Drugs of the Future 1998, 23(6): 591-597

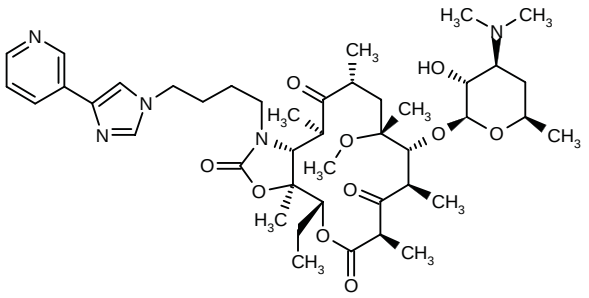
CCC: 0377-8282/98

HMR-3647

Ketolide Antibacterial

RU-66647

11,12-Dideoxy-3-des(2,6-dideoxy-3-C,3-*O*-dimethyl-α-L-altropyranosyloxy)-6-*O*-methyl-3-oxo-12,11-(oxycarbonylimino)-N^{11}-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]erythromycin A



$C_{43}H_{65}N_5O_{10}$ Mol wt: 812.01

CAS: 173838-31-8

EN: 230662

Synthesis

The selective mesylation of 2'-*O*-acetyl-3-des(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-ribohexopyranosyloxy)-6-*O*-methyl-3-oxoerythromycin A (I) with methanesulfonic anhydride in pyridine gives the expected 11-*O*-methanesulfonyl derivative (II), which is treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetone to yield the 10,11-didehydro derivative (III). The acylation of (III) with carbonyl diimidazole (IV) by means of NaH in THF affords the 12-*O*-acyl derivative (V) (1), which is finally cyclocondensed with 4-[4-(3-pyridyl)imidazol-1-yl]butylamine (VI) in hot acetonitrile (2, 3). Scheme 1.

The starting compound 4-[4-(3-pyridyl)imidazol-1-yl]butylamine (VI) is obtained as follows: The condensation of *N*-(4-bromobutyl)phthalimide (VII) with 4-(3-pyridyl)imidazole (VIII) by means of NaH in DMF gives *N*-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]phthalimide (IX), which is then treated with hydrazine in refluxing ethanol (2, 3). Scheme 1.

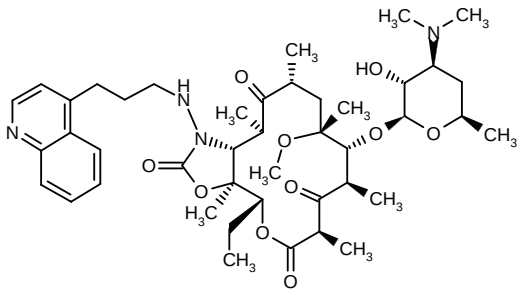
Description

Crystals, m.p. 187-8 °C (2, 3).

Introduction

The ketolides are a newer class of antimicrobial compounds. These broad-spectrum, semisynthetic macrolide compounds are characterized by a 3-keto function that replaces the α-L-cladinose moiety typically found in the erythronolide A ring in other macrolide compounds. Like the macrolides, streptogramins, lincomycin and chloramphenicol, the ketolides target ribosomes with high affinity for the 50S subunit of the organelle and subsequently inhibit bacterial protein synthesis. Although their sites of action are very similar, the subtle differences between them are sufficient to result in fundamentally different spectrums of activity (4). The ketolides are especially effective against respiratory pathogens, with a spectrum that encompasses Gram-positive, Gram-negative and atypical bacteria (*Legionella*, *Mycoplasma*, *Chlamydia*), *H. influenzae* and multidrug-resistant pneumococci (5).

As part of the ongoing search for antibacterial agents to treat infections caused by macrolide-resistant streptococci, scientists at Hoechst Marion Roussel synthesized a group of new ketolides with activity against macrolide-lincosamide-streptogramin B-resistant pneumococci and identified an early compound, RU-004 (HMR-3004) [I], which displayed good activity during extensive preclinical testing (6). Further optimization of these 11,12-cyclo-disubstituted ketolides eventually culminated in the discovery of the more potent compound, HMR-3647 (RU-66647), which was selected for further testing (7).



