ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 1, pp. 129–136. © Pleiades Publishing, Ltd., 2020.

Synthesis and Antimicrobial Study of New Fused Thiazolo[3,2-*b*]triazine, Triazolo[4,3-*b*]triazine, and 1,2,4-Triazinone Derivatives

M. F. El-Shehry[a, b], F. A. A. El-Hag[c], and E. F. Ewies[d,*]

[a] *Pesticide Chemistry Department, National Research Centre, Dokki, Giza, 12622 Egypt*

[b] *Pharmacy Department, Al-Zahrawi University College, Karbala, 56001 Iraq*

[c] *Department of Chemistry of Natural and Microbial Products, National Research Centre, Dokki, Giza, 12622 Egypt*

[d] *Organometallic and Organometalloid Chemistry Department, National Research Centre, Dokki, Giza, 12622 Egypt*

**e-mail: ewiesfawzy@yahoo.com; ef.ewies@nrc.sci.eg*

Received July 9, 2019; revised November 10, 2019; accepted November 22, 2019

Abstract—6-[2-(Furan-2-yl)ethyl]-3-sulfanylidene-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**1**) reacted with chloroacetone to give *S*-acetonyl derivative which cyclized in ethanol under reflux to afford 6-[2-(furan-2-yl)-ethyl]-3-methyl-7*H*-[1,3]thiazolo[3,2-*b*][1,2,4]triazin-7-one. 2,4-Bis(furan-2-carbonyl)-6-[2-(furan-2-yl)-ethyl]-3-sulfanylidene-3,4-dihydro-1,2,4-triazin-5(2*H*)-one and 3-amino-6-[2-(furan-2-yl)ethyl]-2-{[6-(2-(furan-2-yl)ethyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl]sulfanyl}-3-methyl-7*H*-[1,3]thiazolo[3,2-*b*][1,2,4]-triazin-7-one were prepared by reaction of **1** with furoyl chloride and dibromoacetonitrile, respectively. Compound **1** also reacted with formaldehyde and with formaldehyde and benzylamine to give 2-hydroxymethyl and 2-(benzylaminomethyl) derivatives. The alkylation of **1** with methyl iodide, followed by treatment with hydrazine hydrate, afforded 6-[2-(furan-2-yl)ethyl]-2-hydrazinyl-1,2,4-triazin-5(2*H*)-one. Reactions of the latter with aromatic aldehydes and formic acid furnished 3-aryl- and 3-unsubstituted 6-[2-(furan-2-yl)ethyl][1,2,4]tri-azolo[4,3-*b*][1,2,4]triazin-7(1*H*)-ones, respectively, and triacetyl and tetrabromophthalazinyl derivatives were obtained by reacting hydrazinyltriazinone with acetic anhydride and tetrabromophthalic anhydride. The newly synthesized compounds were evaluated for their antimicrobial activity against some bacterial and fungal strains.

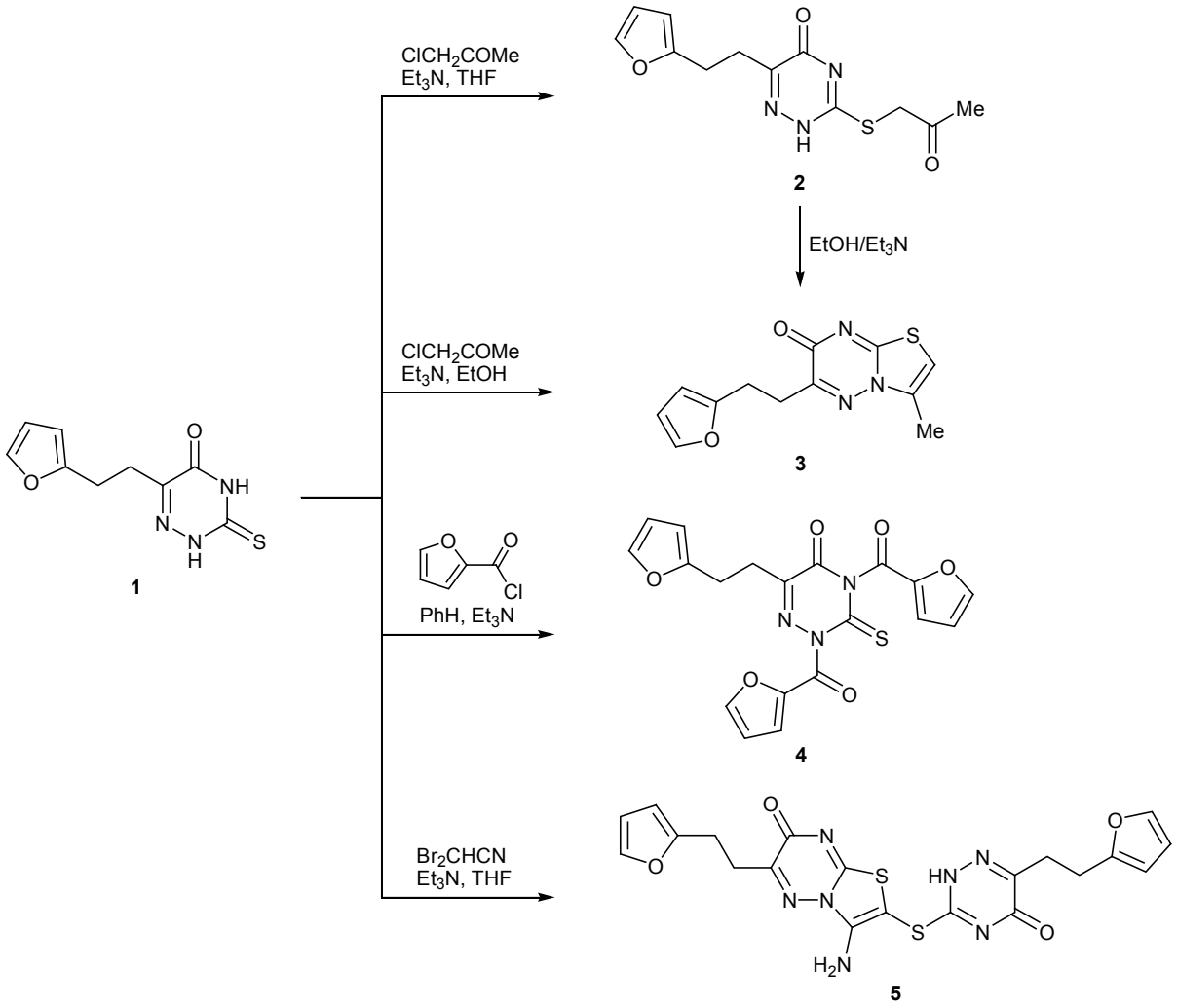
Keywords: 6-(2-furylvinyl)-3-thioxo-1,2,4-triazinones, thiazolo[3,2-*b*]triazinones, hydrazinotriazinone, triazolo[4,3-*b*]triazinones, antimicrobial activity.

