Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 13, pp. 1671-1676, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00282-5

SYNTHESIS AND STRUCTURE–ACTIVITY RELATIONSHIPS OF NOVEL THF 1β-METHYLCARBAPENEMS

Yang-I Lin,* Panayota Bitha, Subas M. Sakya, Timothy W. Strohmeyer, Zhong Li, Ving J. Lee, Stanley A. Lang, Jr., Youjun Yang, Niraja Bhachech, William J. Weiss, Peter J. Petersen, Nilda V. Jacobus, Karen Bush, Raymond T. Testa, and Francis P. Tally

Wyeth-Ayerst Research, Division of American Home Products Corporation, Infectious Diseases Research Section, Pearl River, N.Y. 10965

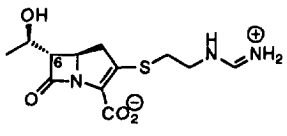
Abstract: A series of twelve highly active aminomethyl-THF 1β-methylcarbapenems **3a–l** were synthesized. Of these, carbapenems **3a–f** demonstrated a spectrum of antimicrobial activity comparable to those of imipenem and meropenem with the exception of only moderate anti-pseudomonal activity. Most importantly, they demonstrated moderate intrinsic oral activity against an *E. coli* infection in mice. © 1997 Elsevier Science Ltd.

Introduction

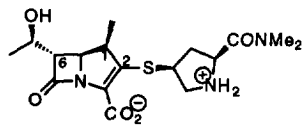
Until recently, imipenem[1,2] was the only carbapenem available for clinical use in the United States. Of all the β-lactam antibiotics in clinical use, it has the broadest spectrum of antimicrobial activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria, including many resistant clinical isolates. It is not only highly stable to hydrolysis by most serine β-lactamases, but also an effective inhibitor of these serine β-lactamases. However, imipenem has four drawbacks. First, it is highly sensitive to renal dehydropeptidase (DHP) inactivation, thus requiring co-administration with cilastatin, a dehydropeptidase inhibitor. Second, it has convulsive potential, particularly in patients with impaired renal function and underlying CNS disease. Third, it is not orally active. Fourth, it has a half-life of only one hour. The second generation carbapenem, meropenem, which has antimicrobial activity very similar to that of imipenem and was recently approved for use, addresses the first two concerns.[1,3] Therefore, our objective has been to develop the next generation of carbapenems, equal in activity to the clinically effective parenteral carbapenems, imipenem and meropenem, and having pharmacokinetic advantages such as oral activity and longer half-life.

The structure–activity relationships of imipenem and meropenem are well documented.[1,4] The 6α-hydroxyethyl group is responsible for high stability to hydrolysis by most serine β-lactamases and for high

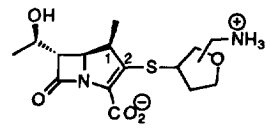
serine β-lactamase inhibitory activity, thus distinguishing imipenem and meropenem from classical β-lactam antibiotics such as penicillins and cephalosporins. The 1β-methyl group of meropenem is responsible for both the high chemical stability as well as stability to hydrolysis by renal dehydropeptidases, thus distinguishing meropenem from the first generation carbapenem, imipenem. In looking for sites for further structural modification, the 2-position appeared to be the only place that would allow considerable variation without compromising the antimicrobial activity and therefore, became the target of our investigation. Since hundreds of substituted tetrahydrofuranylthiols can be readily obtained by the modification of carbohydrates, extensive efforts were directed toward the synthesis of novel THF 1β-methylcarbapenems with pharmacokinetic and/or microbiological advantages, resulting in aminomethyl-THF 1β-methylcarbapenems **3** as the major synthetic targets. These dipeptide-like compounds were made with the objective of obtaining carbapenems with enhanced activity against Gram-negative bacteria and with oral activity, both mediated through the use of peptide transport systems.[5] Here we report the synthesis and structure–activity relationships of aminomethyl-THF 1β-methylcarbapenems **3**.[6]



