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)

Mohamed R. Shaaban[a,b] and Ahmed H. M. Elwahy[a]*

[a]Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt
[b]Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah Almukkarramah, Saudi Arabia
*E-mail: aelwahy@hotmail.com

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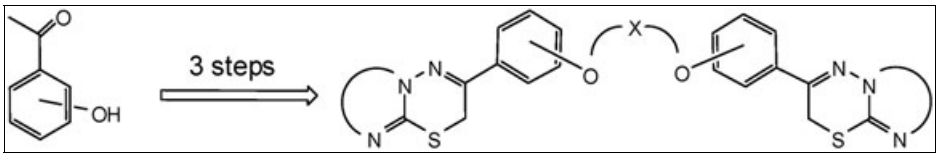

A synthesis of bis(α-bromo ketones) **5a-c** and **6b,c** was accomplished by the reaction of bis(acetophenones) **3a-c** and **4b,c** with *N*-bromosuccinimide in the presence of *p*-toluenesulfonic acid (*p*-TsOH). Treatment of **5a-c** and **6b,c** with each of 4-amino-3-mercapto-1,2,4-triazoles **9a,b** and 4-amino-6-phenyl-3-mercapto-1,2,4-triazin-5(4*H*)-ones **13** in refluxing ethanol afforded the novel bis(*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) **10a-d** and **11a-c** as well as bis(*as*-triazino[3,4-*b*][1,3,4]thiadiazines) **14a-c** and **15**, respectively, in good yields. Compounds **11b** and **11c** underwent $NaBH_4$ reduction in methanol to give the target 1,ω-bis{4-(6,7-dihydro-3-substituted-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl) phenoxy}butanes **12a** and **12b** in 42 and 46% yields, respectively.

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INTRODUCTION

Bis-heterocyclic compounds with a suitable alkyl 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, that 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].

In recent decades, the synthesis and pharmacological activities of 1,2,4-triazoles and their heterocyclic fused analogues (e.g., triazolothiadiazoles and triazolothiadiazines) have attracted much attention because they display a variety of medical applications such as antibacterial, antifungal, anticancer, antitumor, anticonvulsant, anti-inflammatory, antimicrobial activity and analgesic properties [12–26].

In addition, 1,2,4-triazines and their fused derivatives have been widely studied in terms of their synthetic xmethodologies and reactivity since some of these derivatives were reported to have promising biological activities [27–35].

α-Bromo ketones are valuable compounds, which are useful in the synthesis of a variety of heterocycles [36–40] as well as in other synthetic applications including cross aldol condensations [41], enaminoketones [42] and Favorskii rearrangements [43,44]

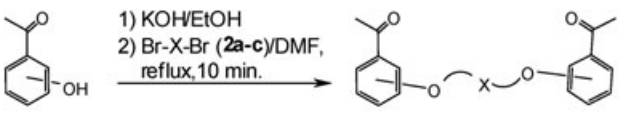
In general, α-bromo carbonyl compounds can be conventionally obtained by the reaction of carbonyl compounds with various reagents such as bromine [45], copper (II) bromide [46,47], dioxane dibromide [48] tetrabutylammonium tribromide [49], and polymer-supported pyridinium bromide perbromide [50]. In addition, the *N*-bromosuccinimide (NBS) has been classically utilized for the α-bromination of ketones via radical process promoted by radical initiators such as AIBN and benzoyl peroxide in CCl_4 [51].

Keeping the above facts in mind and in continuation of our interest in the synthesis of bis(heterocycles) [52–59], we describe herein a simple and efficient route for the synthesis of novel bis(α-bromo ketones) and studied their synthetic utilities as key intermediates for the synthesis of novel bis(*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) as well as bis(*as*-triazino[3,4-*b*][1,3,4]thiadiazines).

RESULTS AND DISCUSSION

In search of an expedient pathway to prepare the target bis(α-bromo ketones) **5a-c** and **6b,c** our attention focused on bis(acetophenones) **3a-c** and **4a-c** as precursors which could be obtained by the reaction of the potassium salt 2-hydroxyacetophenone **1a** and 4-hydroxyacetophenones **1b** with the appropriate dibromoalkanes **2a-c** in boiling DMF (Scheme 1).

