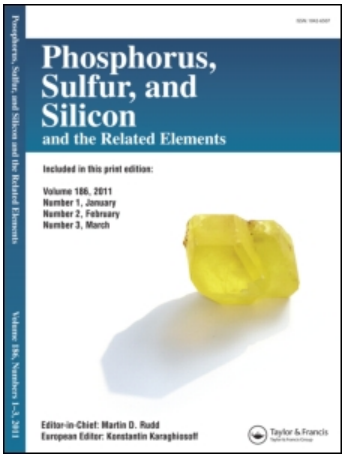

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Synthesis and Biological Evaluation of Some Novel N , N '-Bis-(1,2,4-Triazin-4-Yl)Dicarboxylic Acid Amides and Some Fused Rings with 1,2,4-Triazine Ring

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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL *N,N′*-BIS-(1,2,4-TRIAZIN-4-YL)-DICARBOXYLIC ACID AMIDES AND SOME FUSED RINGS WITH 1,2,4-TRIAZINE RING

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Some of novel N,N′*-bis-(1,2,4-triazin-4-yl)dicarboxylic acid amides (**2–5**) and thiadiazolo[2,3-*b*][1,2,4]triazin-7-yl carboxylic acid derivatives (**6**,**7**) were prepared by heating 4-amino-6-methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine (**1**) with different dicarboxylic acids (oxalic, malonic, fumaric, maleic, succinic, and phthalic acids respectively) in $POCl_3$. Refluxing **1** with 1-chloro-2,4-dinitrobenzene in DMF yielded 3-methyl-6-nitro-10*H*-benzo[1,2,4]thiadiazino[2,3-*c*][1,2,4]triazin-4-one (**8**). Condensation of **1** with 2,4-pentandione in refluxing acetic acid furnished 6-methyl-4-(1-methyl-3-oxobut-1-enylamino)-3-thioxo-3,4-dihydro-2H-[1,2,4]triazin-5-one (**9**). 3,8-Dimethyl[1,2,4] triazino[3,4-*b*][1,3,4]thiadiazine-4,7-dione (**11**) was prepared by refluxing **1** with 2-bromopropionyl bromide in anhydrous benzene to afford the corresponding* N*-acetylated derivative **10**, which was cyclized by using triethylamine. Also, some triazinylquinazolinones **13a**,**b** were obtained by fusion of **1** with 6-bromo(and/or 6,8-dibromo)-2-methyl-3,1-benzoxazin-4*H*-ones.*

Keywords: 1-Chloro-2,4-dinitrobenzene; 2-bromopropionyl bromide; 2,4-pentanedione; 1,2,4-triazine; 3,1-benzoxazin-4*H*-ones; anti-HBV activity; dicarboxylic acids

INTRODUCTION

1,2,4-Triazines have many applications in the biological field. A number of this class of compounds acts as antimicrobial,[1] antiviral,[2] antiinflamatory, and antimalarial agents.[3–5] 4-Amino-1,2,4-triazin-5(4*H*)-one

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derivatives have attracted considerable interest because of their herbicidal activities[6] and important intermediates for the preparation of fused 1,2,4-triazinone heterocycles.[7]

