Bis(α-bromo ketones): Versatile Precursors for Novel Bis(*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) and Bis(thiazoles)

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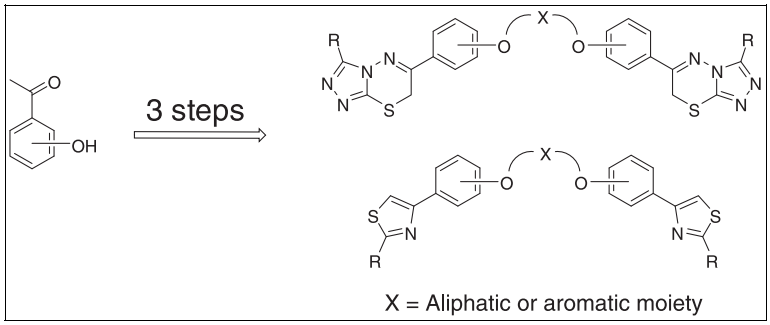

A synthesis of novel bis(*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) **4–6** in which the triazolothiadiazine is linked to the benzene core through the thiadiazine ring *via* phenoxymethyl spacers was reported. First attempt to synthesize **4–6** by the reaction of the appropriate bis(acetophenones) with 4-amino-3-mercapto-1,2,4-triazole derivatives using an acidified acetic acid method were unsuccessful. On the other hand, reaction of the corresponding bis(α-bromoketones) with 4-amino-3-mercapto-1,2,4-triazole derivatives afforded **4–6** in good yields. The reaction pathway is assumed to involve S-alkylation to give bis(aminotriazole) intermediates, followed by intramolecular cyclocondensation to give **4–6**. The successful isolation of the corresponding bis(aminotriazole) intermediates provides strong evidence for the proposed mechanism. The novel bis(thiazoles) **23–36**, linked to alkyl or aryl spacers can also be synthesized by reaction of the appropriate bis(bromoacetyl) compounds **12a–c** and **14–19** with the corresponding thioamide derivatives **20–22.**

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INTRODUCTION

Bis-heterocyclic compounds with a suitable spacer constitute an important class of compounds and their various types of activities, especially, as antitumor [1] and as antimicrobial [2], have been studied. These activities, which result in their pharmacological utility, have been reported to be enhanced when different functionalities or substitutions are present on the two heterocyclic moieties in the bis-compound [3–11].

Moreover, the synthesis and pharmacological activities of 1,2,4-triazoles and their heterocyclic fused analogs (e.g., triazolothiadiazoles and triazolothiadiazines) have attracted much attention in recent decades because they display a variety of medical applications such as antibacterial, antifungal, anticancer, antitumor, anticonvulsant, anti-inflammatory, antimicrobial activity, and analgesic properties [12–26]. Furthermore, thiazole derivatives have also attracted increasing attention due to their numerous pharmacological applications and biological activities, such as anti-inflammatory, analgesic, antimicrobial, anti-HIV, antihypertensive, and herbicidal activity [27–37].

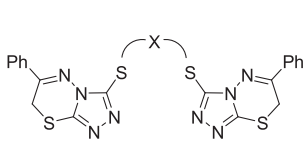
Recently, we reported the synthesis of bis(triazolothiadiazines) **1** and **2** in which the triazolothiadiazine moieties are attached to a benzene core or alkyl spacer through the triazole ring *via* thioether group. We have also reported the synthesis of bis(triazolothiadiazines) **3** in which the triazolothiadiazine moieties are linked to alkyl spacer through the thiadiazine ring *via* phenoxy group (Chart 1) [38–40]. Preliminary evaluation of the biological activities of **1–3** indicates that bis(triazolothiadiazines) of type **3** are more effective.

As a continuation of this work, we describe herein simple and efficient routes for the synthesis of novel bis (*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) **4–6** in which the triazolothiadiazine are linked to the benzene core through the thiadiazine ring via phenoxymethyl group (Chart 2).

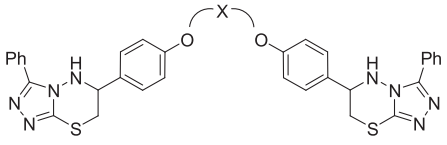
RESULTS AND DISCUSSION

Recently, El-Sherief *et al*. reported the synthesis of *s*-triazolo[3,4-*b*][1,3,4]thiadiazines **9a–g** by the reaction of 4-amino-3-mercapto-5-phenyl-*s*-triazole **7a** with aromatic ketones **8a–g** containing active α-hydrogens as a methyl group using an acidified acetic acid method [41]. The advantages of this method are short reaction time, one-pot reaction, and direct use of ketones without the formation phenacyl bromides (Scheme 1).

