A42867, A NOVEL GLYCOPEPTIDE ANTIBIOTIC

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A42867 is a new glycopeptide antibiotic of the ristocetin-vancomycin class active against aerobic and anaerobic Gram-positive bacteria. A42867 is produced by a strain of *Nocardia* nov. sp. ATCC 53492. A42867 was isolated during a screening program aimed at the discovery of new members of this glycopeptide class of antibiotics, by affinity chromatography based on an acyl-D-alanyl-D-alanine probe. The structure of A42867 was elucidated by fast atom bombardment MS, high field 2D ^{1}H NMR spectroscopy, and HPLC analysis of the hydrolyzed carbohydrates. A42867 differs from vancomycin in the sugar portion and in the presence of only one chlorine atom in the peptide core. Its biological activity on Gram-positive aerobic and anaerobic bacteria is similar to that of other antibiotics of this group.

The increased frequency of antibiotic-resistant Gram-positive bacteria has led to a renewed interest in the clinical use of glycopeptide antibiotics, which are highly effective against these species. A screening program aimed at the discovery of new glycopeptide antibiotics was developed based on the selective affinity of glycopeptides for the peptidoglycan precursor terminating with the D-alanyl-D-alanine moiety[1,2]. The method involves affinity chromatography of fermentation broths through an aminocaproyl-Sepharose matrix to which the dipeptide D-alanyl-D-alanine was coupled[3]. This method allows the detection of glycopeptide antibiotics also when co-produced in fermentation broth with antibiotics having different mechanisms of action and thus represents an advantage over the antagonism screen technique previously described by RAKE *et al.*[4].

By this means we isolated several strains producing antibiotics of the glycopeptide class. Among these a *Nocardia* strain was found to produce a new member of the vancomycin family. This new antibiotic, A42867, is active *in vitro* and *in vivo* against Gram-positive bacteria. This paper describes the isolation, taxonomy and fermentation of the producing strain as well as the isolation, structure elucidation, and biological properties of the antibiotic.

Isolation of the Producing Strain

The actinomycete strain which produces A42867 was isolated from a soil sample collected in Italy by the procedure described by HIRSCH and CHRISTENSEN[5] using CZAPEK glucose as basal agar medium for selection of actinomycetes. This strain has been deposited at the American Type Culture Collection (ATCC) under the accession No. ATCC 53492.

Taxonomy of the Producing Strain

Cultural and Physiological Characteristics

To examine the cultural and physiological characteristics, the organism was cultivated on the various standard media suggested by SHIRLING and GOTTLIEB[6] and on several media recommended

Table 1. Cultural and physiological characteristic of ATCC 53492 strain.

Culture medium	Characteristics
Medium No. 2	Abundant growth, wrinkled surface
(yeast extract - malt extract agar)	Color brown 15/H/11
	Soluble yellow pigment
Medium No. 3	Moderate growth, smooth surface
(oatmeal agar)	Color orange 12/L/12
	Trace white aerial mycelium
Medium No. 4	Abundant growth, wrinkled surface
(inorganic salts - starch agar)	Color dark orange 13/L/12
	Trace white aerial mycelium
Medium No. 5	Abundant growth, wrinkled surface
(glycerol - asparagine agar)	Color dark orange 13/L/12
	Trace white aerial mycelium
Medium No. 6	Moderate growth, slightly wrinkled surface
(peptone - yeast extract - iron agar)	Color apricot 10/F/9
Medium No. 7	Abundant growth, wrinkled surface
(tyrosine agar)	Color brown 15/H/11
	Trace white aerial mycelium
CZAPEK - sucrose agar	Moderate growth, smooth surface
	Color yellow orange 9/G/8
	Trace aerial mycelium
Oatmeal agar	Abundant growth, slightly wrinkled surface
	Color orange 12/F/10
	Trace white aerial mycelium
	Trace of rose soluble pigment
HICHEY and TRESNER's agar	Abundant growth, wrinkled surface
	Color golden 9/I/6
Calcium malate agar	Abundant growth, wrinkled surface
	Color pale yellow 10/C/4
	Trace white aerial mycelium
BENNETT's agar	Abundant growth, wrinkled surface
	Color brown 15/H/11
Glucose - asparagine agar	Moderate growth, slightly crusty surface
	Color yellow 10/L/5
Nutrient agar	Abundant growth, smooth surface
	Color yellow orange 9/G/6
Skim milk agar	Abundant growth, smooth surface
	Color peach 9/I/5
Egg albumin agar	Moderate growth, smooth surface
	Colorless
	Trace aerial mycelium
SABOURAUD agar	No growth
Potato agar	Abundant growth, wrinkled surface
	Color yellow 10/L/7
	Trace white aerial mycelium
	Soluble rose pigment
Water agar	Very scant growth, smooth surface
	Colorless
	Good formation of white aerial mycelium
Soil agar	Moderate growth, smooth surface
	Colorless
	Abundant formation of aerial mycelium
Glucose - Tryptose agar	Abundant growth, wrinkled surface
	Color yellow 10/L/7