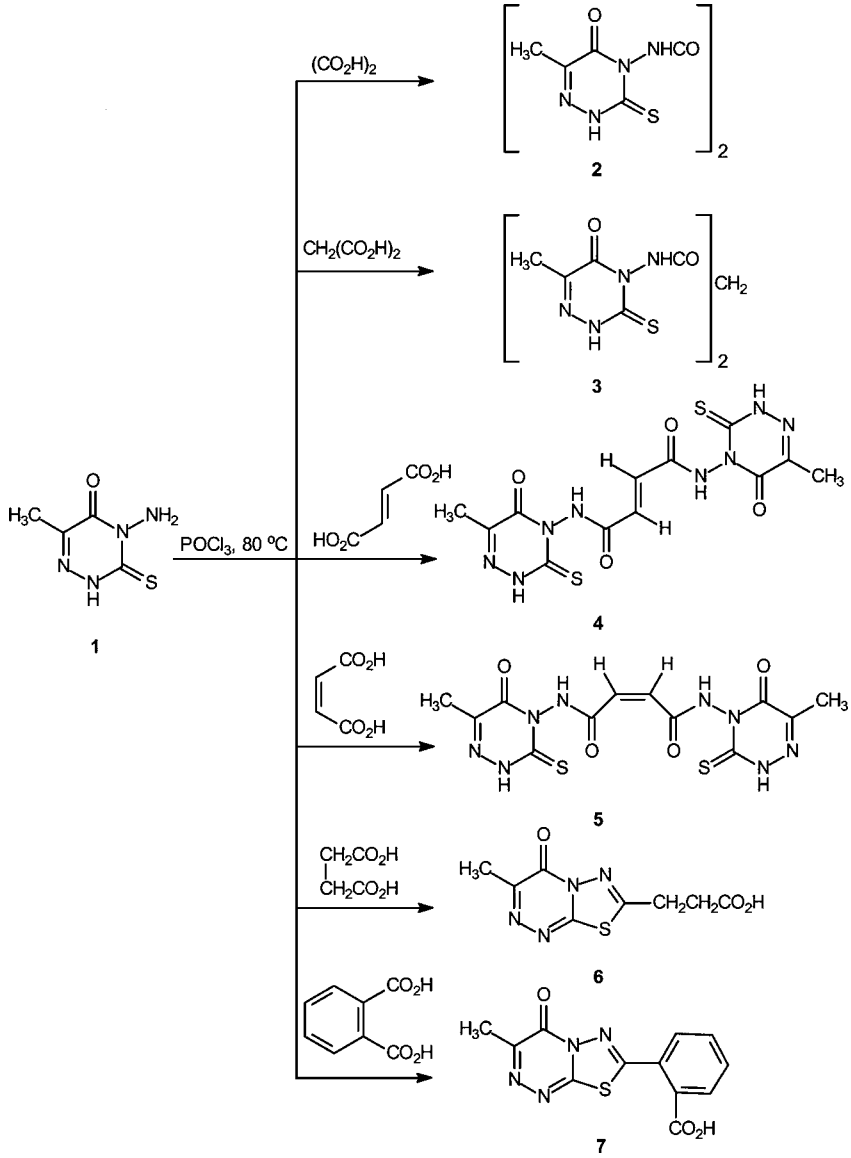
The reaction of monocarboxylic acids with 4-amino-6-substituted-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine in $POCl_3$ to afford the corresponding thiadiazolo[2,3-*b*][1,2,4]triazine derivatives was achieved.[8–10] In this article, the reaction of dicarboxylic acids with 4-amino-6-methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine (**1**) was tried as well as some related reactions to afford fused rings with **1** were given. All the new compounds prepared were tested for their activity against Hepatitis B Virus (HBV).

RESULTS AND DISCUSSION

Heating compound **1** with dicarboxylic acids, namely oxalic, malonic, fumaric and maleic acids, respectively, in $POCl_3$ at 85°C gave the corresponding diamide derivatives **2–5**. Treatment of **1** with succinic and phthalic acids, respectively, under the same reaction conditions afforded the thiadiazolo[2,3-*b*][1,2,4]triazin-7-yl carboxylic acid derivatives **6**,**7**. ^{1}H NMR spectra of compounds **2–5** showed the existence of triazine-NH signals as singlets in the range of 13.74–13.93 ppm, while NHCO signals were observed as broad singlets in the range of 11.19–12.24 ppm. The CH=CH groups of compounds **4** and **5** were found as doublets at 7.19 (J = 14.8 Hz) and 7.25 ppm (J = 8.2 Hz) respectively. Mass spectral analysis of compound **4** showed the molecular ion peak M^+ at m/z = 384. ^{1}H NMR spectra of compounds **6**,**7** showed the disappearance of triazine-NH and in compound **1** and the existence of COOH signals as broad singlets at 12.20 and 11.16 ppm respectively (Scheme 1).

