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SYNTHESIS AND ANTIVIRAL AND ANTITUMOR ACTIVITIES OF 2*H*-[1,2,3]TRIAZOLO[4,5-*d*]PYRIMIDINES AND 1*H*-, 2*H*-, AND 3*H*-[1,2,3]TRIAZOLO[4,5-*d*]PYRIMIDIN-5(4*H*)-ONE-7(6*H*)-THIONES

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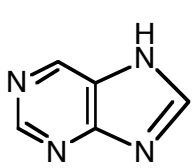
Abstract – This paper describes a facile synthesis of 2-aryl-2*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**3a-o**) and 7-amino-2-aryl-5-phenyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines (**6a-e**) prepared by oxidative cyclization of 6-amino-5-arylazopyrimidine-2,4(1*H*,3*H*)-diones (**2a-o**) and 4,6-diamino-5-arylazo-2-phenylpyrimidines (**5a-e**) with $CuSO_4$, respectively, and a reliable thionation of [1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**3a,e,f**, **7a,b** and **9**) accomplished by the reaction with phosphorous pentasulfide or Lawesson's reagent as well as evaluation of their antiviral and antitumor activities in vitro.

INTRODUCTION

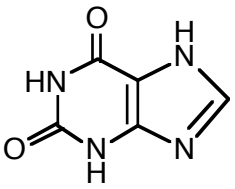
Fused pyrimidines and purines have been utilized as mimics of the naturally occurring xanthines and nucleic acid bases. A large number of purines (**I**), xanthines (**II**) and their analogues are known to possess wide biological activities, *e.g.*, antiviral[1] and anti-tumor activities[2] as well as xanthine oxidase inhibitory activities.[3] Therefore, in the past few decades much effort has been expended in the search for effective antineoplastic and antiviral agents, and for this purpose the structure of natural purines has been modified resulting in potent antagonists in biological systems.[4] Similarly, the positional alternations of different substituents on xanthine have resulted in several potent antagonists for potency and selectivity in biological systems.[5] Beside, the compounds (**III** and **IV**) substituted by sulfur for oxygen at the 6-position of guanine and hypoxanthine resulted in potential activity[6] against a wide

spectrum of rodent tumors, leukemia and adenocarcinoma 755 test system. Substituted 6-thioxanthines (**V**) have also aroused considerable attention for their biological activities.[7] The comparative study of 8-azapurine (**VI**) and 8-azaxanthine (**VII**) to purine and xanthine is not sufficient to explore the biological activities in this area.

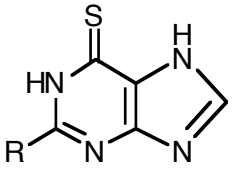
A program on synthesis of fused pyrimidine derivatives[8] for biological evaluation has been in progress in our laboratory. Just recently we have communicated[9] the synthesis of 3-alkyl/aryl-3*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones and their regioselective alkylation, and these compounds were found very low toxic. On the contrary, the 2-substituted 2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*, 6*H*)-diones have been reported[10] as potential antagonists of adenosine receptors. However, so many 2-substituted derivatives have not been synthesized yet for the biological evaluation. Therefore, in the present paper we would like to report the synthesis of 2-aryl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**VIII**) and 7-amino-2-aryl-5-phenyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines (**IX**) along with the study of thionation of 1*H*-, 2*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones with the evaluation of their antiviral and antitumor activities.



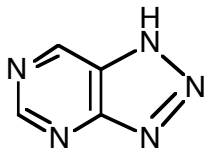
purine (**I**)



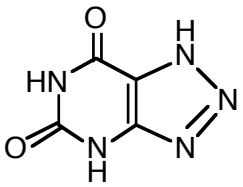
xanthine (**II**)



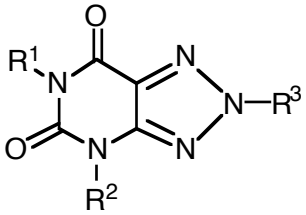
R = NH_2 (**III**), R = H (**IV**)
R = OH (**V**)



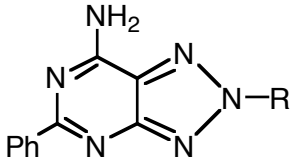
8-azapurine (**VI**)



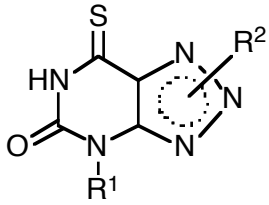
8-azaxanthine (**VII**)



(**VIII**)



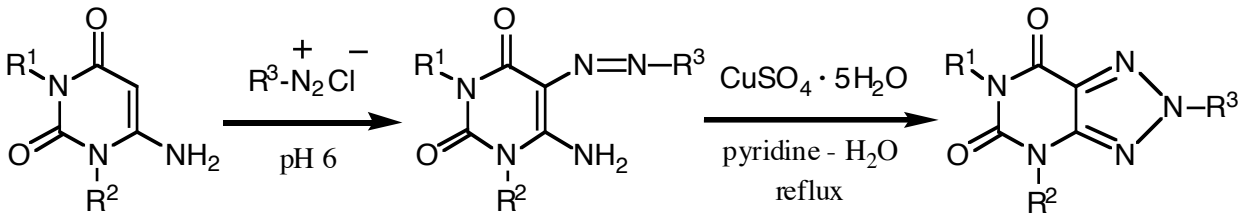
(**IX**)



(**X**)

RESULTS AND DISCUSSION

The key intermediate, 6-amino-5-arylazopyrimidine-2,4(1*H*,3*H*)-diones (**2a-o**) were prepared from 6-aminouracils (**1a-d**) according to the modified procedure outlined previously.[11] Namely, treatment of 6-aminouracils (**1a-d**) with appropriate diazotized aromatic amines at pH 6 afforded the corresponding 5-arylazo derivatives (**2a-o**) in quantitative yield as shown in Scheme 1 and Tables 1 and 2. For the conversion of 6-amino-5-arylazopyrimidine derivatives into 2-aryl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine derivatives, several procedures have been reported previously, *e.g.,* heating,[12] chromic acid oxidation,[13]

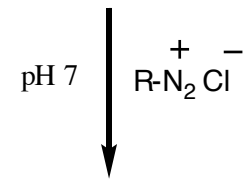


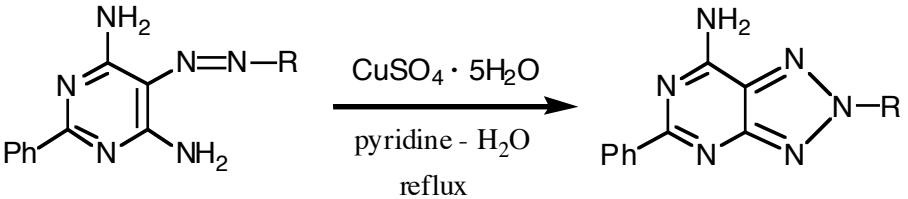
1a-d **2a-o** **3a-o**

a: $R^1 = R^2 = H$
b: $R^1 = Me$, $R^2 = H$
c: $R^1 = H$, $R^2 = Me$
d: $R^1 = R^2 = Me$

