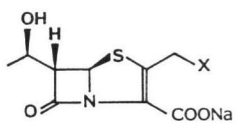
A NEW CLASS OF PENEMS, THE 2-HETEROCYCLYL(THIO)METHYL DERIVATIVES

Sir:

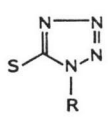
Within our primary program specifically oriented to the synthesis of new "2-CH_2–X" penem compounds[1], we have been engaged in an extensive work[2,3] directed towards the simultaneous insertion of the thienamycin and cephalosporin side chains into the penem nucleus. In practice, the conceptual operation of incorporating the heterocyclyl(thio)methyl groups characterizing the most important cephalosporins into the 6-hydroxyethylpenem framework gave rise to a novel class of β-lactam antibiotics **1** of remarkable antibacterial action[4]. According to WOODWARD's strategy[5], compounds of formula **1** were first approached from a 4-acetoxyazetidinone and the suitable heterocyclic thioethanthioic acids. More recently, however, we devised a straightforward and general route exploiting the pivotal hydroxymethylpenems **2a**~**c**[2,3] as common intermediates. For instance, reaction of **2c** with mesyl chloride (CH_2Cl_2, triethylamine, −40°C, few minutes), followed by aqueous $NaHCO_3$ work-up, afforded the mesyl derivative **2d**; IR ($CHCl_3$) cm^{-1} 1795, 1705, 1590, 1360, 1175; UV $\lambda_{max}^{CHCl_3}$ nm (ε) 328 (6,250). Sequential displacement with the heterocyclylthiol **3**[6] (THF, triethylamine, 0°C, 3 hours), desilylation ($Bu_4NF \cdot 3H_2O$ 3 mol equiv, AcOH 9 mol equiv, THF, 25°C, 20 hours) and Pd-mediated transallylation[7] with sodium 2-ethylhexanoate gave **1t**, isolated after reverse-phase chromatography (Merck LiChroprep RP-18, water); ^1H NMR (90 MHz, D_2O) δ 1.30 (3H, d, J=6 Hz, CH_3CH), 3.77 (1H, dd, J=1.8 and 6.5 Hz, H-6), 4.18 (1H, m, H-8), 4.55 (2H, br s, CH_2S), 5.50 (1H, d, J=1.8 Hz, H-5), 6.50 (1H, s, Ar); IR (KBr) cm^{-1} 3500~3150, 1760, 1660, 1625; UV $\lambda_{max}^{H_2O}$ nm (ε) 262 (11,170), 299 (10,180).

The *in vitro* antimicrobial activity of the new penems against a selection of most representative Gram-positive and Gram-negative bacteria is reported in Table 1. Apart from the tetrazole-carboxylic acid derivatives **1c**, **d**, all compounds were particularly active against Gram-positive bacteria, whereas activity against Gram-negative strains, being inferior by at least one order of magnitude, ranged from moderate to good. The tetrazole (**1a**, **b**, **e**~**g**) and triazinone (**1o**, **p**) derivatives ranked among the most interesting compounds for broadness of antibacterial spectrum, specific activity and resistance to β-

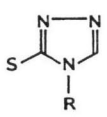


1 (a ~ u)

X :

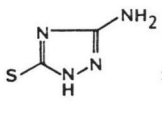


a R = H
b R = CH_3
c R = CH_2COONa
d R = CH_2CH_2COONa

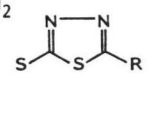


e R = $CH_2CH_2CONH_2$
f R = CH_2CH_2CN
g R = $CH_2CH_2\overset{+}{N}HMe_2$ (Inner salt)

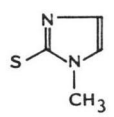
h R = H
i R = CH_2CH_3



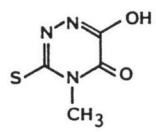
j



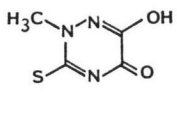
k R = NH_2
l R = CH_3
m R = SCH_2COONa



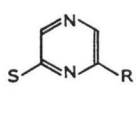
n



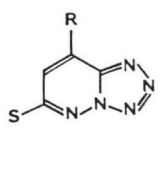
o



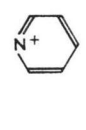
p



q R = H
r R = OCH_3



s R = H
t R = NH_2



u (Inner salt)

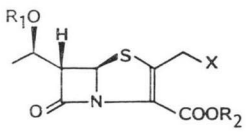
Table 1. *In vitro* antibacterial activity[a,b] of penems.

