5-Cyano-6-aryluracil and 2-Thiouracil Derivatives as Potential Chemotherapeutic Agents. IV

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A series of 5-cyano-6-aryluracils and 2-thiouracils **1a-h** has been prepared and alkylated to 1,3-dialkyluracils **2a-d** and 2-alkylthiouracils, **3**, **4** and **6**, by electrophilic substitution with alkyl halides. Reaction of **1b** with dibromoethane and 1,3-dibromopropane gave the corresponding bicyclic products, 7-aryl-6-cyano-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-ones **5a,b** and 8-aryl-7-cyano-3,4-dihydro-2*H*-pyrimido[2,3-*b*][1,3]thiazin-6-ones **5c-g**. Nucleophilic substitution on **6** with hydrazine led to **7** which on refluxing with formic acid gave 5-aryl-6-cyano-8-methyl-*s*-triazolo[3,4-*b*]pyrimidin-7-ones (**9**), while with acetic and propionic acids only 2-acylhydrazino-3-methyl-4-oxo-5-cyano-6-arylpyrimidines **8a,b** were isolated. The hydrazine **7** undergoes cyclization with acetylacetone and methyl dimethylmercaptoacrylate providing 2-(pyrazol-1-yl)-3-methyl-4-oxo-5-cyano-6-substituted pyrimidines **10**, and **11**. Some of the compounds were screened for antibacterial-, antifungal- and antiviral activities and a few of them showed significant chemotherapeutical activities.

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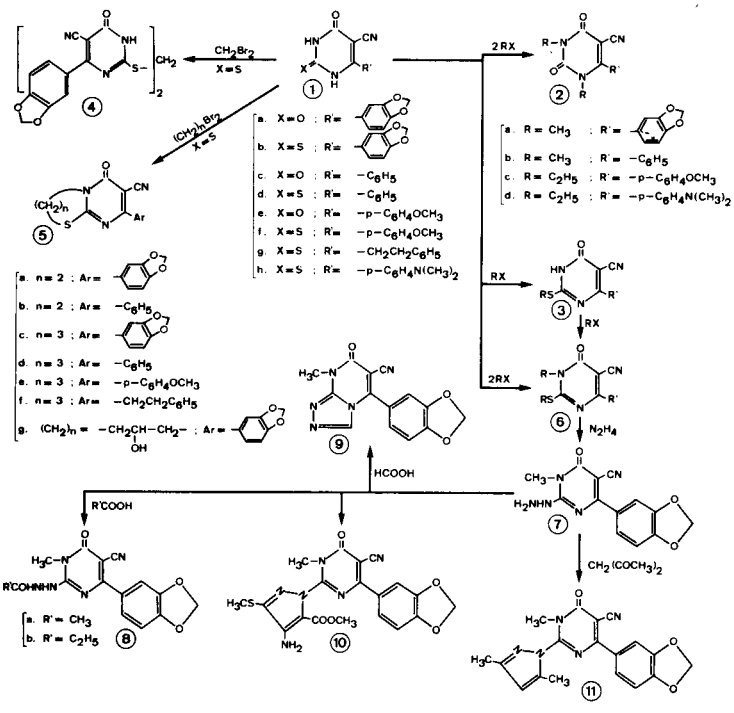
Pyrimidines are among those molecules that make life possible as being some of the building blocks of DNA and RNA. Various analogues of thiopyrimidines such as 2-thiouracil and 2,4-dithiouracil possess systematic fungicidal activity against cucumber powdery mildew caused by *Erysiphe cichoracearum* [1].

A number of 2-(5-nitrofurfurylthio)-4-methylpyrimidines were screened for their fungicidal activity and reported to be active against *Microsporum canis, M. audouini, Trichophyton sulphureum* and *Cryptococcus neoformans*. 2-Thiouracil has also been found to possess some viricidal activity by suppressing the multiplication of infective turnip yellow and tobacco mosaic viruses, [2-6], whereas in tissue culture it was found to be active against influenza and poliomyelitis viruses [7,8]. The antibacterial and anticancer activities of various 2-thiopyrimidines, aminothiopyrimidines and hydroxythiopyrimidines have been studied by various workers, who demonstrated some activity against

SCHEME I



Lactobacillus arabinosus, L. leichannii and sarcoma 180 in mice [1,9,10]. Several 2-alkylthio-4,5,6-trisubstituted pyrimidines showed herbicidal activity against crabgrass, foxtail redroot, pigweed and Jimson weed.