2, 3 **a**: $R^1 = R^2 = H$, $R^3 = 2,6\text{-}Cl_2\text{-}C_6H_3$
b: $R^1 = Me$, $R^2 = H$, $R^3 = 2,6\text{-}Cl_2\text{-}C_6H_3$
c: $R^1 = Me$, $R^2 = H$, $R^3 = 2,4,6\text{-}Cl_3\text{-}C_6H_2$
d: $R^1 = H$, $R^2 = Me$, $R^3 = 2,4\text{-}Cl_2\text{-}C_6H_3$
e: $R^1 = H$, $R^2 = Me$, $R^3 = 2,6\text{-}Cl_2\text{-}C_6H_3$
f: $R^1 = H$, $R^2 = Me$, $R^3 = 2,4,6\text{-}Cl_3\text{-}C_6H_2$
g: $R^1 = R^2 = Me$, $R^3 = 2\text{-}Cl\text{-}C_6H_4$
h: $R^1 = R^2 = Me$, $R^3 = 2\text{-}NO_2\text{-}C_6H_4$
i: $R^1 = R^2 = Me$, $R^3 = 3\text{-}MeO\text{-}C_6H_4$
j: $R^1 = R^2 = Me$, $R^3 = 4\text{-}NC\text{-}C_6H_4$
k: $R^1 = R^2 = Me$, $R^3 = 2,4\text{-}Cl_2\text{-}C_6H_3$
l: $R^1 = R^2 = Me$, $R^3 = 2,6\text{-}Cl_2\text{-}C_6H_3$
m: $R^1 = R^2 = Me$, $R^3 = 3,4\text{-}Me_2\text{-}C_6H_3$
n: $R^1 = R^2 = Me$, $R^3 = 2\text{-}NO_2\text{-}4\text{-}Me\text{-}C_6H_3$
n: $R^1 = R^2 = Me$, $R^3 = 2\text{-}NO_2\text{-}4\text{-}Me\text{-}C_6H_3$
o: $R^1 = R^2 = Me$, $R^3 = 2,4,6\text{-}Cl_3\text{-}C_6H_2$

4





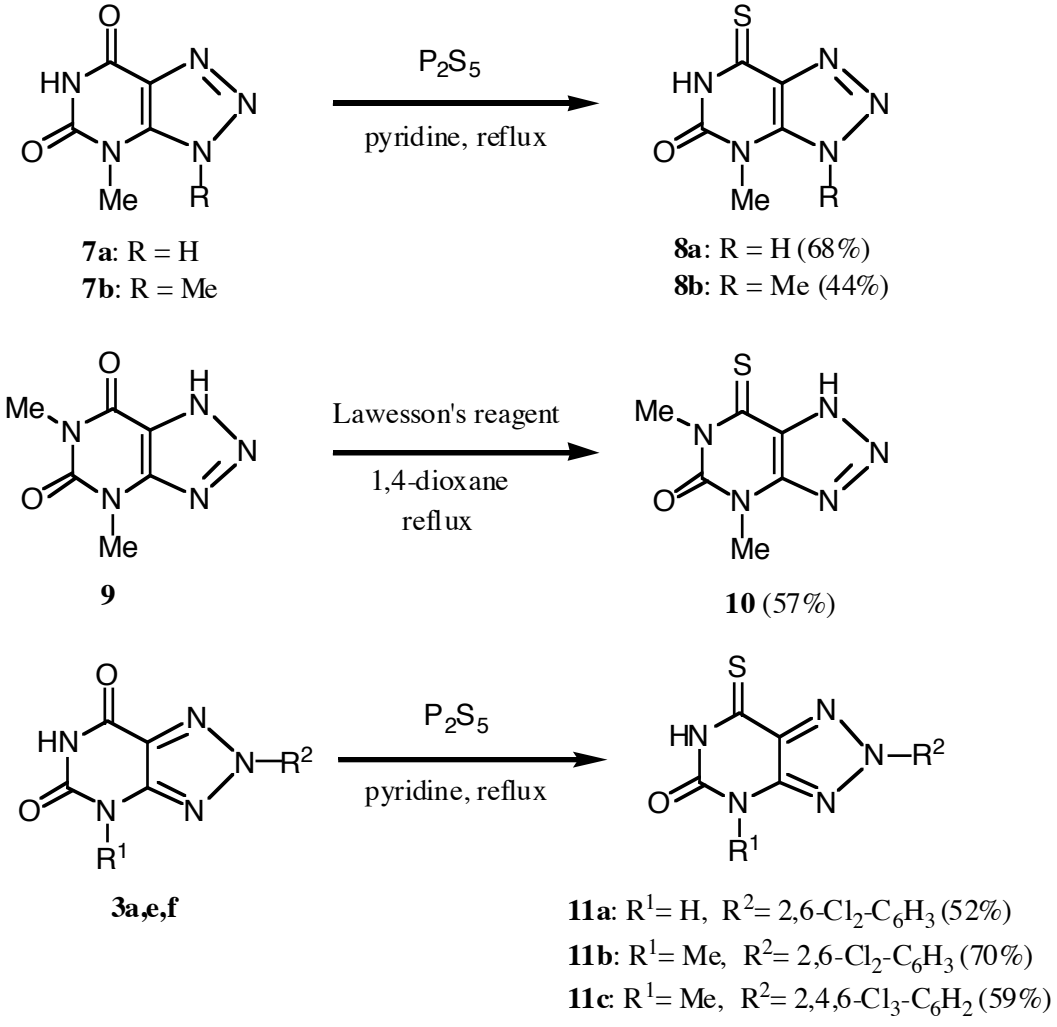
5a-e **6a-e**

5, 6 **a**: R = Ph
b: R = 2-Cl-C_6H_4
c: R = 4-Cl-C_6H_4
d: R = 2,6-Cl_2-C_6H_3
e: R = 3,4,5-MeO_3-C_6H_2

Scheme 1

lead tetraacetate oxidation,[14] oxidation with alkaline copper sulfate,[15] and oxidation with copper sulfate[11,16] in pyridine-water. In the present study, the oxidative cyclization of the 6-amino-5-arylazopyrimidine derivatives (**2a-o**) leading to the formation of 2-aryl-2*H*-[1,2,3]triazolo[4,5-*d*]-pyrimidine-5,7(4*H*,6*H*)-diones (**3a-o**) was accomplished with copper sulfate[16] in pyridine-water in excellent yields (Tables 3 and 4). The 4,6-diamino-5-arylazo-2-phenylpyrimidines (**5a-e**) were also prepared by treating of 4,6-diamino-2-phenylpyrimidine (**4**) with the appropriate diazotized aromatic amines, which on subsequent cyclization with copper sulfate afforded the corresponding 7-amino-2-aryl-5-phenyl-2*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidines (**6a-e**) in good yields (Tables 5 and 6).

Thionation of xanthine[17] and 1,3-dimethylxanthine (theophylline)[18] takes place selectively at the 6-position with phosphorous pentasufide. Sometimes under drastic conditions or with an excess thionating agent[18] it takes place both at the 2- and 6-positions. The thionation of unsubstituted 8-azaxanthine (VII) is not smooth enough. We tried to do the thionation of unsubstituted 8-azaxanthine directly by heating under reflux with phosphorous pentasulfide in pyridine as well as with Lawesson's reagent in 1,4-dioxane. However, these methods were not effective because of less reactivity of 8-azaxanthine toward these reagents. Beside, for longer reaction time and under more drastic conditions, some decomposition of 8-azaxanthine took place. Cresswell *et al*. reported[19] the synthesis of 6-thio-8-azaxanthine by heating 8 -azaxanthine-3-*N*-oxide with phosphorous pentasulfide in pyridine, and they also attained the same 6-thio compound using ammonium salt of 8-azaxanthine instead of 8-azaxanthine-3-*N*-oxide. We now successfully accomplished the thionation of the matylated derivatives, 4-methyl-1*H*- (**7a**) and 3,4-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**7b**), with phosphorous pentasulfide in pyridine at boiling temperature leading to the formation of the corresponding 7-thio derivatives (**8a**, 68% yield; **8b**, 44% yield) (Scheme 2).



