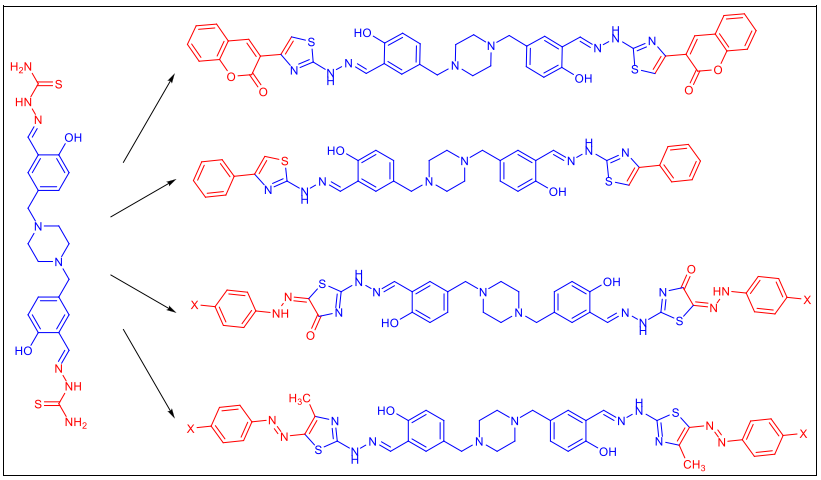
Microwave-Assisted Synthesis of Novel Bis(thiazoles) Incorporating Piperazine Moiety

Ahmed E. M. Mekky* and Sherif M. H. Sanad

Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt
*E-mail: ataher2211@yahoo.com
Received December 6, 2018
DOI 10.1002/jhet.3531
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).



Novel bis(hydrazinecarbothioamide) was prepared by the reaction of 1,4-bis[(3-formyl-4-hydroxyphenyl) methyl]piperazine with thiosemicarbazide. The bis(hydrazinecarbothioamide) was used as a building block for construction of a novel bis(thiazolyl)piperazines *via* its cyclocondensation with a series of each of α-halocarbonyl compounds and hydrazonoyl halides in dimethylformamide in the presence of triethylamine as a catalyst under microwave irradiation. The structure of the newly bis(thiazolyl)piperazine derivatives is elucidated *via* the spectral data as well as elemental analyses.

INTRODUCTION

The synthesis of heterocyclic rings has been an attractive field in therapeutic science. Numerous heterocyclic compounds containing nitrogen and sulfur are used in the development and design of drugs [1]. Piperazine occupies a principal place in medicinal chemistry. It is a vital core scaffold present in many synthetic therapeutically important compounds. The versatility of piperazine nucleus is established by the fact that it is an essential part of many currently notable drugs such as antianginals, antidepressants, antihistamines, antiserotonergics, and antipsychotics. Among the several Food and Drug Administration-approved therapeutic drugs, the piperazine ring was found in Celebrex, rimonabant, and leflunomide (Figure 1) [2–6]. Also, thiazole and its derivatives are one of the heterogeneous ring compounds that are associated with many pharmaceutical and medical applications. Thiazole derivatives demonstrate significant biological properties such antifungal (abafungin), antimicrobial (sulfazole), anti-inflammatory, anticancer, anticonvulsant, anti-HIV, antihypertensive, anti-gout (febuxostat), and antidiabetic activities (Figure 2) [7–14]. In addition, bis-heterocyclic compounds as well as hybrid molecules, whose pharmacophores are integrated into a single molecule, were reported to display various biological activities, especially as fungicidal, antibacterial, tuberculostatic, anthelmintic, and antiamoebic [15–22]. Because of the significant bioactivity and wide range of application of piperazine and thiazole derivatives as well as bis-heterocyclic compounds, several publications reported concerning the synthesis of these derivatives [23–31].

Motivated by the above-mentioned findings, and in continuation of our attention in the synthesis bis(heterocycles) [32–41], we report, herein, the synthetic utilities of the bis(thiosemicarbazone) as key intermediate for the synthesis of novel bis(thiazole), under both microwave irradiation and conventional methods.

RESULTS AND DISCUSSION

Initially, our goal was to hybridize the piperazine unit with thiazole. For this purpose, 1,4-bis[(3-formyl-4-hydroxyphenyl)methyl]piperazine **3** [42] was chosen as

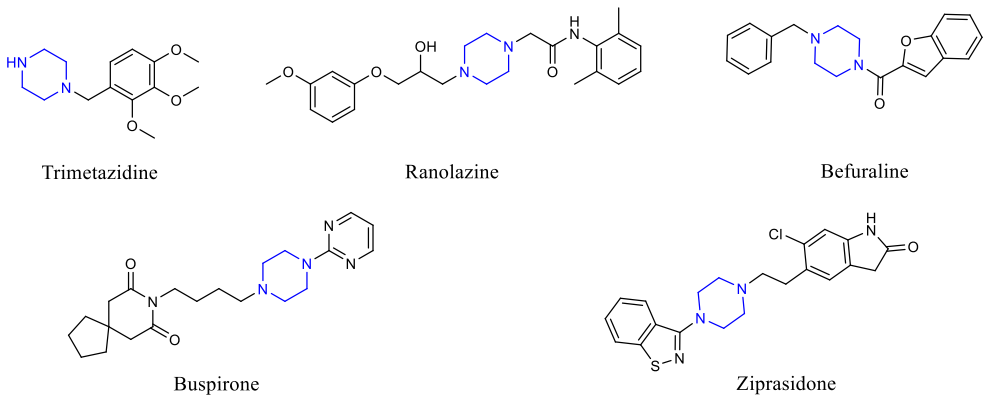


Figure 1. Some pharmaceutical drugs containing piperazine core. [Color figure can be viewed at wileyonlinelibrary.com]