Refluxing compound **1** with 1-chloro-2,4-dinitrobenzene for 2 hours in dimethylformamide afforded 3-methyl-6-nitro-10*H*-benzo [1,2,4]thiadiazino[2,3-*c*][1,2,4]triazin-4-one (**8**) through the elimination of one molecule of hydrogen chloride and one molecule of nitrous acid. Its ^{1}H NMR spectrum showed the presence of CH_3-triazine as a singlet at 3.02 ppm and the three aromatic protons were observed at 7.27 (d, J = 9.6 Hz), corresponding to ortho coupling of *H*-5 with H-7, 8.20 (dd, J = 9.6, 2.5 Hz), to ortho and meta coupling of *H*-7 with H-5 and H-8, and 8.56 (d, J = 2.3 Hz), and to meta coupling of *H*-8 with H-7.[11]Its mass spectrum showed the existence of the molecular ion peak M^+ at m/z = 277.

Compound **1** was condensed with 2,4-pentandione in refluxing glacial acetic acid for 24 h to afford 6-methyl-4-(1-methyl-3-oxobut-1-enylamino)-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazin-5-one (**9**).



SCHEME 1

Its ^{1}H NMR spectrum showed the presence of triazine-NH as a singlet at 13.62 ppm and N*H*–C=CH as a singlet at 11.55 ppm. Its ^{13}C NMR spectrum showed the presence of triazine-CO at 153.07 ppm and *C*OCH$_3$ at 203.59 ppm.

Reaction of compound **1** with 2-bromopropionyl bromide in refluxing anhydrous benzene furnished 2-bromo-*N*-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-yl)propionamide (**10**) which was cyclized by treatment with triethylamine in refluxing anhydrous benzene to give 3,8-dimethyl[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazine-4,7-dione (**11**). The ^{1}H NMR spectrum of compound **10** showed two signals as singlets at 11.53 (N*H*CO) and 13.78 (triazine-NH) ppm. For compound **11**, the thiadiazine-NH signal was found at 10.35 ppm and triazine-NH in compound **1** was not observed.

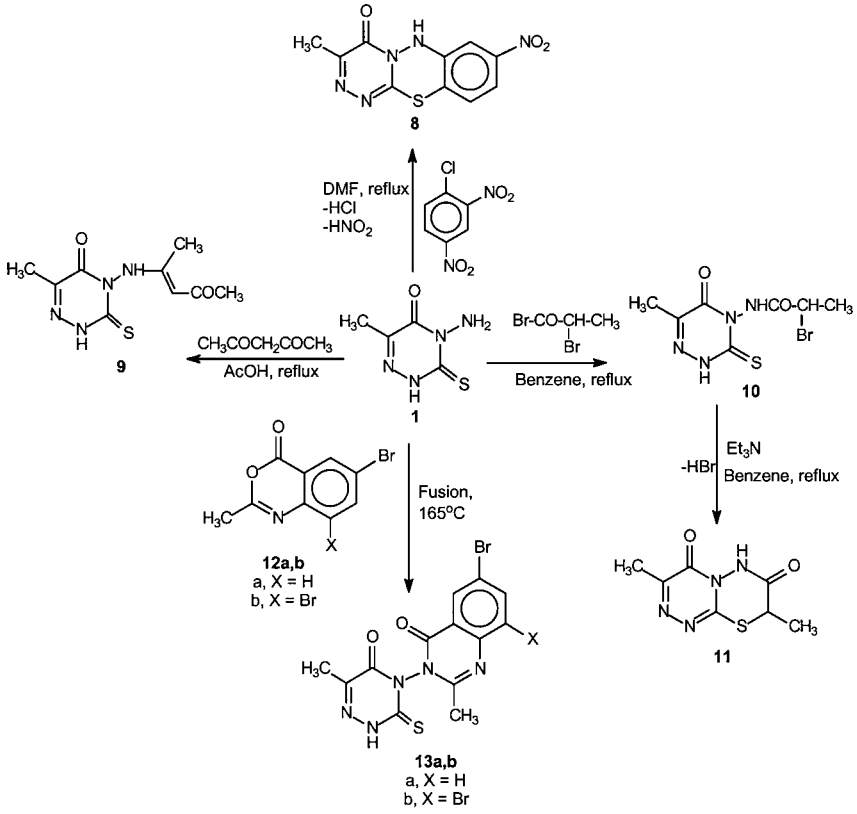
Fusion of compound **1** with 6-bromo-(and/or 6,8-dibromo)-2-methyl-3,1-benzoxazin-4*H*-ones (**12a**,**b**) at 165°C for 3.5 h furnished the corresponding quinazolinone derivatives **13a**,**b** respectively as the sole products (tlc). The ^{1}H NMR spectrum of compound **13a** showed two doublets and one singlet signals corresponding to the three aromatic protons while, for compound **13b** the two aromatic protons were observed as singlets. Only triazine-NH signals were observed for the two products, that confirm the cyclized sructures and not the open ones (Scheme 2).