Chart 1

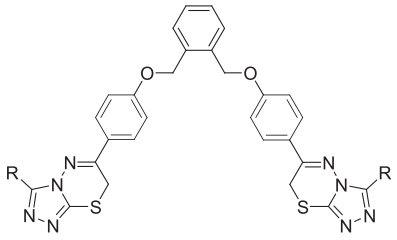


1, X = Aliphatic moiety
2, X = Aromatic moiety



3, X = Aromatic moiety

Chart 2



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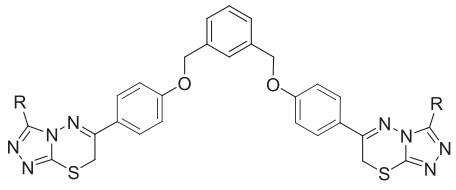

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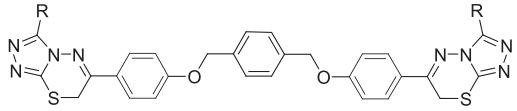

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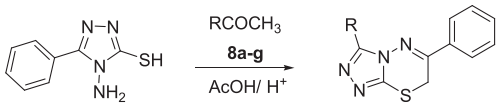
Scheme 1

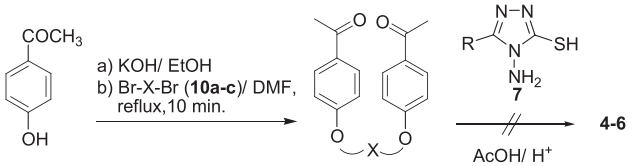


7a

9a-g

9a, R = Ph
b, = C_6H_4-Cl-*p*
c, = C_6H_4-Br-*p*
d, = C_6H_4-CH_3-*p*
e, = C_6H_4-MeO-*p*
f, = C_6H_4-NH_2-*p*
g, = C_6H_4-OH-*p*

Scheme 2



8g

11a-c

11a, X =

b, X =

c, X =

In connection with this findings, we studied the synthesis of bis(acetophenones) **11a–c** by the reaction of the potassium salt of 4-hydroxyacetophenone **8 g** with the appropriate bis(bromomethyl)benzenes **10a–c** in boiling dimethylformamide (DMF). The synthetic utility of **11a–c** as building blocks for novel bis(*s*-triazolo[3,4-*b*][1,3,4] thiadiazines) **4–6** were investigated. Unfortunately, repeated attempts to synthesize **4–6** by the reaction of **11a–c** with 4-amino-3-mercapto-1,2,4-triazole derivatives **7** using an acidified acetic acid method were unsuccessful, and the starting materials were recovered completely unchanged (Scheme 2).

The unsuccessful synthesis of **4–6** from **11a–c** prompted us to study the synthesis of the bis(*α*-bromoketones) **12a–c** as suitable precursors for **4–6**. First attempt to synthesize **12a–c** by bromination of **11a–c** with bromine in acetic acid led to the formation of an unseparable mixture of the bis(*α*-bromoketone) **12** as well as the corresponding undesirable bis(*α*,*α*-dibromoketone). On the other hand, the reaction of **11a–c** with *N*-bromosuccinimide (NBS) in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in acetonitrile afforded the corresponding bis(*α*-bromoketones) **12a–c** as single monobrominated ketones in most instances in high yield (Scheme 3).

Thus, reaction of **12a–c** with 4-amino-3-mercapto-1,2,4-triazole derivatives **7a–c** in ethanol-DMF mixture in the presence of few drops of piperidine as a catalyst under

Scheme 3

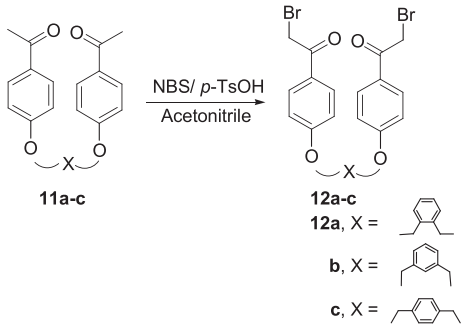
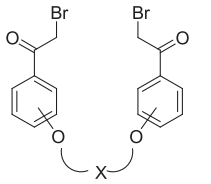


Chart 3



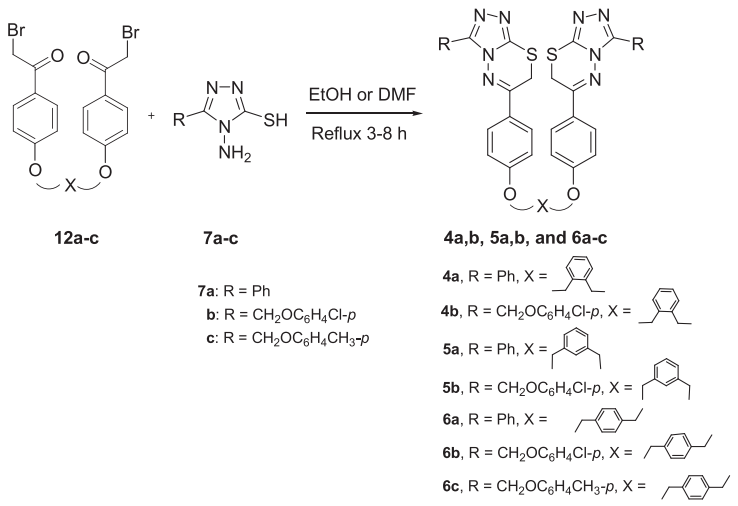
14-19

14, X = $(CH_2)_2$ (*o*-isomer)
15, X = $(CH_2)_3$ (*o*-isomer)
16, X = $(CH_2)_4$ (*o*-isomer)
17, X = $(CH_2)_2$ (*p*-isomer)
18, X = $(CH_2)_3$ (*p*-isomer)
19, X = $(CH_2)_4$ (*p*-isomer)