The therapeutic importance of thiopyrimidines prompted us as a part of a chemotherapeutic research program to synthetize a series of 5-cyano-6-aryluracil- and 2-thiouracil derivatives and to determine their potential chemotherapeutical activities.

Chemistry.

5-Cyano-6-aryluracils **1a,c,e** and 2-thiouracils **1b,d,f-h** were prepared by refluxing an equimolar mixture of ethyl cyanoacetate, potassium carbonate, urea or thiourea with an appropriate aromatic aldehyde in absolute ethanol as described by Kambe *et al.* [11]. Alkylation of uracils in DMF with two equivalents of alkylhalide in the presence of potassium carbonate yielded 1,3-*N*-dialkyluracils. **2**. Alkylation of 2-thiouracils with an equivalent amount of alkylhalide under similar conditions afforded 2-alkylthiouracils **3**. Further alkylation of **3** produced **6**, which was also obtained by direct alkylation of 2-thiouracils with two equivalents of alkylhalide. Nucleophilic substitution of **6** with hydrazine in ethanol led to 2-hydrazino-3-methyl-4-oxo-5-cyano-6-arylpyrimidine **7**, which on refluxing in formic acid cyclized to 5-aryl-6-cyano-8-methyl-*s*-triazolo[3,4-*b*]-pyrimid-7-one **9**, while in acetic or propionic acid noncyclic products **8a,b** were formed. Reaction of **7** with methyl dimethylmercaptocyanoacrylate and pentane-2,4-dione gave respectively 2-(3-methylmercapto-4′-amino-5′-carbomethoxypyrazol-1′-yl)-4-oxo-5-cyano-6-arylpyrimidine **10** and 2-(3′,5′-dimethylpyrazol-1′-yl)-3-methyl-4-oxo-5-cyano-6-arylpyrimidine **11**. Stirring a mixture of **1b** and methylene bromide with potassium carbonate in DMF produced under gentle warming bis(4-oxo-3,4-dihydro-5-cyano-6-aryl-2-thiopyrimidinyl)methane **4**. Heating of **1b** with ethylene bromide in DMF with potassium carbonate, however, gave 7-aryl-6-cyano-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one **5a** while with 1,3-dibromopropane, 8-aryl-7-cyano-3,4-dihydro-2*H*-pyrimido[2,3-*b*][1,3]thiazin-6-ones **5c-f** were obtained.

Chemotherapeutic Evaluation.

The compounds listed in Table I were chemotherapeutically tested by standard methods described earlier [12]. The antibacterial activity was determined *in vitro* with the hole-plate agar diffusion method against gram-positive cocci including *Diplococcus pneumoniae, Micrococcus sp., Staphylococcus aureus, Streptococcus pyogenes, S. viridans,* gram-negative cocci including *Neisseria gonorrhoeae,* gram-negative enteric bacilli *Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella* type C, *Serratia marescens, Shigella flexneri* and the acid-fast bacillum *Myobacterium fortuitum.*

The antifungal activity was determined *in vitro* with the agar dilution method against yeasts including *Candida albicans* and fungi including *Aspergillus flavus, A. fumigatus, A. niger, Microsporum canis, Trichophyton mentagrophytes* and *T. rubrum.* The antiviral activity was determined *in vitro* with the tissue culture method using confluent VERO monolayers in micro-titers plates against one DNA-virus namely *Herpes simplex* and three RNA-viruses including *Coxsackie-, Poliomyelitis-* and *Semliki forest* viruses. The most pronounced antibacterial properties were found in the series of 2,6-substituted-5-cyanothiouracils **3** and for 2-hydrazino-3-methyl-4-oxo-5-cyano-6-(3′,4′-methylenedioxyphenyl)pyrimidine (**7**). 5-Cyano-6-phenethyl-2-thiouracil (**1g**) and some compounds of the 2,3-dihydrothiazolo-[3,2-*a*]pyrimidines and 3,4-dihydro-2*H*-pyrimido[2,3-*b*]-[1,3]thiazines **5** showed appreciable antifungal activities. The latter compounds were also quite active against the gram-negative coccus *N. gonorrhoeae.* Finally an interesting antiviral action against several viruses was noted for 5-cyano-6-(*p*-dimethylaminophenyl)-2-thiouracil (**1h**).

