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

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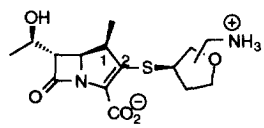
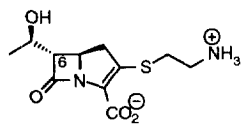
Abstract: Two series of active aminomethyl-THF 1β-methylcarbapenem derivatives were synthesized. In general, they were all slightly less active than their parent compounds and failed to demonstrate enhanced activity against *P. aeruginosa*. © 1997 Elsevier Science Ltd.

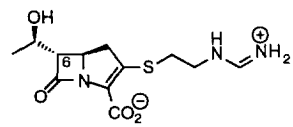
In previous publications,[1] we reported a series of twelve highly active aminomethyl-THF 1β-methylcarbapenems **1**. Many of these carbapenems demonstrated a spectrum of antimicrobial activity comparable to or better than that of imipenem. However, they only demonstrated modest anti-pseudomonal activity comparable to that of thienamycin. Therefore, efforts were directed toward the synthesis of aminomethyl 1β-methylcarbapenem derivatives with enhanced activity against *P. aeruginosa*. Here we report the synthesis and antimicrobial activity of novel THF 1β-methylcarbapenems derived from the aminomethyl-THF 1β-methylcarbapenems **1**.



1: THF Carbapenems



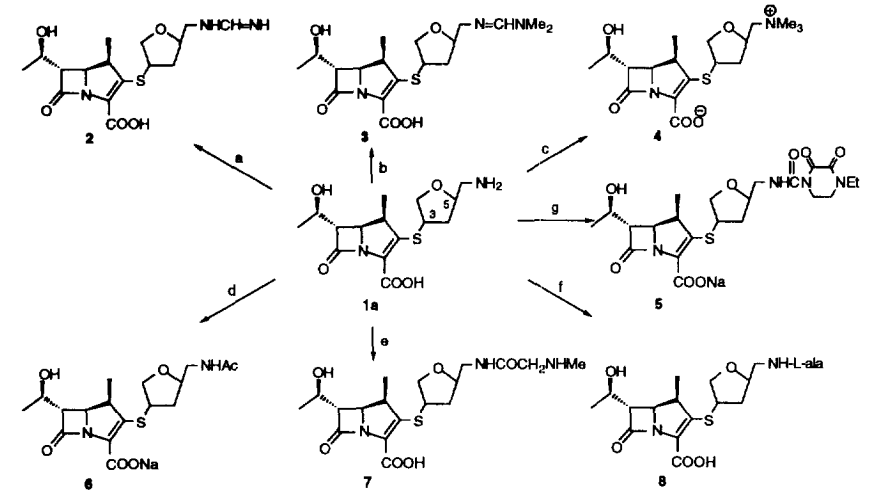
Thienamycin



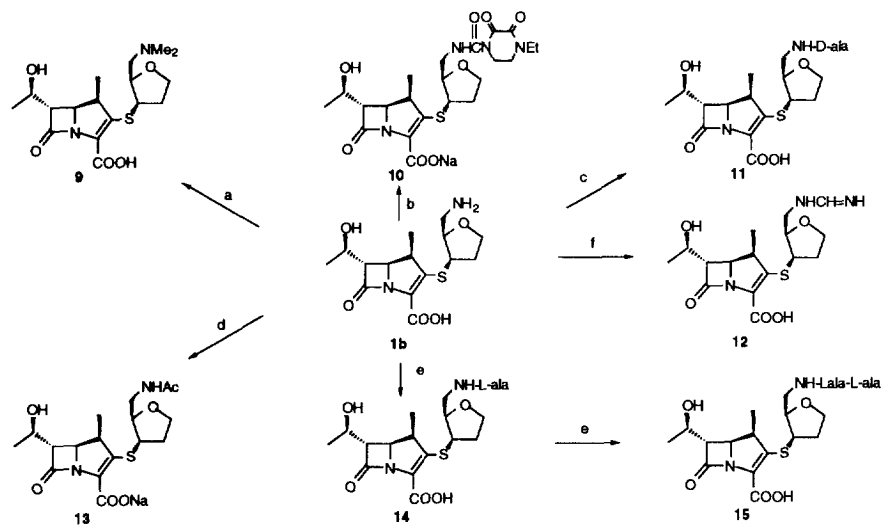
Imipenem

Chemistry

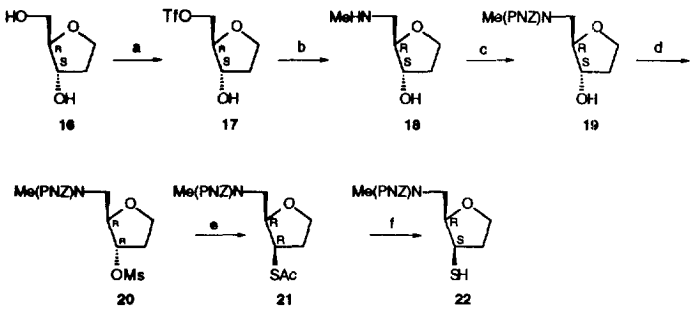
Synthesis of aminomethyl-THF 1β-methylcarbapenems, **1a** and **1b**, was previously described.[1] The carbapenem **1a** is a mixture of diastereomers (3*S*,5*R* and 3*R*,5*S*), and the carbapenem **1b** is optically pure. Transformation of the carbapenems, **1a** and **1b**, to the desired compounds, **2** to **15**, is shown in Schemes 1 and 2. Reaction of the carbapenems, **1a** and **1b**, with the N-carboxyanhydride of an amino acid provided a mixture of