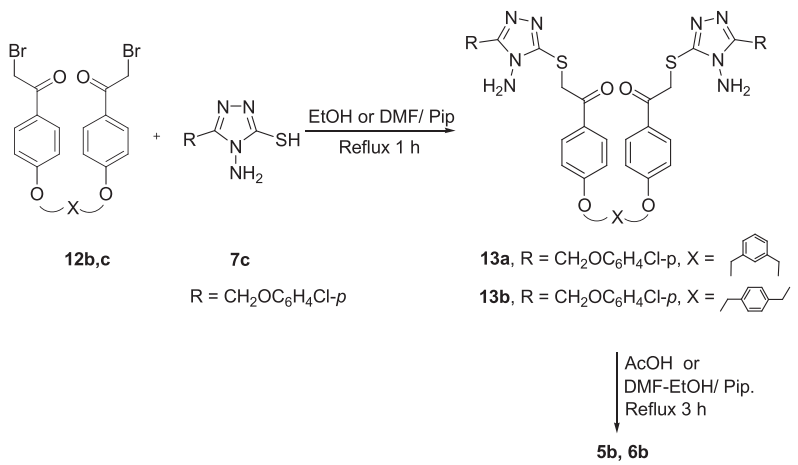
reflux afforded the novel bis(5,6-dihydro-*s*-triazolo[3,4-*b*] thiadiazines) **4–6** in 50–70% yields (Scheme 4).

All of the isolated compounds were characterized by elemental analyses, as well as their spectral data, which agree with the proposed structures. Thus, the disappearance of NH_2 stretching bands in the IR spectra of the triazolothiadiazines

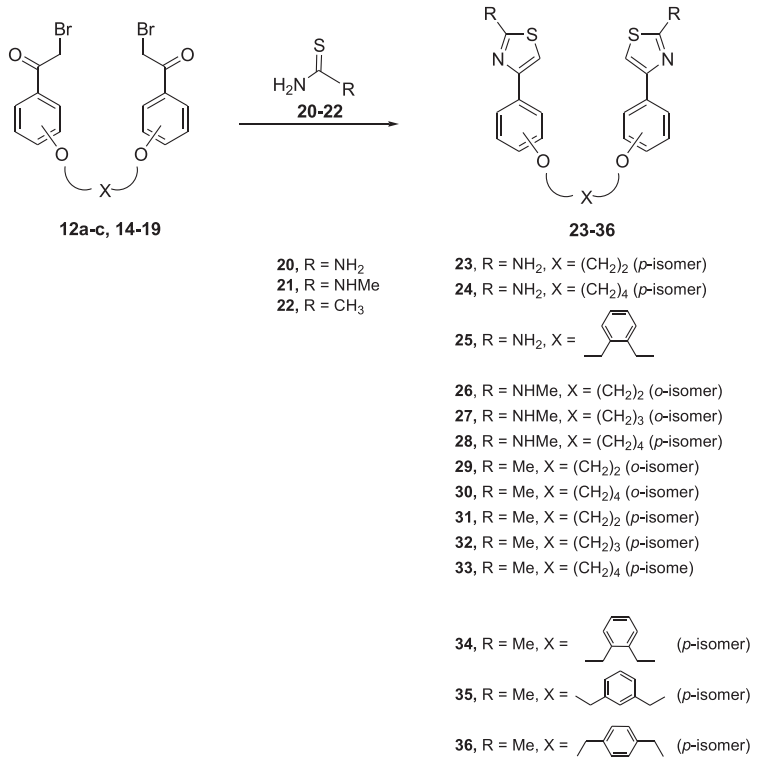
Scheme 4



Scheme 5



Scheme 6



4–6 together with the absence of the characteristic signals belonging to primary amine in their ^{1}H-NMR spectra are evidences for the cyclocondensation of the appropriate bis(α-bromoketones) **12a–c** with aminotriazoles **7a–c**, respectively. In addition, the presence of SCH_2 protons, resonated at (δ) 4.32–4.40 ppm as singlet signals integrating four protons, clearly indicating that ring closure reaction occurred. All other protons were seen at the expected chemical shifts and integral values (See Experimental section).

The reaction pathway is assumed to involve S-alkylation to give bis(aminotriazole) intermediates **13**, followed by intramolecular cyclocondensation to give **4–6**. The corresponding bis(aminotriazoles) **13a,b** could be isolated thereby providing strong evidence for the proposed mechanism. The latter compounds underwent cyclocondensation in refluxing acetic acid or DMF containing few drops of piperidine to give **5b** and **6b**, respectively (Scheme 5).

Encouraged by the results obtained with the aforementioned experiments, we have extended our study to include the synthesis of novel bis(thiazoles) **24–37** by reaction of the appropriate bis(bromoacetyl) compounds **12a–c** as well as **14–19** [40] with the corresponding thioamide derivatives. Compounds **14–19** were recently prepared in our laboratory from the corresponding bis-acetophenones with NBS in acetonitrile (Chart 3).

In a typical experiment, an equimolar amount of bis (bromo) derivatives **12a**, **17** and **19,** and thiourea **20** was reacted in refluxing ethanol to afford the corresponding bis(aminothiazoles) **23–25** (Scheme 6). The reaction was completed within 3–5 h, and the product was obtained in good yields.

In a similar manner, bis(bromo) derivatives **12a–c** and **14–19** were reacted smoothly with *N*-methylthiourea **21** and thioacetamide **22** successfully to give the corresponding bis(thiazole) derivatives **26–36** (Scheme 3).

