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Review Article

Novel fluoroketolides: synthesis and antibacterial activity

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Introduction

Macrolides are a well-known family of oral antibacterial agents active against most relevant bacteria involved in respiratory infections. However, all contemporary macrolides are inactive against macrolide-lincosamide-streptogramin B (MLS_B)-resistant bacteria. Depending on the country, more than 30% of *Streptococcus pneumoniae* are nowadays resistant to macrolides, including clarithromycin and azithromycin (1, 2). Because of the emergence of penicillin-resistant strains, β-lactams can no longer be used as initial therapy. Although new quinolones are more active against pneumococci, they still remain contraindicated in pregnant women or young children.

To overcome the spread of pneumococcal resistance, a major new class of semisynthetic 14-membered-ring macrolide derivatives, called ketolides, has been generated (3). Ketolides are characterized by a keto function at position 3 of the macrolactone ring, replacing the L-cladinose moiety, a neutral sugar long thought to be crucial for antibacterial activity. Structural changes in ketolides render them significantly different from macrolides. First, they are active, with the exception of constitutively MLS_B-resistant *Staphylococcus aureus*, against most of the erythromycin A-resistant Gram-positive cocci expressing the constitutive or inducible *erm* methylase gene and *mef* efflux gene, including constitutively erythromycin A-resistant and penicillin-resistant *S. pneumoniae* (4, 5). In addition, they do not induce MLS_B resistance (6) and they do not select any resistant mutants (7). Finally, they are very stable in acidic medium (3).

Among ketolides, telithromycin (*Ketek*®) (5) from Aventis is the most advanced compound, currently approved in Europe and submitted for approval in the USA. ABT-773 from Abbott is in phase II (Fig. 1). Telithromycin displays strong activity against multidrug-resistant *S. pneumoniae*, staphylococci, streptococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Branhamella pertussis* and intracellular respiratory pathogens, such as *Chlamydia pneumoniae* and *Legionella* spp. (8, 9).

In the search for new ketolides with improved activity, halogen atoms were stereospecifically introduced into the C-2 position, leading to the new group of fluoroketolides. In this review, we describe the synthesis and antibacterial activities of the fluoroketolides published or patented

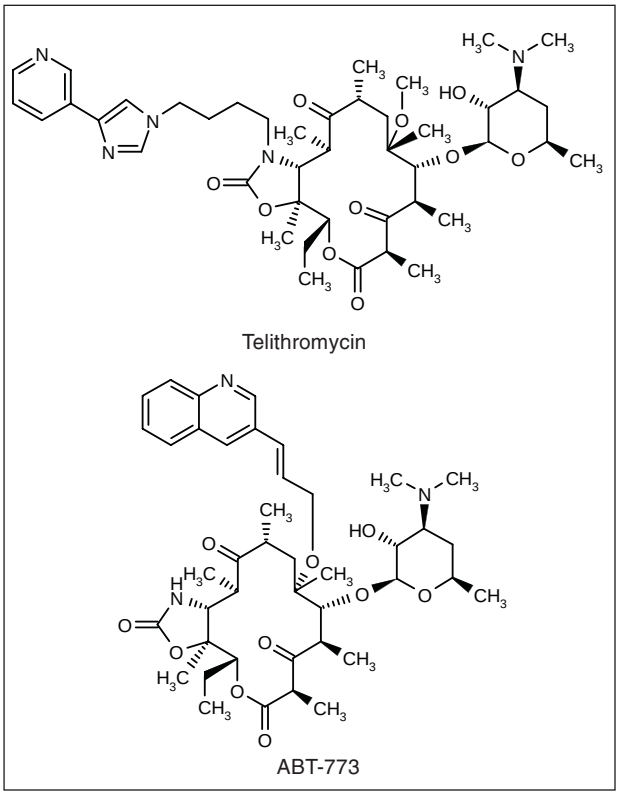


Fig. 1. Ketolides in clinical development.