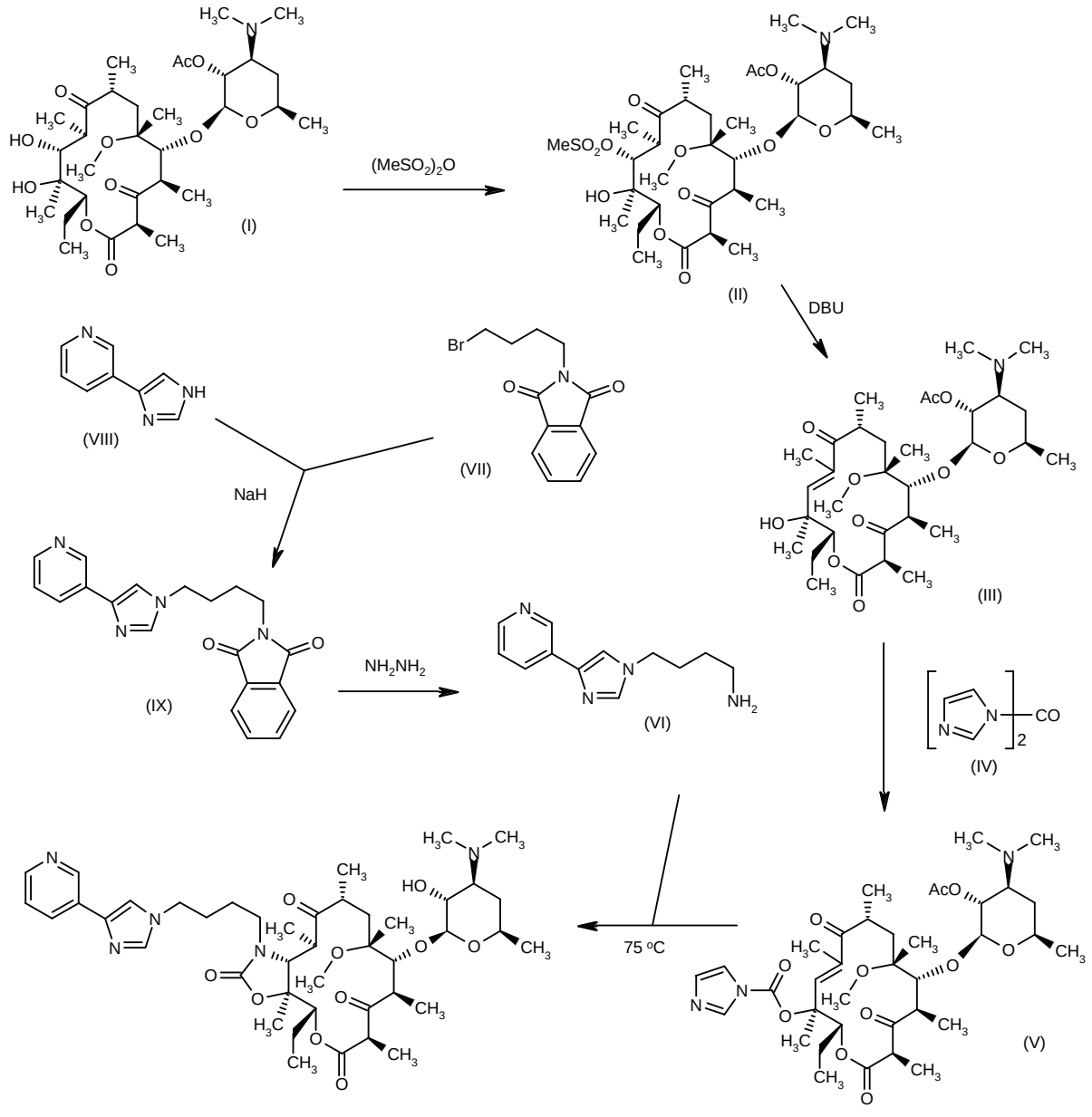
[I]

Pharmacological Actions

Susceptibility to HMR-3647 was tested *in vitro* against 230 penicillin- and erythromycin-susceptible and -resis-

