to give 180 mg (0.483 mmol, 90%) of 11 as a clear oil, which crystallized from methanol/ether, mp 113-115 °C; IR 5.79, 5.95 μm; NMR δ 6.72 (1, d, J = 8.5 Hz, H-2), 6.62 (1, d, J = 8.5 Hz, H-1), 4.65 (1, s, H-5); $[\alpha]^{26}_D$ -317° (c 0.30). Anal. ($C_{20}H_{23}NO_6$) C, H, N.

Noroxycodone (12). A suspension of 150 mg (0.402 mmol) of 11 in 5 mL of 5 N sulfuric acid was refluxed under nitrogen for 12 h. The solution was cooled, made basic with solid sodium bicarbonate, and extracted with chloroform to give 107 mg (0.355 mmol, 88%) of 12 as a solid: mp 170-172 °C (lit.[17] mp 174-175 °C); IR 5.80 μm; NMR δ 6.68 (1, d, J = 8.5 Hz, H-2), 6.60 (1, d, J = 8.5 Hz, H-1), 4.63 (1, s, H-5), 3.87 (3, s, OMe); mass spectrum, m/e 301 (M^+, 20), 117 (71), 103 (100), 101 (85); $[\alpha]^{26}_D$ -232° (c 0.20) [lit.[17] $[\alpha]_D$ -205° (c 0.4)]. An authentic sample of 12 (Mallinckrodt, Inc.) exhibited mp 170-173 °C; $[\alpha]^{26}_D$ -237° (c 0.20).

The hydrochloride salt of 12 was prepared by adding saturated methanolic hydrogen chloride to a solution of 12 in methanol. Subsequent addition of ether gave a precipitate, which was crystallized from methanol/ether to give 12·HCl, mp 280-283 °C dec. Anal. ($C_{17}H_{20}NO_4Cl \cdot CH_3OH$) C, H, N.

Noroxymorphone (1c). A solution of 50 mg (0.134 mmol) of 11 in 0.5 mL of chloroform was added via syringe to a solution of 0.13 mL (1.3 mmol) of boron tribromide in 0.5 mL of chloroform with stirring in an ice bath under nitrogen.[15] The mixture was stirred in the ice bath for 1 h, then a solution prepared from 0.25 mL of concentrated ammonium hydroxide and 1 g of ice was added, and stirring was continued in the cold for 0.5 h. The layers were separated, and the aqueous solution was extracted with chloroform. The combined chloroform solutions were dried and evaporated. To the resulting gum (56 mg) was added 1 mL of 6 N sulfuric acid, and the mixture was refluxed under nitrogen for 12 h. The solution was cooled and basicified with ammonium hydroxide, and the resulting precipitate was isolated by centrifugation and dried under high vacuum to give 57 mg of gray solid.

The crude amine was dissolved in 0.2 mL of 6 N sulfuric acid by warming to 55 °C, then the solution was cooled in an ice bath, and the crystalline salt was isolated by centrifugation. The salt was dissolved in water and basicified with ammonium hydroxide, and the resulting precipitate was again centrifuged and dried to afford 34 mg of noroxymorphone (1c) as an off-white solid. Repetition of the above purification procedure yielded 28 mg (0.098 mmol, 73%) of 1c as a white solid, which did not melt below 300 °C (lit.[18] mp 310-313 °C); NMR (Me_2SO-d_6) δ 6.47 (1, d, J = 8 Hz), 6.41 (1, d, J = 8 Hz), 4.58 (1, s); $[\alpha]^{26}_D$ -179° (c 0.2, 10% HOAc) [lit.[2b] for enantiomer of 1c: mp 290 °C; $[\alpha]^{20}_D$ +150° (c 1.02, 10% HOAc)]. An authentic sample of 1c (Mallinckrodt, Inc.) exhibited an NMR spectrum identical with that of the synthetic material and $[\alpha]^{26}_D$ -199° (c 0.2, 10% HOAc).

