The Preparation and Antitumor Properties of Acylated Derivatives of 6-Thiopurine Ribosides[1]

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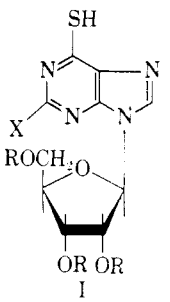
In connection with the study of the possible role of hydrolytic enzymes, acylated derivatives of 6-thiopurine ribosides were prepared by *direct acylation* of the corresponding parent compounds. Antitumor evaluation of these derivatives indicated that the carcinostatic properties vary with the nature of the acyl groups.

The antitumor activities of 6-mercaptopurine riboside [9-(β-D-ribofuranosyl)purine-6-thiol, thioinosine (I, X = H, R = H)] and thioguanosine [2-amino-9-(β-D-ribofuranosyl)purine-6-thiol (I, X = NH_2, R = H)] are well known.[2] Recently, the acyl derivatives of a number of pyrimidine (and azapyrimidine) nucleosides,[3] purine nucleosides,[2a,4] and nucleoside antibiotics[5] have been actively studied by many investigators. These acyl derivatives, because of their greater lipid solubility, were reported to have a drastically altered oral absorption pattern.[3,5] Consequently, acylation of these nucleosides would modify the transport characteristics through the cell membrane.[6]



I

One of the major problems involved with the use of 6-mercaptopurine and related derivatives is the rapid transformation of the drug to other inactive metabolites, which are then rapidly excreted.[7] Suppression of the degradative enzymatic action by the concurrent administration of another drug is one approach to this problem recently described by Elion and co-workers[7c] An alternative method is to administer the drug in a form which is slowly converted *in vivo* to the desired active form. Such a compound would, undoubtedly, have many clinical advantages. Therefore the synthesis and investigation of selected derivatives of 6-thiopurine ribosides has been undertaken.

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)purine-6-thiol (I, X = H, R = $COCH_3$) and the 2-amino analog (I, X = NH_2, R = $COCH_3$) have previously been prepared by refluxing triacetylribosides of the corresponding 6-chloropurine with thiourea in ethanol.[4b] Fox, *et al.*,[2a] prepared 9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)purine-6-thiol (I, X = H, R = COC_6H_5) and the corresponding 2-amino derivative (I, X = NH_2, R = COC_6H_5) by the thiation of the benzoylated inosine and guanosine, respectively, with phosphorus pentasulfide. In our laboratories these compounds as well as other acyl derivatives were prepared by direct acylation of the corresponding 6-thiopurine ribosides by a modified Schotten–Baumann reaction[2a,8] using acyl chlorides and pyridine. The products thereby obtained are of high purity and yields of the acylated derivatives are generally quite good (Table I). It is interesting to note that the amino group of thioguanosine was not acylated under the present reaction condition.

Preliminary antitumor screening results[9] of these compounds are listed in Table II. These data indicated that (1) the acetylated derivatives possess very encouraging activity at low doses; (2) activity is relinquished with long chain acylated derivatives; (3) the substituted benzoyl derivatives are quite active in CA-755 and possess much lower toxicity. With the testing data presently available, a comparison of the maximum tolerated dose (MTD) of 6-mercaptopurine riboside,[10,11] thioguanosine,[11] and their acylated derivatives reveals that (1) the acylated derivatives of 6-mercaptopurine riboside are not superior to the parent compound, and (2) the acylated derivatives of thioguanosine, particularly the substituted benzoyl derivatives, are found to possess more than ten times the MTD value of the parent compound.

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service (Contract No. SA-43-ph-3025).

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(9) The biological testing was performed by the Screening Contractors of the Cancer Chemotherapy National Service Center.

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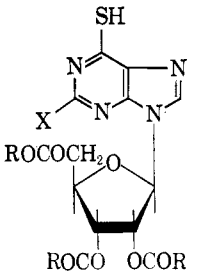
TABLE I