For the formation of compounds **13a**,**b**, the following mechanism could be postulated: First attack of the lone pair of electrons of the amino group of **1** on the lactone linkage of compounds **12a**,**b** to afford the intermediates **A** and **B** followed by internal nucleophilic attack to give **C** which suffered elimination of water to give **13a**,**b** (Scheme 3).

ANTI-HBV ACTIVITY

The hepatoplastoma cell line HepG2-2.2.15 was used to evaluate the antiviral effect of the tested compounds against HBV.[12] The cells were incubated in growth medium (RPMI-1640, 10% heat-inactivated fetal-calf serum (FCS) and antibiotic) at 37°C, 5% CO_2, with and without test compounds. The average production HBV virion DNA from cell cultures with addition of different concentration of test compound was expressed relatively to HBV virion DNA in cultures without the compound. Quantitation of HBV-DNA was done using a semiquantitative PCR followed by DIG PCR ELISA as previously decribed.[13] The cytotoxic effect of the compounds was accessed by culturing the HepG2-2.2.15 cells in the presence of compounds as for the antiviral assay. The viability of the cells were analysed using a MTT-assay.

Compound **7** showed moderate inhibition of viral replication with a 50% inhibitory concentration $IC_{50} = 98\ \mu M$ and 50% cytotoxic concentration $CC_{50} > 100\ \mu M$, while compounds **2**, **4**, **5**, **6**, **8**, **10**, and

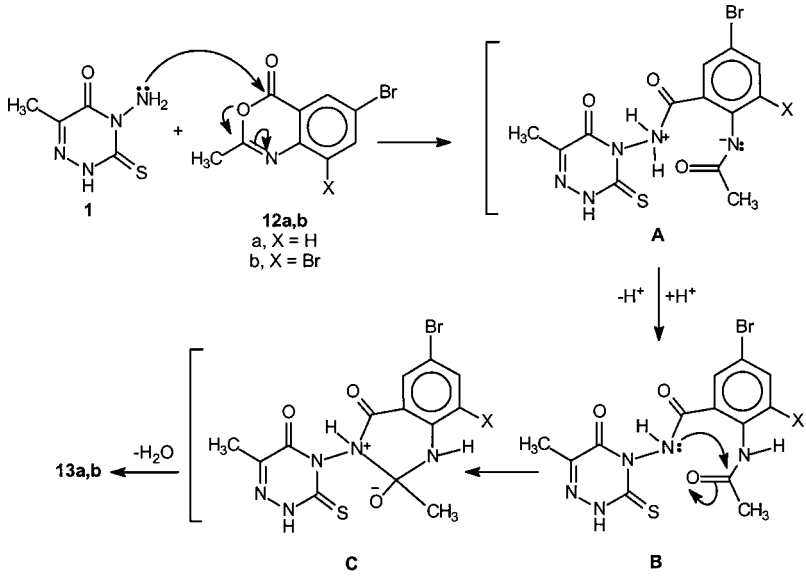


SCHEME 2

11 were neither active against HBV nor cytotoxic. Compounds **3**, **9**, **13a**, and **13b** were not active but were cytotoxic to the HepG2-2.2.15 cells.