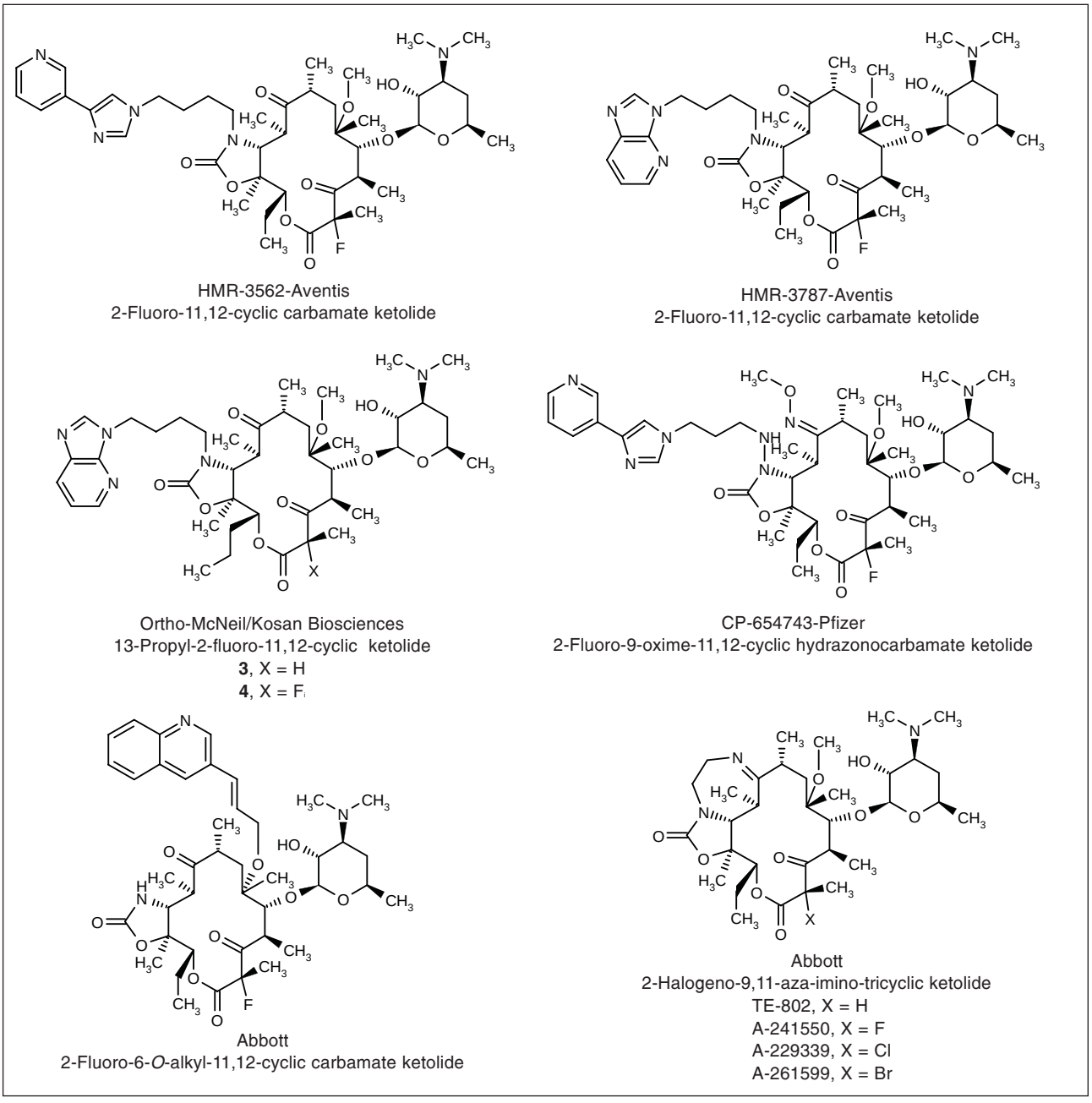


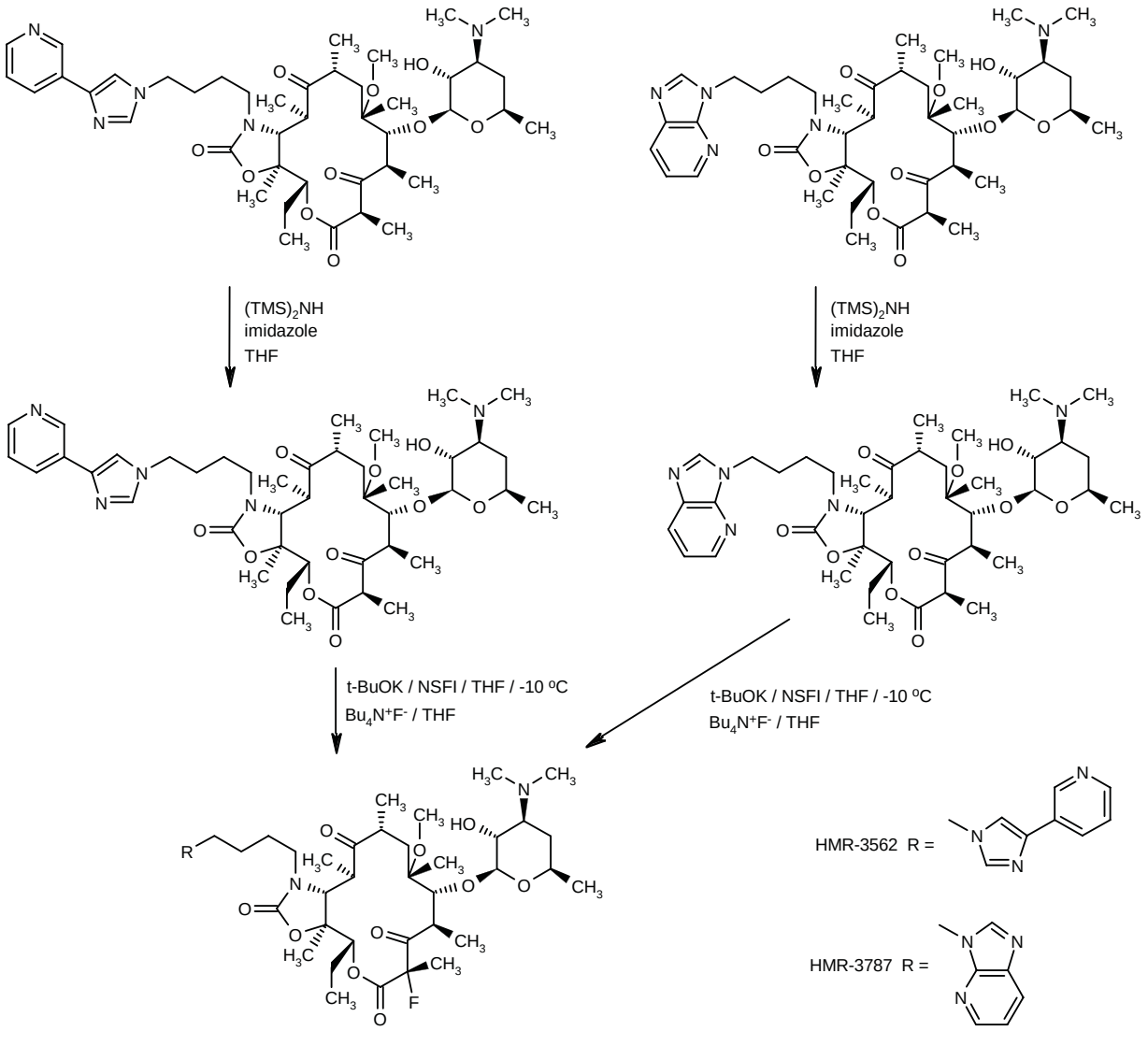
Fig. 2. 2-Halogeno ketolides.