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Purine Acyclic Nucleosides. Nitrogen Isosteres of 9-[(2-Hydroxyethoxy)methyl]guanine as Candidate Antivirals

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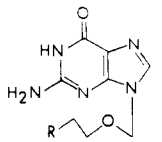
A number of nitrogen analogues of 9-[(2-hydroxyethoxy)methyl]guanine [acylovir, Zovirax] containing amine functions in the side chain were synthesized and tested for antiviral activity. These purine acyclic nucleosides were prepared by reaction of tris(trimethylsilyl)guanine or 2,6-diaminopurine sodium salt with the chloromethyl ethers prepared from *N*-(2-hydroxyethyl)phthalimide, *N*-[2-(2-hydroxyethoxy)ethyl]phthalimide, or *N*-(2-hydroxyethyl)oxazolidin-2-one to give the N-blocked intermediates **5**-**8**. Deprotection with hydrazine or by alkaline hydrolysis gave 9-[(2-aminoethoxy)methyl]guanine (**9**), 9-[(2-aminoethoxy)methyl]-2,6-diaminopurine (**10**), 9-[[2-(2-aminoethoxy)ethoxy]methyl]guanine (**11**), and 9-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]guanine (**12**). When tested against herpes simplex virus type 1, only **9** was active with an IC_{50} = 8 μM. Little or no activity was observed against a range of other DNA and RNA viruses.

Acyclovir [9-[(2-hydroxyethoxy)methyl]guanine, Zovirax (1)] is a potent antiherpetic drug with activity against



1, R = OH
2, R = OCH_2CH_2OH

herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).[1,2] This purine acyclic nucleoside contains an acyclic side chain which mimics the cyclic carbohydrate of natural nucleosides. Although acyclovir (1) is essentially nontoxic to uninfected host cells, it possesses potent antiviral activity in cells infected with HSV.[2,3] This selective toxicity is related to acyclovir (1) being a substrate for HSV-encoded thymidine kinase.[4] Phosphorylation to the monophosphate occurs preferentially in HSV-infected cells, with subsequent selective inhibition of viral replication.[2,4]

A number of pyrimidine acyclic nucleosides analogous to acyclovir (1) were found to have little or no in vitro antiviral activity.[5,6] An extended chain analogue, **2**, of

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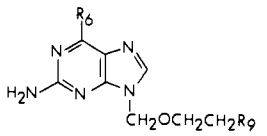
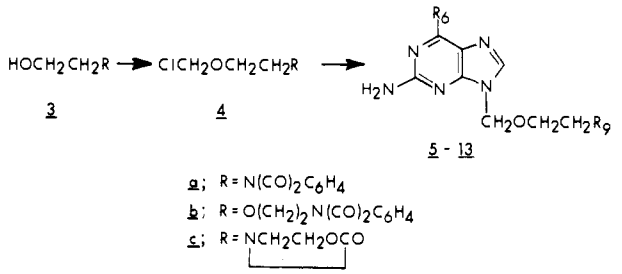
Table I. Derivatives of 9-Substituted Purines



no.	R_6	R_9	methods	% yield	mp, °C	formula[a]
5	OH	$N(CO)_2C_6H_4$	A	90	240 dec[b]	$C_{16}H_{14}N_6O_4 \cdot H_2O$
6	NH_2	$N(CO)_2C_6H_4$	exp	60	240-242[c]	$C_{16}H_{15}N_7O_3$
7	OH	$O(CH_2)_2N(CO)_2C_6H_4$	A	90	181-182[b,d]	$C_{18}H_{18}N_6O_5 \cdot 0.5H_2O$
8	OH	NCH_2CH_2OCO	A	3[e]	222-224	$C_{11}H_{14}N_6O_4 \cdot H_2O$
9	OH	NH_2	B	56	174-176 eff[f]	$C_8H_{12}N_6O_2 \cdot CH_3CO_2H \cdot H_2O$
10	NH_2	NH_2	B	53	175-178[g]	$C_8H_{13}N_7O \cdot CH_3CO_2H \cdot 0.5H_2O$
11	OH	$OCH_2CH_2NH_2$	B	11[h]	186-190	$C_{10}H_{16}N_6O_3 \cdot CH_3CO_2H$
12	OH	$NHCH_2CH_2OH$	exp	22[h]	173-176	$C_{10}H_{16}N_6O_3$
13	OH	$NHC(O)CH_3$	exp	36[g]	240-242 dec	$C_{10}H_{14}N_6O_3$