ACYLATED 6-THIOPURINE RIBOSIDES



Compound no.	X	R	Formula	Recryst. solvents[a]	M.p., °C.	% yield	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N	Ultraviolet absorption (mμ) pH 1 λmax	pH 1 ε	pH 11 λmax	pH 11 ε
1	H	CH_3	$C_{16}H_{18}N_4O_7S$	A + B	252–253[b]	90	46.8	4.4	13.6	46.9	4.4	13.7	320	25,800	236	13,500
															309	23,800
2	H	$CH_3(CH_2)_2$	$C_{22}H_{30}N_4O_7S$	C	206–207	61	53.4	6.1	11.3	53.1	6.2	11.1	320	22,200	237	10,400
															309	20,800
3	H	$(CH_3)_2CH$	$C_{22}H_{30}N_4O_7S$	D	205–207	60	53.4	6.1	11.3	53.2	6.2	11.7	320	29,700	236	15,800
															310	28,000
4	H	$CH_3(CH_2)_3$	$C_{25}H_{36}N_4O_7S$[c]	C	190–192	56	55.1	6.8	10.3	55.3	6.9	10.4	321	23,100	237	12,500
															309	23,700
5	H	$CH_3(CH_2)_{10}$	$C_{46}H_{72}N_4O_7S$	C	212–214	74	66.5	9.4	6.7	66.7	9.4	6.5	320	24,000	234	14,100
															310	22,400
6	H	$CH_3(CH_2)_{16}$	$C_{64}H_{114}N_4O_7S$	E	221–222	84	70.8	10.5	5.2	70.8	10.5	5.0	322	27,600	234	19,000
															311	27,100
7	H	$CH_3(CH_2)_7CH{=}CH(CH_2)_7$	$C_{64}H_{108}N_4O_7S$	D + F	202–206	71	71.4	10.0	5.2	71.5	10.0	5.3	321	26,700	235	16,200
															310	24,200
8	H	C_6H_5	$C_{31}H_{24}N_4O_7S$	C	219–221[d]	69	62.4	4.0	9.4	62.7	4.1	9.4	228	41,700	310	23,800
													320	25,000		
9	H	*p*-ClC_6H_4	$C_{31}H_{21}Cl_3N_4O_7S$	(1) A + B, (2) C	239–240	83	53.2	3.0	8.0	53.2	3.1	8.0	245	40,600	238	39,800
													322	20,300	310	16,400
10	H	*p*-$O_2NC_6H_4$	$C_{31}H_{21}N_7O_{13}S$	E	172–176	91	50.9	2.9	13.4	50.8	3.4	13.6	264	33,500	234	21,600
													320	27,400	305	32,800
11	H	*p*-$CH_3OC_6H_4$	$C_{34}H_{30}N_4O_{10}S$	C	176–177	94	59.5	4.4	8.2	59.4	4.6	8.3	261	40,500	236	24,400
													323	22,000	258	46,400
															310	23,300
12	NH_2	CH_3	$C_{16}H_{19}N_5O_7S$[c]	E	203–205[e]	75	44.3	4.6	16.1	44.4	4.7	16.3	264	3,800	251	8,300
													344	15,100	317	13,600
13	NH_2	C_2H_5	$C_{19}H_{25}N_5O_7S$	C	209–211	61	48.8	5.4	15.0	48.9	5.6	14.7	264	7,000	251	16,600
													343	22,000	317	20,100
14	NH_2	$CH_3(CH_2)_2$	$C_{72}H_{31}N_5O_7S$	C	217–218	79	51.8	6.1	13.7	51.9	6.3	13.4	264	8,600	252	13,200
													342	17,800	318	19,900
15	NH_2	$(CH_3)_2CH$	$C_{22}H_{31}N_5O_7S$	C	211–213	68	51.8	6.1	13.7	51.5	6.1	13.6	264	7,900	250	13,200
													344	24,000	317	21,400
16	NH_2	$CH_3(CH_2)_{14}$	$C_{58}H_{103}N_5O_7S$[f]	D	170–172	89	67.6	10.2	6.8	67.7	10.5	6.8	262	19,000	250	26,200
													343	34,700	318	30,800
17	NH_2	C_6H_5	$C_{31}H_{25}N_5O_7S$	E	225–228[g]	58	60.9	4.1	11.5	60.5	4.5	11.1	227	39,700	250	16,500
													266	10,400	317	20,800
													344	21,800		
18	NH_2	*p*-$CH_3C_6H_4$	$C_{34}H_{31}N_5O_7S$[c]	C	212–214	83	61.6	4.8	10.6	61.8	5.0	10.2	245	60,300	244	43,000
													340	20,900	318	24,300
19	NH_2	*p*-ClC_6H_4	$C_{31}H_{22}Cl_3N_5O_7S$	C + D	227–228	87	52.0	3.1	9.8	51.6	3.1	9.8	246	44,300	244	41,400
													340	20,000	323	14,300
20	NH_2	*p*-$O_2NC_6H_4$	$C_{31}H_{22}N_8O_{13}S$[f]	B + E	191–195	75	48.7	3.1	14.7	48.8	3.4	15.1	263	35,600	253	31,400
													344	24,200	273	31,400
															314	27,700
21	NH_2	*p*-$CH_3OC_6H_4$	$C_{34}H_{31}N_5O_{10}S$[h]	C	173–176	64	55.6	4.8	9.5	55.4	4.6	9.8	261	44,200	256	50,000
													344	19,800	318	19,800

