Discovery and Structure–Activity Relationship of a Series of 1-Carba-1-dethiacephems Exhibiting Activity against Methicillin-Resistant *Staphylococcus aureus*

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Received February 18, 1993

The synthesis and antimicrobial activity of several new 1-carba-1-dethiacephalosporins is described. The discovery of unique activity of some of the analogues against methicillin-resistant *Staphylococcus aureus* led to the development of a structure–activity relationship designed to optimize this activity. The results of this investigation along with the pharmacokinetic characteristics of select compounds are described.

With the introduction of Lorabid (loracarbef; 1, Figure 1) as a commercial product, the carbacephems have established themselves as a new class of β-lactam antibiotics available for clinical use.[1] Our efforts in the carbacephem arena have led us to the discovery of a group of compounds which not only display broad-spectrum antibacterial activity but have unique activity against methicillin-resistant *Staphylococcus aureus*. In this report, we detail our efforts to optimize this activity while maintaining pharmacokinetic characteristics suitable for clinical utility.

The carbacephem nucleus is unique in its ability to provide derivatives which are hydrolytically stable relative to comparable cephalosporin analogues,[2] which have a sulfur in the 1-position. Thus, 3-substituted-1-carbacephems such as the 3-sulfonyl-1-carbacephems[3] or 3-quaternary ammonium[4] 1-carbacephems (2 and 3, Figure 1) have been prepared and evaluated even though the corresponding cephem derivatives would not be anticipated to be particularly stable. With the consideration of enhanced stability in mind, we set out to prepare a series of 1-carbacephems bearing an aromatic sulfide directly attached to C-3 of the nucleus.[5]

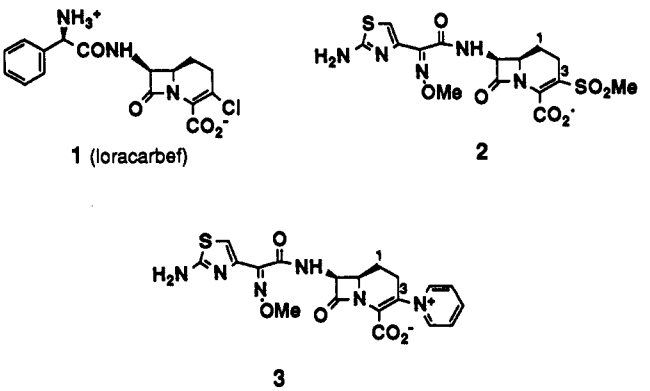
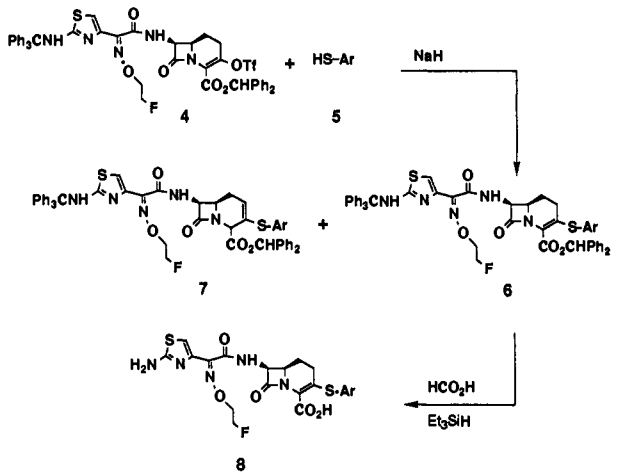


Figure 1.

Chemistry

In order to explore the structure–activity relationships of 3-substituted-1-carbacephems bearing a sulfur atom at the 3-position, we utilized the chemistry depicted in Scheme I. Thus, the previously described[4] enol triflate 4 was reacted with the desired thiol 5 in the presence of base to provide the 3-substituted derivative 6. This conversion was sometimes complicated by formation of the Δ^2 adduct (7) which could be separated via chromatography. Removal of the blocking groups present in 6 gave rise to the desired product 8, suitable for antibacterial evaluation. Purification of the final compounds was typically accomplished by reverse-phase chromatography of the sodium salts. Utilizing this synthetic sequence, we were able to prepare a large number of aromatic and heteroaromatic sulfides due to the availability of the corresponding mercaptans. For thiols which were not commercially available, literature procedures were followed for their preparation.