since the first report of 2-fluorination in 1997 (10). The two fluoroketolides HMR-3562 and HMR-3787, which are both as active as telithromycin but show improved activity against streptococci and enterococci, will be overviewed (Fig. 2).

Chemistry

Fluoroketolides such as HMR-3562 and HMR-3787 were synthesized from their corresponding ketolide as starting material. Fluorination in C-2 was achieved in 3 steps, as shown in Scheme 1. First, quantitative silylation of the 2'-alcohol with $(TMS)_2NH$/imidazole gave a protected intermediate that was reacted with t-BuOK and *N*-fluorobenzenesulfonimide (NSFI) as fluorinating reagent, to obtain after desilylation with $Bu_4N^+F^-$ the desired fluoroketolides HMR-3562 and HMR-3787 in 83% and 56% yield, respectively. The stereochemistry of the reaction was demonstrated by synthesizing HMR-3562 according to an alternative way starting from the fluoroenone **2** (Scheme 2). The starting enone **1** was first

Scheme 1: Synthesis of HMR 3562 and HMR 3787

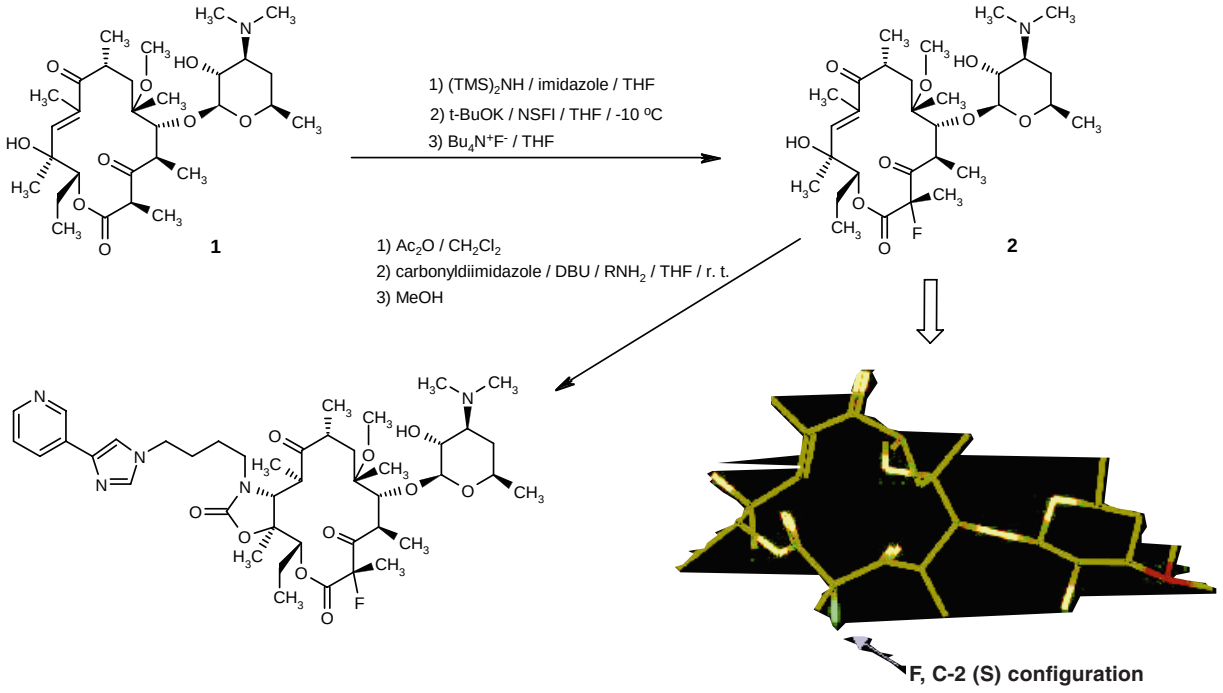


fluorinated to give the corresponding 2-fluoroketolide in 69% yield (11). This compound was then crystallized and the absolute stereochemistry of C-2 determined. Finally, after acetylation in 2', **2** was reacted with carbonyldiimidazole and DBU in THF and the corresponding 4-[4-(3-pyridyl)imidazolyl]lbutylamine added to generate HMR-3562 in 67% yield. As the two different synthetic pathways yielded the same compound [^{1}H NMR, especially 2-Me δ (ppm) 1.79 (d, $J_{H,F}$= 21.5 Hz, 3H), and melting point = 118 ºC], the absolute *S*-configuration was attributed to HMR-3562 (Scheme 2). This methodology has been applied to the synthesis of several other 2-fluoro-11,12-cyclic carbamate ketolides (12-16).