by WAKSMAN[7]. The media were incubated at 28°C and examined after 1 to 3 weeks of growth (see Table 1). Color names used in this study were assigned according to MAERZ and PAUL[8]. Strain ATCC 53492 grew well on most of the agar media with the exception of SABOURAUD agar where no growth was observed and water agar where growth was very scant. The ability of the organism to utilize different carbon sources was investigated according to PRIDHAM and GOTTLIEB[9]; no growth was observed on rhamnose and cellulose, while on raffinose and sucrose scanty growth was observed. The strain tolerated temperatures ranging from 22 to 40°C, with an optimum range of growth between 28 and 37°C. At temperatures higher than 45°C no growth was observed, while at 20°C the growth was slow and very scanty. The growth-permissive pH range was from 5 to 9. The physiological characteristics of strain A42867 are as follows: Positive for H_2S formation, litmus milk peptonization, tyrosine reaction, and hydrolysis starch; negative for casein hydrolysis, Ca-malate solubilization, nitrate reduction, cellulose decomposition, and litmus milk coagulation.

Morphological Characteristics

The morphological characteristics were determined by light microscopy after 7 to 21 days of growth at 28°C. The substrate mycelium was composed of branched hyphae which fragmented into bacillary elements in older cultures. The aerial mycelium was well developed only on soil agar and water agar. Examination of soil agar plates showed the presence of long and straight aerial hyphae which sometimes formed knots or nest-like tangles.

Chemotaxonomical Studies

Strain ATCC 53492 was cultured in V6 medium (glucose 2%, beef extract 0.5%, autolyzed peptone 0.5%, hydrolyzed casein 0.3% and NaCl 0.15%), on a rotary shaker (200 rpm) at 28°C for 3 days. The harvested mycelium was washed with distilled water and dried with ethanol. Amino acids[10] and sugars[11] were released by acid hydrolysis and separated by cellulose TLC[12]. Whole cell analysis revealed the presence of *meso*-diaminopimelic acid, arabinose and galactose, indicating that strain ATCC 53492 is an actinomycete of cell wall type IV-A[13]. On the basis of its morphological characteristics and cell wall composition we classified this strain in the actinomycete genus *Nocardia*.

Antibiotic Production

For antibiotic production, strain ATCC 53492, grown on oatmeal agar slants, was inoculated into a culture medium having the following composition: Glucose 2%, yeast extract 0.2%, soybean meal 0.8% NaCl 0.1% and $CaCO_3$ 0.4%. The same medium was used for all fermentation steps. Fermentation of 200 liters was carried out at 28°C with an air flow of 0.5 liter/liter/minute at 250 rpm. Antibiotic production was monitored by microbiological assay using the well agar diffusion method with *Bacillus subtilis* ATCC 6633 as test organism. Maximum antibiotic production was reached after 72~96 hours of fermentation at 28°C. At that time there was complete glucose depletion and the pH was 7.4~7.6.

Isolation of the Antibiotic

The fermentation broth (200 liters) was processed on a rotary filter using a filter aid. The filtered broth was adjusted to pH 7.5 and added to 1 liter of D-Ala-D-Ala-aminocaproyl-Sepharose-4B preswollen matrix[3] and stirred gently overnight at room temperature. The resin was recovered by filtration and washed with about 10 liters of 0.5% (w/v) Tris-HCl buffer pH 7.5 containing 5% (w/v) NaCl

and then with water (4×5 liters). The broth and the washings were discarded. The product, selectively bound to the resin, was eluted with 1.5% (w/v) ammonium hydroxide (4×5 liters), concentrated and lyophilized to obtain a crude powder. The crude was dissolved in 2 liters of 2 M NaCl, adjusted to pH 7.5 and filtered. The filtrate was applied at 500 ml/hour to a 1-liter column of pre-swollen D-Ala-D-Ala-aminocaproyl-Sepharose-4B previously equilibrated with 0.04 M borate buffer, pH 7.5, containing 2 M NaCl and 0.6% of Triton X-100 (Baker). The column was washed with 8 liters of 8 M urea (pH 7.5) at a flow rate of 500 ml/hour and eluted with 70 liters of aqueous NaOH at pH 10; 1 liter fractions were collected.