EXPERIMENTAL

Melting points were measured in an open capillary tube and were uncorrected. The NMR spectra were recorded on a Bruker 250 FT NMR spectrometer, and tetramethylsilane was the internal standard. Mass spectra were recorded using electron ionization (EI) on a Varian Mat 311A spectrometer. The IR spectra were recorded on a Perkin-Elmer 1720 spectrometer. The microanalyses were measured at the microanalysis unit, Faculty of Science, Tanta University.



SCHEME 3

4-Amino-6-methyl-4-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine (**1**) was prepared by dropwise addition of pyruvic acid to thiocarbohydrazide in boiling water.[14]

General Procedure for Preparation of *N,N′*-bis-(6-methyl-5-oxo-3-thioxo-2,3,5-trihydro-1,2,4-triazin-yl)diamide Derivatives 2–5 and 3-methyl-4-oxo-4*H*-[1,2,4]thiadiazolo-[2,3-*b*][1,2,4]triazine-7-carboxylic Acid Derivatives 6,7

Compound **1** (1.58 g, 10 mmol) and dicarboxylic acids (if any, 10 mmol) in $POCl_3$ (15 mL) were heated at 85°C for 6 h. The reaction mixture was concentrated to 1/3 volume under reduced pressure and cooled. Water (20 mL) was added dropwise at 0°C to the reaction mixture, and the solid product that formed was filtered off and recrystallized. Using oxalic, malonic, fumaric, and maleic acids afforded *N*,*N*′-bis-(6-methyl-5-oxo-3-thioxo-2,3,5-trihydro-1,2,4-triazin-4-yl)diamide derivatives **2–5**, respectively. Using succinic and phthalic acids afforded 3-methyl-4-oxo-4*H*-[1,2,4]thiadiazolo [2,3-*b*][1,2,4]triazin-7-yl-carboxylic acid derivatives **6**,**7** respectively.

N,*N*′-Bis-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-1,2,4-triazin-4-yl) oxalamide (**2**): Recrystallized from 1,4-dioxane; yield 35%; m.p. >300°C; IR (KBr) $\nu = 3423$ (NH), 3165 (CO*NH*), 1691(CO), 1604 (*CO*NH), 1515 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) $\delta = 2.23$ (s, 3H, CH_3), 12.24 (s, 1H,

NHCO), 13.93 (s, 1H, NH) ppm. Anal. Calcd. for $C_{10}H_{10}N_8O_4S_2$: C, 32.43; H, 2.72; N, 30.26. Found: C, 32.33; H, 2,68; N, 30.14.

N,*N*′-Bis-(6-methyl-5-oxo-3-thioxo-2,3,5-trihydro-1,2,4-triazin-4-yl) malonamide (**3**). The compound was recrystallized from MeOH; yield 63%; m.p. 294–296°C; IR (KBr) ν = 3433 (NH), 3204 (NHCO), 1727 (CO), 1687 (CONH), 1501 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 2.18 (s, 3H, CH_3), 3.52 (s, 2H, CH_2), 11.19 (s, 1H, NHCO), 13.74 (s, 1H, NH) ppm; Ms, m/z = 384 (M^+, 4%), 158 (100%); Hrms for $C_{11}H_{12}N_8O_4S_2$: 383.9874, requires 384.0422.

