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(12) J. K. Landquist and G. J. Stacey, *J. Chem. Soc.*, 2822 (1953).
(13) Evidently diborane reduction of chloroacetaldehyde oxime [W. Meister, *Ber.*, 40, 3442 (1907)] produced a mixture of 2-chloroethylhydroxylamine and 2-chloroethylamine.
(14) R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2109 (1959).
(15) C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, 31, 4067 (1966).
(16) T. O. Hennessey and J. R. Edwards, *Vet. Rec.*, 90, 187 (1972).
(17) M. L. Edwards, R. E. Bambury, and H. W. Ritter, *J. Med. Chem.*, 18, 637 (1975).
(18) USAN name for *N*-(2-hydroxyethyl)-α-(5-nitro-2-furyl)-nitrone.
(19) Silica gel was purchased from Gebr. Hermann, D. 5000 Köln-Ehrenfeld, Grüner Weg 8-10, West Germany, under the name Kieselegel.
(20) J. D. Johnston, U.S. Patent 3 344 022 (1967).
(21) Attempts to purify them by several recrystallizations were unsuccessful.

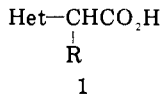
β-Lactam Antibiotics Derived from Nitrogen Heterocyclic Acetic Acids. 1. Penicillin Derivatives

M. L. Edwards,* R. E. Bambury, and H. W. Ritter

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215. *Received September 1, 1976*

In an attempt to synthesize antibacterial agents effective against gram-negative bacteria, penicillin derivatives were prepared from substituted and unsubstituted 1,4-dihydro-2-oxopyridine-1-acetic acids, 1,4-dihydro-4-oxopyridine-1-acetic acids, and 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acids. The unsubstituted derivatives displayed moderate activity against gram-negative bacteria; however, substitution (alkyl, chloro, nitro, acetyl, and cyano) on the heterocyclic ring of these acetic acids and (alkyl, phenyl) in the α position decreased the activity of the penicillin derivatives against gram-negative organisms.

One of the goals of our antibiotic research program is the synthesis of a parenterally effective broad-spectrum penicillin. Our route to this goal was side-chain modification, i.e., coupling novel carboxylic acids with 6-aminopenicillanic acid (6-APA). We synthesized a number of acids with the general structure 1 (Table I), in which an acetic acid residue is bonded to the nitrogen in a heterocyclic ring. This publication will discuss the synthesis of the nitrogen heterocyclic acetic acids, the coupling of the acids to 6-APA, and the antibacterial activity of the resulting derivatives.



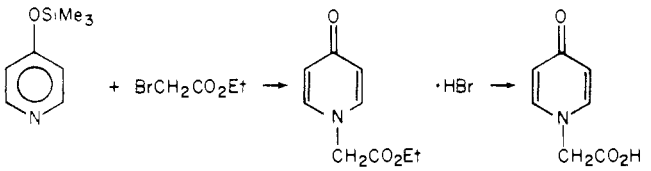
1

A variety of routes was utilized in the synthesis of the heterocyclic acids. The most direct route (method B, Table I) was the reaction of the hydroxy-substituted heterocycle with chloroacetic acid in aqueous alkali. In several examples, a two-step sequence was utilized: reaction of the hydroxy-substituted heterocycle with ethyl bromoacetate in ethanol which contained 1 equiv of potassium hydroxide, followed by hydrolysis of the ester (method A). For compound 18, the sequence illustrated by Scheme I was the most convenient preparation. The 2,4-pyrimidinedione-1-acetic acids with acetyl or cyano groups at C-5 were prepared by the procedure of Shaw and co-workers[1,2] (Scheme II).

The acids prepared were coupled with 6-APA by the mixed anhydride, acid chloride, or imidazolide technique. The penicillin derivatives are tabulated in Table II. These derivatives all assayed (I_2 titration) a minimum of 75% pure and gave spectra (IR, NMR) which were in agreement with the assigned structure.

