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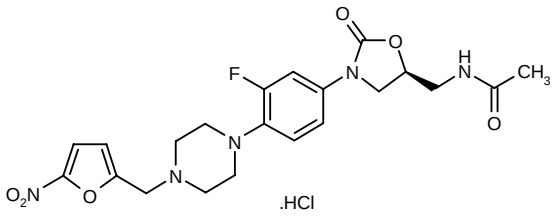
CCC: 0377-8282/2003

RBx-7644

Oxazolidinone Antibacterial

Ranbezolid Hydrochloride

N-[3-[3-Fluoro-4-[4-(5-nitrofuran-2-ylmethyl)piperazin-1-yl]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide monohydrochloride



$C_{21}H_{24}FN_5O_6.HCl$

Mol wt: 497.9085

CAS: 392659-39-1

CAS: 392659-38-0 (as free base)

EN: 316064

Abstract

RBx-7644 (ranbezolid hydrochloride) is an extended-spectrum oxazolidinone that not only retains the excellent activity of linezolid against important Gram-positive pathogens, but also displays exquisite activity against all anaerobes (Gram-positive or Gram-negative) tested and has significant inhibitory activity against slime-producing and glass-adherent bacteria. Like linezolid, RBx-7644 has a novel mode of action, binding to the 50S ribosomal subunit and preventing it from forming a complex with the 30S subunit and initiation factors, resulting in blockade of the initiation of protein biosynthesis in prokaryotes. Due to its novel mode of action, RBx-7644 is active against pathogens that have acquired resistance to existing drugs. RBx-7644 was highly active by both the oral and parenteral routes in mouse models of infection and displayed good oral bioavailability in mice, rats and dogs. In phase I studies, oral RBx-7644 was rapidly absorbed, safe and well tolerated. Its profile suggests potentially expanded indications for use and a reduced liklihood for resistance development.

