PROPERTIES OF MM 13902 AND OTHER CARBAPENEM ANTIBIOTICS *IN VITRO* AND *IN VIVO*

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The carbapenem antibiotics, which include the olivanic acids and the thienamycins, have a broad-spectrum of antibacterial activity but only thienamycin itself shows appreciable activity against *Pseudomonas aeruginosa*. The zwitterionic nature of thienamycin was reproduced in the olivanic acid series by preparing the deacetyl derivatives of MM 17880 and MM 22380 — compounds NA 26975 and NA 26978. The latter derivative showed anti-pseudomonas activity and had an antibacterial spectrum similar to thienamycin itself. In contrast the *O*-sulfated analogue, NA 26975, was no more active than the parent compound against *P. aeruginosa*. Both deacetyl compounds were more stable than the parent natural products to a mouse kidney enzyme preparation and gave higher urinary recoveries in the mouse.

Pharmacokinetic studies with MM 13902 in various animal species showed that the compound was rapidly eliminated from the blood and gave only low urinary recoveries. Similar findings were observed also in human volunteers given MM 13902. The nephrotoxicity reported for thienamycin/MK 0787 in the rabbit was not seen with the olivanic acids MM 13902, MM 17880, MM 22382 and MM 22383 when tested under the same conditions.

Over thirty naturally occurring β-lactam compounds based on the carbapenem ring system have now been reported. These include the olivanic acids[1,2], thienamycin and the epithienamycins[3,4], the PS-5 series of compounds[5,6], the carpetimycins[7,8], and the asparenomycins[9]. As a rule the carbapenems are broad-spectrum antibiotics that are stable to a wide range of bacterial β-lactamases. However, as part of our evaluation programme, we have shown that most of the compounds are readily degraded by animal kidney homogenates, and recently, workers at Merck Sharp & Dohme have reported that this degradation is caused by a kidney enzyme, renal dipeptidase-1[4]. As a result of this metabolism, carbapenem antibiotics give only low urinary recoveries *in vivo*[4,9]. Further studies on thienamycin and its *N*-formimidoyl derivative have shown that the compounds are nephrotoxic in the rabbit and, like cephaloridine, large doses cause significant increases in levels of blood urea nitrogen (BUN) and serum creatinine[10].

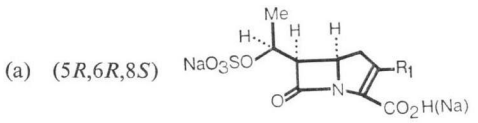
A previous publication[11] compared the properties of some of the carbapenem antibiotics *in vitro* with emphasis on the structure activity relationships between the olivanic acids and the thienamycins. Further studies on these compounds including their stability to a mouse kidney enzyme preparation; the urinary recovery obtained in the mouse and behaviour in the rabbit nephrotoxicity test are reported here. In addition some *in vivo* properties of MM 13902 in other animal species and the data obtained in human volunteers are described.

Materials and Methods

Compounds

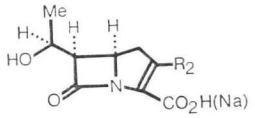
The naturally occurring olivanic acids were prepared by fermentation of *Streptomyces olivaceus*

Fig. 1. Structure of carbapenem antibiotics.



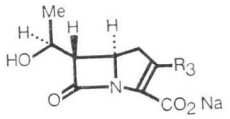
(a) (5*R*,6*R*,8*S*)

Compound	R_1
MM 4550	$-SCH=CHNHCOCH_3$ (t, ^+S)
MM 13902	$-SCH=CHNHCOCH_3$ (t)
MM 17880	$-SCH_2CH_2NHCOCH_3$
NA 26975A	$-SCH_2CH_2NH_2$



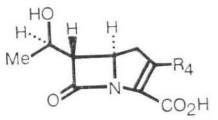
(b) (5*R*,6*R*,8*S*)

Compound	R_2
MM 22380	$-SCH_2CH_2NHCOCH_3$
MM 22382	$-SCH=CHNHCOCH_3$ (t)
NA 26978	$-SCH_2CH_2NH_2$



(c) (5*R*,6*S*,8*S*)

Compound	R_3
MM 22381	$-SCH_2CH_2NHCOCH_3$
MM 22383	$-SCH=CHNHCOCH_3$ (t)



