Synthesis, Characterization, and Biological Activity of Some Aza-Uracil Derivatives

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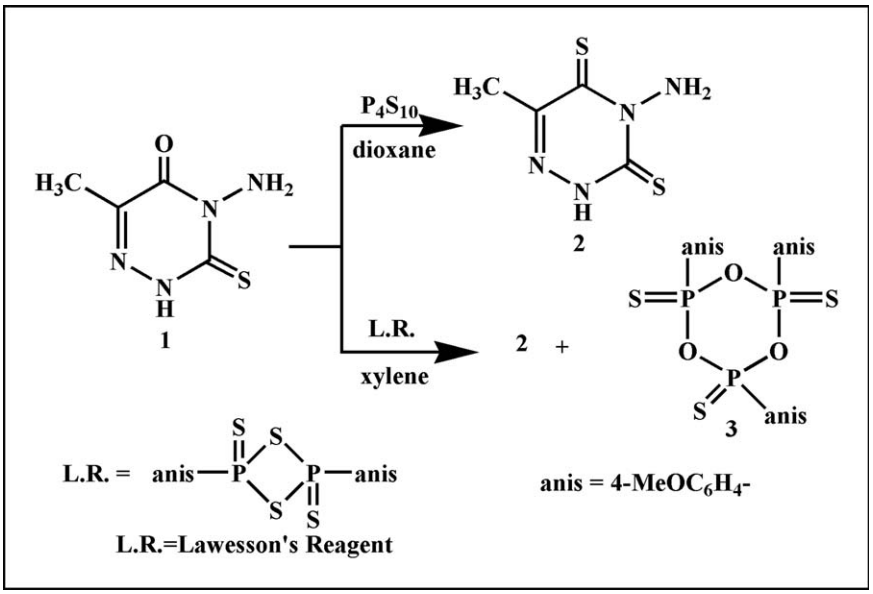

Thiation of **1** by LR gave the corresponding 3,5-dithioxo derivative **2** and the trimer **3**. Methylation of **1** afforded the S-methyl derivative **4**. Compound **1** was fused with 6-bromo-2-phenyl-benzo[1,3-d]oxazin-4-one **(5)** and gave **6**. Condensation of **1** with some acid derivatives **7a-d** and/or **8a-c** yielded thiadiazolo-triazine derivatives **9a-d** and **10a-c**. Compounds **9a,c** and **10c** were hydrolyzed to furnish **11a-c.** Acetylation of **14** afforded mono- and diacetyl-derivatives **15** and **16**. Benzoylation of **14** afforded mono- and dibezoyl-derivatives **17** and **18**. **14** with some aromatic aldehydes yielded **19a–c**. Reacting **14** with phenyl (iso- and/or isothio-) cyanate gave the urea derivatives **20a,b.** Thiation of **14** with P_4S_{10} furnished **21**. The newly synthesized compounds were tested as antimicrobial agents.

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INTRODUCTION

Compounds containing the 1,2,4-triazine moiety are found in natural sources and many of them showed important biological activities. Azaribine-antiviral drug is structurally based on the 1,2,4-triazine heterocyclic system [1]. Condensed 1,2,4-triazines found application as pharmaceuticals, herbicides, pesticides, and dyes [2–6]. 1,2,4-Triazines were reported to posses anti-HIV, anticancer [7–10], antihypertensive, anesthetic, antidepressant, tranquilizer, sedative, muscle relaxant [10,11], herbicidal, selective weed control in wheat, antibacterial, antiviral, antifungal, anti-inflammatory, anticonvulsant activities as well as carragreen-inducededema inhibitor. [10,11]. Moreover, some substituted 1,2,4-triazino[5,6-b]indole derivatives act as antiviral and anticancer agents [12]. All these facts encouraged us to continue in this direction and synthesize some new 1,2,4-triazine derivatives to explore their biological activity as antibacterial and antifungal agents.

DISCUSSION

When 4-amino-6-methyl-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazin-5-one **(1)** [13] reacted with P_4S_{10} in anhydrous dioxane [14] or 2,4-bi-(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent, LR) in anhydrous xylene, it gave the corresponding 3,5-dithioxo derivative **2**. In case of using LR, by-product **3** could be detected and isolated [15]. The synthesis of 4-amino-6-methyl-3-methylsulfanyl-4*H*-[1,2,4]triazin-5-one **(4)** was described earlier by J. Lee and W. W. Paudler [16] and others [17,18] (Fig. 1).