Scheme 1



1a,b **3a-c, 4a-c**

3a-c (*o*-isomer)	X
a	$(CH_2)_2$
b	$(CH_2)_3$
c	$(CH_2)_4$
4a-c (*p*-isomer)	**X**
a	$(CH_2)_2$
b	$(CH_2)_3$
c	$(CH_2)_4$

First attempts to synthesize **5a** and **6b** by bromination of **3a** and **4b** with Br_2 in acetic acid led to the formation of a mixture of the bis(α-bromo ketones) **5a** and **6b** as well as the undesirable bis(α,α-dibromoketones) **7a** and **8b** (Scheme 2). The ^{1}H NMR spectra of the reaction products indicated the presence of CH_2–Br protons, resonated at δ 4.39–4.49 ppm as singlet signals integrating four protons, and $CHBr_2$ protons, resonated at δ 6.66–6.96 ppm as singlet signals integrating two protons. Unfortunately, all attempts to separate the two products were unsuccessful.

On the other hand, the reaction of **3a-c** and **4b,c** with NBS in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in acetonitrile afforded the corresponding bis(α-bromo ketones) **5a-c** and **6b,c** as single monobrominated ketones in most instances in high yield (Scheme 3).

The synthetic utility of compounds **5a-c** and **6b,c** as building blocks for novel bis(5,6-dihydro-*s*-triazolo[3,4-*b*] thiadiazines) **10a-d** and **11a-c** is outlined in Scheme 4. 4-Amino-3-mercapto-1,2,4-triazole derivatives **9a,b** were chosen as ideal heterocyclic reagents. The amino and mercapto groups of these compounds serve as readily accessible nucleophilic centers for the preparation of *N*-bridged heterocycles. Thus, reaction of **5a-c** and **6b, c** with **9a,b** in anhydrous ethanol under reflux afforded **10a-d** and **11a-c** in 58–95% yields.

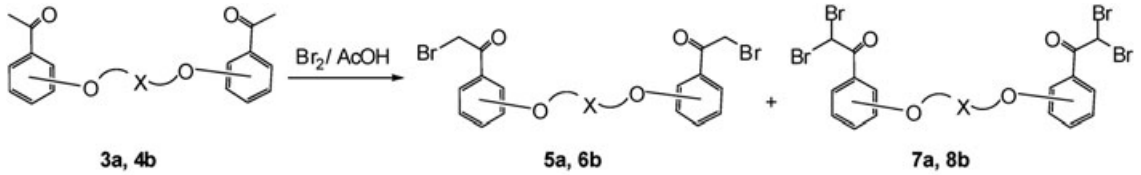
Compounds **11b** and **11c** underwent $NaBH_4$ reduction in methanol to give the target 1,ω-bis{4-(6,7-dihydro-3-substituted-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl) phenoxy}butanes **12a,b** in 60–65% yields (Scheme 5).

Similarly, a series of 1,2,4-triazino[3,4-*b*][1,3,4]thiadiazin-4-ones **14a-c** and **15** have been synthesized in 63–72% yield by the reaction of 4-amino-6-phenyl-3-mercapto-1,2,4-triazin-5(4*H*)-ones **14a-c** and **15** with the appropriate bis(α-bromo ketones) **5a-c** and **6c** in refluxing ethanol (Scheme 6).

All compounds were characterized by their melting points, elementary analysis, IR, ^{1}H NMR and mass spectra. The spectral data agree with the proposed structures. Thus, the disappearance of NH_2 stretching bands in the IR spectra of triazolothiadiazines **10a-d** and **11a-c** as well as triazinothiadiazin-4-ones **14a-c** and **15**, together with the disappearance of the characteristic peaks belonging to primary amine in their ^{1}H NMR spectra are evidences for the cyclocondensation of the appropriate bis(α-bromo ketones) with each of **9a,b** and **13**, respectively. In addition, the presence of SCH_2 protons, resonated at δ 4.24–4.57 ppm as singlet signals integrating four protons, clearly indicated that ring closure reaction occurred. All other protons were seen at the expected chemical shifts and integral values. Compounds **12a** and **12b** showed in their ^{1}H-NMR spectra a well resolved doublet signal for N^5-H, two dd singlet for C^7-Ha and C^7-He and a multiplet signal for C^6-H. The two protons of C^7–H_2 (for compound **12a** and **12b**) each appears as dd as a result of the geminal coupling (^2J = 12.6 Hz) as well as the vicinal coupling constants with C^6-H. The large vicinal coupling constants $^3J_{5,6}$ = 8.7–9.3 Hz, $^3J_{6,7}$ = 8.7 Hz indicate *trans* relationship of N^5-H, C^6-H and C^6-H, C^7-Ha. On the other hand, the small vicinal coupling constant $^3J_{6,7e}$ = 2.7–3.0 Hz indicate the *cis* relationship of C^6-H, C^7-He.