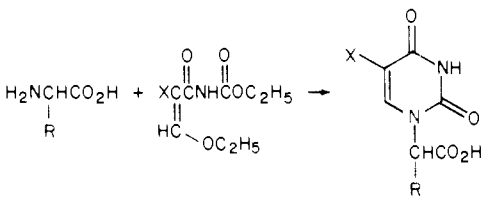
Although we synthesized a variety of acids, the most interesting antibacterial activity was found with derivatives of three classes: 1,2-dihydro-2-oxopyridine-1-acetic acids, 1,4-dihydro-4-oxopyridine-1-acetic acids, and 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acids (Table III). The compounds were evaluated against fatal infections in

Scheme I



20 18

Scheme II



R = H, CH_2, Ph; X = CN, C(=O)CH_3

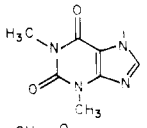
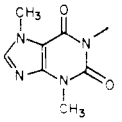
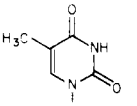
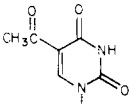
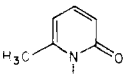
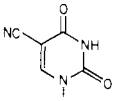
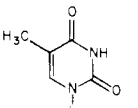
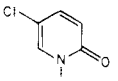
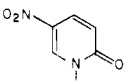
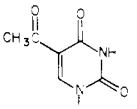
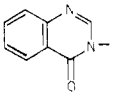
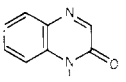
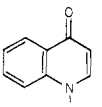
mice using four bacteria, two gram positive (*Staphylococcus aureus* and *Streptococcus pneumoniae*) and two gram negative (*Salmonella schottmuelleri* and *Escherichia coli*). The compounds were not all evaluated simultaneously so comparisons between compounds will be qualitative in nature.

The penicillins derived from acids other than the three groups of main interest exhibited minimal activity against gram-negative organisms (compounds **21–24**). Those derived from the 2-pyridone acids (**25–30**) demonstrated activity against *Salmonella*, but *E. coli* activity was lost on substitution of the pyridone ring (**26**, **28–30**) or in the α position (**27**). A similar structure–activity relationship was observed in the 4-pyridone and 2,4-pyrimidinedioneacetic acid series. Optimum activity appeared to be in the unsubstituted derivatives in all three cases.

Several of the compounds were designed to be resistant to destruction by β-lactamase by insertion of groups in the α position of the side chain[3] (**27**, **38**, and **39**) or on the heterocyclic ring (**26**). All compounds were evaluated in

Table I. Heterocyclic Acetic Acids

Het-CH(R)-CO_2H

No.	Het	R	Method[a]	Mp, °C, or ref	No.	Het	R	Method[a]	Mp, °C, or ref
2		H	A	*b*	12		H	B	*h*
3		H	B	*c*	13		H	B	*i*
4		H	A	*d*	14		H	C	*j*
5		H	B	*e*	15		H	C	*k*
6		CH_3	B	214-216 dec	16		CH_3	A	260-262
7		H	B	227-229					
8		H	A	219-223	17		C_6H_5	C	*j*
10		H	A	*f*	18		H	D	263-264.5
11		H	A	*g*	19		H	B	278-279

[a] Method A = ethyl bromoacetate and heteroamide, KOH in ethanol, followed by aqueous base hydrolysis. Method B = nitrogen heterocycle and chloroacetic acid in aqueous KOH. Method C = ethoxyamide and glycine. Method D = trimethylsilyl ether of 4-hydroxypyridine and ethyl bromoacetate, followed by aqueous HCl hydrolysis. [b] J. Klasa, *Arch. Pharm. (Weinheim, Ger.)*, **288**, 114 (1955). [c] E. Merk, O. Wolfes, and E. Kornick, German Patent 352980; *Chem. Abstr.*, 17, 1307 (1932). [d] H. Lawson and D. H. Miles, *Chem. Ind. (London)*, 461 (1958). [e] R. Adams and H. W. Schrecker, *J. Am. Chem. Soc.*, 71, 1186 (1949). [f] B. R. Baker, U. S. Patent 2648665 (to American Cyanamide); *Chem. Abstr.*, **48**, 1439 (1954). [g] F. Cuiban, M. Ionescu, H. Bala, and M. Steresca, *Bull. Soc. Chim. Fr.*, 356 (1963). [h] B. R. Baker and E. B. Cheda, *J. Pharm. Sci.*, 54, 25 (1965). [i] J. L. Rabinowitz and S. Gurin, *J. Am. Chem. Soc.*, 75, 5758 (1953). [j] See ref 1. [k] See ref 2.