Scheme I



In Vitro Evaluation

The initial group of aryl and heteroaryl sulfides prepared is shown in Table I along with their MICs (in μg/mL) against a variety of Gram-positive and Gram-negative organisms. Although these compounds represent very potent antimicrobial agents, there was little advantage seen for any of the compounds when compared with currently marketed antibacterials such as cefotaxime. Importantly, none of the new carbacephalosporin analogues demonstrated any significant activity against strains of *Pseudomonas* or methicillin-resistant *S. aureus* (MRSA; strain X400) (Table I). For these reasons we chose not to pursue further development of these derivatives.[6]

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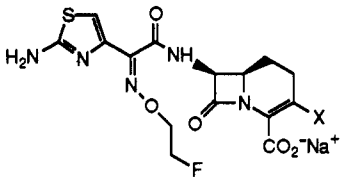
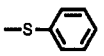
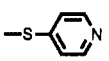
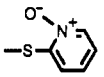
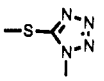
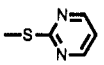
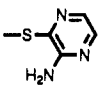
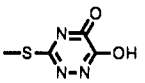
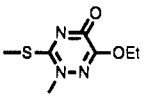
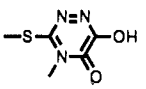
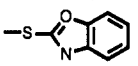
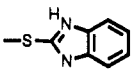
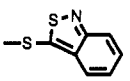
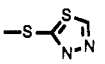
Table I[a]



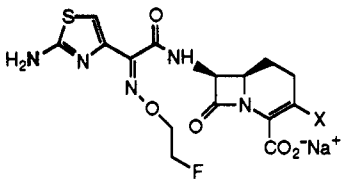
compd	X	LY#	*S. aureus* X1.1	*S. aureus* X400	*S. aureus* S13E	*S. epi.* 270	*S. epi.* 222	*S. pn.* PARK	*H. i.* C.L.	*E. c.* EC14	*K.* X26	*E. cl.* EB5	Pseudomas X239	Pseudomas PS18
methicillin			2	64	8	4	4	0.5	4	>128	32	>128	>128	>128
cefotaxime			2	64	8	8	2	0.015	0.015	0.03	<0.008	0.25	8	16
9		LY275837	0.5	128	64	2	2	0.015	0.03	0.5	0.03	4	128	64
10		LY233687	0.5	64	32	2	1	<0.008	0.015	0.06	0.015	0.5	16	64
11		LY242436	2	128	64	8	2	0.15	0.015	0.125	0.06	2	>128	128
12		LY233742	0.5	>128	128	4	2	0.015	0.015	0.06	<0.008	0.5	16	>128
13		LY269879	2	128	32	8	4	0.03	0.03	0.125	0.015	1	>128	>128
14		LY209841	0.5	>128	32	4	1	<0.008	0.015	0.125	0.015	1	128	16
15		LY269756	4	>128	>128	32	8	0.06	0.03	0.06	0.06	0.5	>128	>128
16		LY269092	0.5	>128	128	16	4	0.03	0.03	0.5	0.06	2	128	>128
17		LY242789	0.5	128	64	8	2	0.015	0.03	0.06	0.06	0.5	32	32
18		LY206513	0.125	64	2	2	1	<0.008	0.03	0.25	0.015	1	32	32
19		LY206514	2	128	16	8	2	<0.008	0.015	0.125	0.015	1	32	32
20		LY242551	4	>128	>128	32	8	<0.008	0.03	0.5	0.06	4	>128	>128
21		LY231301	0.125	64	32	2	0.5	<0.008	0.03	0.25	0.03	0.5	32	16
22		LY206967	0.125	64	16	0.06	0.5	<0.008	0.015	0.03	0.015	0.5	>128	32