[a] All compounds were analyzed for C, H, and N; the presence of H_2O was indicated in the NMR spectra. [b] Recrystallized from 2-MeOEtOH. [c] Recrystallized from 2-MeOEtOH-EtOH. [d] Melted at 139-140 °C and resolidified. [e] Recrystallized from H_2O and then EtOH. [f] Recrystallized from EtOH-H_2O. [g] Recrystallized from EtOH. [h] Recrystallized from EtOH-H_2O-C_6H_6.

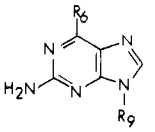
Scheme I



acyclovir (1) has been reported to have antiherpetic activity in vitro, albeit weaker than that of acyclovir (1).[7] In another prototype, replacement of the 5'-hydroxyl function of 5-iodo-2'-deoxyuridine by an amino group produced an analogue with selective activity against HSV-1.[8,9] In an attempt to find other purine acyclic nucleosides with activity comparable to acyclovir (1), we have prepared several analogues of 1 and 2 that contain nitrogen in place of the ether or hydroxyl oxygens of the acyclic side chain. Their synthesis and evaluation for antiviral activity are described herein.

Chemistry. Since the initial reports[1,2,10] on the biological activity of acyclic nucleosides, several papers have been published that describe synthetic entries to this new class of compound.[5,6,11-19] These methods encompass the use of chloromethyl ethers,[5,6,11,16] iodomethyl ethers,[13-15] or acetoxymethyl ethers[18,19] for introduction of the side chain. The chloromethyl ether entry was selected for synthesis of the purine acyclic nucleosides **9–12** (Table I), which were prepared in three steps from **4a–c** as outlined in Scheme I. The intermediate chloromethyl ethers **4b** and **4c** were prepared from alcohols **3b** and **3c**[20] with paraformaldehyde and hydrogen chloride as described for **4a**.[21] The guanine intermediates **5**, **7**, and **8** (Table I) were prepared by alkylation of tris(trimethylsilyl)guanine[22] with **4a–c**. The diaminopurine analogue **6** was made by alkylation of the sodium salt in DMF. The phthaloyl protective groups were cleaved with hydrazine, followed by workup with 5% aqueous AcOH, to give **9–11**. (The conventional aqueous HCl workup gave a product that was contaminated with guanine.) The oxazolidinone ring in **8** was opened with aqueous NaOH to give the desired **12**

Table II. Activity against Herpes Simplex Virus Type I by Compounds 1 and 9-13[a]



no.	R_6	R_9	plaque inhibn result[b]	IC_{50}, μM
9	OH	$CH_2OCH_2CH_2NH_2$	+	8
10	NH_2	$CH_2OCH_2CH_2NH_2$	–	
11	OH	$CH_2OCH_2CH_2OCH_2CH_2NH_2$	–	
12	OH	$CH_2OCH_2CH_2NHCH_2CH_2OH$	–	
13	OH	$CH_2OCH_2CH_2NHCOCH_3$	–	
1[c]	OH	$CH_2OCH_2CH_2OH$	+	0.1

[a] For methodology, see ref 1, 22, and 23. [b] + = active; – = inactive at 50 μg per disk. [c] Acyclovir.

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in low yield. Acetylation of 9 with acetic anhydride gave the acetamido derivative 13.

Biological Results and Discussion

The acyclic nucleoside analogues 9–12 were tested for cytotoxicity against Detroit 98 and mouse L cells in cell culture.[23] None exhibited any significant cytotoxicity when tested at 10^{-4} M.

