyl)benzo[d]-thiazole (8)

A mixture of 1-(benzofuran-2-yl)-2-bromoethanone **(2b)** (1 mmol) and 2-(1-(benzo[*d*]-thiazol-2-yl)ethylidene)hydrazinecarbothioamide **(4a)** (1 mmol) was dissolved in ethanol

(20 mL), containing TEA (1 mL). The reaction mixture was heated at reflux for 3 h. The solid product which formed was filtered off and recrystallized from DMF/EtOH to afford the title compounds **8** as brown powder (70% yield), mp. 248–250 °C; IR: (potassium bromide) 3425 (NH), 1558 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO) δ 2.45 (s, 3H, CH_3), 7.10 (s, 1H, benzofuran-3-H), 7.45–7.61 (m, 5 H, ArH & thiazole-5-H), 7.89–8.09 (m, 4H, ArH), 12.20 (s, 1H, NH); ms: *m/z* (%) 390 (M^+). Anal. Calcd. for $C_{20}H_{14}N_4OS_2$: C, 61.52; H, 3.61; N, 14.35; S, 16.42. Found: C, 60.98; H, 3.41; N, 14.29; S, 16.33%.

References

[1] Ghonim, A. E.; Ligresti, A.; Rabbito, A.; Mahmoud, A. M.; Di Marzo, V.; Osman, N. A.; Abadi, A. H. Structure-Activity Relationships of Thiazole and Benzothiazole Derivatives as Selective Cannabinoid CB2 Agonists with *In Vivo* Anti-Inflammatory Properties. *Eur. J. Med. Chem.* **2019**, *180*, 154–170. DOI: 10.1016/j.ejmech.2019.07.002.

[2] Anuradha; Patel, S.; Patle, R.; Parameswaran, P.; Jain, A.; Shard, A. Design, Computational Studies, Synthesis and Biological Evaluation of Thiazole-Based Molecules as Anticancer Agents. *Eur. J. Pharm. Sci.* **2019**, *134*, 20–30. DOI: 10.1016/j.ejps.2019.04.005.

[3] Liaras, K.; Geronikaki, A.; Glamočlija, J.; Ćirić, A.; Soković, M. Thiazole-Based Chalcones as Potent Antimicrobial Agents. Synthesis and Biological Evaluation. *Bioorganic Med. Chem.* **2011**, *19*, 3135–3140. DOI: 10.1016/j.bmc.2011.04.007.

[4] Piechowska, K.; Świtalska, M.; Cytarska, J.; Jaroch, K.; Łuczykowski, K.; Chałupka, J.; Wietrzyk, J.; Misiura, K.; Bojko, B.; Kruszewski, S.; et al. Discovery of Tropinone-Thiazole Derivatives as Potent Caspase 3/7 Activators, and Noncompetitive Tyrosinase Inhibitors with High Antiproliferative Activity: Rational Design, One-Pot Tricomponent Synthesis, and Lipophilicity Determination. *Eur. J. Med. Chem.* **2019**, *175*, 162–171. DOI: 10.1016/j.ejmech.2019.05.006.

[5] Wang, Y.; Wu, C.; Zhang, Q.; Shan, Y.; Gu, W.; Wang, S. Design, Synthesis and Biological Evaluation of Novel β-Pinene-Based Thiazole Derivatives as Potential Anticancer Agents via Mitochondrial-Mediated Apoptosis Pathway. *Bioorg. Chem.* **2019**, *84*, 468–477. DOI: 10.1016/j.bioorg.2018.12.010.

[6] Qin, Y. J.; Wang, P. F.; Makawana, J. A.; Wang, Z. C.; Wang, Z. N.; Yan-Gu; Jiang, A. Q.; Zhu, H. L. Design, Synthesis and Biological Evaluation of Metronidazole-Thiazole Derivatives as Antibacterial Inhibitors. *Bioorganic Med. Chem. Lett.* **2014**, *24*, 5279–5283. DOI: 10.1016/j.bmcl.2014.09.054.