A. Graul, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of HMR-3647



tant strains of pneumococci, and the activity of the ketolide was compared to that of various other antibiotics, including erythromycin, azithromycin, clarithromycin, roxithromycin, rokitamycin, clindamycin, pristinamycin, ciprofloxacin, sparfloxacin, imipenem, doxycycline and chloramphenicol. HMR-3647 displayed potent activity against all the strains tested (MIC_{90}s = 0.03 and 0.25 µg/ml for erythromycin-susceptible and -resistant strains, respectively). MIC_{90}s for the other macrolides were only significant in the case of erythromycin-susceptible organisms. Of all the macrolides tested, HMR-3647 showed the best time-kill kinetics against 11 erythromycin-sensitive and -resistant strains; only pristinamycin showed more rapid killing (8).

The compound displayed potent antipneumococcal activity *in vitro*, even against penicillin-resistant strains of *Streptococcus pneumoniae*, with better activity than that of quinupristin/dalfopristin, erythromycin, clindamycin and

other related compounds based on time-kill kinetics (9-13). Killing curves showed reductions of 5.2-5.9 logs at 2 h after drug exposure in penicillin- and erythromycin-susceptible strains and 3.1-3.5 logs at 2 h after drug exposure in penicillin- and erythromycin-resistant strains. The postantibiotic effect of HMR-3647 was estimated to be 7 h (12).

HMR-3647 showed excellent *in vitro* activity against respiratory pathogens (14), including *Chlamydia pneumoniae* (MIC_{90} = 0.25 μg/ml) (15), and against clinical isolates of *Enterococcus* spp., including vancomycin-resistant strains (MIC_{90} range ≤ 0.03-4.0 μg/ml) (16). It also showed potential in the treatment of sexually transmitted and pelvic inflammatory infections, and skin and soft tissue infections (17), and was active against *Legionella* spp. (MIC_{90} = 0.03 μg/ml) (18, 19) and *Toxoplasma gondii* (IC_{50} = 3.92-0.13 μg/ml after 24-72 h of exposure) (20).

The potent *in vitro* activity of HMR-3647 against *Staphylococcus aureus* and coagulase-negative staphylococci indicates that the compound deserves further evaluation for the treatment of staph infections (21). It was also found to possess favorable activity against *Corynebacterium diphtheriae* (MIC_{90} = 0.008 mg/l), a reemergent pathogen of clinical significance in Eastern Europe, and other coryneform bacteria from clinical samples (22, 23). The *in vitro* activity of HMR-3647 as compared to 12 other compounds, including erythromycin A, against strains of Gram-positive bacteria indicates that the compound has potential in the treatment of anaerobic infections (24, 25).

HMR-3647 also demonstrated potent activity against 90 strains of lactic acid bacteria, including 60 strains of *Lactobacillus*, 12 of *Leuconostoc* and 18 of *Pediococcus*, giving an average MIC_{90} of 0.015 μg/ml (range ≤ 0.0007-4.0 μg/ml) (26). Its activity was also proven against Gram-positive strains with acquired resistance to erythromycin (27-30), as well as other multidrug-resistant strains (31). Efficacy was furthermore demonstrated against *Bordetella pertussis* and *B. parapertussis* (MIC_{90} = 0.03 μg/ml), with more potent activity than reference macrolides and ansamycins (32). During the course of *in vitro* testing, HMR-3647 was consistently more active than erythromycin and similar in activity to clindamycin (33, 34). The low MICs against many strains tested, together with the postantibiotic effect of HMR-3647, indicate that it will have an increased dosing interval (35).

The excellent activity of HMR-3647 against *S. pneumoniae* and *S. aureus* was demonstrated in mice. In a thigh infection in neutropenic mice, HMR-3647 was active against both *S. aureus* and macrolide-susceptible *S. pneumoniae*, being 1.5-, 2.5- and 4-fold more active than azithromcyin, clarithromycin and roxithromycin, respectively; it was also active against macrolide-resistant *S. pneumoniae* in this model (36, 37). Based on the good activity seen in neutropenic mice, a subsequent study was designed to evaluate the impact of neutrophils on the *in vivo* activity of HMR-3647 and other ketolides. Neutropenic and nonneutropenic mice infected with *S. pneumoniae* were treated for 24 h with either HMR-3647 or HMR-3004 (0.29-75 mg/kg in 4 divided doses). The potency of the ketolides was enhanced 1.8- to 24-fold in the presence of neutrophils, with the most significant increase in potency observed in the case of *S. pneumoniae* strains resistant to both erythromycin and clindamycin. The potency of HMR-3647 increased by 1.8- to 4.4-fold in erythromycin-susceptible and erythromycin-resistant, clindamycin-susceptible strains in the presence of neutrophils (38).