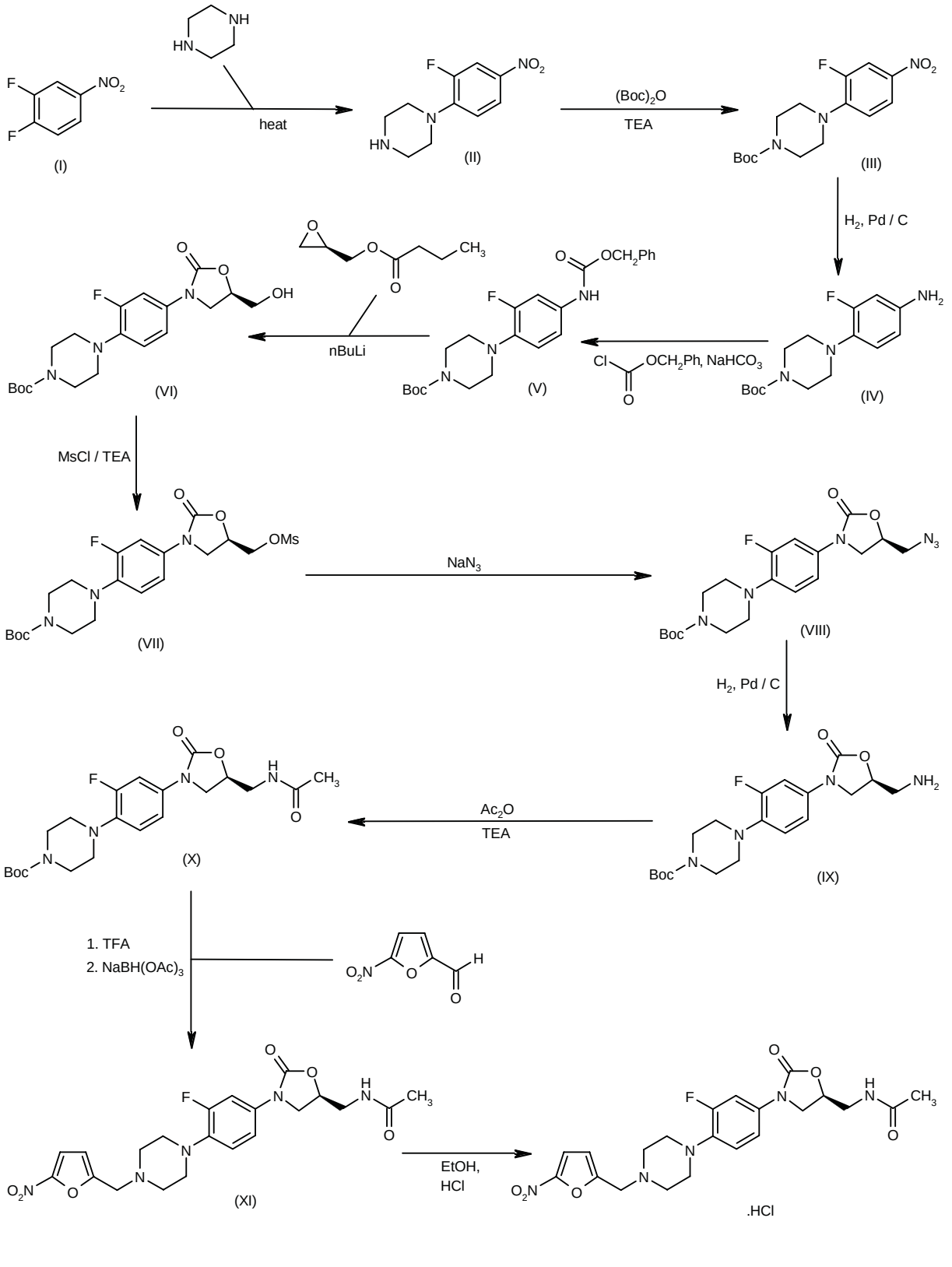
Synthesis

The antibacterial activity of RBx-7644 is due to the 5(*S*)-acetamidomethyl configuration at the oxazolidinone ring, and thus, asymmetric synthesis of only the 5(*S*)-enantiomer was desirable (Scheme 1):

3,4-Difluoronitrobenzene (I) is condensed with piperazine in acetonitrile to give 4-(2-fluoro-4-nitrophenyl)-piperazine (II) as a light yellow compound. Compound (II) is dissolved in dichloromethane and triethylamine, followed by the addition of Boc-anhydride, to provide compound (III). 4-(*tert*-Butoxycarbonyl)-1-(2-fluoro-4-nitrophenyl)piperazine (III), upon hydrogenation with H_2 over Pd/C in methanol at 50 psi, yields 4-(*tert*-butoxycarbonyl)-1-(2-fluoro-4-aminophenyl)piperazine (IV) as a dark solid. Compound (IV) reacts with benzylchloroformate in dry THF in the presence of solid sodium bicarbonate to afford the desired compound (V). 4-(*tert*-Butoxycarbonyl)-1-[2-fluoro-4-(benzyloxycarbonylamino)phenyl]piperazine (V), upon treatment with *n*-BuLi and (*R*)-glycidyl butyrate at –78 °C, gives the desired (*R*)-(–)-3-[3-fluoro-4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]phenyl]-5-(hydroxymethyl)-2-oxazolidinone (VI). The hydroxymethyl compound (VI) is treated with methanesulfonyl chloride in dichloromethane in the presence of triethylamine to give (*R*)-(–)-3-[3-fluoro-4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]phenyl]-5-(methylsulfonyloxymethyl)-2-oxazolidinone (VII). The sulfonyl derivative (VII) is treated with sodium azide in dimethylformamide to provide the azide (VIII) as a white solid. (*R*)-(–)-3-[3-Fluoro-4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl]-5-(azidomethyl)-2-oxazolidinone (VIII), upon hydrogenation with H_2 over Pd/C at 45 psi, gives (*S*)-(–)-3-[3-fluoro-4-[4-(*tert*-butoxycarbonyl)-piperazin-1-yl]phenyl]-5-(aminomethyl)-2-oxazolidinone (IX). The aminomethyl compound (IX), upon treatment with acetic anhydride in dichloromethane in the presence of triethylamine, affords the acetamide

Ashok Rattan. Ranbaxy Research Laboratories, Microbiology, New Drug Discovery Research, Plot 20, Sector 18, 122002 Gurgaon, Haryana, India.

Scheme 1: Synthesis of RBx-7644



derivative (X). The acetamidomethyl-oxazolidinone derivative (X), upon treatment with trifluoroacetic acid, gives (*S*)-(−)-3-[3-fluoro-4-(1-piperazinyl)phenyl]-5-(acetamidomethyl)-2-oxazolidinone, which, without isolation, is treated with 5-nitro-2-furaldehyde in the presence of sodium triacetoxy borohydride to provide compound (XI). Compound (XI), upon treatment with ethanolic HCl, affords RBx-7644 as a light yellow crystalline solid.

Introduction

In recent years, there has been a worldwide increase in infections caused by pathogens resistant to multiple microbial agents. This problem is more acute in the hospital setting, where methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Enterococcus faecalis* have emerged as the major problem bacteria. In the community, infections caused by penicillin- and macrolide-resistant *Streptococcus pneumoniae* are also proving to be a major problem.