[7] Prajapati, N. P.; Patel, K. D.; Vekariya, R. H.; Patel, H. D.; Rajani, D. P. Thiazole Fused Thiosemicarbazones: Microwave-Assisted Synthesis, Biological Evaluation and Molecular Docking Study. *J. Mol. Struct.* **2019**, *1179*, 401–410. DOI: 10.1016/j.molstruc.2018.11.025.

[8] Chen, C.; Song, J.; Wang, J.; Xu, C.; Chen, C.; Gu, W.; Sun, H.; Wen, X. Synthesis and Biological Evaluation of Thiazole Derivatives as Novel USP7 Inhibitors. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 845–849. DOI: 10.1016/j.bmcl.2017.01.018.

[9] Lu, Y.; Li, C. M.; Wang, Z.; Ross, C. R.; Chen, J.; Dalton, J. T.; Li, W.; Miller, D. D. Discovery of 4-Substituted Methoxybenzoyl-Aryl-Thiazole as Novel Anticancer Agents: Synthesis, Biological Evaluation, and Structure-Activity Relationships. *J. Med. Chem.* **2009**, *52*, 1701–1711. DOI: 10.1021/jm801449a.

[10] Popsavin, M.; Kojić, V.; Spaić, S.; Svirčev, M.; Bogdanović, G.; Jakimov, D.; Aleksić, L.; Popsavin, V. Popsavin, V. 2-Substituted Thiazole-4-Carboxamide Derivatives as Tiazofurin Mimics: Synthesis and in Vitro Antitumour Activity. *Tetrahedron.* **2014**, *70*, 2343–2350. DOI: 10.1016/j.tet.2014.02.035.

[11] Karuvalam, R. P.; Haridas, K. R.; Nayak, S. K.; Guru Row, T. N.; Rajeesh, P.; Rishikesan, R.; Kumari, N. S. Design, Synthesis of Some New (2-Aminothiazol-4-Yl)Methylester

Derivatives as Possible Antimicrobial and Antitubercular Agents. *Eur. J. Med. Chem.* **2012**, *49*, 172–182. DOI: 10.1016/j.ejmech.2012.01.008.

[12] Khan, I.; Ibrar, A.; Abbas, N. Triazolothiadiazoles and Triazolothiadiazines-Biologically Attractive Scaffolds. *Eur. J. Med. Chem.* **2013**, *63*, 854–868. DOI: 10.1016/j.ejmech.2013.01.060.

[13] Sever, B.; Altintop, M. D.; Kuş, G.; Özkurt, M.; Özdemir, A.; Kaplancikli, Z. A. Indomethacin Based New Triazolothiadiazine Derivatives: Synthesis, Evaluation of Their Anticancer Effects on T98 Human Glioma Cell Line Related to COX-2 Inhibition and Docking Studies. *Eur. J. Med. Chem.* **2016**, *113*, 179–186. DOI: 10.1016/j.ejmech.2016.02.036.

[14] Kamel, M. M.; Megally Abdo, N. Y. Synthesis of Novel 1,2,4-Triazoles, Triazolothiadiazines and Triazolothiadiazoles as Potential Anticancer Agents. *Eur. J. Med. Chem.* **2014**, *86*, 75–80. DOI: 10.1016/j.ejmech.2014.08.047.

[15] Kaplancikli, Z. A.; Turan-Zitouni, G.; Özdemir, A.; Revial, G. New Triazole and Triazolothiadiazine Derivatives as Possible Antimicrobial Agents. *Eur. J. Med. Chem.* **2008**, *43*, 155–159. DOI: 10.1016/j.ejmech.2007.03.019.

[16] Aytaç, P. S.; Durmaz, I.; Houston, D. R.; Çetin-Atalay, R.; Tozkoparan, B. Novel Triazolothiadiazines Act as Potent Anticancer Agents in Liver Cancer Cells through Akt and ASK-1 Proteins. *Bioorg. Med. Chem.* **2016**, *24*, 858–872. DOI: 10.1016/j.bmc.2016.01.013.

[17] Kumar, D.; Narayanam, M. K.; Chang, K. H.; Shah, K. Synthesis of Novel Indolyl-1,2,4-Triazoles as Potent and Selective Anticancer Agents. *Chem. Biol. Drug Des.* **2011**, *77*, 182–188. DOI: 10.1111/j.1747-0285.2010.01051.x.