Promising activity was also observed in murine models of severe community-acquired pneumonia resulting from infection by erythromycin-resistant pneumococci (MIC = 0.3 mg/l), *Haemophilus influenzae* (MIC = 0.3-1.2 mg/ml) or atypical bacteria. HMR-3647 showed good pulmonary diffusion and a slightly longer half-life than those of reference macrolides in the same model (39-41). Based on its activity against these common respiratory pathogens, HMR-3647 appears to be a very promising candidate for the treatment of infections caused by difficult-to-treat respiratory pathogens (40, 41).

Good activity was seen in a model of disseminated *Mycobacterium avium* disease in beige mice that were treated with HMR-3647 (100, 200 or 400 mg/kg/day), resulting in significant and dose-dependent reductions in bacterial load in the blood, liver and spleen as compared to controls (42).

Clinical efficacy in the treatment of toxoplasmosis, such as that encountered in transplant recipients, has also been suggested based on the promising results obtained in a murine model of *Toxoplasma gondii* infection, in which 100% of mice infected with cysts were protected with the compound at a dose of 30 mg/kg/day x 10 days (43). The activity against *T. gondii* of HMR-3647 was enhanced significantly when administered in combination with other drugs typically used to treat this infection, such as atovaquone, clindamycin or sulfadiazine (44).

Based on the demonstrated efficacy of HMR-3647 against *Bacteroides fragilis in vitro*, the *in vivo* activity of the compound in treating experimental abdominal abscesses caused by *B. fragilis* in mice was studied. Preliminary data indicate that the compound, administered at doses of 1.25 or 2.0 mg b.i.d., was at least as effective as clindamycin and more effective than either metronidazole or cefotetan (45).

Based on bacterial counts obtained after 24 h of treatment with HMR-3647 in neutropenic mice infected with *S. pneumoniae*, and on the 80-100% survival in drug-treated animals as compared to 100% mortality in untreated infected controls, it appears that survival results with longer courses of therapy can be predicted from bacterial counts at 24 h (46).

Development of bacterial resistance to the effects of antibacterial agents is a known hazard of their use. Thus, an *in vitro* study was conducted in order to determine the selection of HMR-3647-resistant mutants of *S. pneumoniae* and *S. aureus*. The results of the study indicate that, if used at adequate dosages, there is very little likelihood

of developing resistance during drug therapy with HMR-3647 (47).

Pharmacokinetics and Pharmacodynamics

An *in vitro* pharmacodynamic study was conducted to determine the time-kill kinetics and postantibiotic effect of HMR-3647 on respiratory pathogens, enterococci and *Bacteroides fragilis*. Time-kill kinetics indicated that the compound is primarily bacteriostatic, with slow bactericidal activity observed only at much higher concentrations. A significant postantibiotic effect was observed with all strains tested, although with considerable variation between strains and species, ranging from 1.2-8.2 h at concentrations 10 times the MIC (48).

The *in vivo* pharmacodynamics and single-dose pharmacokinetics of HMR-3647 were tested in mice infected with *S. pneumoniae*. The compound, administered as subcutaneous doses of 4.68, 18.8 and 75 mg/kg, gave respective half-life values of 89.7, 149 and 205 min, and respective AUC values of 10.6, 30.2 and 80.4 mg.h/l. The dose-response curve was affected only slightly by lengthening the dosing interval. The AUC/MIC ratio obtained for the drug, which was found to be the factor that best correlated with efficacy, indicated that once-daily dosing will be appropriate with this ketolide in human studies (49).

