Bioorganic & Medicinal Chemistry Letters, Vol.3, No.11, pp. 2253-2254, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

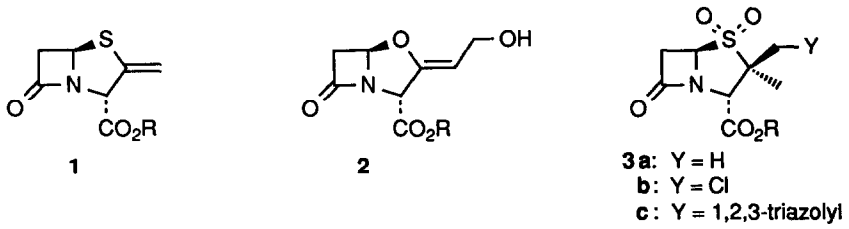
2-SUBSTITUTED PENEMS, NEW CANDIDATES FOR CEPHALOSPORINASE INHIBITORS

Hideo Tanaka, Yutaka Kameyama, Shin-ichi Sumida, and Sigeru Torii*
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700, Japan

(*Received* 1 *April* 1993)

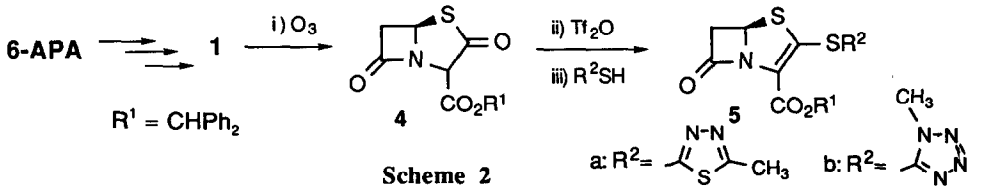
Abstract: Upon preliminary bioassay experiments, C(2)-substituted penems **5** exhibit promising activities particularly against *E. Cloacae* (cephalosporinase).

The first discovery of the potent ß-lactamase inhibitory activities of clavulanic acid **2** in 1976,[1] has made a tremendous impact on antibacterial chemotherapy. Meanwhile, in 1978, English reported that penicillanic acid 1,1-dioxide (sulbactam) **3a** exhibits a ß-lactamase inhibitory activity comparable to that of clavulanic acid **2**.[2] These findings have induced many synthetic efforts toward the development of new ß-lactamase inhibitors. The inhibitors explored so far, involving BL-P2013 (**3b**, Y = Cl) [3] and YTR-830H (**3c**, Y = 1,2,3-triazolyl),[4] have mainly been elaborated by chemical modification of the penam 1,1-dioxide framework **3a**.



Scheme 1

Incidentally, the 2-*exo*-methylenepenam framework **1** represents a structural hybrid of those of clavulanic acid **2**, sulbactam **3a** and its analogues **3b** and **3c**. One can, therefore, hope that the 2-*exo*-methylenepenam **1** might exhibit a potent inhibitory activity toward ß-lactamases. Furthermore, the 2-*exo*-methylenepenam **1** is a new strategic intermediate which can open new entries to ß-lactam antibiotics and ß-lactamase inhibitors through manipulation of the 2-*exo*-methylene moiety. The first synthesis of the 2-*exo*-methylenepenam **1** was recently attained by our group.[5] The success in opening the facile synthetic route to **1**, in turn, enabled us to demonstrate a convenient access to 2-substituted penems **5** based on manipulation of the 2-*exo*-methylene moiety of **1** as illustrated in Scheme 2.[5] Herein, we describe the preliminary experiment to assay the inhibitory propaties of the 2-substituted penems **5a** and **5b** (R^1 = Na) against ß-lactamases, such as TEM-1, CTX-1, *E. Cloacae*, and *P. Aeruginosa*.