(d) (5*R*,6*S*,8*R*)

Compound	R_4
Thienamycin	$-SCH_2CH_2NH_2$
N-Acetyldehydro-thienamycin	$-SCH=CHNHCOCH_3$ (t)
N-Formimidoyl thienamycin (MK 0787)	$-SCH_2CH_2N=C(H)-NH_2$

ATCC 31365 as described previously[1,2]. Compounds NA 26975A and NA 26978A were prepared in our Research Laboratories from MM 17880 and MM 22380 respectively as described previously[12,13]. Thienamycin was a gift from Dr. J. BIRNBAUM of Merck Sharp and Dohme Research Laboratories. The compounds described in this paper are shown in Fig. 1.

Minimum Inhibitory Concentrations (MIC)

The MIC values of the test compounds were determined in broth in microtitre trays as described previously[11].

Crude Kidney Enzyme Preparation

Mouse kidneys were sliced into small pieces and suspended in 0.05 M 3-(*N*-morpholino)propane sulfonic acid (MOPS) buffer at pH 7.0. The suspension was homogenized for 3 periods of 30 seconds with 30-second intervals, using an IKA Ultra-Turrax TP 18/2 homogeniser (Janke and Kuntzel, IKA Products, Belmont, Surrey, England). The homogenate was submitted to ultrasonication using an MSE 100 watt Ultrasonic disintegrator (MSE Scientific Instruments, Crawley, Sussex, U.K.) for a total of 90 seconds in 3 equal periods with a 30-second interval between each treatment. Both the homogenization and ultrasonication were performed in iced water. The sonicated tissue was centrifuged at 2,200× *g* for 15 minutes and the supernatant fluid used as the crude enzyme preparation and stored at −20°C. The concentration of kidney enzyme was adjusted to give a standard rate of degradation of MM 13902.

Stability Assay

Reaction mixtures containing 0.2 ml of test compound (or MM 13902) at 200 μg/ml and 0.2 ml kidney enzyme preparation (or MOPS buffer alone) were prepared. Samples (20 μl) were removed at time 0 and at frequent intervals during incubation at 37°C and assayed without further treatment for residual antibiotic by high performance liquid chromatography (HPLC). The HPLC was carried out using a Waters 6000A pump, U6K injector and reverse phase C18 μ-Bondapak Column (Waters Associates Ltd., Northwich, U.K.). A guard column packed with CO-pell ODS (Whatman Chemical Separation Division, Maidstone, Kent, U.K.) was included to prolong column life. The compounds were detected at 300 nm by a Cecil 212 UV spectrophotometer (Cecil Instruments, Cambridge, U.K.) using an 8 μl flow cell with a 10-mm path length which was linked to a potentiometric chart recorder.

The column eluant was based on 0.05 M ammonium dihydrogen phosphate buffer (pH 4.7) containing from 3~10% acetonitrile and pumped at 1.5~2 ml/minute. The concentration of acetonitrile in the mobile phase and the flow rate were adjusted to give a retention time for the test compound of about 4 minutes. At the wavelength used there was little interference from other UV-absorbing components in the kidney preparation.

The stability of MM 13902 was arbitrarily assigned the value 1.0 and the stability of the test compound was expressed as the rate of inactivation of test compound (μg/ml/minute) divided by the rate of inactivation of MM 13902 (μg/ml/minute). Thus, compounds having a stability figure of >1.0 were proportionally more stable than MM 13902 and *vice versa*.

Plasma Levels and Urinary Recoveries in Animals

Mice: MM 13902 was dosed subcutaneously at 50 mg/kg to groups of five male MF-1 strain albino mice (19~21 g). Blood was collected in heparinised tubes at various time intervals after dosing and centrifuged at 12,000$\times g$ for 1 minute. Antibiotic concentrations were determined by microbiological assay using *Bacillus subtilis* against standards prepared in normal mouse plasma. To determine urinary recovery, six groups of five mice were dosed orally with 1 ml water and given 50 mg/kg of test compound by subcutaneous injection. Urine was collected over 0~1 hour, 1~2 hour and 2~4 hour periods and assayed against standards prepared in 0.05 M phosphate buffer.

