SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF MONOCARBAMS LEADING TO U-78608

Sir:

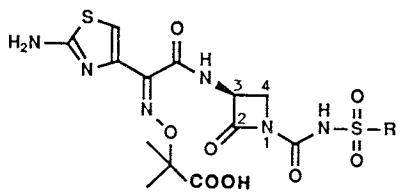
Monocarbams are totally synthetic monocyclic β-lactam antibacterial agents which have, as their salient structural feature, a substituted sulfonylaminocarbonyl activating group at the N-1 position. The seminal studies in this area were conducted by workers at the Squibb Institute for Medical Research.[1] In 1985 BREUER *et al.*[2] reported the synthesis and antibacterial activity of pirazmonam (**1**), a monocarbam incorporating an iron-chelating hydroxypyridone residue[3] into its N-1 sulfonylaminocarbonyl activating group. This compound retains many of the positive attributes of its progenitor, aztreonam, but displays remarkably improved activity against *Pseudomonas aeruginosa*. Apparently the potentiating hydroxypyridone group allows pirazmonam to behave as a siderophore mimic.[4] This characteristic enhances penetration of the outer membrane of Gram-negative bacteria *via* utilization of siderophore transport mechanisms.[5]

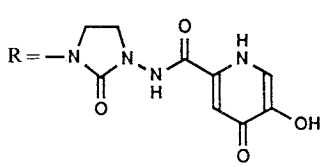
Our own efforts in the monocarbam field have focused on the development of novel linkages between the β-lactam's proximal N-1 sulfonylaminocarbonyl activating moiety and the distal hydroxypyridone group. Herein we describe the results of this structure-activity relationship study which led to the selection of U-78608 (**2**) as a candidate for further development. As we preliminarily reported, U-78608 exhibits potent activity against aerobic Gram-negative bacteria.[6]

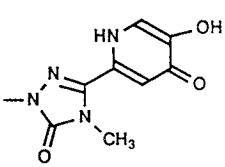
Synthetic protocols for preparing the various protected hydroxypyridone-containing subunits of the nascent sulfonylaminocarbonyl activating group are outlined in Scheme 1. The known kojic acid derivatives **3**[3] and **4**[7] were reacted with appropriate semicarbazides and/or 4-amino-1,2,4-triazol-5-ones[8,9] under standard conditions to provide the adducts **5**~**7** in excellent yield. The semicarbazide derivatives **5** (R_2=H, CH_3) underwent smooth cyclization/dehydration under basic conditions[8] to afford the corresponding triazolones **8**.

Final assembly of the targeted monocarbams was accomplished *via* the convergent synthetic procedure depicted in Scheme 2. To this end the β-lactams **9**[10] were reacted with chlorosulfonyl isocyanate (CSI) in dichloromethane to give the CSI adducts **10**. These derivatives were then treated with THF solutions of compounds **11**, previously prepared by silylating **5**~**8** with excess *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (MSTFA), concentration *in vacuo*, and reconstitution in THF. In this way the crude protected monocarbams **12** were obtained in good yield. Purification was usually delayed until after the benzyl group was removed by hydrogenolysis. At this point the substrates were converted to their sodium salts and chromatographed over Diaion HP-20 resin. These materials were then treated with TFA to remove the remaining protecting groups and chromatographed over Diaion HP-20 to afford the desired monocarbam antibiotics (see Fig. 1). In this way the title compound, U-78608 (**2**), was obtained in 60% overall yield from **9**.