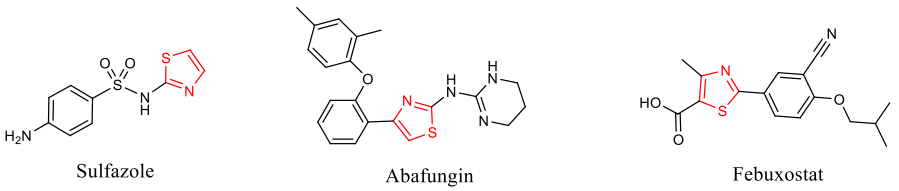


Figure 2. Some biologically active drugs containing thiazole core. [Color figure can be viewed at wileyonlinelibrary.com]

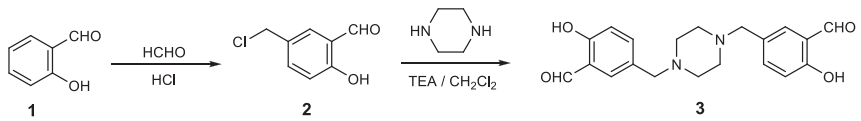
the main intermediate, which was easily obtained from 5-(chloromethyl)-2-hydroxybenzaldehyde **2** and piperazine in dichloromethane and triethylamine (TEA). Compound **2** was obtained from the reaction of salicylaldehyde and formaldehyde in the presence of concentrated hydrochloric acid [43] (Scheme 1).

The reaction of bis(2-hydroxybenzaldehyde) **3** with thiosemicarbazide **4** was carried out in dioxane in the presence of a few drops of glacial acetic acid under microwave irradiation produces one product that has been identified as bis(hydrazinecarbothioamide) **5** within 10 min (Scheme 2).

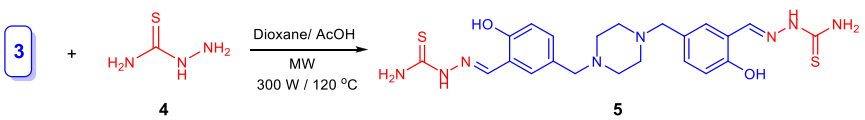
The elemental analysis and spectral data were fully consistent with the given structure **5**. For example, its ^{1}H-NMR spectrum presented two singlet signals at δ 2.43 and 3.58 due to piperazine and methylene protons, two doublet and one singlet signals in the region δ 6.95–7.63 due to aromatic protons, and a singlet signal at δ 8.35 due to one methine proton, in addition to three D_2O-exchangeable singlet signals at δ 8.10, 9.92, and 11.43 due to NH_2, OH, and NH protons, respectively.

The bis(hydrazinecarbothioamide) **5** has stimulated us to study its synthetic facilities as a building block for construction of a novel bis(thiazoles) *via* the cyclocondensation with α-halocarbonyl compounds and hydrazonoyl halides, respectively. Thus, the reaction of the bis(hydrazinecarbothioamide) **5** with chloroacetone **6** in dimethylformamide (DMF) under microwave irradiation in the presence of TEA as a catalyst afforded bis(thiazolyl)piperazine **7** (Scheme 3). The infrared (IR)

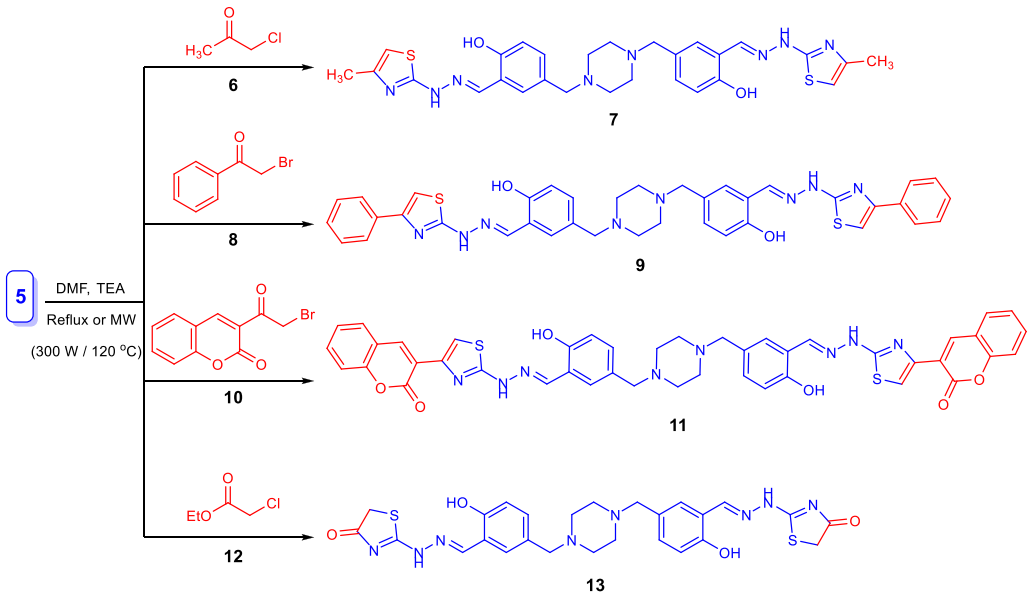
Scheme 1. Synthesis of bis(2-hydroxybenzaldehyde) **3**.