Rats: MM 13902 was administered subcutaneously at 100 mg/kg to six male Sprague-Dawley rats (130~150 g). Blood was collected from the tail vein and treated as described above. Six rats were given 5 ml water orally and a dose of MM 13902 subcutaneously for the urinary recovery experiment.

Rabbits: MM 13902 was dosed subcutaneously at 100 mg/kg to five New Zealand White rabbits (2.1~2.5 kg). Blood was collected from the marginal ear vein and treated as described previously. To determine urinary recovery three rabbits were dosed orally with 20 ml water followed by a subcutaneous injection of MM 13902.

Dogs: MM 13902 was administered intramuscularly at 50 mg/kg to one male and one female beagle (9.5 kg). Blood was collected from a leg vein and treated as described previously. Urinary recovery was determined in 1 beagle dog which was given 300 ml water orally prior to an intramuscular injection of MM 13902. Urine was collected by catheterization at 1 hour and 2 hours after dosing.

Squirrel Monkeys: Two male and two female squirrel monkeys (600~1,000 g) were dosed subcutaneously with MM 13902 at 25 mg/kg. Blood was collected from a leg vein and treated as described previously. Urinary recovery was determined in three male and three female monkeys which were given 10 ml water orally followed by a subcutaneous injection of MM 13902. Urine was collected at 0~1 hour, 1~3 hours and 3~5 hours after dosing.

Human Volunteer Studies

Doses of MM 13902 of 25 mg, 50 mg, 125 mg and 250 mg were injected intramuscularly into the outer quadrant of the gluteus maximus to groups of three healthy volunteers. All the people participating in the studies were male, aged between 18 and 45 years. Any people with known penicillin hypersensitivity or who had received medication within the previous seven days were excluded from the study. The concentrations of MM 13902 in serum and urine samples were determined by microbiological assay against *B. subtilis* ATCC 6633.

Serum Binding Determination

Solutions of MM 13902 (10 μg/ml) were prepared in sterile serum from various animal species and also in pooled human serum. These solutions were subjected to centrifugal ultrafiltration through Amicon Centriflo CF50A membrane cones (Amicon Ltd., Woking, Surrey, U.K., and the concentration of antibiotic in the ultrafiltrate determined by bioassay.

Nephrotoxicity Studies

The olivanic acids MM 13902, MM 17880, MM 22382 and MM 22383, and cephaloridine were administered subcutaneously at 180 mg/kg to groups of four New Zealand White rabbits (1.5~2.9 kg). Blood was removed from the marginal ear vein immediately prior to dosing and again after 48 hours. The samples were centrifuged at 1,700$\times g$ for 15 minutes, and the concentrations of urea and

creatinine in the sera were examined using the appropriate test kits (Boehringer Corporation (London) Ltd., Lewes, Sussex, U.K.).

Results

Activity *In Vitro*

The activity of the naturally occurring carbapenems MM 17880 and MM 22380 and the corresponding deacetyl derivatives NA 26975 and NA 26978 are shown in Table 1. The results show that deacetylation of MM 22380 led to improved activity against *Pseudomonas aeruginosa,* a strain of *Escherichia coli* producing R-TEM β-lactamase and the Gram-positive cocci tested. Indeed the antibacterial spectrum and potency of NA 26978 closely resembled that of thienamycin. In contrast compound NA 26975 (deacetyl MM 17880) was not active against *P. aeruginosa* although it showed slightly improved Gram-positive activity compared to the parent compound.

Table 1. Activity *in vitro* of some naturally occurring carbapenems and their deacetyl analogues.

Organism	MIC (μg/ml)				
	MM 17880	NA 26975	MM 22380	NA 26978	Thienamycin
Escherichia coli (amp[a]-sensitive)	0.2	0.2	0.2	0.4	0.2
E. coli (amp-resistant, R-TEM)	0.8	0.4	25	0.8	0.4
Klebsiella pneumoniae	0.4	0.4	0.8	0.4	0.4
Proteus mirabilis	0.4	0.8	0.8	1.6	3.1
Pseudomonas aeruginosa	100	100	>100	3.1	3.1
Staphylococcus aureus	1.6	0.4	0.4	0.08	0.04
Streptococcus faecalis	6.2	3.1	1.6	0.8	1.6

[a] Ampicillin.