In conclusion we synthesized new series of bis(α-bromo ketones) via the reaction of bis(acetophenones) with NBS in the presence of *p*-TsOH in acetonitrile. The synthetic utility of these compounds as building blocks for novel bis(5,6-dihydro-*s*-s-triazole[3,4-*b*]thiadiazines) as well as

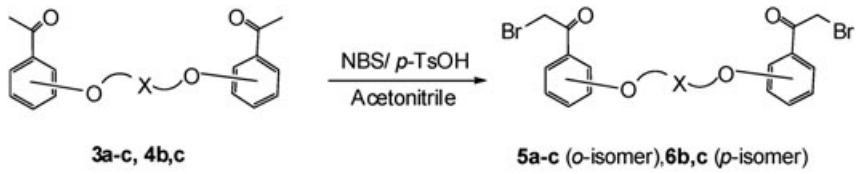
Scheme 2



3a, 4b **5a, 6b** **7a, 8b**

3a, X = $(CH_2)_2$ **5a**, X = $(CH_2)_2$ **7a**, X = $(CH_2)_2$
4b, X = $(CH_2)_3$ **6b**, X = $(CH_2)_3$ **8b**, X = $(CH_2)_3$

Scheme 3



3a-c, 4b,c

5a-c (*o*-isomer),**6b,c** (*p*-isomer)

5a-c (*o*-isomer)	X
a	$(CH_2)_2$
b	$(CH_2)_3$
c	$(CH_2)_4$
6b,c (*p*-isomer)	X
b	$(CH_2)_3$
c	$(CH_2)_4$

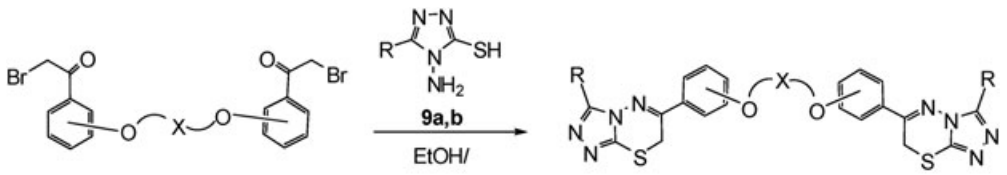
bis(*as*-triazino[3,4-*b*][1,3,4] thiadiazines) have been investigated. The novel starting bis(α-bromo ketones) would open a new access to a variety of heterocyclic systems with possible pharmaceutical properties. The new synthesized bis (fused heterocycles) offer an advantage of their easy synthesis on a large scale in a simple procedure from inexpensive starting materials and we believe that they should be useful compounds with potentially high pharmacological and biological activities.

EXPERIMENTAL

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 ^1H and ^{13}C NMR spectra were determined on a Varian Mercury VX 300 NMR spectrometer using 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** and 1,ω-bis(4-acetylphenoxy) alkanes **4a,b** were prepared according to published procedures [53,60].

