Bioorganic & Medicinal Chemistry Letters, Vol.3, No.11, pp. 2187-2192, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

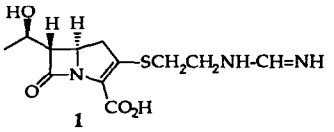
THE SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 2-PARA-QUATERNARY AMMONIOMETHYLPHENYL-CARBAPENEMS.**

Frank DiNinno,* David A. Muthard, and Thomas N. Salzmann
Merck Research Laboratories
Department of Synthetic Chemical Research
PO Box 2000
Rahway, New Jersey 07065

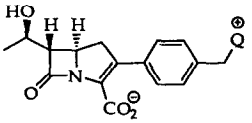
(*Received* 1 *April* 1993)

Abstract: The synthesis and *in vitro* antibacterial activity of 2-phenylcarbapenems bearing a spacer linked heteroaromatic or heterocyclic quaternized moiety are discussed. In general, this class of antibiotics was found to possess antibacterial activity superior to the parent natural product, thienamycin, except for *Ps. aeruginosa*, and were less susceptible to degradation by the DHP-I enzyme.

The clinical success of Primaxin,®[1] a product of these laboratories which is comprised of the first broad spectrum carbapenem antibiotic, imipenem (**1**), and cilastatin, a DHP-I inhibitor, has generated enormous commercial interest to improve on its properties. Currently, no less than three new carbapenems, panipenem,[2] meropenem,[3] and biapenem,[4] are undergoing clinical trials as parenterally administered, broad spectrum antibiotics. Like the parent, natural product thienamycin,[5] all of these derivatives possess a sulfur atom at C-2 of the carbapenem nucleus and thus this area has received extensive investigation.[6] In contrast, relatively few studies have been reported which focus on analogous carbon based substituents,[7] and only the most recently disclosed class of tricyclic carbapenems, known as tribactams,[8] exemplify C-2 carbon systems which have led to a clinical candidate; GV104326[9] and the hexetil ester, GV118819,[10] are reportedly under development as an injectable and orally absorbable antibiotic, respectively. In this report, attention is again drawn to the virtues of 2-arylcarbapenems,[7a] for potential use in antimicrobial therapy, as chemically and metabolically stable, highly active representatives of the class.



1

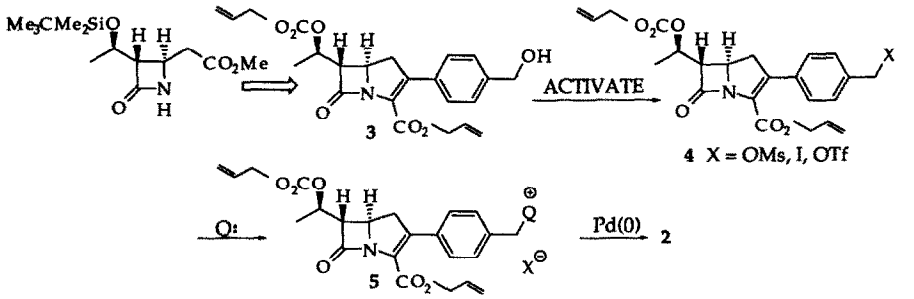


2a Q = NH_3
2b Q = NH-CH=NH_2

As part of our continuing effort to further exploit the unparalleled, intrinsic activity of the carbapenem nucleus,[11] our attention became focused on 2-phenylcarbapenems (**2**) which possess a cationic moiety at a benzylic position. Compounds of this type include the parent amine[7a] **2a** and the analogous formamidine derivative[12] **2b**, which have been shown to exhibit markedly improved *in vitro* potency (except for *Ps. aeruginosa*) and DHP-I (porcine) stability over thienamycin. We sought to extend the nature of the charged center to include heterocyclic

and heteroaromatic derived quaternary moieties, already commonplace in cephalosporin research and also reported in a similarly related series of penems,[13] with the hope of finding an exquisitely active derivative that might serve as a clinically and cost effective alternative for Cefoxitin.®