Stability to a Mouse Kidney Preparation and Recovery in Mouse Urine

The rate of degradation of MM 13902 in the presence of mouse kidney was determined by HPLC. It was found that a 100 μg/ml solution lost potency at a rate of 1.5 μg/ml/minute when incubated in a 1% crude enzyme preparation at 37°C. This rate of degradation was assigned as arbitrary value of 1.0 and the stability of other carbapenem antibiotics relative to MM 13902 is shown in Table 2. It will be seen that the other sulfated derivatives, MM 4550 and MM 17880, and the (6*S*, 8*S*)-hydroxyl compounds, MM 22381 and MM 22383, were either similar to or slightly more stable than MM 13902 whereas the (6*R*, 8*S*)-hydroxyl compounds, MM 22380 and MM 22382, were less stable. The deacetyl analogues NA 26975, NA 26978 and thienamycin on the other hand were from five to seven-fold more stable than MM 13902.

Table 2. Stability of carbapenems in mouse kidney homogenate and percentage recovered in mouse urine.

Compound	Stability relative to MM 13902 in 1% mouse kidney	% Urinary recovery 0~4 hours
MM 13902	1.0	1.3
MM 4550	1.2	0.9
MM 17880	1.7	1.9
NA 26975	5.0	8.0
MM 22380	0.5	0.7
NA 26978	7.2	10.2
MM 22381	1.4	0.7
MM 22382	0.1	0.2
MM 22383	1.9	0.7
Thienamycin	6.7	25[a]

[a] Value reported in the reference 4.

The urinary recoveries of the test compounds after subcutaneous administration to mice are

Table 3. Some pharmacokinetic parameters of MM 13902 in animal species and in human volunteers.

Species	Dose (mg/kg) and route	Mean concentration (μg/ml) at minutes after dose							$T_{1/2\beta}$ (minutes)	% Unbound in serum/plasma	% Urinary recovery
		5	15	30	45	60	90	120			
Mouse	50 s.c.	9.2	2.4	<0.3	—	—	—	—	4.5	60	1.3
Rat	100 s.c.	24.2	8.9	2.4	1.9	<1.0	—	—	10.6	43	7.2
Rabbit	100 s.c.	—	30	16	10.4	7.5	3.6	2.1	31	43	3.5
Dog	50 i.m.	—	13.3	10.6	7.8	4.9	2.1	1.0	27	53	0.3
Squirrel monkey	25 s.c.	—	38.8	23.5	12.0	5.2	1.0	0.6	16.5	53	1.7
Human volunteers	250[a] i.m.	—	5.4	6.2	4.6	3.7	1.8	1.2	40.7	41	1.8

[a] Administered as a single 250 mg dose.

also shown in Table 2. Only 1% or less of the *N*-acetylated compounds was recovered in the urine whereas 8~10% of the dose of the deacetyl derivatives, NA 26975 and NA 26978, was obtained.

Pharmacokinetic Properties of MM 13902

The pharmacokinetic properties of MM 13902 have been studied in various animal species and the results obtained are shown in Table 3. It can be seen that in the mouse the compound produced low levels and was rapidly eliminated ($t_{1/2}$=4.5 minutes). Somewhat higher and more persistent levels were found in the rat, rabbit, dog and squirrel monkey, and in these species the elimination half-lives were of the order 11~30 minutes. The urinary recovery of MM 13902 in animals was low and ranged from 0.3% in the dog to 7% in the rat. The binding of MM 13902 to serum proteins of the test species was about 50%.

Single doses of MM 13902 of 25 mg, 50 mg, 125 mg and 250 mg were administered intramuscularly to human volunteers and the serum levels obtained at the top dose are shown in Table 3. The peak level (6.0 μg/ml) occurred at 30 minutes, thereafter the levels decreased to 1.2 μg/ml at 2 hours. The elimination half-life at this dose was 40 minutes. As was found in experimental animals, the percentage urinary recovery in man was low. The mean value obtained during the study was 1.8% with a range of between 0.1% and 5.3%.

Nephrotoxicity Studies

The effects of a large intravenous dose of the olivanic acids or of cephaloridine on kidney function as estimated by the levels of blood urea nitrogen and serum creatinine in the rabbit are illustrated in Table 4. The results show that cephaloridine gave significant evidence of nephrotoxicity whereas the olivanic acids MM 13902, MM 17880, MM 22382 and MM 22383 gave no such effects.