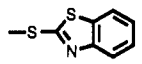
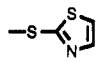
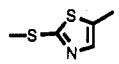
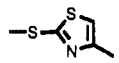
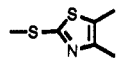
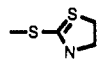
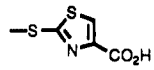
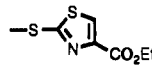
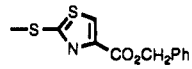
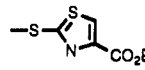
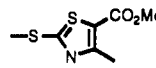
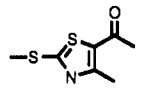
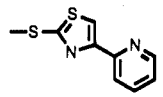
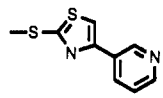
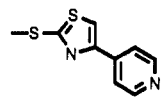
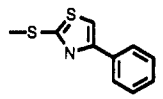
[a] *S. epi.* = *Staphylococcus epidermidis*, *S. pn.* = *Streptococcus pneumoniae*, *H. i.* = *Haemophilus influenzae*, *E. c.* = *Escherichia coli*, *K.* = *Klebsiella*, *E. cl.* = *Enterbacter cloacae*.

Of the several diverse heterocyclic sulfide derivatives prepared, we included a selection of 2-thiazole compounds such as benzothiazole **23** (Table II). The *in vitro* antimicrobial results for this compound (LY274516) immediately caught our attention due to the activity displayed against MRSA. The relevance of this virulent organism in the nosocomial setting along with the paucity of treatment modalities[7] prompted us to explore this unique activity in depth. We began by preparing a series of monocyclic 3-thiathiazole derivatives (Table II, **24–38**). We were surprised to find that none of these analogues, except for the 4-phenyl derivative **38** (LY274797), were significantly active against the resistant strains of *S. aureus*. We concluded from this structure–activity study that a relatively large, lipophilic group attached to the thiazole ring would be required for activity against MRSA (assuming at this level that the thiazole ring was important for this activity; compare **18** and **19**, Table I, with **24**). On the basis of this assumption, we redirected our synthetic efforts to preparing 1-carbacephalosporins substituted in the 3-position with a sulfur-linked benzothiazole substituent.

The initial group of compounds prepared in the benzothiazole series is shown in Table III (**39–42**). We were very encouraged by the activity displayed against MRSA, especially with the nitro-substituted derivative **42**

Table II[a]



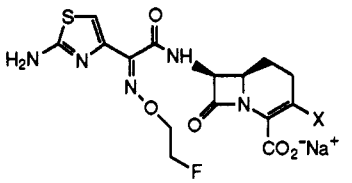
compd	X	LY#	*S. aureus* X1.1	*S. aureus* X400	*S. aureus* S13E	*S. epi.* 270	*S. epi.* 222	*S. pn.* PARK	*H. i.* C.L.	*E. c.* EC14	*K.* X26	*E. c.* EB5	*Pseudomas* X239	*Pseudomas* PS18
methicillin			2	64	8	4	4	0.5	4	>128	32	>128	>128	>128
cefotaxime			2	64	8	8	2	0.015	0.015	0.03	<0.008	0.25	8	16
23		LY274516	0.125	4	4	0.5	0.25	<0.008	0.03	0.25	0.03	1	16	128
24		LY275588	0.25	64	16	4	0.5	<0.008	<0.008	0.125	<0.008	1	128	32
25		LY209597	0.5	128	32	4	1	<0.008	<0.008	0.5	0.03	2	64	32
26		LY209075	0.5	64	4	4	0.5	<0.008	<0.008	0.25	<0.008	2	64	32
27		LY233070	0.5	32	4	2	1	<0.008	0.015	0.5	0.06	4	8	64
28		LY242260	0.5	64	16	2	1	<0.008	<0.008	0.125	0.015	1	<128	64
29		LY242259	2	>128	128	8	4	0.015	0.015	0.25	0.25	4	>128	128
30		LY206969	1	32	16	2	2	<0.008	0.06	0.5	0.06	4	>128	128
31		LY209562	0.25	32	8	2	0.5	<0.008	0.03	0.25	0.015	2	128	64
32		LY209563	0.5	64	16	4	1	<0.008	0.03	0.5	0.03	4	>128	128
33		LY209245	0.25	128	16	8	2	<0.008	0.06	2	0.125	8	>128	>128
34		LY209347	0.5	128	32	8	2	<0.008	0.06	1	0.125	8	>128	>128
35		LY219233	0.25	32	16	2	0.5	<0.008	0.03	0.5	0.03	2	32	64
36		LY209732	0.25	32	8	2	0.5	<0.008	0.015	0.25	0.03	2	>128	64
37		LY209733	0.125	32	8	2	0.5	<0.008	0.03	0.25	0.03	2	>128	>128
38		LY274797	0.125	4	4	0.5	0.25	<0.008	0.03	0.25	0.015	1	8	64