7a: R = H
7b: R = Me

8a: R = H (68%)
8b: R = Me (44%)

9

10 (57%)

3a,e,f

11a: R^1= H, R^2= 2,6-Cl_2-C_6H_3 (52%)
11b: R^1= Me, R^2= 2,6-Cl_2-C_6H_3 (70%)
11c: R^1= Me, R^2= 2,4,6-Cl_3-C_6H_2 (59%)

Scheme 2

Thus, the compounds (**7a**,**b**) replaced by a methyl group for the hydrogen atom at the 4-position of [1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones facilitate the thionation at the 7-position. Nishigaki *et al.* reported[20] that heating 4,6-dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (8-azatheophylline) (**9**) with an excess phosphorous pentasulfide in pyridine at boiling temperature afforded the dithionated compound, 5,7-dimethyl[1,2,3]thiadiazolo[5,4-*d*]pyrimidin-4(5*H*)-one-6(7*H*)-thione, exclusively *via* the υ-triazole-thiadiazole rearrangement of the 5,7-dithione intermediate. When we carried out the thionation of 8-azatheophylline (**9**) with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) instead of phosphorous pentasulfide in 1,4-dioxane at boiling temperature, the desired 4,6-dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**10**) was obtained in 57% yield. The IR spectrum of compound (**10**) showed the characteristic maximum absorption bands at 3100 and 1700 cm^{-1} due to NH and C=O group, respectively. The ^{1}H-NMR spectrum exhibited chemical shifts at δ 3.62 and 3.79 attributed to 6-N-CH_3 and 4-N-CH_3 protons, respectively, though the signal assigned to 3-NH proton did not appear due to high acidity. The spectral and microanalysis data for compound (**10**) were quite satisfactory to assign the mono thionation without any ring rearrangement. We also successfully accomplished the thionation of 2-ary-2*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**3a**,**e**,**f**) with phosphorous pentasulfide in pyridine at boiling temperature to afford the corresponding 7-thio derivatives (**11a,** 52% yield; **11b**, 70% yield; **11c**, 59% yield). Cresswell *et al*. reported[19] that the thionation of 8-azaxanthine, 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione-4-*N*-oxide, took place at the 7-position. Hence, considering the above observation it can be said that the thionation of [1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**7a**,**b**, **9** and **3a**,**e**,**f**) happened exclusively at the 7-position in the same manner as xanthine.

BIOLOGICAL EVALUATION

The compounds (**3a-o**, **6a-e**, **8a**,**b** and **11a**,**b**) were evaluated for antiviral activity in vitro against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) according to the known procedure.[24,25] The results are summarized in Table 7. The potency of antiviral activity of each compound is expressed as a minimum inhibitory concentration (ED_{50}) required to reduce virus plaque formation by 50% under experimental conditions. 7-Amino-2-aryl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines (8-azaadenines) (**6a**,**b**,**d**,**e**) exhibited their activity against both types of virus at the concentration >4 μg/mL. 4,6-Dimethyl-2-(4-methyl-2-nitrophenyl)-2*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**3n**) also exhibited activity at the same concentration. Compounds (**3b**,**d-j**,**m**,**o** and **6c**) showed activity against both herpes virus at higher concentration (>20 μg/mL). Other compounds did do show any activity up to 100 μg/mL.

Antineoplastic activities of the test compounds were also evaluated against CCRF-HSB-2 and KB cells according to the modified MTT assay[26] for cellular growth and survival application method developed by

Mosmann[27] in vitro. The results, *i.e.* the 50% inhibitory concentration [IC_{50} (μg/mL)] of each compound against both cells are summarized in Table 7. Among the all compounds, 8-azaadenine derivatives (**6a–e**) showed more potent activities against these tumor cells, though these compounds were not equally active against both cells. For example, compounds (**6a** and **6c**) exhibited more potency against KB cell at the concentration 2.3 μg/mL and 4.8 μg/mL than against CCRF-HSB-2 cell at the concentration 6.8 μg/mL and 47.0 μg/mL, respectively. Compound (**6b**) showed nearly equal activity against CCRF-HSB-2 (8.2 μg/mL) and KB cells (9.4 μg/mL). Most of 8-azaxanthines (**3a–o**) and their thioxo derivatives (**8a**,**b**, **11a**,**b**) showed very week activities at the concentration 30-60 μg/mL.

Since 8-azaxanthines and 8-azaadenines have a great deal of coincidence in structure and reactivity with xanthines and adenines, their positional and chemical alternation may result in potent antagonist in biological system. Therefore, a number of 8-azaxanthines and 8-azaadenines were prepared and tested for their antiviral and antitumor activity in vitro. 8-Aazaadenine derivatives showed somewhat antiviral and antitumor activities, but 8-azaxanthines and 6-thio-8-azaxanthines were less active compounds. Therefore, the sulfur at 6-position of 8-azaxanthines did not improve their antiviral or antitumor activity. Further analogues syntheses and evaluation of their biological activities are in progress.

EXPERIMENTAL

Mps were determined on a Yanagimoto micro-melting point hot stage apparatus and were uncorrected. Microanalyses were measured using a Yanako CHN Corder MT-5-apparatus. IR spectra were obtained on a JASCO FT/IR-200 spectrophotometer in Nujol mulls. ^{1}H-NMR spectra were recorded using a VXR 300 MHz spectrometer and chemical shift values were expressed in δ values (ppm) relative to tetramethylsilane as an internal standard. Coupling constants are given in Hz and signals are quoted as follows: s, singlet; d, doublet; t, triplet; br, broad; m, multiplet. All reagents were of commercial quality from freshly opened containers and were used without further purification. Reaction progress was monitored by analytical thin-layer chromatography (TLC) on pre-coated glass plates (silica gel 60 F_{254} Plate-Merck) using the solvent systems of A (AcOEt) and B [*n*-hexane : AcOEt (1:1)] unless being cited in the table and products were visualized by UV light. Column chromatography was accomplished on Daisogel IR-60 (63/210 mesh, Daiso Co.). Most of physical and spectral data for the products prepared here are summarized in the Tables 1-6.

General procedure for 6-amino-5-arylazopyrimidine-2,4(1*H*,3*H*)-diones (2a-o)

A mixture of aromatic amine (5.7 mmol), conc. HCl (12 mL) and water (5 mL) was slightly warmed to convert to the amine hydrochloride. Then, the mixture was cooled in an ice bath with stirring and

Table 1. Physical and analytical data for compounds (**2a-o**)

Compd No.	Yield (%)	Appearance (shape of crystals)	Mp[a] (°C)	Formula (R_f)[b]	Analysis (%) Calcd (Found) C	H	N
2a	94	yellow (powder)	>300	$C_{10}H_7N_5O_2Cl_2 \cdot 1/8H_2O$ (0.13)	39.72 (40.09	2.42 2.43	23.16 22.77)
2b	89	yellow (powder)	266-267	$C_{11}H_9N_5O_2Cl_2$ (0.33)	42.06 (41.68	2.89 2.94	22.29 22.33)
2c	91	yellow (powder)	>300	$C_{11}H_8N_5O_2Cl_3$ (0.40)	37.90 (38.16	2.31 2.45	20.09 19.94)
2d	89	orange (powder)	>300	$C_{11}H_9N_5O_2Cl_2$ (0.42)	42.06 (41.88	2.89 2.89	22.29 22.32)
2e	87	yellow (needles)	270-271	$C_{11}H_9N_5O_2Cl_2$ (0.45)	42.06 (42.02	2.89 2.93	22.29 22.09)
2f	93	yellow (powder)	284-285	$C_{11}H_{83}N_5O_2Cl \cdot 1/4H_2O$ (0.48)	37.42 (37.62	2.43 2.40	19.84 19.52)
2g[c]	81	yellow (needles)	>300	$C_{12}H_{12}N_5O_2Cl$ (0.56)	49.07 (48.67	4.12 4.11	23.84 23.73)
2h	86	orange (needles)	>300	$C_{12}H_{12}N_6O_4 \cdot 1/3H_2O$ (0.57)	46.45 (46.71	4.11 3.97	27.09 26.74)
2i	78	yellow (powder)	252-253	$C_{13}H_{15}N_5O_3$ (0.45)	53.97 (53.82	5.23 5.03	24.21 24.10)
2j	91	yellow (powder)	289-290	$C_{13}H_{12}N_6O_2 \cdot 1/6H_2O$ (0.41)	54.35 (54.64	4.33 4.41	29.25 28.97)
2k	90	orange (needles)	277-278	$C_{12}H_{11}N_5O_2Cl_2 \cdot 1/2H_2O$ (0.62)	42.75 (42.70	3.59 3.49	20.77 20.85)
2l	89	orange (needles)	240-241	$C_{12}H_{11}N_5O_2Cl_2 \cdot 2/3H_2O$ (0.61)	42.37 (42.55	3.65 3.49	20.59 20.58)
2m[d]	72	orange (needles)	285-286	$C_{14}H_{17}N_5O_2$ (0.55)	58.52 (58.53	5.96 5.65	24.37 24.17)
2n	82	orange (needles)	300-301	$C_{13}H_{14}N_6O_4 \cdot 1/8H_2O$ (0.46)	48.71 (48.46	4.48 4.37	26.22 26.49)
2o	84	yellow (powder)	288-289	$C_{12}H_{10}N_5O_2Cl_3$ (0.48)	39.75 (39.89	2.78 2.89	19.31 19.58)

[a]All compounds were recrystallized from 75% aqueous DMF.
[b]Solvent system for TLC: AcOEt. [c]Ref. 21. [d]Ref. 22.

treated with a cold solution of $NaNO_2$ (6.7 mmol) in water (4 mL) for *ca.* 30 min. After the excess nitrous acid was destroyed with urea, the resulting solution was poured into ice water (100 mL) containing $NaHCO_3$ (10 g) and the pH of the solution was adjusted to *ca.* 6 with $NaHCO_3$. A solution of 6-aminouracils (**1a-d**) (5.0 mmol) in hot water was added to the appropriate diazonium chloride solution under stirring and the reaction mixture was stirred at rt for 30 min. Then, the resulting solution was warmed at 50–60 °C for a few min, cooled to room temperature with stirring and kept for overnight.