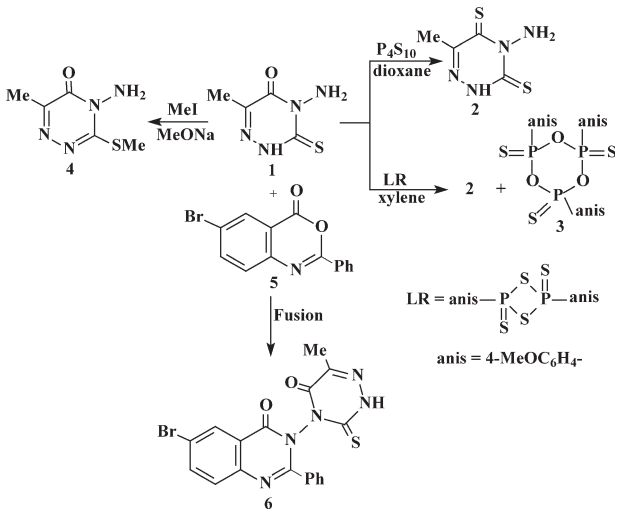
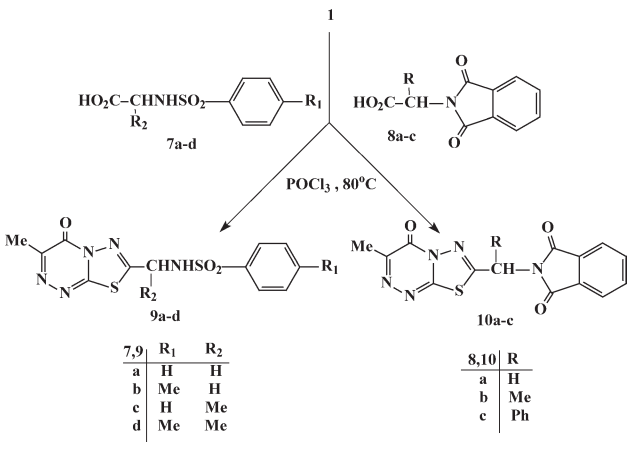


Figure 1. The reaction of **1** with Lawesson's reagent.

El-Barbary *et al*. [19] have reported that aminotriazines can be condensed with bezoxazones to afford the corresponding quinazolinyl derivatives. Accordingly, fusion of **1** with **5** in oil bath at 165°C furnished 6-bromo-3-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4] triazin-4-yl)- 2-phenyl-3*H*-quinazolin-4-one (**6**) (Fig. 1).

The structure of **6** was deduced from spectroscopic and elemental analyses. Its mass spectrum showed the molecular ion peak M^+ at m/z 442 and the base peak at m/z = 441, the ions at 300 (11.46, $C_{14}H_8BrN_2O^+$), 220 (3.32, $C_{14}H_8N_2O^+$) and 142 (2.92, $C_4H_4N_3OS^+$) were observed. Its ^{13}C NMR spectrum supported the structure, which showed the signals at δ 156.03 (C=O), in the range 121.36–139.57 (C_{arom}) ppm.

In view of the possible pharmacological activity of new purine analogues, a series of 1,3,4-thiadiazolo[2,3-*c*]-1,2,4-triazines were reported in the literature [20]. A number of 1,3,4-thiadiazoles showed antibacterial properties similar to those of well-known sulphonamide drugs [21]. The thiadiazole nucleus which incorporates a N—C—S linkage exhibits a large number of biological activities [22].



7,9	R_1	R_2
a	H	H
b	Me	H
c	H	Me
d	Me	Me

8,10	R
a	H
b	Me
c	Ph

Figure 2. Condensation of **1** with *N*-benzene sulfonylglycine derivatives and/or *N*-phthalimidoglycine derivatives.

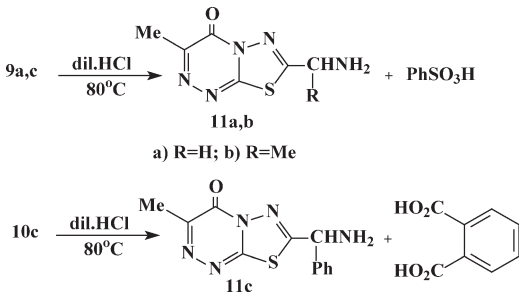


Figure 3. Acidic hydrolysis of **9a,c** and **10c**.

Condensation of **1** with *N*-benzene sulfonylglycine derivatives **7a–d** and/or *N*-phthalimidoglycine derivatives **8a–c** [23] yielded the new thiadiazolotriazines **9a–d** and **10a–c,** respectively (Fig. 2).

The IR spectra of compounds **9a–d** and **10a–c** showed no absorption bands related to NH_2 and NH groups, thus confirming the bi-cyclic ring formation. The C=O stretching frequency was appeared at the range υ 1695–1720 cm^{-1}.

The mass spectrum of compound **9c** showed the molecular ion peak M^+ at 351.39, which corresponds to the expected molecular formula, its ^1H NMR spectrum showed absence of a singlet at d 6.00 ppm assigned to NH_2 group and showed a singlet (1H) at d 8.12 ppm assigned to NH proton and its ^{13}C NMR spectrum supported the structure which showed the signals at δ 31.15 ($\underline{C}H_3CH$), 40.94 ($\underline{C}HCH_3$), at the range 126.44–139.95 ($\underline{C}_{arom}$) ppm.

Compounds **9a,c** were hydrolyzed by heating with dil. HCl and furnished 7-aminomethyl-3-methyl[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-4-one and 7-(1-aminoethyl)-3-methyl[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-4-one **(11a,b),** respectively as well as benzene sulfonic acid (Fig. 3). The IR spectra of compounds **11a,b** showed bands at 3248 and 3358 cm^{-1} related to NH_2 groups.

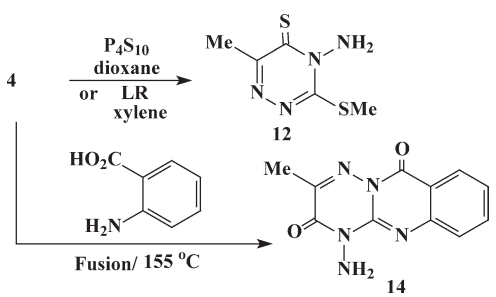


Figure 4. Synthesis of compound **14**.