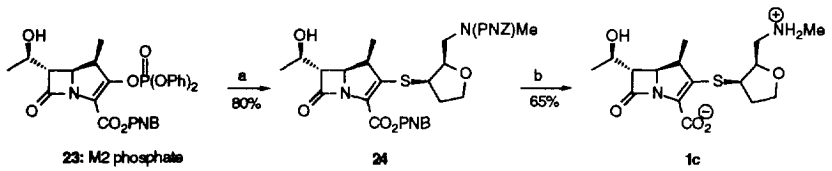
Scheme 1 (a) EtOCH=NH·HCl/pH 7.0 phosphate buffer; (b) $Me_2NCH(OPr\text{-}i)_2$/pH 8.5 phosphate buffer; (c) Me_2SO_4/pH 8.5 phosphate buffer; (d) AcCl/$(i\text{-}Pr)_2NEt/CH_2Cl_2$; (e)  /pH 8.5 phosphate buffer; (f)  /pH 8.5 phosphate buffer; (g)  /$(i\text{-}Pr)_2NEt/CH_2Cl_2$.



Scheme 2 (a) 37% aq $CH_2O/H_2O/Pt_2O$; (b)  /$(i\text{-}Pr)_2NEt/CH_2Cl_2$; (c)  /pH 8.5 phosphate buffer; (d) AcCl/DMF/TEA; (e) PNZ-L-ala-OSu/pH 8.5 phosphate buffer/dioxane; (f) EtCH=NH·HCl/pH 7.0 phosphate buffer.



Scheme 3 (a) $Tf_2O/Py/CH_2Cl_2$; (b) $MeNH_2$/*p*-Dioxane; (c) PNZCl/*i*-Pr_2NEt/CH_2Cl_2; (d) MsCl/TEA/CH_2Cl_2; (e) KSAc/DMF/Toluene; (f) NaOH/MeOH



Scheme 4 (a) **22**/*i*-Pr_2NEt/CH_3CN; (b) H_2/10%Pd on C/pH 6.0

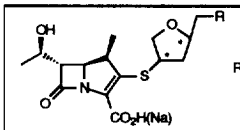
mono- and dipeptide derivatives, which were separated by reverse-phase chromatography.[1(b),2] The monopeptide derivatives can also be prepared by reaction of **1a** or **1b** with the PNZ-protected O-Su ester of an amino acid.[3] Thus, reaction of **1b** with the PNZ-protected O-Su ester of L-alanine gave monopeptide **14** and reaction of **14** with the PNZ-protected O-Su ester of L-alanine gave dipeptide **15**. Quarternary amine derivative **4** was obtained by exhaustive methylation of the carbapenem **1a** with dimethyl sulfate. The tertiary amine derivative **9** was prepared by reductive methylation of the carbapenem **1b**. These THF carbapenems are quite stable at room temperature between pH 6 and 8 with a half life of ca. 400 to ca. 200 h but their stability steeply declines outside of this range.[4] Therefore, the reactions in 0.1 M buffer solution (NaH_2PO_4-Na_2HPO_4) were carried out at 0 °C, particularly those at pH 8.5, and the reactions in methylene chloride were carried out at room temperature. The secondary amine derivative **1c** was prepared according to Schemes 3 and 4.

Results and Discussion

Imipenem, the formamidine derivative of thienamycin, retains the antibacterial spectrum of thienamycin and exhibits enhanced activity against *P. aeruginosa*.[5] However, formamidine derivatives **2**, **3**, and **12** were slightly less active against some microorganisms including *P. aeruginosa* than the parent compounds, **1a** and **1b**.

Table 1 **3,5-Disubstituted THF Carbapenems**

In vitro activity (MIC; μg/mL)



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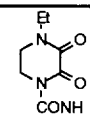