CONCLUSIONS

We developed a simple method for the synthesis of bis (triazolothiadiazinyl)arenes. The triazolothiadiazine moiety in the novel compounds are linked to benzene core *via* phenoxy group. Attempts to synthesize these compounds directly from the corresponding bis ketones according to recently published results were unsuccessful. Confirmation of the suggested mechanism for the synthesis of these compounds by isolation of the intermediates bis (triazoles) was reported. We have also synthesized a series of novel bis(thiazoles), linked to alkyl or aryl spacers. Full characterization of these compounds is reported. The new synthesized compounds are interesting both in their own right as unusual molecules and for their promising pharmacological and biological activities. They offer an advantage

of their easy synthesis in a simple one step or two steps procedure from inexpensive starting materials.

EXPERIMENTAL

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus and were not corrected. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3–300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were determined on a Varian Mercury VX 300 NMR spectrometer using tetramethylsilane TMS as an internal standard and DMSO-d_6 as a solvent. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. 1,ω-bis(2-acetylphenoxy)alkanes **3a–c** were prepared using a modified procedure to a published method [42–45].

1,ω-Bis(4-acetylphenoxy)benzenes 11a–c

General procedure. 4-Hydroxyacetophenone **9g** (10 mmol) was dissolved in a hot ethanolic KOH solution (prepared by dissolving 0.56 g (10 mmol) of KOH in 10 mL of absolute ethanol), and the solvent was then removed in vacuo. The remaining material was dissolved in DMF (10 mL), and the appropriate dibromides (5 mmol) were added. The reaction mixture was refluxed for 10 min during which KBr was separated. The solvent was then removed in vacuo, and the remaining materials were poured onto crushed ice. The crude precipitate of bis(acetylphenoxy)benzenes **11a–c** were recrystallized from ethanol.

1,2-Bis(4-acetylphenoxymethyl)benzene (11a). (93% Yield), mp 136 °C (ethanol); IR (cm^{-1}): 1666 (C═O); MS: *m/z* 374 (M$^+$, 57.9%), 357 (14.36%), 239 (100%); ^{1}H-NMR (DMSO): δ 2.50 (s, 6H), 5.33 (s, 4H), 7.11 (d, 4H, J = 6.9 Hz), 7.37–7.40 (m, 2H), 7.53–7.54 (m, 2H), 7.90 (d, 4H, J = 7 Hz). Anal. calcd for $C_{24}H_{22}O_4$ (374.43): C, 76.99; H, 5.92. Found: C, 77.14; H, 5.93.

1,3-Bis(4-acetylphenoxymethyl)benzene (11b). (90% Yield), mp 140 °C (ethanol) (ref. [42] 139–140 °C).

1,4-Bis(p-acetylphenoxymethyl)benzene (11c). (92% Yield), mp 200–202 °C (ethanol) (ref. [43] 181–182 °C).

Synthesis of bis(α-bromoacetophenones) (12a–c)

General procedure. To a stirred solution of bis(acetophenone) derivatives **11a–c** (10 mmol) and p-TsOH (5.6 g, 20 mmol) in acetonitrile (50 mL) was slowly added NBS (3.6 g, 20 mmol). The reaction mixture was heated under reflux with stirring for 1–2 h then left to cool to room temperature. The solvent was evaporated in vacuo, and the residue was dissolved in chloroform (50 mL), washed with water (2 × 20 mL), and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid was recrystallized from benzene or ethyl acetate to afford the corresponding bis(α-bromoketone) derivatives **12a–c**, respectively.

1,2-Bis(4-bromoacetylphenoxymethyl)benzene (12a). (96% Yield), mp 132 °C (ethylacetate); IR (cm^{-1}): 1662 (C═O); ^{1}H-NMR (DMSO): δ 4.81 (s, 4H), 5.36 (s, 4H), 7.15 (d, 4H, J = 8.7 Hz), 7.41 (m, 2H, ArH's), 7.54 (m, 2H, ArH's), 7.97 (d, 4H, J = 8.7 Hz). Anal. calcd for $C_{24}H_{20}Br_2O_4$ (529.97): C, 54.16; H, 3.79; Br, 30.03. Found: C, 54.42; H, 3.81; Br, 29.93.

1,3-Bis(4-bromoacetylphenoxymethyl)benzene (12b). (90% Yield), mp 108–110 °C (ethylacetate); IR (cm^{-1}): 1668 (C═O); ^{1}H-NMR (DMSO): δ 4.82 (s, 4H), 5.25 (s, 4H), 7.15 (d, 4H, J = 9.15 Hz), 7.44–7.45 (m, 3H, ArH's), 7.57 (s, 1H), 7.98 (d, 4H, J = 6.9 Hz). Anal. calcd for $C_{24}H_{20}Br_2O_4$ (529.97): C, 54.16; H, 3.79; Br, 30.03. Found: C, 54.28; H, 3.61; Br, 30.11.

1,4-Bis(4-bromoacetylphenoxymethyl)benzene (12c). (95% Yield), mp 140–142 °C (ethylacetate); IR (cm^{-1}): 1681 (C═O); ^{1}H-NMR (DMSO): δ 4.83 (s, 4H), 5.24 (s, 4H), 7.10–8.07 (m, 12H, ArH's). Anal. calcd for $C_{24}H_{20}Br_2O_4$ (529.97): C, 54.16; H, 3.79; Br, 30.03. Found: C, 53.89; H, 3.62; Br, 29.74.