an in vitro assay[4] against two penicillin-resistant strains of *Staph. aureus*. At 1000 μg/mL, **26** exhibited a definite zone of inhibition and compounds **24**, **25**, **27**, **30**, **31**, **33**, and **34** exhibited zones of partial inhibition. It appeared that in these series, a methyl group at the 6 position of the pyridine ring was preferable to a methyl group in the α position of the side chain (compare **26** and **27**). In summary, we have prepared several series of penicillin derivatives, of which a few examples have shown broad-spectrum antibacterial activity in experimental infections in mice.

Experimental Section

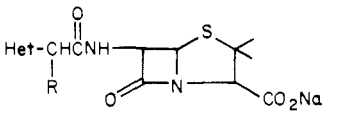
Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined in pressed KBr disks. Intermediates were characterized by C, H, and N combustion analysis and the values were ±0.4% of the theoretical values. The penicillins were characterized by spectra (IR and NMR) and purity was checked by iodine titration (75% or better).

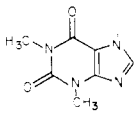
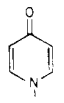
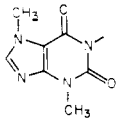
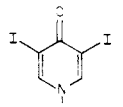
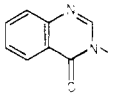
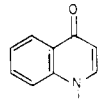
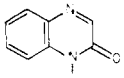
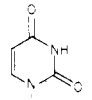
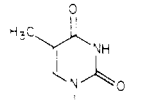
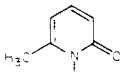
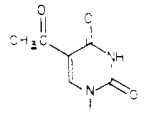
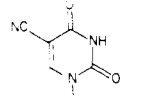
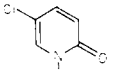
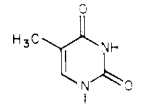
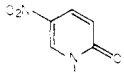
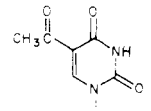
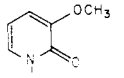
2-[(1,2-Dihydro-2-oxopyridin)-1-yl]propionic Acid (6). A mixture of 50% KOH (100 mL) and 2-hydroxypyridine (20 g, 0.2 mol) was stirred at reflux temperature while 2-bromopropionic acid (30 g, 0.2 mol) was added dropwise over 30 min. The mixture was stirred at reflux temperature another hour, chilled, acidified, and filtered. The product was recrystallized from methyl alcohol to give 6.5 g of solid: mp 214–216 °C dec; IR 1740, 1650, 1559, 1220, 770, and 720 cm^{-1}; NMR (Me_2SO-d_6) δ 1.57 (d, J = 7 Hz, 3 H), 5.22 (q, J = 7 Hz, 1 H), 6.1–6.58 (m, 2 H), and 7.27–7.82 (m, 2 H). Anal. ($C_8H_9NO_3$) C, H, N.

[(1,2-Dihydro-5-nitro-2-oxopyridin)-1-yl]acetic Acid (8). A mixture of methanol (300 mL), sodium methoxide (10.8 g, 0.2 mol), and 2-hydroxy-5-nitropyridine (28 g, 0.2 mol) was stirred at reflux temperature under an N_2 atmosphere while ethyl bromoacetate (33.2 g, 0.2 mol) was added dropwise. The mixture was stirred at reflux temperature for 20 h and filtered. The filtrate was chilled and filtered. The precipitate was recrystallized to give 31 g of ethyl [(1,2-dihydro-5-nitro-2-oxopyridin)-1-yl]acetate (**40**): mp 112–114 °C; IR (KBr) 1760, 1690, 1620, 1570, 1520, 1360, 1220, 1130, 1100, 845, 760, and 655 cm^{-1}; NMR (Me_2SO-d_6-Me_4Si) δ 1.4 (t, J = 4 Hz, 3 H), 4.42 (q, J = 4 Hz, 2 H), 6.75 (d, J = 5 Hz, 1 H), 8.28 and 8.42 (d, J = 2 Hz, 1 H), and 9.4 (d, J = 2 Hz, 1 H). Anal. ($C_9H_{10}N_2O_5$) C, H, N.