Vancomycin has been the drug of choice for infections caused by Gram-positive cocci, but there are major drawbacks to its use, one of which is its lack of oral bioavailability, necessitating administration by the intravenous route. The emergence of vancomycin-resistant enterococci (VRE) cautions against the indiscriminate use of vancomycin in the intensive care unit. However, it is with the recent emergence of vancomycin-intermediate *S. aureus* (VISA) that the situation has become even more alarming, with experts raising the possibility of a return to the preantibiotic era.

One approach would be to discover and develop new classes of antimicrobials which are completely synthetic in nature. This would ensure that the target pathogens have no prior exposure, and therefore no preexisting resistance to the drug. The (*S*)-3-aryl-5-acetamidomethyl-2-oxazolidinones, first discovered and reported in 1987, are a novel class of totally synthetic antibacterial agents. Oxazolidinones have a number of intriguing attributes, including: 1) a unique mechanism of action that involves inhibition of protein synthesis at a very early stage, providing a lack of cross-resistance with existing antimicrobials; 2) a spectrum of activity that includes a number of important bacterial species; 3) activity in animal models of human infection when administered by either the oral or the parenteral route; and 4) sufficient structural latitude to allow for activity and/or toxicity modifications.

Linezolid was the first antibacterial drug in a new class now available for the treatment of infections associated with vancomycin-resistant *Enterococcus faecium* (VREF), including bloodstream infections, hospital-acquired pneumonia and complicated skin and skin structure infections, including cases due to MRSA. Although the most frequently reported side effects attributed to linezolid in clinical studies were headache, nausea, diarrhea and vomiting, the decrease in platelet counts observed in laboratory tests in patients receiving linezolid is of particular concern.

For linezolid, preclinical data demonstrate dose- and time-dependent myelosuppression, as evidenced by bone marrow hypocellularity, decreased hematopoiesis and decreased levels of circulating erythrocytes, leukocytes and platelets. The hematopoietic effects occurred at doses of 40 and 80 mg/kg/day in dogs and rats, respectively, exposures approximately 0.6 times and equal to the expected human exposure based on AUC, respectively. These hematopoietic effects were reversible, although in some studies reversal was incomplete within the duration of the recovery period.

RBx-7644 is a new synthetic extended-spectrum oxazolidinone antibiotic which shows excellent aqueous solubility and is therefore suitable for both oral and intravenous use, as well as an improved tolerability profile in preclinical studies.

Pharmacological Actions

Transcription and translation have proved to be valuable targets for antibiotic discovery. A number of marketed antibiotics inhibit bacterial growth through inhibition of prokaryotic RNA transcription and protein translation. Like linezolid, RBx-7644 has a novel mode of action, binding to the 50S ribosomal subunit and preventing it from forming a complex with the 30S subunit and initiation factors. The result is blockade of the initiation of protein biosynthesis in prokaryotes, a target not exploited by any previous antibiotic. Most existing protein synthesis inhibitors, such as chloramphenicol, macrolides, ketolides and tetracyclines, inhibit peptide elongation, and the aminoglycosides cause misreading of mRNA, leading to the synthesis of defective proteins.

An *in vitro* cell-free transcription and translation assay was used to establish the mechanism of action of RBx-7644. The commercially available *Escherichia coli* S30 extract system for circular DNA (Promega) was used for this purpose. The translation of the luciferase reporter gene was monitored by measuring luminescence. It was demonstrated that, like linezolid, RBx-7644 inhibited cell-free transcription-coupled translation in *E. coli* with an IC_{50} of approximately 10 μM.

The *in vitro* evaluation of the antibacterial spectrum and potency of RBx-7644 against cliniccal isolates has been extensive. It includes initial studies conducted by Ranbaxy Laboratories and numerous studies conducted in academic and clinical laboratories in both India and the U.S. To date, RBx-7644 susceptibility data are available against 1,541 bacterial isolates.

RBx-7644 demonstrates a spectrum covering primarily Gram-positive microorganisms, inhibiting all strains of staphylococci (including MRSA and methicillin-resistant *Staphylococcus epidermidis* [MRSE]), enterococci (including vancomycin-resistant strains) and pneumococci (including penicillin-intermediate and penicillin-resistant strains) at a concentration of 2 μg/ml or less. This compound also demonstrates significant activity against *Bacillus* spp. at a concentration of 0.6 μg/ml, as

Table I: In vitro activity of RBx-7644 against target pathogenic microorganisms.