Synthesis of 1,ω-bis(2-acetylphenoxy)alkanes 3a-c and 1, ω-bis(4-acetylphenoxy)alkanes 4a-c. 2-Hydroxyacetophenone **1a** or 4-hydroxyacetophenone **1b** (10 mmol) was dissolved in 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

Scheme 4

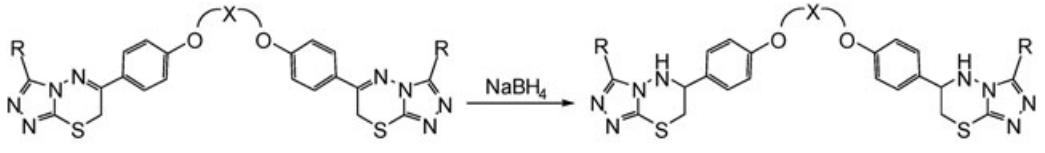


5a-c (*o*-isomer),**6b,c** (*p*-isomer)

10a-d (*o*-isomer),**11a-c** (*p*-isomer)

10a-d (*o*-isomer)	X	R
a	$(CH_2)_2$	C_6H_5
b	$(CH_2)_2$	CH_3
c	$(CH_2)_3$	C_6H_5
d	$(CH_2)_4$	C_6H_5
11a-c (*p*-isomer)	X	R
a	$(CH_2)_3$	C_6H_5
b	$(CH_2)_4$	C_6H_5
c	$(CH_2)_4$	CH_3

Scheme 5



12a,b	X	R
a	$(CH_2)_4$	C_6H_5
b	$(CH_2)_4$	CH_3

(10 mL) and the appropriate dibromides (5 mmol) was 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 was poured onto crushed ice. The crude precipitates of bis(acetylphenoxy)alkanes **3a-c** and **4a-c** were recrystallized from ethanol [53,60].

Synthesis of bis(α-bromo ketones) 5a-c and 6b,c. To a stirred solution of bis(acetophenone) derivatives **3a-c** or **4b,c** (l0 mmol) and *p*-TsOH (5.6 g, 20 mmol) in acetonitrile (50 mL) was slowly added NBS (3.6 g, 20 mmol). After addition of NBS was complete, the reaction mixture was refluxed 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 to afford the corresponding bis(α-bromo ketone) derivatives **5a-c** and **6b,c**, respectively.

1,2-bis(2-bromoacetylphenoxy)ethane 5a. Yield (68%), mp 105°C; IR: (potassium bromide) 1675 (C=O) cm^{-1}; ^1H NMR: δ 4.55 (s, 4H), 4.74 (s, 4H), 7.07 (t, 2H, *J* = 9 Hz), 7.27 (d, 2H, *J* = 9 Hz), 7.59 (t, 2H, *J* = 9 Hz), 7.70 (d, 2H, *J* = 9 Hz); ^{13}C NMR: δ 25.14, 29.47, 89.42, 113.49, 121.14, 123.43, 129.9, 136.70, 187.87; ms: *m/z* (%) 458 (M^++4, 1.3), 456 (M^++2, 2.6), 454 (M^+, 1.35), 361 (44), 241(45), 147 (45), 121 (69), 92 (100). *Anal*. Calcd. for $C_{18}H_{16}Br_2O_4$: C, 47.40; H, 3.54. Found: C, 47.38; H, 3.56.

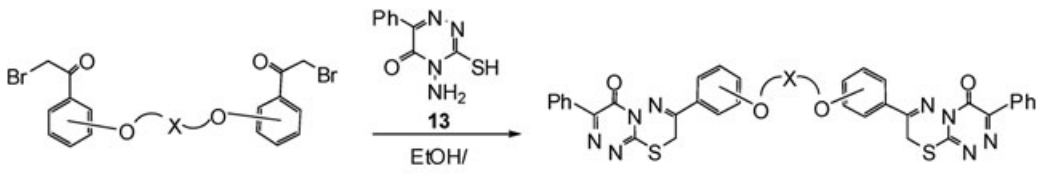
1,2-bis(2-bromoacetylphenoxy)propane 5b. Yield 83%, mp 88–89 °C; IR: (potassium bromide) 1675 (C=O) cm^{-1}; ^1H NMR: δ 2.28–2.39 (m, 2H), 4.3 (t, 4H), 4.78 (s, 4H), 7.06 (t, 2H, *J* = 9 Hz), 7.22 (d, 2H, *J* = 9 Hz), 7.58 (t, 2H, *J* = 9 Hz), 7.69 (d, 2H, *J* = 9 Hz); ^{13}C NMR: δ 28.10, 28.31, 65.52, 89.5, 113.20, 126.18, 128.98, 129.9, 133.51, 191.69; ms: *m/z* (%) 472 (M^++4, 0.43), 470 (M^++2, 0.82), 468 (M^+, 0.52), 377 (25), 255 (26), 175 (70), 121 (100). *Anal.* Calcd. for $C_{19}H_{18}Br_2O_4$: C, 48.54; H, 3.86. Found: C, 48.57; H, 3.88.