[a] Recrystallization solvents: (A) water, (B) acetone, (C) ethyl acetate, (D) methanol, (E) ethanol, and (F) dichloromethane. [b] Lit.[4b] m.p. 255–256°. [c] Hemihydrate. [d] Lit.[2a] m.p. 206–214°. [e] Lit.[4b] m.p. 209–211°. [f] Hydrate. [g] Lit.[2a] m.p. 223.5–227.5.° [h] Dihydrate.

Experimental[12]

General Preparation of Acyl Derivatives of 6-Mercaptopurine Riboside and Thioguanosine (see Table I).—To a stirred suspension of 0.02 mole of mercaptopurine riboside in 250 ml. of anhydrous pyridine was added 0.08 mole of the appropriate acid chloride. The resulting solution was heated at 50–60° for 3 hr. while stirring. The solvent was then removed *in vacuo* (below 50°) and the residue was treated with 500 ml. of distilled water. The crystallized product was filtered and recrystallized from appropriate solvents (see Table I). Drying was accomplished at 100° (0.1 mm.).

A shorter reaction time (1 or 2 hr.) or lower temperature resulted in the recovery of either starting material or mono- or diacylated derivatives.

In the case of R = $CH_3(CH_2)_7CH{=}CH(CH_2)_7$ or *p*-$CH_3C_6H_4$ and X = H or NH_2, the water, which was added to induce the crystallization of the residue, was decanted and the semisolid residue crystallized upon the addition of 200 ml. of anhydrous methanol.

Attempted recrystallizations of unbranched acyl derivatives (R = $CH_3CH_2CH_2$ through $CH_3(CH_2)_7CH{=}CH(CH_2)_7$) from nonpolar solvents (ether, heptane, or benzene) caused the formation of a gel. This difficulty was overcome by recrystallizing these compounds from more polar solvents.

(12) All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer.

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Table II

Preliminary Antitumor Screening Results of Acylated 6-Thiopurine Ribosides

Compound no.	Test system	Dose (mg./kg.)	Survivors	Animal wt. diff. (T − C)	Tumor wt. (mg.) or survival (days) Test	Control	Slope[a]	ED_{50}[b]	% (T/C)
1	SA-180	100.0	6/6	0.3	98	1002			9
		100.0	6/6	1.7	135	1101			12
	CA-755	240.0	0/10						
		120.0	1/10	−4.9	0	1245			
		60.0	10/10	−5.0	0	1245			0
		30.0	9/10	−3.2	0	1245			0
		30.0	9/10	−4.0	8	1155			0
		15.0	10/10	−3.5	34	1155			2
		7.5	10/10	−0.9	43	1155			3
		3.7	10/10	−3.7	80	1155			6
		1.8	10/10	−1.7	173	1155			14
		1.8	10/10	−1.8	524	1657			31
		0.9	10/10	−0.3	1021	1657			61
		0.4	9/10	0.2	1553	1657			93
	LE-1210	60.0	6/6	−3.1	13.7	8.8			155
		60.0	6/6	−4.2	13.2	8.4			157
		90.0	6/6	−4.6	11.5	8.4			136
		60.0	6/6	−3.9	12.0	8.4			142
		40.0	6/6	−3.0	12.7	8.4			151
		26.0	6/6	−2.8	11.3	8.4			134
		13.0	6/6	0.4	9.5	8.4			113
	KB (Cell culture)	w.					−0.84	2.4×10^{0}	
							−0.82	4.3×10^{0}	
2	SA-180	500.0	0/6						
		125.0	6/6	−5.3	414	1395			29
		125.0	6/6	−0.5	663	1372			48
		125.0	4/6	−3.8	415	1841			22
	CA-755	100.0	10/10	−6.2	5	1015			0
	LE-1210	100.0	6/6	−4.7	13.3	8.8			151
	KB	w.					−0.69	7.2×10^{-1}	
							−1.16	2.6×10^{-1}	
3	SA-180	500.0	0/6						
		125.0	6/6	−5.0	114	1019			11
	KB	w.					−1.00	2.7×10^{-1}	
4	SA-180	500.0	4/6	−2.9	123	1119			10
		500.0	5/6	−5.4	340	1440			23
		500.0	5/6	0.6	1026	1372			74
		500.0	4/6	−0.8	778	1841			42
5	SA-180	500.0	7/7	−0.7	1240	722			171
	CA-755	400.0	9/10	−1.3	1699	1951			87
	LE-1210	400.0	6/6	0.8	10.7	11.0			97
	KB (Cell culture)	w.					−0.75	1.0×10^{2}	
6	SA-180	500.0	6/6	−0.8	892	1269			70
	CA-755	400.0	8/10	−2.5	1100	1425			77
	LE-1210	400.0	6/6	−0.7	9.3	9.3			100
7	SA-180	500.0	7/7	0.2	559	722			77
	CA-755	400.0	8/10	−0.7	1118	1951			57
	LE-1210	400.0	6/6	−0.4	11.7	11.5			101
	KB	w.						M 1.0×10^{2}	
9	SA-180	500.0	3/6	−2.3	693	665			
		250.0	6/7	−2.5	1242	1209			102
	CA-755	200.0	10/10	−3.6	378	1738			21
		200.0	9/10	−2.5	246	1257			19
		200.0	10/10	−3.4	31	1683			1
		200.0	9/10	−3.1	407	1882			21
		200.0	6/10	−2.4	334	1425			
		200.0	7/10	−3.8	79	1586			4
		200.0	9/10	−3.3	131	1345			9
	LE-1210	200.0	6/6	−1.7	11.0	8.9			123
	KB	w.					−0.62	6.2×10^{1}	
10	SA-180	500.0	4/7	−5.8	459	722			
		250.0	7/7	−1.6	399	862			46
		250.0	7/7	−3.8	463	676			68