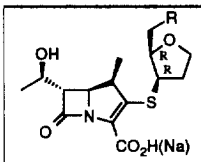
		NH_2	NHCH=NH	N=CHNMe$_2$	$^+NMe_3$		NHAc	NHCOCH$_2$-NHMe	NH-L-ala	imipenem
		1a	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
ORGANISM	Strain									
E. coli	ATCC 25922	≤ 0.06	≤ 0.06	0.12	0.25	2.00	≤ 0.06	≤ 0.06	≤ 0.06	0.12
E. coli	GC 2205	≤ 0.06	≤ 0.06	0.12	0.25	0.25	≤ 0.06	≤ 0.06	≤ 0.06	0.12
E. coli	GC 1792	0.06	≤ 0.06	0.12	0.25	4.0	0.12	≤ 0.06	≤ 0.06	≤ 0.06
E. cloacae	GC 2209	≤ 0.06	≤ 0.06	0.12	0.25	8.0	0.50	≤ 0.06	0.25	≤ 0.06
C. freundii	GC 2211	0.06	≤ 0.06	0.50	1.0	32	2.0	0.25	1.0	0.25
M. morganii	GC 2213	0.25	0.50	2.0	4.0	16	0.50	0.25	1.0	1.0
A. calcoaceticus	GC 756	1.0	2.0	16	16	128	8.0	2.0	8.0	0.25
P. aeruginosa	ATCC 27853	4.0	8.0	16	32	>128	64	32	32	1.0
P. aeruginosa	GC 1544 OprD-	8.0	16	32	64	128	128	32	64	16
X. maltophilia	GC 562	>128	>128	>128	>128	>128	>128	>128	>128	>128
S. aureus	ATCC 29213	≤ 0.06	≤ 0.06	0.12	0.12	0.50	0.12	≤ 0.06	0.12	≤ 0.06
S. aureus	GC 2220 MRSA	8.0	8.0	16	16	32	16	16	8.0	1.0
E. faecalis	GC 842	2.0	2.0	8.0	8.0	16	8.0	4	4.0	1.0
E. faecium	GC 1182	128	128	>128	>128	>128	>128	>128	>128	64
Rel. hydrolysis by hog DHP		19	NT**	NT	NT	13	4	NT	10	100

* Diastereomers

** Not tested

Table 2 **2R,3R-Disubstituted THF Carbapenems**

In vitro activity (MIC; μg/mL)



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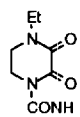

		NH_2	NHMe	NMe_2		NH-D-ala	NHCH=NH	NHAc	NH-L-ala	(NH-L-ala)$_2$
		1b	**1c**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
ORGANISM	Strain									
E. coli	ATCC 25922	≤ 0.06	≤ 0.06	0.03	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06
E. coli	GC 2205	≤ 0.06	≤ 0.06	0.06	≤ 0.06	≤ 0.06	0.12	≤ 0.06	≤ 0.06	0.12
E. coli	GC 1792	≤ 0.06	≤ 0.06	0.06	≤ 0.06	0.12	≤ 0.06	0.12	≤ 0.06	≤ 0.06
E. cloacae	GC 2209	≤ 0.06	≤ 0.06	≤ 0.12	≤ 0.06	0.25	≤ 0.06	0.50	0.25	2.0
C. freundii	GC 2211	≤ 0.06	0.12	0.25	0.12	1.0	0.50	2.0	1.0	8.0
M. morganii	GC 2213	0.50	0.50	0.50	0.50	1.0	1.0	0.50	1.0	2.0
A. calcoaceticus	GC 756	2.0	4.0	4.0	2.0	8.0	8.0	16	16	32
P. aeruginosa	ATCC 27853	8.0	8.0	16	16	64	16	128	32	64
P. aeruginosa	GC 1544 OprD-	16	32	32	32	64	32	>128	64	>128
X. maltophilia	GC 562	>128	>128	>128	>128	>128	>128	>128	>128	>128
S. aureus	ATCC 29213	≤ 0.06	≤ 0.06	0.06	≤ 0.06	≤ 0.06	≤ 0.06	0.12	0.12	1.0
S. aureus	GC 2220 MRSA	1.0	1.0	4.0	8.0	8.0	4.0	16	8.0	64
E. faecalis	GC 842	0.50	0.50	1.0	4.0	2.0	2.0	8.0	4.0	4.0
E. faecium	GC 1182	64	>64	64	>128	>128	128	>128	>128	>128
Rel. hydrolysis by hog DHP		8.5	10	7.5	9	3	18	4	12	13

Protein OprD of the *P. aeruginosa* outer membrane is known to facilitate the specific permeation of some amino acids such as lysine and arginine across this membrane barrier.[6] Since imipenem resembles some of these amino acids, it can use the protein OprD to go through the outer membrane of *P. aeruginosa*. However, mono- and dipeptide derivatives **7**, **8**, **11**, **14**, and **15** had poor anti-pseudomonas activity due to poor uptake through OprD protein channel and against other microorganisms they were less active than the parent compounds, **1a** and **1b**. The anti-pseudomonas activity of piperacillin is due to the presence of the 4-ethyl-2,3-dioxo-1-piperazinecarboxamido moiety,[7] but derivatives, **5** and **10**, containing the piperacillin side chain did not demonstrate anti-pseudomonas activity. Acyl derivatives, **6** and **13**, also did not demonstrate anti-pseudomonas activity. Methylation (compound **1c**) slightly decreased the antimicrobial activity against Gram-negative bacteria and dimethylation (compound **9**) further decreased the antimicrobial activity. Quaternary derivative **4** was also less active than the parent compound **1a**.

None of the compounds exhibited acceptable activity against methicillin-resistant *S. aureus* (GC 2220); 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 due to the presence of the 1β-methyl moiety.

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