Organism	n	Drug	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Geometric mean MIC
Gram-positive cocci	371	RBx-7644	1	2	0.947
		Linezolid	2	2	1.434
		Vancomycin	1	32	1.342
Staphylococcus aureus	201	RBx-7644	1	2	1.273
		Linezolid	2	2	1.701
		Vancomycin	1	1	0.898
MSSA	48	RBx-7644	1	2	1.059
		Linezolid	2	2	1.782
		Vancomycin	1	1	0.794
MRSA	152	RBx-7644	2	2	1.351
		Linezolid	2	2	1.674
		Vancomycin	1	1	0.938
Coagulase-negative staphylococci	54	RBx-7644	0.5	2	0.364
		Linezolid	1	2	1.053
		Vancomycin	1	2	1.167
Enterococcus faecalis	33	RBx-7644	1	2	1.26
		Linezolid	2	2	1.49
		Vancomycin	4	32	6.088
Enterococcus faecium	37	RBx-7644	2	4	1.821
		Linezolid	2	2	1.428
		Vancomycin	32	32	14.845
Streptococcus pneumoniae	31	RBx-7644	0.25	1	0.342
		Linezolid	1	2	0.939
		Vancomycin	0.25	0.5	0.261
*Streptococcus pneumoniae**	264	RBx-7644	0.25	1	0.403
		Linezolid	1	2	1.289
		Vancomycin	0.25	0.25	0.226
Haemophilus influenzae	10	RBx-7644	16	32	6.926
		Linezolid	8	16	7.511
		Vancomycin	32	32	32
Moraxella catarrhalis	3	RBx-7644	-	2	0.79
		Linezolid	-	8	5.04
		Vancomycin	-	32	32
Neisseria gonorrhoeae	17	RBx-7644	2	16	1.03
		Linezolid	8	16	6.264
		Vancomycin	16	16	10.217
Anaerobes	30	RBx-7644	0.032	0.25	0.055
		Linezolid	1	2	0.977
		Vancomycin	16	32	7.127
Anaerobes*	306	RBx-7644	0.032	0.25	0.037
		Linezolid	1	4	1.134
		Metronidazole	0.5	2	0.48

*Conducted at Prof. Applebaum's laboratory, U.S.A.

well as *Moraxella catarrhalis* (MIC_{90} = 2 μg/ml) and mycobacteria (1-5).

RBx-7644 demonstrates moderate activity (MIC_{90} = 16-32 μg/ml) against *Haemophilus influenzae* and *Neisseria gonorrhoeae*. As other oxazolidinones, RBx-7644 is inactive against members of the *Enterobacteriaceae* family and *Pseudomonas*. Against anaerobic bacteria, RBx-7644 demonstrates significant *in vitro* activity. It is a potent inhibitor of Gram-positive anaerobes (MIC = 0.03-0.25 μg/ml), and it also has significant activity against Gram-negative anaerobes (*e.g.*, MIC = 0.06-0.12 μg/ml against *Bacteroides* spp.) (1, 4, 6). A summary of the activity of RBx-7644 against key target species is shown in Table I.

The *in vitro* susceptibility results for RBx-7644 were tested against 479 consecutive clinical isolates of Gram-positive pathogens from several institutes in various parts of India (5). The key species identified as pathogenic organisms in samples of pus, blood, urine, bone curettings, vaginal and wound swabs, swabs from surgical wound and graft sites, *etc.*, consisted mainly of *S. aureus*, *S. pneumoniae*, enterococci, coagulase-negative staphylococci (CoNS), group A streptococci (GAS), group B streptococci and *Bacillus* spp. The results demonstrated that, irrespective of the underlying resistance to other antibiotics, all clinical isolates were sensitive to RBx-7644, as estimated by a disk diffusion technique with a bacterial inhibition zone diameter of ≥ 19 mm.

In vitro activity was also tested at Hershey Medical Center, U.S.A., against 118 methicillin-resistant staphylococci (59 *S. aureus* and 59 CoNS), 264 *S. pneumoniae*

Table II: In vitro activity of RBx-7644 against anaerobic bacteria.

