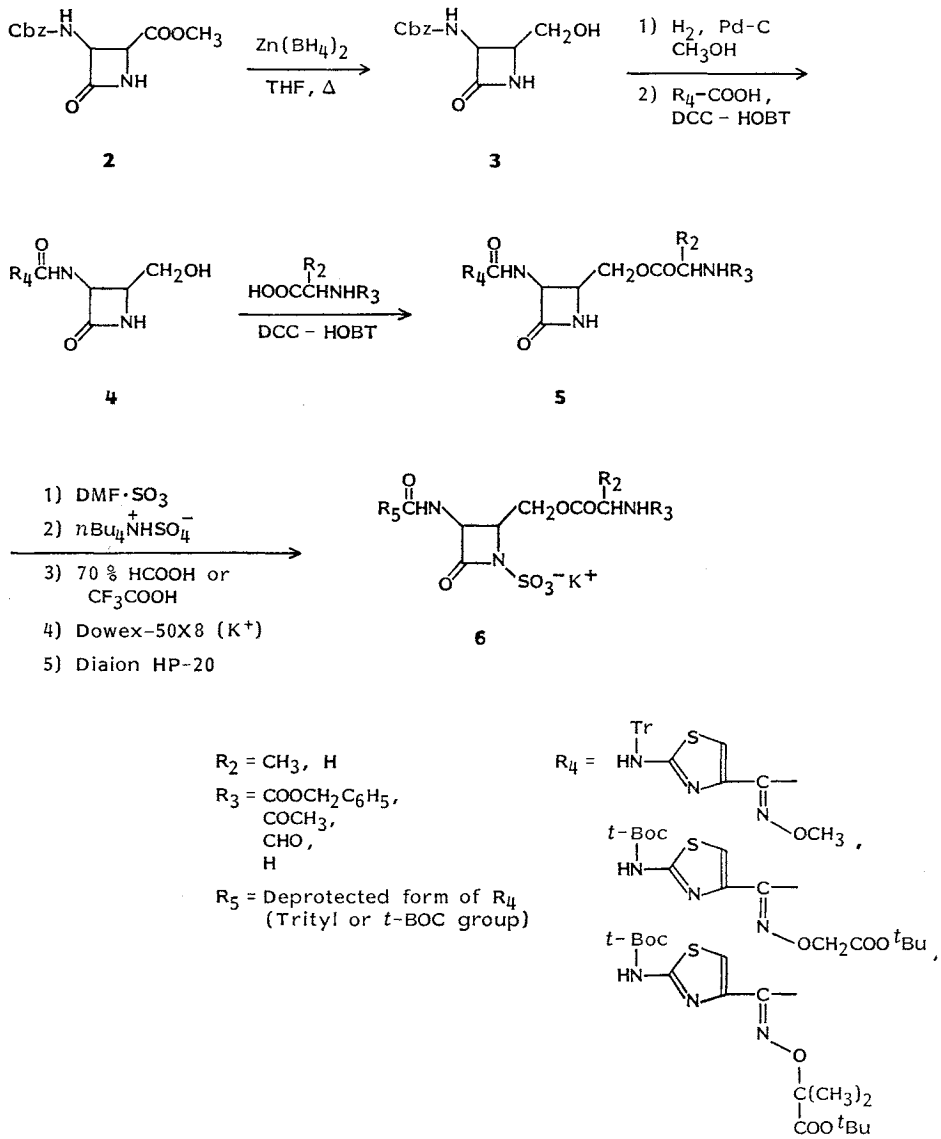
SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF C-4-AMINO ACID SUBSTITUTED MONOBACTAM ANALOGS

Sir:

Since the discovery of the new monocyclic β-lactam compounds, extensive efforts have been made to improve the biological activities of this class of β-lactam compounds by various research groups.[1,2] Considering the peptide nature of the β-lactam compounds we thought it would be interesting to introduce the various amino acid moieties at C-4 of the monobactam as shown in general formula **1**.