Toxicity

HMR-3647 was administered to healthy mice at doses of up to 300 mg/kg/day for 10 days in order to determine its potential toxic effects. Animals treated at this dose level did not show signs of weight loss or any other indications of toxicity (43).

Clinical Studies

HMR-3647 is currently in phase I clinical testing, and is expected to progress to phase II/III during the spring or summer of 1998 (50).

Manufacturer

Hoechst Marion Roussel (FR).

References

1. Agouridas, C., Bonnefoy, A., Chantot, J.-F., Le Martret, O., Denis, A. (Roussel-Uclaf). *Erythromycin derivs., their process of preparation and their application as medicaments.* CA 2102457, EP 596802, FR 2697523, FR 2707088, JP 94220082, US 5527780.

2. Agouridas, C., Chantot, J.-F., Denis, A., Govin D'Ambrieres, S., Le Martret, O. (Roussel Uclaf). *Novel erythromycin derivs., method for their preparation and their use as drugs.* EP 680967, FR 2719587, JP 96053489, US 5635485, WO 9529929.

3. Agouridas, C., Chantot, J.-F., Denis, A., Govin D'Ambrieres, S., Le Martret, O. (Roussel Uclaf). *Novel erythromycin derivs., their process of preparation and their application as medicines.* FR 2732684.

4. Agouridas, C., Collette, P., Mauvais, P., Chantot, J.F. RU 004: *Preliminary studies on the mechanism of action.* 35th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, San Francisco) 1995, Abst F170.

5. Agouridas, C., Bonnefoy, A., Chantot, J.F. *In vitro antibacterial activity of RU 004, a novel ketolide highly active against respiratory pathogens.* 35th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, San Francisco) 1995, Abst F158.

6. Agouridas, C., Benedetti, Y., Denis, A., Le Martret, O., Chantot, J.F. *Ketolides: A new distinct class of macrolide antibacterials – Synthesis and structural characteristics of RU 004.* 35th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, San Francisco) 1995, Abst F157.

7. Chantot, J.F., Agouridas, C., Bonnefoy, A. *In vitro antibacterial activity of HMR 3647, a new ketolide highly active against respiratory pathogens.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.12.

8. Pankuch, G.A., Visalli, M.A., Jacobs, M.R., Appelbaum, P.C. *Susceptibilities of penicillin- and erythromycin-susceptible and -resistant pneumococci to HMR 3647 (RU 66647), a new ketolide, compared with susceptibilities to 17 other agents.* Antimicrob Agents Chemother 1998, 42: 624-30.

9. Barry, A.L., Brown, S.D., Fuchs, P.C. *Antipneumococcal activity of a ketolide (HMR 3647) and seven related drugs in vitro.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-107.

10. Pankuch, G.A., Jacobs, M.R., Appelbaum, P.C. *Antipneumococcal activity (MIC) of RU 66647, a new ketolide, compared to 16 other agents.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-108.

11. Visalli, M.A., Jacobs, M.R., Appelbaum, P.C. *Antipneumococcal activity of HMR 3647 (RU 66647), a new ketolide, compared to other drugs, by time-kill.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-109.

12. Negri, M.C., Morosini, M.I., Loza, E., Meseguer, M.A., Almaraz, F., Baquero, F. *The novel ketolide HMR3647 is highly active on antibiotic-susceptible and -resistant Streptococcus pneumoniae.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-110.

13. Barry, A.L., Fuchs, P.C., Brown, S.D. *Antipneumococcal activities of a ketolide (HMR 3647), a streptogramin (quinupristin-dalfopristin), a macrolide (erythromycin), and a lincosamide (clindamycin).* Antimicrob Agents Chemother 1998, 42: 945-6.

14. Agouridas, C., Bonnefoy, A., Chantot, J.F. *In vitro antibacterial activity of HMR-3647, a novel ketolide highly active against respiratory pathogens.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-112.

15. Roblin, P.M., Hammerschlag, M.R. *In vitro activity of a new ketolide antibiotic, HMR 3647, against Chlamydia pneumoniae.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-248.

16. Hoban, D., Karlowsky, J., Weshnoweski, B., Kabani, A., Zhanel, G. *In vitro activity of a new ketolide HMR 3647 against geographically diverse Canadian isolates of Enterococcus spp.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-119.