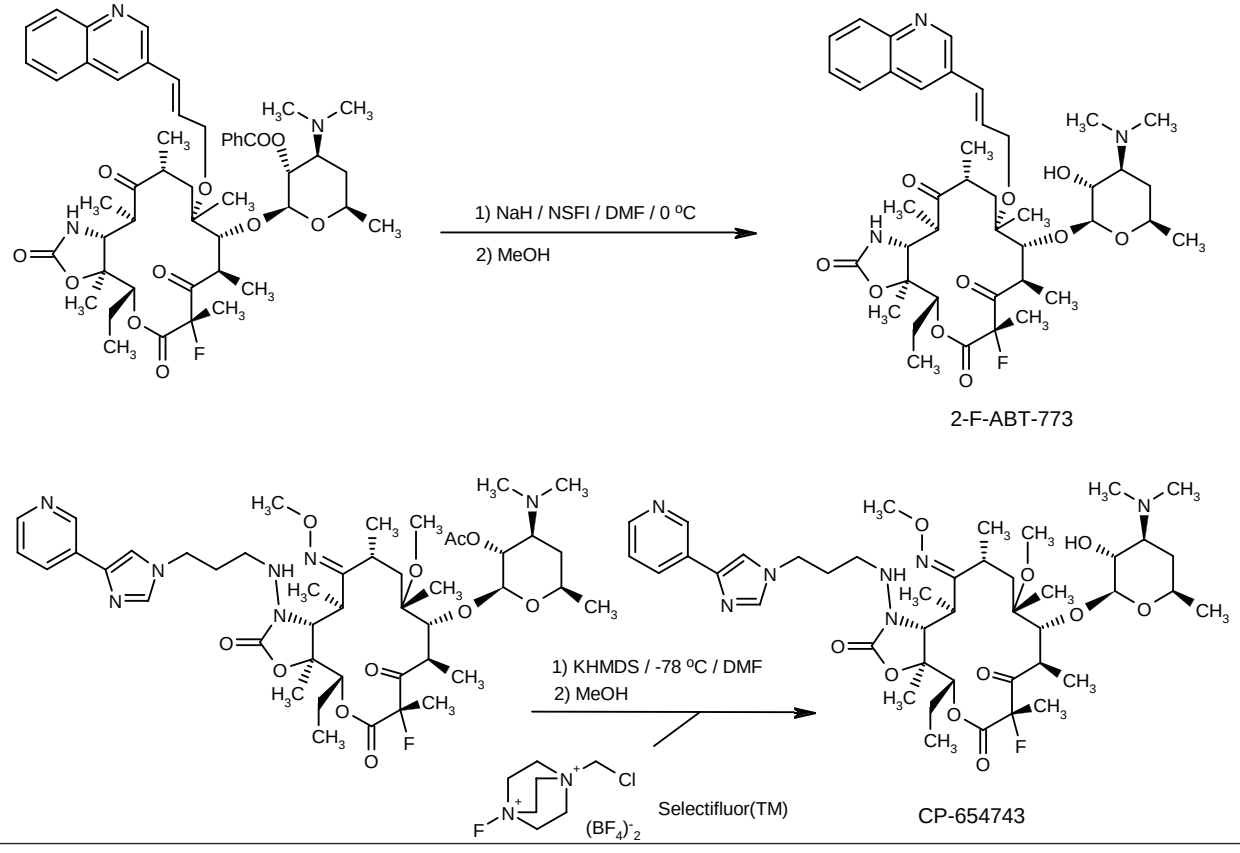
As shown in Scheme 3, the fluorination reaction was also reported using NSFI and sodium hydride (10, 17-19), or Selectifluor™ and KHMDS (20, 21).

Regarding the introduction of other halogen atoms in the telithromycin series, a chlorine atom was easily introduced by radical chlorination using *N*-chlorosuccinimide with AIBN at 40 ºC (11). RU-74234 was obtained in 38% yield as a single isomer of unknown stereochemistry. In the azaimino tricyclic ketolide series (17), chlorination was reported with Cl_3CCCl_3 in the presence of sodium carbonate in *N*-methylpyrrolidone (Scheme 4). Finally, in the same series, a bromine atom was added by using pyridine HBr_3 as electrophile (19).