DOI: 10.1134/S1070428020010200

Many recent publications showed that uncondensed and condensed heterocyclic systems bearing the 1,2,4-triazine moiety had different biological activities [1], e.g., anti-HIV [2, 3], anticancer [3], biocidal [4], antimicrobial [5–7], analgesic, and anti-inflammatory [8, 9]. Taking into account the broad spectrum of biological activities, the present study continues our previous work [10–16] in the field of synthesis of various non-fused and fused heterocyclic compounds having reactive functional groups and their biological activity. Herein we report the synthesis of some heterocycles incorporating triazine moiety in order to discover compounds with better biological activity.

The starting material was 6-[2-(furan-2-yl)ethyl]-3-sulfanylidene-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**1**) which was prepared according to [17]. Compound **1** smoothly reacted with an equimolar amount of choloroacetone in tetrahydrofuran (THF) containing a few drops of triethylamine to give *S*-acetonyl derivative **2**. When the reaction of **1** with chloroacetone was carried out in anhydrous ethanol in presence of triethylamine, thiazolotriazinone derivative **3** was obtained in one step reaction without intermediate isolation of **2**. Compound **3** was also synthesized by refluxing **2** with triethylamine in anhydrous ethanol (Scheme 1). The reaction of **1** with 2 equiv of furoyl chloride in anhydrous benzene gave the corresponding 2,4-difuroyl derivative **4**. In the reaction of **1** with an equimolar amount of dibromoacetonitrile in THF in the presence of triethylamine we isolated 3-aminothiazolotriazin-7-

Scheme 1.



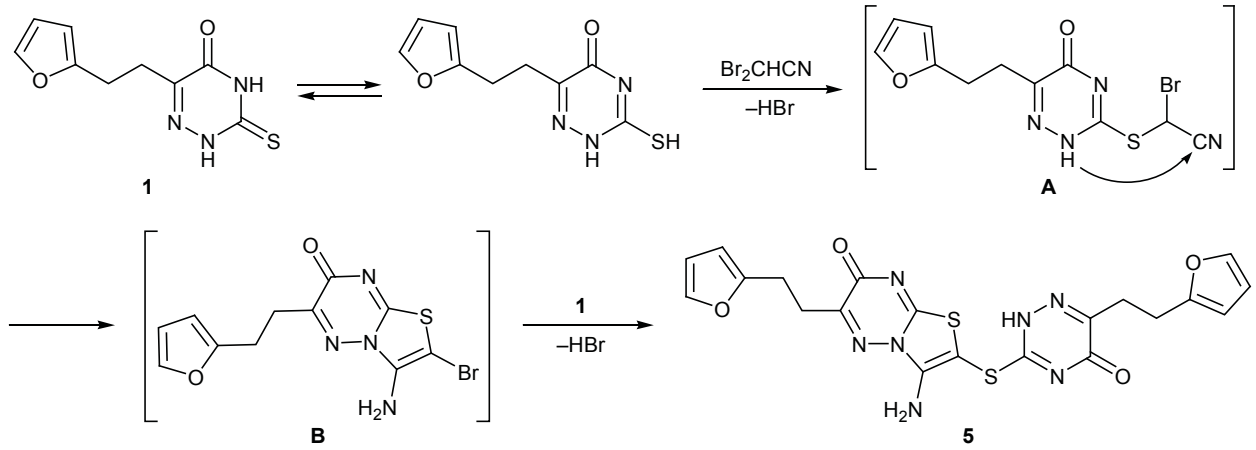
one **5**. The analytical and spectral data were in a good agreement with the assigned structures **2**–**5** (see Experimental).