17. Felmingham, D., Robbins, M.J., Leakey, A., Cooke, R., Dencer, C., Salman, H., Ridgway, G.L., Grüneberg, R.N., Bryskier, A. *The comparative in vitro activity of HMR 3647, a ketolide antimicrobial, against clinical bacterial isolates.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-116.

18. Smith, R.P., Baltch, A.L., Ritz, W., Franke, M., Michelsen, P. *Antibacterial effect of ketolides HMR3004 and HMR3647 against intracellular Legionella pneumophila (L. pn.).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-249.

19. Schülin, T., Wennersten, C.B., Ferraro, M.J., Moellering, R.C. Jr., Eliopoulos, G.M. *Susceptibility of Legionella spp. to ketolide HMR 3647 and other newer antimicrobials.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-250.

20. Araujo, F., Khan, A., Bryskier, A., Remington, J. *Ketolides are active against Toxoplasma gondii*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-251.

21. Kitzis, M.D., Goldstein, F.W., Bismuth, R., Miegi, M., Acar, J.F. *Comparative in vitro activity of HMR 3647, a new ketolide antibiotic, against S. aureus (SA) and coagulase negative staphylococci (CNS).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-111.

22. Engler, K.H., Warner, M., George, R.C. *In vitro susceptibility of Corynebacterium diphtheriae to HMR 3647, a new macrolide.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-124.

23. Martinez-Martinez, L., Pascual, A., Suarez, A.I., Perea, E.J. *In vitro activities of ketolide HMR 3647, five macrolides, and clindamycin against coryneform bacteria isolated from clinical samples.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-246.

24. Ednie, L., Jacobs, M., Appelbaum, P. *Anti-anaerobic activity of the ketolide RU 66647 compared to 12 other compounds*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-122.

25. Ednie, L.M., Jacobs, M.R., Appelbaum, P.C. *Comparative antianaerobic activities of the ketolides HMR 3647 (RU 66647) and HMR 3004 (RU 64004).* Antimicrob Agents Chemother 1997, 41: 2019-22.

26. Torres, C., Zarazaga, M., Tenorio, C., Saenz, Y., Portillo, A., Baquero, F. *Susceptibility of Lactobacillus, Leuconostoc, and Pediococcus to ketolide HMR 3647 and other antibiotics.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-247.

27. Schülin, T., Wennersten, C.B., Moellering, R.C. Jr., Eliopoulos, G.M. *In vitro activity of HMR 3647 in comparison with erythromycin A against Gram-positive bacteria.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-113.

28. Marie-Bigot, C., Decre, D., Muller, C., Salgado, E., Bergogne-Berezin, E. *In vitro activity of a novel ketolide antimicrobial agent HMR3647 compared to erythromycin (ERY), roxithromycin (ROX), azithromycin (AZI) and clarithromycin (CLA).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-117.

29. Soriano, F., Calvo, R., Fernandez-Roblas, R. *In vitro activity of ketolide HMR 3647 (RU 66647) against Grampositive bacilli.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-118.

30. Dediste, A., Vlaes, L., Tridiani, R., Devaster, J.-M., Vandamme, P., Butzler, J.-P. *In vitro activity of ketolides RU004 and 647 and five other antibiotics against Arcobacter butzleri.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-245.

31. Malathum, K.T., Coque, T., Singh, K.V., Murray, B.E. *Studies of a new ketolide, HMR3647, against multiresistant Gram-positive cocci.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-115.

32. Hoppe, J.E., Bryskier, A. *In vitro susceptibilites of Bordetella pertussis and Bordetella parapertussis to two ketolides (HMR 3004 and HMR 3647), four macrolides (azithromycin, clarithromycin, erythromycin A, and roxithromycin), and two ansamycins (rifampin and rifapentine).* Antimicrob Agents Chemother 1998, 42: 965-6.

33. Reig, M., Moreno, A., Baquero, F. *Activity of the new ketolide HMR3647 against anaerobic bacteria.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-121.

34. Jones, R.N., Biedenbach, D.J. *Antimicrobial activity of RU-66647, a new ketolide.* Diagn Microbiol Infect Dis 1997, 27: 7-12.