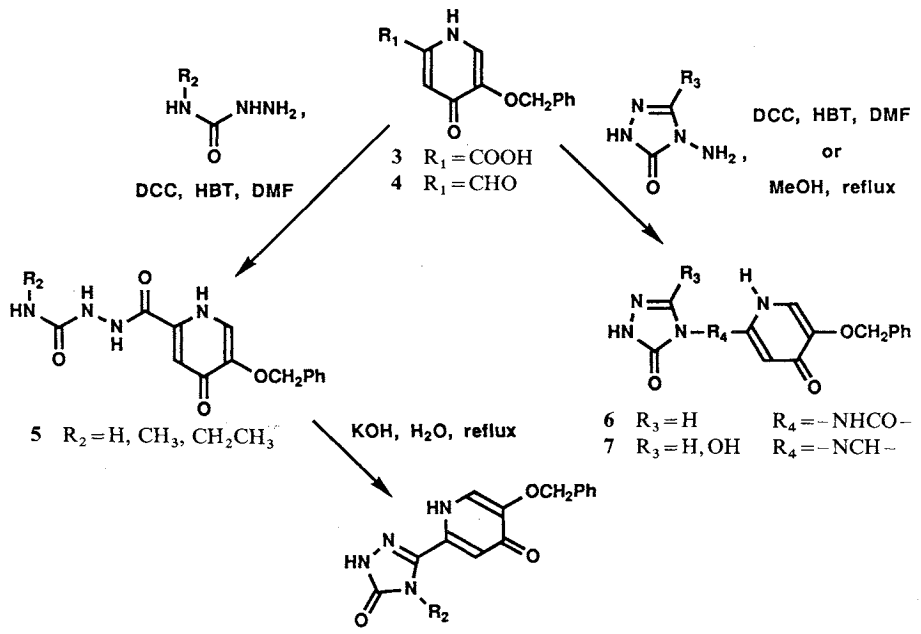
U-78608 (disodium salt) was a white amorphous solid with the following characteristics: $[\alpha]_D^{25}+5.2°$ (*c* 0.52, H_2O); IR (film) cm^{-1} 3403, 1785, 1714, 1626, 1573, 1542, 1360, 1303, 1231, 1199, 1164; UV $\lambda_{max}^{H_2O}$ nm (ε) 220 (43,380), 250 (25,300), 280 (15,940); ^1H NMR (300 MHz, DMSO-d_6) δ 11.12 (1H, d, J=8.3 Hz), 7.94, (1H, s), 7.43 (1H, s), 7.19 (1H, br s), 6.78 (1H, s), 5.15 (1H, m), 3.81 (1H, t, J=6.5 Hz), 3.45~3.37 (1H, partially obscured dd), 3.42 (3H, s), 1.49 (3H, s), 1.41 (3H, s); FAB-MS *m/z* 699.0646



1 (Pirazmonam) 

2 (U-78608) 

Scheme 1.



DCC: Dicyclohexylcarbodiimide, HBT: 1-hydroxybenzotriazole.

Scheme 2.

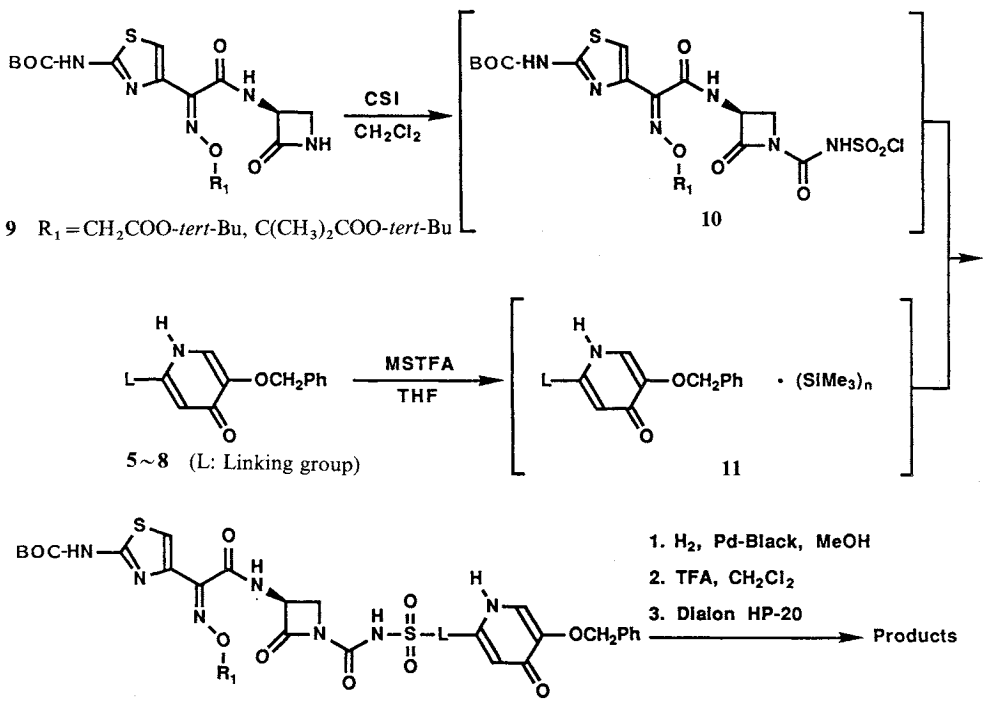
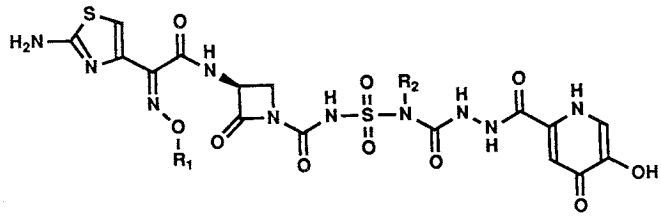
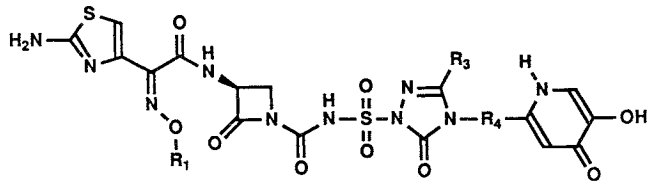