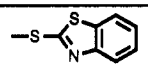
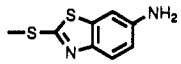
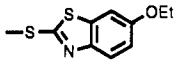
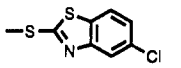
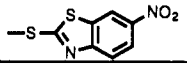
[a] *S. epi.* = *S. epidermidis*, *S. pn.* = *S. pneumoniae*, *H. i.* = *H. influenzae*, *E. c.* = *E. coli*, *K.* = *Klebsiella*, *E. cl.* = *E. cloacae*.

(LY275858). The parent benzothiazole derivative **23** (LY274516) and the nitro-substituted derivative **42** were selected on the basis of this initial screening for more in-depth microbiological and pharmacokinetic evaluation.

The effect of salt concentration on the MIC of cephalosporins determined against MRSA *in vitro* has been documented.[8] We investigated this effect on the activity of these new 1-carbacephalosporins, the results of which are shown in Table IV. The MIC for each compound (in μg/mL) against a heteroresistant strain of *S. aureus* (ST430) is shown. As evidenced by the data, the new carbacephalosporins **23** and **42** maintain their good activity in the presence or absence of salt. It is felt that this characteristic is indicative of "real" activity against methicillin-resistant strains since in the absence of 4% NaCl, many β-lactams are known to give false-positive *in*

Table III[a]



compd	X	LY#	S. aureus X1.1	S. aureus X400	S. aureus S13E	S. epi. 270	S. epi. 222	S. pn. PARK	H. i. C.L.	E. c. EC14	K. X26	E. cl. EB5	Pseudomas X239	Pseudomas PS18
23		LY274516	0.125	4	4	0.5	0.25	<0.008	0.03	0.25	0.03	1	16	128
39		LY206517	0.25	16	4	1	1	<0.008	0.03	0.25	0.03	2	>128	128
40		LY206515	0.25	8	8	0.5	1	<0.008	0.125	1	0.06	4	>128	128
41		LY206516	0.125	8	4	0.5	0.5	<0.008	0.06	0.25	0.06	2	>128	64
42		LY275858	0.06	2	2	0.5	0.5	<0.008	0.03	0.25	0.06	1	>128	64

[a] *S. epi.* = *S. epidermidis*, *S. pn.* = *S. pneumoniae*, *H. i.* = *H. influenzae*, *E. c.* = *E. coli*, *K.*, *Klebsiella*, *E. cl.* = *E. cloacae*.

Table IV

compd	MICs (μg/mL) vs MRSA (ST430) trypticase soy broth (TSB)	TSB + 4% NaCl	IC_{50} for binding to PBP2a (μg/mL)
methicillin	8	256	456
nafcillin	0.25	32	200
23 (LY274516)	0.5	1	3.5
42 (LY275858)	0.5	1	0.85

Table V

compound	sensitive (ST446)		heteroresistant (ST430)		homoresistant (ST447)	
salt concn	0%	4%	0%	4%	0%	4%
methicillin	1	1	8	256	>512	>512
nafcillin	0.25	0.25	1	64	128	128
42 (LY275858)	0.25	0.25	1	1	1.9	1.9

vitro results.[9] Further studies demonstrate that **42** was active against both the heteroresistant strain as well as homoresistant *S. aureus* (Table V).