35. Jacobs, M.R., Bajaksouzian, S., Chuang, J., Ronchetti, M.P., Appelbaum, P.C. *Postantibiotic effect of the ketolide HMR 3647 (RU 66647) on Gram positive cocci.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-253.

36. Vesga, O., Andes, D., Craig, W.A. *Comparative in vivo activity of HMR 3647, azithromzyin (AZ), clarithromycin (CL), and roxithromycin (RX) against S. pneumoniae (SP) and Staphylococcus aureus (SA).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-258.

37. Vesga, O., Craig, W.A. *Impact of macrolide resistance on the in vivo activity of a new ketolide, HMR 3647, against S. pneumoniae (SP) and S. aureus (SA).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-259.

38. Andes, D., Vesga, O., Craig, W. *Impact of neutrophils on the antimicrobial activity of ketolides in an animal infection model.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.19.

39. Rajagopalan-Levasseur, P., Vallee, E., Agouridas, C., Chantot, J.F., Bonnefoy, A., Bryskier, A., Carbon, C. *HMR 3647: Activity against erythromycin-resistant pneumococci and Haemophilus influenzae in murine pneumonia models.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-260.

40. Agouridas, C., Bonnefoy, A., Chantot, J.F. *In vivo antibacterial activity of HMR 3647, a novel ketolide highly active against respiratory pathogens.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-257.

41. Agouridas, C., Bonnefoy, A., Chantot, J.F. *In vivo antibacterial activity of HMR 3647, a novel ketolide highly active against respiratory pathogens.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.11.

42. Bermudez, L.E., Kolonoski, P., Wu, M., Young, L.S. *Efficacy of the ketolide HMR3647 in the treatment of disseminated Mycobacterium avium infection in mice.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.17.

43. Araujo, F.G., Khan, A.A., Slifer, T.L., Bryskier, A., Remington, J.S. *The ketolide antibiotics HMR 3647 and HMR 3004 are active against Toxoplasma gondii in vitro and in murine models of infection.* Antimicrob Agents Chemother 1997, 41: 2137-40.

44. Araujo, F.G., Khan, A.A., Bryskier, A., Remington, J.S. *Combinations of ketolides with other therapeutic agents are active against Toxoplasma gondii.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 5.18.

45. Thadepalli, H., Chuah, S.K., Thadepalli, F., Gollapudi, S. *HMR 3647 in the treatment of Bacteroides fragilis experimental abdominal abscess.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.14.

46. Craig, W.A., Andes, D., Vesga, O. *Is in-vivo activity of ketolides by bacterial counts at 24 hrs predictive of survival with prolonged therapy?* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.18.

47. Bonnefoy, A., Agouridas, C., Chantot, J.F. *HMR 3647: Antibacterial activity of resistance.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.24.

48. Boswell, F.J., Andrews, J.M., Wise, R. *Pharmacodynamic properties of HMR 3647, a novel ketolide, on respiratory pathogens, enterococci and Bacteroides fragilis demonstrated by studies of time-kill kinetics and postantibiotic effect.* J Antimicrob Chemother 1998, 41: 149-53.

49. Vesga, O., Bonnat, C., Craig, W.A. *In vivo pharmacodynamic activity of HMR 3647, a new ketolide.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-255.

50. *HMR-3647 development status.* Hoechst Marion Roussel Company Communication 1998, May 8.

Additional References

Biedenbach, D.J., Jones, R.J. *In vitro evaluation of new ketolides, RU-64004 and RU-66647 against macrolide-resistant Gram-positive pathogens.* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F221.

Hoechst – A new structure, a new chapter. Future: The Hoechst Magazine 1997, March, 61-5.

Wise, R., Andrews, J.M. *The in vitro activity of the new ketolide HMR 3647 against a wide range of clinical isolates.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-114.

Wexler, H.M., Molitoris, E., Finegold, S.M. *In vitro activity of HMR 3647 (RU 66647) compared to azithromycin (AZ), clarithromycin (CL), erythromycin (ER), and roxithromycin (RO).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-120.

Boswell, F.J., Andrews, J.M., Wise, R. *Pharmacodynamic properties of HMR 3647, a novel ketolide demonstrated by studies of time-kill kinetics and postantibiotic effect.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-254.