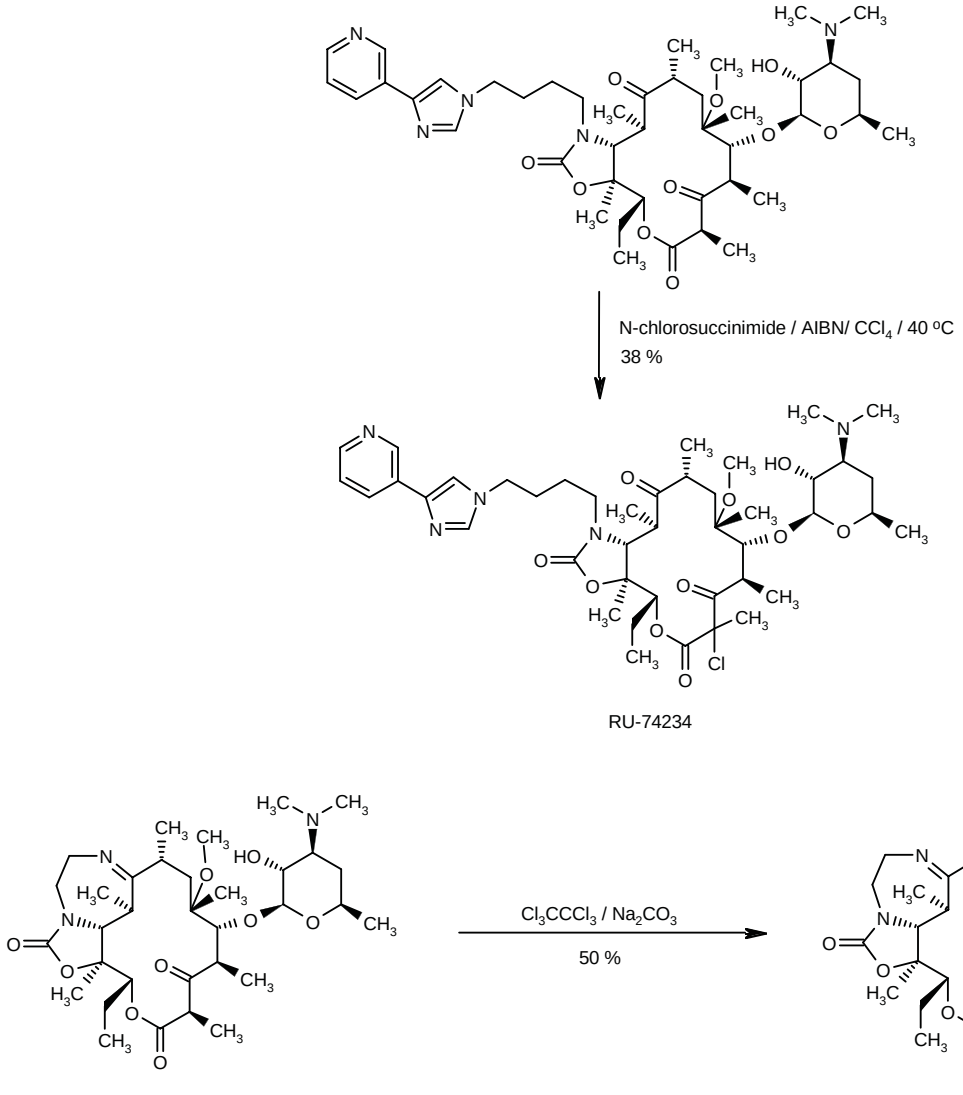
Scheme 2: Alternate Synthesis of HMR-3562 and Absolute Configuration of C-2



Scheme 3: Synthesis of 2-F-ABT-773 and CP-654743



Scheme 4: Synthesis of 2-Chloro Ketolides



Fluoroketolides: structure-activity relationships

In addition to the 3-keto function, the most important features for *in vitro* and *in vivo* activities of ketolides are the 11,12-cyclic carbamate moiety and the heteroaryl side-chain, generally linked to the ketolide backbone by the carbamate nitrogen or the 6-hydroxy. All these groups are also present in different series synthesized by Abbott, *e.g.*, 6-*O*-substituted ketolides (22) and azaimino tricyclic ketolides (23). With the exception of 2,3-anhydro derivatives (24), very little was known about the relative importance of position 2 for the overall activity of ketolides. To address this question, the chemical reactivity of the 1,3-β-keto-ester function of ketolides was exploited to modify the C-2 position in the 11,12-cyclic carbamate series. This approach has allowed us to introduce halogen atoms such as chlorine and fluorine in position 2 and to demonstrate that, within the ketolide class, position 2 tolerates only a fluorine atom to retain good antibacterial activity.

2-Fluoro-11,12-cyclic carbamate ketolides (telithromycin series)

In the 11,12-cyclic carbamate series, the replacement of a C2-hydrogen atom with a fluorine gave two compounds, HMR-3562 and HMR-3787, that demonstrated very good activities against strains susceptible to erythromycin A (25). Furthermore, they were effective against inducibly erythromycin A-resistant *S. aureus* and *S. pneumoniae,* as well as constitutively erythromycin A-resistant *S. pneumoniae*. HMR-3562 and HMR-3787 were equal or superior to azithromycin and telithromycin

Table I: In vitro *activity of 2-halogeno ketolides in the 11,12-cyclic carbamate series (from ref. 11, 25, 26).*

	MIC (μg/ml)								
	S. aureus EryS 011UC4	*S. aureus* EryRi 011GO25i	*S. aureus* EryRc 011B20	*S. pyogenes* EryS 02A1UC1	*S. pneumoniae* EryS 032UC1	*S. pneumoniae* EryRc 030PW23c	*S. pneumoniae* EryRc 030SJ1	*S. pneumoniae* EryRi 030SJ5i	*H. influenzae* β-lactamase + 351HT3
Azithromycin	0.3	>40	>40	0.6	0.15	>40	>40	>40	1.2
Clarithromycin	0.3	>40	>40	0.08	0.04	>40	>40	>40	5
Telithromycin	0.04	0.08	>40	0.02	0.02	0.04	0.02	0.02	1.2
HMR-3562	0.02	0.08	>40	0.02	0.02	0.02	0.02	0.02	1.2
RU-74234*	0.6	>40	>40	0.04	0.04	1.2	5	0.6	2.5
HMR-3787	0.04	0.08	>40	0.02	0.02	0.04	0.08	0.02	0.6

EryS: erythromycin A-susceptible; EryRc: erythromycin A constitutive MLS_B resistance; EryRi: erythromycin A inducible MLS_B resistance. *see Scheme 4.