Synthesis of bis(triazolo[3,4-b]thiadiazine) derivatives 4a,b, 5a,b, and 6a–c

General procedure. Method A: to a solution of **12a–c** (10 mmol) in EtOH/DMF [50 mL (30:20)] containing few drops of piperidine, aminotriazolethiol **7a–c** (20 mmol) was added. The reaction mixture was heated under reflux for 5 h. The solvent was then removed in vacuo, and the remaining solid was diluted with ice-cold water (100 mL). The precipitate obtained was collected and crystallized from the proper solvent to give compounds **4a,b**, **5a,b,** and **6a–c**.

Method B: A solution of **13a,b** (10 mmol) in EtOH/DMF [50 mL (30:20)] containing few drops of piperidine, or AcOH (20 mL), was heated under reflux for 2 h. The solvent was then removed in vacuo, and the remaining solid was diluted with ice-cold water (100 mL). The precipitate obtained was collected and crystallized from the proper solvent to give compounds **5b** and **6b,** respectively.

6-(4-(2-((4-(3-Phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)phenoxy)methyl)-benzyloxy)-phenyl)-3-phenyl-7H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazine (4a). (55% Yield), mp 248–250 °C; IR (cm^{-1}): 1601 (C═N); MS: *m/z* 718 (M$^+$, 4.6%), 307 (100%), 103 (49.8%), 79 (48.6%); ^{1}H-NMR (DMSO): δ 4.38 (s, 4H), 5.36 (s, 4H), 7.20–7.23 (d, 4H, J = 9 Hz), 7.38–7.43 (m, 4H), 7.53–7.56 (m, 6H), 7.95–7.99 (m, 4H), 7.99–8.02 (m, 4H). Anal. calcd for $C_{40}H_{30}N_8O_2S_2$ (718.85): C, 66.83; H, 4.21; N, 15.59; S, 8.92. Found: C, 66.71; H, 3.89; N, 15.73; S, 8.66.

6-(4-(2-((4-(3-((4-Chlorophenoxy)methyl)-7H-[1,2,4]triazolo [3,4-b][1,3,4]-thiadiazin-6-yl)phenoxy)methyl)benzyloxy)phenyl)-3-((4-chlorophenoxy)methyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine (4b). (63% Yield), mp 132–134 °C; IR (cm^{-1}): 1602 (C═N); MS: *m/z* 848 (M$^+$+2, 7.5%), 846 (M$^+$, 15.2%), 354 (17.2%), 97 (53.5%), 69 (60.3%), 57 (100%), 55 (87.3%); ^{1}H-NMR (DMSO): δ 4.38 (s, 4H), 5.30 (s, 4H), 5.35 (s, 4H), 6.95–6.98 (m, 4H), 7.07–7.09 (m, 4H), 7.17 (d, 4H, J = 8.7 Hz), 7.35–7.43 (m, 2H), 7.46–7.52 (m, 2H), 7.93 (d, 4H, J = 8.4 Hz). Anal. calcd for $C_{42}H_{32}Cl_2N_8O_4S_2$ (847.79): C, 59.50; H, 3.80; Cl, 8.36; N, 13.22; S, 7.56. Found: C, 59.37; H, 3.59; Cl, 8.12; N, 13.16; S, 7.44.

6-(4-(3-((4-(3-Phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)phenoxymethyl)-benzyloxy)-phenyl)-3-phenyl-7H-[1,2,4] triazolo[3,4-b][1,3,4]-thiadiazine (5a). (50% Yield), mp 245–247 °C (acetic acid); IR (cm^{-1}): 1599 (C═N); MS: *m/z* 718 (M$^+$, 0.1%), 308 (53.7%), 276 (100%), 119 (88%), 103 (96%); ^{1}H-NMR (DMSO): δ 4.40 (s, 4H), 5.24 (s, 4H), 7.20 (d, 4H, J = 8.7 Hz), 7.43–7.47 (m, 4H), 7.53–7.58 (m, 6H), 7.96–8.03 (m, 8H). Anal. calcd for $C_{40}H_{30}N_8O_2S_2$ (718.85): C, 66.83; H, 4.21; N, 15.59; S, 8.92. Found: C, 66.49; H, 3.88; N, 15.23; S, 8.67.

6-(4-(3-((4-(3-((4-Chlorophenoxy)methyl)-7H-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazin-6-yl)phenoxy)-methyl)benzyloxy)phenyl)-3-((4-chlorophenoxy)methyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine (5b). (70% Yield), mp 128–130 °C; IR (cm^{-1}): 1597 (C═N); MS: *m/z* 848 (M$^+$+2, 8.3%), 846 (M$^+$, 8.2%), 240 (100%), 136 (60.7%), 78 (69.7%); ^{1}H-NMR (DMSO): δ 4.40 (s, 4H), 5.23 (s, 4H), 5.38 (s, 4H), 7.10–7.94 (m, 20H,

ArH's). Anal. calcd for $C_{42}H_{32}Cl_2N_8O_4S_2$ (847.79): C, 59.50; H, 3.80; Cl, 8.36; N, 13.22; S, 7.56. Found: C, 59.22; H, 3.68; Cl, 7.94; N, 12.91; S, 7.52.

6-(4-(4-((4-(3-Phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)phenoxy)methyl)-benzyloxy)-phenyl)-3-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (6a). (55% Yield), mp 252–254 °C (acetic acid); IR (cm^{-1}): 1600 (C═N); MS: *m/z* 718 (M^+, 3.5%), 213 (7.3%), 98 (86.3%), 80 (100%), 55 (51.1%); ^{1}H-NMR (DMSO): δ 4.32 (s, 4H), 5.20 (s, 4H), 7.14–7.99 (m, 22H, ArH's); ^{13}C-NMR: δ 22.50, 69.21, 115.51, 125.71, 126.07, 127.85, 128.65, 129.20, 130.07, 136.28, 142.48, 151.43, 155.37, 161.26, 171.89. Anal. calcd for $C_{40}H_{30}N_8O_2S_2$ (718.85): C, 66.83; H, 4.21; N, 15.59; S, 8.92. Found: C, 66.51; H, 3.87; N, 15.24; S, 8.69.