All the other compounds tested exhibited only a weak or no chemotherapeutical activity *in vitro* against the test microorganisms.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The nmr spectra were recorded on a Varian T-60 spectrophotometer in DMSO-d_6 using TMS as internal standard. Mass spectra were determined on a Nuclide 12-90-G mass spectrometer.

5-Cyano-6-(3′,4′-methylenedioxyphenyl)uracil (**1a**).

A mixture of urea (3 g, 0.05 mole), ethyl cyanoacetate (5.7 g, 0.05 mole), piperonal (7.5 g, 0.05 mole) and potassium carbonate (7 g, 0.051 mole) in absolute ethanol (100 ml) was refluxed overnight, cooled and filtered. The precipitate was dissolved in hot water and neutralized with glacial acetic acid. The precipitate was filtered off, washed with water and dried, 40%, mp 295-298°.

Anal. Calcd. for $C_{12}H_7N_3O_4$: C, 56.03; H, 2.72; N, 16.34. Found: C, 56.21; H, 2.65; N, 12.42.

5-Cyano-6-phenyluracil (**1c**).

This compound was prepared by refluxing an equimolar mixture of urea, ethyl cyanoacetate, benzaldehyde and potassium carbonate in ethanol for 12 hours and isolated as described in the preceding experiment, mp 285-288°, lit [11] mp 287-288°.

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.28; N, 19.72. Found: C, 61.78; H, 3.42; N, 19.64.

5-Cyano-6-(p-anisyl)uracil (**1e**).

An equimolar quantity of urea, ethyl cyanoacetate, anisaldehyde (*p*-) and potassium carbonate in ethanol provided **1e**, which was crystallized from water, 52%, mp 225-230°; ms: m/z 243 ($M^{+\cdot}$).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.70; N, 17.28. Found: C, 59.38; H, 3.85; N, 17.31.

5-Cyano-6-(3′,4′-methylenedioxyphenyl)-2-thiouracil (**1b**).

A mixture of thiourea (7.6 g), ethyl cyanoacetate (11.3 g), piperonal (15 g) and potassium carbonate (13.9 g) in 150 ml of ethanol was refluxed overnight and cooled. The precipitate thus obtained was filtered off and washed with ethanol. The precipiate was dissolved in water at 70-80°, fil-

Table I

IN VITRO Chemotherapeutical Activity

A.	Antibacterial activity [a]	
	Compound No.	Bacteria
	1. High activity	
	3b	*E. coli*
	3e	*D. pneumoniae, Micrococcus sp., S. aureus, S. pyogenes, S. viridans, M. fortuitum, E. coli*
	5a, 5c	*N. gonorrhoeae*
	7	*D. pneumoniae, Micrococcus sp., S. aureus, S. pyogenes, S. viridans M. fortuitum, N. gonorrhoeae, E. coli, K. pneumoniae, P. vulgaris, P. aeruginosa, S. marescens*
	2. Weak activity	
	3b	*D. penumoniae*
	3c	*D. pneumoniae, E. coli*
	6c	*Micrococcus sp., E. coli*
	3. No activity	**1g, 1h, 4, 5g, 6b, 8b, 9, 10** and **11**
B.	Antifungal activity [b]	
	Compound No.	Fungi
	1. High activity	
	1g	*A. niger, M. canis, T. mentagrophytes*
	5a	*A. flavus, A. niger, M. cansi, T. mentagrophytes*
	5c	*A. flavus, A. fumigatus, A. niger, M. canis, T. mentagrophytes*
	2. Weak activity	
	4	*A. niger, M. canis*
	6c	*M. canis*
	8b	*C. albicans*
	3. No activity	**1h, 3b, 3c, 3e, 5g, 6b, 7, 9, 10**, and **11**.
C.	Antiviral activity [c]	
	Compound No.	Viruses
	1. Small activity	
	5c	Coxsackie 10 (50 μg/ml), polio (50 μg/ml)
	1h	Coxsackie 10^2 (50 μg/ml), polio 10^2 (3.12 μg/ml), herpes simplex 10^2 (12.5 μg/ml)
	2. No activity	**1g, 3b, 3c, 3e, 4, 5a, 5g, 6b, 6c, 7, 8b, 9, 10**, and **11**