Compound	S.a.	S.a.+	D.p.	S.p.	S.f.	E.c.	E.c.+	K.a.	K.a.+	E.cl.	E.cl.+	P.m.	P.v.	C.f.	S.m.	P.a.
1a	0.17	0.17	0.06	0.06	32	0.25	0.35	0.5	0.5	0.7	16	1.4	1	2.8	4	>32
b	0.01	0.01	0.006	0.01	5.7	0.17	0.17	0.25	0.35	0.35	2.8	0.25	0.12	4	4	>32
c	1	1	1	1.4	>32	1	1	2	5.7	1.4	>32	1.4	1.4	n.t.	n.t.	>32
d	1.4	1	1	1.4	>32	0.35	1	1	1.4	0.7	>32	0.5	1.4	n.t.	n.t.	>32
e	0.01	0.02	0.008	0.01	8	0.17	0.17	0.25	0.25	0.5	5.7	1.4	0.5	2.8	2	>32
f	0.01	0.06	0.008	0.01	8	0.5	0.5	0.5	0.5	1	8	0.5	0.25	n.t.	n.t.	>32
g	0.03	0.08	0.008	0.008	16	0.7	0.5	0.7	1	0.7	1	1	1	n.t.	n.t.	>32
h	0.17	0.17	0.02	0.04	22.6	2.8	2.8	8	4	8	32	11.3	4	22.6	22.6	>32
i	0.03	0.06	0.01	0.01	8	1.4	1	2	4	5.7	32	4	1.4	8	11.3	>32
j	0.12	0.12	0.008	0.06	16	2	1	1	2	4	8	4	2	8	8	>32
k	0.03	0.12	0.01	0.03	2	8	8	4	8	8	32	4	32	n.t.	n.t.	>32
l	0.06	0.12	0.01	0.03	16	8	16	8	32	32	>32	16	>32	n.t.	n.t.	>32
m	0.17	0.17	0.01	0.06	22.6	2.8	4	11.3	8	4	>32	2	0.5	>32	32	>32
n	0.06	0.12	0.01	0.03	16	1.4	1	11.3	2.8	2	11.3	5.7	2	8	11.3	>32
o	0.03	0.06	0.008	0.01	8	0.5	0.5	2	1.4	2	32	1	0.5	>32	16	>32
p	0.08	0.08	0.01	0.04	8	0.25	0.25	1	1.4	0.17	22.6	0.25	0.17	4	5.7	>32
q	0.01	0.01	0.004	0.008	2.8	5.7	5.7	16	22.6	22.6	32	4	2	16	32	>32
r	0.01	0.01	0.008	0.004	5.7	>32	>32	>32	>32	>32	>32	>32	8	n.t.	n.t.	>32
s	0.004	0.004	0.002	0.002	2.8	0.12	0.25	2	5.7	2.8	16	1	0.17	n.t.	n.t.	>32
t	0.004	0.01	0.008	0.002	2	2	2	2	8	8	16	0.5	0.5	n.t.	n.t.	>32
u	0.01	0.01	0.008	0.01	16	8	8	5.7	16	4	1.4	>32	32	2	32	11.3

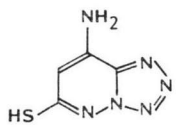
[a] MICs (μg/ml, geometric mean values of two determinations) were determined by the standard two fold serial microdilution technique in Isosensitest broth (final volume 100 μl) using an inoculum of $1 \sim 2 \times 10^5$ colony forming units/ml.

[b] Organisms included in this Table are: S.a. *Staphylococcus aureus* Smith; S.a.+ *S. aureus* 39/2 (penicillinase producer); D.p. *Streptococcus pneumoniae* ATCC 6301; S.p. *S. pyogenes* C 203; S.f. *S. faecalis* ATCC 6057; E.c. *Escherichia coli* 1507; E.c.+ *E. coli* TEM (producer of plasmid mediated β-lactamase); K.a. *Klebsiella aerogenes* 1522E; K.a.+ *K. aerogenes* 1082E (producer of chromosomally mediated β-lactamase); E.cl. *Enterobacter cloacae* 1321E; E.cl.+ *E. cloacae* P99 (producer of chromosomally mediated β-lactamase); P.m. *Proteus mirabilis* ATCC 9921; P.v. *P. vulgaris* X20; C.f. *Citrobacter freundii* F. 51; S.m. *Serratia marcescens* 200; P.a. *Pseudomonas aeruginosa* G.

n.t.: Not tested.



2 (a ~ d)



3

a $R_1=SiMe_2Bu^t$, $R_2=pNB$, X=OH
b $R_1=CO_2pNB$, $R_2=pNB$, X=OH
c $R_1=SiMe_2Bu^t$, $R_2=allyl$, X=OH
d $R_1=SiMe_2Bu^t$, $R_2=allyl$, $X=OSO_2CH_3$
(pNB=*p*-nitrobenzyl)

Table 2. *In vitro* activity[a] of six 2-heterocyclylthiomethyl penems against 20 strains of methicillin-resistant *Staphylococcus aureus*.