6-(4-(4-((4-(3-((4-Chlorophenoxy)methyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazin-6-yl)phenoxy)methyl)benzyloxy)phenyl)-3-((4-chlorophenoxy)methyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (6b). (57%, Method A, % Method B), 198–200 °C; IR (cm^{-1}): 1598 (C═N); MS: *m/z* 848 (M^++ 2, 1.2%), 847 (M^+, 0.8%), 339 (2.2%), 245 (100%), 84 (57.5%); ^{1}H-NMR (DMSO): δ 4.40 (s, 4H), 5.22 (s, 4H), 5.38 (s, 4H), 7.12–7.95 (m, 20H, ArH's). Anal. calcd for $C_{42}H_{32}Cl_2N_8O_4S_2$ (847.79): C, 59.50; H, 3.80; Cl, 8.36; N, 13.22; S, 7.56. Found: C, 50.19; H, 3.64; Cl, 8.41; N, 12.88; S, 7.44.

6-(4-(4-((4-(3-((p-Tolyloxy)methyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)phenoxy)-methyl)benzyloxy)phenyl)-3-((p-tolyloxy)methyl)-7H-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazine (6c). (65% Yield), mp 90–92 °C (acetic acid); IR (cm^{-1}): 1600 (C═N); MS: *m/z* 806 (M^+, 3.4%), 402 (7.5%), 107 (100%), 79 (21.7%); ^{1}H-NMR (DMSO): δ 2.23 (s, 6H), 4.39 (s, 4H), 5.23 (s, 4H), 5.31 (s, 4H), 6.96–7.95 (m, 20H, ArH's). Anal. calcd for $C_{44}H_{38}N_8O_4S_2$ (806.95): C, 65.49; H, 4.75; N, 13.89; S, 7.95. Found: C, 65.11; H, 4.43; N, 13.91; S, 7.84.

Synthesis of bis(aminotriazoles) (13a,b). To a solution of **12b,c** (10 mmol) in EtOH/DMF [50 mL (30:20)] containing few drops of piperidine, aminotriazole **7c** (20 mmol) was added. The reaction mixture was heated under reflux for 2 h. The solvent was then removed in vacuo, and the remaining solid was diluted with ice-cold water (100 mL). The precipitate obtained was collected and crystallized from the proper solvent to give compounds **13a,b**.

1,1′-(4,4′-(1,3-Phenylenebis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-(4-amino-5-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone) (13a). (75% Yield), mp 202–204 °C; IR (cm^{-1}): 1670 (C═O), 3170–3313 (NH_2); MS: *m/z* 883 (M^+, 45.4%), 882 (8.7%), 555 (51.3%), 320 (48.2%), 128 (100%); ^{1}H-NMR (DMSO): δ 4.84 (s, 4H), 5.17 (s, 4H), 5.25 (s, 4H), 6.08 (s, 4H), 7.09–8.02 (m, 20H, ArH's). Anal. calcd for $C_{42}H_{36}Cl_2N_8O_6S_2$ (883.82): C, 57.08; H, 4.11; Cl, 8.02; N, 12.68; S, 7.26. Found: C, 55.79; H, 3.84; Cl, 7.71; N, 12.45; S, 7.19.

1,1′-(4,4′-(1,4-Phenylenebis(methylene))bis(oxy)bis(4,1-phenylene))bis(2-(4-amino-5-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone) (13b). (70% Yield), mp 182–184 °C; 1671 (C═O), 3171–3316 (NH_2); MS: *m/z* 883 (M^+, 4.8%), 882 (11.3%), 211 (58.4%), 64 (100%), 54 (98.4%); ^{1}H-NMR (DMSO): δ 4.84 (s, 4H), 5.17 (s, 4H), 5.24 (s, 4H), 6.07 (br, 4H), 7.09–8.02 (m, 20H, ArH's). Anal. calcd for $C_{42}H_{36}Cl_2N_8O_6S_2$ (883.82): C, 57.08; H, 4.11; Cl, 8.02; N, 12.68; S, 7.26. Found: C, 56.63; H, 3.78; Cl, 7.81; N, 12.47; S, 6.92.

Synthesis of bis(thiazole) derivatives (23–36)

General procedure. A mixture of the appropriate bis (bromoacetophenone) compounds **12a–c** and **14–19** (0.01 mol), thiourea, *N*-mehtylthiourea, or thioacetamide (0.02 mol) in ethanol or ethanol/dioxane was heated under reflux for 3–5 h. The solid obtained upon cooling was filtered, collected, and recrystallized from acetic acid to give the corresponding bis (thiazole) products **23–36**.

5-(4-(2-(4-(2-Aminothiazol-5-yl)phenoxy)ethoxy)phenyl)thiazol-2-amine (23). (60% Yield), mp 301 °C; IR (cm^{-1}): 3231–3181 (NH_2);MS: *m/z* 410 (M^+, 100%) 218 (47%), 191 (72%); ^{1}H-NMR (DMSO): δ 3.57 (br, 4H), 4.36–4.39 (m, 4H), 7.03–7.77 (m, 8H, ArH's), 7.74 (s, 2H). Anal. calcd for$C_{20}H_{18}N_4O_2S_2$ (410.09): C, 58.52; H, 4.42; N, 13.65. Found: C, 57.98; H, 4.16; N, 13.41.

