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In Vitro Activities of BAL9141, a Novel Broad-Spectrum Pyrrolidinone Cephalosporin, against Gram-Negative Nonfermenters

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The activities of BAL9141 (formerly Ro 63–9141), a novel pyrrolidinone-3-ylidenemethyl cephalosporin, against 244 strains of gram-negative nonfermenters were evaluated. The overall MIC at which 50% of isolates are inhibited (MIC_{50}) and the overall MIC_{90} were 2 and 64 μg/ml, respectively, which are similar to those of imipenem, lower than those of the other cephalosporins tested, amoxicillin, and the ticarcillin-clavulanic acid combination, and much higher than those of ciprofloxacin. BAL9141 shows species-dependent activity in vitro against a variety of gram-negative nonfermentative pathogens.

BAL9141 (formerly Ro 63–9141) is a novel pyrrolidinone-3-ylidenemethyl cephalosporin that consistently has activity against methicillin-resistant strains of *Staphylococcus* spp. but that exhibits promising in vitro and in vivo activities against a variety of gram-negative pathogens (1). The purpose of this study was to evaluate the activity of BAL9141 against a broad range of aerobic gram-negative glucose-nonfermentative rods.

(Part of this work was presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, Calif., 1998 [R. Zbinden, V. Puenter, and A. von Graevenitz, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-19, 1998].).

The MICs of BAL9141 and nine other antimicrobials were determined by the NCCLS agar dilution method on non-cation-adjusted Mueller-Hinton agar (Becton Dickinson Microbiology Systems, Cockeysville, Md.) for 244 gram-negative nonfermenters that were collected through 1995 in the Department of Medical Microbiology, University of Zurich, Zurich, Switzerland, and a reference strain, *Pseudomonas aeruginosa* ATCC 27853 (5). A 0.5 McFarland suspension in phosphate-buffered saline was diluted 1/10 to obtain the desired inoculum of 10^7 CFU/ml. A multipoint inoculator was used to deliver 10^4 CFU per spot to each test plate and to control plates without antibiotics. Cultures were incubated at 35°C for 20 h in an aerobic atmosphere in accordance with the NCCLS methodology (5). BAL9141 of known potency was supplied by F. Hoffmann-La Roche, Basel, Switzerland (courtesy of P. Hebeisen). The other compounds were obtained from commercial sources. Identification of the isolates studied was in accordance with recommended methods (4).

The MICs of BAL9141 and the other antimicrobial agents are shown in Table 1. The modal MIC of BAL9141 for *P. aeruginosa* ATCC 27853 was 2 μg/ml; the MICs of the other antimicrobial agents for *P. aeruginosa* fell within expected ranges (6). The MICs at which 50% of isolates are inhibited (MIC_{50}s) and MIC_{90}s for all 244 strains were 2 and 64 μg/ml, respectively, for BAL9141; 8 and 64 μg/ml, respectively, for cefepime; 64 and >64 μg/ml, respectively, for cefotetan; 8 and >64 μg/ml, respectively, for cefozopran; 8 and >64 μg/ml, respectively, for ceftazidime; 8 and >64 μg/ml, respectively, for ceftriaxone; 32 and >64 μg/ml, respectively, for amoxicillin-clavulanic acid; 32 and >64 μg/ml, respectively, for ticarcillin-clavulanic acid; 1 and 64 μg/ml, respectively, for imipenem; and 0.25 and 4 μg/ml, respectively, for ciprofloxacin. Table 2 shows the cumulative in vitro activities of BAL9141 and the comparator drugs against 244 gram-negative nonfermenters.