Table 2. IR and ^{1}H-NMR spectroscopic data for compounds (**2a-o**)

Compd No.	[ν_{max} (Nujol)/cm^{-1}][a]	δ_H[300 MHz; $(CD_3)_2SO$; Me_4Si)
2a	*3260*, 3145, 3080 (NH) 1720, 1695 (C=O)	7.25 (1H, t, J = 8.1, Ar-*p*H), 7.50 (2H, d, J = 8.1, Ar-*m*H), 7.80 and 10.24 (each 1H, each s, NH_2), 10.87 (2H, s, 2 x NH)
2b	3260, 3120, *3080* (NH) 1720, 1685 (C=O)	3.18 (3H, s, CH_3), 7.25 (1H, t, J = 8.1, Ar-*p*H), 7.49 (2H, d, J = 8.1, Ar-*m*H), 7.77 and 10.19 (each 1H, each s, NH_2), 11.23 (1H, s, NH)
2c	3255, *3160*, 3080 (NH) 1740, 1620 (C=O)	3.20 (3H, s, CH_3), 7.55 (2H, s, Ar-H), 7.82 and 10.21 (each 1H, each s, NH_2), 11.22 (1H, br s, NH)
2d	3320, 3200, 3065 (NH) 1720, 1685 (C=O)	3.32 (3H, s, CH_3), 7.39 (1H, dd, $J_{3',5'}$ = 1.8, $J_{5',6'}$ = 8.7, 5'-H), 7.57 (1H, d, J = 1.8, 3'-H), 7.78 (1H, d, J = 8.4, 6'-H), 9.06 and 11.20 (each 1H, each s, NH_2), 12.24 (1H, s, NH)
2e	3220, 3120, 3080 (NH) 1725, 1655 (C=O)	3.31 (3H, s, CH_3), 7.23 (1H, d, J = 8.1, Ar-*p*H), 7.47 (2H, d, J = 8.1, Ar-*m*H), 8.89 and 11.12 (each 1H, each br s, NH_2), 11.52 (1H, s, NH)
2f	3180, 3070 (NH) 1730, 1680 (C=O)	3.32 (3H, s, CH_3), 7.59 (2H, s, Ar-H), 8.99 and 11.22 (each 1H, each s, NH_2), 11.53 (1H, br s, NH)
2g	3245, *3160* (NH) 1720, 1625 (C=O)	3.29 (3H, s, 3-N-CH_3), 3.40 (3H, s, 1-N-CH_3), 7.25 (1H, dt, $J_{4',6'}$ = 1.5, $J_{3',4'}$ = $J_{4',5'}$ = 7.5, 4'-H), 7.37 (1H, dt, $J_{3',5'}$ = 1.5, $J_{4',5'}$ = $J_{5',6'}$ = 7.5, 5'-H), 7.49 (1H, dd, $J_{3',5'}$ = 1.5, $J_{3',4'}$ = 7.8, 3'-H), 7.80 (1H, dd, $J_{4',6'}$ = 1.5, $J_{5',6'}$ = 8.1, 6'-H), 8.95 and 12.25 (each 1H, each s, NH_2)
2h	3255, *3180* (NH) 1720, 1630 (C=O)	3.27 (3H, s, 3-N-CH_3), 3.37 (3H, s, 1-N-CH_3), 7.44 (1H, dt, $J_{4',6'}$ = 1.2, $J_{3',4'}$ = $J_{4',5'}$ = 7.8, 4'-H), 7.72 (1H, dt, $J_{3',5'}$ = 1.2, $J_{4',5'}$ = $J_{5',6'}$ = 7.8, 5'-H), 7.91-7.97 (2H, m, 3'- and 6'-H), 9.18 and 12.05 (each 1H, each s, NH_2)
2i	3300 (NH) 1705, 1625 (C=O)	3.26 (3H, s, 3-N-CH_3), 3.37 (3H, s, 1-N-CH_3), 3.82 (3H, s, O-CH_3), 6.83 (1H, d, J = 7.5, 5'-H), 7.21-7.34 (3H, m, 2'-, 4'- and 6'-H), 8.62 and 11.79 (each 1H, each s, NH_2)
2j	3360, 3250 (NH) 1720, 1650 (C=O)	3.27 (3H, s, 3-N-CH_3), 3.39 (3H, s, 1-N-CH_3), 7.80 (4H, d, J = 6.0, Ar-H), 8.91 and 11.89 (each 1H, each s, NH_2)
2k	3245, *3160* (NH) 1700, 1630 (C=O)	3.27 (3H, s, 3-N-CH_3), 3.38 (3H, s, 1-N-CH_3), 7.41 (1H, dd, $J_{3',5'}$ = 1.5, $J_{5',6'}$ = 9.0, 5'-H), 7.60 (1H, d, J = 1.5, 3'-H), 7.77 (1H, d, J = 9.0, 6'-H), 9.08 and 12.15 (each 1H, each s, NH_2)
2l	*3200*, *3120* (NH) 1710, 1635 (C=O)	3.26 (3H, s, 3-N-CH_3), 3.39 (3H, s, 1-N-CH_3), 7.20-7.26 (1H, m, 4'-H), 7.46 (2H, dd, $J_{3',5'}$ = 1.2, $J_{3',4'}$ = $J_{4',5'}$ = 8.1, 3'- and 5'-H), 8.89 and 11.49 (each 1H, each s, NH_2)
2m	3260, *3200* (NH) 1695, 1610 (C=O)	2.26 and 2.29 (each 3H, each s, 2 x Ar-CH_3), 3.25 (3H, s, 3-N-CH_3), 3.36 (3H, s, 1-N-CH_3), 7.18 (1H, d, J = 8.1, 5'-H), 7.39 (1H, dd, $J_{2',6'}$ = 1.8, $J_{5',6'}$ = 8.1, 6'-H), 7.44 (1H, d, J = 1.8, 2'-H), 8.53 and 11.76 (each 1H, each br s, NH_2)
2n	3300, *3180* (NH) 1705, 1620 (C=O)	2.56 (3H, s, Ar-CH_3), 3.26 (3H, s, 3-N-CH_3), 3.39 (3H, s, 1-N-CH_3), 7.53 (1H, d, J = 8.1, 6'-H), 7.91 (1H, dd, $J_{3',5'}$ = 2.1, $J_{5',6'}$ = 8.4, 5'-H), 8.23 (1H, d, J = 2.1, 3'-H), 8.78 and 11.63 (each 1H, each s, NH_2)
2o	3210, 3140 (NH) 1720, 1620 (C=O)	3.23 (3H, s, 3-N-CH_3), 3.37 (3H, s, 1-N-CH_3), 7.67 (2H, s, Ar-H), 8.97 and 11.38 (each 1H, each s, NH_2)

[a] The IR absorption value in italic refers to wave numbers at which shoulder or inflexion occurs in the absorption.

The solid deposited was collected by filtration and washed well with water to afford the corresponding 5-arylazo derivatives (**2a-o**) as shown in Tables 1 and 2.