1,2-bis(2-bromoacetylphenoxy)butane 5c. Yield 92%, mp. 145°C; IR: (potassium bromide) 1670 (C=O) cm^{-1}; ^1H NMR: δ 2.00–2.01 (m, 4H), 4.18 (brs, 4H), 4.75 (s, 4H), 7.05 (t, 2H, *J* = 9 Hz), 7.20 (d, 2H, *J* = 9 Hz), 7.55 (t, 2H, *J* = 9 Hz), 7.68 (d, 2H, *J* = 9 Hz); ms: *m/z* (%) 486 (M^++4, 0.01), 484 (M^++2, 0.05), 482 (M^+, 0.02), 325 (0.74), 215 (0.04), 137 (16), 121(59), 55 (100). *Anal*. Calcd. for $C_{20}H_{20}Br_2O_4$: C, 49.61; H, 4.16. Found: C, 49.60; H, 4.18.

1,2-bis(4-bromoacetylphenoxy)propane 6b. Yield 85%, mp. 165°C; IR: (potassium bromide) 1674 (C=O) cm^{-1}; ^1H NMR: δ 2.22 (brs, 2H), 4.21 (brs, 4H), 4.71(s, 4H), 7.07 (d, 4H, *J* = 9 Hz), 7.95 (d, 4H, *J* = 9 Hz); ms: *m/z* (%) 472 (M^++4, 1.04), 470 (M^++2, 1.4), 468 (M^+, 0.52), 430 (0.7), 375 (12), 297 (30), 241 (9), 149 (35), 121 (100). *Anal*. Calcd. for $C_{19}H_{18}Br_2O_4$: C, 48.54; H, 3.86. Found: C, 48.55; H, 3.85.

1,2-bis(2-bromoacetylphenoxy)butane 6c. Yield 95%, mp. 158°C; IR: (potassium bromide) 1671 (C=O) cm^{-1}; ^1H NMR: δ 2.01–2.09 (m, 4H), 4.18 (brs, 4H), 4.71 (s, 4H), 7.06 (d, 4H, *J* = 9 Hz), 7.93 (d, 4H, *J* = 9 Hz); ^{13}C NMR: δ 25.53, 30.95, 67.57, 114.32, 114.48, 126.63, 129.9, 189.67; ms: *m/z* (%) 486 (M^++4, 0.16), 484 (M^++2, 0.97), 482 (M^+, 0.87), 352 (18), 323 (32), 271 (26), 207 (100), 121 (47). *Anal.* Calcd. for $C_{20}H_{20}Br_2O_4$: C, 49.61; H, 4.16. Found: C, 49.63; H, 4.17.

Scheme 6



14a-c (*o*-isomer)	X
a	$(CH_2)_2$
b	$(CH_2)_3$
c	$(CH_2)_4$
15 (*p*-isomer),	X = $(CH_2)_4$

Synthesis of bis(triazolothiadiazines) 10a-d and 11a-c and bis (triazinothiadiazines) 14a-c and 15. ***General procedure.*** A mixture of the appropriate bis(α-bromoacetophenone) **5a-c** or **6b,c** (5 mmol), and the corresponding aminotriazolthiol or aminotriazinethiol derivative **9a,b** or **13** (10 mmol) in absolute ethanol was heated at refluxing temperature for 2 h. The reaction mixture was then cooled and the resulting precipitate was collected by filtration, washed thoroughly with ethanol and dried. Recrystallization from dioxane/DMF afforded the corresponding bis(fused heterocycle) derivatives **10a-d**, **11a-d**, **14a-c**, and **15** in 54–95% yield.