[18] Mavrova, A. T.; Wesselinova, D.; Tsenov, Y. A.; Denkova, P. Synthesis, Cytotoxicity and Effects of Some 1,2,4-Triazole and 1,3,4-Thiadiazole Derivatives on Immunocompetent Cells. *Eur. J. Med. Chem.* **2009**, *44*, 63–69. DOI: 10.1016/j.ejmech.2008.03.006.

[19] Liu, Y.; Xia, Y.; Fan, Y.; Maggiani, A.; Rocchi, P.; Qu, F.; Iovanna, J. L.; Peng, L. N-Aryltriazole Ribonucleosides with Potent Antiproliferative Activity against Drug-Resistant Pancreatic Cancer. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2503–2507. DOI: 10.1016/j.bmcl.2010.02.104.

[20] Bhat, K. S.; Poojary, B.; Prasad, D. J.; Naik, P.; Holla, B. S. Synthesis and Antitumor Activity Studies of Some New Fused 1,2,4-Triazole Derivatives Carrying 2,4-Dichloro-5-Fluorophenyl Moiety. *Eur. J. Med. Chem.* **2009**, *44*, 5066–5070. DOI: 10.1016/j.ejmech.2009.09.010.

[21] Chand, K.; Rajeshwari; Hiremathad, A.; Singh, M.; Santos, M. A.; Keri, R. S. A Review on Antioxidant Potential of Bioactive Heterocycle Benzofuran: Natural and Synthetic Derivatives. *Pharmacol. Reports.* **2017**, *69*, 281–295. DOI: 10.1016/j.pharep.2016.11.007.

[22] Heravi, M. M.; Zadsirjan, V.; Hamidi, H.; Tabar Amiri, P. H. Total Synthesis of Natural Products Containing Benzofuran Rings. *RSC Adv.* **2017**, *7*, 24470–24521. DOI: 10.1039/c7ra03551a.

[23] Ono, M.; Kung, M.-P.; Hou, C.; Kung, H. F. Benzofuran Derivatives as Aβ-Aggregate-Specific Imaging Agents for Alzheimer's Disease. *Nucl. Med. Biol.* **2002**, *29*, 633–642. DOI: 10.1016/S0969-8051(02)00326-8.

[24] Dawood, K. M. Benzofuran Derivatives: A Patent Review. *Expert Opin. Ther. Pat.* **2013**, *23*, 1133–1156. DOI: 10.1517/13543776.2013.801455.

[25] Sashidhara, K. V.; Modukuri, R. K.; Sonkar, R.; Rao, K. B.; Bhatia, G. Hybrid Benzofuran-Bisindole Derivatives: New Prototypes with Promising anti-Hyperlipidemic Activities. *Eur. J. Med. Chem.* **2013**, *68*, 38–46. DOI: 10.1016/j.ejmech.2013.07.009.

[26] Khanam, H.; Shamsuzzaman, Bioactive Benzofuran Derivatives: A Review. *Eur. J. Med. Chem.* **2015**, *97*, 483–504. DOI: 10.1016/j.ejmech.2014.11.039.

[27] Abdelhafez, O. M.; Ahmed, E. Y.; Amin, K. M.; Ali, H. I.; Abdalla, M. M. Design, Synthesis and Anticancer Activity of Benzofuran Derivatives Targeting VEGFR-2 Tyrosine Kinase. *RSC Adv.* **2014**, *4*, 11569–11579. DOI: 10.1039/c4ra00943f.

[28] Iversen, L.; Gibbons, S.; Treble, R.; Setola, V.; Huang, X. P.; Roth, B. L. Neurochemical Profiles of Some Novel Psychoactive Substances. *Eur. J. Pharmacol.* **2013**, *700*, 147–151. DOI: 10.1016/j.ejphar.2012.12.006.

[29] Bogazzi, F.; Tomisti, L.; Bartalena, L.; Aghini-Lombardi, F.; Martino, E. Amiodarone and the Thyroid: A 2012 Update. *J. Endocrinol. Investig.* **2012**, *35*, 340–348. DOI: 10.3275/8298.