The fractions were assayed by the well agar diffusion assay and by HPLC analysis on a reverse phase column (C18 Ultrasphere, Beckman) using a gradient acetonitrile-phosphate buffer as mobile phase with UV detection at 254 nm. Microbiologically active fractions with similar HPLC profiles were pooled, concentrated, and lyophilyzed yielding 0.6 g of pure antibiotic. The HPLC profile of pure A42867 shows that this antibiotic is produced as a single component, in contrast with the majority of the glycopeptide antibiotics of this class which are produced as a mixture of related factors.

Structure Determination

Acid base ionization studies were carried out in two different solvents and indicated the presence of the six ionizable functions reported in Table 2.

The UV spectra at different pH values showed that the ionization of the phenolic groups is responsible for the variations, as shown in Table 3. The terminal carboxyl and methylamino groups do not contribute to the UV variation. This behavior is similar to that observed with vancomycin.

The IR spectrum of A42867 was very similar to those of other glycopeptides and shows the characteristic bands of glucosides, phenols and amides (Fig. 1).

Fast atom bombardment (FAB)-MS showed an abundant quasimolecular ion $(M+H)^+$ at *m/z* 1,560, in agreement with the molecular weight calculated on the basis of elemental analysis data. The elemental analysis showed: C 53.3, H 5.9, N 9.0, Cl 2.2; calcd C 55.4, H 5.55, N 8.07, Cl 2.27, corresponding to the empirical formula $C_{72}H_{86}O_{28}N_9Cl$, MW 1,560.816.

The presence of glucose and rhamnose was indicated by the HPLC analysis (RP-18 column, gradient of aqueous acetic acid - acetonitrile, UV detection at 254 nm) of the dansyl derivatized hydrochloric acid hydrolysate of A42867, using a mixture of dansyl derivatized authentic sugars as reference standards[14]. Under these conditions, D-(+)-glucose and D-(+)-rhamnose were detected in a 1:1 molar ratio, while the amino sugars were not detectable.

Some fragments were observed in the FAB-MS, shown in Fig. 2, that allowed us to confirm the

Table 2. Ionization data for A42867.

	MCS - H_2O (4:1)	H_2O	Assignment
pK 1	4.7	3.4	COOH
pK 2	6.2	7.2	$HN-CH_3$
pK 3	8.6	8.9	Vancosamine NH_2
pK 4~6 (average value)	10.7	10.6	Phenolic OH's
Isoelectric point (calcd)		8.1	

An excess of 0.1 N HCl was added to solutions of A42867 in methyl cellosolve (MCS) - H_2O and in H_2O, which were then titrated with 0.1 N KOH.

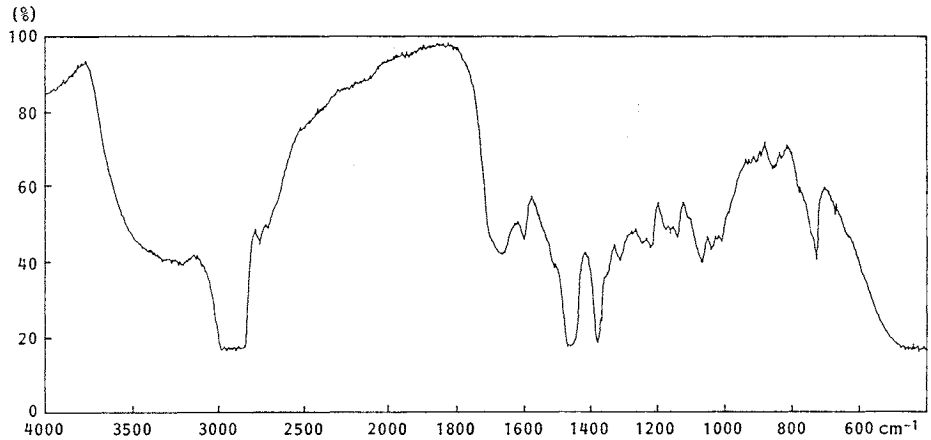
presence of rhamnose, glucose and vancosamine moieties. In particular, the ion at *m/z* 1,253 indicated the loss of the rhamnosylglucose moiety from (M+H), suggesting that a glucose moiety is directly bound to the peptide core. In the low mass region of the spectrum (not shown in Fig. 2) there were no peaks due to the cleavage of the peptide chain, as in the case of vancomycin[15] and other glycopeptides[16].