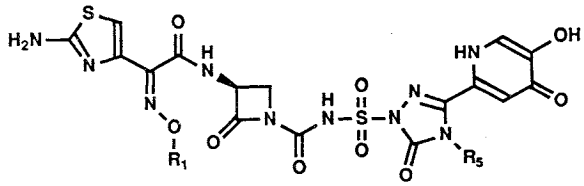
Fig. 1. Monocarbams prepared.



13 $R_1=CH_2COOH$ $R_2=H$
14 $R_1=C(CH_3)_2COOH$ $R_2=H$
15 $R_1=CH_2COOH$ $R_2=CH_3$
16 $R_1=C(CH_3)_2COOH$ $R_2=CH_3$
17 $R_1=CH_2COOH$ $R_2=CH_2CH_3$
18 $R_1=C(CH_3)_2COOH$ $R_2=CH_2CH_3$



19 $R_1=CH_2COOH$ $R_3=H$ $R_4=-NHCO-$
20 $R_1=C(CH_3)_2COOH$ $R_3=H$ $R_4=-NHCO-$
21 $R_1=C(CH_3)_2COOH$ $R_3=H$ $R_4=-NCH-$
22 $R_1=C(CH_3)_2COOH$ $R_3=OH$ $R_4=-NCH-$



23 $R_1=C(CH_3)_2COOH$ $R_5=H$
2 (U-78608) $R_1=C(CH_3)_2COOH$ $R_5=CH_3$

Table 1. MICs (μg/ml)[a].

Compound	*S.a*	*S.p.*	*C.f.*	*E.cl.*	*E.c.*	*K.o.*	*K.p.*	*P.v.*	*S.m.*	*P.a.*-1	*P.a.*-2
13	>128	>128	2	64	0.25	4	2	4	1	4	16
14	>128	128	0.5	32	0.06	0.5	0.5	0.25	0.5	2	2
15	>128	>128	1	64	0.5	2	2	4	1	2	8
16	>128	128	1	32	0.5	2	0.25	0.125	1	2	4
17	>128	>128	2	128	0.5	8	8	8	2	16	64
18	>128	>128	0.5	32	0.25	0.5	0.5	0.25	0.5	2	16
19	> 64	64	0.06	16	<0.008	0.25	0.25	0.125	0.03	2	2
20	>128	128	0.06	16	<0.015	0.125	0.25	0.03	0.03	0.125	0.25
21	> 64	64	0.125	64	<0.008	0.25	0.25	0.06	0.06	0.5	1
22	> 64	> 64	0.125	8	0.03	0.25	1	0.125	0.125	4	4
23	> 64	> 64	0.03	4	<0.008	0.03	0.25	0.03	0.015	0.5	0.5
2 (U-78608)	> 64	> 64	0.03	4	<0.008	0.015	0.125	0.015	≤0.008	0.125	0.125
Pirazmonam	> 64	64	0.06	16	<0.008	0.25	0.125	0.06	0.03	0.06	0.06
Aztreonam	> 64	> 64	0.06	16	0.06	16	0.015	0.015	0.125	4	4