[30] Bakunova, S. M.; Bakunov, S. A.; Wenzler, T.; Barszcz, T.; Werbovetz, K. A.; Brun, R.; Hall, J. E.; Tidwell, R. R. Synthesis and in Vitro Antiprotozoal Activity of Bisbenzofuran Cations. *J. Med. Chem.* **2007**, *50*, 5807–5823. DOI: 10.1021/jm0708634.

[31] Dawson, P.; Opacka-Juffry, J.; Moffatt, J. D.; Daniju, Y.; Dutta, N.; Ramsey, J.; Davidson, C. The Effects of Benzofury (5-APB) on the Dopamine Transporter and 5-HT2-Dependent Vasoconstriction in the Rat. *Prog. Neuro-Psychopharmacology Biol. Psych.* **2014**, *48*, 57–63. DOI: 10.1016/j.pnpbp.2013.08.013.

[32] Kumbhare, R. M.; Kosurkar, U. B.; Janaki Ramaiah, M.; Dadmal, T. L.; Pushpavalli, S. N.; Pal-Bhadra, M. Synthesis and Biological Evaluation of Novel Triazoles and Isoxazoles Linked 2-Phenyl Benzothiazole as Potential Anticancer Agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5424–5427. DOI: 10.1016/j.bmcl.2012.07.041.

[33] Hiyoshi, H.; Goto, N.; Tsuchiya, M.; Iida, K.; Nakajima, Y.; Hirata, N.; Kanda, Y.; Nagasawa, K.; Yanagisawa, J. 2-(4-Hydroxy-3-Methoxyphenyl)-Benzothiazole Suppresses Tumor Progression and Metastatic Potential of Breast Cancer Cells. *Sci Rep.* **2014**, *4*, 7095. doi:10.1038/srep07095.

[34] Xie, X.; Yan, Y.; Zhu, N.; Liu, G. Benzothiazoles Exhibit Broad-Spectrum Antitumor Activity: Their Potency, Structure-Activity and Structure-Metabolism Relationships. *Eur. J. Med. Chem.* **2014**, *76*, 67–78. DOI: 10.1016/j.ejmech.2014.02.007.

[35] Kamal, A.; Syed, M. A. H.; Mohammed, S. M. Therapeutic Potential of Benzothiazoles: A Patent Review (2010 – 2014). *Expert Opin. Ther. Pat.* **2015**, *25*, 335–349. DOI: 10.1517/13543776.2014.999764.

[36] Sharma, P. C.; Sinhmar, A.; Sharma, A.; Rajak, H.; Pathak, D. P. Medicinal Significance of Benzothiazole Scaffold: An Insight View. *J. Enzyme Inhib. Med. Chem.* **2013**, *28*, 240–266. DOI: 10.3109/14756366.2012.720572.

[37] Cano, N. H.; Ballari, M. S.; López, A. G.; Santiago, A. N. New Synthesis and Biological Evaluation of Benzothiazole Derivates as Antifungal Agents. *J. Agric. Food Chem.* **2015**, *63*, 3681–3686. DOI: 10.1021/acs.jafc.5b00150.

[38] Patel, R. V.; Park, S. W. Catalytic N-Formylation for Synthesis of 6-Substituted-2-Benzothiazolylimino-5-Piperazinyl-4-Thiazolidinone Antimicrobial Agents. *Res. Chem. Intermed.* **2015**, *41*, 5599–5609. DOI: 10.1007/s11164-014-1684-8.

[39] Hazra, K.; Nargund, L. V. G.; Rashmi, P.; Chandra, J. N. N. S.; Nandha, B.; Harish, M. S. Synthesis and Comparative Study of anti-Mycobacterium Activity of a Novel Series of Fluoronitrobenzothiazolopyrazoline Regioisomers. *Arch. Pharm. Pharm. Med. Chem.* **2012**, *345*, 137–146. DOI: 10.1002/ardp.201100072.