[a] Antibacterial activity of 60 μg/ml product is comparable to that of the standards used (50 μg/ml penicillin G and 100 μg/ml neomycin). [b] Antifungal activity of 150 μg/ml is comparable to that of the standard used (100 U/ml nystatin). [c] Antiviral activity in tissue culture expressed as the reduction factor of the viral titer (**12b**).

tered off and neutralized with glacial acetic acid. The light yellow precipitate was filtered off and washed with water. It was crystallized from a DMF-water mixture, yielding 10.5 g, mp 218-225° dec; ms: m/z 273 ($M^{+\cdot}$).

Anal. Calcd. for $C_{12}H_7N_3O_3S$: C, 52.75; H, 2.56; N, 15.38. Found: C, 53.01; H, 2.62; N, 15.45.

5-Cyano-6-phenyl-2-thiouracil (**1d**).

This compound was prepared in 40% yield by reacting an equimolar mixture of thiourea, ethyl cyanoacetate, potassium carbonate and benzaldehyde in ethanol, mp 298-300°, lit [11] mp 300-302°.

5-Cyano-6-(*p*-anisyl)-2-thiouracil (**1f**).

This compound was synthesized from thiourea, ethyl cyanoacetate, *p*-anisaldehyde and potassium carbonate as described earlier, 52%, mp 245-247°, lit [11], 280-281°; ms: m/z 259 ($M^{+\cdot}$).

Anal. Calcd. for $C_{12}H_9N_3O_2S$: C, 55.60; H, 3.47; N, 16.22. Found: C, 55.62; H, 3.65; N, 16.32.

5-Cyano-6-phenethyl-2-thiouracil (**1g**).

This compound was isolated in 40% yield by reacting thiourea, ethyl cyanoacetate, dibromocinnamaldehyde and potassium carbonate in ethanol, mp 230-232°; ms: m/z 257 ($M^{+\cdot}$).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.70; H, 4.28; N, 16.34. Found: C, 60.82; H, 4.35; N, 16.52.

5-Cyano-6-(*p*-dimethylaminophenyl)-2-thiouracil (**1h**).

This compound was prepared from thiourea, ethyl cyanoacetate, *p*-dimethylaminobenzaldehyde and potassium carbonate in ethanol, mp 265-267°, lit [11], mp 287-288°.

1,3-Dimethyl-5-cyano-6-(3',4'-methylenedioxyphenyl)uracil (**2a**).

A solution of **1a** (2.6 g) in 20 ml of DMF was stirred overnight with potassium carbonate and methyl iodide under gentle wraming. The reaction mixture was diluted with water and the resulting precipitate was filtered off, washed with water and crystallized from a water-DMF mixture, mp 200-201°; ms: m/z 285 ($M^{+\cdot}$).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 59.12; H, 4.35; N, 14.68.

1,3-Dimethyl-5-cyano-6-phenyluracil (**2b**).

This compound was prepared from **1c** by *N*-methylation with methyl iodide as described in the preceding experiment, 48%, mp 170-173°.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.73; H, 4.56; N, 17.42. Found: C, 64.83; H, 4.62; N, 17.35.

1,3-Diethyl-5-cyano-6-(*p*-anisyl)uracil (**2c**).

This compound was synthesized from **1e** and ethyl iodide in DMF with potassium carbonate and isolated as described earlier, 45%, mp 75°.

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.21; H, 5.68; N, 14.04. Found: C, 64.36; H, 5.45; N, 14.25.

1,3-Diethyl-5-cyano-6-(*p*-dimethylaminophenyl)uracil (**2d**).

N-Ethylation of **1h** with ethyl iodide according to the preceding procedure gave the title compound, 35%, mp 100-101°.

Anal. Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.38; H, 6.41; N, 17.95. Found: C, 65.55; H, 6.62; N, 18.12.