BAL9141 was particularly active against *Agrobacterium radiobacter*, *Alcaligenes faecalis*, *Bordetella bronchiseptica*, *Moraxella* spp., *Ochrobactrum anthropi*, *Pseudomonas oryzihabitans*, *Ralstonia pickettii*, and *Weeksella virosa*. The results of our study of the activities of BAL9141 against *P. aeruginosa* and *Acinetobacter* spp. were by and large in agreement with those of Hebeisen et al. (1), except that, across the board, our pathogens were more susceptible than the selected isolates used by those investigators. Our results for the other antimicrobials are in line with those obtained by Jones et al. (2), Klein et al. (3), Spangler et al. (7), and von Graevenitz and Bucher (8).

The overall activities of BAL9141 against the glucose-nonfermentative gram-negative rods tested were most similar to those of imipenem in terms of MIC_{50}s and MIC_{90}s. Imipenem, however, had clearly superior activity against *Achromobacter xylosoxidans*, *Acinetobacter baumannii*, *Brevundimonas vesicularis*, *Burkholderia cepacia*, *Comamonas acidovorans*, *P. aeruginosa*, *Pseudomonas stutzeri*, and *W. virosa*. For the other species tested, their activities were similar. Cefepime was more active against *Chryseobacterium indologenes* and *Sphingomonas* spp. and, to some extent, was also more active against *P. aeruginosa*. Cefozopran was, overall, as active as cefepime. With the exception of ceftazidime against *B. cepacia*, *C. acidovorans*, and *P. aeruginosa*, the expanded-spectrum and broad-spectrum cephalosporins were less active than BAL9141 or the penicillin-clavulanic acid combinations.

While imipenem and ciprofloxacin have greater potencies against most of the organisms tested, BAL9141, cefepime, and cefozopran, in decreasing order, appear to be potent enough to

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TABLE 1. Comparative in vitro activities of BAL9141 against 244 gram-negative nonfermenters