Scheme 2. Synthesis of bis(hydrazinecarbothioamide) **5**. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 3. Synthesis of bis(thiazolyl)piperazines **7**, **9**, **11** and bis(4-oxothiazolyl)piperazine **13**. [Color figure can be viewed at wileyonlinelibrary.com]



spectrum of the bis(thiazolyl)piperazine **7** revealed an absorption band at 3413 and 3224 cm^{-1} due to (OH) and (NH), respectively. Its NMR showed the presence of a characteristic singlet signal at δ 8.80 due to methine proton (–N=CH–). All other protons were seen at the expected chemical shifts and integral values (see the Experimental section).

Analogously, 2-bromo-1-phenylethanone **8** and 3-(2-bromoacetyl)-2*H*-chromen-2-one **10** were reacted with bis(hydrazinecarbothioamide) **5** in DMF, under microwave irradiation, in the presence of a catalytic amount of TEA, which afforded bis(thiazolyl)piperazines **9** and **11**, respectively. Moreover, ethyl chloroacetate **12** reacted with **5** under the same conditions to give the corresponding bis(4-oxothiazolyl)piperazine **13** (Scheme 3). The reaction time and the yield are shown in Table 1.

A second series of bis(thiazolyl)piperazine derivatives was prepared by a related pathway (Scheme 4). Thus, the cyclocondensation of compound **5** with hydrazonoyl chlorides **14a–e** in DMF under microwave irradiation, in the presence of TEA, gave bis(arylazothiazolyl)piperazine derivatives **15a–e** (Scheme 4). The structure of this series of bis(arylazothiazolyl)piperazines **15a–e** was established on the basis of spectral data and elemental analysis. Accordingly, the ^{1}H-NMR spectrum of bis(phenylazothiazolyl)piperazine **15a**, as a typical example, showed three singlet signals at δ 2.43, 2.60, and 3.58 due to piperazine, methyl, and methylene protons, accompanied by aromatic proton signals in the region δ 6.82–7.63 and a singlet signal at δ 8.78 due to methine proton, in addition to two D_2O-exchangeable singlet signals identified as OH and NH protons at δ 10.66 and 10.70, respectively. In addition, the mass spectrum of **15a** showed a molecular ion peak at *m/z* = 784. An additional justification for the structure of the aforementioned reaction products comes from the treatment of benzene diazonium chloride **16** with bis(thiazolyl)piperazines **7** in pyridine afforded a product identical in all respects with **15a**.

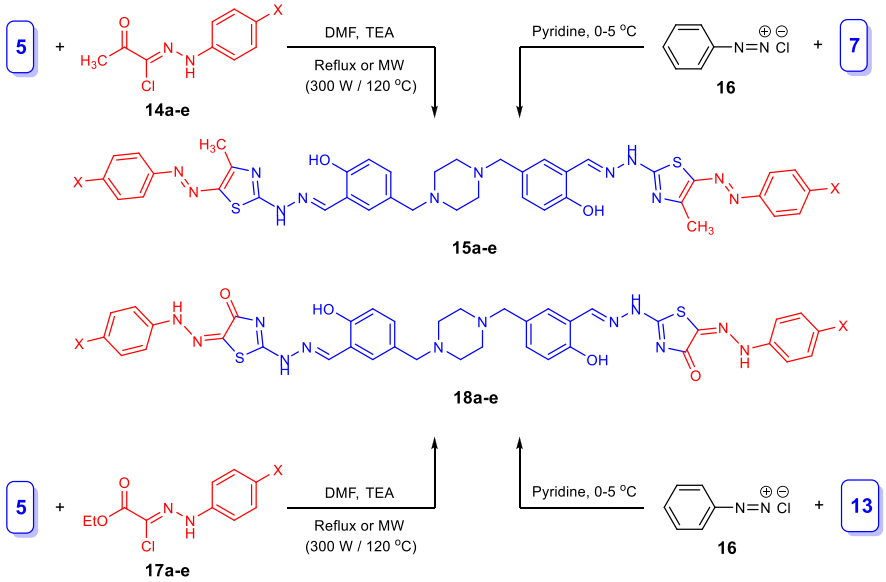
Similarly, treatment of bis(hydrazinecarbothioamide) **5** with the appropriate hydrazonoyl chlorides **17a–e** in DMF containing TEA under microwave irradiation afforded bis(5-arylhydrazono-4-oxothiazolyl)piperazines

Table 1

Synthesis of bis(thiazolyl)piperazines **7**, **9**, **11** and bis(4-oxothiazolyl)piperazine **13**, under both microwave irradiation and conventional method.

		Microwave irradiation 300 W/120°C		Conventional method	
Entry	Compound	Time (min)	Yield (%)	Time (h)	Yield (%)
1	**7**	15	93	3	88
2	**9**	10	96	2	90
3	**11**	10	98	1.5	95
4	**13**	15	90	3	82

Scheme 4. Synthesis of bis(arylazothiazolyl)piperazines **15a–e** and bis(5-arylhydrazono-4-oxothiazolyl)piperazines **18a–e**. [Color figure can be viewed at wileyonlinelibrary.com]



18a–e (Scheme 4). The structures of the formed products **18a–e** were elucidated by elemental analyses and spectral data (see the Experimental section). Again, the structure was confirmed by alternative synthesis. Thus, the coupling of bis(4-oxothiazolyl)piperazine **13** with benzene diazonium chloride **16** in pyridine yielded the same product **18a**.

Finally, to find the effect of microwave irradiation on the synthesis of this series of bis(thiazole) derivatives, all previous reactions were carried out under the same conditions without microwave irradiation (Tables 1 and 2). It was noticed that the reaction time increased substantially and that yield of the products decreased. Consequently, microwave irradiation was found to have supportive effect on the synthesis of bis(thiazole) derivatives by decreasing the time of aforementioned reactions from 1.5–6 h in conventional procedure to 10–45 min. Also, an obvious improvement is seen in yields of reactions under microwave irradiations.