Table II: In vitro *activity of C-13 propyl-2-fluoroketolides (from ref. 15).*

	MIC (μg/ml)				
	S. aureus ATCC29213	*E. faecalis* ATCC29212	*S. pneumoniae* ATCC49619	*E. coli* OC2605	*H. influenzae* OC4883
3, X =H	0.25	0.12	0.03	4	4
4, X =F	0.12	0.03	0.015	2	0.25

Table III: In vitro *activity of 2-fluoro-ABT-773 (from ref. 17).*

	MIC (μg/ml)					
	S. pyogenes EryS EES61	*S. pyogenes* EryRc 930	*S. pneumoniae* EryRc 5979	*S. pneumoniae* EryS ATCC6303	*S. pneumoniae* EryR 5649 efflux	*H influenzae* DILL AmpR
Erythromycin A	0.05	>100	>100	0.06	16	4
ABT-773	0.03	1	16	0.03	0.25	2
2-F-ABT-773	0.03	0.25	1	0.03	0.25	1

EryS: erythromycin A-susceptible; EryR: erythromycin A-resistant; EryRc: erythromycin A constitutive MLS_B resistance.

against *H. influenzae* (Table I). In contrast, the 2-chloro analog of telithromycin RU-74234 was clearly less active than the parent compound, particularly against erythromycin A-resistant *S. pneumoniae*. Due to their attractive profiles, the HMR compounds were further evaluated *in vitro* and *in vivo* against several respiratory pathogens (see below).

The rapid development of engineering of polyketide synthase genes has recently allowed scientists at Kosan Biosciences and Ortho-McNeil to obtain several new 13-substituted ketolides such as **3** (15, 16). One of these new derivatives was fluorinated to give the corresponding 13-propyl fluoroketolide **4**. This fluorinated ketolide **4** was slightly more active against Gram-positive bacteria but demonstrated markedly improved activity against the Gram-negative pathogen *H. influenzae* (Table II).

2-Fluoro-6-O-alkyl-11,12-cyclic carbamate ketolides (ABT-773 series)

A recent patent describes the synthesis of several 6-*O*-alkylketolides (17). Similar to the HMR-3562 series, the introduction of a fluorine atom in position 2 of ABT-773 resulted in improved activity against constitutively erythromycin A-resistant *S. pneumoniae* and *S. pyogenes* (Table III).

2-Halogeno-9,11-azaimino tricyclic ketolides

In different series such as the 9,11-azaimino tricyclic ketolides (17, 19), the beneficial effect of a fluorine atom (A-241550) compared to a hydrogen (TE-802) was also noted. A chlorine (A-229339) in position 2 was also shown to be detrimental for antibacterial activity (Table IV).

2-Fluoro-11,12-cyclic hydrazonocarbamate ketolides

The 2-fluoro-11,12-hydrazonocarbamate analog of telithromycin CP-654743 was recently described (20). However, this fluoroketolide did not demonstrate any significant improvement over telithromycin (Table V).

Table IV: In vitro *activity of 2-halogeno ketolides of the 9,11-azaimino tricyclic series (from ref. 19)*.

	MIC (µg/ml)					
	S. aureus EryS 6538P	*S. aureus* EryRi A5177	*S. aureus* EryRc A5278	*S. pyogenes* EryS EES641	*S. pneumoniae* EryS ATCC6303	*S. pneumoniae* EryR 5649 efflux
Erythromycin A	0.2	3.1	>100	0.06	0.06	32
TE-802	0.2	0.2	>100	0.125	0.06	0.5
A-241550	0.1	0.1	>100	0.03	0.03	0.5
A-229339	25	25	>100	4	4	4

EryS: erythromycin A-susceptible; EryR: erythromycin A-resistant, EryRc: erythromycin A constitutive MLS_B resistance; EryRi: erythromycin A inducible MLS_B resistance.

Table V: In vitro *activity of 2-fluoro-11,12-cyclic hydrazonocarbamate CP-654743 (from ref. 20).*

	MIC (µg/ml)						
	S. aureus EryS 1116	*S. pyogenes* EryRc 1079	*S. pyogenes* EryR 1064 efflux	*S. pneumoniae* EryS 1016	*S. pneumoniae* EryR 5649 efflux	*S. pneumoniae* EryRc 1095	*H. influenzae* 1116
Erythromycin A	0.2	>100	16	0.05	32	>100	4
Telithromycin	0.05	4	1	0.025	0.5	0.025	2
CP-654743	0.05	4	0.5	0.006	0.5	0.025	2

EryS: erythromycin A-susceptible; EryR: erythromycin A-resistant; EryRc: erythromycin A constitutive MLS_B resistance.

Table VI: In vitro *antibacterial activity of HMR-3787 and HMR-3562 (µg/ml; from ref. 26, 27).*