Drug	All anaerobes (n=305)	*Bacteroides fragilis* (n=75)	*Prevotella* and *Porphyromonas* (n=57)	*Fusobacterium* spp. (n=36)	*Peptostrepto-coccus* spp. (n=52)	*Clostridum perfringens* (n=20)	*Clostridium difficile* (n=10)
RBx-7644	0.5	0.125	0.25	1	0.016	0.06	0.03
Linezolid	4	4	2	1	2	2	2
Quinupristin/dalfopristin	>8	8	4	>8	1	0.5	2
Amoxicillin	128	>128	64	2	0.5	0.25	2
Amoxicillin + clavulanic acid	2	8	2	2	0.5	<0.125	2
Clindamycin	8	>32	32	16	1	1	>32
Metronidazole	4	1	2	0.5	2	1	0.5
Vancomycin	>16	>16	>16	>16	1	1	4
Teicoplanin	>16	16	8	>16	0.125	0.125	0.25
Imipenem	1	1	0.06	1	0.125	0.25	4
Gatifloxacin	4	8	4	4	2	1	2
Moxifloxacin	2	8	4	4	2	0.5	2

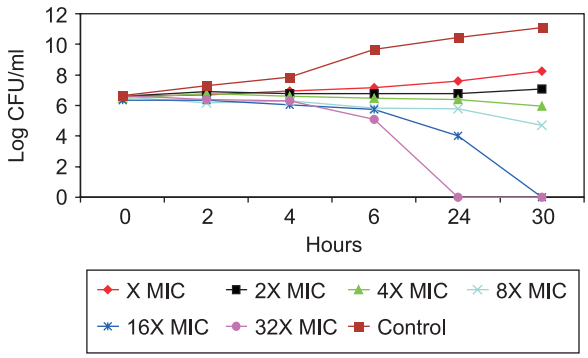


Fig. 1. Kill kinetics of RBx-7644 against MRSA 562 at various MIC levels.

(including 90 penicillin-sensitive, 92 penicillin-intermediate, 82 penicillin-resistant, 110 erythromycin-resistant and 26 quinolone-resistant strains) and 306 anaerobes (including 75 *B. fragilis*, 57 *Prevotella/Porphyromonas*, 36 fusobacteria, 52 *Peptostreptococcus*, 41 Gram-positive non-spore-forming rods and 45 clostridia). Results indicated that RBx-7644 was active against all methicillin-resistant staphylococci, with an MIC_{90} of 2 µg/ml, and against all strains of *S. pneumoniae*, irrespective of susceptibility to penicillin, erythromycin or quinolones. Moreover, its activity was 1-3 dilutions better than linezolid. Against anaerobes, RBx-7644 was by far the most active molecule (2-4, 6, 7) (Table II).

To study the dynamic interaction between RBx-7644 and the target pathogens, killing kinetics were investigated at different concentrations of drug (Fig. 1). The activity was essentially bacteriostatic and concentration-independent, although there was a hint of concentration-dependent killing at higher concentrations after prolonged exposure of the bacteria to the drug. The target pathogens studied included MRSA and MRSE, *E. faecium* and *S. pneumoniae*.

The effects of inoculum size, pH and the presence of protein on the MIC values of RBx-7644 were evaluated in different experiments using the agar dilution method and Gram-positive bacteria. The MIC of RBx-7644 did not increase by more than a 1-fold dilution, even with a 2 log increase in the inoculum size. Similar effects were also observed with linezolid. The MIC of RBx-7644 did not change when the pH varied between 5.5 and 8.5, nor in the presence of either 25% serum or 5% human albumin. Similar effects were observed with linezolid.

The *in vitro* postantibiotic effect (PAE) of RBx-7644 was dependent upon both duration of exposure and drug concentration. Exposure of MRSA strain 562 to RBx-7644 for 1 and 2 h at 8 x MIC produced a PAE of 3 and 5 h, respectively. In the same set of experiments, linezolid demonstrated a PAE of 2 and 3 h following exposure to 8 x MIC for 1 and 2 h, respectively. The PAE was shorter for vancomycin. The PAE of RBx-7644 was also assessed in a neutropenic murine thigh infection caused by *S. aureus* (MRSA strain 562) and was found to be 2.8 and 3.2 h, respectively, at doses of 25 and 75 mg/kg, respectively. Similarly, in the same animal model, RBx-7644 at doses of 25 and 75 mg/kg demonstrated an *in vivo* PAE of 5 and 8 h, respectively, against infections due to *S. pneumoniae* AB34, and of 7 and 8 h, respectively, against infections caused by CoNS strain 879 (8) (Fig. 2).

The effect of combining RBx-7644 with other antimicrobials was examined by calculating the fractional inhibitory concentration index (FIC index) using the following formula: FIC index = A + B MICA MICA.