The structure of A42867 was further studied by NMR spectroscopy, using modern 2D techniques. The assignment of most of the hydrogen atoms based on coupling experiments are

Table 3. UV bands (λ_{max}, nm) and absorptions (*a*) of A42867 in water solution at different pH values.

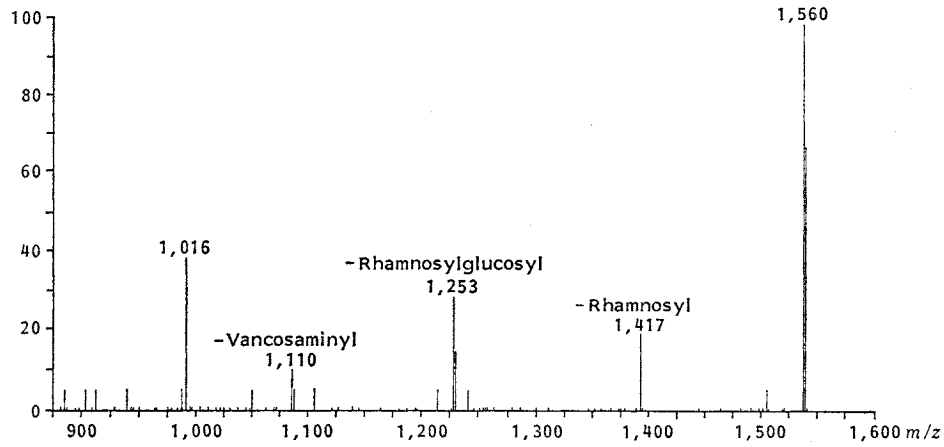
	λ_{max} (nm)	*a* (1 mg/ml, 1 cm)
0.1 N HCl		
~pH 7.4	282	3.57
pH 9.0	282	3.52
	305	1.18
0.1 N KOH	265 (sh)	7.39
	305	4.44

Fig. 1. IR spectrum of A42867 in mineral oil.