General procedure for 2-aryl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (3a-o)

A mixture of 6-amino-5-arylazopyrimidine-2,4(1*H*,3*H*)-diones (**2a-o**) (2.6 mmol), $CuSO_4 \cdot 5H_2O$ (2.7 g), water (8 mL) and pyridine (16 mL) was heated under reflux for 3–4 h. Then, water (130 mL) was added to the reaction mixture and the mixture was made weak acidity with dilute HCl. Upon cooling to rt, the solid deposited was collected by filtration and washed well with water, which was recrystallized from an appropriate organic solvent to afford the corresponding 2-aryl-2*H*-triazolopyrimidine derivatives (**3a-o**) as shown in Tables 3 and 4.

General procedure for 4,6-diamino-5-arylazo-2-phenylpyrimidines (5a-e)

A warmed solution of 4,6-diamino-2-phenylpyrimidines (**4**) (3.0 mmol) in water (30 mL) containing conc. HCl (1 mL) was added to the diazonium chloride solution prepared from an appropriate aromatic amine (3.6 mmol) in the manner described above for the 5-azo derivatives (**2a-o**). After the reaction mixture was stirred at rt for 30 min, the pH of the reaction mixture was adjusted to *ca.* 7 with $NaHCO_3$. Then, the mixture was stirred at rt for an additional 1 h and kept for overnight. The solid deposited was collected by filtration and washed well with water to afford the corresponding 5-azo derivatives (**5a-e**) as shown in Tables 5 and 6.

General procedure for 7-amino-2-aryl-5-phenyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidines (6a-e)

A mixture of 4,6-diamino-5-arylazo-2-phenylpyrimidines (**5a-e**) (1.2 mmol), $CuSO_4 \cdot 5H_2O$ (1.25 g), water (5 mL) and pyridine (10 mL) was heated under reflux for 3–4 h. Then, water (100 mL) was added to the reaction mixture. After cooling to rt, the mixture was acidified with AcOH and kept for overnight. The solid deposited was collected by filtration, washed well with water and recrystallized from a mixture of *n*-hexane and ethyl acetate to afford the corresponding 2-aryl-2*H*-triazolopyrimidine derivatives (**6a-e**) as shown in Tables 5 and 6.

4-Methyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (8a)

A mixture of 4-methyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**7a**)[9] (2.0 g, 11.97 mmol) and P_2S_5 (5.85 g, 26.33 mmol) in pyridine (100 mL) was heated under reflux for 4 h. After the reaction was complete, the solution was evaporated *in vacuo* and water (50 mL) was added to the residue. The resulting suspension was heated at 100 °C under stirring for 30 min. Upon cooling to room temperature, the solid deposited was collected by filtration, dissolved in 0.5N NaOH and reprecipitated with 3N HCl.

Table 3. Physical and analytical data for compounds (**3a-o**)

Compd No.	Yield (%)	Appearance (shape of crystals)	Mp[a] (°C)	Formula (R_f)[b]	Analysis (%) Calcd (Found) C	H	N
3a	75	colorless (needles)	>300	$C_{10}H_5N_5O_2Cl_2$ (0.18)	40.29 (40.09	1.69 1.89	23.49 23.34)
3b	69	pale yellow (powder)	>300	$C_{11}H_7N_5O_2Cl_2 \cdot 2/5H_2O$ (0.39)	41.38 (41.56	2.46 2.64	21.93 21.66)
3c	72	pale yellow (powder)	287-288	$C_{11}H_6N_5O_2Cl_3$ (0.51)	38.12 (37.95	1.75 1.84	20.21 20.34)
3d	75	colorless (powder)	292-293	$C_{11}H_7N_5O_2Cl_2 \cdot 1/7H_2O$ (0.38)	41.98 (42.18	2.33 2.44	22.26 22.00)
3e	83	colorless (powder)	244-245	$C_{11}H_7N_5O_2Cl_2$ (0.40)	42.33 (42.31	2.26 2.44	22.44 22.31)
3f	84	colorless (prisms)	300-301	$C_{11}H_6N_5O_2Cl_3 \cdot 1/6H_2O$ (0.47)	37.80 (37.88	1.83 1.86	20.03 19.79)
3g	81	colorless (powder)	157-158	$C_{12}H_{10}N_5O_2Cl$ (0.48)	49.41 (49.34	3.46 3.52	24.01 24.26)
3h	86	orange (plates)	184-185	$C_{12}H_{10}N_6O_4 \cdot 1/10H_2O$ (0.34)	47.40 (47.29	3.38 3.40	27.64 27.73)
3i	76	yellow (needles)	178-179	$C_{13}H_{13}N_5O_3$ (0.50)	54.35 (53.97	4.56 4.58	24.38 24.47)
3j	82	pale yellow (needles)	224-225	$C_{13}H_{10}N_6O_2$ (0.42)	55.32 (55.12	3.57 4.03	29.77 29.81)
3k	76	colorless (powder)	182-183	$C_{12}H_9N_5O_2Cl_2 \cdot 1/4H_2O$ (0.55)	43.59 (43.60	2.90 2.82	21.18 21.16)
3l	83	colorless (prisms)	221-222	$C_{12}H_9N_5O_2Cl_2$ (0.53)	44.19 (43.98	2.78 2.88	21.47 21.64)
3m	73	pale yellow (powder)	203-204	$C_{14}H_{15}N_5O_2$ (0.59)	58.94 (58.59	5.30 5.30	24.55 24.87)
3n	82	colorless (needles)	206-207	$C_{13}H_{12}N_6O_4$ (0.45)	49.37 (49.35	3.82 3.86	26.57 26.85)
3o	78	colorless (powder)	214-215	$C_{12}H_8N_5O_2Cl_3 \cdot 1/3H_2O$ (0.63)	39.32 (39.22	2.38 2.32	19.10 19.03)

[a]All compounds were recrystallized from AcOEt except for **3a** and **3d**, which were recrystallized from AcOEt-EtOH. [b]Solvent system for TLC: *n*-hexane : AcOEt (1:1 v/v).

The resulting precipitate was collected by filtration, washed with cold water and recrystallized from ethanol to afford the 7-thioxo derivative (**8a**) (1.48 g, 68%) as orange needles, mp 222-224 °C; R_f (A) 0.15; IR (Nujol) ν_{max}/cm^{-1}: 3180, 3090 (NH), 1680 (C=O); ^{1}H-NMR [$(CD_3)_2SO$] δ 3.45 (3H, s, 4-N-CH_3), 12.66 (1H, s, 6-NH), 15.80 (1H, br s, 3-NH); *Anal.* Calcd for $C_5H_5N_5OS$: C, 32.78; H, 2.75; N, 38.23. Found: C, 32.53; H, 2.74; N, 37.90.

Table 4. IR and ^{1}H-NMR spectroscopic data for compounds (**3a-o**)