This communication discusses the preparation of this series of monobactams and their structure-activity relationships.

Scheme 1.



R_2 = CH_3, H

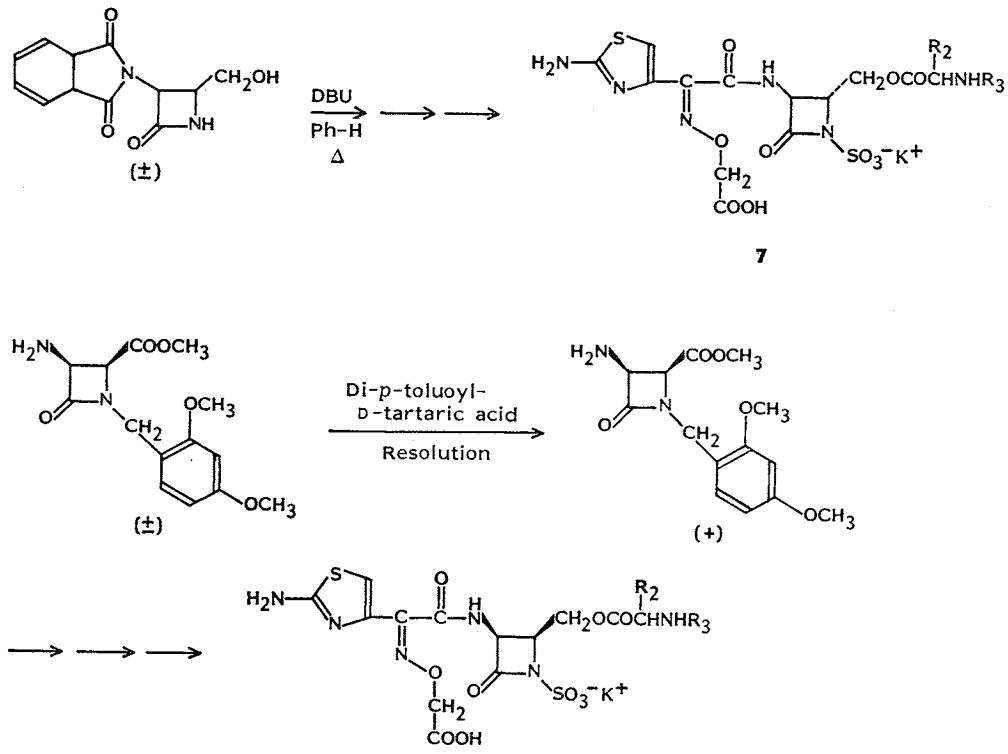
R_3 = $COOCH_2C_6H_5$, $COCH_3$, CHO, H

R_5 = Deprotected form of R_4 (Trityl or *t*-BOC group)

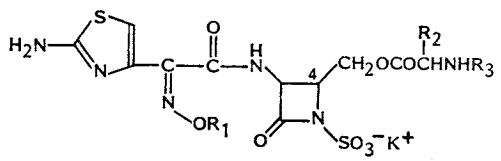
Cbz=benzyloxycarbonyl
DCC=Dicyclohexylcarbodiimide
HOBT=Hydroxybenztriazole

t-BOC=*tert*-Butoxycarbonyl
Tr=triphenylmethyl

Scheme 2.



DBU=1,8-Diazabicyclo[5.4.0]undec-7-ene



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The C-4 amino acid-substituted monobactams were prepared as outlined in Scheme 1. Racemic carbomethoxyazetidinone (**2**)[3] was reduced by zinc borohydride to obtain the C-4 hydroxymethyl azetidinone (**3**). Catalytic hydrogenation followed by coupling with the appropriate C-3 aminoacyl side chain produced oxime-aminothiazole azetidinone (**4**). The amino acid moiety was introduced at C-4 by use of the DCC-HOBT method to obtain β-lactam compound **5**. Sulfonation on the lactam ring nitrogen atom followed by tetra-*N*-butyl ammonium salt formation, deprotection, cation exchange to give the potassium salt and purification through Diaion HP-20 resin afforded *cis*-(±)-monobactam **6**.