Organism (no. of strains) and drug	MIC (μg/ml)		
	Range	50%	90%
Achromobacter xylosoxidans subsp. *denitrificans* and *A. xylosoxidans* subsp. *xylosoxidans* (17)			
BAL9141	1–32	4	16
Cefepime	2–>64	32	>64
Cefotetan	32–>64	>64	>64
Cefozopran	8–>64	>64	>64
Ceftazidime	1–32	8	16
Ceftriaxone	1–>64	64	>64
Amoxicillin-clavulanic acid	8–>64	32	>64
Ticarcillin-clavulanic acid	2–64	8	64
Imipenem	0.25–4	2	4
Ciprofloxacin	1–32	4	8
Acinetobacter baumannii (10)			
BAL9141	0.5–>64	2	16
Cefepime	1–>64	8	32
Cefotetan	32–>64	64	>64
Cefozopran	1–64	8	32
Ceftazidime	2–>64	8	64
Ceftriaxone	4–>64	16	64
Amoxicillin-clavulanic acid	32–>64	64	>64
Ticarcillin-clavulanic acid	1–>64	64	>64
Imipenem	0.25–4	0.5	0.5
Ciprofloxacin	≤0.06–>64	0.25	0.25
Acinetobacter iwoffii (10)			
BAL9141	≤0.06	≤0.06	≤0.06
Cefepime	≤0.06–1	≤0.06	0.5
Cefotetan	0.5–64	4	32
Cefozopran	≤0.06–0.5	≤0.06	≤0.06
Ceftazidime	≤0.06–8	0.5	4
Ceftriaxone	≤0.06–4	1	2
Amoxicillin-clavulanic acid	≤0.06–8	2	8
Ticarcillin-clavulanic acid	0.25–8	2	4
Imipenem	≤0.06–0.13	≤0.06	0.13
Ciprofloxacin	≤0.06	≤0.06	≤0.06
Agrobacterium radiobacter (10)			
BAL9141	≤0.06–0.5	0.13	0.25
Cefepime	1–8	2	8
Cefotetan	0.25–8	4	8
Cefozopran	1–16	4	8
Ceftazidime	4–64	64	64
Ceftriaxone	1–32	4	16
Amoxicillin-clavulanic acid	0.25–16	16	16
Ticarcillin-clavulanic acid	4–16	8	16
Imipenem	≤0.06–1	0.25	0.25
Ciprofloxacin	≤0.06–1	≤0.06	0.5
Alcaligenes faecalis (10)			
BAL9141	0.25–8	0.5	2
Cefepime	0.25–>64	8	8
Cefotetan	0.5–>64	2	>64
Cefozopran	0.5–>64	8	16
Ceftazidime	2–16	4	8
Ceftriaxone	0.13–>64	0.25	>64
Amoxicillin-clavulanic acid	8–64	16	64
Ticarcillin-clavulanic acid	4–16	8	8
Imipenem	≤0.06–4	0.5	4
Ciprofloxacin	≤0.06–4	1	4
Bordetella bronchiseptica (10)			
BAL9141	0.06–8	2	4
Cefepime	0.25–64	16	32
Cefotetan	8–>64	>64	>64
Cefozopran	0.25–>64	32	32
Ceftazidime	1–32	16	32
Ceftriaxone	0.5–>64	>64	>64
Amoxicillin-clavulanic acid	8–64	16	64
Ticarcillin-clavulanic acid	4–>64	16	32
Imipenem	0.13–2	1	2
Ciprofloxacin	≤0.06–2	1	2
Brevundimonas vesicularis (14)			
BAL9141	1–>64	4	>64
Cefepime	0.25–32	8	32
Cefotetan	8–>64	32	>64
Cefozopran	1–>64	8	>64
Ceftazidime	0.5–>64	32	>64
Ceftriaxone	0.5–>64	4	>64
Amoxicillin-clavulanic acid	4–>64	8	>64
Ticarcillin-clavulanic acid	4–>64	16	>64
Imipenem	0.25–>64	0.5	>64
Ciprofloxacin	0.25–16	4	16
Burkholderia cepacia (14)			
BAL9141	0.5–64	8	64
Cefepime	≤0.06–32	8	32
Cefotetan	8–>64	64	>64
Cefozopran	16–>64	64	>64
Ceftazidime	2–32	16	16
Ceftriaxone	4–>64	16	64
Amoxicillin-clavulanic acid	>64	>64	>64
Ticarcillin-clavulanic acid	>64	>64	>64
Imipenem	≤0.06–16	8	8
Ciprofloxacin	1–4	1	4
Chryseobacterium indologenes (14)			
BAL9141	0.25–>64	16	64
Cefepime	≤0.06–16	1	4
Cefotetan	4–>64	>64	>64
Cefozopran	0.5–>64	4	>64
Ceftazidime	4–32	8	32
Ceftriaxone	8–64	64	64
Amoxicillin-clavulanic acid	0.5–>64	32	>64
Ticarcillin-clavulanic acid	2–>64	>64	>64
Imipenem	≤0.06–>64	16	>64
Ciprofloxacin	≤0.06–2	0.5	0.5
Chryseobacterium meningosepticum (10)			
BAL9141	8–64	32	64
Cefepime	8–64	32	64
Cefotetan	64–>64	>64	>64
Cefozopran	16–>64	32	64
Ceftazidime	64–>64	>64	>64
Ceftriaxone	32–>64	64	>64
Amoxicillin-clavulanic acid	32–>64	>64	>64
Ticarcillin-clavulanic acid	>64	>64	>64
Imipenem	32–64	32	64
Ciprofloxacin	0.5–8	1	2
Comamonas acidovorans (10)			
BAL9141	1–32	4	16
Cefepime	8–>64	8	64
Cefotetan	4	4	4
Cefozopran	4–>64	16	64
Ceftazidime	0.5–4	1	2
Ceftriaxone	1–64	8	32
Amoxicillin-clavulanic acid	32–>64	>64	>64
Ticarcillin-clavulanic acid	8–>64	64	>64
Imipenem	0.25–4	1	2
Ciprofloxacin	≤0.06–0.5	0.13	0.25
Moraxella spp. (10) (except *M. catarrhalis*)			
BAL9141	≤0.06–0.25	≤0.06	0.13
Cefepime	≤0.06–2	0.5	1
Cefotetan	0.13–8	1	8
Cefozopran	≤0.06–1	0.5	1
Ceftazidime	≤0.06–8	2	4
Ceftriaxone	≤0.06–0.5	≤0.06	0.5
Amoxicillin-clavulanic acid	0.13–1	0.25	0.5
Ticarcillin-clavulanic acid	≤0.06–4	0.5	1
Imipenem	≤0.06–0.25	≤0.06	0.13
Ciprofloxacin	≤0.06–0.13	≤0.06	0.13