The mechanism of formation of 3-aminothiazolotriazin-7-one **5** is depicted in Scheme 2. The alkylation of the thiol tautomer of **1** with dibromoacetonitrile gives intermediate **A** with elimination of hydrogen bromide due to basic medium. Intermediate **A** undergoes cyclization via nucleophilic attack of the nitrogen lone pair on the cyano carbon atom to produce intermediate 3-amino-2-bromothiazolotriazinone **B**, which is alkylated with the second molecule of **1**, yielding final product **5**.

In an attempt to prepare polyfunctionalized heterocycles, the reaction of **1** with formaldehyde was conducted under different conditions. When compound **1** was treated with formaldehyde in glacial acetic acid, the product was hydroxymethyltriazinone **6**, whereas the Mannich reaction of **1** with equimolar amounts of benzylamine and formaldehyde in methanol afforded benzylaminomethyl derivative **7**. In addition, compound **1** was reacted with an equimolar amount of methyl iodide in 10% ethanolic potassium hydroxide; 3-(methylsulfanyl)triazinone **8** was thus obtained in good yield. When compound **8** was treated with hydrazine hydrate in boiling ethanol in the presence of triethylamine, 3-hydrazinyltriazinone **9** was formed (Scheme 3).

The reaction of **9** with aromatic aldehydes in absolute ethanol in the presence of piperidine as a catalyst yielded the corresponding 3-aryltriazolotriazinones **10a** and **10b**. 3-Unsubstituted analog **11** was obtained in good yield by heating compound **9** in boiling formic acid. Furthermore, treatment of **9** with acetic anhydride under reflux afforded triacetyl derivative **12**. Compound **9** also reacted with tetrabromophthalic anhy-

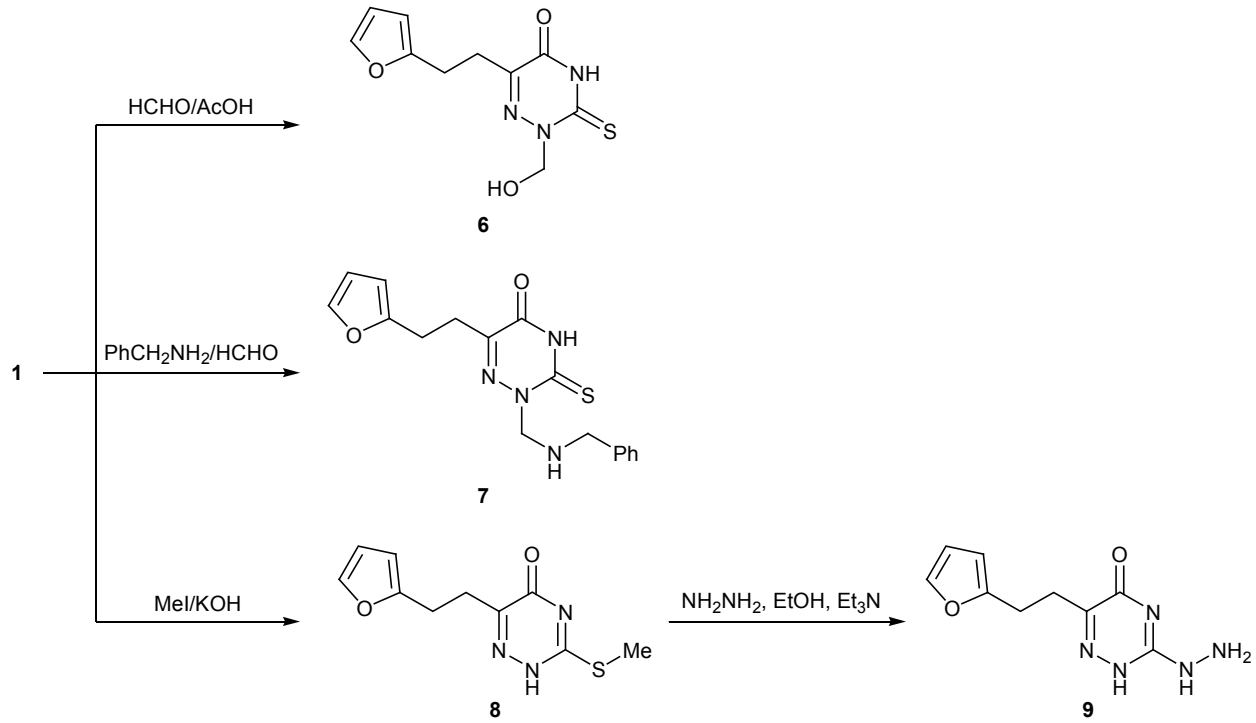
Scheme 2.