Compound	MIC (μg/ml)		
	Geometric mean	For 90% of isolates	Range
1d	9.5	32	2 ~>32
g	1.5	4	0.25~ 8
k	0.9	2	0.25~>32
p	1.6	4	0.5 ~ 4
q	0.5	2	≤0.06~ 32
t	0.2	1	≤0.06~ 16

a) Susceptibility tests were performed by the agar dilution method in Mueller Hinton medium (Oxoid) according to NCCLS directions (Standard methods for dilution antimicrobial susceptibility tests for bacteria which grow aerobically. NCCLS proposed standard: PMS-7. National Committee for Clinical Laboratory Standards, Villanova, Pa., 1980).

lactamases; on the other hand introduction of the pyridinium moiety (**1u**) brought forth activity against *Pseudomonas aeruginosa*. A few representatives were also evaluated against a number of clinical isolates of methicillin-resistant *Staphylococcus aureus* (Table 2); remarkably, five out of the six compounds tested showed good *in vitro* potency.

Preliminary *in vivo* results indicated that penems **1** are endowed with interesting and variable levels of therapeutic activity in the treatment of experimental infections in mice. For instance, ED_{50} values of 4.0 and 0.13 (cumulative dose, mg/kg) were observed following subcutaneous administration of, respectively, **1b** and **1u** to mice intraperitoneally infected with *Streptococcus pyogenes* C 203 (LD_{99} equivalent amount; treatments 30 and 120 minutes after infection); penem FCE 22101[3], *in vitro* equiactive with these compounds against the same strain, gave a value of 3.2 in a parallel experiment. A full evaluation of this promising class of antibiotics is now in advanced progress in our laboratories and will be reported in a forthcoming paper.

GIOVANNI FRANCESCHI*
MARCO ALPEGIANI
ANGELO BEDESCHI
MAURIZIO FOGLIO
ETTORE PERRONE

Farmitalia Carlo Erba SpA
Ricerca & Sviluppo Chimico
Via dei Gracchi, 35
20146 Milan, Italy

GIUSEPPE MEINARDI
SILVIO GRASSO
IVO DE CARNERI

Farmitalia Carlo Erba SpA
Ricerca & Sviluppo Biologico
Via C. Imbonati, 24
20159 Milan, Italy

(Received February 15, 1984)

References

1) FRANCESCHI, G.; M. FOGLIO, F. ARCAMONE, A. SANFILIPPO & G. SCHIOPPACASSI: Antibacterial activity of novel broad-spectrum "(5*R*)-penem" derivatives. J. Antibiotics 33: 453~454, 1980
2) FOGLIO, M.; C. BATTISTINI, F. ZARINI, C. SCARAFILE & G. FRANCESCHI: Synthesis of new orally absorbed penem esters, structurally related to thienamycin and cephamycins. Heterocycles 20: 1491~1494, 1983
3) FRANCESCHI, G.; M. FOGLIO, M. ALPEGIANI, C. BATTISTINI, A. BEDESCHI, E. PERRONE, F. ZARINI, F. ARCAMONE, C. DELLA BRUNA & A. SANFILIPPO: Synthesis and biological properties of sodium (5*R*, 6*S*, 8*R*)-6α-hydroxyethyl-2-carbamoyloxymethyl-2-penem-3-carboxylate (FCE 22101) and its orally absorbed esters FCE 22553 and FCE 22891. J. Antibiotics 36: 938~941, 1983
4) MEINARDI, G.; S. GRASSO, I. DE CARNERI, M. FOGLIO, E. PERRONE, A. BEDESCHI, M. ALPEGIANI & G. FRANCESCHI: A new class of penems: 6α-Hydroxyethyl-2-heterocyclylthiomethyl derivatives. Abstracts of Papers of 23rd Intersci. Conf. on Antimicrob. Agents Chemother., No. 985, Las Vegas, 1983
5) LANG, M.; K. PRASAD, W. HOLICK, J. GOSTELI, I. ERNEST & R. B. WOODWARD: The penems, a new class of β-lactam antibiotics. 2. Total syn-

thesis of racemic 6-unsubstituted representatives. J. Am. Chem. Soc. 101: 6296~6301, 1979

6) NANNINI, G.; E. PERRONE, D. SEVERINO, F. CASABUONA, A. BEDESCHI, F. BUZZETTI, P. N. GIRALDI, G. MEINARDI, G. MONTI, A. CERIANI & I. DE CARNERI: Cephalosporins. III. Synthesis and structure-activity relationships of 7-vinylenethioacetamidocephalosporins with a tetrazolo-pyridazine at the 3-position. J. Antibiotics 34: 1456~1468, 1981

7) JEFFREY, P. D. & S. W. MCCOMBIE: Homogeneous, palladium (O)-catalyzed exchange deprotection of allylic esters, carbonates, and carbamates. J. Org. Chem. 47: 587~590, 1982