Ethyl [(1,2-dihydro-5-nitro-2-oxopyridin)-1-yl]acetate (40) (11.3 g, 0.05 mol) was added to 100 ml of 1 N NaOH and the mixture was stirred at 50 °C for 1.5 h and chilled and the pH of the solution was adjusted to 2.5 with 1 N HCl. The acidified solution was concentrated to 100 mL (at reduced pressure), chilled, and filtered. The precipitate was dissolved in aqueous $NaHCO_3$ and precipitated by the addition of 1 N HCl to give 3.5 g of product: mp 219–223 °C; IR (KBr) 3450, 1680, 1520, 1470, 1360,

Table II



No.	Het	R	Method of prepn[a]	I_2 titration,[b] %	No.	Het	R	Method of prepn[a]	I_2 titration,[b] %
21		H	A	80	31		H	C	78
22		H	A	83	32		H	C	86
23		H	A	92	33		H	C	86
24		H	C	98	34		H	B	76
25		H	B	80	35		H	C	93
26		H	C	92	36		H	C	76
27		CH_3	B	73	37		H	C	80
28		H	C	112	38		CH_3	C	89
29		H	C	103	39		C_6H_5	C	98
30		H	C	87					

[a] Method A = acid chloride. Method B = mixed anhydride. Method C = carbonyldiimidazole. [b] U.S. Pharmacopeia, 14th revision, Mack Publishing Co., Easton, Pa., 1970, p 429.

1195, 1170, 845, 765, and 660 cm^{-1}; NMR (Me_2SO-d_6–Me_4Si) δ 4.72 (s, 2 H), 6.55 (d, J = 5 Hz, 1 H), 8.07 and 8.17 (d, J = 2 Hz, 1 H), 8.07 and 8.17 (d, J = 2 Hz, 1 H), 9.17 (d, J = 2 Hz, 1 H). Anal. ($C_7H_6N_2O_5$) C, H, N.

1,4-Dihydro-4-oxopyridine-1-acetic Acid (18). Ethyl bromoacetate (25 mL) was added to 4-trimethylsilyloxypyridine[5] (9 g) and the mixture was kept under an N_2 atmosphere until the exothermic reaction subsided. The mixture solidified after 2 min. After the mixture had cooled to room temperature, 500 mL of ether was added and the ether suspension was filtered. The white solid was recrystallized from isopropyl alcohol to give 8 g of ethyl 1,4-dihydro-4-oxopyridineacetate hydrobromide (41): mp 195 °C; IR (KBr) 1750, 1650, 1520, 1240, 1215, 1195, 1030, and 855 cm^{-1}; NMR (Me_2SO-d_6–Me_4Si) δ 1.32 (t, J = 6 Hz, 3 H), 4.31 (q, J = 6 Hz, 2 H), 5.7 (s, 2 H), 7.55 (d, J = 6 Hz, 2 H), 8.91 (d, J = 6 Hz, 2 H), 10.51 (br s, 1 H). Anal. ($C_9H_{11}NO_3$·HBr) C, H, N.

A solution of ethyl 1,4-dihydro-4-oxopyridineacetate hydrobromide (41) (786 g, 3 mol) in concentrated HCl (3.2 L) was heated at reflux for 1.5 h. The solution was concentrated to 600 mL and poured into 600 mL of THF. The solid was filtered off and air-dried to give 552.5 g of pyridoneacetic acid hydrochloride. This solid was dissolved in 275 mL of H_2O and a solution of KOH (134.7 g) in water (275 mL) was added. The mixture was heated 20 min on a steam bath, chilled, and filtered. The solid was dried at 100 °C in vacuo to give 297 g of 18: mp 163–264.5 °C dec; IR (KBr) 3450, 1650, 1550, 1450, 1400, 1210, and 865 cm^{-1}; NMR (TFA) δ 4.91 (s, 2 H), 67.03 (d, J = 6 Hz, 2 H), 7.97 (d, J = 6 Hz, 2 H). Anal. N, H; C: calcd, 54.90; found, 54.31.