Similarly, Compound **10c** was hydrolyzed by diluted HCl and the corresponding amino derivative 7-(amino-phenylmethyl)-3-methyl[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-4-one **(11c)** was formed. The isolation of phthalic acid gave an additional proof for the formation of **11c** (Fig. 3).

Compound **12** could be synthesized by refluxing **4** with either P_4S_{10} in anhydrous dioxane [14] or LR in anhydrous xylene without formation of any other products (Fig. 4). Badawy *et al*. [24] have synthesized compound **14** by reacting **4** with 2-aminobenzoic acid. (Fig. 4).

The amino group in compound **14** is a versatile moiety and could be used for producing new heterocyclic derivatives. Thus, refluxing **14** with acetic anhydride in glacial acetic acid gave the mono- and di-acetyl products *N*-(3-methyl-2,10-dioxo-2*H*,10*H*-1,4,4a,9-tetraazaanthracen-1-yl)acetamide **(15)** and *N*-acetyl-*N*-(3-methyl-2,10-dioxo-2*H*,10*H*-1,4,4a,9-tetraazaanthracen-1-yl) acetamide **(16)** (Fig. 5).

Similarly, the mono- and di-benzoyl products *N*-(3-methyl-2,10-dioxo-2*H*,10*H*-1,4,4a,9-tetraazaanthracen-1-yl)benzamide **(17)** and *N*-benzoyl-*N*-(3-methyl-2,10-dioxo-2*H*,10*H*-1,4,4a,9-tetraazaanthracen-1-yl)benzamide **(18)** were obtained when compound **14** was refluxed with benzoyl chloride in anhydrous pyridine (Fig. 5).

The Schiff bases 1-(benzylideneamino)-3-methyl-1*H*-1,4,4a,9-tetraazaanthracene-2,10-dione **(19a),** 1-[(2-chloro-benzylidene)amino]-3-methyl-1*H*-1,4,4a,9-tetraaza-anthracene-2,10-dione **(19b)** and/or 3-methyl-1-[(thiophen-2-ylmethylene)amino]-1*H*-1,4,4a,9-tetraazaanthracene-2,10-dione **(19c)** could be synthesized by condensation of compound **14** with some aromatic aldehydes, namely: benzaldehyde, 2-chloro-benzaldehyde and thiophene-2-carboxaldehyde in DMF (Fig. 5).

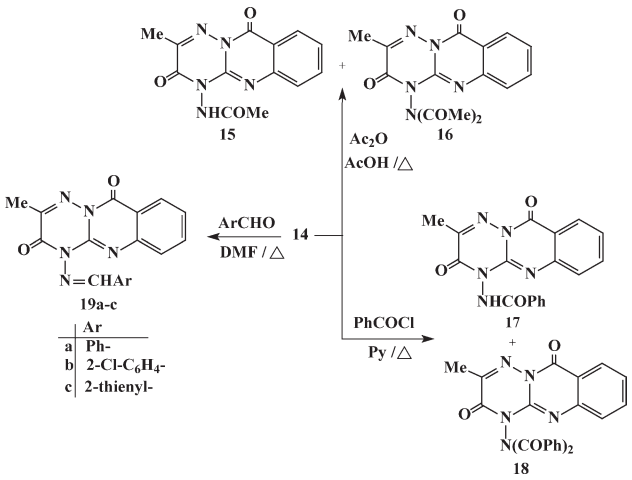


Figure 5. The amino group in compound **14**, a versatile moiety, can be used for producing new heterocyclic derivatives.

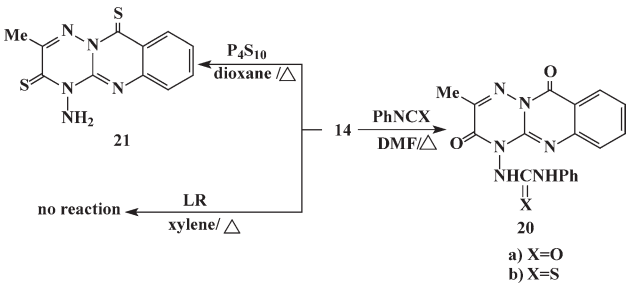


Figure 6. Thiation of compound **14**.

The ^{1}H NMR spectra of **19a–c** showed a singlet (1H, CHAr) in the range 8.7–9.3 ppm.

Refluxing **14** with phenyl (iso- and/or isothio-)cyanate in DMF gave 1-(3-methyl-2,10-dioxo-2*H*,10*H*-1,4,4a,9-tetraazaanthracen-1-yl)-3-phenylurea **(20a)** and 1-(3-methyl-2,10-dioxo-2*H*,10*H*-1,4,4a,9-tetraazaanthracen-1-yl)-3-phenylthiourea **(20b)** (Fig. 6).

The ^{1}H NMR spectrum of compound **20b** showed a doublet at d 8.19 ppm assigned to two NH protons which appeared in the IR spectrum at 3188 and 3436 cm^{-1}.