Labro, M.T., Vazifeh, D., Abdelghaffar, H. *Effect of the new ketolide HMR-3647 on human neutrophil (PMN) function in vitro.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-256.

Wu, M., Kolonoski, P., Bermudez, L.E., Young, L.S. *Efficacy of two ketolides, HMR3004 and HMR3647, in treatment of disseminated M. avium (MAC) disease in beige mice.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-261.

Barry, A.L., Fuchs, P.C., Brown, S.D. *Tentative interpretive criteria for HMR 3647 disk diffusion susceptibility tests.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.01.

Visalli, M., Jacobs, M., Appelbaum, P. *Antipneumococcal activity of HMR 3647, a new ketolide, compared to other drugs, by time-kill.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.02.

Pankuch, G., Jacobs, M., Appelbaum, P. *Antipneumococcal activity (MIC) of HMR 3647, a new ketolide, compared to 16 other agents*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.03.

Hoban, D., Palatnick, L., Weshnoweski, B., Cox, L., Balko, T., Karlowsky, J., Zhanel, G. *The novel ketolide HMR 3647 is highly active against worldwide isolates of Streptococcus pneumoniae and Streptococcus pyogenes.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.04.

Giovanetti, F., Biavasco, F., Marchetti, F., Varaldo, P.E. *In vitro activity of the ketolide HMR 3647 against erythromycin-susceptible and erythromycin resistant isolates of Streptococcus pyogenes.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.05.

Cocuzza, C.E., Tomasini, A., Renzetti, D., Primavera, A., Santini, L., Marchetti, F., Mattina, R. *Ketolide (HMR 3647) in vitro activity on 4000 strains of S. pyogenes isolated in Northen Italy.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.06.

Felmingham, D., Robbins, M.J., Clark, S., Mathias, I., Bryskier, A. *The comparative in vitro activity of HMR3647 against speciated coagulase negative Staphylococcus spp.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.07.

Hamilton-Miller, J.M.T., Shah, S. *Comparative activity vs Gram-positive cocci in vitro of ketolide HMR3004*. 4th Int Conf

Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.08.

Jacobs, M.R., Bajaksouzian, S., Chuang, J., Ronchetti, M.P., Appelbaum, P.C. *Postantibiotic effects of the ketolide HMR 3647 on macrolide-susceptible and -resistant Gram positive cocci.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.09.

Hoban, D., Palatnick, L., Balko, T., Zhanel, G., Kabani, A., Karlowsky, J. *In vitro activity of a novel ketolide HMR 3647 and comparative macrolides against worldwide Haemophilus influenzae (HI) isolates.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.10.

Hoppe, J.E., Bryskier, A. *In vitro susceptibility of Bordetella pertussis and B. parapertussis to the ketolides HMR 3004 and HMR 3647, to the macrolides azithromycin, clarithromycin, erythromycin A, and roxithromycin and to the ansamycins rifampicin and rifapentine.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.13.

Ednie, L., Jacobs, M., Appelbaum, P. *Anti-anaerobic activity of the ketolide HMR 3647 compared to 12 other compounds.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.15.

Hammerschlag, M.R., Roblin, P.M. *In vitro activity of a new ketolide antibiotic, HMR 3647, against Chlamydia pneumoniae.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.16.

Anderson, R., Mokgobu, I., Theron, A.J., Feldman, C. *In vitro assessment of the anti-oxidative interactions of the ketolide antimicrobial agent RU-64004 with human neutrophils.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.20.

Labro, M.T., Vazifeh, D., Bryskier, A. *Uptake of a new ketolide, HMR-3647, by human neutrophils in vitro*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.21.

Feldman, C., Anderson, R., Theron, A.J., Ramafi, G., Cole, P.J., Wilson, R. *Ketolide HMR 3004 attenuates the effects of bioactive phospholipids (PL) on human ciliated epithelium in vitro.* 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.22.

Collette, P., Douthwaite, S., Mankin, A., Mauvais, P. *Similarities and differences in ketolide and macrolide interaction within two distinct domains of 23S ribosomal RNA*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 1.23.