CONCLUSION

In conclusion, we introduce an effective synthetic pathway for a series of novel bis(thiazolyl)piperazines, bis(4-oxothiazolyl)piperazine, bis(arylazothiazolyl)piperazines, and bis(5-arylhydrazono-4-oxothiazolyl)piperazines under microwave irradiation *via* cyclocondensation of bis(hydrazinecarbothioamide) with appropriate α-halocarbonyl compounds and hydrazonoyl halides. Microwave irradiation gave access to high yields of bis(thiazole) in a short reaction time than did

Table 2

Synthesis of bis(arylazothiazolyl)piperazines **15a–e** and bis(5-arylhydrazono-4-oxothiazolyl)piperazines **18a–e**, under both microwave irradiation and conventional method.

			Microwave irradiation 300 W/120°C		Conventional method	
Entry	Compound	X	Time (min)	Yield (%)	Time (h)	Yield (%)
1	**15a**	H	30	92	5	80
2	**15b**	CH_3	30	95	5	85
3	**15c**	OCH_3	30	82	5	77
4	**15d**	Cl	15	95	4	90
5	**15e**	COOEt	45	85	6	70
6	**18a**	H	30	88	5	78
7	**18b**	CH_3	15	90	4	84
8	**18c**	OCH_3	30	80	5	68
9	**18d**	Cl	30	92	5	57
10	**18e**	COOEt	45	80	5	66

conventional heating. The structure of the novel bis(thiazole) series was established by spectral data in addition to alternative synthesis.

EXPERIMENTAL

All organic solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck (Merck KGaA, Darmstadt, Germany). These chemicals were used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile attenuated total reflectance sampling accessory on the Nicolet iS10 Fourier transform IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Mercury (Varian, Inc., Palo Alto, CA) at 300 and 75 MHz, respectively, spectrophotometer using tetramethylsilane as an internal standard and DMSO-d_6 as solvent; and chemical shifts were expressed as δ ppm units. Mass spectra were recorded on a GC-MS-QP1000EX spectrometer using inlet type at 70 eV. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series. Microwave experiments were performed using CEM Discover & Explorer SP microwave apparatus (300 W), utilizing 35-mL capped glass reaction vessels automated power control based on temperature feedback. Hydrazonoyl halides **14a**–**e** and **17a**–**e** [44] were prepared according to the reported literature.

Synthesis of 1,4-bis[(3-((2-carbamothioylhydrazineylidene) methyl)-4-hydroxyphenyl)methyl]piperazine (5). A mixture of bis(aldehyde) **3** (1 mmol) and thiosemicarbazide **4** (2 mmol), in dioxane (10 mL) in the presence of few drops of acetic acid, was placed in process vial and was irradiated by microwave with a power of 300 W to reach a reaction temperature of 120°C under autogenerated pressure for 10 min. The formed solid was filtered off, washed with ethanol, and recrystallized from DMF as colorless crystals (78%); mp 264–266°C; IR (υ cm^{-1}): 3401, 3235, 3161, 1605, 1532; ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 8H, 4 CH_2), 3.58 (s, 4H, 2 CH_2), 6.95–7.63 (m, 6H, Ar-H), 8.10 (s, 4H, 2 NH_2), 8.35 (s, 2H, 2 –N=CH–), 9.92 (s, 2H, 2 OH), 11.43 (s, 2H, 2 NH); MS (*m*/*z*): 500 (M^+); Anal. for $C_{22}H_{28}N_8O_2S_2$ (500.6): C, 52.78; H, 5.64; N, 22.38; S, 12.81. Found: C, 53.01; H, 5.41; N, 22.56; S, 12.77%.

Synthesis of bis(thiazolyl)piperazines 7, 9, 11 and bis(4-oxothiazolyl)piperazine 13. ***Method "A" (microwave method).*** A mixture of bis(hydrazinecarbothioamide) **5** (1 mmol) and each of chloroacetone **6**, phenacyl bromide **8**, 3-(2-bromoacetyl)-2*H*-chromen-2-one **10**, or ethyl chloroacetate **12** (2 mmol) in DMF (10 mL) in the presence of TEA (0.5 mL) was placed in process vial and was irradiated by microwave with a power of 300 W to reach a reaction temperature of 120°C under autogenerated pressure for 10–15 min. The formed solid was filtered off, washed with ethanol, and recrystallized from DMF.

Method "B" (conventional method). A mixture of bis(hydrazinecarbothioamide) **5** (1 mmol) and each of chloroacetone **6**, 2-bromo-1-phenylethanone **8**, 3-(2-bromoacetyl)-2*H*-chromen-2-one **10**, or ethyl chloroacetate **12** (2 mmol) in DMF (20 mL) in the presence of TEA (0.5 mL) was heated at reflux for 1.5–3 h. The formed solid was filtered off, washed with ethanol, and recrystallized from DMF.

1,4-Bis[(4-hydroxy-3-((2-(4-methylthiazol-2-yl) hydrazineylidene)methyl)phenyl)methyl]piperazine (7). Beige crystals; mp 242–244°C; IR (υ cm^{-1}): 3413, 3224, 2945, 1608, 1480; ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 8H, 4 CH_2), 2.59 (s, 6H, 2 CH_3), 3.58 (s, 4H, 2 CH_2), 6.55–7.52 (m, 8H, Ar-H), 8.80 (s, 2H, 2 –N=CH–), 10.70 (s, 2H, 2 OH), 10.78 (s, 2H, 2 NH); MS (*m*/*z*): 576 (M^+); Anal. for $C_{28}H_{32}N_8O_2S_2$: C, 58.31; H, 5.59; N, 19.43; S, 11.12. Found: C, 58.54; H, 5.68; N, 19.69; S, 11.02%.