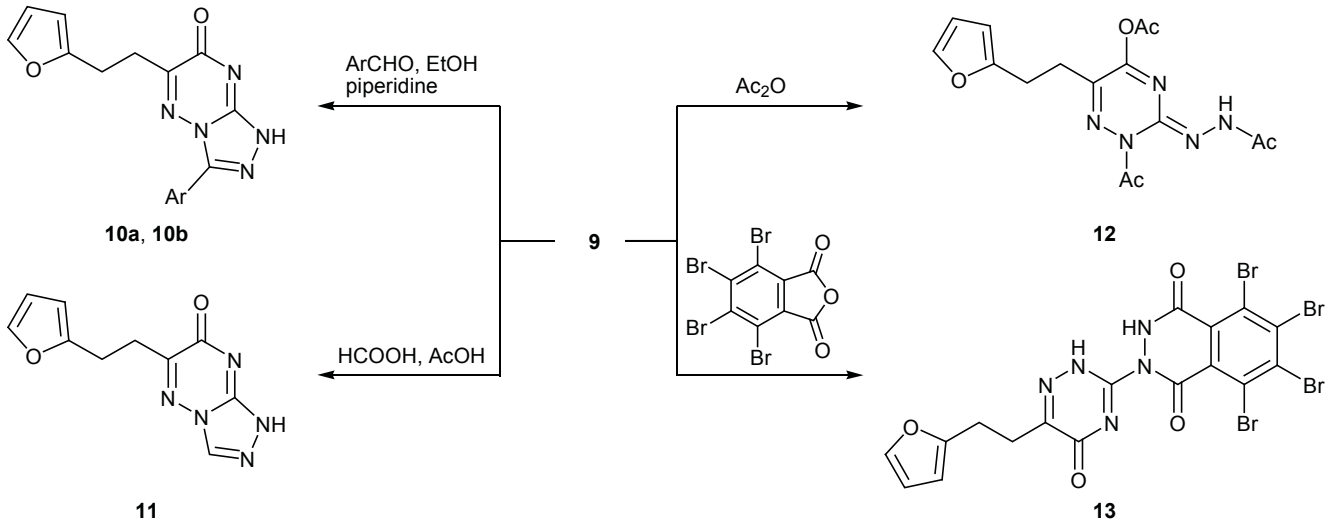
dride in glacial acetic acid to produce triazinyl-substituted tetrabromophthalazinedione **13** (Scheme 4).

The newly synthesized compounds were screened to determine their *in vitro* antimicrobial activity against three pathogenic gram-positive bacteria, two pathogenic gram-negative bacteria, and one fungal culture (*Candida albicans*) in comparison to penicillin (antibacterial drug) and nizo-arm (antifungal drug) as reference drugs. The results are presented in Table 1. Most of the tested triazine derivatives **1**–**13** showed moderate to significant antimicrobial activity as compared to the reference drugs. Thiazolotriazinone **3**, 3-aminothiazolotriazin-7-one **5**, dihydrotriazolotriazinones **10a** and **10b**, and triazinyltetrabromophthalazinedione **13** exhibited significant antibacterial and antifungal activity, while methylsulfanyltriazinone **8** and triacetyl derivative **12** displayed antifungal activity. The other derivatives exhibited moderate antibacterial and antifungal activity with the inhibition zone diameters ranging from 8 to 30 mm/mg versus 15, 25, 32, 40 mm/mg for penicillin and 35 and 45 mm/mg for nizo-arm. Hydrazine derivative **9** and 2,4-bis-furoyl derivative **4** showed a weak antimicrobial activity or were completely inactive. Further modification and

Scheme 3.



Scheme 4.



10, Ar = 2-$O_2NC_6H_4$ (**a**), 4-$O_2NC_6H_4$ (**b**).

optimization are needed to get new candidates of more significant antimicrobial activity against various types of bacteria and fungi.

EXPERIMENTAL

All chemicals were supplied by either Fluka or Aldrich and were used without further purification. All melting points were measured in open capillary tubes using an Electrothermal 9100 apparatus and are uncorrected. Elemental microanalyses were carried out using a Vario Elementar analyzer at the Microanalytical Unit, Central Services Laboratory, National Research Centre (Dokki, Giza, Egypt) and were found within ± 0.4% of the theoretical values. The FT-IR spectra were recorded with a Perkin Elmer Frontier spectrometer. The ^1H and ^{13}C NMR spectra (300 and 75 MHz, respectively) were recorded at room temperature on a Bruker Avance TM 300 spectrometer as solutions in DMSO-d_6; the chemical shifts were measured relative to the residual proton (δ 2.50 ppm) and carbon signals (δ_C 39.51 ppm) of the solvent. The mass spectra were

Table 1. Antimicrobial activities (inhibition zone diameter, mm/mg) of compounds **1**–**13** against Gram-positive and Gram-negative bacteria and fungi