An FIC index of 0.5 or less was interpreted as synergy, 0.5-4 as indifference/additive effect and > 4 as antagonism. RBx-7644 combined with other common antibacterial drugs such as aztreonam (FIC = 1), amikacin (FIC = 2), ceftriaxone (FIC = 2), clarithromycin (FIC = 0.75), quinupristin/dalfopristin (FIC = 0.75) and vancomycin (FIC = 2) produced primarily an additive/indifferent response when tested *in vitro* against *S. aureus* or *E. coli*. No antagonism was observed with any drug.

Linezolid is active against nearly all clinically relevant Gram-positive pathogens, with MIC_{90} values of 2-4 µg/ml, but within months of clinical use resistance has been reported in VRE and MRSA. The common feature in both reports is the presence of a foreign body (catheter) in

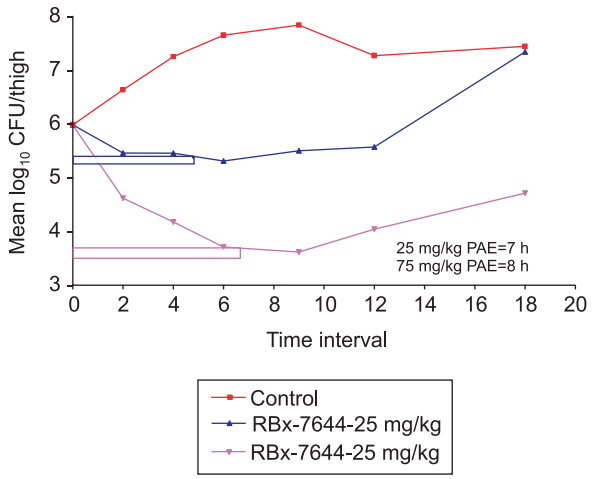


Fig. 2. *In vivo* postantibiotic effect of RBx-7466 against CoNS 879.

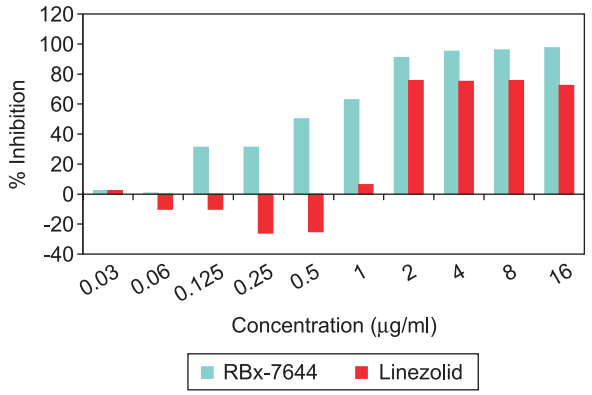


Fig. 3. Inhibition of biofilm formation (MRSA 1026/99).

these patients, leading to treatment failure and development of resistant mutants. To assess the potential for the development of resistance to RBx-7644, the effects of linezolid and RBx-7644 on inhibition of biofilm formation by MRSA 1026/99 and MRSE 654 were studied. The findings are depicted in Figures 3 and 4.

The change in the MIC of linezolid, vancomycin, quinupristin/dalfopristin and RBx-7644 in a glass-adherent bacteria model using MRSE 879 bacteria was investigated. The results can be seen in Table III.

Using NCCLS methods, the MIC of RBx-7644 was determined by an agar dilution method against 275 Gram-positive clinical isolates and 3 ATCC QC strains. Simultaneously, disk diffusion tests were performed using 5-, 15- and 30-µg disks. In order to determine the QC ranges against *S. aureus* ATCC 25923, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619, MIC and disk diffusion tests were performed on 12 different days. The MIC for all Gram-positive bacteria tested was ≤ 4 µg/ml, with an MIC_{90} of 2 µg/ml. The 30-µg disk resulted in a zone diameter of ≥ 19 mm for each of these isolates. With QC strains, for *S. aureus* ATCC 25923 the MIC range was 0.5-2 µg/ml and zone diameter 19-24 mm, for *E. faecalis* ATCC 29212 the MIC range was 1-4 µg/ml and zone diameter 19-24 mm, and for *S. pneumoniae* ATCC 49619 the MIC range was 0.125-0.5 µg/ml and zone diameter 29-34 mm. The susceptibility of staphylococci, enterococci and streptococci thus appears to be monomodal. Zone diameter breakpoints of ≥19 mm (MIC ≤ to 4 µg/ml) for susceptibility were recommended (5).