[40] Mir, F.; Shafi, S.; Zaman, M. S.; Kalia, N. P.; Rajput, V. S.; Mulakayala, C.; Mulakayala, N.; Khan, I. A.; Alam, M. S. Sulfur Rich 2-Mercaptobenzothiazole and 1,2,3-Triazole Conjugates as Novel Antitubercular Agents. *Eur. J. Med. Chem.* **2014**, *76*, 274–283. DOI: 10.1016/j.ejmech.2014.02.017.

[41] Takasu, K.; Inoue, H.; Kim, H. S.; Suzuki, M.; Shishido, T.; Wataya, Y.; Ihara, M. Rhodacyanine Dyes as Antimalarials. 1. Preliminary Evaluation of Their Activity and Toxicity. *J. Med. Chem.* **2002**, *45*, 995–998. DOI: 10.1021/jm0155704.

[42] Siddiqui, N.; Rana, A.; Khan, S. A.; Haque, S. E.; Alam, M. S.; Ahsan, W.; Ahmed, S. Synthesis of 8-Substituted-4-(2/4-Substituted Phenyl)-2H-[1,3,5]Triazino[2,1-b][1,3]Benzothiazole-2-Thiones and Their Anticonvulsant, anti-Nociceptive, and Toxicity Evaluation in Mice. *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 1344–1350. DOI: 10.3109/14756360902888176.

[43] Munirajasekhar, D.; Himaja, M.; Mali, S. V. A Facile and Efficient Synthesis of 2-(5-(4-Substitutedphenyl)-4, 5-Dihydro-3-Phenylpyrazol-1-Yl)-6-Substitutedbenzothiazoles and Their Biological Studies. *J. Heterocyclic Chem.* **2014**, *51*, 459–465. DOI: 10.1002/jhet.1618.

[44] Henary, M.; Paranjpe, S.; Owens, E. A. Substituted Benzothiazoles: Synthesis and Medicinal Characteristics. *Heterocyclic Commun.* **2013**, *19*, 89–99. DOI: 10.1515/hc-2013-0026.

[45] Prakash, O.; Aneja, D. K.; Hussain, K.; Lohan, P.; Ranjan, P.; Arora, S.; Sharma, C.; Aneja, K. R. Synthesis and Biological Evaluation of Dihydroindeno and Indeno [1,2-e] [1,2,4]Triazolo [3,4-b] [1,3,4]Thiadiazines as Antimicrobial Agents. *Eur. J. Med. Chem.* **2011**, *46*, 5065–5073. DOI: 10.1016/j.ejmech.2011.08.019.

[46] Palekar, V. S.; Damle, A. J.; Shukla, S. R. Synthesis and Antibacterial Activity of Some Novel Bis-1,2,4-Triazolo[3,4-b]-1,3,4-Thiadiazoles and Bis-4-Thiazolidinone Derivatives from Terephthalic Dihydrazide. *Eur. J. Med. Chem.* **2009**, *44*, 5112–5116. DOI: 10.1016/j.ejmech.2009.07.023.

[47] Demirbas, N.; Karaoglu, S. A.; Demirbas, A.; Sancak, K. Synthesis and Antimicrobial Activities of Some New 1-(5-Phenylamino-[1,3,4] Thiadiazol-2-Yl)Methyl-5-Oxo-[1,2,4]Triazole and 1-(4-Phenyl-5-Thioxo-[1,2,4] Triazol-3-Yl)Methyl-5-Oxo-[1,2,4]Triazole Derivatives. *Eur. J. Med. Chem.* **2004**, *39*, 793–804. DOI: 10.1016/j.ejmech.2004.06.007.

[48] Clemons, M.; Coleman, R. E.; Verma, S. Aromatase Inhibitors in the Adjuvant Setting: Bringing the Gold to a Standard? *Cancer Treat. Rev.* **2004**, *30*, 325–332. DOI: 10.1016/j.ctrv.2004.03.004.

[49] Sumangala, V.; Poojary, B.; Chidananda, N.; Arulmoli, T.; Shenoy, S. Facile Synthesis, Cytotoxic and Antimicrobial Activity Studies of a New Group of 6-Aryl-3-[4-(Methylsulfonyl)Benzyl]-7H-[1,2,4]Triazolo[3,4-b][1,3,4] Thiadiazines. *Eur. J. Med. Chem.* **2012**, *54*, 59–64. DOI: 10.1016/j.ejmech.2012.04.024.