Compound no.	*B. cereus*	*S. aureus*	*S. typhimurium*	*E. coli*	*P. aeruginosa*	*C. albicans*
1	10	12	30	10	15	15
2	20	15	20	10	25	20
3	21	30	35	12	15	20
4	5	5	10	10	12	15
5	20	30	30	12	30	20
6	12	20	20	15	35	25
7	15	10	25	10	25	15
8	20	25	30	12	40	25
9	0	0	10	10	12	15
10a	20	30	40	15	35	20
10b	10	25	35	15	40	25
11	15	20	10	10	30	20
12	20	25	30	8	45	35
13	23	32	45	12	25	30
Penicillin	25	32	40	15	–	–
Nizo-arm	–	–	–	–	45	35

measured with a GC Finnigan MAT SSQ-7000 mass spectrometer. The progress of reactions and the purity of the isolated compounds were monitored by TLC on silica gel-precoated aluminum sheets (Type 60, F 254, Merck, Darmstadt, Germany); spots were visualized by exposure to a UV lamp at λ 254 nm for a few seconds. The reported yields are based upon pure materials isolated by column chromatography. The solvents used were dried and purified according to conventional procedures.

6-[2-(Furan-2-yl)ethyl]-3-sulfanylidene-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (1). 2-Furaldehyde was condensed in 3 N sodium hydroxide with pyruvic acid to obtain 2-furfurylidenepyruvic acid, mp 109–112°C, which was converted to the corresponding thiosemicarbazone, mp 168–171°C, and the latter was subjected to cyclization by refluxing in 5% sodium carbonate to give compound **1**, mp 267–269°C. The analytical and spectral data were in agreement with those reported in [17].

6-[2-(Furan-2-yl)ethyl]-3-[(2-oxopropyl)sulfanyl]-1,2,4-triazin-5(2*H*)-one (2). A mixture of compound **1** (0.01 mol, 2.21 g) and chloroacetone (0.01 mol, 0.92 mL) in anhydrous tetrahydrofuran (20 mL) containing triethylamine (1 mL) as a catalyst was stirred for 4 h. The solvent was evaporated under reduced pressure, and the residue was triturated with cold water, followed by acidification with dilute hydrochloric acid. The precipitate was filtered off and crystallized from methanol. Yield 1.94 g (70%), mp 202–204°C. IR spectrum (KBr), ν, cm^{-1}: 3220 (NH), 1685, 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.79 s (3H, $COCH_3$), 2.81 t and 2.96 t (2H each, CH_2), 3.75 s (2H, CH_2), 6.42–7.61 m (3H, H_{Fu}), 7.46 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.3 and 25.6 (CH_2), 27.1 (CH_3), 39.5 (CH_2), 107.1, 112.0, 138.4, 141.2, 156.3 (C_{arom}), 156.9 (C^5=O), 202.1 (Me**C**=O). Mass spectrum: *m*/*z* 279 (I_{rel} 69%) $[M]^+$. Found, %: C 51.55; H 4.73; N 15.01. $C_{12}H_{13}N_3O_3S$. Calculated, %: C 51.60; H 4.69; N 15.04; S 11.48. *M* 279.07.

6-[2-(Furan-2-yl)ethyl]-3-methyl-7*H*-[1,3]thiazolo[3,2-*b*][1,2,4]triazin-7-one (3). A mixture of **1** (0.01 mol, 2.21 g) and chloroacetone (0.01 mol, 0.92 mL) in anhydrous ethanol (30 mL) containing a few drops of triethylamine was refluxed for 2 h. The mixture was cooled and acidified with dilute hydrochloric acid, and the solid product was collected by filtration and crystallized from ethanol. Yield 1.95 g (75%), mp 208–210°C. IR spectrum (KBr): ν 1675 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 2.85 t and 2.97 t (2H each, CH_2), 6.04–7.15 m (4H, 2-H, H_{Fu}). ^{13}C NMR spectrum, δ_C, ppm: 11.1 (CH_3), 23.1 and 25.2 (CH_2), 102.1, 106.9, 112.2, 134.4, 141.2, 146.2, 156.2 (C_{arom}), 157.9 (C=O). Mass spectrum: *m*/*z* 261 (I_{rel} 25%) $[M]^+$. Found, %: C 55.20; H 4.20; N 16.11. $C_{12}H_{11}N_3O_2S$. Calculated, %: C 55.16; H 4.24; N 16.08; S 12.27. *M* 261.06.