The *in vivo* activity of RBx-7644 was assessed in numerous animal models, including systemic, pulmonary and localized infection models in mice. In these studies, the predominant routes of administration were oral and intravenous, although subcutaneous administration was also employed in some instances. The selection of models was intended to support specific clinical claims being sought for RBx-7644. RBx-7644 was highly effective in mouse models of Gram-positive infections, including methicillin-sensitive *S. aureus* (MSSA), MRSA, MRSE, group A streptococci (GAS), *S. pneumoniae* and *E. faecalis*. Its activity is equal or superior to that of linezolid, vancomycin and Synercid (quinupristin/dalfopristin). Similar results were obtained in murine models of skin and skin structure infections caused by MRSA, GAS and group B streptococci, and in pulmonary infections caused by *S. pneumoniae* or MRSA. The activity of the drug was best (in mice) when administered more frequently rather than when the total dose was administered as a single

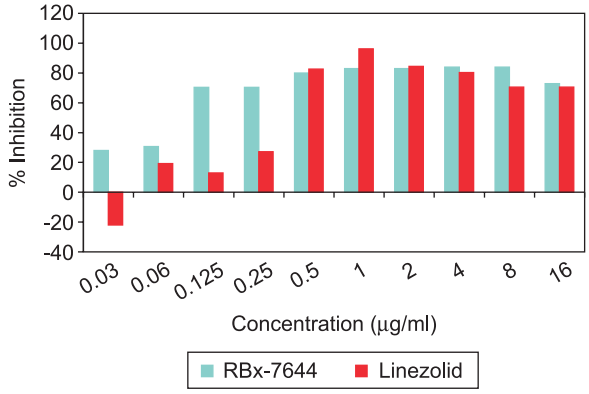


Fig. 4. Inhibition of biofilm formation (MRSE 654).

Table III: Change in MIC between bacteria in suspension and on sintered glass.

Drug	MIC in broth (µg/ml)	MIC on sintered glass adherent bacteria (µg/ml)
RBx-7644	0.5	2
Linezolid	2	32
Synercid	0.5	2
Vancomycin	2	8

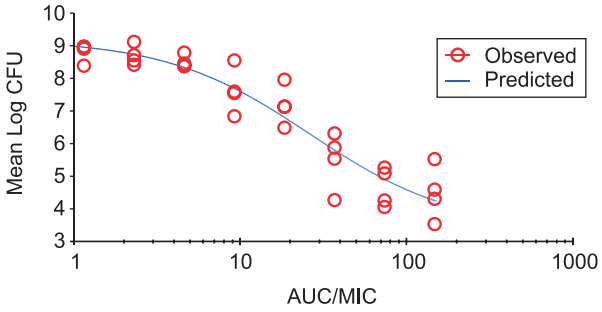


Fig. 5. Effect of AUC/MIC *versus* mean log CFU/thigh.

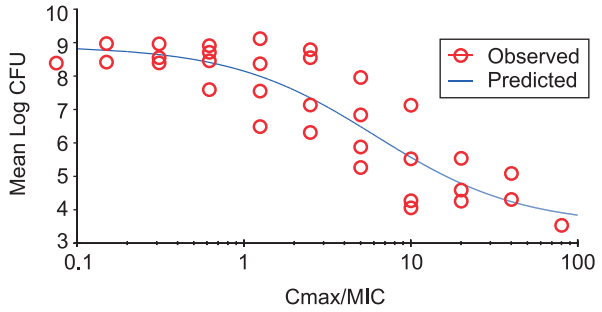


Fig. 6. Effect of C_{max} *versus* mean log CFU/thigh.

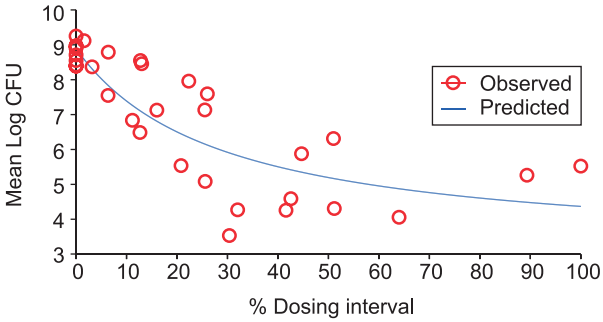


Fig. 7. Effect of dosing interval on mean CFU/thigh.

bolus dose. To investigate the effect of RBx-7644 on foreign body infections, catheter pieces were dipped in bacterial suspension and implanted into rats. Rats were dosed orally at different time intervals and bacterial load after treatment was determined. RBx-7644 decreased bacterial load in a dose-dependent manner (9).