5-(4-(4-(4-(2-Aminothiazol-5-yl)phenoxy)butoxy)phenyl)thiazol-2-amine (24). (65% Yield), mp 285 °C; IR (cm^{-1}): 3299–3184 (NH_2);MS: *m/z* 438 (M^+, 11%), 246 (42%), 57 (100%);^{1}H-NMR (DMSO): δ 1.88–1.92 (m, 4H), 4.09–4.12 (m, 4H), 4.10 (s, 4H), 7.03–7.67 (m, 8H, ArH's), 7.05 (s, 2H); ^{13}C-NMR (DMSO): δ25.27,67.53, 100.51, 114.87, 120.54, 127.28, 159.37, 168.16, 170.09. Anal. calcd for $C_{22}H_{22}N_4O_2S_2$ (438.12): C, 60.25; H, 5.06; N, 12.78. Found: C, 59.79; H, 4.82; N, 12.41.

5-(4-(2-((4-(2-Aminothiazol-5-yl)phenoxy)methyl)benzyloxy)phenyl)thiazol-2-amine (25). (55% Yield), mp 250–252 °C (acetic acid); IR (cm^{-1}): 3223 (br, NH_2); MS: *m/z* 486.1 (M^+, 10.2%), 295 (25.6%), 192 (100%), 150 (46.3%), 64 (54.5%); ^{1}H-NMR (DMSO): δ 3.76 (br, 4H), 5.30 (s, 4H), 7.06 (s, 2H), 7.09–7.73 (m, 12H, ArH's). Anal. calcd for$C_{26}H_{22}N_4O_2S_2$ (486.12): C, 64.17; H, 4.56; N, 11.51. Found: C, 63.81; H, 4.23; N, 11.58.

5-(2-(2-(2-(2-(Methylamino)thiazol-5-yl)phenoxy)ethoxy)phenyl)-N-methylthiazol-2-amine (26). (63% Yield), mp 282–284 °C;IR (cm^{-1}): 3174 (NH);: *m/z* 438 (M^+, 36%), 260 (72%), 149 (100%);^{1}H-NMR (DMSO): δ 2.91 (s, 6H), 3.72 (br, 2H), 4.46 (s, 4H), 7.05–7.70 (m, 8H, ArH's), 7.09 (s, 2H); Anal. calcd for $C_{22}H_{22}N_4O_2S_2$ (438.12): C, 60.25; H, 5.06; N, 12.78. Found: C, 59.91; H, 5.18; N, 12.66.

5-(2-(3-(2-(2-(Methylamino)thiazol-5-yl)phenoxy)propoxy)phenyl)-N-methylthiazol-2-amine (27). (58% Yield), mp 178–180 °C;IR (cm^{-1}): 3349 (NH);: *m/z* 452 (M^+, 100%), 246 (74%);^{1}H-NMR (DMSO): δ 2.18–2.22 (m, 2H), 2.96–3.05 (m, 6H), 3.79 (br, 2H),4.17–4.21 (m, 4H),7.00–7.08–7.69 (m, 10H, ArH's); Anal. calcd for $C_{23}H_{24}N_4O_2S_2$ (452.13): C, 61.04; H, 5.34; N, 12.38. Found: C, 60.71; H, 5.18; N, 12.27.

5-(4-(4-(4-(2-(Methylamino)thiazol-5-yl)phenoxy)butoxy)phenyl)-N-methylthiazol-2-amine (28). (70% Yield), mp 258 °C;IR (cm^{-1}): 3224 (NH);: *m/z* 466 (M^+, 100%), 177 (59%), 149 (64%);^{1}H-NMR (DMSO): δ 1.88–1.90 (m, 4H), 3.00 (s, 6H), 3.56 (br, 2H), 4.03–4.10 (m, 4H), 6.98–7.77 (m, 8H, ArH's), 7.02 (s, 2H); Anal. calcd for $C_{24}H_{26}N_4O_2S_2$ (466.15): C, 61.78; H, 5.62; N, 12.01. Found: C, 61.41; H, 5.55; N, 11.89.

5-(2-(2-(2-(2-Methylthiazol-5-yl)phenoxy)ethoxy)phenyl)-2-methylthiazole (29). (72% Yield), mp 263–265 °C; MS: *m/z* 408 (M^+, 4.4%), 407 (6.6%), 217 (15%), 190 (17.6%), 79 (100%), 63 (46.9%); ^{1}H-NMR (DMSO): δ 2.70 (s, 6H), 4.58 (s, 4H), 7.02-7.33 (m, 6H, ArH's), 7.82 (s, 2H), 7.14 (d, 2H, $J = 7.8$ Hz). Anal. calcd for $C_{22}H_{20}N_2O_2S_2$ (408.1): C, 64.68; H, 4.93; N, 6.86. Found: C, 64.96; H, 4.72; N, 6.98.