On the other hand, thiation of compound **14** with phosphorus pentasulfide in anhydrous boiling dioxane furnished 1-amino-3-methyl-1*H*-1,4,4a,9-tetraazaanthracene-2,10-dithione **(21)** as the sole product (tlc) (Fig. 6). The IR spectrum of **21** showed two sharp bands at υ 1695 and 1773 cm^{-1} related to the presence of two C=S groups and no absorption bands for C=O groups.

Surprisingly, in our hands, trying to thiate compound **14** by its treatment with LR in anhydrous boiling xylene, we have obtained starting material unreacted (Fig. 6).

BIOLOGICAL ACTIVITY REPORT

The newly synthesized compounds were screened for their *in vitro* antibacterial activities using the cut plug method [25] against the gram positive bacteria (*Bacillus subtilius* and *Staphylococcus aureus*) and the gram negative bacteria (*Escherichia coli*, *Salmonella typhae* and *Klebsilla sp*.) and antifungal activity against yeast (*Candida albicans*) using Chloramophenicol and Streptomycin as standard drugs. The results are summarized and illustrated in Table 1.

The results revealed that most of the tested compounds showed antibacterial and antifungal (anticandidal) activity with varying magnitudes. The zone of inhibition above 7 mm in diameters was taken as a positive result.

Compounds **9a**, **11a, 20a** showed the highest activity against all the tested bacteria and yeast. However, other compounds showed low and/or no antibacterial or antifungal activity. These differences varied according to

Table 1

Diameters of inhibition zones (mm) of newly synthesized 1,2,4-triazines against different test bacteria on nutrient agar and yeast after 24 hr by the cut-plug method on nutrient agar at 35–37°C.

	Test organisms					
Cpd.	*Escherichia coli*	*Bacillus subtilus*	*Staphylococcus aurus*	*Salmonella typhae*	*Klebsilla sp.*	*Candida albicans*
Chloramophenicol (30 μgm)	20	20	38	—	23	—
Streptomycin (10 μgm)	14	23	12	—	11	—
(1)	—	17	—	7	40	9
(4)	10	—	—	—	9	—
(6)	12	—	20	20	—	—
(9a)	17	15	15	20	10	20
(9b)	—	15	—	12	8	15
(9c)	—	—	—	—	—	11
(9d)	—	—	—	—	—	—
(10a)	15	18	—	18	13	12
(10b)	12	—	—	—	—	—
(10c)	—	—	—	25	9	11
(11a)	20	20	20	20	11	20
(11b)	10	—	10	—	—	12
(11c)	13	—	13	10	15	—
(14)	8	7	9	20	—	16
(15)	—	—	—	—	—	—
(16)	10	—	22	10	—	—
(17)	10	—	10	—	—	12
(18)	—	—	—	—	—	—
(19a)	10	—	—	—	15	—
(19b)	—	—	—	22	—	10
(19c)	27	—	9	10	—	7
(20a)	12	15	17	15	12	25
(20b)	15	—	20	15	—	—
(21)	—	—	—	9	7	8

the differences in the structure of the cell wall of the tested organism and the structure of compound.

EXPERIMENTAL

All melting points are uncorrected and performed by the open capillary melting point apparatus. Microanalyses were performed by Microanalysis Unit, Faculty of Science, Tanta University, Egypt. IR spectra were recorded with a Perkin-Elmer spectrometer. The NMR spectra were recorded on a Bruker 300 MHz and Bruker 200 MHz spectrometer using TMS as an internal standard, DMSO and $CHCl_3$ as solvents. Mass spectra (ms) were recorded using electron ionization (E.I.) on a Varian Mat 311A spectrometer.

Compounds **1** [13], **2** & **12** [14], **4** [16–18], and **14** [24], were prepared according to known methods.

Formation of 6-bromo-3-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-yl)-2-phenyl-3*H*-quinazolin-4-one (6). A mixture of compound **1** (1.58 g, 0.010 mole) and **5** (3.02 g, 0.010 mole) was fused at 165°C in an oil bath for 3 h (tlc). The reaction mixture was cooled and titrated with ethanol (10 mL), filtered off and chromatographed on a column of silica gel with chloroform:ethanol (9:1, v/v) to yield 1.33 g (30%), mp 276–278°C; IR (potassium bromide): 1693 (CN), 2919 (CH), 3088 (Ph), 3241 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 3.40 (s, 1H, SH), 7.52-8.50 (m, 8H, H_{arom}); ^{13}C NMR (DMSO-d_6): δ16.92 (CH_3-6'), 145.44 (C-3'), 147.48 (C-6'), 151.04 (C-2), 156.03 (C-4), 172.98 (C-5'), 121.36, 128.64, 130.08 and 139.57 (C_{arom}); ms**:** m/z 442 (34), 441 (100), 300 (11), 220 (3), 153 (10), 142 (3), 127 (1), 77 (23). Anal. Calcd. For $C_{18}H_{12}BrN_5O_2S$: C, 48.88; H, 2.73; N, 15.83. Found: C, 48.93; H, 2.72; N, 16.25.

Condensation of compound 1 with mono carboxylic acid derivatives 7a–d and 8a–c: Formation of compounds 9a–d and 10a–c. ***General procedure.*** Compound **1** (1.58 g, 0.010 mole) and mono carboxylic acids (if any, 0.010 mole) in $POCl_3$ (15 mL) were heated at 85°C for 6–8 h (tlc). The solvent was concentrated to its 1/3 volume under reduced pressure (5 mL) and cooled water (20 mL) was added drop wise at (0°C) to the above reaction mixture and the solid product formed was filtered off and recrystallized from DMF/water.