1,4-Bis[(4-hydroxy-3-((2-(4-phenylthiazol-2-yl) hydrazineylidene)methyl)phenyl)methyl]piperazine (9). Colorless crystals; mp > 300°C; IR (υ cm^{-1}): 3430, 3325, 3121, 2915, 1611, 1564, 1484; ^{1}H-NMR (DMSO-d_6): δ 2.44 (s, 8H, 4 CH_2), 3.57 (s, 4H, 2 CH_2), 6.72–7.80 (m, 18H, Ar-H), 8.29 (s, 2H, 2 –N=CH–), 10.00 (s, 2H, 2 OH), 12.07 (s, 2H, 2 NH); Anal. for $C_{38}H_{36}N_8O_2S_2$ (700.8): C, 65.12; H, 5.18; N, 15.99; S, 9.15. Found: C, 65.36; H, 5.01; N, 15.74; S, 9.33%.

1,4-Bis[(4-hydroxy-3-((2-(4-(2-oxo-2*H*-*chromen*-3-*yl*) *thiazol*-2-*yl*)*hydrazineylidene*)*methyl*)*phenyl*)*methyl*]*piperazine* *(11).* Colorless crystals; mp > 300°C; IR (υ cm^{-1}): 3436, 3220, 3122, 2915, 1701, 1575, 1491; ^{1}H-NMR (DMSO-d_6): δ 2.44 (s, 8H, 4 CH_2), 3.57 (s, 4H, 2 CH_2), 6.76–7.75 (m, 16H, Ar-H), 8.34 (s, 2H, 2 –N=CH–), 8.51 (s, 2H, 2 coumarin-CH-4), 10.04 (s, 2H, 2 OH), 12.14 (s, 2H, 2 NH); MS (*m*/*z*): 836 (M^+); Anal. for $C_{44}H_{36}N_8O_6S_2$: C, 63.14; H, 4.34; N, 13.39; S, 7.66. Found: C, 63.01; H, 4.58; N, 13.47; S, 7.51%.

1,4-Bis[(4-hydroxy-3-((2-(4-oxo-4,5-dihydrothiazol-2-yl) hydrazineylidene)methyl)phenyl)methyl]piperazine (13). Colorless crystals; mp 228–230°C; IR (υ cm^{-1}): 3434, 2919, 1716, 1645, 1490; ^{1}H-NMR (DMSO-d_6): δ 2.44 (s, 8H, 4 CH_2), 3.57 (s, 4H, 2 CH_2), 3.97 (s, 4H, 2 thiazole-H5), 6.87–7.56 (m, 6H, Ar-H), 8.61 (s, 2H, 2 –N=CH–), 10.59 (s, 2H, 2 OH), 10.66 (s, 2H, 2 NH); Anal. for $C_{26}H_{28}N_8O_4S_2$ (580.6): C, 53.78; H, 4.86; N, 19.30; S, 11.04. Found: C, 53.98; H, 4.99; N, 19.08; S, 10.89%.

Synthesis of bis(arylazothiazolyl)piperazines 15a-e and bis(5-arylhydrazono-4-oxothiazolyl)piperazines 18a–e. ***Method "A" (microwave method).*** A mixture of bis(hydrazinecarbothioamide) **5** (1 mmol) and each of

hydrazonoyl chlorides **14a–e** or **17a–e** (2 mmol) in DMF (10 mL) in the presence of TEA (0.5 mL) was placed in process vial and was irradiated by microwave with a power of 300 W to reach a reaction temperature of 120°C under autogenerated pressure for 15–45 min. The formed solid was filtered off, washed with ethanol, and recrystallized from DMF.

Method "B" (conventional method). A mixture of bis(hydrazinecarbothioamide) **5** (1 mmol) and each of hydrazonoyl chlorides **14a–e** or **17a–e** (2 mmol) in DMF (10 mL) in the presence of TEA (0.5 mL) was heated at reflux for 4–6 h. The formed solid was filtered off, washed with ethanol, and recrystallized from DMF.

Method "C" (coupling method). A benzene diazonium chloride solution **16** (2 mmol) was prepared *via* the addition of sodium nitrite solution of (0.2 g into 2 mL of water) to aniline hydrochloride (2 mmol in 2 mL of concentrated HCl) with stirring in ice bath. The obtained solution was then poured to a solution of each of compound **7** or **13** (1 mmol) in pyridine (15 mL) with stirring for 2 h at 0–5°C. The reaction mixture was stirred for additional 4 h in ice bath and then left for 24 h at 4°C in a refrigerator. The solids obtained were filtrated and recrystallized from DMF to give the corresponding **15a** and **18a**.

1,4-Bis[(4-hydroxy-3-((4-methyl-5-(phenyldiazenyl)thiazol-2-ylhydrazineylidene)methyl)phenyl)methyl]piperazine (15a). Red crystals; mp > 300°C; IR (υ cm^{-1}): 3415, 3224, 2962, 1607, 1481; ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 8H, 4 CH_2), 2.60 (s, 6H, 2 CH_3), 3.58 (s, 4H, 2 CH_2), 6.82–7.63 (m, 16H, Ar-H), 8.78 (s, 2H, 2 –N═CH–), 10.66 (s, 2H, 2 OH), 10.70 (s, 2H, 2 NH); MS (*m*/*z*): 784 (M^+); Anal. for $C_{40}H_{40}N_{12}O_2S_2$: C, 61.21; H, 5.14; N, 21.41; S, 8.17. Found: C, 61.47; H, 5.18; N, 21.24; S, 8.33%.