Compd No.	[ν_{max}(Nujol)/cm^{-1}]	δ_H(300 MHz; $CDCl_3$; Me_4Si)
3a	3185, 3070 (NH), 1730, 1700 (C=O)	7.47-7.50 (3H, m, Ar-H), 9.80 (1H, s, 6-NH), 11.73 (1H, s, 4-NH)
3b	3200 (NH), 1740, 1680 (C=O)	3.47 (3H, s, N-CH_3), 7.47-7.52 (3H, m, Ar-H), 11.42 (1H, s, NH)
3c	3205 (NH), 1740, 1680 (C=O)	3.47 (3H, s, N-CH_3), 7.52 (2H, s, Ar-H), 11.16 (1H, s, NH)
3d	3200 (NH), 1730 (CO)	3.56 (3H, s, N-CH_3), 7.46 (1H, dd, $J_{3',5'}$ = 2.4, $J_{5',6'}$ = 8.7, 5'-H), 7.63 (1H, d, J = 2.4, 3'-H), 7.65 (1H, d, J = 8.7, 6'-H), 11.18 (1H, s, NH)
3e	3180 (NH), 1735, 1690 (C=O)	3.60 (3H, s, N-CH_3), 7.50-7.54 (3H, m, Ar-H), 11.20 (1H, s, NH)
3f	3200 (NH), 1740, 1695 (C=O)	3.55 (3H, s, N-CH_3), 7.58 (2H, s, Ar-H), 11.30 (1H, s, NH)
3g	1730, 1680 (C=O)	3.49 (3H, s, 6-N-CH_3), 3.63 (3H, s, 4-N-CH_3), 7.42-7.52 (2H, m, 4'- and 5'-H), 7.61 (1H, dd, $J_{3',5'}$ = 1.8, $J_{3',4'}$ = 7.2, 3'-H), 7.66 (1H, dd, $J_{4',6'}$ = 2.1, $J_{5',6'}$ = 7.5, 6'-H)
3h	1725, 1675 (C=O)	3.48 (3H, s, 6-N-CH_3), 3.58 (3H, s, 4-N-CH_3), 7.67 (1H, dt, $J_{4',6'}$ = 1.5, $J_{3',4'}$ = $J_{4',5'}$ = 7.8, 4'-H), 7.79 (1H, dt, $J_{3',5'}$ = 1.5, $J_{4',5'}$ = $J_{5',6'}$ = 7.8, 5'-H), 7.94-7.99 (2H, m, 3'- and 6'-H)
3i	1730, 1680 (C=O)	3.49 (3H, s, 6-N-CH_3), 3.65 (3H, s, 4-N-CH_3), 3.91 (3H, s, O-CH_3), 6.97 (1H, ddd, J = 0.9, J = 2.7 and J = 8.1, 4'-H), 7.40 (1H, t, J = 8.1, 5'-H), 7.70 (1H, t, J = 2.4, 2'-H), 7.74 (1H, ddd, J = 0.9, J = 2.1 and J = 8.1, 6'-H)
3j	1735, 1685 (C=O)	3.50 (3H, s, 6-N-CH_3), 3.66 (3H, s, 4-N-CH_3), 7.84 (2H, d, J = 8.7, Ar-*m*H), 8.31 (2H, d, J = 8.7, Ar-*o*H)
3k	1730, 1690 (C=O)	3.50 (3H, s, 6-N-CH_3), 3.63 (3H, s, 4-N-CH_3), 7.44 (1H, dd, $J_{3',5'}$ = 2.1, $J_{5',6'}$ = 8.7, 5'-H), 7.62 (1H, d, J = 2.4, 3'-H), 7.64 (1H, d, J = 8.4, 6'-H)
3l	1730, 1680 (C=O)	3.51 (3H, s, 6-N-CH_3), 3.64 (3H, s, 4-N-CH_3), 7.49-7.54 (3H, m, Ar-H)
3m	1730, 1680 (C=O)	2.33 and 2.36 (each 3H, each s, 2 x Ar-CH_3), 3.49 (3H, s, 6-N-CH_3), 3.65 (3H, s, 4-N-CH_3), 7.27 (1H, d, J = 8.1, 5'-H), 7.86 (1H, dd, $J_{2',6'}$ = 2.1, $J_{5',6'}$ = 8.1, 6'-H)), 7.95 (1H, d, J = 2.1, 2'-H)
3n	1730, 1685 (C=O)	2.69 (3H, s, Ar-4'-CH_3), 3.50 (3H, s, 6-N-CH_3), 3.67 (3H, s, 4-N-CH_3), 7.54 (1H, d, J = 8.4, 6'-H), 8.32 (1H, dd, $J_{3',5'}$ = 2.1, $J_{5',6'}$ = 8.4, 5'-H), 8.78 (1H, d, J = 2.1, 3'-H)
3o	1730, 1675 (C=O)	3.50 (3H, s, 6-N-CH_3), 3.62 (3H, s, 4-N-CH_3), 7.53 (2H, s, Ar-H)

3,4-Dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (8b)

A mixture of 3,4-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**7b**)[9] (0.50 g, 2.76 mmol) and P_2S_5 (1.23 g, 5.52 mmol) in pyridine (30 mL) was heated under reflux for 3 h. Then, the solution was evaporated *in vacuo* and water (10 mL) was added to the residue. The resulting suspension was heated at 100 °C for 20 min. Upon cooling to rt, the deposited precipitate was collected by filtration and purified by column chromatography on silica gel using a mixture of *n*-hexane and ethyl acetate (1:1)

Table 5. Physical and analytical data for compounds (**5a-e** and **6a-e**)

Compd No.	Yield (%)	Appearance (shape of crystal)	Mp[a] (°C)	Formula (R_f)[b]	Analysis (%) Calcd (Found) C	H	N
5a[c]	86	orange (powder)	>300	$C_{16}H_{14}N_6 \cdot 1/4H_2O$ (0.60)	65.18 (65.47	4.96 5.06	28.50 28.18)
5b	85	orange (powder)	241-242	$C_{16}H_{13}N_6Cl$ (0.58)	59.17 (59.08	4.03 4.18	25.88 26.04)
5c	88	oragne (needles)	237-238	$C_{16}H_{13}N_6Cl$ (0.65)	59.17 (58.83	4.03 4.09	25.88 26.17)
5d	92	orange (powder)	>300	$C_{16}H_{12}N_6Cl_2$ (0.66)	53.50 (53.39	3.37 3.36	23.40 23.15)
5e	82	yellow (powder	290-291	$C_{19}H_{20}N_6O_3 \cdot 1/4H_2O$ (0.40)	59.29 (59.57	5.37 5.36	21.83 21.59)
6a[c]	72	pale orange (prisms)	281-282	$C_{16}H_{12}N_6$ (0.51)	66.66 (66.35	4.20 4.40	29.15 29.53)
6b	74	pale orrange (needles)	234-235	$C_{16}H_{11}N_6Cl$ (0.45)	59.54 (59.80	3.44 3.71	26.04 26.09)
6c	69	pale yellow (powder)	>300	$C_{16}H_{11}N_6Cl$ (0.55)	59.54 (59.32	3.44 3.65	26.04 26.00)
6d	79	pale yellow (powder)	292-293	$C_{16}H_{10}N_6Cl_2 \cdot 1/6H_2O$ (0.49)	53.35 (53.46	2.89 3.06	23.33 23.09)
6e	81	orange (needles)	211-212	$C_{19}H_{18}N_6O_3 \cdot 1/8\ H_2O$ (0.34)	59.95 (59.84	4.83 4.86	22.08 22.16)

[a]Compounds (**5a-e**) were recrystallized from 75% aqueous DMF and compounds (**6a-e**) were recrystallized from *n*-hexane-AcOEt. [b]Solvent system for TLC: *n*-hexane : AcOEt (1:1 v/v). [c]Ref. 23.

as eluting solvent to afford the 7-thioxo derivative (**8b**) (0.24 g, 44%) as pale yellow powdery crystals, mp 253-254 °C; R_f (A) 0.39; IR (Nujol) ν_{max}/cm^{-1}: 3130 (NH), 1720 (C=O); ^{1}H-NMR [$(CD_3)_2SO$] δ : 3.61 (3H, s, 4-N-CH_3), 4.26 (3H, s, 3-N-CH_3), 12.71 (1H, s, 6-NH); *Anal.* Calcd for $C_6H_7N_5OS \cdot 1/12H_2O$: C, 36.26; H, 3.64; N, 35.24. Found: C, 36.02; H, 3.51; N, 35.43.