Mechanistically, we were interested in determining whether these novel β-lactams act via inhibition of penicillin binding proteins (PBPs). Indeed, a strong correlation has been established for the binding affinity of antibacterials to PBP2a[11] and *in vivo* activity[12] against resistant strains. We were pleased to find that these compounds bind to PBP2a with IC_{50}s that correlate well to the observed MICs against the resistant strains (Table IV).

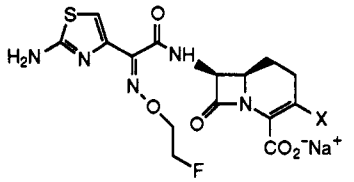
Our enthusiasm for **23** and **42** as potential clinical candidates was soon tempered by the discovery that the compounds exhibit an extremely high level of binding to proteins in human plasma. Although the effect of protein binding on antibacterial efficacy has been debated[10] and some clinically utilized cephalosporins such as ceftriaxone are characterized by high serum binding, it was evident that we would need to reduce the degree of serum binding of these compounds (estimated to be >99.2%) in order to obtain a reasonable candidate for clinical trials.

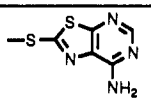
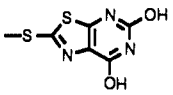
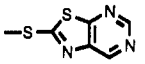
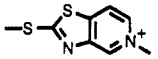
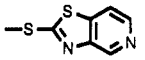
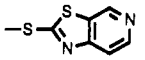
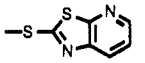
In an attempt to lower the protein binding of the lead benzothiazoles, we set out to synthesize compounds bearing heterocyclic-fused thiazoles tethered to the 3-position of the 1-carbacephalosporin with a sulfur atom. Our hypothesis predicted lower lipophilicity of these derivatives compared with the benzothiazoles, which we felt could lower the plasma protein binding potential. Table VI displays some of the derivatives prepared. We were pleased to find that **43** (LY242914) demonstrated less protein binding than the lead benzofused derivatives. Unfortunately, the activity against MRSA decreased along with the high protein binding. Compounds **43–46** likewise did not exhibit activity against MRSA although **46** (LY242942) was determined to have even less serum binding than **43**. We were delighted to find, however, that the pyridinothiazoles **47–49** did show good MRSA activity with lowered serum binding. In particular, our attention was directed to **47** (LY206763) as the best of the three. The expanded *in vitro* microbiological evaluation of **47** indicated that it is a very potent compound against various strains of MRSA (Table VII). As was the case with our previous lead compounds **23** and **42**, compound **47** exhibited good affinity for the PBP2a enzyme (IC_{50} = 2 μg/mL), which correlates rather well with the *in vitro* MIC against several strains of MRSA.

Pharmacokinetic Evaluation

Plasma protein binding was determined for **47** and is compared to other β-lactams in Table VIII. Although its binding was high (96.6% in human plasma), it was anticipated that the free drug levels obtained would be sufficient to provide therapeutic efficacy. The pharmacokinetic evaluation of **47** was conducted in rats and monkeys. In rats dosed intravenously with 20 mg/kg of **47**, the half-life was determined to be 35.1 min with a C_{max} of 56.7 μg/mL. The urinary recovery (as total antibacterial activity) was 37.2% of the administered dose. In monkeys dosed intravenously with 30 mg/kg of **47**, the half-life was found to be 58.4 min with a C_{max} of 342.8 μg/mL. The urinary recovery was 46.8% of the administered dose. Figure 2 graphically represents the data for rats and monkeys. Figure 3 shows the pharmacokinetic profile of **47** in monkeys compared with historical data obtained for ceftriaxone and cefoperazone.