TABLE II (*Continued*)

Compound no.	Test system	Dose (mg./kg.)	Survivors	Animal wt. diff. (T − C)	Tumor wt. (mg.) of survival (days) Test	Control	Slope[a]	ED_{50}[b]	% (T/C)
10	CA-755	200.0	9/10	−4.9	22	1951			1
		200.0	10/10	−5.7	23	1239			1
		200.0	8/10	−5.0	0	985			0
	LE-1210	200.0	6/6	−3.1	13.6	9.2			147
		200.0	6/6	−1.6	14.0	8.8			159
	KB	w.					−0.97	3.6×10^{1}	
11	SA-180	500.0	4/6	−1.9	520	665			78
	CA-755	400.0	9/10	−5.9	0	1738			0
		400.0	4/10	−5.5	5	1683			
		400.0	10/10	−6.1	0	1257			0
		400.0	8/10	−5.4	68	1882			3
		400.0	8/10	−7.0	8	1345			0
		400.0	10/10	−6.2	38	1423			2
	LE-1210	400.0	6/6	−1.1	9.8	8.9			110
	KB	w.					−0.93	1.9×10^{0}	
12	SA-180	50.0	2/6	−8.3	75	1164			
		33.0	4/6	−5.8	131	1164			11
		22.0	4/6	−6.7	35	1164			3
		15.0	6/6	−5.5	72	1164			6
		6.6	6/6	−3.2	210	1164			18
		4.4	6/6	−0.9	80	1164			6
		3.0	5/6	−3.0	148	1164			12
	CA-755	120.0	0/10						
		30.0	0/10						
		15.0	2/10	−4.5	0	896			
		7.5	8/10	−3.2	0	896			0
		3.0	10/10	−1.6	8	896			0
		1.0	10/10	−1.1	100	896			11
		0.5	10/10	−0.5	851	1223			69
		0.2	9/10	0.4	948	1223			77
		0.1	10/10	0.5	1060	1223			86
	LE-1210	7.5	6/6	1.2	12.5	9.2			135
		11.2	6/6	−4.8	14.3	8.1			176
		7.5	6/6	−4.3	13.2	8.1			162
		5.0	6/6	−3.5	13.2	8.1			162
		3.3	6/6	−2.6	10.3	8.1			127
		1.6	6/6	−0.3	9.5	8.9			106
	KB	w.					−0.99	3.6×10^{0}	
	Hep-2	w.					−1.2	3.6×10^{0}	
	(Cell line)	w.					−1.35	2.2×10^{0}	
	Hep-2/6MP	w.						M 1.0×10^{2}	
	(Cell line)	w.						M 1.0×10^{2}	
13	SA-180	250.0	0/6						
		63.0	1/6	−4.1	80	1440			
		15.0	6/6	0.0	582	1372			42
		15.0	5/6	−1.2	590	1841			32
	KB	w.						L 1.0×10^{0}	
14	SA-180	500.0	0/6						
		125.0	0/6						
		31.0	6/6	1.0	735	1372			53
	CA-755	25.0	7/10	−3.7	25	641			3
	LE-1210	25.0	6/6	−2.7	11.8	8.3			142
	KB	w.					−1.20	2.8×10^{-1}	
15	SA-180	500.0	0/6						
	KB	w.					−0.91	2.0×10^{-1}	
16	SA-180	500.0	5/6	1.1	650	725			89
	CA-755	400.0	10/10	−2.8	1100	2182			50
		400.0	8/10	−2.6	271	1035			26
	LE-1210	400.0	6/6	−1.0	8.7	9.0			96
	KB	w.					−0.27	3.9×10^{1}	
18	SA-180	500.0	6/6	−0.9	608	725			83
	CA-755	400.0	10/10	−4.8	166	2182			7
		400.0	10/10	−2.5	229	1035			22
	LE-1210	400.0	6/6	−1.3	9.7	9.0			107
	KB	w.					−0.48	8.3×10^{1}	

