NEW ETHER OXIME DERIVATIVES OF ERYTHROMYCIN A

A STRUCTURE-ACTIVITY RELATIONSHIP STUDY

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The discovery of roxithromycin is the result of a rational and scientific process, based on the fact that at least one reason for erythromycin A's resorption variability after oral administration was its instability in the gastric juice. This instability is due to the reactivity of the ketone in position 9 in acidic medium and one chemical approach was to mask it by an oxime function. Both stereoisomers of this oxime were isolated. Direct *O*-alkylation of this oxime allowed access to various ether oxime derivatives and of the latter the *E* stereoisomers were more interesting than the *Z* ones. The choice of the nature of the oxime substitution was made according to the lipophilic or hydrophilic character of the aliphatic ether chain and these alterations were mainly carried out by introducing heteroatoms into this chain. These different derivatives were classified in 5 groups according to the chemical nature of the chain: Aliphatic, aromatic and nitrogen-, oxygen- and sulfur-containing chains. Two classes, those containing a nitrogen or an oxygen in the ether side chains, showed differential *in vitro*/*in vivo* antibiotic activities, with improved bioavailability. Some preliminary pharmacokinetic data confirmed this improvement and led to the selection of five candidates, from which roxithromycin emerged as the best compound.

Since its discovery by MCGUIRE *et al.*[1] in 1952, erythromycin A (ERY) has been the most widely used and effective macrolide antibiotic against many diseases, especially respiratory tract infections including atypical pneumonia due to *Legionella pneumophila*, *Mycoplasma pneumoniae* or *Chlamydia* spp. Another useful indication of erythromycin is in sexually transmitted diseases, where it proves its efficiency in the treatment of non-gonococcal urethritis due to *Ureaplasma urealyticum* and *Chlamydia trachomatis*. These striking results are obtained despite unsatisfactory pharmacokinetics with a wide variability in the resorption according to the individual, an observation which is valid for all macrolides[2]. ERY derivatives (esters and salts) were prepared in an attempt to improve the performance, but results were disappointing. This fact led to research for new ERY derivatives retaining the same antibacterial spectral activity, but showing an improved bioavailability.

ERY (I) is an orally administered antibiotic and the main reason for its resorption variability and consequently the low antibiotic level in the serum is its instability in the gastric juice. It is well known that in acidic conditions ERY gives first an internal enolic ether and secondly an internal ketal by reaction with the ketone in position 9 and hydroxylic groups in positions 6 and 12 (Fig. 1)[3]. Neither product exhibits antibiotic activity[4] and this ketal formation is irreversible. An obvious way of preventing this internal ketalization was to block or transform the ketone group into another functional group.

The transformation of the ketone in position 9 to an oxime was a possible way of preventing internal ketalization. ERY oximes had already been described[5,6] as well as the ester derivatives, but as the ethers were practically unexplored, we decided to prepare various ether oximes. The choice of the nature of the oxime substitution was made as a function of the lipophilic or hydrophilic character and this was carried

Fig. 1. Acid degradation of ERY.