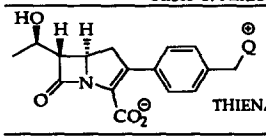
SCHEME

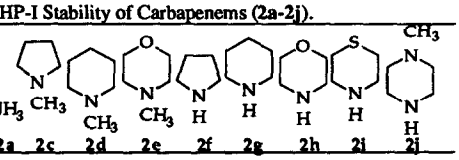


The general approach to the synthesis of molecules **2** is outlined in the Scheme in which the key doubly protected carbapenem synthon **3** [14] was prepared by a modification of the route detailed by Guthikonda.[7f] Suitable activation of the hydroxyl group of **3** allowed for ready displacement at the benzylic center by nucleophiles, Q, to afford stable salts **5**. Typically, two primary modes of activation were employed: first, conversion of the alcohol **3** to the corresponding mesylate **4** (X=OMs) was accomplished by the procedure of Crossland and Servis,[15] (MsCl, Et_3N, 0°C, CH_2Cl_2) which in turn, was converted to the more reactive iodide derivative **4** (X=I) via the Finkelstein reaction (NaI, acetone, 0°C). Secondly, with nucleophiles that were compatible with triflic anhydride, the alcohol in CH_2Cl_2 solvent, at ice-water bath temperatures, was treated with 2.2 equivalents of the nucleophile and triflic anhydride to directly afford **5**, presumably *via* the intermediacy of the *in situ* formed, highly reactive benzyl triflate **4** (X=OTf) which was not detected. Displacement reactions of iodide **4** were usually performed in acetonitrile at ambient temperature. With sluggish nucleophiles, a rate enhancement could be achieved by the addition of silver triflate to yield triflate salts **5** and silver iodide. Finally, the removal of the two allyl derived protecting groups was simultaneously accomplished by the palladium(0) catalyzed method of McCombie and Jeffrey[16] to provide the target class **2**. Generally, compounds **5** in mixtures of CH_2Cl_2 and EtOAc, at room temperature or below, were exposed to 1.1 equivalents each of 2-ethyl hexanoic acid and its potassium salt in the presence of 60 mole% triphenylphosphine and 20 mole% tetrakistriphenylphosphine palladium(0) in an inert atmosphere and aged for 3-5 hours. In most cases, rapid precipitation was observed, however, it was initially determined that premature collection of the precipitate gave mixtures of products **2** and partially deprotected carboxylate intermediate.

Our initial experiments utilized heterocyclic bases such as N-methyl pyrrolidine, piperidine, and morpholine, which gave high yields of salts **5** employing the triflic anhydride *in situ* activation procedure. Subsequent deprotections provided derivatives **2c-2e** in 30-40% isolated yields after purification by reverse phase chromatography. Although this type of charged arylcarbapenem, commonly referred to as a "hard quat", also possessed potent *in vitro* activity (Table 1), especially against the *Enterococcus*, *Serratia* , and *Proteus* species, they exhibited unacceptable

Table 1. Antibacterial Activity and DHP-I Stability of Carbapenems (2a-2j).





Organisms	MIC (μg/ml)[c]	THIENAMYCIN	IMIPENEM 1	2a	2c	2d	2e	2f	2g	2h	2i	2j
				Relative Potency, Thienamycin = 1[a]								
S. aureus (4)	0.03		1.8	1.5	0.9	0.8	0.8	0.6	0.6	0.6	0.9	0.4
Enterococcus (3)	3.6		1.5	9.2	13.9	14.9	10.6	12.1	6.1	8.6	9.2	5.7
E. coli (5)	0.37		1.6	3.5	3.2	5.3	2.0	2.8	2.5	3.5	2.3	3.0
Enterobacter (6)	0.67		1.8	11.0	7.5	8.0	5.7	5.7	4.0	5.3	3.2	4.9
Klebsiella (5)	0.88		1.5	3.2	2.6	1.9	2.3	2.1	1.4	1.4	1.3	1.0
Serratia (2)	0.93		1.8	5.3	26.0	11.3	7.5	9.8	5.7	8.0	7.5	7.0
Proteus (5)	1.9		1.6	6.5	8.6	9.8	6.1	8.0	8.6	10.6	7.0	9.2
Pseudomonas (5)	1.79		4.0	0.02	0.03	0.03	0.02	0.07	0.05	0.03	0.03	0.04
DHP - I Susceptibility[b]	1.0		0.85	0.02	0.03	0.03	0.02	0.04	0.03	0.13	0.13	0.12