Imipenem/Merck
First Generation



Meropenem/Sumitomo/Zeneca
Second Generation

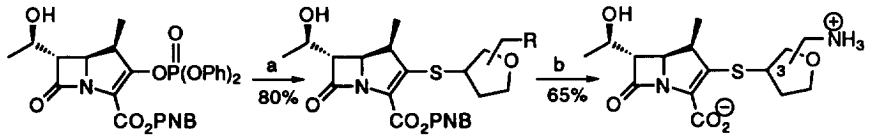


3: THF Carbapenems

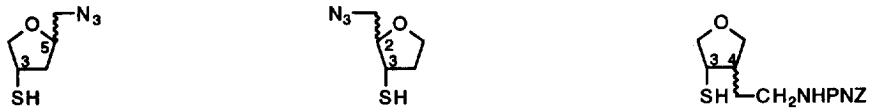
Chemistry

A series of ten positional and configurational isomers of azidomethyl and PNZ-protected aminomethyl tetrahydrofuranylthiols **4a-l** were synthesized.[6(a), 6(f)] PNB-protected carbapenems **2a–l** were synthesized by the reaction of phosphate ester **1** with the thiols **4a–l** in acetonitrile in the presence of N,N-diisopropylethylamine. Zwitterionic carbapenems **3a–l** were synthesized by reductive hydrogenation with 10% palladium on charcoal at pH 6. Under these conditions, the azido moiety was reduced to the primary amino group and the PNB and PNZ moieties deprotected (Scheme 1). Carbapenems **3a–b** are each a mixture of diastereomers. A mixture of diastereomeric carbapenems **3i** and **3j** obtained from the reaction of the phosphate ester **1** with the racemic thiol **4i–j** followed by hydrogenation of the PNB-protected carbapenem **2i–j** was

successfully separated by C_{18} reverse phase chromatography; carbapenems **3k** and **3l** were similarly prepared. The assignment of stereochemistry of carbapenems **3i–l** is tentative. The most interesting and optically pure carbapenem **3f** (CL191,121) was synthesized from diol **5** in seven steps in 15% overall yield as illustrated in Scheme 2. Diol **5** ($[\alpha]^{25}_D = +47°\pm1$; c = 1.1% in H_2O)[7] was obtained in two steps from 2-deoxy-D-ribose. Since the ditriflate of the diol **5** is chemically unstable, the triflate group was introduced one at a time to provide a higher overall yield.



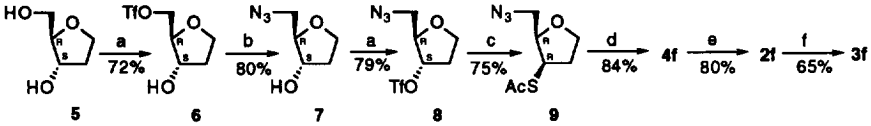
Scheme 1: (a) 4/*i*-Pr$_2$NEt/CH$_3$CN, rt; (b) H$_2$/10%Pd on C/pH 6.0, rt



4a: racemic; *trans*
4b: racemic; *cis*
4c: 3*R*, 5*S*; *trans*
4d: 3*R*, 5*R*; *cis*
4e: 3*S*, 5*S*; *cis*

4f: 2*R*, 3*R*; *cis*
4g: 2*R*, 3*S*; *trans*
4h: 2*S*, 3*S*; *cis*

4i-j: racemic; *cis*
4k-l: racemic; *trans*



Scheme 2: (a) 1 equiv. Tf$_2$O/Py/CH$_2$Cl$_2$, -20 °C; (b) nBuNN$_3$/CH$_2$Cl$_2$, -20 °C; (c) KSAc/MeCN, 0 °C; (d) MeONa/MeOH, 0 °C; (e) 1/*i*-Pr$_2$NEt/CH$_3$CN, rt; (f) H$_2$/10%Pd on C/pH 6.0, rt

Results and Discussion

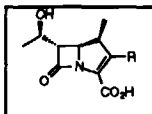
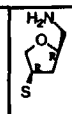
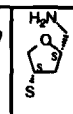
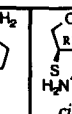
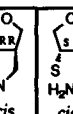
As shown in Table 1,[8] twelve aminomethyl-THF 1β-methylcarbapenems **3a–l** exhibited antimicrobial activity against a spectrum of Gram-positive and Gram-negative bacteria, including those producing specific β-lactamases. In the 3,5-disubstituted series, the stereochemistry of the substituents on the THF ring had little effect on the antimicrobial activity. These 3,5-disubstituted compounds **3a–e** were almost equally active. Against Gram-positive and Gram-negative microorganisms, they demonstrated a spectrum of activity comparable to those of imipenem and meropenem with the exception of only moderate anti-pseudomonal activity. Decreased activity in *P. aeruginosa* (ATCC 27853) appeared to be due to poor uptake through OprD protein channel.[6d,9] Loss of the OprD protein channel in *P. aeruginosa* (GC 1544) markedly affects the activity of imipenem but has little effect upon the antipseudomonal activity of the compounds **3a–e**. However, in the 2,3- and 3,4-disubstituted series, the stereochemistry of the substituents on the THF ring had a pronounced effect on the antimicrobial activity. The activity between cis and trans compounds could differ as much as 16 fold, with cis compounds more active than the trans compounds. Among these compounds, carbapenem **3f** (CL191,121) had the best activity against Gram-positive organisms, particularly against *E. faecalis*. Most importantly, the compounds **3a**, **3b**, and **3f** demonstrated moderate intrinsic oral activity (ED_{50} = 2-4 mg/kg) against an *E. coli* infection in mice and were about 20 times more efficacious than imipenem when dosed orally.[6e] None of the compounds exhibited acceptable activity against methicillin-resistant *S. aureus* (GC2220); none exhibited activity against *E. faecium* or *X. maltophilia*. As expected, these THF 1β-methylcarbapenems all demonstrated better stability than imipenem to hydrolysis by hog renal dehydropeptidase and do not require coadministration with a dehydropeptidase inhibitor.