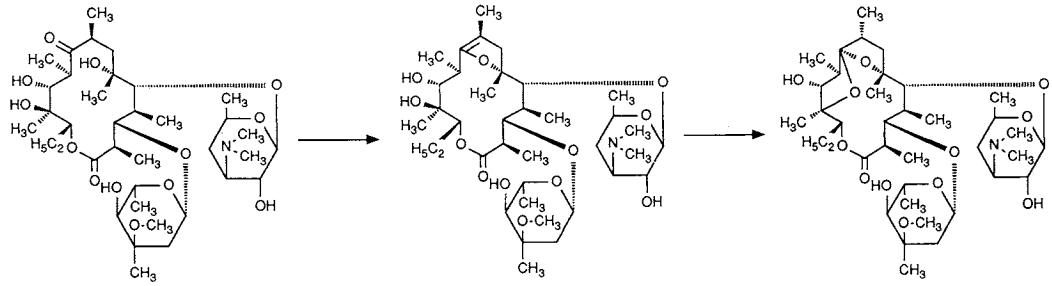
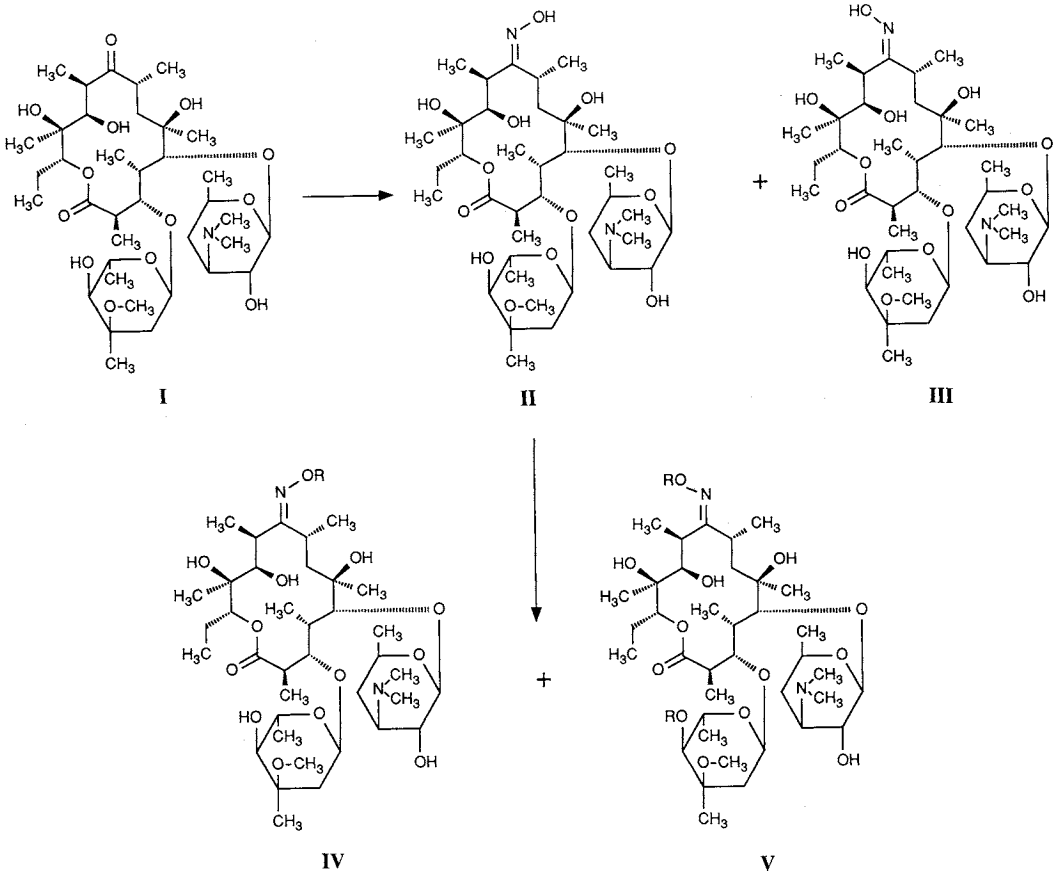


Fig. 2. Synthesis of ether oxime derivatives of ERY.



out mainly by introducing heteroatoms into the aliphatic ether chain, with the aim of studying structure-activity and bioavailability relationships. From a strategic point of view, we decided to systematically evaluate the activities of all products both *in vitro* and *in vivo* in the mouse in comparison with ERY, aiming at detecting the best improvement of bioavailability.

Chemistry

ERY belongs to the 14-membered macrolide class with two carbohydrates (an amino sugar, desosamine and a neutral one, cladinose). This complex molecule is unstable in acidic medium but relatively stable in