N-(3-methyl-4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-ylmethyl)benzene sulfonamide (9a). Yield 2.01 g (62%); mp 119–121°C; IR (potassium bromide): 1617 (CN), 1709 (CO), 2922 (CH), 3056 (Ph), 3353 and 3554 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3-3), 4.50 (s, 2H, CH_2), 7.50-8.00 (m, 5H, H_{arom}), 9.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 17.44 (CH_3-3), 42.42 (CH_2), 148.67 (C-3), 154.16 (C-9), 159.72 (C-6), 163.95 (C-4), 126.96, 129.71, 133.33, and 139.95 (C_{arom}). Anal. Calcd. For $C_{12}H_{11}N_5O_3S_2$: C, 42.72; H, 3.29; N, 20.76. Found: C, 40.22; H, 3.31; N, 20.22.

4-Methyl-N-(3-methyl-4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4] triazin-7-ylmethyl) benzenesulfonamide (9b). Yield 1.47 g (42%); mp 209–211°C; IR (potassium bromide): 1632 (CN), 1705 (CO), 2932 (CH), 3126 (Ph), 3398 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3-3), 3.42 (s, 3H, CH_3-4), 4.53 (s, 2H, CH_2), 7.50-8.03 (m, 4H, H_{arom}), 9.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 17.44 (CH_3-3), 21.25 (CH_3-4'), 42.41 (CH_2), 148.65 (C-3), 154.13 (C-9), 159.73 (C-6), 163.93 (C-4), 127.07, 130.06, 137.08 and 143.73 (C_{arom}). Anal. Calcd. For $C_{13}H_{13}N_5O_3S_2$: C, 44.43; H, 3.73; N, 19.93. Found: C, 43.52; H, 3.61; N, 19.70.

N-[1-(3-methyl-4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl)ethyl]benzene sulfonamide (9c). Yield 2.9 g (75%); mp 171–173°C; IR (potassium bromide): 1553 (CN), 1695 (CO), 2932 (CH), 3070 (Ph), 3218 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3-3), 3.22, 3.41 (m, 4H, CH_3CH—), 7.51-7.90 (m, 5H, H_{arom}), 8.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 17.11 (CH_3-3), 31.15 (CH_3CH), 40.94 ($CHCH_3$), 148.52 (C-6), 153.49 (C-3), 159.89 (C-9), 161.73 (C-4), 126.44, 129.24, 132.52 and 139.95 (C_{arom}); ms: m/z 351 (0.31), 169 (7), 168 (100), 156 (2), 95 (23). Anal. Calcd. For $C_{13}H_{13}N_5O_3S_2$: C, 44.43; H, 3.73; N, 19.93. Found: C, 43.86; H, 3.57; N, 19.85.

4-Methyl-N-[1-(3-methyl-4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1, 2,4]triazin-7-yl)ethyl] benzenesulfonamide (9d). Yield 3.02 g (83%); mp 221–223°C; IR (potassium bromide): 1598 (CN),1699 (CO), 2914 (CH), 3139 (Ph), 3385 and 3558 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3-3), 3.22 (m, 4H, CH_3CH—), 3.40 (s, 3H, CH_3-4), 7.31-7.70 (m, 4H, H_{arom}), 7.99 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 17.10 (CH_3-3), 20.92 (CH_3-4'), 31.12 (CH_3CH), 40.93 ($CHCH_3$), 148.28 (C-3), 153.44 (C-9), 159.89 (C-6), 161.78 (C-4), 126.50, 129.60, 137.13, and 142.83 (C_{arom}). Anal. Calcd. For $C_{14}H_{15}N_5O_3S_2$: C, 46.02; H, 4.14; N, 19.16. Found: C, 45.50; H, 4.01; N, 18.77.

2-(3-Methyl-4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-ylmethyl)isoindole-1,3-dione (10a). Yield 2.64 g (81%); mp 320–322°C; IR (potassium bromide): 1609 (CN), 1720 (CO), 2925 (CH), 3099 (Ph) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3-3), 4.50 (s, 2H, CH_2), 7.91–8.21 (m, 4H, H_{arom}); ^{13}C NMR (DMSO-d_6): δ 16.74 (CH_3-3), 147.50 (C-3), 151.17 (C-9), 164.69 (C-6), 167.17 (C-4), 174.65 (CONCO), 123.39, 131.59 and 134.79 (C_{arom}). Anal. Calcd. For $C_{14}H_9N_5O_3S$: C, 51.37; H, 2.77; N, 21.40. Found: C, 50.91; H, 2.87; N, 20.87.

2-[1-(3-Methyl-4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl)ethyl]isoindole-1,3-dione (10b). Yield 3.06 g (90%); mp 248–250°C; IR (potassium bromide): 1705 (CO), 1614 (CN), 2929 (CH), 3054 (Ph) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.40 (s, 7H, CH_3-3, $CHCH_3$), 7.92 (m, 4H, H_{arom}); ^{13}C NMR (DMSO-d_6): δ 17.40 (CH_3-3), 29.58 (CH_3CH), 36.20 ($CHCH_3$), 153.87 (C-9), 161.85 (C-4), 167.97 (CONCO), 123.50, 131.83 and 134.84 (C_{arom}); ms: m/z 341 (56), 195 (4), 167 (6), 160 (100), 159 (2), 147 (13), 77 (20). Anal. Calcd. For $C_{15}H_{11}N_5O_3S$: C, 52.78; H, 3.25; N, 20.52. Found: C, 52.53; H, 3.27; N, 20.44.