(*E*)-But-2-enedioic acid bis-[(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-1,2,4-triazin-4-yl)amide] (**4**). The compound was separated as a pure material from hot methanol; yield 48%; m.p. 292–294°C; IR (KBr) ν = 3421 (NH), 3193 (CO*NH*), 2898 (CH=CH), 1679 (CO), 1601 (CO*NH*), 1501 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 2.21 (s, 3H, CH_3), 7.19 (d, 1H, J = 14.8 Hz, *trans*-CH=CH) 11.69 (s, 1H, NHCO), 13.82 (s, 1H, NH) ppm; Hrms for $C_{12}H_{12}N_8O_4S_2$: 396.2026, requires 396.2048.

(*Z*)-But-2-enedioic acid bis-[(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-yl)amide] (**5**). The compound was separated as a pure material from hot MeOH; yield 42%; m.p. 260–262°C; IR (KBr) ν = 3425 (NH), 3038 (CO*NH*), 2921 (CH=CH), 1700 (CO), 1619 (*CO*NH), 1553 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 2.22 (s, 3H, CH_3), 7.25 (d, 1H, *J* = 8.2 Hz, *cis*-CH=CH) 11.72 (s, 1H, NHCO), 13.84 (s, 1H, NH) ppm. Anal. Calcd. for $C_{12}H_{12}N_8O_4S_2$: C, 36.36; H, 3.05; N, 28.27. Found: C, 36.21; H, 3.04; N, 28.15

3-(3-Methyl-4-oxo-4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-7-yl)-propionic acid (**6**). The compound was recrystallized from DMF–H_2O; yield 53%; m.p. 238–240°C. IR (KBr) ν = 3224 (OH), 1700 (COO), 1633 (CO), 1513 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 2.07 (s, 3H, CH_3), 3.21–3.44 (m, 4H, CH_2CH_2), 12.20 (br s, 1H, COOH) ppm. Anal. Calcd. for $C_8H_8N_4O_3S$: C, 40.00; H, 3.36; N, 23.32. Found: C, 39.98; H, 3.35; N, 23.11.

2-(3-Methyl-4-oxo-4*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-7-yl) benzoic acid (**7**). The compound was recrystallized from DMF–H_2O; yield 45%; m.p. 235–237°C; IR (KBr) ν = 3170 (OH), 1737 (COO), 1602 (CO), 1484 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 2.22 (s, 3H, CH_3), 7.57–8.24 (m, 4H, Ar), 11.16 (br s, 1H, COOH) ppm. Anal. Calcd. for $C_{12}H_8N_4O_3S$: C, 50.00; H, 2.80; N, 19.43. Found: C, 49.92; H, 2.78; N, 19.01.

3-Methyl-6-nitro-10H-benzo[1,2,4]thiadiazino[2,3-*c*]-[1,2,4]triazin-4-one (8)

Compound **1** (1.58 g, 10 mmol) and 1-chloro-2,4-dinitrobenzene (2 g, 10 mmol) in DMF (25 mL) was refluxed for 2 h. The reaction mixture

was cooled to room temperature and poured on ice cold water (100 mL). The solid product that formed was filtered off and recrystallized from petroleum ether (60–80°C) to give 1.3 g of 8; yield 47%; m.p. 68–70°C; IR (KBr) ν = 3101 (NH), 1603 (CO), 1501 (C=N), 1331 (NO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 3.02 (s, 3H, CH_3), 7.27 (d, 1H, J = 9.6 Hz, H_{arom}), 8.20 (dd, 1H, J = 9.6, 2.5 Hz, H_{arom}), 8.56 (d, 1H, J = 2.3 Hz, H_{arom}) ppm; ^{13}C NMR [DMSO-d_6] δ = 42.6 (CH_3), 117.95, 124.12, 127.66 (C_{arom}), 134.95 (C-3), 135.44 (C-4), 149.21 (N=C–S) ppm; Ms, m/z : 277 (M^+, 16%), 166 (100%). Anal. Calcd. for $C_{10}H_6N_5O_3S$: C, 43.48; H, 2.19; N, 28.70. Found: C, 43.13; H, 2.12; N, 28.46.