1,4-Bis[(4-hydroxy-3-((4-methyl-5-(*p*-tolyldiazenyl)thiazol-2-ylhydrazineylidene)methyl)phenyl)methyl]piperazine (15b). Red crystals; mp > 300°C; IR (υ cm^{-1}): IR (υ cm^{-1}): 3414, 3221, 2954, 1604, 1485; ^{1}H-NMR (DMSO-d_6): δ 2.24 (s, 6H, 2 CH_3), 2.43 (s, 8H, 4 CH_2), 2.58 (s, 6H, 2 CH_3), 3.58 (s, 4H, 2 CH_2), 6.82–7.61 (m, 14H, Ar-H), 8.84 (s, 2H, 2 –N═CH–), 10.68 (s, 2H, 2 OH), 10.85 (s, 2H, 2 NH); Anal. for $C_{42}H_{44}N_{12}O_2S_2$ (813.0): C, 62.05; H, 5.46; N, 20.67; S, 7.89. Found: C, 62.14; H, 5.20; N, 20.96; S, 7.65%.

1,4-Bis[(4-hydroxy-3-((4-methyl-5-((4-methoxyphenyl)diazenyl)thiazol-2-ylhydrazineylidene)methyl)phenyl)methyl]piperazine (15c). Red crystals; mp > 300°C; IR (υ cm^{-1}): IR (υ cm^{-1}): 3414, 3220, 2957, 1603, 1480; ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 8H, 4 CH_2), 2.60 (s, 6H, 2 CH_3), 3.58 (s, 4H, 2 CH_2), 3.76 (s, 6H, 2 OCH_3), 6.86–7.68 (m, 14H, Ar-H), 8.86 (s, 2H, 2 –N═CH–), 10.46 (s, 2H, 2 OH), 10.66 (s, 2H, 2 NH); MS (*m*/*z*): 845 (M^+); Anal. for $C_{42}H_{44}N_{12}O_4S_2$: C, 59.70; H, 5.25; N, 19.89; S, 7.59. Found: C, 59.92; H, 5.44; N, 19.76; S, 7.43%.

1,4-Bis[(4-hydroxy-3-((4-methyl-5-((4-chlorophenyl)diazenyl)thiazol-2-yl hydrazineylidene)methyl)phenyl)methyl]piperazine (15d). Red crystals; mp > 300°C; IR (υ cm^{-1}): 3417, 3220, 2954, 1605, 1480; ^{1}H-NMR (DMSO-d_6): δ 2.44 (s, 8H, 4 CH_2), 2.59 (s, 6H, 2 CH_3), 3.57 (s, 4H, 2 CH_2), 6.85–7.63 (m, 14H, Ar-H), 8.75 (s, 2H, 2 –N═CH–), 10.74 (s, 2H, 2 OH), 10.86 (s, 2H, 2 NH); Anal. for $C_{40}H_{38}Cl_2N_{12}O_2S_2$ (853.8): C, 56.27; H, 4.49; N, 19.69; S, 7.51. Found: C, 56.42; H, 4.33; N, 19.84; S, 7.64%.

1,4-Bis[(4-hydroxy-3-((4-methyl-5-((4-ethoxycarbonylphenyl)diazenyl)thiazol-2-ylhydrazineylidene)methyl)phenyl)methyl]piperazine (15e). Red crystals; mp > 300°C; IR (υ cm^{-1}): IR (υ cm^{-1}): 3414, 3222, 2941, 1700, 1604, 1483; ^{1}H-NMR (DMSO-d_6): δ 1.30 (t, J = 7.2 Hz, 6H, 2 $CH_2C\underline{H}_3$), 2.43 (s, 8H, 4 CH_2), 2.60 (s, 6H, 2 CH_3), 3.57 (s, 4H, 2 CH_2), 4.26 (q, J = 7.2 Hz, 4H, 2 $C\underline{H}_2CH_3$), 6.83–7.88 (m, 14H, Ar-H), 8.66 (s, 2H, 2 –N═CH–), 10.72 (s, 2H, 2 OH), 10.97 (s, 2H, 2 NH); Anal. for $C_{46}H_{48}N_{12}O_6S_2$ (929.0): C, 59.47; H, 5.21; N, 18.09; S, 6.90. Found: C, 59.29; H, 5.08; N, 18.26; S, 6.77%.

1,4-Bis[(4-hydroxy-3-((2-(5-(2-phenylhydrazineylidene)-4-oxo-4,5-dihydrothiazol-2-yl)hydrazineylidene)methyl)phenyl)methyl]piperazine (18a). Yellow crystals; mp 286–288°C; IR (υ cm^{-1}): 3436, 3254, 2912, 1705, 1634, 1543, 1484; ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 8H, 4 CH_2), 3.58 (s, 4H, 2 CH_2), 6.89–7.66 (m, 16H, Ar-H), 8.71 (s, 2H, 2 –N═CH–), 10.50 (s, 2H, 2 OH), 10.61 (s, 2H, 2 NH), 12.62 (s, 2H, 2 NH); MS (*m*/*z*): 788 (M^+); Anal. for $C_{38}H_{36}N_{12}O_4S_2$: C, 57.85; H, 4.60; N, 21.31; S, 8.13. Found: C, 57.72; H, 4.35; N, 21.44; S, 8.26%.