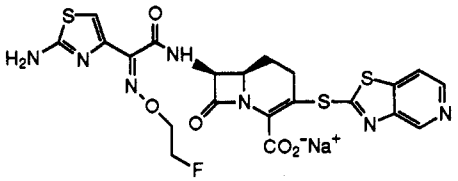
Table VI[a]



compd	X	LY#	*S. aureus* X1.1	*S. aureus* X400	*S. aureus* S13E	*S. epi.* 270	*S. epi.* 222	*S. pn.* PARK	*H. i.* C.L.	*E. c.* EC14	*K.* X26	*E. cl.* EB5	Pseudomas X239	Pseudomas PS18
43		LY242914	0.125	32	16	2	0.5	<0.008	0.03	0.25	0.03	1	>128	64
44		LY242933	2	128	16	8	2	<0.008	<0.008	0.06	0.06	1	>128	64
45		LY209961	0.125	16	8	2	0.5	<0.008	0.03	0.25	0.03	2	128	128
46		LY242942	2	128	16	8	2	0.15	0.06	0.25	0.03	4	32	32
47		LY206763	0.125	4	0.5	2	0.5	<0.008	0.03	0.06	0.03	1	32	32
48		LY219054	0.125	8	4	2	0.5	<0.008	0.015	0.25	0.06	2	>128	64
49		LY242438	0.25	16	8	4	1	<0.008	0.03	0.25	0.03	2	>128	64

[a] *S. epi.* = S. epidermidis, *S. pn.* = *S. pneumoniae*, *H. i.* = *H. influenzae*, *E. c.* = *E. coli*, *K.* = *Klebsiella*, *E. cl.* = *E. cloacae*.

Table VII



strain	MIC (μg/mL) against MRSA: TSB	TSB + 4% NaCl
ST430	0.5	1
geometric mean for 31 strains of MRSA		2.6

Table VIII.[a] **In Vitro Plasma Protein Binding**

compound	percent bound: mouse	rat	monkey	human
206763	88.5	95.0	98.5	96.6
275858	96.9	98.3		>99.2
206967	36.2	63.1	49.1	36.0
ceftriaxone		88.5		94.0

[a] Test compound concentration = 20 μg/mL.

The exciting results presented herein are a prelude to definitive *in vivo* data in a suitable animal model. Should the results of such a study prove positive, consideration will be given for possible clinical evaluation of **47** in human subjects.

Experimental Section

All reactions described herein were performed under an inert atmosphere of dry nitrogen in flame-dried glassware unless otherwise noted. All reagents were used as supplied unless stated otherwise. Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz with a General Electric QE-300 instrument, at 270 MHz with a Brucker W-M instrument, and at 90 MHz with a JOEL FX-90 instrument. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane. IR spectra were recorded on a Nicolet MX-1 FT-IR, optical rotations were measured on a Perkin-Elmer 241 spectrometer, and UV spectra were obtained on a Cary 219. The mass spectral data were obtained on either a CEC-21-140 or a Varian MAT-731 spectrometer. All MPLC separations were conducted on Merck Lobar columns (LiChroprep RP-18) with the help of a Fluid Metering Inc. pump. Analytical HPLC separations were performed on a Varian chromatographic system utilizing a MicroPak MCH-5N-cap 15 cm × 4 mm column and a variable-wavelength UV detector set to record at 254 nm.

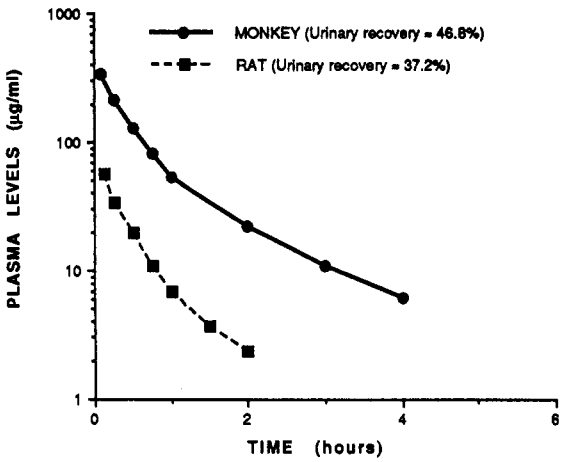


Figure 2. Plasma levels of antibacterial activity in rats (20 mg/kg) and monkeys (30 mg/kg) following iv administration.

General Procedure for the Preparation of 1-Carba-1-dethiacephems. The compounds described in this report were prepared according to the method outlined below.