2-Methylmercapto-3-methyl-4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**6a**, R = CH_3).

To a solution of **1b** (2.0 g) in DMF (20 ml), potassium carbonate and methyl iodide were added and stirred for 3 hours. The reaction mixture was diluted with water and the precipitate was filtered off. The product thus obtained was crystallized from methanol yielding 2.1 g (95%), mp 240°; ms: m/z 301 ($M^{+\cdot}$), 286 (M^+ -CH_3), 254 (M^+ -SCH_3); nmr (DMSO-d_6): δ 2.73 (s, SCH_3), 3.53 (s, N-CH_3), 6.3 (s, CH_2), 7.2-7.96 (m, C_6H_3).

Anal. Calcd. for $C_{14}H_{11}N_3O_3S$: C, 55.81; H, 3.65; N, 13.95. Found: C, 55.72; H, 3.73; N, 14.22.

2-Ethylmercapto-3-ethyl-4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)-pyrimidine (**6b**, R = C_2H_5).

A mixture of **1b** (0.7 g), potassium carbonate (0.5 g) and ethyl iodide (0.7 g) in DMF (10 ml) was stirred overnight at room temperature and worked up as described in the preceding experiment. The crude product was crystallized from methanol, yielding 0.23 g, mp 131°.

Anal. Calcd. for $C_{16}H_{15}N_3O_3S$: C, 58.36; H, 4.56; N, 12.77. Found: C, 58.40; H, 4.48; N, 12.78.

2-*n*-Propylmercapto-3-*n*-propyl-4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**6c**, R = *n*-C_3H_7).

A solution of **1b** (0.5 g) in DMF (10 ml) was stirred with potassium carbonate and after a while *n*-propyl iodide was added. The resulting mixture was stirred overnight under gentle warming and finally diluted with water. The reaction mixture was extracted with ether, drioed over calcium chloride and filtered. The filtrate was evaporated to dryness which gave a viscous liquid. Trituration with petroleum ether gave a light yellow crystalline solid, 0.13 g, mp 110°; ms: m/z 357 ($M^{+\cdot}$), 315 (M^+ -C_3H_6), 314 (M^+ -C_3H_7), 300 (M^+ -NC_3H_7), 272 (300-CO).

Anal. Calcd. for $C_{18}H_{19}N_3O_3S$: C, 60.50; H, 5.32; N, 11.76. Found: C, 60.26; H, 5.23; N, 11.63.

The aqueous phase of the reaction mixture was acidified with acetic acid which gave a yellow solid. The precipitate was filtered off, washed with water and crystallized from a chloroform-methanol mixture as 2-*n*-propylmercapto-4-oxo-3,4-dihydro-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**3a**), 0.14 g, mp 235°; nmr (DMSO-d_6): δ 1.0 (t, CH_3), 1.73 (m, CH_2), 3.2 (t, CH_2), 6.13 (s, CH_2), 7-7.67 (m, C_6H_3).

Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.14; H, 4.13; N, 13.33. Found: C, 56.96; H, 3.98; N, 13.24.

Other compounds prepared according to this procedure are listed in Table II.

2-Cyanomethylmercapto-4-oxo-3,4-dihydro-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**3b**).

A solution of **1b** (0.5 g) in DMF (10 ml) was stirred with chloroacetonitrile (0.2 g) and potassium carbonate (0.5 g) under gentle warming overnight. The reaction mixture was diluted with water and filtered. The filtrate was neutralized with acetic acid and the yellow precipitate thus obtained was filtered off, washed with water and finally crystallized from a DMF-water mixture, yielding 0.2 g, mp 187°; ms: m/z 312 ($M^{+\cdot}$), 286 (M^+ -CN), 240 (M^+ -SCH_2CN); nmr (DMSO-d_6): δ 2.1 (s, CH_2), 6.17 (s, -OCH_2O), 7.03-7.75 (m, C_6H_3).

Anal. Calcd. for $C_{14}H_8N_4O_3S$: C, 53.85; H, 2.56; N, 17.95. Found: C, 54.02; H, 2.58; N, 17.91.

Other compounds prepared according to the same procedure are listed in Table III.