The key pharmacokinetic/pharmacodynamic efficacy correlate for RBx-7644 in a mouse thigh infection model of MRSA 562 was found to be the amount of time the serum concentration exceeded the MIC (T > MIC). Efficacy was achieved when drug concentrations were maintained above the MIC for 40% of the dosing interval (10) (Figs. 5-7).

A total of 58 receptors and 5 enzyme targets, along with effects in many relevant *in vitro* and *in vivo* animal models representing different physiological systems, were studied for predicting the side effect profile. It was concluded that RBx-7644 is a safe compound. The few undesired effects observed were not considered important, as they appeared only at very high concentrations, which may not be relevant to human administration, or were seen only in *in vitro* systems. The effects of RBx-7644 on MAO-A, pentobarbitone sleeping time and gastric emptying are similar to those reported for linezolid. RBx-7644 displayed an LD_{50} of 2113.72 mg/kg in mice and 1519.4 mg/kg in rats by the oral route.

Doses used for 28-day repeated-dose toxicity studies in rats were 20, 50 and 125 mg/kg/day as a solution in water, given by oral gavage. The degree and extent of exposure of RBx-7644 following equally divided twice-daily doses at 8-h intervals were dose-dependent, with no indication of autoinduction/inhibition of drug-metabolizing enzymes. All animals were in good health during administration and recovery periods. The drug was well tolerated throughout the experiment. The no-effect dose level (NOEL) of RBx-7644 in Wistar rats after repeated doses for 28 consecutive days was 50 mg/kg/day (11).

In 28-day repeated-dose oral toxicity studies in dogs, doses of 20, 40 and 80 mg/kg/day were well tolerated by all animals. At the end of the administration period, hematological examination revealed a decrease in red blood cells only at the highest dose in males. These values returned to normal during recovery. The NOEL was considered to be 40 mg/kg/day in dogs (11).

RBx-7644 did not show any genotoxic potential in the bacterial reverse-mutation (Ames) assay, in vitro chromosomal aberrations in cultured human lymphocytes, or in the in vivo bone marrow micronucleus and bone marrow chromosomal aberration tests in Swiss albino mice (11).

Pharmacokinetics and Metabolism

RBx-7644 is mainly metabolized by CYP 3A4 in human liver microsomes. It shows partial inhibition (25-50%) of CYP 2E1 at concentrations of 7-200 µM. The IC50 for CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 was > 200 µM. Six *in vitro* metabolites were observed upon incubating RBx-7644 with mouse and rat liver microsomes and one major metabolite has been identified.

The pharmacokinetics of RBx-7644 were evaluated in mice, rats and dogs after oral and intravenous administration. The absolute bioavailability of the compound was 126.7% in mice, 107.3% in rats and 65.85% in dogs. The total body clearance of RBx-7644 in mice, rats and dogs was 1.3, 0.73 and 0.45 l/kg/h, respectively. The apparent volume of distribution was found to be 1.9, 2.3, 3.9 l/kg in mice, rats and dogs, respectively, and the mean terminal half-life was 1.25, 1.86 and 5.83 h, respectively. Urinary recovery of unchanged compound was about 25% in male rats at 24 h after oral dosing. The exposure in all

species was dose-proportional over the range of doses evaluated, with no gender-based differences.

In rats, twice-daily oral or i.v. dosing of RBx-7644 at 8-h intervals for 28 days indicated no gender differences and no accumulation. The exposure was dose-proportional, with no indication of autoinduction or inhibition. There was 70% less exposure after oral compared to after i.v. dosing.

A 28-day toxicokinetic study of RBx-7644 was conducted in dogs in the dose range of 20-80 mg/kg p.o. administered twice daily at 8-h intervals. The results indicated that there was minimal accumulation after doses of 20 and 40 mg/kg, but at 80 mg/kg the C_{max} increased by 2.6-fold and the AUC by 1.9-fold. No gender differences were seen.

Clinical Studies

A phase I study was conducted in the U.K. to investigate the safety, tolerability and pharmacokinetics of single oral doses of RBx-7644 in healthy male subjects. The results of the study suggested that RBx-7644 is safe and well tolerated, with a maximum tolerated dose in healthy male subjects of 600 mg. RBx-7644 administered as single doses had no significant effect on the cardiovascular system, hepatic, renal and metabolic functions. RBx-7644 shows linear kinetics across the dose range tested and is rapidly absorbed ($t_{max} \approx 1$ h). The mean terminal plasma half-life was dose-independent (1.52-1.76 h), and the C_{max} and AUC showed dose proportionality up to 800 mg; T > MIC (2 μg/ml) after a single 800-mg dose was nearly 5 h.

Source

Ranbaxy Laboratories Ltd. (IN).

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