When 9–13 were tested by means of plaque-inhibition tests against HSV-1 in cell culture,[1,24,25] only 9 was active at 50 μg per disk. When this activity was quantitated using the plaque-reduction assay,[1,26] an IC_{50} = 8 μM was obtained (Table II). This amino analogue 9 is 80-fold less active than the clinically useful purine acyclic nucleoside, acyclovir (1).[1-3] Little or no activity was observed for 9–13 against two other DNA viruses (vaccinia virus, adenovirus type 5) or a range of RNA viruses comprising rhinovirus 1B, Mengo, Semliki Forest, measles, corona, influenza, and respiratory syncytial virus.[1]

Fyfe et al. have studied a number of nucleoside analogues as substrates and/or inhibitors of HSV-1 encoded thymidine kinase.[4,27] They have reported that nucleoside analogues in which the mechanism of antiherpes activity is the same for acyclovir (1) bind to and are good substrates for HSV-1 encoded thymidine kinase.[4,27] The amino analogue 9 had a low affinity for the thymidine kinase but was inactive as a substrate. These results show that the mechanism of antiherpetic activity of 9 is different from that of acyclovir (1). If 9 is antiviral as its nucleotide, then phosphorylation is accomplished by a different enzyme. Alternatively, the weak activity of 9 may be due to in vitro deamination to generate low levels of acyclovir (1).

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and are uncorrected. UV spectra were measured on a Unicam SP 800 spectrophotometer. NMR data were recorded on Varian XL-100-15-FT and T-60 spectrometers using Me_4Si as an internal standard. Each analytical sample had spectral data compatible with its assigned structure, gave combustion values for C, H, and N within 0.4% of theoretical, and moved as a single spot on TLC. TLC's were performed on Eastman Chromagram sheets of cellulose (C), polyamide (P), alumina (A), or silica gel (S) with fluorescent indicator using EtOAc/hexane, 2:1 (solvent 1); CH_2Cl_2/hexane, 1:1 (solvent 2); MeOH (solvent 3); CH_3CN/H_2O, 7:1 (solvent 4); C_6H_6/EtOH, 3:1 (solvent 5); 5% aqueous $(NH_4)_2SO_4$/PrOH/NH_4OH/H_2O, 6:1:1.5:1.5 (solvent 6); or NH_4OH/H_2O/EtOH, 1:1:18 (solvent 7).

***N*-[2-(2-Hydroxyethoxy)ethyl]phthalimide (3b).** A mixture of 10.0 g (95.1 mmol) of 2-(2-aminoethoxy)ethanol and 14.23 g (96.1 mmol) of phthalic anhydride was stirred until a clear viscous oil was formed. The oil was heated on a steam bath for 1.5 h, cooled, and partitioned between 125 mL of chloroform and 50 mL of a 5% aqueous $NaHCO_3$. The chloroform layer was dried ($MgSO_4$), treated with charcoal, filtered, and spin-evaporated in vacuo to a light yellow oil, yield 21.1 g (95%), of sufficient purity for the next step. A 3.0-g sample of the oil was dissolved in 50 mL of $CHCl_3$ and washed with 25 mL of 0.1 N HCl. The $CHCl_3$ solution was dried ($MgSO_4$), concentrated, and distilled, giving an oil that [bp 153–160 °C (0.10 torr)] solidified to give 2.22 g (74%) of 3b: bp 153–160 °C (0.10 torr); mp 61–63 °C; TLC (S, solvent 1; A, solvent 2); NMR ($CDCl_3$) δ 7.55–8.00 (m, 4 H, ArH), 4.07–3.43 (m, 8 H, 2 CH_2CH_2), 2.77 (s, 1 H, OH). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

***N*-[2-[2-(Chloromethoxy)ethoxy]ethyl]phthalimide (4b).** A stirred dispersion of 14.1 g (60.0 mmol) of 3b and 1.83 g (20.3 mmol) of paraformaldehyde in 140 mL of 1,2-dichloroethane was saturated with dry HCl at −10 °C. After 1 h the solution was dried with $CaCl_2$, filtered, and spin-evaporated in vacuo to give 4b in quantitative yield as a clear oil, which was used without further purification: NMR ($CDCl_3$) δ 7.95 (m, 4 H, ArH), 5.44 (s, 2 H, OCH_2Cl), 4.10–3.55 (m, 8 H, 2 CH_2CH_2).