Organisms (No. of isolates)	Clarithromycin	HMR-3787	HMR-3562
Staphylococcus aureus Ery (73)			
Range	0.01-0.6	0.002-0.04	0.002-0.08
MIC_{50}/MIC_{90}	0.15/0.15	0.04/0.04	0.04/0.08
Staphylococcus aureus EryRi (50)			
Range	1.2->40	0.01-0.15	0.04-0.6
MIC_{50}/MIC_{90}	>40/>40	0.04/0.08	0.08/0.15
Coagulase-negative *Staphylococcus* spp. EryS (30)			
Range	0.01-0.3	0.01-0.08	0.01-0.08
MIC_{50}/MIC_{90}	0.08/0.15	0.04/0.04	0.04/0.04
Coagulase-negative *Staphylococcus* spp. EryRi (16)			
Range	1.2->40	0.01-0.3	0.02-0.3
MIC_{50}/MIC_{90}	2.5/>40	0.04/0.08	0.08/0.3
Streptococcus pyogenes (Lancefield group A) (23)			
Range	0.008-8	0.008-0.25	0.015-0.25
MIC_{50}/MIC_{90}	0.03/8	0.008/0.25	0.03/0.25
Viridans *Streptococcus* spp. (35)			
Range	0.008->128	0.004-0.25	0.008-0.12
MIC_{50}/MIC_{90}	1/>128	0.03/0.15	0.03/0.06
Haemophilus influenzae (90)			
Range	0.08-10	0.04-1.2	0.15-2.5
MIC_{50}/MIC_{90}	5/10	0.6/1.2	0.6/1.2
Moraxella catarrhalis (45)			
Range	0.01-2.5	0.01-2.5	0.005-5
MIC_{50}/MIC_{90}	0.08/0.15	0.04/0.08	0.08/0.08

EryS: erythromycin A-susceptible; EryRi: erythromycin A inducible MLS_B resistance.

Fluoroketolides: biological evaluation of HMR-3562 and HMR-3787

Extended in vitro *activity (Tables VI-IX)*

HMR-3562 and HMR-3787 were shown to be 2-4 times more active than clarithromycin against staphylococci susceptible to erythromycin A. It is worth noting that the MIC values of fluoroketolides against erythromycin A-susceptible and inducibly erythromycin A-resistant strains of *S. aureus* or coagulase-negative staphylococci are very similar (11, 26, 27). No activity was observed against constitutively erythromycin A-resistant staphylococci (Table I). On the other hand, these two compounds

Table VII: In vitro *antipneumococcal activity of HMR-3787 and HMR-3562 (μg/ml; from ref. 26, 27).*

Organisms (No. of isolates)	Clarithromycin	HMR-3787	HMR-3562
Streptococcus pneumoniae EryS (80)			
Range	<=0.002-0.6	0.002-0.02	0.002-0.02
MIC_{50}/MIC_{90}	0.01/0.08	0.005/0.01	0.002/0.005
Streptococcus pneumoniae EryR (103)			
Range	0.3->40	0.01/0.08	
0.002-1.2	0.002-0.15		
MIC_{50}/MIC_{90}	>40/>40	0.04/1.2	0.005/0.08
Streptococcus pneumoniae PenR (58)			
Range	0.01->40	0.002-1.2	0.0020.15
MIC_{50}/MIC_{90}	2.5/>40	0.01/0.3	0.002/0.02
Streptococcus pneumoniae EryR (*ermB*) (13)*			
Range		0.005/0.15	0.001/0.02
MIC_{50}/MIC_{90}		0.01/0.04	0.001/0.01
Streptococcus pneumoniae EryR (*mefE*) (7)*			
Range	0.3/>40		0.01/0.08

*Unpublished results. EryS: erythromycin A-susceptible; EryR: erythromycin A-resistant; EryRc: erythromycin A constitutive MLS_B resistance; EryRi: erythromycin A inducible MLS_B resistance; PenR: penicillin-resistant.

Table VIII: In vitro *antienterococcal activity of HMR-3787, HMR-3562 and reference antibiotics (μg/ml; from ref. 26).*

Organisms (No. of isolates)	Erythromycin A	Azithromycin	Clarithromycin	HMR-3787	HMR-3562
E. faecium EryS (11)					
Range	0.01-0.6	0.15-5	0.04-1.2	0.005-0.02	0.002-0.02
MIC_{50}/MIC_{90}	0.6/0.6	2.5/2.5	0.6/0.6	0.005/0.01	0.005/0.005
E. faecium EryR (29)					
Range	5->40	10->40	2.5->40	0.01-5	0.01-0.6
MIC_{50}/MIC_{90}	>40/>40	>40/>40	>40/>40	2.5/5	0.3/0.6
E. faecalis EryS (39)					
Range	0.01-0.6	0.08-5	0.04-1.2	0.002-0.01	0.002-0.005
MIC_{50}/MIC_{90}	0.3/.6	2.5/5	0.3/0.6	0.005/0.01	0.002/0.005
E. faecalis EryR (12)					
Range	1.2->40	2.5->40	0.6->40	0.005-5	0.002-0.6
MIC_{50}/MIC_{90}	>40/>40	>40/>40	>40/>40	0.04/5	0.04/0.3

EryS: erythromycin A-susceptible; EryR: erythromycin A-resistant.

Table IX: In vitro *activity of HMR-3787and HMR-3562 against* Chlamydia, Mycoplasma *and* Mycobacterium *(μg/ml; from ref. 27).*