Table II

2,3,6-Substituted-5-cyano-thiouracils **6**

Compound No.	R	R'	Mp °C	Molecular Formula	Elemental Analysis (%) Calcd. C	H	N	Found C	H	N
6d	-CH_3	C_6H_5-	174	$C_{13}H_{11}N_3OS$	60.70	4.28	16.34	60.64	4.35	16.53
6e	-C_2H_5	C_6H_5-	152	$C_{15}H_{15}N_3OS$	63.16	5.25	14.74	63.35	5.45	14.89
6f	-CH_3	$C_6H_5CH_2CH_2$-	100	$C_{15}H_{15}N_3OS$	63.16	5.26	14.74	63.26	5.38	14.65
6g	-CH_3	*p*-CH_3O-C_6H_4-	197	$C_{14}H_{13}N_3O_2S$	58.53	4.53	14.63	58.34	4.68	14.38
6h	$C_6H_5CH_2$-	*p*-CH_3O-C_6H_4-	110	$C_{26}H_{21}N_3O_2S$	71.07	4.78	9.57	71.34	4.56	9.83
6i	CH_2=CH-CH_2-	*p*-CH_3O-C_6H_4-	85	$C_{18}H_{17}N_3O_2S$	63.72	5.01	12.39	63.81	4.92	12.45
6j	$C_6H_5CH_2CH_2$-	*p*-CH_3O-C_6H_4-	110	$C_{28}H_{25}N_3O_2S$	71.95	5.35	8.99	72.15	5.48	9.23
6k	-CH_3	*p*-$(CH_3)_2NC_6H_4$-	183	$C_{15}H_{16}N_4OS$	60.00	5.33	18.66	60.12	5.62	18.46
6l	$C_6H_5CH_2$-	*p*-$(CH_3)_2NC_6H_4$-	120	$C_{27}H_{24}N_4OS$	71.68	5.31	12.39	71.72	5.45	12.48

Table III

2,6-Substituted-5-cyano-thiouracils **3**

Compound No.	R	R'	Mp °C	Molecular Formula	Elemental Analysis (%) Calcd. C	H	N	Found C	H	N
3c	-CH_2CONH_2	*m,p*-$CH_2O_2C_6H_3$-	221	$C_{14}H_{10}N_4O_4S$	50.91	3.03	16.92	50.97	3.01	16.92
3d	-CH_2CH_2OH	*m,p*-$CH_2O_2C_6H_3$-	305-310	$C_{14}H_{10}N_3O_4S$	53.16	3.16	13.29	53.42	3.34	13.12
3e	*p*-Cl-$C_6H_4CH_2$-	*m,p*-$CH_2O_2C_6H_3$-	225	$C_{19}H_{12}N_3O_3SCl$	57.36	3.02	10.57	56.97	2.95	10.56
3f	-CH_2CN	-$CH_2CH_2C_6H_5$	113	$C_{15}H_{12}N_4OS$	60.81	4.05	18.92	60.72	4.32	19.12
3g	-CH_2CN	*p*-$CH_3OC_6H_4$-	195	$C_{14}H_{10}N_4O_2S$	56.37	3.36	18.79	56.32	3.54	18.65

2-Hydrazino-3-methyl-4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**7**).

To a suspension of **6** (R = CH_3) (0.2 g) in ethanol (8 ml), hydrazine (1 ml) was added and the mixture was refluxed for 5 hours. After cooling and dilution with water a brown precipitate was obtained, which was filtered off and crystallized from DMF-ether as a brown solid; tlc showed a single spot, 0.15 g, mp 263° dec.

Anal. Calcd. for $C_{13}H_{11}N_5O_3$: C, 54.73; H, 3.86; N, 24.58. Found: C, 54.50; H, 3.82; N, 24.63.

2-Acetylhydrazino-3-methyl-4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**8a**).

A mixture of **7** (0.2 g) and acetic acid (5 ml) was refluxed for 20 hours. The reaction content was cooled and filtered. The crude material obtained was crystallized from a DMF-water mixture, 0.15 g, mp 285°; ms: m/z 327 ($M^{+\cdot}$), 285 (M^+ -CH_2CO), 284 (M^+ -CH_3CO), 270 (M^+ -CH_3NCO), 255 (270-CH_3); nmr (DMSO-d_6): δ 1.97 (s, CH_3), 3.37 (s, CH_3), 6.11 (s, CH_2), 6.97-7.61 (m, C_6H_3).