1,4-Bis[(4-hydroxy-3-((2-(5-(2-(*p*-tolyl)hydrazineylidene)-4-oxo-4,5-dihydrothiazol-2-yl)hydrazineylidene)methyl)phenyl)methyl]piperazine (18b). Yellow crystals; mp 255–257°C; IR (υ cm^{-1}): 3437, 3246, 2919, 1703, 1638, 1546, 1490; ^{1}H-NMR (DMSO-d_6): δ 2.25 (s, 6H, 2 CH_3), 2.44 (s, 8H, 4 CH_2), 3.58 (s, 4H, 2 CH_2), 6.86–7.74 (m, 14H, Ar-H), 8.74 (s, 2H, 2 –N═CH–), 10.68 (s, 2H, 2 OH), 10.84 (s, 2H, 2 NH), 12.70 (s, 2H, 2 NH); MS (*m*/*z*): 816 (M^+); Anal. for $C_{40}H_{40}N_{12}O_4S_2$: C, 58.81; H, 4.94; N, 20.57; S, 7.85. Found: C, 58.96; H, 4.74; N, 20.71; S, 7.95%.

1,4-Bis[(4-hydroxy-3-((2-(5-(2-(4-methoxyphenyl)hydrazineylidene)-4-oxo-4,5-dihydrothiazol-2-yl)hydrazineylidene)methyl)phenyl)methyl]piperazine (18c). Yellow crystals; mp 258–260°C; IR (υ cm^{-1}): 3437, 3244, 2933, 1704, 1632, 1549, 1496; ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 8H, 4 CH_2), 3.57 (s, 4H, 2 CH_2), 3.75 (s, 6H, 2 OCH_3), 6.84–7.65 (m, 14H, Ar-H), 8.70 (s, 2H, 2 –N═CH–), 10.47 (s, 2H, 2 OH), 10.66 (s, 2H, 2 NH), 12.49 (s, 2H, 2 NH); Anal. for $C_{40}H_{40}N_{12}O_6S_2$ (848.9): C, 56.59; H, 4.75; N, 19.80; S, 7.55. Found: C, 56.32; H, 4.52; N, 19.98; S, 7.67%.

1,4-Bis[(3-((2-(5-(2-(4-chlorophenyl)hydrazineylidene)-4-oxo-4,5-dihydrothiazol-2-yl)hydrazineylidene)methyl)-4-hydroxyphenyl)methyl]piperazine (18d). Yellow crystals;

mp > 300°C; IR (υ cm^{-1}): 3432, 3240, 2923, 1701, 1644, 1545, 1491; ^{1}H-NMR (DMSO-d_6): δ 2.44 (s, 8H, 4 CH_2), 3.57 (s, 4H, 2 CH_2), 6.88–7.62 (m, 14H, Ar-H), 8.65 (s, 2H, 2 –N═CH–), 10.55 (s, 2H, 2 OH), 10.64 (s, 2H, 2 NH), 12.64 (s, 2H, 2 NH); Anal. for $C_{38}H_{34}Cl_2N_{12}O_4S_2$ (857.7): C, 53.21; H, 4.00; N, 19.60; S, 7.48. Found: C, 53.44; H, 4.14; N, 19.38; S, 7.24%.

1,4-Bis[(3-((2-(5-(2-(4-ethoxycarbonylphenyl) hydrazineylidene)-4-oxo-4,5-dihydrothiazol-2-yl) hydrazineylidene)methyl)-4-hydroxyphenyl)methyl] piperazine (18e). Yellow crystals; mp 270–272°C; IR (υ cm^{-1}): 3438, 3252, 2921, 1716, 1635, 1550, 1493; ^{1}H-NMR (DMSO-d_6): δ 1.31 (t, J = 7.2 Hz, 6H, 2 $CH_2\underline{CH_3}$), 2.43 (s, 8H, 4 CH_2), 3.58 (s, 4H, 2 CH_2), 4.26 (q, J = 7.2 Hz, 4H, 2 $\underline{CH_2}CH_3$), 6.85–7.94 (m, 14H, Ar-H), 8.73 (s, 2H, 2 –N═CH–), 10.57 (s, 2H, 2 OH), 10.91 (s, 2H, 2 NH), 12.79 (s, 2H, 2 NH); Anal. for $C_{44}H_{44}N_{12}O_8S_2$ (933.0): C, 56.64; H, 4.75; N, 18.01; S, 6.87. Found: C, 56.75; H, 4.63; N, 18.21; S, 6.69%.

REFERENCES AND NOTES

[1] Acheson, R. M. An Introduction to the Chemistry of Heterocyclic Compounds, 3rd ed.; Wiley InterScience: India, 2009.

[2] Lassen, J. F.; Holm, N. R.; Stankovic, G.; Lefèvre, T.; Chieffo, A.; Hildick-Smith, D.; Pan, M.; Darremont, O.; Albiero, R.; Ferenc, M.; Louvard, Y. EuroIntervention 2014, 10, 545.

[3] Boksay, I. J.; Popendiker, K.; Weber, R. O.; Soeder, A. Arzneimittelforschung 1979, 29, 193.

[4] Gastpar, M.; Gastpar, G.; Gilsdorf, U. Pharmacopsychiatry 1985, 18, 351.

[5] Howland, R. H. J Psychosoc Nurs Ment Health Serv 2015, 53, 21.

[6] Mattei, C.; Rapagnani, M. P.; Stahl, S. M. J Cent Nerv Syst Dis 2011, 3, 1.

[7] Siddiqui, N.; Arshad, M. F.; Ahsan, W.; Alam, M. S. Int J Pharm Sci Drug Res 2009, 1, 136.

