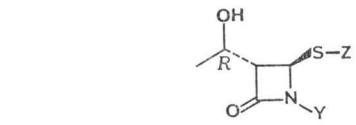
A NEW CLASS OF 2-HETEROCYCLYL-ALKYLTHIOPENEMS

Sir:

Penems are a unique class of synthetic β-lactams, which are potent, broad-spectrum antibiotics. Since the first announcement[1] a decade ago, several publications have appeared in the literature[2~15] on new and improved synthetic methodologies to construct a variety of novel penems. At least three candidates, Sch 29482[16], Sch 34343[17] and FCE 22101[18], have been advanced to the clinical trials. Here, as part of a continuing program, we wish to report a new series of 2-heterocyclylalkylthiopenems, which are by far one of the most active series of penems synthesized.

The synthetic route employed for the title compounds is essentially the same as that developed in our laboratories[19] for the production of Sch 34343. Thus, conversion of 3*S*,4*R*,5*R*-*S*-trityl azetidinone (**1**) to its *N*-alkylated product **2** using allyl iodoacetate, followed by trityl deblocking with silver nitrate afforded the silver thiolate **3** in over 90% yield. Trityl deblocking to the free thiol **4** may also be achieved by reduction with zinc in acidic medium: NMR ($CDCl_3$) δ 5.9 (1H, m), 5.3 (2H, m), 5.0 (1H, dd, J=3, 9 Hz, coupled with SH), 4.55 (2H, m), 4.2 (1H, d, J=18 Hz, NCH_2), 4.15 (1H, m), 3.75 (1H, d, J=18 Hz), 3.2 (1H, dd, J=3, 6 Hz), 2.1 (1H, d, J=9 Hz, SH), 1.35 (3H, d, J=6 Hz). Selective thiocarbonylation using either thiocarbonyl diimidazole or β-naphthyl thiochloroformate goes exceedingly efficiently (>95%) on the silver thiolate **3** to generate the corresponding intermediate **5** or **6**, set for cyclization. Upon treatment with a strong non-nucleophilic base *e.g.* lithium bis hexamethyl silyl amide in the presence of a silylating agent (BSA) to transiently protect the hydroxyl group, effected rapid ring closure forming the versatile thione **7**. Alkylation of the thione **7** in situ or after isolation afforded the novel penems **8**. Palladium (O) catalyzed deblocking of the ester group[20] to form the acid or its salt **9** proceeded efficiently.

As can be seen from Table 1, the *N*-substituted imidazole and triazole derivatives have the best overall antibiotic activity. A two carbon spacing between the sulfur and nitrogen atoms appears to impart optimum activity, *e.g.* compounds **10** and **11**, **24** and **25** (this pattern largely holds true with a variety of other penems synthesized in these laboratories). The presence of amino, carboxylic acid (ionizable groups) or highly lipophilic groups adversely affects the



1 Y = H, Z = CPh_3

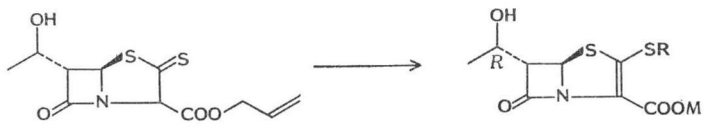
2 Y = CH_2COO–allyl, Z = CPh_3

3 Y = CH_2COO–allyl, Z = Ag

4 Y = CH_2COO–allyl, Z = H

5 Y = CH_2COO–allyl, Z = imidazole-thiocarbonyl

6 Y = CH_2COO–allyl, Z = naphthyl-O-thiocarbonyl



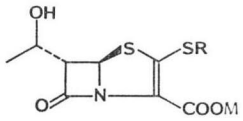
7

8 M = Allyl

9 M = H or Na^+

R See Table 1

Table 1. *In vitro* antibacterial activity of selected penems.



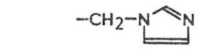
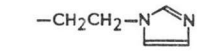
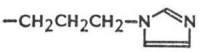
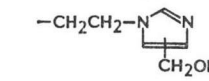
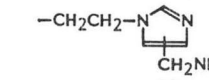
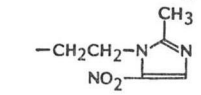
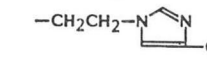
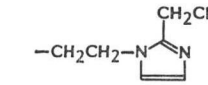
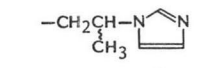
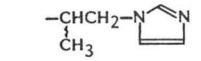
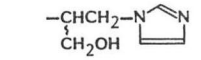
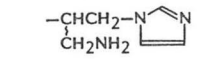
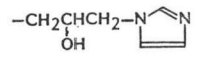
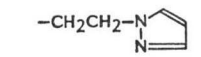
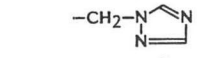
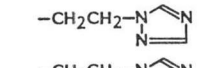
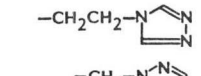
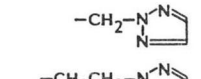
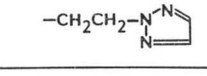
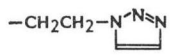
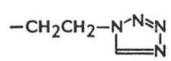
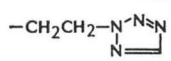
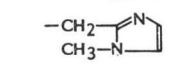
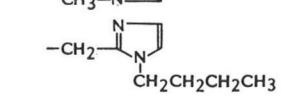
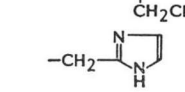
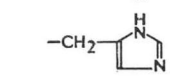
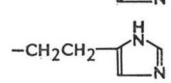
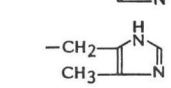
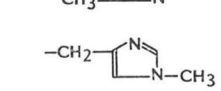
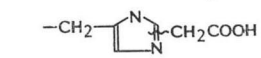
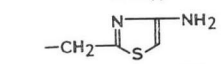
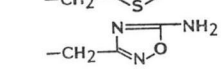
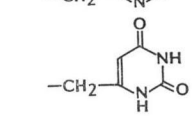
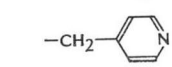
Compound	R	Geometric mean MICs	
		Gram-positive	Gram-negative
10		0.08	0.63
11		0.061	0.135
12		0.08	1.25
13		0.17 0.17	0.19 (0.2) (1,4-isomer) 0.307 (1,5-isomer)
14		0.41 0.38	2.2 (1,4-isomer) 2.24 (1,5-isomer)
15		0.22	39.3
16		0.063	0.307
17		0.065	1.14
18		0.16	1.3
19		0.078	0.24*
20		0.17	0.46
21		1.6	3.0
22		0.15	0.77
23		0.44	8.0
24		0.44	1.6
25		0.15	0.42
26		0.3	0.42
27		0.37	7.8
28		0.24	7.9