Synthesis of peptidic prodrugs of aminomethyl-THF 1β-methyl carbapenems **3** is the subject of the following communication.[10]

Acknowledgments: The authors would like to thank Dr. Andrew Berks for an extensive patent literature research at the beginning of the project and Ms. Eugenia Delos Santos for her superb technical assistance.

Table 1 Aminomethyl-THF 1β-Methylcarbapenems

In vitro activity (MIC; μg/mL)

	R													Imipenem	Meropenem
		3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**		
ORGANISM	Strain														
E. coli	ATCC 25922	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	0.50	0.50	≤ 0.06	0.12	0.25	0.50	0.12	≤ 0.06
E. coli	GC 2205	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	0.12	≤ 0.06	0.25	0.50	0.12	0.12	0.25	0.50	0.12	≤ 0.06
E. coli	GC 1792	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	0.50	0.50	≤ 0.06	0.12	0.25	0.50	≤ 0.06	≤ 0.06
E. cloacae	GC 2209	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	0.50	0.25	≤ 0.06	0.12	0.25	0.50	≤ 0.06	≤ 0.06
C. freundii	GC 2211	≤ 0.06	≤ 0.06	≤ 0.06	0.12	0.12	≤ 0.06	1.0	0.50	0.25	0.50	1.0	1.0	0.25	≤ 0.06
M. morganii	GC 2213	0.25	0.50	0.25	0.50	0.50	0.50	2.0	2.0	2.0	2.0	4.0	4.0	1.0	≤ 0.06
A. calcoaceticus	GC 756	1.0	2.0	1.0	2.0	2.0	2.0	2.0	4.0	2.0	16	16	8.0	0.25	0.50
P. aeruginosa	ATCC 27853	4.0	8.0	2.0	16	8.0	8.0	16	4.0	16	16	32	16	1.0	0.25
P. aeruginosa	GC 1544 OprD-	8.0	16	8.0	32	16	16	32	16	32	32	64	64	16	4.0
X. maltophilia	GC 562	>128	>128	>128	>128	>128	>128	>64	>128	>128	>128	>128	>128	>128	>128
S. aureus	ATCC 29213	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	0.06	0.12	≤ 0.06	0.12	0.12	0.12	≤ 0.06	≤ 0.06
S. aureus	GC 2220 MRSA	8.0	4.0	8.0	8.0	4.0	1.0	4.0	8.0	4.0	16	16	16	1.0	8.0
E. faecalis	GC 842	2.0	2.0	2.0	4.0	4.0	0.50	8.0	4.0	2.0	8.0	8.0	8.0	1.0	2.0
E. faecium	GC 1182	128	128	>128	>128	128	64	>64	128	128	>128	>128	>128	64	>128
ED50*** SOD SSC	*E. coli*	3.7 0.27	3.5 0.28	NT	NT	NT	3.8 0.34	NT	NT	NT	NT	NT	NT	79 0.67	NT
Rel. hydrolysis by hog DHP		19	10	NT**	10	7.3	8.5	18	4.5	< 1	<1	39	37	100	28

* A mixture of diastereomers (**3a** and **3b**).
** Not Tested.
*** mg/kg; Imipenem/cilastatin was used as the reference drug.
SOD = single oral dose; SSC = single subcutaneous dose.