6-[2-(3,4-Dihydro-4-oxoquinazolin-3-yl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid Sodium Salt (23) (Method A). Oxalyl chloride (12 g, 0.1 mol) was added to a suspension of the potassium salt of 3,4-dihydro-4-oxoquinazoline-3-acetic acid (12 g, 0.05 mol) in hydrocarbon-stabilized $CHCl_3$ (250 mL). The mixture was stirred under an N_2 atmosphere overnight and then chilled to −35 °C. A chilled solution of the bis(tetramethylsilyl) derivative of 6-APA [prepared from 10.8 g (0.05 mol) of 6-APA and hexamethyldisilizane] and triethylamine (5 g, 0.05 mol) in $CHCl_3$ (100 mL) was added dropwise over 30 min. The reaction mixture was stirred at −10 °C for 1 h and allowed to warm to room temperature. Dioxane (350 mL) was added and the solution was filtered to remove the precipitated triethylamine hydrochloride. The filtrate was treated with 2 mL of water, stirred for 30 min, and filtered to remove unreacted 6-APA. The filtrate was treated with 25 mL of a 2 N solution of sodium 2-ethylhexanoate and 1 L of ether. The resulting mixture was filtered and the precipitate was re-

Table III. ED_{50} (mg/kg) of Penicillin Derivatives[a]

No.	Gram positive[b]		Gram negative[b]	
	S.a.	S.p.	S.s.	E.c.
21	3.5	47	>100	>100
22	2.5	5.2	>100	>100
23	1.2	6.0	>100	>100
24	<1.0	3.2	100	>100
25	<1.0	5.3	11	30
26	19	19	52	>100
27	6.7	6.8	100	>100
28	<1.0	10	6.5	>100
29		4.4	37	>100
30	32	3.6	29	>100
31	14	2.8	19	31
32	1.0	5.6	16	>100
33	1.0	5.3	36	>100
34	<1.0	2.4	28	36
35	<1.0	5.2	44	68
36	<1.0	4.3	19	>100
37	1.1	6.7	16	100
38	<1.0	10	48	>100
39	<10	19.3	>100	>100
Penicillin G	1.0	10		
Ampicillin				25
Chloromycetin			50	

[a] Each compound was given to mice infected with a fatal infection. Doses of 1, 10, or 100 mg/kg were given in four doses at −1, +1, +19, and +25 h. The challenge was given at 0 h. ED_{50} calculated according to L. J. Reed and H. Muench, *Am. J. Hyg.*, 27, 493, 497 (1938). [b] *S.a.* = *Staphylococcus aureus; S.p.* = *Streptococcus pneumoniae; S.s.* = *Salmonella schottmuelleri; E.c.* = *Escherichia coli.*

dissolved in methanol (150 mL, some insoluble material, filtered off) and reprecipitated with ether: yield of reprecipitated product 6.8 g; mp 219–221 °C dec; IR (KBr) 1760, 1670, 1620, and 770 cm^{-1}; NMR (D_2O–DSS) δ 1.58 (d, J = 4 Hz, 6 H), 4.27 (s, 1 H), 4.88 (s, 2 H), 5.62 (s, 2 H), 7.5–8.3 (m, 5 H); iodine titration 92.2%.

3,3-Dimethyl-6-[2-[2-oxo-1(2*H*)-pyridyl]acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid Sodium Salt (25) (Method B). A solution of 1,2-dihydro-2-oxopyridine-1-acetic acid (3.1 g, 0.02 mol) and triethylamine (2 g, 0.02 mol) in DMF (50 mL) was chilled to −25 °C. Ethyl chloroformate (2.17 g, 0.02 mol) was added and the mixture was stirred at −25 °C for 30 min. A chilled solution of bis(Me_3-6-APA) [from 4.3 g (0.02 mol) of 6-APA and hexamethyldisilazine] in $CHCl_3$ (50 mL) was added and the mixture was stirred at −20 °C for 1 h and allowed to come to room temperature. Dioxane (100 mL) was added, and the mixture was filtered. Water (0.2 mL) was added to the filtrate; the mixture was stirred for 30 min and filtered free of unreacted 6-APA. Ten milliliters of a 2 N butanol solution of sodium 2-ethylhexanoate and 1 L of ether were added to the filtrate. The precipitated product was filtered off, dissolved in methanol (100 mL), and reprecipitated by the addition of ether. The yield was 3.6 g of white powder, which decomposed over a 20 °C range beginning at 120 °C: IR (KBr) 1780, 1660, 1610, 1580, 1540, 1400, 1320, and 765 cm^{-1}; NMR (D_2O–DSS) δ 1.60 (d, J = 6 Hz, 6 H), 4.25 (s, 1 H), 4.8 (s, 2 H), 5.57 (s, 2 H), 6.4–6.8 (m, 2 H), 7.5–7.9 (m, 2 H); iodine titration 80.3%.