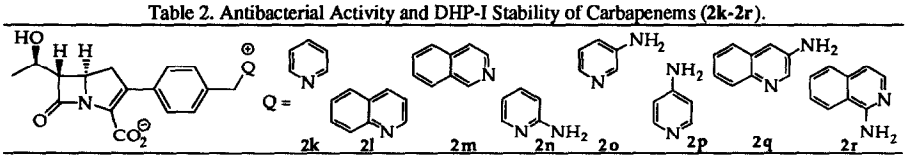
[a] Agar disc diffusion assay. Activities are relative to thienamycin and are expressed as indices derived from the indicated number of strains in each species. See ref. 7f. [b] DHP-I (porcine) susceptibility is given relative to imipenem = 0.85. See ref. 19. [c] MIC of thienamycin is given as reference.

levels of acute toxicity in mice,[17] which precluded further investigation. In contrast, the analogous heterocyclic amines provided zwitterionic counterparts **2f-2j** that offered a greater degree of safety and exhibited similar antimicrobial activity, as also evidenced in Table 1. It was interesting to note in this series of derivatives that introduction of a heteroatom into the nitrogen containing heterocycle **2h-2j** led to an increase in susceptibility of the carbapenem to the DHP-I enzyme.

Concurrent with this exploration was the use of heteroaromatic bases such as pyridine and the quinolines, which were more extensively studied as a result of the improved Gram positive and *Serratia* spp. activities, as shown in Table 2, and the absence of acute toxicity effects. These compounds **2k-2m** were readily prepared from iodide **4** and small excesses of nucleophiles. Similarly prepared were pyridinium, quinolinium, and isoquinolinium compounds **2n-2r**

possessing a ring substituted amino group which in some cases (**2n, 2p, 2r**) participated in charge dispersal through conjugation. As can be seen from the activity reported in Table 2, the

Table 2. Antibacterial Activity and DHP-I Stability of Carbapenems (**2k-2r**).

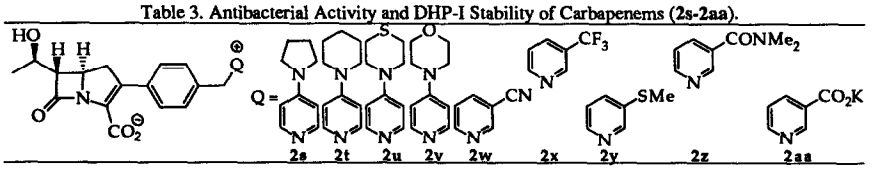


Organisms	Relative Potency, Thienamycin = 1[a]							
S. aureus (4)	1.3	1.5	1.3	1.3	2.3	1.1	1.9	1.3
Enterococcus (3)	13.0	24.3	24.3	21.1	17.1	24.3	12.1	9.2
E.coli (5)	3.5	6.1	7.5	2.8	7.5	7.0	3.7	2.7
Enterobacter (6)	7.0	8.6	11.3	6.1	11.3	11.3	3.7	2.3
Klebsiella (5)	4.3	1.2	2.0	2.6	4.3	2.3	0.9	0.7
Serratia (2)	9.8	27.9	36.8	11.3	22.6	29.9	9.2	3.7
Proteus (5)	9.8	13.0	17.1	8.0	14.9	16.0	9.2	3.7
Pseudomonas (5)	0.1	0.07	0.07	0.08	0.1	0.2	0.05	0.05
DHP - I Susceptibility[b]	0.07	0.07	0.08	0.11	0.09	0.14	0.09	0.14