1,2-Bis{2-(3-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)phenoxy}ethane 10a. Yield 78%, mp. 250°C; IR: (potassium bromide) 1608 (C=N) cm^{-1}; ^1H NMR: δ 4.18 (s, 4H), 4.53 (s, 4H), 7.06 (t, 2H, *J* = 9 Hz), 7.28 (d, 2H, *J* = 9 Hz), 7.48–7.59 (m, 8H), 7.94–7.98 (m, 6H); ms: *m/z* (%) 642 (M^+, 5), 403 (16.4), 309 (6.8), 217 (5.4), 177 (100), 76 (75.5). *Anal*. Calcd. for $C_{34}H_{26}N_8O_2S_2$: C, 63.53; H, 4.08; N, 17.43. Found: C, 63.50; H, 4.11; N, 17.48.

1,2-Bis{2-(3-methyl-7 H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)phenoxy}ethane 10b. Yield 58%, mp. 243°C; IR: (potassium bromide) 1608 (C=N) cm^{-1}; ^1H NMR: δ 2.49 (s, 6H), 4.18 (s, 4H), 4.53 (s, 4H), 7.09 (t, 2H, *J* = 9 Hz), 7.27 (d, 2H, *J* = 9 Hz), 7.53 (t, 2H, *J* = 9 Hz), 7.94 (d, 2H, *J* = 9 Hz); ms: *m/z* (%) 518 (M^+, 13), 484 (11.4), 304 (8.8), 213 (7.4), 76 (75.5). *Anal*. Calcd. for $C_{24}H_{22}N_8O_2S_2$: C, 55.58; H, 4.28; N, 21.61. Found: C, 55.60; H, 4.26; N, 21.63.

1,3-Bis{2-(3-phenyl-7 H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)phenoxy}propane 10c. Yield 73%, mp. 265°C; IR: (potassium bromide) 1600 (C=N) cm^{-1}; ^1H NMR: δ 2.27–2.31 (m, 2H), 4.24 (t, 4H), 4.32 (s, 4H), 7.01 (t, 2H, *J* = 9 Hz), 7.20 (d, 2H, *J* = 9 Hz), 7.48–7.54 (m, 8H), 7.94–7.97 (m, 6H); ms: *m/z* (%) 656 (M^+, 2), 484 (27.0), 369 (1.6), 308 (4.3), 261 (12.1), 177 (100), 104 (63.9). *Anal*. Calcd. for $C_{35}H_{28}N_8O_2S_2$: C, 64.01; H, 4.30; N, 17.06. Found: C, 63.98; H, 4.33; N, 17.07.

1,4-Bis{2-(3-phenyl-7 H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)phenoxy}butane 10d. Yield 83%, mp. 260°C; IR: (potassium bromide) 1605 (C=N) cm^{-1}; ^1H NMR: δ 1.92–1.98 (m, 4H), 4.16–4.23 (m, 4H), 4.22 (s, 4H), 7.03 (t, 2H, *J* = 9 Hz), 7.16 (d, 2H, *J* = 9 Hz), 7.48–7.64 (m, 8H), 7.93–7.95 (m, 6H); ms: *m/z* (%) 670 (M^+, 19), 646 (100), 309 (3.0), 177 (100), 118 (51.0), 76 (52.0). *Anal*. Calcd. for $C_{36}H_{30}N_8O_2S_2$: C, 64.46; H, 4.51; N, 16.70. Found: C, 64.45; H, 4.53; N, 16.72.

1,3-Bis{4-(3-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)phenoxy}propane 11a. Yield 70%, mp. 248°C; IR: (potassium bromide) 1602 (C=N) cm^{-1}; ^1H NMR: δ 2.22 (brs, 2H), 4.23(brs, 4H), 4.38(s, 4H), 7.11(d, 4H, *J* = 9 Hz), 7.53–7.55(m, 6H), 7.94–8.01(m, 8H); ^{13}C NMR: δ 22.58, 28.36, 64.63, 115.04, 125.51, 126.00, 127.83, 128.68, 129.44, 144.00, 150.10 151.41, 155.46, 161.48; ms: *m/z* (%) 656 (M^+, 5), 630 (15.4), 369 (6.8), 177 (5.4), 104 (12.1). *Anal*. Calcd. for $C_{35}H_{28}N_8O_2S_2$: C, 64.01; H, 4.30; N, 17.06. Found: C, 64.03; H, 4.31; N, 17.05.