5-(2-(4-(2-(2-Methylthiazol-5-yl)phenoxy)butoxy)phenyl)-2-methylthiazole (30). (66% Yield), mp 234 °C; ^{1}H-NMR (DMSO): δ 2.02 (br, 4H), 2.48 (s, 6H), 4.19 (s, 4H), 6.99–7.32 (m, 6H, ArH's), 7.88 (s, 2H), 8.07–8.09 (m, 2H, ArH's). Anal. calcd for $C_{24}H_{24}N_2O_2S_2$ (436.13): C, 66.02; H, 5.54; N, 6.42. Found: C, 65.71; H, 5.23; N, 6.11.

5-(4-(2-(4-(2-Methylthiazol-5-yl)phenoxy)ethoxy)phenyl)-2-methylthiazole (31). (80% Yield), mp 216 °C; MS: *m/z* 408 (M^+, 33.6%), 353 (56.9%), 80 (100%), 64 (72.5%); ^{1}H-NMR (DMSO): δ 2.69 (s, 6H), 4.36 (s, 4H), 7.04 (d, 4H, $J = 6.9$ Hz), 7.75 (s, 2H), 7.86 (d, 4H, $J = 6.9$ Hz). Anal. calcd for $C_{22}H_{20}N_2O_2S_2$ (408.1): C, 64.68; H, 4.93; N, 6.86. Found: C, 64.47; H, 4.66; N, 6.95.

5-(4-(3-(4-(2-methylthiazol-5-yl)phenoxy)propoxy)phenyl)-2-methylthiazole (32). (58% Yield), mp 176 °C; MS: *m/z* 422 (M^+, 28.6%), 421 (100%), 232 (55.5%), 121 (28.5%); ^{1}H-NMR (DMSO): δ 2.18–2.20 (m, 2H), 2.69 (s, 6H), 4.17-4.21 (m, 4H), 7.00 (d, 4H, $J = 7.8$ Hz), 7.66 (s, 2H), 7.84 (d, 4H, $J = 8.1$ Hz). Anal. calcd for $C_{23}H_{22}N_2O_2S_2$(422.11): C, 65.37; H, 5.25; N, 6.63. Found: C, 64.96; H, 5.48; N, 6.59.

5-(4-(4-(4-(2-Methylthiazol-5-yl)phenoxy)butoxy)phenyl)-2-methylthiazole (33). (83% Yield), mp 173 °C; ^{1}H-NMR (DMSO): δ 1.88–1.91 (m, 4H), 2.68 (s, 6H), 4.06–4.07 (m, 4H), 6.98 (d, 4H, $J = 7.8$ Hz), 7.72 (s, 2H), 7.84 (d, 4H, $J = 8.1$ Hz); Anal. calcd for $C_{24}H_{24}N_2O_2S_2$(436.13): C, 66.02; H, 5.54; N, 6.42. Found: C, 65.73; H, 5.12; N, 6.55.

5-(4-(2-((4-(2-Methylthiazol-5-yl)phenoxy)methyl)benzyloxy) phenyl)-2-methylthiazole (34). (88% Yield), mp 190–192 °C; IR (cm^{-1}):1604 (C═N); MS: *m/z* 484 (M^+, 28.9%), 294 (100%), 293 (50.5%), 104 (63.4%); ^{1}H-NMR (DMSO): δ 2.70 (s, 6H), 5.285 (s, 4H), 7.09 (d, 4H, $J = 8.4$ Hz), 7.36–7.56 (m, 4H, ArH's), 7.74 (s, 2H), 7.85 (d, 4H, $J = 8.4$ Hz). Anal. calcd for $C_{28}H_{24}N_2O_2S_2$ (484.13): C, 69.39; H, 4.99; N, 5.78. Found: C, 68.85; H, 4.73; N, 5.56.

5-(4-(3-((4-(2-Methylthiazol-5-yl)phenoxy)methyl)benzyloxy) phenyl)-2-methylthiazole (35). (65% Yield), mp 153–155 °C (acetic acid); IR (cm^{-1}): 1606 (C═N); MS: *m/z* 484 (M^+, 1.9%), 395 (49.7%), 372 (49.7%), 278 (50.7%), 128 (100%); ^{1}H-NMR (DMSO): δ 2.66 (s, 6H), 5.13 (s, 4H), 7.04 (d, 4H, $J = 9.3$ Hz), 7.40–7.53 (m, 4H, ArH's), 7.64 (s, 2H), 7.82 (d, 4H, $J = 9$ Hz); ^{13}C-NMR: δ 18.79, 69.17, 111.88, 114.80, 115.15, 127.13, 127.45, 129.29, 137.24, 153.40, 158.11, 165.40. Anal. calcd for $C_{28}H_{24}N_2O_2S_2$ (484.13): C, 69.39; H, 4.99; N, 5.78. Found: C, 69.66; H, 5.25; N, 5.42.

5-(4-(4-((4-(2-Methylthiazol-5-yl)phenoxy)methyl)benzyloxy) phenyl)-2-methylthiazole (36). (68% Yield), mp 230 °C (acetic acid); IR (cm^{-1}): 1605 (C═N); MS: *m/z* 484 (M^+, 15.5%), 294 (48.2%), 190 (74.6%), 104 (100%); ^{1}H-NMR (DMSO): δ 2.66 (s, 6H), 5.12 (s, 4H), 7.03 (d, 4H, $J = 6.9$ Hz), 7.45–7.47 (m, 4H, ArH's), 7.66 (s, 2H), 7.82 (d, 4H, $J = 6.9$ Hz). Anal. calcd for$C_{28}H_{24}N_2O_2S_2$ (484.13): C, 69.39; H, 4.99; N, 5.78. Found: C, 68.97; H, 5.22; N, 5.46.

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