Anal. Calcd. for $C_{15}H_{13}N_5O_4$: C, 55.04; H, 3.97; N, 21.41. Found: C, 55.21; H, 3.65; N, 21.65.

2-Propionylhydrazino-3-methyl-4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**8b**).

A solution of **7** (0.2 g) in propionic acid (5 ml) was refluxed for 3 hours, cooled and filtered. The precipitate was crystallized from DMF-water, yielding 0.15 g, mp 287°; nmr (DMSO-d_6): δ 1.1 (t, CH_3), 2.78 (m, CH_2), 3.38 (s, CH_3), 6.13 (s, CH_2), 7.63-6.65 (m, C_6H_3).

Anal. Calcd. for $C_{16}H_{15}N_5O_4$: C, 56.30; H, 4.34; N, 20.53. Found: C 56.22; H, 4.50; N, 20.65.

6-Cyano-5-(3',4'-methylenedioxyphenyl)-8-methyl-1,2,4-triazolo[3,4-*b*]pyrimidin-7-one (**9**).

A solution of **7** (0.2 g) in formic acid (5 ml) was refluxed for 4 hours, cooled and poured into water. The precipitate thus obtained was filtered off and crystallized from a DMF-water mixture, yielding 0.12 g, mp 275°.

Anal. Calcd. for $C_{14}H_9N_5O_3$: C, 56.95; H, 3.05; N, 23.73. Found: C, 57.21; H, 3.34; N, 23.73.

2-(3'-Methylmercapto-4'-amino-5'-carbomethoxy-1'-yl)-3-methyl-4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**10**).

A mixture of **7** (0.2 g) and methyl dimethylmethylmercaptoacrylate (0.2 g) in DMF (5 ml) was refluxed for 5 hours, cooled and added to methanol under stirring, which gave a yellow precipitate. It was filtered off, washed from water and crystallized from a DMF-water mixture, yielding 0.15 g, mp 300°.

Anal. Calcd. for $C_{19}H_{16}N_6O_5S$: C, 51.82; H, 3.63; N, 19.09. Found: C, 51.86; H, 3.76; N, 18.98.

2-(3',5'-Dimethylpyrazol-1'-yl)-4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidine (**11**).

This compound was prepared from **7** (0.2 g) and acetylacetone (0.2 g) in DMF (5 ml) with a few drops of acetic acid and worked up as described in the preceding experiment, to yield 0.2 g, mp 252°.

Anal. Calcd. for $C_{18}H_{15}N_5O_3$: C, 61.89; H, 4.30; N, 20.06. Found: C, 61.98; H, 4.52; N, 20.32.

Bis[4-oxo-5-cyano-6-(3',4'-methylenedioxyphenyl)pyrimidin-2-yl]mercaptomethane (**4**).

A mixture of **1b** (0.5 g), methylene bromide (0.17 g) and potassium carbonate (0.5 g) in DMF (10 ml) was stirred with a little warming for 3 hours and stirring was continued overnight. Water was added to the reaction mixture and the solid thus obtained was filtered off and crystallized from a DMF-methanol mixture, yielding 0.2 g, mp 265°; ms: m/z 558 ($M^{+\cdot}$).

Anal. Calcd. for $C_{25}H_{14}N_6O_6S_2 \cdot 0.5H_2O$: C, 52.91; H, 2.64; N, 14.8. Found: C, 53.22; H, 3.02; N, 15.08.

6-Cyano-7-(3',4'-methylenedioxyphenyl)-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**5a**).

A mixture of **1b** (0.5 g), dichloroethane (0.2 g) and potassium carbonate (0.5 g) in 10 ml of DMF was heated at 85-90° for 3 hours, cooled and poured slowly on cold water with stirring. The precipitate thus obtained was filtered off, washed with water and finally crystallized from a DMF-water mixture; tlc showed single spot, 0,4 g, mp 220°; nmr (DMSO-d_6): δ 3.6 (t, CH_2), 4.47 (t, CH_2), 6.13 (s, CH_2), 7-7.6 (m, C_6H_3).