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TABLE 1—*Continued*

Organism (no. of strains) and drug	MIC (μg/ml)		
	Range	50%	90%
Ochrobactrum anthropi (10)			
BAL9141	0.5–2	1	2
Cefepime	8–64	16	64
Cefotetan	16–>64	64	>64
Cefozopran	4–>64	16	>64
Ceftazidime	64–>64	>64	>64
Ceftriaxone	2–>64	8	>64
Amoxicillin-clavulanic acid	32–>64	>64	>64
Ticarcillin-clavulanic acid	64–>64	>64	>64
Imipenem	1–2	1	2
Ciprofloxacin	≤0.06–0.5	0.5	0.5
Oligella ureolytica (10)			
BAL9141	0.25–>64	0.5	>64
Cefepime	0.25–>64	4	16
Cefotetan	0.13–>64	64	>64
Cefozopran	1–>64	2	>64
Ceftazidime	0.5–>64	16	>64
Ceftriaxone	≤0.06–64	4	64
Amoxicillin-clavulanic acid	0.25–>64	8	>64
Ticarcillin-clavulanic acid	0.25–>64	8	>64
Imipenem	≤0.06–>64	0.5	64
Ciprofloxacin	≤0.06–1	0.5	0.5
Pseudomonas aeruginosa (15)			
BAL9141	0.25–64	8	32
Cefepime	1–16	4	16
Cefotetan	>64	>64	>64
Cefozopran	0.5–16	2	16
Ceftazidime	2–32	4	8
Ceftriaxone	2–>64	>64	>64
Amoxicillin-clavulanic acid	>64	>64	>64
Ticarcillin-clavulanic acid	8–>64	>64	>64
Imipenem	0.13–32	2	4
Ciprofloxacin	≤0.06–2	0.13	2
Pseudomonas oryzihabitans (10)			
BAL9141	≤0.06–2	0.13	0.25
Cefepime	≤0.06–>64	0.13	8
Cefotetan	0.5–>64	2	32
Cefozopran	≤0.06–>64	0.13	0.5
Ceftazidime	0.13–>64	0.5	2
Ceftriaxone	0.13–>64	0.5	32
Amoxicillin-clavulanic acid	2	2	2
Ticarcillin-clavulanic acid	0.13–>64	2	64
Imipenem	0.13–2	0.13	0.25
Ciprofloxacin	≤0.06–0.5	≤0.06	0.5
Pseudomonas stutzeri (12)			
BAL9141	≤0.06–16	1	16
Cefepime	≤0.06–>64	0.25	>64
Cefotetan	≤0.06–>64	2	16
Cefozopran	≤0.06–>64	0.25	>64
Ceftazidime	≤0.06–>64	1	>64
Ceftriaxone	0.13–>64	2	>64
Amoxicillin-clavulanic acid	0.25–16	8	16
Ticarcillin-clavulanic acid	0.25–>64	8	64
Imipenem	0.06–1	0.5	0.5
Ciprofloxacin	≤0.06	≤0.06	≤0.06
Ralstonia pickettii (10)			
BAL9141	1–4	2	4
Cefepime	1–4	2	4
Cefotetan	8–>64	>64	>64
Cefozopran	0.25–4	2	4
Ceftazidime	2–16	8	16
Ceftriaxone	≤0.06–0.25	0.25	0.25
Amoxicillin-clavulanic acid	1–>64	>64	>64
Ticarcillin-clavulanic acid	2–>64	>64	>64
Imipenem	≤0.06–2	1	2
Ciprofloxacin	≤0.06–0.25	0.13	0.25
Sphingomonas spp. (10)			
BAL9141	4–16	8	16
Cefepime	2–16	2	8
Cefotetan	64–>64	64	>64
Cefozopran	0.5–16	4	16
Ceftazidime	2–>64	16	>64
Ceftriaxone	1–32	8	16
Amoxicillin-clavulanic acid	8–32	16	32
Ticarcillin-clavulanic acid	8–>64	>64	>64
Imipenem	0.5–>64	32	64
Ciprofloxacin	≤0.06–4	0.25	2
Stenotrophomonas maltophilia (15)			
BAL9141	0.5–>64	>64	>64
Cefepime	4–>64	>64	>64
Cefotetan	8–>64	64	>64
Cefozopran	32–>64	>64	>64
Ceftazidime	4–>64	64	>64
Ceftriaxone	>64	>64	>64
Amoxicillin-clavulanic acid	8–>64	>64	>64
Ticarcillin-clavulanic acid	16–>64	>64	>64
Imipenem	8–>64	>64	>64
Ciprofloxacin	0.5–8	4	8
Weeksella virosa (15)			
BAL9141	≤0.06–2	≤0.06	2
Cefepime	0.5–16	4	16
Cefotetan	0.5–8	2	4
Cefozopran	0.25–32	0.25	8
Ceftazidime	0.25–8	1	4
Ceftriaxone	0.5–4	2	4
Amoxicillin-clavulanic acid	≤0.06–0.5	0.13	0.5
Ticarcillin-clavulanic acid	0.13–16	0.25	1
Imipenem	≤0.06–0.13	≤0.06	≤0.06
Ciprofloxacin	<0.06–0.13	<0.06	0.13