Organisms (No. of isolates)	Clarithromycin	HMR-3787	HMR-3562
Chlamydia pneumoniae (5)			
Range	all 0.06	0.06-0.12	all 0.06
Mycoplasma pneumoniae (20)			
Range	0.002/0.008	0.00025-0.0005	0.00025-0.0005
MIC_{50}/MIC_{90}	0.004/0.004	0.0005/0.0005	0.0005/0.0005
Mycobacterium avium intracellulare (25)			
Range	1-32	4-128	8-128
MIC_{50}/MIC_{90}	4/8	32/32	64/64

were reported to be very active against several species of streptococci (Table VI), including erythromycin A-resistant *S. pneumoniae* (11, 25-27), with MIC_{50} values for HMR-3562 and HMR-3787 of 0.005 and 0.04 μg/ml, respectively (Table VII). In addition, no difference was observed in the behavior of HMR-3562 against penicillin-resistant strains of *S. pneumoniae* (25, 26), with MIC_{50} values < 0.002 μg/ml (Table VII). The high antibacterial activity of HMR-3562 and HMR-3787 was also demonstrated against isolates of *S. pneumoniae* harboring the *ermB* methylase genes or *mefE* efflux genes (unpublished data, 27, 28) (Table VII). For both HMR-3562 and HMR-3787, MICs against enterococci (25, 26) (Table VIII) were slightly higher against *Enterococcus faecium* than against *Enterococcus faecalis* (MIC_{50} = 0.04-0.3 and 0.04-2.5 μg/ml, respectively). Against *H. influenzae*, HMR-3562 and HMR-3787 displayed similar activity to azithromycin, all strains being inhibited at a concentration

Table X: Comparative in vivo *antibacterial activities of HMR-3562 and HMR-3787 in a murine septicemia model (from ref. 29, 30).*

Strains	Phenotype	Drug	MIC (mg/l)	PD_{50} (mg/kg)
S. aureus	EryS	Clarithromycin	0.02	12
		HMR-3562	0.01	9
		HMR-3787	0.01	15.4
	EryRi	Clarithromycin	>40	12.4
	Oxacillin-resistant	HMR-3562	0.04	3.7
		HMR-3787	0.04	6.6
S. pneumoniae	EryRc	Clarithromycin	>40	>40
	Oxacillin-resistant	HMR-3562	0.001	2
		HMR-3787	0.6	3
	EryRi	Clarithromycin	>40	>50
		HMR-3562	≤ 0.02	4.4
		HMR-3787	0.08	29.4
	EryS	Clarithromycin	0.01	49
		HMR-3562	0.001	15
		HMR-3787	nd	17
S. pyogenes	EryS	Clarithromycin	0.08	2
		HMR-3562	≤ 0.01	1.5
		HMR-3787	≤ 0.02	<1.5
S. agalactiae	EryS	Clarithromycin	0.02	<3.5
		HMR-3562	nd	2
		HMR-3787	nd	2.7
H. influenzae	Ampicillin-R	Clarithromycin	10	>150
	(β-Lactamase -)	HMR-3562	1.2	64
		HMR-3787	1.2	44
	Ampicillin-R	Clarithromycin	2.5	>100
	(β-Lactamase +)	HMR-3562	0.6	56
		HMR-3787	0.6	59
E. faecalis	EryS	HMR-3562	nd	6
		HMR-3787	nd	6
E. faecium	EyS vanR teiR	HMR-3562	0.02	6.5
E. faecium	EryR vanR teiR	HMR-3562	0.15	14.8
E. faecium	EryR vanR teiR	HMR-3562	0.15	21.8

EryS: erythromycin A-susceptible; EryR: erythromycin A-resistant; EryRc: erythromycin A constitutive MLS_B resistance; EryRi: erythromycin A inducible MLS_B resistance; nd: not determined; VanR: vancomycin-resistant; TeiR: teicoplanin-resistant.

that did not exceed 2.5 μg/ml. Activities against *M. catarrhalis* (26, 27) were similar to those of commercially available macrolides (Table VI). While both ketolides were shown to be as active as clarithromycin against *Chlamydia,* they were 10 times more active against *Mycoplasma pneumoniae* and 4-8 times less active against *Mycobacterium avium intracellula*re (27) (Table IX).

In vivo *activity (Table X)*

In mice with septicemia caused by Gram-positive cocci susceptible to erythromycin A, HMR-3562 and HMR-3787, administered orally, demonstrated efficacy similar to that of clarithromycin but superior to that of erythromycin A. In septicemia caused by erythromycin A-resistant strains of *S. aureus* and *S. pneumoniae*, HMR-3562 and HMR-3787 were also very active, with effective doses ranging between 2 and 4.4 mg/kg and 3 and 29.4 mg/kg, respectively, a range similar to that found against erythromycin A-susceptible pathogens. In addition, it was recently reported that HMR-3562 and HMR-3787 demonstrated high therapeutic effficacy against *E. faecium,* including vancomycin-resistant strains, and *E. faecalis* (29, 30). Finally, in acute or subacute murine pneumonia models, HMR-3787 and virginamycin were reported to be equipotent, whereas HMR-3562 was reported to be the most bactericidal compound against constitutively MLS_B-resistant *S. pneumoniae* (31).

Against *H. influenzae*-induced systemic infections, the ketolides were systematically more potent than erythromycin A or clarithromycin, which displayed PD_{50} values higher than 100 mg/kg. In addition, PD_{50} values for HMR-3562 and HMR-3787 were 2-4 times lower than those found for azithromycin in the case of both tested ampicillin-resistant strains (30).

Conclusions

Fluoroketolides are a new subfamily of ketolides displaying a similar antibacterial profile to telithromycin. They generally possess improved activity against erythromycin A-resistant *S. pneumoniae* and *S. pyogenes,* including both *ermB* and *mefE* phenotypes. Finally, they also demonstrate very good activity against enterococci,

including vancomycin-resistant *E. faecium*. Taken together, these data suggest that fluoroketolides could become promising new agents for the treatment of respiratory pathogens resistant to erythromycin A.

Preliminary safety and pharmacokinetic studies are in progress with HMR-3562 and HMR-3787.

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