[50] Salem, M. E.; Darweesh, A. F.; Farag, A. M.; Elwahy, A. H. M. Synthesis and Structures of Novel Multi-Armed Molecules Involving Benzene as a Core and 4-Phenylthiazole, 4-Pyrazolylthiazole, or Thiadiazole Units as Arms. *J. Heterocyclic Chem.* **2017**, *54*, 586–595. DOI: 10.1002/jhet.2629.

[51] Abdelmoniem, A. M.; Elwahy, A. H. M.; Abdelhamid, I. A. Bis (Indoline-2,3-Diones): Versatile Precursors for Novel Bis (2', 6'- Dicarbonitrile) Derivatives. *Arkivoc.* **2016**, *2016*, 304–312. DOI: 10.3998/ark.5550190.0017.324.

[52] M. Abdella, A.; H. M. Elwahy, A.; A. Abdelhamid, I. Multicomponent Synthesis of Novel Bis(2-Amino-Tetrahydro-4H-Chromene-3- Carbonitrile) Derivatives Linked to Arene or Heteroarene Cores. *Curr. Org. Synth.* **2016**, *13*, 601–610. DOI: 10.2174/1570179413999151211115100.

[53] Shaaban, M. R.; Elwahy, A. H. M. Bis(α-Bromo Ketones): Versatile Precursors for Novel Bis (s-Triazolo[3,4-b] [1,3,4]Thiadiazines) and Bis (as-Triazino[3,4-b] [1,3,4]Thiadiazines). *J. Heterocyclic Chem.* **2012**, *49*, 640–645. DOI: 10.1002/jhet.861.

[54] Abdelmoniem, A. M.; Ghozlan, S. A. S.; Abdelmoniem, D. M.; Elwahy, A. H. M.; Abdelhamid, I. A. Facile One-Pot, Three-Component Synthesis of Novel Bis-Heterocycles Incorporating 5H-Chromeno[2,3-b]Pyridine-3-Carbonitrile Derivatives. *J. Heterocyclic Chem.* **2017**, *54*, 2844–2849. DOI: 10.1002/jhet.2890.

[55] Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. 3,4-Bis(Bromomethyl)Thieno[2,3-b]Thiophene: Versatile Precursors for Novel Bis(Triazolothiadiazines), Bis(Quinoxalines), Bis(Dihydrooxadiazoles), and Bis(Dihydrothiadiazoles). *J. Heterocyclic Chem.* **2016**, *53*, 1113–1120. DOI: 10.1002/jhet.2373.

[56] Salem, M. E.; Darweesh, A. F.; Farag, A. M.; Elwahy, A. H. M. 2-Bromo-1-(1H-Pyrazol-4-Yl)Ethanone: Versatile Precursors for Novel Mono-, Bis- and Poly{6-(1H-Pyrazol-4-Yl)-[1,2,4]Triazolo[3,4-b][1,3,4]Thiadiazines}. *Tetrahedron.* **2016**, *72*, 712–719. DOI: 10.1016/j.tet.2015.12.024.

[57] Hebishy, A. M. S.; Abdelhamid, I. A.; Elwahy, A. H. M. Synthesis of Novel Bis(Nicotinecarbonitrile) Derivatives. *Arkivoc.* **2018**, *2018*, 97–108. DOI: 10.24820/ark.5550190.p010.367.

[58] Hebishy, A. M. S.; Elgemeie, G. H.; Elwahy, A. H. M. Novel Bis(2-Cyanoketene-S,S-/S,N-Acetals): Versatile Precursors for Novel Bis(Aminopyrazole) Derivatives. *J. Heterocyclic Chem.* **2019**, *56*, 1581–1587. DOI: 10.1002/jhet.3536.

[59] Hebishy, A. M. S.; Abdelhamid, I. A.; Elwahy, A. H. M. Synthesis of Novel Bis(Dihydropyridine) and Terpyridine Derivatives. *Arkivoc* **2018**, *2018*, 109–123. DOI: 10.24820/ark.5550190.p010.498.