***N*-[2-(Chloromethoxy)ethyl]oxazolidin-2-one (4c).** This compound was prepared from 26.24 g (200 mmol) of *N*-(2-hydroxyethyl)oxazolidin-2-one[20] (3c), 6.00 g (66.7 mmol) of paraformaldehyde, and 650 mL of 1,2-dichloroethane as described for 4b to give an oil, which was used without further purification: NMR ($CDCl_3$) δ 5.47 (s, 2 H, OCH_2Cl).

Method A. 9-[(2-Phthalimidoethoxy)methyl]guanine (5). A mixture of 8.022 g (53.07 mmol) of guanine, 5.82 g (44.04 mmol) of ammonium sulfate, and 500 mL of hexamethyldisilazane under N_2 was refluxed with strring for 20 h. The resultant solution was spin-evaporated in vacuo to an oil that was twice dissolved in 100 mL of toluene and reevaporated. To this clear oil in 50 mL of toluene was added 17.00 g (79.6 mmol) of 4a[21] and 23 mL (165.0 mmol) of Et_3N. The mixture was refluxed with stirring for 29 h, cooled, and spin-evaporated in vacuo to give a dark brown oil. The oil was digested for 40 min with 400 mL of ethanol to give a solid: yield 17.83 g (90%); mp ~141 °C dec. Recrystallization from 2-MeOEtOH gave the analytical sample: mp slow dec above 240 °C; TLC (S, solvent 3; A, solvent 4); NMR (Me_2SO-d_6) δ 13.85 (br s, 1 H, lactam NH), 7.83 (s, 4 H, ArH), 7.75 (s, 1 H, C-8), 6.45 (br s, 2 H, NH_2), 5.33 (s, 2 H, NCH_2O), 3.73 (br s, 4 H, CH_2CH_2). Anal. ($C_{16}H_{14}N_6O_4 \cdot H_2O$) C, H, N.

2,6-Diamino-9-[(2-phthalimidoethoxy)methyl]purine (6). A solution of 3.45 g (21.7 mmol) of 2,6-diaminopurine monohydrate in 250 mL of DMF was dried with 3 Å molecular sieves. The mixture was filtered under a blanket of nitrogen and spin-evaporated to a volume of 70 mL. To this solution was added 0.95 g (23.0 mmol) of sodium hydride (57% dispersion in mineral oil). The mixture was stirred for 15 h, and a solution of 5.20 g (21.7 mmol) of 4a[21] in 37 mL of dimethylformamide was added dropwise. After 6 h the solvent was removed under reduced pressure to give a solid, which was dispersed in 50 mL of MeOH–H_2O, collected, and dried: yield 4.60 g (60%); mp ~225 °C. Recrystallization from 2-MeOEtOH–EtOH gave the analytical sample: mp 240–242 °C; TLC (S, solvent 5 and A, solvent 4); NMR (Me_2SO-d_6) δ 7.85 (s, 4 H, ArH), 7.78 (s, 1 H, C-8), 6.64 (br s, 2 H, NH_2), 5.77 (br s, 2 H, NH_2), 5.35 (s, 2 H, NCH_2O), 3.73 (s, 4 H, CH_2CH_2). Anal. ($C_{16}H_{15}N_7O_3$) C, H, N.