6-[2-[2-Oxo-1(2*H*)-quinoxalinyl]acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid Sodium Salt (24) (Method C). A solution of 1,2-dihydro-2-oxoquinoxaline-1-acetic acid (3.3 g, 0.016 mol) in DMF (20 mL) was chilled to −10 °C and carbonyldiimidazole (2.6 g, 0.016 mol) was added. The mixture was stirred at 0 °C under an N_2 atmosphere for 20 min, warmed to room temperature, and placed under a vacuum for 5 min (to remove the CO_2 liberated during the imidazolide formation). A solution of 6-APA (3.5 g, 0.016 mol) and triethylamine (3.2 g, 0.032 mol) in $CHCl_3$ (100 mL) was added and the reaction mixture was stirred for 18 h under an N_2 atmosphere. Eight milliliters of a 2 N butanol solution of sodium 2-ethylhexanoate and 1 L of ether were added. The mixture was filtered and the product was reprecipitated from methanol with ether to give 3.5 g of white powder: mp 227–229 °C dec; IR (KBr) 1770, 1660, 1620, and 760 cm^{-1} NMR (D_2O–DSS) δ 1.58 (d, J = 5 Hz, 6 H), 4.3 (s, 1 H), 5.05 (s, 2 H), 5.55 (s, 2 H), 7.15–8.9 (m, 4 H), 8.2 (s, 1 H); iodine titration 98%.

References and Notes

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(5) Prepared from chlorotrimethylsilane, triethylamine, and 4-hydroxypyridine in toluene (reflux, 18 h).

Tetramisole Analogues as Inhibitors of Alkaline Phosphatase, an Enzyme Involved in the Resistance of Neoplastic Cells to 6-Thiopurines

Kuldeep K. Bhargava, Men H. Lee,[1] Yow-Mei Huang, Linda S. Cunningham, Krishna C. Agrawal, and Alan C. Sartorelli*

Department of Pharmacology and Section of Developmental Therapeutics, Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut 06510.

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A series of tetramisole derivatives was synthesized and tested for inhibitory activity against alkaline phosphatase which was partially purified from a murine ascitic neoplasm resistant to 6-thiopurines (Sarcoma 180/TG). These agents included derivatives substituted with halogens, CH_3, or NO_2 groups at either the meta or para position of the phenyl ring of tetramisole and 2,3-dehydrotetramisole. The phenyl ring of tetramisole and 2,3-dehydrotetramisole was also replaced by a naphthyl ring, and the phenyl ring of 2,3-dehydrotetramisole was substituted by a thienyl ring system. The presence of both the thiazolidine and dihydroimidazole rings of tetramisole was found to be essential for enzyme inhibitory activity. Substitution of a naphthyl for the phenyl group and dehydrogenation at the 2,3 position of the thiazolidine ring were found to significantly enhance inhibitory activity for alkaline phosphatase. Tests employing (*S*)-(−)-6-(4-bromophenyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole oxalate in combination with 6-thioguanine demonstrated that the inhibitor of alkaline phosphatase was capable of increasing the toxicity of 6-thioguanine to Sarcoma 180/TG cells in tissue culture.

We have provided evidence[2-4] which demonstrates that the acquisition of insensitivity to the antileukemic 6-thiopurines (i.e., 6-mercaptopurine and 6-thioguanine) by the murine neoplasm Sarcoma 180/TG and by acute lymphocytic leukemia cells of man is at least in part due to an increase in the activity of a particulate-bound alkaline phosphatase(s) which causes an elevation in the rate of degradation of the active tumor-inhibitory nucleotide