[60] Elwahy, A. H. M. A New Approach for the Design of Novel Hexa-Host Molecules. *Tetrahedron Lett.* **2001**, *42*, 5123–5126. DOI: 10.1016/S0040-4039(01)00950-9.

[61] Abdelhamid, I. A.; Darweesh, A. F.; Elwahy, A. H. M. Synthesis and Characterization of Poly(2,6-Dimethyl-4-Phenyl-1,4-Dihydropyridinyl)Arenes as Novel Multi-Armed Molecules. *Tetrahedron Lett.* **2015**, *56*, 7085–7088. DOI: 10.1016/j.tetlet.2015.11.015.

[62] Salem, M. E.; Darweesh, A. F.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. 2-Bromo-1-(1H-Pyrazol-4-Yl)Ethanone: Versatile Precursor for Novel Mono- and Bis[Pyrazolylthiazoles]. *J. Heterocyclic Chem.* **2017**, *54*, 226–234. DOI: 10.1002/jhet.2571.

[63] Mohamed, M. F.; Darweesh, A. F.; Elwahy, A. H. M.; Abdelhamid, I. A. Synthesis, Characterization and Antitumor Activity of Novel Tetrapodal 1,4-Dihydropyridines: P53 Induction, Cell Cycle Arrest and Low Damage Effect on Normal Cells Induced by Genotoxic Factor H2O2. *RSC Adv.* **2016**, *6*, 40900–40910. DOI: 10.1039/c6ra04974e.

[64] Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A. Salicylaldehyde Derivatives as Building Blocks in the Synthesis of Useful Open Chain and Macrocyclic Crown Compounds. *J. Chem. Res.* **1998**, 548–549. DOI: 10.1039/a802440e.

[65] Elwahy A. H. M. ; Sarhan, R. M.; Badawy, M. A. Synthesis and Characterization of Poly([1,2,4]Triazolyl- and [1,2,4]Triazolo[3,4-b][1,3,4]Thiadiazinylsulfanylmethyl)Arenes: Novel Multi-Armed Molecules. *Curr. Org. Synth.* **2013**, *10*, 786–790. DOI: 10.2174/1570179411310050008.

[66] Salem, M. E.; Hosny, M.; Darweesh, A. F.; Elwahy, A. H. M. Synthesis of Novel Bis- and Poly(Aryldiazenylthiazoles). *Synth. Commun.* **2019**, *49*, 2319–2329. DOI: 10.1080/00397911.2019.1620283.

[67] Salem, M. E.; Darweesh, A. F.; Shaaban, M. R.; Elwahy, A. H. M. Synthesis of Novel Bis- and Poly(Hydrazinylthiazole) Linked to Benzofuran or Benzothiazole as New Hybrid Molecules. *Arkivoc.* **2019**, *2019*, 73–88. DOI: 10.24820/ark.5550190.p010.810.

[68] Hosny, M.; Salem, M. E.; Darweesh, A. F.; Elwahy, A. H. M. Synthesis of Novel Bis(Thiazolylchromen-2-One) Derivatives Linked to Alkyl Spacer via Phenoxy Group. *J. Heterocyclic Chem.* **2018**, *55*, 2342–2348. DOI: 10.1002/jhet.3296.

[69] Salem, M. E.; Ahmed, A. A.; Darweesh, A. F.; Kühn, O.; Elwahy, A. H. M. Synthesis and DFT Calculations of 2-Thioxo-1,2-Dihydropyridine-3-Carbonitrile as Versatile Precursors for Novel Pharmacophoric Hybrid Molecules. *J. Mol. Struct.* **2019**, *1176*, 19–30. DOI: 10.1016/j.molstruc.2018.08.031.

[70] Salem, M. E.; Darweesh, A. F.; Elwahy, A. H. M. 2-Mercapto-4,6-Disubstituted Nicotinonitriles: Versatile Precursors for Novel Mono- and Bis[Thienopyridines]. *J. Sulfur Chem.* **2018**, *39*, 525–543. DOI: 10.1080/17415993.2018.1471143.