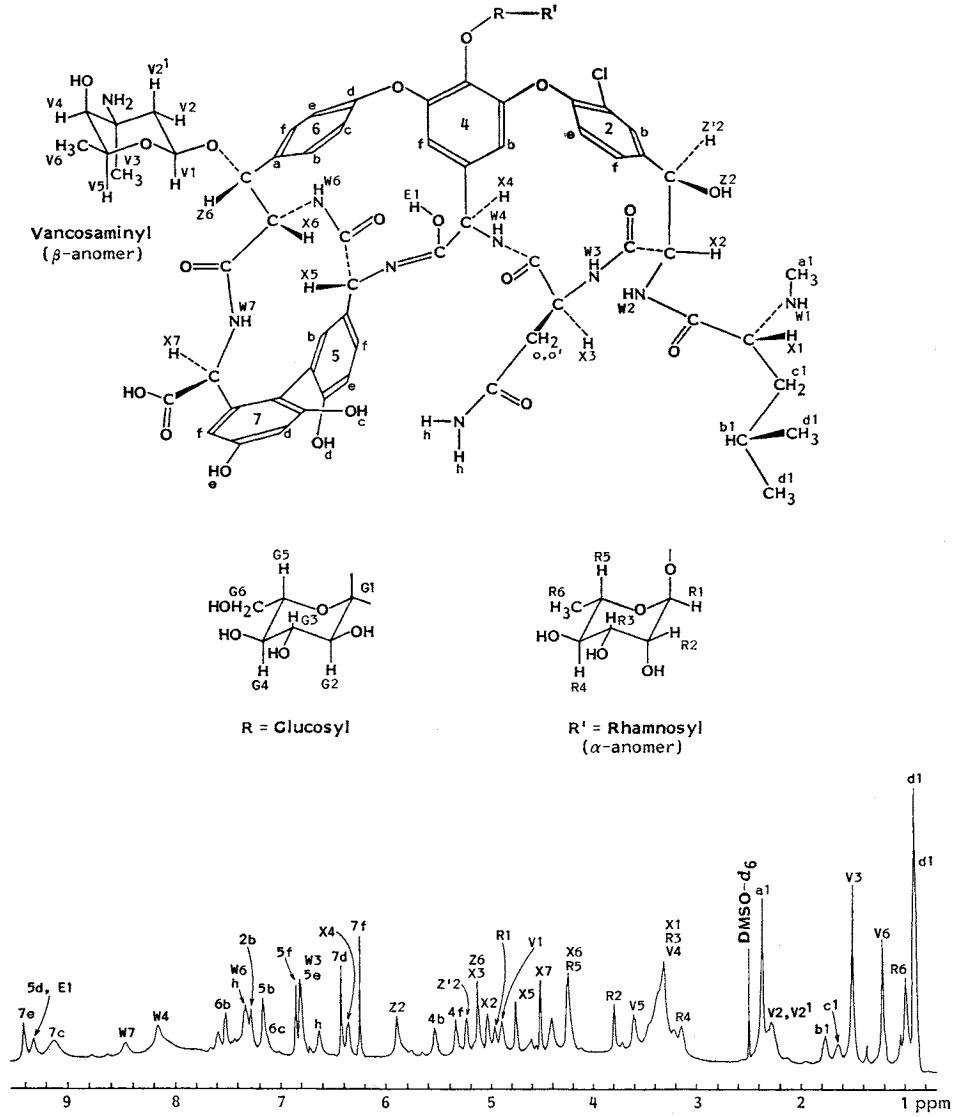
IR spectrum of A42867 in mineral oil taken on a Perkin-Elmer 580 spectrometer.

Fig. 2. FAB-MS of A42867.



FAB-MS of A42867 condition: Matrix thioglycerol - glycerol (2 : 1), ionizing gas Xe at 8 keV, accelerating voltage 6 kV, instrument VG 70-250.

Fig. 3. ^{1}H NMR spectrum of A42867 in DMSO-d_6.



^{1}H NMR spectrum of A42867 in DMSO-d_6 with TMS as internal reference recorded at 500 MHz with a Bruker 500 AM spectrometer.

reported in Fig. 3 and Table 4. These data, in comparison with those from the literature, established that A42867 is a tricyclic glycopeptide antibiotic, which has an aglycone moiety similar to that of vancomycin; one chlorinated β-hydroxytyrosine, one β-hydroxytyrosine, three substituted phenylglycines, one *N*-methylleucine and one aspartic acid amide linked in a seven-membered peptide chain in the same sequence as that of vancomycin. A42867 differs from vancomycin in having; vancosamine (β-anomer) in position z6, rhamnosylglucose in position 4d and only one chlorine atom in position 2c. Furthermore, 2D NMR studies of the linkage between amino acids 4 and 5, showed an unusual tautomeric amide-isoamide equilibrium[17]. As in vancomycin two ether bonds and a carbon-carbon bond join, respectively, aromatic rings 2-4-6 and 5-7.

Table 4. Assignment of the main signals of the ^1H NMR spectrum based on scalar and dipolar coupling studies carried out by COSYPHDQ and NOESYPH experiments.

Proton[a]	ppm	Proton	ppm
7e	9.39	Z6, X3	5.12
5d, E1	9.32	X2	5.01
7c	9.12	R1	4.95
W7	8.45	V1	4.88
W4	8.15	X5	4.75
6b	7.49	X7	4.52
h	7.32, 6.63	X6, R5	4.22
W6	7.32	R2	3.79
2b	7.24	V5	3.59
5b	7.16	X1, R3, V4	3.30
5f	6.84	R4	3.14
5e, W3	6.79	a1	2.34
7d	6.40	V2, V2[1]	2.27
X4	6.35	b1	1.75
7f	6.23	c1	1.62
(Z2)-OH	5.88	V3	1.50
4b	5.52	V6	1.20
4f	5.33	R6	0.98
Z'2	5.21	d1	0.89, 0.86

[a] The nomenclature used here and in Fig. 3 is that proposed by BARNA *et al.*[24].
COSYPHDQ: Correlation spectroscopy phase sensitive double quantum filter.
NOESYPH: Nuclear Overhauser phase sensitive effect.