2,4-Bis(furan-2-carbonyl)-6-[2-(furan-2-yl)-ethyl]-3-sulfanylidene-3,4-dihydro-1,2,4-triazine-5(2*H*)-one (4). A mixture of **1** (0.01 mol, 2.21 g) and furoyl chloride (0.02 mol, 2.60 mL) in THF (20 mL) containing triethylamine (1 mL) was refluxed for 1 h. The mixture was evaporated under reduced pressure, the residue was triturated with cold water and acidified with dilute aqueous HCl, and the solid was filtered off and crystallized from methanol. Yield 1.84 g (45%), mp 251–253°C. IR spectrum (KBr), ν, cm^{-1}: 1700, 1675, 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.75 t and 2.92 t (2H each, CH_2), 6.02–8.06 m (9H, H_{Fu}). ^{13}C NMR spectrum, δ_C, ppm: 24.1 and 25.5 (CH_2), 106.1, 111.9, 112.2, 117.2, 118.3, 138.4, 140.5, 141.2, 144.9, 146.2, 156.2, 156.3 (C_{arom}), 156.5 157.9 (Fu**C**=O), 162.3 (C^5=O), 170.3 (C=S). MS (*m*/*z*): Mass spectrum: *m*/*z* 411 (I_{rel} 25%) $[M]^+$. Found, %: C 55.50; H 3.15; N 10.26. $C_{19}H_{13}N_3O_6S$. Calculated, %: C 55.47; H 3.19; N 10.21; S 7.79. *M* 411.05.

3-Amino-6-[2-(furan-2-yl)ethyl]-2-({6-[2-(furan-2-yl)ethyl]-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl}-sulfanyl)-7*H*-[1,3]thiazolo[3,2-*b*][1,2,4]triazin-7-one (5). A solution of dibromoacetonitrile (0.01 mol, 2.0 mL) in THF (5 mL) was added dropwise over a period of 30 min to a stirred solution of **1** (0.02 mol, 4.42 g) in THF (15 mL) containing triethylamine (1 mL) at 80°C, and the mixture was stirred for further 3 h. The mixture was evaporated under reduced pressure, the residue was acidified with dilute aqueous HCl, and the solid product was collected by filtration and crystallized from methanol. Yield 4.31 g (90%), mp > 300°C. IR spectrum (KBr), ν, cm^{-1}: 3320, 3200 (NH, NH_2), 1690, 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.67 t, 2.79 t, 3.02 t, and 3.30 t (2H each, CH_2), 3.40 br.s (2H, NH_2), 6.07–7.31 m (6H, H_{Fu}), 13.61 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.1, 23.6, 24.1, 25.5 (CH_2); 107.2, 112.1, 112.3, 133.1, 138.4, 141.5, 142.2, 144.9, 146.2, 156.2, 156.3 (C_{arom}); 157.5, 158.9 (C=O), 166.3 (C–S). Mass spectrum: *m*/*z* 481 (I_{rel} 30%) $[M - 2]^+$. Found, %: C 49.63; H 3.50; N 20.32. $C_{20}H_{17}N_7O_4S_2$. Calculated, %: C 49.68; H 3.54; N 20.28; S 13.26. *M* 483.08.

6-[2-(Furan-2-yl)ethyl]-2-(hydroxymethyl)-3-sulfanylidene-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (6). A mixture of compound **1** (0.01 mol, 2.21 g) and

37% aqueous formaldehyde solution (5 mL) in glacial acetic acid (30 mL) was refluxed for 4 h. The mixture was cooled and poured onto crushed ice under stirring, and the solid product was filtered off and crystallized from acetic acid. Yield 1.76 g (70%), mp > 300°C. IR spectrum (KBr), ν, cm^{-1}: 3250 (OH), 3200 (NH), 1700 (C=O). ^1H NMR spectrum, δ, ppm: 2.68 t and 3.01 t (2H each, CH_2), 5.27 s (2H, CH_2), 6.23–7.13 m (3H, H_{Fu}), 13.10 s (1H, NH), 13.51 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 23.6 and 25.5 (CH_2), 75.5 (CH_2OH), 107.5, 112.4, 141.2, 142.5 (C_{arom}), 156.5 (C=O), 176.3 (C=S). Mass spectrum: *m*/*z* 253 (I_{rel} 55%) $[M]^+$. Found, %: C 47.45; H 4.33; N 16.63. $C_{10}H_{11}N_3O_3S$. Calculated, %: C 47.42; H 4.38; N 16.59; S 12.66. *M* 253.05.

2-[(Benzylamino)methyl]-6-[2-(furan-2-yl)ethyl]-3-sulfanylidene-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (7). A mixture of compound **1** (0.01 mol, 2.21 g) and methanol (30 mL) was treated with 37% aqueous formaldehyde solution (0.01 mol, 0.3 mL), benzylamine (0.01 mol, 1.07 mL) and dilute aqueous HCl (25 mL). The mixture was refluxed for 3 h and left overnight, and the solid product was collected by filtration and crystallized from acetic acid. Yield 2.72 g (80%), mp 225–226°C. IR spectrum (KBr), ν, cm^{-1}: 3240, 3200 (NH), 1700 (C=O). ^1H NMR spectrum, δ, ppm: 2.70 t and 3.02 t (2H each, CH_2), 3.57 s (2H, C**H**$_2$Ph), 3.87 s (2H, CH_2), 4.60 s (1H, NH), 6.01–7.61 m (8H, H_{arom}, H_{Fu}), 13.50 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.1, 25.6, 51.1, 62.5 (CH_2); 107.5, 112.4, 126.1, 127.5, 128.6, 140.2, 141.5, 153.2, 156.2 (C_{arom}), 157.5 (C=O), 177.3 (C=S). Mass spectrum: *m*/*z* 342 (I_{rel} 50%) $[M]^+$. Found, %: C 59.60; H 5.25; N 16.39. $C_{17}H_{18}N_4O_2S$. Calculated, %: C 59.63; H 5.30; N 16.36; S 9.36. *M* 342.12.