1,4-Bis{4-(3-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)phenoxy}butane 11b. Yield 92%, mp. 240°C; IR: (potassium bromide) 1608 (C=N) cm^{-1}; ^1H NMR: δ 1.92 (brs, 4H), 4.16 (brs, 4H), 4.41 (s, 4H), 7.12 (d, 4H, *J* = 9 Hz), 7.54–7.59 (m, 6H), 7.96–8.03 (m, 8H); ms: *m/z* (%) 670 (M^+, 23), 464 (30.6), 357 (100), 276 (19.4), 139 (44.4), 80 (97.2). *Anal*. Calcd. for $C_{36}H_{30}N_8O_2S_2$: C, 64.46; H, 4.51; N, 16.70. Found: C, 64.44; H, 4.52; N, 16.71.

1,4-bis{4-(3-methyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)phenoxy}butane 11c. Yield 95%, mp. 280°C; IR: (potassium bromide) 1609 (C=N) cm^{-1}; ^1H NMR: δ 1.92 (brs, 4H), 2.56 (s, 6H),4.17 (brs, 4H), 4.41(s, 4H), 7.12 (d, 4H, *J* = 9 Hz), 8.02 (d, 4H, *J* = 9 Hz); ms: *m/z* (%) 546 (M^+, 20), 276 (19.4), 121 (44.4), 55 (85.2). *Anal*. Calcd. for $C_{26}H_{26}N_8O_2S_2$: C, 57.12; H, 4.79; N, 20.50. Found: C, 57.13; H, 4.81; N, 20.48.

1,2-Bis{2-(3-phenyl-[1,2,4]triazino[3,4-b][1,3,4]thiadiazin-4 (8H)-on-7-yl)phenoxy}ethane 14a. Yield 63%, mp. 220°C; IR: (potassium bromide) 1650 (C=O), 1602 (C=N) cm^{-1}; ^1H NMR: δ 4.17 (s, 4H), 4.57 (s, 4H), 7.10 (t, 2H, *J* = 9 Hz), 7.30 (d, 2H, *J* = 9 Hz), 7.46–7.61 (m, 8H), 8.03–8.05 (m, 6H); ms: *m/z* (%) 698 (M^+, 5), 582 (3.5), 304 (66.3), 201 (30.2), 157 (12.8), 103 (100). *Anal*. Calcd. for $C_{36}H_{26}N_8O_4S_2$: C, 61.88; H, 3.75; N, 16.04. Found: C, 61.89; H, 3.74; N, 16.06.

1,3-Bis{2-(3-phenyl-[1,2,4]triazino[3,4-b][1,3,4]thiadiazin-4 (8H)-on-7-yl)phenoxy}-propane 14b. Yield 68%, mp. 200°C; IR: (potassium bromide) 1642 (C=O), 1602 (C=N) cm^{-1}; ^1H NMR: δ 2.22 (brs, 2H), 4.24 (brs, 4H), 4.40 (s, 4H), 7.12–7.16 (m, 4H), 7.55–7.57 (m, 8H), 7.96–8.02 (m, 6H); ms: *m/z* (%) 712 (M^+, 13), 393 (15.8), 276 (16.8), 205 (65.4), 127 (12.1), 103 (100), 76 (75.5). *Anal*. Calcd. for $C_{37}H_{28}N_8O_4S_2$: C, 62.35; H, 3.96; N, 15.72. Found: C, 62.33; H, 3.97; N, 15.75%.

1,4-Bis{2-(3-phenyl-[1,2,4]triazino[3,4-b][1,3,4]thiadiazin-4 (8H)-on-7-yl)phenoxy}butane 14c. Yield 70%, mp. 165°C; IR: (potassium bromide) 1645 (C=O) cm^{-1}, 1602 (C=N); ^1H NMR: δ 1.95 (brs, 4H), 4.20 (brs, 4H), 4.24 (s, 4H), 7.07 (t, 2H, *J* = 9 Hz), 7.23 (d, 2H, *J* = 9 Hz), 7.50–7.56 (m, 8H), 8.07–8.10 (m, 6H); ms: *m/z* (%) 726 (M^+, 5), 403 (15.4), 307 (6.8), 220 (5.4), 192 (12.1), 161 (25.8), 121 (19.3), 104 (100), 77 (75.5). *Anal*. Calcd. for $C_{38}H_{30}N_8O_4S_2$: C, 62.79; H, 4.16; N, 15.42. Found: C, 62.78; H, 4.17; N, 15.43%.