2-[(3-Methyl-4-oxo-4H-[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-7-yl)phenylmethyl] isoindole-1,3-dione (10c). Yield 3.06 g (76%); mp 117–119°C; IR (potassium bromide): 1605 (CN), 1713 (CO), 2928 (CH), 3028 (Ph) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.52 (s, 4H, CH_3-3, CHPh), 7.31 (m, 5H, CH Ph). 7.90-8.13 (m, 4H, H_{arom}); ^{13}C NMR (DMSO-d_6): δ 17.45 (CH_3-3), 36.05 (CHPh), 148.72 (C-3), 154.28 (C-9), 161.95 (C-4), 167.13 (CONCO), 123.99, 127.51, 128.84, 130.79, and 135.84 (C_{arom}). Anal. Calcd. For $C_{20}H_{13}N_5O_3S$: C, 59.55; H, 3.25; N, 17.36. Found: C, 59.11; H, 3.08; N, 16.92.

Hydrolysis of compounds 9a,c and 10c: Formation of compounds 11a–c. Thirty milliliter of 30% HCl was added to compounds **9a,c** and /or **10c** (0.010 mole) then heated at 80°C 5 h (tlc). The reaction mixture was allowed to cool to room temperature, diluted with water (30 mL) and neutralized with ammonia solution. The solid obtained was filtered off, dried and recrystallized from DMF/water to give compounds **11a–c.**

7-Aminomethyl-3-methyl[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-4-one (11a). Yield 1.64 g (83%); mp 179-181 °C; IR (potassium bromide): 1614 (CN), 2922 (CH), 3248 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3-3), 3.67 (s, 2H, CH2), 5.64 (s, 2H, NH_2). Anal. Calcd. For $C_6H_7N_5OS$: C, 36.54; H, 3.58; N, 35.51. Found: C, 36.44; H, 3.37; N 35.29.

7-(1-Aminoethyl)-3-methyl[1,3,4]thiadiazolo[2,3-c][1,2,4]triazin-4-one (11b). Yield 1.94 g (92%); mp 212–213°C; IR (potassium bromide): 1629 (CN), 2923 (CH), 3290 and 3358 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.15 (s, 3H, CH_3-3), 3.69 (s, 3H, $CHCH_3$), 4.35 (s, 1H, $CHNH_2$), 5.55 (s, 2H, NH_2). Anal. Calcd. For $C_7H_9N_5OS$: C, 39.80; H, 4.29; N, 33.15. Found: C, 39.73; H, 4.18; N, 33.07.

7-(Aminophenylmethyl)-3-methyl[1,3,4]thiadiazolo[2,3-c][1,2, 4]triazin-4-one (11c). Yield 2.21 g (81%); mp 240–242°C; IR (potassium bromide): 1605 (CN), 1694 (C=O), 3247 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.64 (s, 3H, CH_3-3), 3.41 (s, 3H, CH_3-4), 4.27 (s, 1H, $CHNH_2$), 5.56 (s, 2H, NH_2), 7.02-7.61 (m, 5H, H_{arom}). Anal. Calcd. For $C_{12}H_{11}N_5OS$: C, 52.74; H, 4.06; N, 25.62. Found: C, 52.63; H, 3.89; N, 25.57.

Acetylation of compound 14: Formation of compounds 15 and 16. Compound **14** (2.43 g, 0.010 mole) was refluxed with a mixture of acetic acid (15 mL) and acetic anhydride (5 mL) for 1 h (tlc). The solvent was evaporated till dryness under reduced pressure. The residue was chromatographed on a column of silica gel petroleum ether:ethylacetate (3:1, v/v) to give **15** and **16.**

N-(3-methyl-2,10-dioxo-2H,10H-1,4,4a,9-tetraazaanthracen-1-yl)acetamide (15). Yield 1.2 g (85%); mp 255–257°C; IR (potassium bromide): 1599 and 1725 (2CO), 2928 (CH), 3014 (Ph), 3234 (NH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.60 (s, 3H, CH_3CO), 3.81 (s, 3H, CH_3-3), 7.42-7.91 (m, 4H, H_{arom}), 8.43 (s, 1H, NHCO). Anal. Calcd. For $C_{13}H_{11}N_5O_3$: C, 54.74; H, 3.89; N, 24.55. Found: C, 54.30; H, 3.97; N, 24.61.

N-acetyl-N-(3-methyl-2,10-dioxo-2H,10H-1,4,4a,9-tetraazaanthracen-1-yl)acetamide (16). Yield 1.37 g (84%); mp 264–266°C; IR (potassium bromide): 1603 and 1728 (2CO), 2936 (CH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.50 (s, 3H, CH_3-3), 3.31 (s, 6H, $2CH_3CO$), 7.50-7.92 (m, 4H, H_{arom}). Anal. Calcd. For $C_{15}H_{13}N_5O_4$: C, 55.05; H, 4.00; N, 21.40. Found: C, 54.86; H, 4.08; N, 21.33.