[71] Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. 3. 4-Dimethyl-2,5-Functionalized Thieno[2,3-b]Thiophenes: Versatile Precursors for Novel Bis-Thiazoles. *J. Sulfur Chem.* **2015**, *36*, 124–134. DOI: 10.1080/17415993.2014.975131.

[72] Salama, S. K.; Darweesh, A. F.; Abdelhamid, I. A.; Elwahy, A. H. M. Microwave Assisted Green Multicomponent Synthesis of Novel Bis(2-Amino-Tetrahydro-4H-Chromene-3-Carbonitrile) Derivatives Using Chitosan as Eco-Friendly Basic Catalyst. *J. Heterocyclic Chem.* **2017**, *54*, 305–312. DOI: 10.1002/jhet.2584.

[73] Abd El-Fatah, N. A.; Darweesh, A. F.; Mohamed, A. A.; Abdelhamid, I. A.; Elwahy, A. H. M. Experimental and Theoretical Study on the Regioselective Bis- and

Polyalkylation of 2-Mercaptonicotinonitrile and 2-Mercaptopyrimidine-5-Carbonitrile Derivatives. *Tetrahedron.* **2017**, *73*, 1436–1450. DOI: 10.1016/j.tet.2017.01.047.

[74] El-Fatah, N. A. A.; Darweesh, A. F.; Mohamed, A. A.; Abdelhamid, I. A.; Elwahy, A. H. M. Regioselective Synthesis and Theoretical Studies of Novel Bis(Tetrahydro[1,2,4]Triazolo[5,1-b]Quinazolin-8(4H)-Ones) Catalyzed by ZnO Nanoparticles. *Monatsh. Chem.* **2017**, *148*, 2107–2122. DOI: 10.1007/s00706-017-2040-7.

[75] Elwahy, A. H. M.; Shaaban, M. R. Synthesis of Heterocycles Catalyzed by Iron Oxide Nanoparticles. *Heterocycles.* **2017**, *94*, 595–655. DOI: 10.3987/REV-16-854.

[76] Elwahy, A. H. M.; Shaaban, M. R. Synthesis of Heterocycles and Fused Heterocycles Catalyzed by Nanomaterials. *RSC Adv.* **2015**, *5*, 75659–75710. DOI: 10.1039/c5ra11421g.

[77] Abdella, A. M.; Moatasim, Y.; Ali, M. A.; Elwahy, A. H. M.; Abdelhamid, I. A. Synthesis and anti-Influenza Virus Activity of Novel Bis(4H-Chromene-3-Carbonitrile) Derivatives. *J. Heterocyclic Chem.* **2017**, *54*, 1854–1862. DOI: 10.1002/jhet.2776.

[78] Elwahy, A.; Abdelhamid, I.; Sanad, S.; Kassab, R. Microwave Assisted Multi-Component Synthesis of Novel Bis(1,4-Dihydropyridines) Based Arenes or Heteroarenes. *Heterocycles.* **2016**, *92*, 910–924. DOI: 10.3987/com-16-13441.

[79] Hoggarth, E. 938. 2-Benzoyldithiocarbazinic Acid and Related Compounds. *J. Chem. Soc.* **1952**, 4811–4817. DOI: 10.1039/JR9520004811.

[80] Beyer, H.; Kröger, C.-F.; Busse, G. Über 1.2.4-Triazole, I Die Reaktion Von Thiocarbohydrazid Und Thiosemicarbazid Mit Aliphatischen Carbonsäuren Und Ihren Derivaten. *Justus Liebigs Ann. Chem.* **1960**, *637*, 135–145. DOI: 10.1002/jlac.19606370111.

[81] Xu, P.-F.; Sun, X.-W.; Zhang, L.-M.; Zhang, Z.-Y. A Facile Synthesis of Bis(4-Amino-5-Mercapto-1,2,4-Triazol-3-Yl)Alkanes and Bis(5-Mercapto-4H-1,2,4-Triazol-3-Yl)Alkanes. *J. Chem. Res.* **1999**, 170–171. DOI: 10.1039/a808351g.