TABLE II (*Continued*)

Compound No.	Test system	Dose (mg./kg.)	Survivors	Animal wt. diff. (T − C)	Tumor wt. (mg.) or survival (days) Test	Control	Slope	ED_{50}[b]	% (T/C)
19	SA-180	500.0	0/6						
		125.0	6/6	−1.4	620	1395			44
		125.0	4/6	2.1	925	1372			67
	CA-755	100.0	8/10	−4.9	0	1423			0
	LE-1210	100.0	6/6	−3.7	13.0	9.3			139
20	SA-180	125.0	6/6	−1.5	258	1227			21
		125.0	2/7	2.2	600	600			
		125.0	0/6						
		125.0	0/6						
		93.0	6/6	−0.3	194	1372			14
		93.0	0/6						
		93.0	3/6	−2.7	285	1097			
		500.0	0/6						
		125.0	5/6	−6.2	400	1104			36
		125.0	4/6	−6.4	258	874			29
		125.0	6/6	1.5	258	1227			21
	KB	w.						L 1.0×10^0	
		w.					−1.20	3.0×10^{-1}	
21	SA-180	500.0	6/6	−2.5	355	1467			24
		500.0	3/6	−5.8	263	1104			
		500.0	2/6	−5.1	355	874			
		250.0	5/6	−2.0	716	1227			58
		250.0	5/7	0.1	542	600			90
	CA-755	200.0	5/10	−3.5	0	1586			
		100.0	7/10	−6.5	0	1345			0
	LE-1210	200.0	6/6	−2.7	10.7	9.3			115
	KB	w.						L 1.0×10^0	
		w.					−0.74	6.6×10^{-1}	

[a] Slope: change of response for each one-log change of dose. [b] ED_{50}: the dose that inhibits growth to 50% of control growth. For materials tested by weight (w. in dose column), ED_{50} is expressed in μg./ml.: L = less than; M = more than.

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Aminonucleosides. II.[1] 3′-Amino-3′-deoxyinosine and 3′-Amino-3′-deoxyadenosine 1-N-Oxide

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3′-Amino-3′-deoxyadenosine (I) from *Helminthosporium* sp. has been converted directly to 3′-amino-3′-deoxyinosine (II) enzymatically and has been oxidized to 3′-amino-3′-deoxyadenosine 1-N-oxide (III).

Recently we identified an antitumor agent from *Helminthosporium* sp. No. 215 as 3′-amino-3′-deoxyadenosine (I).[2] At least nine other "unusual" purine nucleosides have been obtained from natural sources: Angustmycin A,[3] nucleocidin,[4] cordycepin,[5] nebularin,[6] psicofuranine,[7] crotonoside,[8] puromycin,[9] the aminonucleoside[10] from puromycin and homocitrullylaminoadenosine.[11] Of the nine, seven (Angustmycin A, puromycin, purmomycin aminonucleoside, cordycepin, nebularine, crotonoside, and psicofuranine) have antitumor properties, six at nontoxic dose levels; for the others (nucleocidin and homocitrullylaminoadenosine), no data have been published.[12]

Undoubtedly for this reason, interest in chemically

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