TABLE 2. Cumulative in vitro activities of BAL9141 and comparator drugs against 244 gram-negative nonfermenters

Compound(s)	% strains inhibited by:			
	2 μg/ml	4 μg/ml	8 μg/ml	16 μg/ml
BAL9141	52	65	73	83
Cefepime[a]	20	26	37	48
Cefotetan	18	27	39	42
Cefozopran	38	47	57	67
Ceftazidime[a]	30	43	56	73
Ceftriaxone[a]	32	44	51	58
Amoxicillin-clavulanic acid[b]	20	26	37	48
Ticarcillin-clavulanic acid[c]	19	24	35	47
Imipenem[d]	69	76	80	82
Ciprofloxacin[e]	84	95	97	99

be of clinical utility against most of the species evaluated apart from *Stenotrophomonas maltophilia* and *Chryseobacterium* spp. All compounds tested were inactive against *S. maltophilia* and *Chryseobacterium meningosepticum* (the activity of ciprofloxacin was borderline).

[a] NCCLS-approved susceptibility breakpoint for *P. aeruginosa* and other nonmembers of the family *Enterobacteriaceae* (6), 8 μg/ml.

[b] NCCLS-approved susceptibility breakpoint for ampicillin-sulbactam (6), 8/4 μg/ml.

[c] NCCLS-approved susceptibility breakpoint for nonmembers of the family *Enterobacteriaceae*, 16/2 μg/ml; NCCLS-approved susceptibility breakpoint for *P. aeruginosa*, 64/2 μg/ml.

[d] NCCLS-approved susceptibility breakpoint for *P. aeruginosa* and other nonmembers of the family *Enterobacteriaceae* (6), 4 μg/ml.

[e] NCCLS-approved susceptibility breakpoint (6), 1 μg/ml.

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