Monobactam **6** was obtained as a diastereomeric mixture except in the case of glycine.

We also prepared *trans*-(±)-monobactam **7** and chiral monobactam **8** *via* epimerization and resolution,[4] respectively (Scheme 2).

Results and Discussion

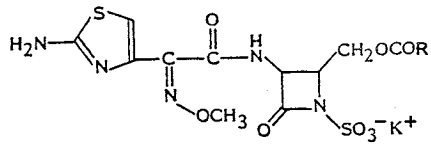
In general, as the C-4 substituents become more hydrophilic and smaller in size, the activity against Gram-negative organisms increases. We believe that this is very well in line with the studies which correlate the polarity and size of the molecules with the permeability of the outer membrane of the cells.[5~7]

More hydrophilic ammonium compounds (**6i**, **6j**) were thought to increase the Gram-negative activity. However, the activity is just comparable (**6f** vs. **6i**) or even slightly lower than that of the *N*-formyl compounds (**6h** vs. **6j**).

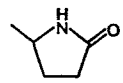
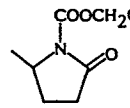
D-Amino acid analog (**6h**) shows 2-fold more activity than L-analog (**6g**) both *in vitro* and *in*

Table 1. Effects of C-4 substituents on the activity.

(A) Aminothiazole methoxime C-3 side chain.



(Racemic)

6	R	MIC (μg/ml)[a]			
		Streptococcus pneumoniae UC 41[b]	*Escherichia coli* UC 311	*Klebsiella pneumoniae* UC 58	*Pseudomonas aeruginosa* UC 9191
6a	 (U-69,938B diastereomeric mixture)	32	2	1	128
6b	 (U-71,090B diastereomeric mixture)	8	16	8	>128
6c	$CH_2NHCOOCH_2C_6H_5$ (U-71,091B)	4	16	8	128
6d	$CH_2NHCOCH_3$ (U-71,092B)	16	0.5	0.25	32
6e	CH_2NHCHO (U-71,093B)	16	<0.12	<0.12	8

[a] Minimum inhibitory concentrations (MIC) were determined by a 2-fold dilution in Mueller-Hinton agar; inoculum of 10^4 cfu.

[b] UC is a registered trademark of The Upjohn Company.

vivo. We cannot at this time relate this result to any single parameter such as the configuration of the amino acid.

The methoxime side chain compound (**6e**) shows stronger activity against Gram-positive bacteria than do the oximecarboxylic acid side chain compounds (**6f, 6k**) though their activities are only moderate.

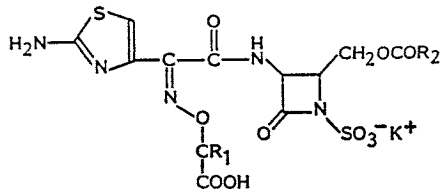
Both methoxime and oximeacetic acid compounds (**6e, 6f**) have comparable *in vitro* activities against Gram-negative organisms except *Pseudomonas aeruginosa*. In the case of *P. aeruginosa*, the oximeacetic acid compound (**6f**) is superior to the methoxime side chain compound (**6e**). Despite the comparable potent *in vitro* activity, the methoxime compound (**6e**) does not show good *in vivo* activity while both oximecarboxylic acid compounds (**6f, 6k**) have good *in vivo* activity. This was somewhat surprising considering the fact that methoxime aminothiazole has been used successfully in the cephalosporin antibiotics (example; cefotaxime).

The activity of the oximeisobutyric acid side chain compound (**6k**) is decreased markedly relative to that of the oximeacetic acid side chain compound (**6f**). This oximeisobutyric acid side chain also has been used successfully in the cephalosporins (example; ceftazidime) and aztreonam. It is difficult to understand this discrepancy although the oximeisobutyric acid side chain must be more hydrophobic than the oximeacetic acid side chain.