6-Methyl-4-(1-methyl-3-oxobut-1-enylamino)-3-thioxo-3,4-dihydro-2H-1,2,4-triazin-5-one (9)

Compound **1** (1.58 g, 10 mmol) and 2,4-pentandione (1.1 mL, 10 mmol) in glacial AcOH (40 mL) were refluxed for 20 h. The solvent was evaporated under reduced pressure and the residual solid was recrystallized from MeOH to give 1.1 g of **9**; yield 42%; m.p. 185–187°C; IR (KBr) ν = 3410 (NH), 3102 (NH–C=CH), 3074 (NH–C=*CH*), 1713 (*CO*), 1605 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 1.78 (s, 3H, C*H*$_3$–C–NH), 2.15 (s, 3H, CH_3), 2.33 (s, 3H, $COCH_3$), 5.36 (s, 1H, C*H*=C–CH_3), 11.55 (s, 1H, N*H*–C–CH_3), 13.62 (s, 1H, NH) ppm; ^{13}C NMR [DMSO-d_6] δ = 16.83 (CH_3), 19.38 (CH_3), 30.22 (CH_3CO), 97.54 (CH), 147.89 (C=*C*–NH), 153.07 (C-5), 170.06 (C-4), 175.68 (C-2), 203.59 (CH_3*C*O) ppm; Ms, m/z : 240 (M^+, 49%), 183 (100%). Anal. Calcd. for $C_9H_{12}N_4O_2S$: C, 44.99; H, 5.03; N, 23.32. Found: C, 44.45; H, 4.93; N, 23.13.

2-Bromo-N-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3H-1,2,4-triazin-4-yl)propionamide (10)

A mixture of compound **1** (1.58 g, 10 mmol) and 2-bromopropionyl bromide (1.1 mL, 10 mmol) was refluxed in anhydrous benzene (40 mL) for 0.5 h. The reaction mixture was cooled. The solid product that formed was filtered off, dried, and chromatographed on a column of silica gel (petroleum ether–ethyl acetate, 2/1, v/v) to give 2.5 g of **10**; yield 85%; m.p. 166–168°C; IR (KBr) ν = 3426 (NH), 3199 (CO*NH*), 1683 (CO), 1614 (*CO*NH), 1515 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 1.88 (t, 3H, J = 7.2 Hz, CHC*H*$_3$), 2.23 (s, 3H, *CH*$_3$), (q, 1H, J = 7.2 Hz, *CH*CH_3), 11.53 (s, 1H, NHCO), 13.78 (s, 1H, NH) ppm; Hrms for $C_7H_9BrN_4O_2S$: 291.9841, requires 291.9629.

3,8-Dimethyl-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazine-4,7-dione (11)

Compound **10** (1.96 g, 5 mmol) was refluxed with Et_3N (0.5 mL, 10 mmol) in anhydrous benzene (20 mL) for 2 h. The solvent was

evaporated till dryness under reduced pressure and the residual solid was chromatographed on a column of silica gel (petroleum ether–ethyl acetate, 2/1, v/v) to give 0.75 g of 3,8-dimethyl-6*H*-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazine-4,7-dione (**11**); yield 71%; m.p. 195–197°C; IR (KBr) ν = 3434 (CO*NH*), 1730 (CO), 1678 (*CO*NH), 1540 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) $\delta = 1.92$ (t, 3H, $J = 7.2$ Hz, CHCH_3), 2.23 (s, 3H, CH_3), 4.42 (q, 1H, $J = 7.2$ Hz, C*H*CH_3), 10.35 (s, 1H, NH); Hrms for $C_7H_8N_4O_2S$: 211.9897, requires 212.036797.

2-Methyl-3-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-3H-quinazolin-4-ones (13a,b)

A mixture of compound **1** (0.8 g, 5 mmol) and 6-bromo-(and/or 6,8-dibromo)-2-methyl-3,1-benzoxazin-4*H*-ones (**12a**,**b**)[15,16] (5 mmol) was fused at 165°C for 3.5 h. The reaction mixture was cooled to room temperature, treated with EtOH (10 mL), filtered off, and recrystallized from EtOH.