Scheme 2

The inhibitory activities of **5a** and **5b** together with those of YTR-830H,[4] which is a currently used potent ß-lactamase inhibitor, are summarized in Table 1. The bioassay results shows that the inhibitory activities of **5a** and **5b** against all the ß-lactamases tested so far are ca. 2~20 fold less than YTR-830H. Nevertheless, it is of interest to note that the inhibitory abilities of **5a** and **5b** at low concentration (0.1- 0.66 μg/ml) against *E. Cloacae* (Cephalosporinase) are almost comparable to those of YTR-830H. These facts lead us in conclusion that the 2-substituted penems **5** can be remarked as a promising leading compound in future research for developing a new class of inhibitors against ß-lactamase, particularly cephalosporinase. We believe that further structural manipulation of the 2-*exo*-methylenepenam **1** and/or the 2-substituted penems **5** might provide new candidates of ß-lactamase inhibitors. We believe that further structural manipulation of the 2-*exo*-methylenepenam **1** and/or the 2-substituted penems **5** might provide new candidates of ß-lactamase inhibitors.

Table 1 ß-Lactamase Inhibitory Activity[a),†]

Enzyme type	Enzyme activity (U/ml)	Substrate[b)]	Inhibitor dose (μg/ml)	Inhibition percentage (%) YTR-830H	**5a** [c)]	**5b**
TEM-1	1.6328	ABPC	10	100	6	28
			0.1	93	--	2
CTX-1	0.7363	CER	10	96	12	19
			0.1	98	--	--
E. Cloacae	1.1517	CER	10	96	14	45
			0.1	7	8	10
P. Aeruginosa	1.0352	CER	10	98	0	16
			0.1	14	--	--

a) Preincubation : 30 ℃, 5 min. Determined by UV method.
b) ABPC: Ampicillin; CER: Cephaloridine.
c) Inhibitor dose: 6.6 or 0.66 μg/ml.
† The activity tests of inhibitors were performed in the Kodama Laboratory, Taiho Pharmaceutical Co., Ltd., Kamikawa, Kodama, Saitama 367-02, Japan.

References

1 Howarth, T. T.; Brown, A. J.; King, T. J. *J. Chem. Soc. Chem. Commun.* **1976**, 266.
2 English, A. R.; Retsema, J. A.; Girard, A. E.; Lynch, J. E.; Barth, W. E. *Antimicrob. Agents Chemother.* **1978**, *14*, 414. Volkmann, R. A.; Carroll, R. D.; Drolet, R. B.; Elliott, M. L.; Moore, B. S. *J. Org. Chem.*, **1982**, *47*, 3344. Brenner, D. G.; Knowles, J. R. *Biochemistry* **1984**, *23*, 5833.
3 Gottstein, W. J.; Crast, L. B.; Graham, R. G.; Hayner, J. U.; Mcgregor, D. N. *J. Med. Chem.* **1981**, *24*, 1531.
4 Aronoff, S. C.; Jacobs, M. R.; Labrozzi, P. H.; Yamabe, S. *J. Antimicrob. Chemother.* **1986**, *18*, 271. Jacobs, M. R.; Aronoff, S. C.; Johenning, S.; Shlaes, D. M.; Yamabe, S. *Antimicrob. Agents Chemother.* **1886**, *29*, 980. Gutmann, L.; Kitzis, M. D.; Yamabe, S.; Acar, J. F. *Antimicrob. Agents Chemother.* **1986**, *29*, 955. Micetich, R. G.; Maiti, S. N.; Spevak, P.; Hall, T. W.; Yamabe, S.; Ishida, N.; Tanaka, M.; Yamazaki, T.; Nakai, A.; Ogawa, K. *J. Med. Chem.* **1987**, *30*, 1469.
5 Tanaka, H.; Kameyama, Y.; Torii, S. *Synlett* **1992**, 878; Tanaka, H.; Kameyama, Y.; Yamauchi, T.; Torii, S.; *J. Chem. Soc. Chem. Commun.* **1992**, 1793.