introduction of this substituent was most beneficial in the pyridine series, regardless of ring position and thereby charge delocalization. On the other hand, an overall less potent compound was the result in the quinoline series. Owing to this and a pronounced decrease in water solubility, this class of quats was not investigated further.Another slight decrease in the stability toward the DHP-I enzyme was noted for those derivatives **2n, 2p, 2r** in which the amino group was in conjugation with the charge on the ring nitrogen. This observation was further extended to a series of heterocyclicyl substituted pyridinium compounds **2s-2v** depicted in Table 3. Interestingly, in this instance the introduction of the heteroatom in the heterocycle(**2u-2v**) now caused a reversal of the previously noted effect and provided for a more DHP stable entity. Unfortunately, this benefit was offset by a general, significant drop in activity across the antibacterial spectrum. Other substituent effects are exemplified in Tables 3 and 4. In general, electron withdrawing substituents (**2w-2aa**) lead to a reduction in activity compared to the parent pyridinium compound, whereas alkyl (**2ab**) and substituted alkyl groups (**2ac-2ag**) gave varying results depending on the nature of the substituent. All of the compounds however, exhibited good enzymatic stability. Interestingly, the introduction of anionic functions such as carboxylate (**2aa**) and sulfonate (**2ad-2ae**) had a positive, pronounced effect on the activity against *Proteus* spp. Further, the introduction of a methylthiomethyl group at the C-3 position of the pyridine ring

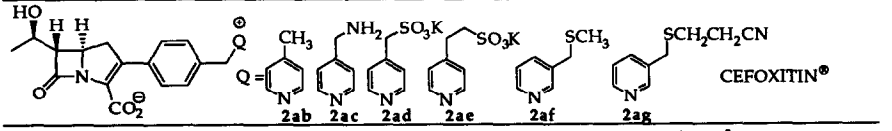
afforded a compound **2af** which exhibited a good balance of potent Gram positive and Gram negative activity along with DHP-I stability.

Table 3. Antibacterial Activity and DHP-I Stability of Carbapenems (**2s-2aa**).



Organisms	Relative Potency, Thienamycin = 1[a]								
S. aureus (4)	0.6	1.1	1.2	0.5	0.9	1.1	2.6	0.3	0.6
Enterococcus (3)	14.9	5.7	4.9	4.6	10.6	8.0	10.6	5.7	5.3
E. coli (5)	3.5	2.8	5.3	4.0	4.0	3.0	4.3	2.3	6.1
Enterobacter (6)	3.0	2.5	4.6	3.0	9.8	5.7	11.3	3.5	12.1
Klebsiella (5)	0.8	0.5	1.1	0.7	2.1	2.8	3.7	1.1	2.0
Serratia (2)	7.5	2.8	4.9	7.0	11.3	13.0	19.7	4.0	27.9
Proteus (5)	7.5	4.0	7.0	7.5	4.6	3.7	9.2	4.6	27.9
Pseudomonas (5)	0.04	0.05	0.04	0.03	0.1	0.05	0.08	0.04	0.08
DHP - I Susceptibility[b]	0.33	0.11	0.09	0.07	0.06	0.04	0.06	0.05	0.08

Table 4. Antibacterial Activity and DHP-I Stability of Carbapenems (**2ab-2ag**).



Organisms	Relative Potency, Thienamycin = 1[a]						
S. aureus (4)	1.1	0.5	0.5	0.4	1.9	1.0	0.03
Enterococcus (3)	14.9	7.0	3.5	4.3	19.7	8.0	0.06
E. coli (5)	4.6	1.7	6.5	5.7	6.1	8.0	0.1
Enterobacter (6)	9.2	2.6	9.2	7.0	10.6	8.6	0.03
Klebsiella (5)	2.8	0.8	1.6	1.1	3.7	4.6	0.04
Serratia (2)	22.6	6.1	9.8	10.6	29.9	14.9	0.3
Proteus (5)	12.1	4.3	9.8	17.1	6.5	7.0	0.6
Pseudomonas (5)	0.1	0.05	0.04	0.04	0.08	0.08	R
DHP - I Susceptibility[b]	0.06	0.04	0.5	0.06	0.05	0.05	R

It is apparent then that highly potent arylcarbapenems can be obtained by varying the nature of the appended quaternary ammonium group and in the heteroaryl type, the ring substituent. As previously denoted[18] it was not possible to restore the anti-pseudomonal activity of thienamycin

to this class of arylcarbapenems. However, a comparison of its activity with that of the cephalosporin, Cefoxitin® in Table 4 is striking. Thus it appears that further evaluation of this class is warranted and its extension will be the subject of future publications from these laboratories.