6-Bromo-2-methyl-3-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3H-[1,2,4]triazin-4-yl)-3*H*-quinazolin-4-one **13a**. Yield 48%; m.p. 276–278°C; IR (KBr) ν = 3207 (NH), 1697 (CO), 1610 (CO), 1540 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) $\delta = 2.30$ (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.71 (d, 1H, $J = 8.1$ Hz H_{arom}), 8.11 (d, 1H, $J = 8.1$ H_{arom}), 8.24 (s, 1H, H_{arom}), 14.33 (s, 1H, NH) ppm; Hrms for $C_{13}H_{10}BrN_5O_2S$: 378.9954, requires 378.9738.

6,8-Dibromo-2-methyl-3-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-yl)-3*H*-quinazolin-4-one (**13b**); yield 46%; m.p. >300°C; IR (KBr) ν = 3448 (NH), 1690 (CO), 1608 (CO), 1508 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) $\delta = 2.30$ (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 8.24 (s, 1H, H_{arom}), 8.51 (s, 1H, H_{arom}), 14.34 (s, 1H, NH) ppm; Hrms for $C_{13}H_9Br_2N_5O_2S$: 459.8132, requires 459.8843.

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REFERENCES

[1] A. K. Mansour, S. B. Awad, and S. Antown, *Z. Naturforsch*, **B29,** 792 (1974).
[2] W. M. Davidson and W. D. Boykin, *J. Pharm. Sci.*, **65,** 737 (1978).
[3] P. W. Hielman, R. D. Gielman, A. J. Scozzie, R. J. Wayner, M. J. Gollo, and S. Z. Ariyan. *J. Pharm. Sci.*, **69,** 282 (1980).

[4] J. M. Gullso, W. P. Paul, J. R. Wayner, and R. E. Moser. *Ger. Offen.*, 2, 821, 381 (Cl. CO7D253/06), 30 Nov 1978; C.A., **90,** 121664m (1979).
[5] W. B. Lacefield, *Fr. Demande*, 2, 343, 479 (Cl.A61K31/53), 7 Oct. 1977; C.A. **89,** 24372m (1979).
[6] L. C. March, G. S. Bajwa, J. Lee, K. Wasti, and M. M. Joullie, *J. Med. Chem.*, **19,** 845 (1976).
[7] M. Mizutani and Y. Sanemitsu, *J. Heterocycl. Chem.*, **19,** 1577 (1982).
[8] H. Golgolab and L. Hosseini-Gohari, *J. Heterocycl., Chem.*, **10,** 387 (1973).
[9] D. E. Jackman, *J. Heterocycl. Chem.*, **27,** 1053 (1990).
[10] M. M. Heravi, R. A. Ibrahimian, M. Bakavoli, and M. H. Arbabzavar, *Indian J. Chem. Sect. B.*, **36,** 1025 (1997).
[11] D. L. Pavia, G. M. Lampman, and G. S. Kriz, *Introduction to Spectroscopy* (Saunders College Publishing, Philadelphia, 1996), 2nd ed., chap. 5, pp. 232.
[12] B. E. Korba and J. L. Gerin, *Antiviral Res.*, **19,** 55 (1992).
[13] T. Fouad, C. Nielsen, L. Bruun, and E. B. Pedersen, *Sc. J. Az. Med. Fac. (GIRLS)*, **19,** 1173 (1998).
[14] A. Dornow, H. Menzel, and P. Marx, *Chem. Ber.*, **97,** 2173 (1964).
[15] A. S. Wheeler and W. M. Oates, *J. Amer. Chem Soc.*, **32,** 770 (1910).
[16] R. S. Misra, C. Dwivedi, and S. S. Parmar, *J. Heterocycl. Chem.*, **17,** 1337 (1980).