4,6-Dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (10)

A mixture of 4,6-dimethyl-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (9)[9] (0.50 g, 2.76 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent, 0.75 g, 1.86 mmol) in 1,4-dioxane (30 mL) was heated under refluxed for 8 h. An additional Lawesson's reagent (0.60 g, 1.49 mmol) was then added to it and the heating was continued for 6 more hours. After the reaction was complete, the solution was evaporated *in vacuo* and the residue was triturated with AcOEt to give crystals, which were collected by filtration and recrystallized from ethanol to afford the 7-thioxo derivative (**10**) (0.31 g, 57%) as pale yellow powdery crystals, mp 225-226 °C; R_f

Table 6. IR and ^{1}H-NMR spectroscopic data for compounds (**5a-e** and **6a-e**)

Compd No.	[ν_{max} (Nujol)/cm^{-1}]a	δ_H (300 MHz; Me_4Si)b
5a	3460, 3280, *3120,* 3060 (NH)	7.32-7.48 (8H, m, 2 x Ph-*m,p*H and NH_2), 7.93 (2H, d, *J* = 7.8, =N-Ph-*o*H), 8.34-8.40 (4H, m, 2-Ph-*o*H and NH_2)
5b	3480, 3355, 3290, 3180 (NH)	7.35-7.49 (5H, m, Ph-*m,p*H and Ar-4',5'-*H*), 7.61 (1H, dd, $J_{3',5'}$ = 2.4, $J_{3',4'}$ = 6.9, Ar-3'-H), 7.81 (2H, br s, NH_2), 8.21 (1H, dd, $J_{4',6'}$ = 2.7, $J_{5',6'}$ = 7.2, Ar-6'-H), 8.36 (2H, dd, $J_{o,p}$ = 2.4, $J_{o,m}$ = 8.1, Ph-*o*H), 8.67 (2H, br s, NH_2)
5c	3460, 3280, *3120*, 3060 (NH)	7.42-7.48 (5H, m, Ph-*m,p*H and Ar-*m*H), 7.53 (2H, br s, NH_2), 7.99 (2H, d, *J* = 8.7, Ar-*o*H), 8.33-8.37 (2H, m, Ph-*o*H), 8.42 (2H, br s, NH_2)
5d	3460, 3400, 3310, 3260 (NH)	7.18 (1H, t, *J* = 7.8, Ar-*p*H), 7.23 (2H, br s, NH_2), 7.37-7.45 (5H, m, Ph-*m,p*H and Ar-*m*H), 8.39 (2H, dd, $J_{o,p}$ = 2.4, $J_{o,m}$ = 7.5, Ph-*o*H), 8.42 (2H, br s, NH_2)
5e	3480, 3280, 3145, *3100* (NH)	3.70 (3H, s, Ar-*p*-OCH_3), 3.87 (6H, s, 2 x Ar-*m*-OCH_3), 7.26 (2H, s Ar-H), 7.44 (5H, br s, Ph-*o,m*H and NH_2), 8.34 (2H, s, Ph-*o*H), 8.40 (2H, br s, NH_2)
6a	3440, 3320 3200 (NH)	6.46 (2H, s, NH_2), 7.40-7.54 (6H, m, Ph-*m,p*H), 8.28 (2H, d, *J* = 8.4, 2-Ph-*o*H), 8.46-8.49 (2H, m, 5-Ph-*o*H)
6b	3440, 3320, 3200 (NH)	6.37 (2H, s, NH_2), 7.47-7.54 (5H, m, Ar-4',5'H and Ph-*m,p*H), 7.65 (1H, dd, $J_{3',5'}$ = 2.1, $J_{3',4'}$ = 7.5, Ar-3'-H), 7.78 (1H, dd, $J_{4',6'}$ = 2.4, $J_{5',6'}$ = 7.2, Ar-6'-H), 8.52-8.56 (2H, m, Ph-*o*H)
6c	3440, 3320, 3200 (NH)	7.47 (3H, t, *J* = 3.3, Ph-*m,p*H), 7.70 (2H, d, *J* = 9.0, Ar-*m*H), 8.22 (1H, br s, NH), 8.27 (2H, d, *J* = 9.0, Ar-*o*H), 8.41-8.45 (3H, m, Ph-*o*H and NH)
6d	3445, 3320, 3200 (NH)	7.05 (2H, br s, NH_2), 7.48 (3H, t, *J* = 3.3, Ph-*m,p*H), 7.53-7.61 (3H, m, Ar-H), 8.52-8.55 (2H, m, Ph-*o*H)
6e	3320, 3170 (NH)	3.93 (3H, s, Ar-*p*-OCH_3), 4.00 (6H, s, 2 x Ar-*m*-OCH_3), 5.94 (2H, s, NH_2), 7.49 (3H, m, Ph-*m,p*H), 7.65 (2H, s, Ar-H), 8.54-8.57 (2H, m, Ph-*o*H)

[a] The IR absorption values in italic refers to wave numbers at which shoulders or inflexions occur in the absorption. [b] ^{1}H-NMR spectra for compounds (**5a-e**) were measured in $(CD_3)_2SO$, while for compounds (**6a-e**) they were measured in $CDCl_3$.

(A) 0.21; IR (Nujol) ν_{max}/cm^{-1}: 3100 (NH), 1700 (C=O); ^{1}H-NMR [$(CD_3)_2SO$] δ : 3.62 (3H, s, 6-N-CH_3), 3.79 (3H, s, 4-N-CH_3); *Anal.* Calcd for $C_6H_7N_5OS \cdot 1/8H_2O$: C, 36.13; H, 3.66; N, 35.11. Found: C, 36.28; H, 3.64; N, 34.84.

General procedure for 2-aryl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (11a-c)

A mixture of 2-aryl-*2H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**3a,e,f**) (2.0 mmol) and P_2S_5 (0.82 g, 3.7 mmol) in pyridine (40 mL) was heated under reflux for 5 h. Then, an additional P_2S_5 (0.67g, 3.0 mmol) was added to it and the heating was continued for 5 more hours. After the reaction was complete, the solution was evaporated *in vacuo* and water (40 mL) was added to the residue. The resulting suspension was heated at 100 °C with stirring for 40 min. Upon cooling to rt, the deposited precipitate was collected by filtration, dissolved in 0.5N NaOH and reprecipitated with 3N HCl. The resulting precipitate was collected by filtration and washed with water to afford the corresponding 7-

Table 7. Evaluation of antiviral and antitumor activities in vitro for compounds (**3a-o**, **6a-e**, **8a**,**b**, and **11a**,**b**)

Compd No.	Inhibitory concentration against Herpes Simplex Virus [ED_{50} (μg/ml)]		Inhibitory concentration against tumor cell lines [IC_{50} (μg/ml)]	
	HSV-1	HSV-2	CCRF- HSB - 2	KB
3a	>100	>100	49.7	43.8
3b	>20	>20	90.0	>100
3c	n.d.	n.d.	n.d.	n.d.
3d	>20	>20	>100	52.7
3e	>20	>20	76.7	53.5
3f	>20	>20	>100	53.1
3g	>20	>20	42.2	76.1
3h	>20	>20	74.5	61.7
3i	>20	>20	40.0	68.7
3j	>20	>20	65.9	>100
3k	>100	>100	>100	86.4
3l	>100	>100	>100	78.0
3m	>20	>20	60.6	>100
3n	>4	>4	>100	>100
3o	>20	>20	98.9	53.5
6a	>4	>4	6.8	2.3
6b	>4	>4	8.2	9.4
6c	>20	>20	47.0	4.8
6d	>4	>4	49.9	48.0
6e	>4	>4	29.4	94.1
8a	>100	>100	67.0	>100
8b	>100	>100	34.1	87.7
11a	>100	>100	31.9	45.9
11b	>100	>100	58.4	35.5
ACV[a]	0.16	0.16	n.d.	n.d.
Ara-C[b]	n.d.	n.d.	0.07	0.09

[a]ACV: acyclovir. [b]Ara-C: arabinosylcytidine. The n.d. means not done.

thioxo derivatives (**11a-c**), whose physical and spectral data are given below:

i) 2-(2,6-Dichlorophenyl)-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**11a**): yield 52%; yellow needles (from AcOEt); mp 292-293 °C; R_f (B) 0.39; IR (Nujol) ν_{max}/cm^{-1}: 3360, 3140 (NH), 1695 (C=O); ^{1}H-NMR ($CDCl_3$) δ : 7.42-7.51(3H, m, Ar-H), 10.57 (1H, s, 6-NH), 11.85 (1H, br s, 4-NH); *Anal.* Calcd for $C_{10}H_5N_5OCl_2S$: C, 38.23; H, 1.60; N, 22.29. Found: C, 38.50; H, 1.91; N, 21.98.