1,4-Bis{4-(3-phenyl-[1,2,4]triazino[3,4-b][1,3,4]thiadiazin-4 (8H)-on-7-yl)phenoxy}butane 15. Yield 72%, mp. 207°C; IR: (potassium bromide) 1642 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR: δ 1.93 (brs, 4H), 4.18 (brs, 4H), 4.35 (s, 4H), 7.13 (d, 4H, *J* = 9 Hz), 7.47–7.52 (m, 6H), 8.03–8.06 (d, 4H, *J* = 9 Hz), 8.08–8.11 (m, 4H); ms: *m/z* (%) 726 (M^+, 9), 393 (15.4), 276 (6.8), 205(35.4), 127(62.1), 103(100), 76(75.5). *Anal*. Calcd. for $C_{38}H_{30}N_8O_4S_2$: C, 62.79; H, 4.16; N, 15.42. Found: C, 62.81; H, 4.15; N, 15.44%.

Reduction of bis(triazolothiadiazine) derivatives 11b,c. ***General procedure.*** To a stirred hot (40–50 °C) solution of each of **11a** and **11c** (0.7 mmol) in methanol (10 mL) was added sodium borohydride (0.4 g) over a period of 15 min. The reaction mixture was heated under reflux for 1 h. The solvent was then removed *in vacuo* and the remaining solid was collected, washed with water and crystallized from ethanol to give colorless crystals of **12a** and **12b**

1,4-Bis{4-(3-phenyl-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)-phenoxy}butane 12a. Yield 42%, mp. 174°C; IR: (potassium bromide) 3357 (NH), 1608 (C=N) cm^{-1}; ^1H NMR: δ 1.8 (brs, 4H), 3.42 (dd, 2H, ^{3} *J* = 3.0 Hz, ^{2} *J* = 12.6 Hz, H_e-7), 3.51 (dd, 2H, ^{3} *J* = 8.7 Hz, ^{2} *J* = 12.6 Hz, H_a-7), 4.0 (brs, 4H), 4.51–4.58(m, 2 H, 6-H), 6.92 (d, 2H, *J* = 8.7 Hz, NH), 7.14–7.99 (m, 18 H, ArHs) ppm; ms: *m/z* (%) 674 (M^+, 20), 468 (55.6), 357 (100), 276 (18.4), 139 (48.4), 80 (87.2). *Anal*. Calcd. for $C_{36}H_{34}N_8O_2S_2$: C, 64.07; H, 5.08; N, 16.60. Found: C, 64.11; H, 5.05; N, 16.63%.

1,4-Bis{4-(3-methyl-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-6-yl)phenoxy}butane 12b. Yield 46%, mp. 202°C; IR: (potassium bromide) 3429 (NH), 1608 (C=N) cm^{-1}; ^1H NMR: δ 1.8 (brs, 4H), 2.26 (s, 6H, CH_3), 3.35 (dd, 2H, ^3J = 2.7 Hz, ^2J = 12.6 Hz, H_e-7), 3.44 (dd, 2H, ^3J = 8.7 Hz, ^2J = 12.6 Hz, H_a-7), 4.04 (brs, 4H), 4.45–4.50 (m, 2H, 6-H), 6.73 (d, 2H, J = 9.3 Hz, NH), 6.94, 7.35 (2 d, 8H, ArHs) ppm; ms: *m/z* (%) 550 (M^+, 10), 280 (22.4), 121 (49.4), 55 (87.2). *Anal*. Calcd. for $C_{26}H_{30}N_8O_2S_2$: C, 56.71; H, 5.49; N, 20.35. Found: C, 56.74; H, 5.51; N, 20.30%.

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