alkaline solution. The oxime derivative is easily obtained by reaction of ERY with hydroxylamine hydrochloride in a methanol solution in the presence of triethylamine (Fig. 2). This reaction is complete in 24 hours of reflux. The isolated crystallized oxime (**II**) has the *E* configuration (or *syn* to carbon 8 of the macrolide ring) whereas in the crude product, a small proportion of the *Z* isomer (**III**) is present. By treatment in alkaline medium (NaOH, MeOH) it is possible to mainly transform the *E* isomer in the *Z* isomer. This oxime configuration was determined by NMR using proton and ^{13}C chemical shifts and ^{15}N-^{13}C coupling constants. The reactivity of the hydroxylic function of the oxime group enabled selective alkylation by means of alkyl halide in the presence of a base (alkaline carbonate, sodium methoxide or sodium hydride) in a solvent such as acetone, tetrahydrofuran or ethyl ether without protection of other hydroxylic groups. In some cases the desired ethers were prepared in two steps starting from the oxime. At first a reactive ether was obtained such as the bromoethyl or oxiranylmethyl derivatives and the second step was the nucleophilic substitution of the bromine or the nucleophilic opening of the epoxide. It is possible to obtain *O*-alkyl oxime derivatives directly by reacting ERY with *O*-alkylhydroxylamine, but with *O*-methylhydroxylamine, for example, the reaction is incomplete and the yield is low. In some preparations, it was possible to obtain a di-ether derivative (**V**) as a minor product, substituted on the hydroxylic group of the oxime and in the 4″ position on the cladinose residue, whereas no *O*-alkylation was observed in position 2′ of the desosamine. This result is suprising, if compared with the well-known relative reactivity of different hydroxylic groups of ERY. Thus in the acylation reaction, the decreasing order of reactivity of hydroxylic groups is: 2′,4″ and 12[7]. In a recent paper on the preparation of 6-*O*-methyl ERY (TE-031), published results show that, starting from *N*-demethyl ERY N and O protected at 2′ and 3′ by a carbobenzyloxy group, hydroxylic groups in positions 6 and 11 have the same reactivity while the hydroxyl in position 4″ does not react[8].

Various ether oxime derivatives of ERY (**IV**) have been prepared. All these derivatives were classified in 5 groups according to the chemical nature of the ether chain to compare their antimicrobial activities:

— aliphatic ether chain (Table 1)

— aromatic ether chain (Table 2)

— nitrogen in the ether chain (Table 3)

Table 1. Antimicrobial activities of aliphatic oxime ether derivatives.

No.	Oxime ether derivative **IV** R=	*In vitro* activity	*In vivo* activity
1	CH_3	0.68	0.9
2	$-CH_2-CH_2-Br$	0.86	0.4
3	$-CH_2-CH=CH_2$	0.70	0.49
4	$-CH_2-\overset{Cl}{\overset{\vert}{C}}=CH_2$	1.02	<0.5
ERY		1	1
Oxime (**II**)		0.62	0.66

In vitro activity is the ratio of the geometric means of ERY/geometric mean of the ether oxime derivatives' MIC of selected sensitive microorganisms.

In vivo activity is the ratio of PD_{50} of ERY/PD_{50} of the ether oxime derivative (in the mouse).

Table 2. Antimicrobial activities of aromatic oxime ether derivatives.

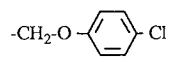
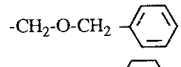
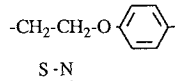
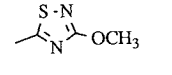
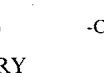
No.	Oxime ether derivative **IV** R=	*In vitro* activity	*In vivo* activity
5		0.83	<0.5
6		0.86	0.69
7		0.98	<0.35
8		0.32	0.73
ERY		1	1

Table 3. Antimicrobial activities of nitrogen-containing oxime ether derivatives.

No.	Oxime ether derivative **IV** R =	*In vitro* activity	*In vivo* activity
9	$-CH_2-CH_2-NH_2$	0.56	<0.3
10	$-CH_2-CH_2-NH-CH_2-CH_3$	1.20	0.5
11	$-CH_2-CH_2-NH-CH(CH_3)_2$	1.58	1.33
12	$-CH_2-CH_2-N(CH_3)_2$	1.19	2.36
13	$-CH_2-CH_2-N(C_2H_5)_2$	1.27	1.55
14	$-CH_2-CH_2-N(CH(CH_3)_2)_2$	1.55	2
15		0.40	1.88
16		1.03	0.76
17		0.96	0.97
18		0.72	0.27
19		0.58	0.67
20	$-CH_2-CH_2-\overset{\uparrow O}{N}(C_2H_5)_2$	0.15	1.66
21	$-CH(CH_3)-CH_2-N(CH_3)_2$	0.95	2.12
22	$-CH(CH_3)-CH_2-N(C_2H_5)_2$	1.48	1.33
23	$-C(CH_3)_2-CH_2-N(C_2H_5)_2$	0.29	2.49
24	$-CH_2-CH_2-CH_2-N(CH_3)_2$	0.82	0.62
25	$-CH_2-CH(OH)-CH_2-N(CH_3)_2$	0.48	0.73
26	$-CH_2-CH(OH)-CH_2-NH-CH(CH_3)_2$	0.76	0.5
27	$-CH_2-C\equiv N$	1.41	0.83
28	$-CH_2-CH_2-C\equiv N$	1.04	<0.5
29	$-CH_2-O-CH_2-CH_2-NH_2$	1.27	<0.75
30	$-CH_2-O-CH_2-CH_2-NH-CH_3$	1.16	0.61
31	$-CH_2-O-CH_2-CH_2-N(CH_3)_2$	1.20	1
32	$-CH_2-O-CH_2-CH_2-N(C_2H_5)_2$	0.78	0.79
33		0.38	0.88
ERY		1	1