6-[2-(Furan-2-yl)ethyl]-3-(methylsulfanyl)-1,2,4-triazin-5(2*H*)-one (8). Methyl iodide (3 mL) was added dropwise with stirring over a period of 2 h at room temperature to a solution of **1** (0.01 mol, 2.21 g) in 10% ethanolic potassium hydroxide. The solution was poured onto crushed ice and acidified with dilute aqueous HCl, and the solid product was filtered off and crystallized from ethanol. Yield 1.64 g (70%), mp 245–247°C. IR spectrum (KBr), ν, cm^{-1}: 3400 (NH), 1695 (C=O). ^1H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 2.60 t and 2.98 t (2H each, CH_2), 6.04–7.12 m (3H, H_{Fu}), 14.00 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.6 (CH_3), 22.5 and 25.5 (CH_2), 107.1, 112.2, 138.2, 141.5 (C_{arom}), 156.5 (C=O), 176.3 (C^3). Mass spectrum: *m*/*z* 237 (I_{rel} 45%) $[M]^+$. Found, %: C 50.65; H 4.64; N 17.75. $C_{10}H_{11}N_3O_2S$. Calculated, %: C 50.62; H 4.67; N 17.71; S 13.51. *M* 237.06.

6-[2-(Furan-2-yl)ethyl]-3-hydrazinyl-1,2,4-triazin-5(2*H*)-one (9). A mixture of **8** (0.01 mol, 2.35 g) and hydrazine hydrate (0.02 mol, 0.5 mL) in ethanol (20 mL) containing four drops of triethylamine was refluxed for 6 h. The solid product was filtered off from the hot mixture and crystallized from DMF. Yield 1.86 g (85%), mp 269–270°C. IR spectrum (KBr), ν, cm^{-1}: 3300–3240 (NH, NH_2), 1700 (C=O). ^1H NMR spectrum, δ, ppm: 2.60 t and 2.98 t (2H each, CH_2), 4.60 br.s (2H, NH_2), 6.02–6.95 m (3H, H_{Fu}), 8.65 s (1H, NH), 12.35 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.3 and 25.2 (CH_2), 107.1, 112.2, 140.2, 141.5, 152.1, 156.1 (C_{arom}), 162.5 (C=O). Mass spectrum: *m*/*z* 221 (I_{rel} 45%) $[M]^+$. Found, %: C 48.82; H 5.05; N 31.63. $C_9H_{11}N_5O_2$. Calculated, %: C 48.86; H 5.01; N 31.66. *M* 221.09.

Reaction of compound 9 with aromatic aldehydes (*general procedure*). A mixture of compound **9** (0.01 mol, 2.19 g) and 2-nitrobenzaldehyde or 4-nitrobenzaldehyde (0.01 mol) in anhydrous ethanol (25 mL) containing a few drops of piperidine was refluxed for 8 h. The mixture was evaporated by half under reduced pressure, and the precipitate was filtered off and crystallized from methanol (**10a**) or acetic acid (**10b**).

6-[2-(Furan-2-yl)ethyl]-3-(2-nitrophenyl)-[1,2,4]-triazolo[4,3-*b*][1,2,4]triazin-7(1*H*)-one (10a). Yield 2.81 g (80%), mp 269–270°C. IR spectrum (KBr), ν, cm^{-1}: 3320, 3300 (NH), 1685 (C=O). ^1H NMR spectrum, δ, ppm: 2.90 t and 3.22 t (2H each, CH_2), 3.38 s (1H, NH), 6.60–8.70 m (7H, C_6H_4, H_{Fu}). ^{13}C NMR spectrum, δ_C, ppm: 23.3 and 25.6 (CH_2), 107.1, 112.2, 123.4, 125.1, 126.2, 129.3, 133.1, 140.2, 141.5, 150.1, 151.1 (C_{arom}), 163.5 (C=O). Mass spectrum: *m*/*z* 352 (I_{rel} 35%) $[M]^+$. Found, %: C 54.58; H 3.40; N 23.80. $C_{16}H_{12}N_6O_4$. Calculated, %: C 54.55; H 3.43; N 23.85. *M* 352.09.

6-[2-(Furan-2-yl)ethyl]-3-(4-nitrophenyl)-[1,2,4]-triazolo[4,3-*b*][1,2,4]triazin-7(1*H*)-one (10b). Yield 2.46 g (70%), mp > 300°C. IR spectrum (KBr), ν, cm^{-1}: 3340, 3320 (NH), 1685 (C=O). ^1H NMR spectrum, δ, ppm: 2.91 t and 3.23 t (2H each, CH_2), 3.39 s (1H, NH), 6.50–8.60 m (7H, C_6H_4, H_{Fu}). Mass spectrum: *m*/*z* 352 (I_{rel} 40%) $[M]^+$. Found, %: C 54.59; H 3.40; N 23.80. $C_{16}H_{12}N_6O_4$. Calculated, %: C 54.55; H 3.43; N 23.85. *M* 352.09.