Method B. 9-[(2-Aminoethoxy)methyl]guanine Acetate (9). A mixture of 0.940 g (2.52 mmol) of 5, 100 mL of EtOH, and 2 mL of hydrazine was refluxed with stirring for 1 h. The hot solution was filtered to remove some yellow insolubles, cooled, and spin-evaporated in vacuo. EtOH was added and the mixture was reevaporated. This treatment was repeated three times. The residual solid was stirred with 50 mL of 3% AcOH in H_2O for 30 min and filtered to remove the solids, which were washed with 15 mL of H_2O. The combined filtrate and wash was spin-evaporated in vacuo at <35 °C to a small volume, diluted with EtOH, and evaporated to dryness. The pasty, white solid was dispersed in a small amount of EtOH and diluted with a few milliliters of Et_2O to give a granular solid, which was collected, washed with EtOH, and dried: yield 0.428 g (56%); mp (sinters ~130 °C) 170–175 °C. Recrystallization from EtOH–H_2O gave the analytical sample: mp (~135 °C melted and resolidified) 174–176 °C (eff); UV (0.1 N HCl) λ_{max} 255 nm (ε 13 300), 275 (sh) (9100); UV (0.1 N NaOH) λ_{max} 257–267 nm (plateau) (ε 11 900); TLC (S, solvent 3; C, solvent 6); NMR (Me_2SO-d_6) δ 7.83 (s, 1 H, C-8), 6.94 (br s, 2 H, purine NH_2), 6.32 (br s, 6 H, exchangeable with D_2O), 5.38 (s, 2 H, NCH_2O), 3.57 (t, 2 H, OCH_2CH_2), 2.82 (t, 2 H, CH_2CH_2N), 1.82 (s, 3 H, CH_3). Anal. ($C_8H_{12}N_6O_2 \cdot CH_3CO_2H \cdot H_2O$) C, H, N.

9-[[2-[(2-Hydroxyethyl)amino]ethoxy]methyl]guanine (12). A solution of 0.815 g (2.16 mmol) of 8 in 5.2 mL of 1 N NaOH was stirred at ambient temperature. After 11 days an additional 0.428 g (10.7 mmol) of solid NaOH was added, and stirring was continued for 3 days. The reaction solution was neutralized with

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1.0 mL of AcOH and spin-evaporated in vacuo. The residue was dissolved in 50 mL of H_2O and applied to a column of Amberlite XAD-2 nonionic polymeric absorbant (200 g, 3.5 × 31 cm). The column was eluted with H_2O to give ten 200-mL fractions containing salt-free **12**. The first two fractions were contaminated with some NaOAc and were rechromatographed. The combined fractions were spin-evaporated in vacuo, giving 0.350 g (49%) of **12** as a white solid. Three recrystallizations from aqueous EtOH with concentration by boiling with continued addition of C_6H_6 gave 0.155 g (22%) of **12**: mp 173–176 °C; TLC (P, solvent 7); UV (0.1 N HCl) λ_{max} 256 nm (ϵ 14 000), 276 (sh) (9500); UV (0.1 N NaOH) λ_{max} 257 nm (ϵ 11 900); NMR (Me_2SO-d_6) δ 7.77 (s, 1 H, C-8), 6.44 (br s, 2 H, NH_2), 5.31 (s, 2 H, NCH_2O), 4.38 (br s, 1 H, NH), 3.6–3.2 (m, 5 H, $2CCH_2N$ + OH), 2.7–2.4 (m, 4 H, $2CCH_2O$). Anal. ($C_{10}H_{16}N_6O_3$) C, H, N.

9-[(2-Acetamidoethoxy)methyl]guanine (13). To a stirred solution of 0.64 g (1.9 mmol) of **9** in 30 mL of pyridine and 10 mL of H_2O was added 0.30 g (2.9 mmol) of acetic anhydride. After 15 h at ambient temperature, the reaction was spin-evaporated in vacuo. The residue was dispersed in EtOH and reevaporated to give a solid, which was collected, washed with Et_2O, and dried: yield 0.37 g (74%); mp 246–256 °C. Recrystallization from EtOH gave the analytical sample: yield 0.18 g (36%); mp 240–242 °C dec; TLC (C, solvent 6); UV (0.1 N HCl) λ_{max} 256 nm (ϵ 12 300); UV (0.1 N NaOH) λ_{max} 257 nm (ϵ 11 100). Anal. ($C_{10}H_{14}N_6O_3$) C, H, N.