Table 5. Antimicrobial activity of A42867.

	MIC (μg/ml)		
	A42867	Teicoplanin	Vancomycin
Staphylococcus aureus Tour	0.25	0.13	0.5
S. haemolyticus L 381[a]	4	4	ND
S. haemolyticus L 382[a]	8	4	ND
S. haemolyticus L 383[a]	1	8	ND
S. haemolyticus L 418[a]	8	8	ND
S. haemolyticus L 602[a]	1	4	ND
S. haemolyticus L 1445[a]	16	8	ND
S. epidermidis ATCC 12228	1	0.5	1
S. epidermidis L 393[a]	1	0.5	ND
S. epidermidis L 408[a]	1	0.25	ND
S. epidermidis L 409[a]	1	0.25	ND
S. epidermidis L 410[a]	0.5	0.25	ND
S. epidermidis L 1480[a]	2	0.25	ND
Streptococcus pyogenes C 203	0.13	0.06	0.5
S. pneumoniae UC 41	0.13	0.06	0.5
S. faecalis ATCC 7080	1	0.13	1
S. mitis L 796[a]	0.25	0.13	0.5
Clostridium perfringens ISS 30543	0.13	0.06	1
C. difficile ATCC 9689	2	0.13	4
Propionibacterium acnes ATCC 6919	0.5	0.13	2
Neisseria gonorrhoeae L 997	>128	32	>128
Haemophilus influenzae ATCC 19418	>128	>128	>128
Escherichia coli SKF 12140	>128	>128	>128
Proteus vulgaris ATCC 881	>128	>128	>128
Pseudomonas aeruginosa ATCC 10145	>128	>128	>128

[a] Clinical isolates.
ND: Not done.

All the chemical and spectroscopic data are in agreement with the structure shown in Fig. 3.

Biological Activity

MIC for *Clostridium difficile* and *Propionibacterium acnes* were determined by agar dilution (inocula 10^4 cfu). MIC for other organisms were determined by microbroth dilution (inocula 10^4 to 10^5 cfu/ml). The cultures were incubated at 37°C for 18~24 hours, except for *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *C. difficile*, and *P. acnes* which were incubated for 48 hours. *N. gonorrhoeae* and *H. influenzae* were incubated in a 5%-CO_2 atmosphere, anaerobes in an anaerobic gas mixture, and all other organisms in an aerobic environment. Media used were: Oxoid Iso-Sensitest broth (Staphylococci, *Streptococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*); Difco Todd-Hewitt broth (other Staphylococci); Difco GC base broth +1% BBL IsoVitaleX (*N. gonorrhoeae*); Difco brain heart infusion broth +1% Difco supplement C (*H. influenzae*); Difco AC medium without agar (*Clostridium perfringens*); Oxoid Wilkins-Chalgren agar (other anaerobes).

A comparison of the antibacterial activity of A42867 with those of vancomycin and teicoplanin is given in Table 5. A42867 is active against Gram-positive bacteria including coagulase-negative Staphylococci. The *in vitro* activity of the three antibiotics was generally quite similar, except that teicoplanin was more active than A42867 against *S. faecalis* and *C. difficile*.

When administered sc to mice infected with *Streptococcus pyogenes*, the ED_{50} of A42867 was calculated to be 1.54 mg/kg.

Discussion

The use of an affinity chromatography method with a bioselective adsorbent allowed detection in fermentation broths of several compounds of the ristocetin-vancomycin glycopeptide class. The same adsorbent was also useful for the recovery of these compounds and was used to isolate and purify A42867, a new glycopeptide.

A42867 belongs to the sub-group of glycopeptides having a tricyclic heptapeptide aglycone. In addition to antibiotics of the vancomycin family, which include monochloro-vancomycin[18] and the M43 series[19], other antibiotics belonging to this sub-group have been recently described: PA/42867[20], izupeptin[21], and eremomycin[22,23].

Structural data differentiated A42867 from all those so far described. In addition, the 2D NMR studies revealed an amide-isoamide tautomeric equilibrium between amino acids 4 and 5 which is a feature never before observed in glycopeptides. This observation will be the subject of a forthcoming paper.

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