[a] MIC; determined by 2-fold dilution in Mueller-Hinton agar; inoculum of 10^4 cfu.

Test organisms and abbreviations: *S.a.*, *Staphylococcus aureus* UC 9218; *S.p.*, *Streptococcus pneumoniae* UC 41; *C.f.*, *Citrobacter freundii* UC 3507; *E.cl.*, *Enterobacter cloacae* UC 9381; *E.c.*, *Escherichia coli* UC 9379; *K.o.*, *Klebsiella oxytoca* UC 9383; *K.p.*, *Klebsiella pneumoniae* UC 58; *P.v.*, *Proteus vulgaris* UC 9679; *S.m.*, *Serratia marcescens* UC 6888; *P.a.*-1, *Pseudomonas aeruginosa* UC 231; *P.a.*-2, *P. aeruginosa* UC 9191.

$(M+H)^+$ (calcd for $C_{21}H_{21}N_{10}O_{11}S_2Na_2$: 699.0628).

The *in vitro* antibacterial activities of the prepared monocarbams are shown in Table 1. As expected, all of the analogs, as well as pirazmonam and aztreonam, displayed a spectrum of activity effectively limited to aerobic Gram-negative bacteria.

Some of the trends with regard to the effects of structural variations on intrinsic activity can be gleaned from an examination of the MIC's for the semicarbazide-derived analogs **13**~**18**. Increased hydrophobic character on the semicarbazide fragment (see R_2) of the monocarbams clearly had a detrimental effect on the potency of the analogs, especially versus *P. aeruginosa*. In addition, the nature of the oxime substituent (R_1) was also seen to play a role in dictating the level of antipseudomonal activity of these compounds. The isobutyric acid-substituted analogs routinely afforded superior *in vitro* activity aginst *P. aeruginosa*, vis-á-vis the corresponding acetic acid-derived congeners.

Another activity trend was noticed in an examination of effects of the linking group between the sulfonylaminocarbonyl activating moiety and the hydroxypyridone terminus of monocarbams **13**~**23** and **2**. The analogs incorporating cyclic triazolone-derived linkers (**19**~**23** and **2**) were usually more active than the corresponding congeners containing acyclic semicarbazide groups (**13**~**18**). Consequently, after focusing the bulk of our attention on monocarbam analogs with modified connections between the potentiating triazolone and hydroxypyridone ring systems, we were able to optimize the potency of this series of analogs with the synthesis of U-78608 (**2**). The most notable structural feature of U-78608 is the direct carbon-carbon bond between the two heterocyclic fragments of its N-1 activating group. U-78608 displayed exquisite activity against aerobic Gram-negative bacteria, especially versus *P. aeruginosa*. The level of activity exhibited by U-78608 was directly comparable or slightly superior to that of pirazmonam against the species examined.[11] The slightly improved potency of U-78608 versus some species may be due to its significantly greater affinity (4-fold) for PBP-3.[12] When compared to aztreonam, U-78608 was found to be significantly more active against *P. aeruginosa*. On the basis of these and other results, U-78608 was selected for further evaluation.

Acknowledgments

The authors are grateful to STEVEN J. BRICKNER, KYOUNG S. KIM, BARNEY J. MAGERLEIN, RICHARD C. THOMAS and DAVID R. WHITE for helpful discussions during the course of this work. We also wish to thank ALICE K. LABORDE, ROBERT J. MOUREY, SCOTT E. TRUESDELL, BETTY H. YAGI and GARY E. ZURENKO for the *in vitro* bioactivity results.

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(Received March 19, 1990)

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