Preparation of Compound 4. Compound 4 was prepared in a manner described in ref 4 utilizing [2-(tritylamino)-4-thiazolyl]-[(2-fluoroethyl)oximino]acetic acid.[13]

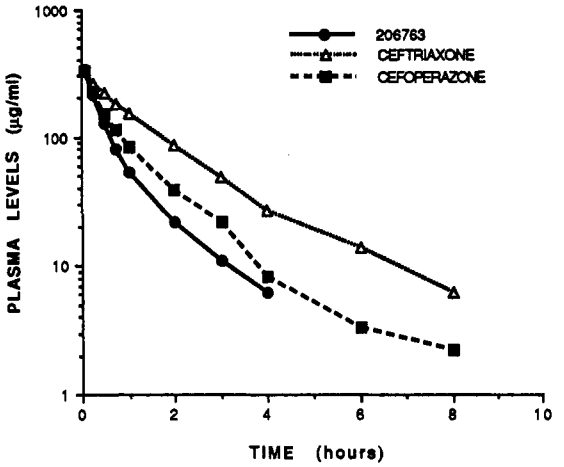


Figure 3. Plasma levels of antibacterial activity in male rhesus monkeys following iv administration of compounds at 30 mg/kg.

Preparation of Compound 6. Sodium hydride (1.6 equiv) and the appropriate heterocyclic thiol (1.5 equiv) were stirred in THF followed by the triflate 4. This solution was allowed to stir overnight at room temperature. The solvent was removed *in vacuo*, and the crude was taken up in CH_2Cl_2, filtered, and purified by flash chromatography on silica using 50–75% EtOAc/hexanes.

Preparation of Compound 8. Triethylsilane (5 equiv) was dissolved in formic acid (1:10) and added to 6. After ca. 1 h, diethyl ether was added, and the volatiles were removed *in vacuo*. The resulting solid was triturated with diethyl ether and purified as the sodium salt by MPLC ($MeOH/H_2O$ solvent system).

Pharmacology. Male Sprague–Dawley rats ($n = 4$) were dosed intravenously with LY206763 at 20 mg/kg in 0.9% saline. Dosing and blood sampling were carried out through an indwelling jugular vein cannula, thus permitting serial sampling from individual rats. Plasma levels and cumulative urinary recoveries were determined from samples collected over a 6-h time course.

Male rhesus monkeys ($n = 4$) were dosed intravenously with test compounds at 30 mg/kg in 0.9% saline. Plasma samples were collected from the cephalic vein over an 8-h time course, along with the 0–24-h cumulative urinary recovery.

Urine was collected in 0.1 M sodium citrate buffer, pH 6.5, from animals placed in metabolism cages. Plasma and urine samples were stored at −70 °C prior to analysis.

Plasma half-life was calculated as $0.693/\beta$, where β is the slope of the terminal portion of the plasma vs time curve. The area under the curve was calculated using Simpson's rule. Urinary recovery was calculated as the percent of the administered dose recovered in the urine.

In vitro plasma protein binding was determined in pooled samples of ICR mouse, Sprague–Dawley rat, rhesus monkey, or human plasma at a drug concentration of 20 µg/mL, using an ultrafiltration technique (Centrifree micropartition system).

Antibiotic concentrations were determined with an agar well diffusion assay (bioassay) employing *Escherichia coli* (ATCC4157) or *Micrococcus luteus* (ATCC9241) as the bacterial test strain. Standard curves from rat, monkey, or human plasma spiked with the compound under study were employed for analysis of plasma samples. Urine samples were analyzed by comparison to a standard curve prepared in 0.1 M sodium citrate buffer, pH 6.5. Urine samples were diluted with citrate buffer so that the drug concentration would fall into the range of the standard curve.

Acknowledgment. The authors would like to express their appreciation to Dr. F. T. Counter and his associates for the antibacterial screening and the Physical Chemistry department for spectral data.

Supplementary Material Available: ^1H NMR, IR, and MS for final compounds reported herein (8 pages). Ordering information is given on any current masthead page.

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