References and Notes

1. (a) Moellering, R. C.; Eliopoulos, G. M.; Sentochnik, D. E. *J. Antimicrob. Chemother.* **1989**, *24(Suppl. A)*, 1. (b) Yazawa, K.; Mikami, Y.; Ohashi, S.; Miyaji, M.; Ichihara, Y.; Nishimura, C. *J. Antimicrob. Chemother.* **1992**, *29*, 169. (c) Sumita, Y.; Nouda, H.; Shinagawa, H.; Yamaga, H.; Sunagawa, M.; *J. Antibiotics* **1995**, *48*, 188. (d) Yang, Y.; Bhachech, N.; Bush, K. *J. Antimicrob. Chemother.* **1995**, *35*, 75. (e) Miyashita, K.; Massova, I.; Taibi, P.; Mobashery, S. *J. Am. Chem. Soc.* **1995**, *117*, 11055.
2. (a) Leanza, W. J.; Wildonger, K. J.; Miller, T. W.; Christensen,. B. G. *J. Med. Chem.* **1979** *22*, 1435. (b) Kropp, H.; Gerckens, L.; Sundelof, J. G.; Kahan,. F. M. *Rev. Infect. Dis.* **1985**, *7 (Suppl 3):* S389.
3. Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiotics* **1990**, *18*, 519.
4. Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles*, **1984**, *21*, 29.
5. (a) Friedman, D. I.; Amidon, G. L. *J. Controlled Release* **1990**, *13*, 141. (b) Lowther, J.; Hammond, S. M.; Russell, K. *J. Antimicrob. Chemother.* **1990**, *25*, 183. (c) Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Ringrose, P. S. *Antimicro. Agents Chemother.* **1979**, *15*, 677. (d) Cheung, K.-S.; Wasserman, S. A.; Dudek, E.; Lerner, S. A.; Johnston, M. *J. Med. Chem.* **1983**, *26*, 1733.
6. (a) Lin, Y.-I; Bitha, P.; Sakya, S. M.; Strohmeyer, T. W.; Feigelson, G. B.; Ziegler, C. B., Jr.; Lee, V. J.; Tally, F. P. *34th Interscience Conference on Antimicrobial Agents and Chemotherapy(ICAAC).* Orlando **1994**. Abstract F70. (b) Lin, Y.-I; Bitha, P.; Sakya, S. M.; Strohmeyer, T. W.; Yang, Y.; Weiss, W. J.; Jacobus, N. V.; Bush, K.; Testa, R. T.; Tally, F. P. *34th ICAAC.* Orlando **1994**. Abstract F72. (c) Weiss, W. J.; Yang, Y.; Petersen, P. J.; Shelofsky, A. G.; Bush, K.; Jacobus, N. V.; Bitha, P.; Lin, Y.-I; Testa, R. T.; Tally, F. P. *34th ICAAC* Orlando **1994**. Abstract F74. (d) Bush, K.; Bhachech, N.; Yang, Y.; Weiss, W. J.; Lin, Y.-I; Testa, R. T.; Tally, F. P. *34th ICAAC.* Orlando **1994**. Abstract F76. (e) Weiss, W. J.; Petersen, P. J.; Jacobus, N. V.; Bitha, P.; Lin, Y.-I; Testa, R. T.; Tally, F. P. *34th ICAAC.* Orlando **1994**. Abstract F78. (f) Lin, Y.-I; Bitha, P.; Sakya, S. M.; Strohmeyer, T. W.; Li, Z; Lee, V. J.; Lang, S. A., Jr., Bush, K.; Testa, R. T. *15th International Congress of Heterocyclic Chemistry.* Taipei, Taiwan 1995. Abstract IL-III-2.
7. Hudsone, G. B.; Baker, R. *J. Org. Chem.* **1967**, *32*, 3650.
8. (a) Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A2. National Committee for Clinical Laboratory Standards, Villanova, PA. (b) Campbell, B. J.; Forrester, L. J.; Zahler, W. L.; Burks, M *J. Biol. Chem.* **1984**, *259*, 14586.
9. (a) Trias, J.; Nikaido, H. *Antimicro. Agents Chemother.* **1990**, *34*, 52. (b) Trias, J.; Nikaido, H. *J. Biol. Chem.* **1990**, *265*, 15680.
10. Lin, Y.-I; Bitha, P.; Sakya, S. M.; Li, Z.; Lang, S. A., Jr.; Yang, Y.; Bhachech, N.; Weiss, W. J.; Petersen, P. J.; Jacobus, N. V.; Bush, K.; Testa, R. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1665.

(*Received in USA* 9 *April* 1997; *accepted* 23 *May* 1997)