— oxygen in the ether chain (Table 4)

— sulfur in the ether chain (Table 5)

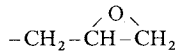
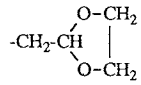
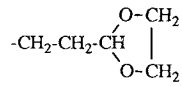
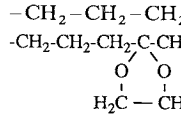
Discussion

Aliphatic and aromatic oxime ether derivatives (Tables 1 and 2) show an *in vitro* activity comparable to that of ERY but their *in vivo* activities are clearly decreased.

Of the 25 nitrogen-containing oxime ether derivatives described (Table 3), 5 compounds are more active than ERY both *in vitro* and *in vivo*, 7 derivatives are only more active *in vitro* and 4 other products are more active *in vivo*, but less active *in vitro* than ERY. The length of the chain is important, as the best results were obtained with an *N*-substituted ethylamine chain (**11**, **12**, **13**, **14** and **22**) compared with longer chains and other substitutions.

Among the 24 oxygen-containing oxime ether derivatives (Table 4), only two compounds (**34** and **38**) are more active than ERY both *in vitro* and *in vivo*, but 10 other ether derivatives show a better *in vivo* activity, although *in vitro* activities are clearly lower than those of ERY. Product **40** should be noted because it is 2 times less active than ERY *in vitro* and yet over 3.5 times more active *in vivo*. This was the

Table 4. Antimicrobial activities of oxygen-containing oxime ether derivatives.

No.	Oxime ether derivative **IV** R=	*In vitro* activity	*In vivo* activity
34	$-CH_2-O-CH_3$	1.27	2.78
35	$-CH_2-O-CH_2-CH_3$	0.71	1.17
36	$-CH_2-O-CH_2-CH_2-CH_3$	0.40	1.4
37	$-C(CH_3)_2-O-CH_3$	0.55	<0.6
38	$-CH_2-O-CH_2-CH_2-Cl$	1.41	2.27
39	$-CH_2-O-CH_2-CH(CH_3)_2$	0.35	0.73
40 (Roxithromycin)	$-CH_2-O-CH_2-CH_2-O-CH_3$	0.51	3.84
41	$-CH_2-O-CH_2-CH_2-O-CH_2-CH_3$	0.60	1.52
42	$-CH_2-CH_2-O-CH_2-CH_3$	0.51	2.35
43	$-CH_2-CH_2-O-CH_2-CH_2OH$	0.67	2.2
44		0.59	<0.37
45		0.42	1.54
46	$-CH_2-CH(OCH_3)_2$	0.39	2.86
47	$-CH_2-CH(OC_2H_5)_2$	0.29	0.69
48		0.24	1.36
49	$-CH_2-CO-O-C(CH_3)_3$	0.28	<1
50	$-CH_2-CO-O-CH_2-CH_3$	0.29	<0.7
51	$-CH_2-COOH$	0.01	nd
52	$-CH_2-CO-C(CH_3)_3$	0.45	1.57
53	$-CH_2-CH_2-CH_2-CO-CH_3$	0.36	0.51
54		0.13	0.73
55	$-CH_2-CHOH-CH_2OH$	0.17	0.71
56	$-CH_2-CHOH-CH_2-O-CO-CH_3$	0.12	<0.7
57	$-CH_2-CHOH-CH_2-O-CH_2-CH_2-OH$	0.12	<0.2
ERY		1	1

nd: Not determined.

Table 5. Antimicrobial activities of sulfur-containing ether chain derivatives.

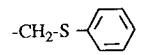
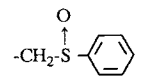
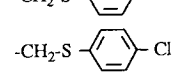
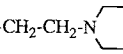
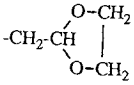
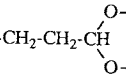
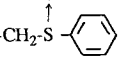
No.	Oxime ether derivative **IV** R=	*In vitro* activity	*In vivo* activity
58	$-CH_2-S-CH_3$	0.92	0.82
59	$-CH_2-\overset{\overset{O}{\uparrow}}{S}-CH_3$	0.33	<0.5
60		0.55	0.82
61		0.45	2.5
62		0.92	<0.75
63	$-CH_2-CHOH-CH_2-S-CH_2-CH_3$	0.56	0.58
ERY		1	1

Table 6. *In vivo* activity in murine infections.