** Dedicated to Professor R. Marshall Wilson on the ocassion of his 25th service anniversary at the University of Cincinnati.

Acknowledgment. We would like to thank H. Kropp and his staff, J. Kahan, J. Huber, J. Sundelof, and L. Gerckens, for microbiological support and DHP-I susceptibility determinations, and G. Reynolds for the preparation of starting material.

References and Notes:

1. Kahan, F.; Kropp, H.; Sundelof, J. G.; & Birnbaum, J. *J. Antimicrob. Chemother.* **1983**, *12*(supp), 1.
2. Inoue, K.; Hamana, Y.; & Mitsuhashi, S. *Chemotherapy*(Tokyo) **1991**, *39*(Suppl. 3), 1.
3. Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; & Kato, M. *J. Antibiotics* **1990**, *43*, 519.
4. Petersen, P. J.; Jacobus, N. V.; Weiss, W. J.; & Testa, R. T. *Antimicrob. Agents Chemother.* **1991**, *35*, 203.
5. Kahan, J.S.;Kahan, F.M.;Goegelman, R.; Currie, S.A.; Jackson, M.; Stapley, E.O.; Miller, T.W.; Miller, A.K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H.B.; & Birnbaum, J. *J. Antibiotics*,**1979**, *32*, 1.
6. Ratcliffe, R. W. & Albers-Schonberg, G. *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R.B., & Gorman, M., Ed.;Academic Press, **1982**; Vol 2, pp 227-313.
7. a) Cama, L.D.; Wildonger, K. J.; Guthikonda, R.; Ratcliffe, R. W.; & Christensen, B. G. *Tetrehedron* **1983**, *39*, 2531; b) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, T.; & Sugawara, S. *J. Antibiotics*, **1984**, *37*, 57; c) Fujimoto, K.; Iwano, Y.; & Hirai, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1363; d) DeVries, J. G.;& Sigmund, G. *Tetrahedron Lett.* **1985**, *26*, 2765; e) Schmitt, S. M.; Salzmann, T. S.; Shih, D. H.; & Christensen, B. G. *J. Antibiotics* **1988**, *41*, 780; f) Guthikonda, R. N.; Cama, L. D., Quesada, M.; Woods, M. F., Salzmann, T. S.; & Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871; g) Wollmann, T. *Recent Advances in the Chemistry of Anti-Infective Agents*, Cambridge, England, July 5-8, **1992**.
8. Perboni, A. *Recent Advances in the Chemistry of Anti-Infective Agents*, Cambridge, England, July 5-8, **1992**.
9. Perboni, A.; Donati, D.; Rossi, T.; Tamburini, B.; Tarzia, G.; & Gaviraghi, G. 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, Ca., October 11-14, **1992**, Abstract #127; Di Modugno, E.; Hammond, S. M.; Xerri, L.; & Gaviraghi, G. *ibid*, Abstract #128; Lowther, J.; Di Modugno, E., Hammond, S. M.; Ratti, E.; & Gaviraghi, G. *ibid*, Abstract #129.
10. Hammond, S. M.; Di Modugno, E.; Lowther, J.; Xerri, L.; & Gaviraghi, G. *ibid*, Abstract #130.
11. Cama, L. & Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 8006; Shih, D. H.; Hannah, J.; & Christensen, B. G. *ibid*, 8004; Sykes, R. B.; *J. Antibiotics* **1982**, *35*, 653.
12. Cama, L., unpublished results.
13. Perrone, E.; Alpegiani, M.; Bedeschi, A.; Giudici, F.; Zarini, F.; Franceschi, G.; Della Bruna, C.; Jabes, D.; & Meinardi, G. *J. Antibiotics*, **1987**, *40*, 1636.
14. All new compounds exhibited spectroscopic properties consistent with the structures given.
15. Crossland, R. K. & Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
16. Jeffrey, P. D. & McCombie, S. W. *ibid* **1982**, *47*, 587.
17. Sundelof, J. and Kropp, H., unpublished results.
18. Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; & Christensen, B. G. *Pure & Appl. Chem.* **1987**, *59*, 455.
19. Kropp, H.; Sundelof, J.; Hajdu, R.; & Kahan, F.M. *Antimicrob. Agents Chemother.* **1982**, *22*, 62.