The overall activity of the *trans*-monobactam isomer (**7**) was much inferior to that of the *cis*-monobactam isomer (**6f**). The chiral molecule (**8**) shows twice the activity of that of the racemic molecule (**6f**). In conclusion, the chiral *N*-formylglycine substituted monobactam (**8**) de-

Table 1. (Continued)

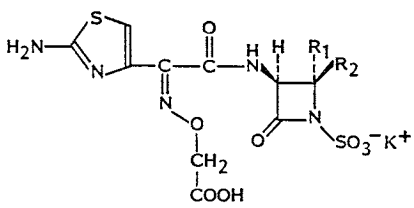
(B) Aminothiazole oximecarboxylic acid C-3 side chain.



(Racemic)

6	R_1	R_2	MIC (μg/ml)[a] *Streptococcus pneumoniae* UC 41[b]	*Escherichia coli* UC 311	*Klebsiella pneumoniae* UC 58	*Pseudomonas aeruginosa* UC 9191
6f	H_2	CH_2NHCHO (U-70,887B)	64	0.125	0.125	16
6g	H_2	CH_3 | CHNHCHO (L) (U-71,055B)	>128	1	1	>128
6h	H_2	CH_3 | CHNHCHO (D) (U-71,056B)	>128	0.5	0.5	128
6i	H_2	CH_2NH_3 (zwitter ion) (U-71,328)	128	0.125	0.125	8
6j	H_2	CH_3 | $CH\text{-}NH_3$ (D) (zwitter ion) (U-71,740)	>128	2	2	128
6k	$(CH_3)_2$	CH_2NHCHO (U-71,699B)	>128	0.5	0.5	128

Table 3. Effects of stereochemistry of C-3 and C-4.



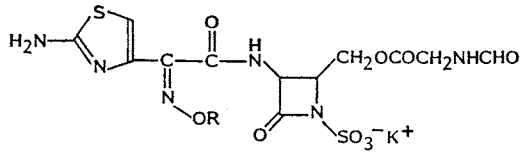
6f (U-70,887B) R_1=H, R_2=CH_2OCCH_2NHCHO (Racemic)

7 (U-71,916B) R_1=CH_2OCCH_2NHCHO, R_2=H (Racemic)

8 (U-71,568B) R_1=H, R_2=CH_2OCCH_2NHCHO (Chiral)

	MIC (μg/ml) *Escherichia coli* UC 311	*Klebsiella oxytoca* UC 9384	*Klebsiella oxytoca* UC 9383	*Serratia marcescens* UC 6888	*Pseudomonas aeruginosa* UC 9191	*Pseudomonas aeruginosa* 30133
6f (U-70,887B)	0.125	0.125	1	0.25	8	16
7 (U-71,916B)	0.125	0.125	16	0.25	128	>128
8 (U-71,568B)	0.06	0.06	0.5	0.25	4	8

Table 2. Effects of C-3 side chain.



(Racemic)

6	R	MIC (μg/ml)							*In vivo* CD_{50} (mg/kg, sc)
		Streptococcus pneumoniae UC 41	*Staphylococcus aureus* UC 6675	*Klebsiella pneumoniae* UC 58	*Escherichia coli* UC 9379	*Pseudomonas aeruginosa* UC 9191	*Pseudomonas aeruginosa* UC 6432	*Serratia marcescens* UC 6888	*E. coli* UC 9451
6e	CH_3 (U-71,093B)	16	128	<0.12	0.25	8	64	1	>50
6f	CH_2COOH (U-70,887B)	64	>128	0.125	0.25	8	16	0.25	6.2~14
6k	CH_3 | $CCOOH$ | CH_3 (U-71,699B)	>128	>128	0.5	1	64	128	1	21.8

monstrates a very potent activity against Gram-negative organisms including *P. aeruginosa*.

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