ii) 2-(2,6-Dichlorophenyl)-4-methyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**11b**): yield 70%; yellow prisms (from *n*-hexane-AcOEt); mp 271-272 °C; R_f (B) 0.53; IR (Nujol) ν_{max}/cm^{-1}: 3300 (NH), 1690 (C=O); ^{1}H-NMR ($CDCl_3$) δ : 3.61 (3H, s, CH_3), 7.49-7.54 (3H, m, Ar-H), 9.50 (1H, s, NH); *Anal.* Calcd for $C_{11}H_7N_5OCl_2S$: C, 40.26; H, 2.15; N, 21.34. Found: C, 40.41; H, 2.32; N, 21.70.

iii) 2-(2,4,6-Trichlorophenyl)-4-methyl-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**11c**): Yield 59%; yellow prisms (from *n*-hexane-AcOEt); mp 256-257 °C; R_f (B) 0.61; IR (Nujol) ν_{max}/cm^{-1}: 3250 (NH), 1685 (C=O); ^{1}H-NMR ($CDCl_3$) δ : 3.60 (3H, s, CH_3), 7.54 (2H, s, Ar-H), 9.44 (1H, s, NH); *Anal.* Calcd for $C_{11}H_6N_5OCl_3S$: C, 36.43; H, 1.67; N, 19.31. Found: C, 36.22; H, 1.79; N, 19.25.

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REFERENCES

1. K. O. Smith, K. S. Galloway, W. L. Kennell, K. K. Ogilvie, and B. K. Radatus, *Antimicrob. Agents Chemother.*, 1982, **22**, 55; D. F. Smee, J. C. Martin, J. P. H. Verheyden, and T. R. Matthews, *Antimicrob. Agents Chemother.*, 1983, **23**, 676; X. Qin, X. Chen, K. Wang, L. Polin, E. R. Kern, J. C. Drach, E. Gullen, Y.-C. Cheng, and J. Zemlicka, *Bioorg. Med. Chem.*, 2006, **14**, 1247.
2. H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel, Jr., *Cancer Res.*, 1959, **19**, 425; *Cancer Res.*, (supplement), 1959, **19**, part 2, 287; G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Cancer Res.,* 1951, **11**, 204.
3. B. R. Baker and W. F. Wood, *J. Med. Chem.*, 1967, **10**, 1101; B. R. Baker, W. F. Wood, and J. A. Kozma, *J. Med. Chem.*, 1968, **11**, 661.
4. A. Bendich, P. J. Russel, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, 1954, **76**, 6073 (see additional references listed there); H. E. Skipper, R. K. Robins, J. R. Thomson, C. C. Cheng, R. W. Brockman, and F. M. Schabel, Jr., *Cancer Res.*, 1957, **17**, 579.
5. S.-A. Kim, M. A. Marshall, N. Melman, H. S. Kim, C. E. Mueller, J. Linden, and K. A. Jacobson, *J. Med. Chem.*, 2002, **45**, 2131; J. W. Daly, W. L. Padgett, and M. T. Shamim, *J. Med. Chem.*, 1986, **29**, 1305; J. Shimada, F. Suzuki, H. Nonaka, and A. Ishii, *J. Med. Chem.*, 1992, **35**, 924; J. W. Daly, W. Padgett, M. T. Shamim, P. Butts-Lamb, and J. Waters, *J. Med. Chem.*, 1985, **28**, 487.
6. D. A. Clarke, F. S. Philips, S. S. Sternberg, C. C. Stock, G. B. Elion, and G. H. Hitchings, *Cancer Res.*, 1953, **13**, 593; J. H. Burchenal, M. L. Murphy, R. R. Ellison, M. P. Sykes, T. C. Tan, L. A. Leone, D. A. Karnof-sky, L. F. Craver, H. W. Dargeon, and C. P. Rhoads, *Blood*, 1953, **8**, 965.
7. K. Bowden and K. R. H. Wooldridge, *Biochem. Pharmacol.*, 1973, **22**, 1015; Y. Ono, K. Ikeda, M. X. Wei, G. R. Harsh; T. Tamiya, and E. A. Chiocca, *Human Gene Therp.*, 1997, **8**, 2043; K. A. Jacobson, L. Kiriasis, S. Barone, B. J. Bradbury, U. Kammula, J. M. Campagne, S. Secunda, J. W. Daly, J. L. Neumeyer, and W. Pfleiderer, *J. Med. Chem.*, 1989, **32**, 1873.

8. T. Nagamatsu, H. Yamada, and K. Shiromoto, *Heterocycles*, 2004, **63**, 9; T. Nagamatsu, H. Yamasaki, T. Fujita, K. Endo, and H. Machida, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3117; T. Nagamatsu and T. Fujita, *Chem. Commun.*, 1999, 1461; T. Nagamatsu, T. Fujita, and K. Endo, *J. Chem. Soc., Perkin Trans. 1*, 2000, 33; T. Nagamatsu, H. Yamasaki, T. Akiyama, S. Hara, K. Mori, and H. Kusakae, *Synthesis*, 1999, 655; T. Nagamatsu, S. Miyazaki, and M. Imaizumi, *PCT Int. Appl. WO 96 26,208* (*Chem. Abstr.*, 1996, **125**, 247848j); T. Nagamatsu, Y. Watanabe, K. Endo, and M. Imaizumi, *PCT Int. Appl. WO 97 06,169* (*Chem. Abstr.*, 1997, **126**, 225313z); T. Nagamatsu, Y. Yamagishi, and F. Yoneda, *Jpn. Kokai Tokkyo koho*, 1977, JP 09 255,681 (C*hem. Abstr.*, 1997, **127**, 336635w).
9. T. Nagamatsu and R. Islam, *Heterocycles*, 2006, **68**, 1811.
10. P. Franchetti, L. Messini, L. Cappellacci, M. Grifantini, A. Lucacchini, C. Martini, and G. Senatore, *J. Med. Chem.*, 1994, **37**, 2970.
11. F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Am. Chem. Soc.*, 1950, **72**, 1816.
12. Charrier, *Gazz. chim. ital.*, 1922, **52**, 261.
13. Zincke, *Ber.*, 1885, **18**, 3136.
14. Y. Maki and E. C. Taylor, *Chem. Pharm. Bull.*, 1972, **20**, 605.
15. Neri, *Gazz. chim. ital.*, 1931, **67**, 610; Charrier and Jorio, *Gazz. chim. ital.*, 1938, **68**, 640.
16. L. W. Hartzel and F. R. Benson, *J. Am. Chem. Soc.*, 1954, **76**, 2263.
17. A. G. Beaman, *J. Am. Chem. Soc.*, 1954, **76**, 5633.
18. R. Rico-Gomez, F. Najera, J. M. L.-Romero, and P. C.-Rudner, *Heterocycles*, 2000, **53**, 2275.
19. R. M. Cresswell, H. K. Maurer, T. Strauss, and G. B. Brown, *J. Org. Chem.*, 1965, **30**, 408.
20. S. Nishigaki, K. Shimizu, and K. Senga, *Chem. Pharm. Bull.*, 1977, **25**, 2790.
21. E. C. Rodriguez, J. R. Sanchez, J. D. D. L. Gonzalez, J. M. S. Peregrin, M. J. Olivier, M. Quiros, and A. L. Beauchamp, *Inorg. Chim. Acta*, 1990, **171**, 151.
22. F. Yoneda, M. Higuchi, and Y. Nitta, *Heterocycles*, 1978, **9**, 1387.
23. S. Narita, T. Kitagawa, and E. Hirai, *Chem. Pharm. Bull.*, 1985, **33**, 4928.
24. H. Machida, S. Sakata, A. Kuninaka, H. Yoshino, C, Nakayama, and M. Saneyoshi, *Antimicrob. Agents Chemother.,* 1979, **16**, 158.
25. H. Machida, S. Sakata, A. Kuninaka, and H. Yoshino, *Antimicrob. Agents Chemother.,* 1981, **20**, 47.
26. S. Miura, Y. Yoshimura, M. Endo, H. Machida, A. Matsuda, M. Tanaka, and T. Sasaki, *Cancer Letters*, 1998, **129**, 103.
27. T. Mosmann, *J. Immunol. Methods*, 1983, **65**, 55.