Table 4. Effects of olivanic acids or cephaloridine on rabbit BUN or serum creatinine levels.

Test compound*	Mean values after 48 hours		
	No. of animals	BUN (mg/100 ml)	Creatinine (mg/100 ml)
Saline (Control)	6	20.1	1.2
Cephaloridine	4	82.5 s	3.7 s
MM 13902	4	14.5 NS	1.1 NS
MM 17880	4	31.2 NS	1.5 NS
MM 22382	3	19.1 NS	1.0 NS
MM 22383	4	20.5 NS	1.4 NS

s=Statistically significantly different ($p=<0.05$) from control.

NS=Not significantly different from control.

* Dosed intravenously at 180 mg/kg.

Discussion

Of the large number of naturally occurring carbapenem antibiotics that have now been reported, only thienamycin has appreciable activity against *P. aeruginosa*. The structural feature of thienamycin conferring anti-pseudomonas activity is the aminoethyl side chain which is acetylated in the other compounds. The aminoethyl analogue of MM 22380 has been prepared (NA 26978) and, like thienamycin, the compound was active against *P. aeruginosa*. However, when other ionic functions were present in NA 26978, for example the *O*-sulfate grouping (as in NA 26975) then anti-pseudomonas activity was no longer observed. Both deacetyl derivatives were more active than corresponding *N*-acetylated compounds, MM 22380 and MM 17880, against Gram-positive bacteria.

In addition to showing improved antibacterial activities, compounds with an aminoethylthio C-3 substituent were more stable than the corresponding *N*-acyl analogues to the renal dipeptidase enzyme. The improved tissue stability values could be correlated with a greater urinary recovery in the mouse. For example, 8~10% of a dose of NA 26975 or NA 26978 was recovered in the urine whereas only 1% or less of the *N*-acetylated parents was obtained. The results obtained with MM 22380 and NA 26978 *in vitro* and *in vivo* agree with those reported by STAPLEY *et al.*[4] for epithienamycin A and its deacetyl derivative. These workers showed also that thienamycin itself gave a mouse urinary recovery of 25% which is in keeping with the tissue stability value that we obtained for the compound (Table 2).

The peak blood levels of MM 13902 in the various animal species were low and the compound was rapidly eliminated. In addition only low urinary recoveries were obtained suggesting that the antibiotic is extensively metabolised *in vivo*. This pattern of rapid elimination and extensive metabolism in animals has been reported previously for thienamycin, however with this compound the corresponding urinary recovery values were higher than those obtained for MM 13902[14].

As was found in experimental animals, blood levels of MM 13902 in human volunteers were low and of short duration. These pharmacokinetic parameters are perhaps disappointing compared with many currently available β-lactam antibiotics but are similar to those reported for intramuscular cefoxitin[15]. The low urinary recovery of MM 13902 in man was also predictable from the animal experiments. The only other carbapenem antibiotic for which human data are available is the thienamycin derivative MK 0787. Pharmacokinetic studies have been reported following intravenous administration and show that MK 0787 was eliminated slightly less rapidly than MM 13902 ($t_{1/2}$=1.0 hour) and was less extensively degraded with 6~31% of the dose being recovered in the urine[16].

A recent Merck patent[10] has reported that large doses of thienamycin and MK 0787 cause kidney damage in the rabbit and claim that this nephrotoxicity is significantly reduced when the compounds are co-administered with a renal dipeptidase inhibitor. The effect may not be associated with all carbapenem compounds as the olivanic acids MM 13902, MM 17880, MM 22382 and MM 22383 do not cause signs of acute nephrotoxicity under the same conditions. It is of some interest that MM 22383, the (8*S*)-isomer of *N*-acetyldehydrothienamycin gave a negative result, as this would indicate that the toxicity of MK 0787/thienamycin is possibly associated with either the (8*R*)-hydroxyethyl moiety or the basic nature of the amino/amidine C-3 substituent.

Previous studies[11] showed that the antibacterial spectrum of MM 13902 *in vitro* compared favourably with the third generation cephalosporins. These data on the other hand show that the pharmacokinetic properties of the compound are less attractive.