Benzoylation of compound 14: Formation of compounds 17 and 18. A mixture of compound **14** (2.43 g, 0.010 mole) and benzoyl chloride (5 mL) in anhydrous pyridine was refluxed for 3 h (tlc). The reaction mixture was worked up as above to give **17** and **18**.

N-(3-methyl-2,10-dioxo-2H,10H-1,4,4a,9-tetraazaanthracen-1-yl)benzamide (17). Yield 1.35 g (78%); mp 270–272°C; IR (potassium bromide): 1603 (CN), 1668 and 1722 (2CO), 3055 (Ph), 3450 (NH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.61 (s, 3H, CH_3-3), 7.40-8.00 (m, 9H, H_{arom}), 8.41 (s, 1H, NHCO). Anal. Calcd. For $C_{18}H_{13}N_5O_3$: C, 62.25; H, 3.77; N, 20.16. Found: C, 61.99; H, 3.58; N, 20.11.

N-benzoyl-N-(3-methyl-2,10-dioxo-2H,10H-1,4,4a,9-tetraazaanthracen-1-yl) benzamide (18). Yield 1.78 g (79%); mp 262–264°C; IR (potassium bromide): 1603 and 1702(2CO),

2923(CH), 3056 (Ph) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.60 (s, 3H, CH_3-3), 7.32-7.91 (m, 14H, H_{arom}). *Anal*. Calcd. For $C_{25}H_{17}N_5O_4$: C, 66.51; H, 3.80; N, 15.51. Found: C, 66.36; H, 3.62; N, 15.46.

Condensation of compound 14 with aldehydes: Formation of compounds 19a–c. To compound **14** (2.43 g, 0.010 mole) in boiling DMF (10 mL) benzaldehyde, 2-chlorobenzaldehyde and/or thiophen-2-carboxaldehyde (0.010 mole) was added. The reaction mixture was refluxed for 3 h (tlc). The reaction mixture was cooled and poured onto ice. The solid obtained was filtered off, dried and recrystallized from DMF/water to afford compounds **19a–c.**

1-(Benzylideneamino)-3-methyl-1H-1,4,4a,9-tetraazaanthracene-2,10-dione (19a). Yield 2.1 g (66%); mp 233–235°C; IR (potassium bromide): 1722 and 1847 (2CO), 1688 (CN), 2923 (CH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.62 (s, 3H, CH_3), 7.41-8.43 (m, 9H, H_{arom}), 8.71 (s, 1H, CHAr). Anal. Calcd. For $C_{18}H_{13}N_5O_2$: C, 65.25; H, 3.95; N, 21.14. Found: C, 65.56; H, 3.74; N, 21.22.

1-[(2-Chlorobenzylidene)amino]-3-methyl-1H-1,4,4a,9-tetraazaanthracene-2,10-dione (19b). Yield 2.19 g (60%); mp 264–266°C; IR (potassium bromide): 1593 and 1706 (2CO), 2923(CH), 3073 (Ph) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H, CH_3-3), 7.42-8.41 (m, 8H, H_{arom}), 9.33 (s, 1H, CHAr). *Anal*. Calcd. For $C_{18}H_{12}ClN_5O_2$: C, 59.11; H, 3.31; N, 19.15. Found: C, 58.67; H, 3.27; N, 19.09.

3-Methyl-1-[(thiophen-2-ylmethylene)amino]-1H-1,4,4a,9-tetraazaanthracene-2,10-dione (19c). Yield 2.19 g (65%); mp 262–264°C; IR (potassium bromide): 1593, 1706 (2CO), 2923 (CH), 3073 (Ph) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.62 (s, 3H, CH_3-3), 7.32-7.41 (m, 4H, H_{arom}), 8.83 (s, 1H, CHAr). Anal. Calcd. For $C_{16}H_{11}N_5O_2S$: C, 56.97; H, 3.29; N, 20.76. Found: C, 56.62; H, 3.37; N, 20.37.

Reaction of compound 14 with phenyl (iso- and/or isothio-)cyanate: Formation of compounds 20a,b. A mixture of phenyl (iso- and/or isothio-)cyanate (0.010 mole) and compound **14** (2.43 g, 0.010 mole) was refluxed in DMF (30 mL) for 3–5 h (tlc). The reaction mixture was cooled and poured onto ice. The solid obtained was filtered off, dried and recrystallized from DMF/water to afford compounds **20a**,**b.**

1-(3-Methyl-2,10-dioxo-2H,10H-1,4,4a,9-tetraazaanthracen-1-yl)-3-phenylurea (20a). Yield 2.57 g (71%); mp 250–252°C; IR (potassium bromide): 1646 and 1793 (2CO), 3057 (Ph), 3284 and 3319 (NH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.25 (s, 3H, CH_3-3), 7.21-7.41 (m, 9H, H_{arom}), 8.13 (s, 2H, 2NH). Anal. Calcd. For $C_{18}H_{14}N_6O_3$: C, 59.67; H, 3.89; N, 23.19. Found: C, 59.47; H, 3.69; N, 23.07.