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Synthesis and β-Lactamase Inhibitory Properties of 2β-(Chloromethyl)-2α-methylpenam-3α-carboxylic Acid 1,1-Dioxide

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Potassium 2β-(chloromethyl)-2α-methylpenam-3α-carboxylate 1,1-dioxide (BL-P2013) and its pivaloyloxymethyl ester were prepared by the conversion of 6-aminopenicillanic acid to *p*-nitrobenzyl 6α-bromo-2,2-dimethylpenam-3α-carboxylate 1-oxide, which was rearranged with benzoyl chloride and quinoline to *p*-nitrobenzyl 6α-bromo-2β-(chloromethyl)-2α-methylpenam-3α-carboxylate in 65% yield. Oxidation and catalytic hydrogenation afforded BL-P2013, which was found to be a potent inhibitor of various bacterial β-lactamases and has been found to protect amoxicillin from β-lactamases in both in vitro and in vivo systems.

The ability of many species of bacteria to produce a β-lactamase which destroys certain β-lactam antibiotics has led to an intensive search for substances that inhibit the action of these protective enzymes. The discovery of clavulanic acid[1] as a potent β-lactamase inhibitor led to the discovery of a variety of new inhibitors which incorporate a β-lactam ring in their structures. Many of these compounds, such as 6-aminopenicillanic acid sulfone,[2] 6β-bromopenicillanic acid,[3] 6α-chloropenicillanic acid sulfone,[4] and various 6β-(acylamino)penicillanic acid sulfones,[5] are relatively simple semisynthetic derivatives of 6-aminopenicillanic acid. The most extensively investigated example of this class is penicillanic acid sulfone (CP-45899),[6] which has been reported to have promising β-lactamase inhibitory properties both in vitro and in vivo. We report here a new example of this class of β-lactamase inhibitor, 2β-(chloromethyl)-2α-methylpenam-3α-carboxylic acid 1,1-dioxide (BL-P2013), which can be prepared from 6-aminopenicillanic acid and which demonstrates high β-lactamase inhibitory activity against a variety of bacterial β-lactamases and which effectively protects amoxicillin from these β-lactamases in both in vitro and in vivo test systems.

Table I. β-Lactamase Inhibitory Properties of Various Compounds against Several Bacterial β-Lactamases

compd	min protective concn,[a] μg/mL		
	K.p.	*S.a.*	*B.f.*
methicillin sulfone	125	>100	
6β-chloropenicillanic acid sulfone	25	>100	
BL-P2013	3.1	3.1	12.5
CP-45899	1.6	12.5	12.5
clavulanic acid	0.1	0.4	6.3

[a] Ability of a compound to inhibit the hydrolysis of an indicator compound, 7-(phenylacetamido)-3-(2,4-dinitrostyryl)-3-cephem-4-carboxylic acid, by β-lactamases from *Klebsiella pneumoniae* A20634 (TEM) (*K.p.*), *Staphylococcus aureus* A9606 (*S.a.*), and *Bacillus fragilis* A22695 (*B.f.*) by the procedure of C. H. O'Callaghan et al., *Antimicrob. Agents Chemother.*, 1, 283–288 (1972). The MPC is the lowest concentration of compound needed to protect the indicator compound from hydrolysis by the β-lactamases within 30 min under standard test conditions.

Chemistry. 6α-Bromopenicillanic acid (**1**) was prepared from 6β-aminopenicillanic acid by the method of Cignarella et al.[7] by substituting hydrobromic acid for hydrochloric acid and was isolated as a *N*,*N*′-dibenzylethylenediammonium salt. This was converted to the sulfoxide **2** with peroxyacetic acid in methylene chloride and isolated as the potassium salt (Scheme I). Esterification with *p*-nitrobenzyl bromide in dimethylacetamide gave the crystalline *p*-nitrobenzyl ester **3**. The rearrangement of

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