[8] Vasu, N.; Goud, B. B. K.; Kumari, Y. B.; Rajitha, B. Rasayan J Chem 2013, 6, 201.

[9] Singh, N.; Bhati, S. K.; Kumar, A. Eur J Med Chem 2008, 43, 2597.

[10] Luzina, E. L.; Popov, A. V. Eur J Med Chem 2009, 44, 4944.

[11] Turan-Zitouni, G.; Chevallet, P.; Kilic, F. S.; Erol, K. Eur J Med Chem 2000, 35, 635.

[12] Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. Eur J Med Chem 2008, 43, 2800.

[13] Satoh, A.; Nagatomi, Y.; Hirata, Y.; Ito, S.; Suzuki, G.; Kimura, T.; Maehara, S.; Hikichi, H.; Satow, A.; Hata, M.; Ohta, H. Bioorg Med Chem Lett 2009, 19, 5464.

[14] Iino, T.; Tsukahara, D.; Kamata, K.; Sasaki, K.; Ohyama, S.; Hosaka, H.; Hasegawa, T.; Chiba, M.; Nagata, Y.; Eiki, J. I.; Nishimura, T. Bioorg Med Chem 2009, 17, 2733.

[15] Hassaneen, H. M.; Shawali, A. S.; Saleh, F. M. J Sulfur Chem 2016, 37, 241.

[16] Shaker, R. M. ARKIVOC 2012, i, 1.

[17] Shawali, A. S.; Sherif, S. M.; El-Merzabani, M. M.; Darwish, M. A. A. J Heterocyclic Chem 2009, 46, 548.

[18] Dolle, R. E. J Comb Chem 2005, 7, 739.

[19] Helal, C. J.; Sanner, M. A.; Cooper, C. B.; Gant, T.; Adam, M.; Lucas, J. C.; Kang, Z.; Kupchinsky, S.; Ahlijanian, M. K.; Tate, B.; Menniti, F. S.; Kelly, K.; Peterson, M. Bioorg Med Chem Lett 2004, 14, 5521.

[20] Soural, M.; Bouillon, I.; Krchnak, V. J Comb Chem 2008, 10, 923.

[21] Csuk, R.; Barthel, A.; Raschke, C.; Kluge, R.; Strohl, D.; Trieschmann, L.; Böhm, G. Arch Pharm (Weinheim) 2009, 342, 699.

[22] Viegas-Junior, C.; Danuello, A.; da Silva Bolzani, V.; Barreiro, E. J.; Fraga, C. A. M. Curr Med Chem 2007, 14, 1829.

[23] Abdelriheem, N. A.; Mohamed, A. M. M.; Abdelhamid, A. O. Molecules 2017, 22, 268.

[24] Gomha, S. M.; Farghaly, T. A.; Mabkhot, Y. N.; Zayed, M. E.; Mohamed, A. M. Molecules 2017, 22, 346.

[25] Abdelhamid, A. O.; Gomha, S. M.; Abdelriheem, N. A.; Kandeel, S. M. Molecules 2016, 21, 929.

[26] Gomha, S. M.; Riyadh, S. M.; Mahmmoud, E. A.; Elaasser, M. M. Chem Heterocycl Compd 2015, 51, 1030.

[27] Gomha, S. M.; Salah, T. A.; Abdelhamid, A. O. Monatsh Chem 2015, 146, 149.

[28] Sayed, M.; Moustafa, H.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. RSC Adv 2016, 6, 10949.

[29] Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. J Sulfur Chem 2015, 36, 124.

[30] Mekky, A. E. M.; Elwahy, A. H. M. J Heterocyclic Chem 2014, 51, E34.

[31] Salem, M. E.; Darweesh, A. F.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. J Heterocyclic Chem 2017, 54, 226.

[32] Mekky, A. E. M.; Saleh, T. S.; Al-Bogami, A. S. Tetrahedron 2013, 69, 6787.

[33] Elneairy, M. A. A.; Mekky, A. E. M.; Ahmed, A. A. M. J Sulfur Chem 2012, 33, 373.

[34] Al-Bogami, A. S.; Mekky, A. E. M. J Heterocyclic Chem 2016, 53, 1554.

[35] Mekky, A. E. M.; Al-Bogami, A. S. J Heterocyclic Chem 2016, 53, 595.

[36] Sanad, S. M. H.; Kassab, R. M.; Abdelhamid, I. A.; Elwahy, A. H. M. Heterocycles 2016, 92, 910.

[37] Hawass, M. A. E.; Sanad, S. M. H.; Ahmed, A. A. M.; Elneairy, M. A. A. J Sulfur Chem 2018, 39, 388.

[38] Sanad, S. M. H.; Abdel Fattah, A. M.; Attaby, F. A.; Elneairy, M. A. A. Can J Chem, 2019, 97, 53. https://doi.org/10.1139/cjc-2017-0721.

[39] Sanad, S. M. H.; Hawass, M. A. E.; Ahmed, A. A. M.; Elneairy, M. A. A. J Heterocyclic Chem 2018, 55, 2823.

[40] Sanad, S. M. H.; Hefny, M. I. M.; Ahmed, A. A. M.; Elneairy, M. A. A. J Heterocyclic Chem 2018, 55, 2046.

[41] Sanad, S. M. H.; Elwahy, A. H. M.; Abdelhamid, I. A. ARKIVOC 2018, vii, 39.

[42] Bagherzadeh, M.; Zare, M. J Coord Chem 2013, 66, 2885.

[43] Guieu, S.; Rocha, J.; Silva, A. M. Synlett 2013, 24, 762.

[44] Farag, A. M.; Algharib, M. S. Org Prep Proced Int 1988, 20, 521.