1-(3-Methyl-2,10-dioxo-2H,10H-1,4,4a,9-tetraazaanthracen-1-yl)-3-phenylthiourea (20b). Yield 3.13 g (83%); mp 350–352°C; IR (potassium bromide): 1665 and 1728 (2CO), 1620 (CS), 3070 (Ph), 3188 and 3436 (NH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.08 (s, 3H, CH_3-3), 8.19 (d, 2H, 2NH), 6.89-7.06 (m, 9H, H_{arom}). Anal. Calcd. For $C_{18}H_{14}N_6O_2S$: C, 57.13; H, 3.73; N, 22.21. Found: C, 57.03; H, 3.54; N, 21.78.

Thiation of compound 14 with P_4S_{10}. ***Formation of 1-amino-3-methyl-1H-1,4,4a,9-tetraazaanthracene-2,10-dithione (21).*** A mixture of compound **14** (2.43 g, 0.010 mole) and P_4S_{10} (2.22 g, 0.005 mole) was refluxed in anhydrous dioxane (20 mL) for 1 h (tlc). The precipitate thus formed was filtered off, washed with cold water, dried, and recrystallized from DMF to yield 1.98 g (72%); mp 276–278°C; IR (potassium bromide): 1611 and 1695 (2CS), 2944 (CH), 3183 (Ph), 3397 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.70 (s, 3H, CH_3), 7.31(s, 2H, NH_2), 7.51-8.42 (m, 4H, H_{arom}). Anal. Calcd. For $C_{11}H_9N_5S_2$: C, 47.98; H, 3.29; N, 25.43. Found: C, 47.55; H, 3.27; N, 25.39.

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REFERENCES AND NOTES

[1] Negwer, M.; Organisch-Chemische Arzneimittel und ihre Synonyma; Akademie—Verlag: Berlin, 1987.

[2] (a) Abdel-Rahman, R. M. Pharmazie 2001, 56, 275. (b) Abdel-Rahman, R. M. Pharmaco 1991, 46, 37.

[3] El-Gendy, Z.; Morsy, J. M.; Allimony, H. A.; Ali, W. R.; Abdel-Rahman, R. M. Pharmazie 2001, 56, 376.

[4] Holla, B. S.; Rao, B. S.; Gonsalves, R.; Sarojini B. K.; Shridhara, K. Pharmaco 2002, 57, 693.

[5] Habib, N. S.; Soliman, R.; Ismail, K.; Hassan, A. M.; Sarg, M. T. Boll Chim Fram 2003, 142, 396.

[6] El Ashry, E. S. H.; Rashed, M.; Taha, E.; Ramadan, E. Adv Heterocycl Chem 1994, 59, 39.

[7] El-Gendy, Z.; Morsy, J. M.; Allimony, H. A.; Ali, W. R.; Abdel-Rahman, R. M. Pharmazie 2001, 56, 376.

[8] El-Gendy, Z.; Morsy, J.; Allimony, H.; Abdel-Rehman, R. Phosphorous Sulphur Silicon Relat Elem 2003, 178, 2055.

[9] Abdel-Rahman, R. M.; Morsy, J. M.; El-Edfawy, S.; Amine, H. A. Pharmazie 1999, 54, 667.

[10] Abdel-Halim, A. M.; El-Gendy, Z.; Abdel-Rahman, R. M. Pharmazie 1995, 50, 726.

[11] El Ashry, E. S. H.; Rashed, N.; Mousaad, A.; Ramadan, E. Adv Heterocycl Chem 1994, 61, 207.

[12] Eshba, N. H.; Salama, H. M.; Labouta, I. M.; Mohsen, A.; Omar, M. Pharmazie 1987, 42, 664.

[13] PridhamT. G.; Shotwell, O. L.; Stodola, F. H.; Lindeufelser, L. A.; Benedict, R. G.; Jackson, R. W. Phytopathology 1956, 46, 575.

[14] Hozien, Z. A. J Chem Res 2000, 3, 401.

[15] Wen, T.; Bau, R.; McKenna, C. E. J Chem Soc Chem Commun 1991,1223.

[16] Lee, J.; Paudler, W. W. J Heterocycl Chem 1972, 9, 995.

[17] Hauptmann, S.; Blattman G.; Schindler, W. J Prakt Chem 1976, 318, 835.

[18] Ulmoskil, E. N.; Rusinov, V. L.; Chupakhim, D. N.; Kusinov, G. L.; Chernychev, A. I.; Aleksandrov, G. G. Khim Geterotsikl Seodin 1987, 11, 1543.

[19] El-Barbary, A. A.; Sakran, M. A.; El-Madani, A. M.; Nielsen, C. J Heterocycl Chem 2005, 42, 1.

[20] Golgolab, H.; Lalezari, I.; Gohari, L. H.; J Heterocycl Chem 1973, 10, 387.

[21] Sandstrom, J.; Katritzky, A. R.; Boulton, A. J. Advances in Heterocyclic Chemistry. Academic Press: New York, 1968.

[22] Omar, A.; Omaima, M. E.; Aboulwafa, M. J Heterocycl Chem 1986, 23, 1339.

[23] Okuda, J.; Inagaki, K.; Miwa, I.; Yashira, T. Chem Pharm Bull 1982, 30, 3244.

[24] Badawy, M. A.; Abdel-Hay, S. A.; Eid, M. M.; Ibrahim, Y. A. Chem Ber 1984, 117, 1083.

[25] Biltz, H. Chem Ber 1905, 38, 1417.