Anal. Calcd. for $C_{14}H_9N_3O_3S$: C, 56.19; H, 3.01; N, 14.05. Found: C, 56.09; N, 2.93; N, 13.94.

6-Cyano-7-phenyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**5b**).

This compound was prepared by heating an equimolar mixture of 5-cyano-6-phenyl-2-thiouracil, dichloromethane and potassium carbonate in DMF and worked up as described in the preceding experiment, 60%, mp 170°.

Anal. Calcd. for $C_{13}H_9N_3OS$: C, 61.17; H, 3.53; N, 16.47. Found: C, 61.23; H, 3.45; N, 16.58.

7-Cyano-8-(3',4'-methylenedioxyphenyl)-3,4-dihydro-2*H*-pyrimido[2,3-*b*]-[1,3]thiazin-6-one (**5c**).

This compound was prepared from **1b** (0.3 g), 1.3-dibromopropane (0.5 ml) potassium carbonate (0.3 g) as described above. The crude product was crystallized from a DMF-water mixture, yielding 0.25 g, mp 186°; nmr (DMSO-d_6): δ 3.33 (s, -CH_2CH_2-), 4.03 (m, CH_2), 6.17 (s, CH_2), 7.03-7.63 (m, C_6H_3).

Anal. Calcd. for $C_{15}H_{11}N_3O_3S$: C, 57.5; H, 3.51; N, 13.42. Found: C, 57.38; H, 3.55; N, 13.06.

7-Cyano-8-phenyl-3,4-dihydro-2*H*-pyrimido[2,3-*b*][1,3]thiazin-6-one (**5d**).

Heating a mixture of 5-cyano-6-phenyl-2-thiouracil, 1,3-dibromopropane and potassium carbonate in equimolar quantities in DMF for 6 hours gave the title compound. The crude material was crystallized from a DMF-water mixture, yielding 65%, mp 202°.

Anal. Calcd. for $C_{14}H_{11}N_3OS$: C, 62.45; H, 4.09; N, 15.61. Found: C, 62.62; H, 4.31; N, 15.83.

8-(*p*-Anisyl)-7-cyano-3,4-dihydro-2*H*-pyrimido[2,3-*b*][1,3]thiazin-6-one (**5e**).

An equimolar mixture of 5-cyano-6-(*p*-anisyl-2-thiouracil, 1,3-dibromopropane and potassium carbonate was heated at 80-90° in DMF for 4 hours and worked up as earlier described, 63%, mp 171°.

Anal. Calcd. for $C_{15}H_{13}N_3O_2S$: C, 60.20; H, 4.35; N, 14.05. Found: C, 60.34; H, 4.23; N, 14.23.

7-Cyano-8-phenylethyl-3,4-dihydro-2*H*-pyrimido[2,3-*b*][1,3]thiazin-6-one (**5f**).

This compound was prepared from 5-cyano-6-phenylethyl-2-thiouracil, 1,3-dibromopropane and potassium carbonate as described in the preceding experiment. The crude material was crystallized from a DMF-water mixture, 60%, mp 120°.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.65; H, 5.05; N, 14.14. Found: C, 64.75; H, 5.34; N, 14.35.

7-Cyano-3-hydroxy-8-(3',4'-methylenedioxyphenyl)-3,4-dihydro-2*H*-pyrimido[2,3-*b*][1,3]thiazin-6-one (**5g**).

1,3-Dibromopropanol-2 was added to a mixture of **1b** (0.5 g) and potassium carbonate (0.5 g) in DMF (10 ml) and heated overnight at 80-90°. The reaction mixture was poured over ice under stirring and filtered. The crude product was crystallized from a DMF-water mixture, yielding 0.51 g, mp 235-237°; nmr (DMSO-d_6): δ 3.57 (t, SCH_2), 4.33 (m, CH), 4.5 (t, NCH_2), 5.77 (OH), 6.15 (s, CH_2), 7-7.63 (m, C_6H_3).

Anal. Calcd. for $C_{15}H_{11}N_3O_4S$: C, 54.71; H, 3.34; N, 12.77. Found: C, 54.58; H, 3.21; N, 12.73.

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