Acknowledgments

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References

1) HOOD, J. D.; S. J. BOX & M. S. VERRALL: Olivanic acids, a family of β-lactam antibiotics with β-lactamase inhibitory properties produced by *Streptomyces* species. II. Isolation and characterisation of the olivanic

acids MM 4550, MM 13902 and MM 17880 from *Streptomyces olivaceus*. J. Antibiotics 32: 295~304, 1979

2) Box, S. J.; J. D. Hood & S. R. Spear: Four further antibiotics related to olivanic acid produced by *Streptomyces olivaceus*: Fermentation, isolation, characterisation and biosynthetic studies. J. Antibiotics 32: 1239~1247, 1979
3) Kahan, J. S.; F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff & J. Birnbaum: Thienamycin, a new β-lactam antibiotic. I. Discovery, taxonomy, isolation and physical properties. J. Antibiotics 32: 1~12, 1979
4) Stapley, E. O.; P. J. Cassidy, J. Tunac, R. L. Monaghan, M. Jackson, S. Hernandez, S. B. Zimmerman, J. M. Mata, S. A. Currie, D. Daoust & D. Hendlin: Epithienamycins — Novel β-lactams related to thienamycin. I. Production and antibacterial activity. J. Antibiotics 34: 628~636, 1981
5) Okamura, K.; S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimauchi, K. Kouno, T. Ishikura & J. Lein: PS-5, a new β-lactam antibiotic from *Streptomyces*. J. Antibiotics 31: 480~482, 1978
6) Sakamoto, M.; H. Iguchi, K. Okamura, S. Hori, Y. Fukagawa & T. Ishikura: PS-5, a new β-lactam antibiotic. II. Antimicrobial activity. J. Antibiotics 32: 272~279, 1979
7) Nakayama, M.; A. Iwasaki, S. Kimura, T. Mizoguchi, S. Tanabe, A. Murakami, I. Watanabe, M. Okuchi, H. Itoh, Y. Saino, F. Kobayashi & T. Mori: Carpetimycins A and B, new β-lactam antibiotics. J. Antibiotics 33: 1388~1390, 1980
8) Imada, A.; Y. Nozaki, K. Kintaka, K. Okonogi, K. Kitano & S. Harada: C-19393 S_2 and H_2, new carbapenem antibiotics. I. Taxonomy of the producing strain, fermentation and antibacterial properties. J. Antibiotics 33: 1417~1424, 1980
9) Kimura, Y.; K. Motokawa, H. Nagata, Y. Kameda, S. Matsuura, M. Mayama & T. Yoshida: Asparenomycins A, B and C, new carbapenem antibiotics. IV. Antibacterial activity. J. Antibiotics 35: 32~38, 1982
10) Merck: European Patent No. 28,778
11) Basker, M. J.; R. J. Boon & P. A. Hunter: Comparative antibacterial properties *in vitro* of seven olivanic acid derivatives: MM 4550, MM 13902, MM 17880, MM 22380, MM 22381, MM 22382 and MM 22383. J. Antibiotics 33: 878~884, 1980
12) Corbett, D. F.: Reaction of olivanic acids with hypobromous acid; The preparation and use of a versatile intermediate, the C-3 thiol. J. Chem. Soc., Chem. Commun. 1981: 803~805, 1981
13) Eglington, A. J.; D. F. Corbett & R. Southgate: Some reactions of the amide function in olivanic acid derivatives. North American Medicinal Chemistry Symposium, Toronto, 1982
14) Kropp, H.; J. G. Sundelof, R. Hajdu & F. M. Kahn: Metabolism of thienamycin and related carbapenem antibiotics by the renal dipeptidase, dehydropeptidase-1. Antimicrob. Agents Chemother. 22: 62~70, 1982
15) Kosmidis, J.; J. M. T. Hamilton-Miller, J. N. G. Gilchrist, D. W. Kerry & W. Brumfitt: Cefoxitin, a new semi-synthetic cephamycin: An *in vitro* and *in vivo* comparison with cephalothin. Bri. Med. J. 4: 653~658, 1973
16) Follarth, F.; A. M. Geddes, P. Spring, G. D. Ball, K. H. Jones, F. Ferber, J. S. Kahan & F. M. Kahan: Tolerability and pharmacokinetics of single doses of *N*-formimidoyl-thienamycin. Abstract 590, 21st Intersci. Conf. Antimicrob. Agents & Chemother., Chicago, 1981