6-[2-(Furan-2-yl)ethyl][1,2,4]triazolo[4,3-*b*]-[1,2,4]triazin-7(1*H*)-one (11). A mixture of **9** (0.01 mol, 2.19 g), glacial acetic acid (20 mL), and formic acid (10 mL) was refluxed for 5 h. The mixture was cooled and poured onto crushed ice with stirring,

and the solid was filtered off, washed with cold water, dried, and crystallized from acetic acid. Yield 1.48 g (65%), mp 221–223°C. IR spectrum (KBr), ν, cm^{-1}: 3150 (NH), 1690 (C=O). ^1H NMR spectrum, δ, ppm: 2.90 t and 3.21 t (2H each, CH_2), 6.09–7.17 m (3H, H_{Fu}), 7.97 s (1H, 3-H), 13.79 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.3 and 24.9 (CH_2), 107.5, 112.6, 134.2, 141.2, 145.1, 156.2 (C_{arom}), 161.5 (C=O). Mass spectrum: *m*/*z* 231 (I_{rel} 15%) $[M]^+$. Found, %: C 51.99; H 3.89; N 30.32. $C_{10}H_9N_5O_2$. Calculated, %: C 51.95; H 3.92; N 30.29. *M* 231.08.

2-Acetyl-3-(2-acetylhydrazinylidene)-6-[2-(furan-2-yl)ethyl]-2,3-dihydro-1,2,4-triazin-5-yl acetate (12). A mixture of **9** (0.01 mol 2.19 g) and acetic anhydride (20 mL) was refluxed for 4 h. The mixture was then poured onto crushed ice, and the solid product was filtered off and crystallized from methanol. Yield 2.24 g (65%), mp 210–212°C. IR spectrum (KBr), ν, cm^{-1}: 3248 (NH), 1740, 1695, 1660 (C=O). ^1H NMR spectrum, δ, ppm: 2.30 t and 3.21 t (2H each, CH_2); 2.51 s, 3.50 s, and 3.73 s (3H, CH_3CO), 6.05–7.18 m (3H, H_{Fu}), 9.85 s (1H, NH). Mass spectrum: *m*/*z* 347 (I_{rel} 20%) $[M]^+$. Found, %: C 51.87; H 4.93; N 20.16. $C_{15}H_{17}N_5O_5$. Calculated, %: C 51.87; H 4.93; N 20.16. *M* 347.12.

5,6,7,8-Tetrabromo-2-{6-[2-(furan-2-yl)ethyl]-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl}-2,3-dihydrophthalazine-1,4-dione (13). A mixture of compound **9** (0.01 mol, 2.19 g) and 3,4,5,6-tetrabromophthalic anhydride (0.01 mol, 4.66 g) in glacial acetic acid (20 mL) was refluxed for 4 h. After cooling, the mixture was poured onto crushed ice, and the solid product was filtered off and crystallized from acetic acid. Yield 4.65 g (70%), mp >300°C. IR spectrum (KBr), ν, cm^{-1}: 3220, 3180 (NH), 1700, 1695, 1685 (C=O). ^1H NMR spectrum, δ, ppm: 2.60 t and 2.98 t (2H each, CH_2), 6.60–7.18 m (3H, H_{Fu}), 12.25 s (1H, NH), 12.90 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.2 and 25.2 (CH_2), 107.1, 112.2, 123.4, 124.1, 133.1, 137.5, 139.2, 139.9, 140.2, 141.5, 154.1, 156.1 (C_{arom}), 158.2, 163.5 (C=O). Mass spectrum, *m*/*z*: 666 (70%), 662 (17%). Found, %: C 30.65; H 1.32; N 10.54. $C_{17}H_9Br_4N_5O_4$. Calculated, %: C 30.62; H 1.36; Br 47.93; N 10.50. *M* 662.74.

Antimicrobial activity. The antimicrobial activities [18–21] of compounds **1**–**13** were studied at the Microbial Chemistry Department, National Research Centre, using the diffusion plate method. A sterilized filter paper disk was saturated with 25 μL of a solution of **1**–**13** or reference drug with a concentration of 1 mg/mL, and the disk was placed onto a plate (9 cm in diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (potato dextrose agar) seeded with a spore suspension of the test organism. After incubation at 37°C for 24 h for bacteria or at 25°C for 72 h for fungi, the diameter of the clear zone of inhibition surrounding the sample was taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter × 100). All measurements were done in methanol as a solvent that has zero inhibition activity. The antimicrobial activity of the new compounds was examined against Gram-positive *Bacillus cereus*, *Staphylococcus aureus*, and *Salmonella typhimurium,* Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa*, and the fungus *Candida albicans*. The obtained results were compared with those for the reference antibiotics purchased from Egyptian markets (Table 1).

ACKNOWLEDGMENTS

The authors thank National Research Centre for financial support during this work and Microbial Chemistry Department, National Research Centre for performing antimicrobial evaluation.

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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