Table 1. (Continued)

Compound	R	Geometric mean MICs	
		Gram-positive	Gram-negative
29		0.15	0.69
30		0.17	0.53
31		0.24	2
32		0.1	0.34
33		0.129	26.5
34		0.27	1.4
35		0.11	0.63
36		0.3	2
37		0.15	0.81
38		0.14	0.68 (1,4-isomer)
39		1.8	1.1 (1,4 or 1,5-isomer)
40		0.2	3.8
41		0.16	1.9
42		0.38	3.8
43		0.13	3.8
44	$CH_2CH_2OCONH_2$ (Sch 34343)	0.15	0.57
45	CH_2CH_3 (Sch 29482)	0.08	0.7
46	FCE 22101	0.16	1.2

* Separated *R* and *S* have comparable activity.

antimicrobial activity, *e.g.* compounds **21**, **39**, **33**. In multi-nitrogen heterocycles such as triazoles and tetrazoles, variation in spectrum and potency was noted depending on the site of *N*-substitution. In general, substitution on the more nucleophilic nitrogen atom seems to be favorable to overall activity, *e.g.* compounds **25** and **26**, **28** and **29**, **30** and **31**. Compounds **32**, **34**, **37**, **38** carbon-linked heterocyclic derivatives also showed excellent antimicrobial activity compared to the reference compounds **44**, **45** and **46**. Extended MICs of some of the selected

Table 2. *In vitro* antibacterial activity of selected penems.

Compound	Geometric mean MICs (μg/ml)*										
	Bacillus	*Escherichia coli*	*Entero-bacter*	*Kleb-siella*	*Morga-nella*	*Provi-dencia*	*Salmo-nella*	*Micrococcus*	*Serratia*	*Staphylo-coccus*	*Entero-coccus faecalis*
11	0.06 (1)	0.14 (11)	0.32 (3)	0.20 (10)	1.0 (1)	0.76 (5)	0.12 (3)	0.12 (1)	1.0 (4)	0.05 (17)	5.6 (2)
13	0.06 (1)	0.09 (11)	0.25 (3)	0.12 (10)	1.0 (1)	0.76 (5)	0.06 (3)	0.12 (1)	1.7 (4)	0.12 (18)	8.0 (2)
16	0.06 (1)	0.24 (11)	0.40 (3)	0.29 (10)	2.0 (1)	1.5 (5)	0.25 (3)	0.25 (1)	1.4 (4)	0.05 (17)	4.0 (2)
19	0.03 (1)	0.12 (11)	0.40 (3)	0.18 (10)	4.0 (1)	2.0 (5)	0.10 (3)	0.12 (1)	2.4 (4)	0.06 (17)	5.7 (2)
20	0.06 (1)	0.25 (11)	0.40 (3)	0.20 (10)	4.0 (1)	3.0 (5)	0.08 (3)	0.12 (1)	4.0 (4)	0.11 (18)	11.3 (2)
25	0.06 (1)	0.19 (11)	0.63 (3)	0.31 (10)	2.0 (1)	0.87 (5)	0.16 (3)	0.12 (1)	3.4 (4)	0.10 (17)	5.7 (2)
32	0.12 (1)	0.41 (10)	1.0 (2)	0.44 (6)	4.0 (1)	2.6 (5)	0.32 (3)	0.25 (1)	2.8 (4)	0.20 (6)	8.0 (2)
44 (Sch 34343)	0.06 (1)	0.30 (11)	1.3 (3)	0.35 (10)	2.0 (1)	0.87 (5)	0.25 (3)	0.06 (1)	4.8 (4)	0.11 (18)	5.7 (2)
46 (FCE 22101)	0.06 (1)	0.68 (11)	3.2 (3)	0.81 (10)	2.0 (1)	2.3 (5)	0.50 (3)	—	5.7 (4)	0.12 (18)	5.7 (2)

Numbers in parentheses indicate the number of strains.

* Mueller-Hinton agar, 24 hours.

penems are shown in Table 2. None of these penems, unlike thienamycin, had any useful pseudomonas activity. More details, including *in vivo* evaluations of this class of highly active penems will be reported in a separate publication.

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