No.	Oxime ether derivative **IV** R=	Staphylococcal septicaemia	Streptococcal septicaemia
12	$-CH_2-CH_2-N(CH_3)_2$	2.36	20
13	$-CH_2-CH_2-N(C_2H_5)_2$	1.55	12
14	$-CH_2-CH_2-N(CH(CH_3)_2)_2$	2	10
15		1.88	5.5
21	$-CH(CH_3)-CH_2-N(CH_3)_2$	2.12	20
22	$-CH(CH_3)-CH_2-N(C_2H_5)_2$	1.33	40
23	$-C(CH_3)_2-CH_2-N(C_2H_5)_2$	2.49	40
20		1.66	1.8
34	$-CH_2-O-CH_3$	2.78	5
35	$-CH_2-O-CH_2-CH_3$	1.17	0.8
38	$-CH_2-O-CH_2-CH_2-Cl$	2.27	0.95
40	$-CH_2-O-CH_2-CH_2-O-CH_3$	3.84	2.3
43	$-CH_2-CH_2-O-CH_2-CH_2OH$	2.2	<0.5
45		1.54	3
46	$-CH_2-CH(OCH_3)_2$	2.86	2
48		1.36	2
52	$-CH_2-CO-C(CH_3)_3$	1.57	3
61		2.5	1.98
ERY		1	1

first evidence of improved bioavailability.

Only one sulfur-containing ether chain derivative (Table 5, **61**) showed an interesting differential activity (*in vitro→in vivo*).

In order to check the different derivatives having improved *in vivo* activity in murine experimental infections caused by *Staphylococcus aureus* 54146, the products were also evaluated in mouse experimental septicaemia induced by *Streptococcus pyogenes* group A A561 (Table 6). Whereas oxygen-containing oxime ether derivatives show the same order of *in vivo* activity in the course of staphylococcal (from 1.17 to 3.84 times more active than ERY) and streptococcal infections (from 2 to 5 times more active than ERY), this is not the case with nitrogen-containing oxime ether derivatives. The *in vivo* activities during infections induced by *S. aureus* remain practically the same (from 1.33 to 2.49 times more active than ERY), but the *in vivo* activities against *S. pyogenes* are clearly improved (from 1.8 to 40 times more active than ERY).

The fact that many derivatives present *in vitro* activities similar to, or more often weaker than, those of ERY and that some of them are more active *in vivo*, demonstrates that these products have a better bioavailability. As pharmacokinetics are important in the assessment of bioavailability, we determined early on some key oral pharmacokinetic properties in comparison to ERY. These preliminary pharmacokinetics only allowed some data to be selected concerning the time (Tmax) and the concentration (Cmax) at the peak and the aspect of the curve in the elimination phase by the concentration 7 hours after administration (C at 7 hours). Table 7 lists some pharmacokinetic parameters for all those compounds which demonstrated a better *in vivo* activity during septicaemia induced by *S. aureus* and *S. pyogenes*. We were looking for an early peak, high Cmax leading after 7 hours to concentrations of the same order of magnitude as MIC values. The oral pharmacokinetic properties of ERY ether oximes reported in the table are better than

Table 7. Oral pharmacokinetic data of ether oximes in the rat (20 mg/kg).

No.	Tmax (hours)	Cmax (μg/ml)	C at 7 hours (μg/ml)	No.	Tmax (hours)	Cmax (μg/ml)	C at 7 hours (μg/ml)
12	2.00	1.90	1.00	**34**	0.50	1.60	0.15
13	1.00	3.80	0.30	**40**	0.25	3.80	0.44
14	1.50	1.18	0.14	**45**	0.75	2.30	1.40
15	0.50	2.30	2.20	**46**	0.25	2.70	1.68
20	2.00	3.05	2.10	**52**	0.50	2.30	0.70
21	1.50	1.43	0.50	**61**	1.00	4.20	0.47
22	2.00	0.70	0.17	ERY	0.20	0.25	Not detectable
23	4.00	0.46	0.23				

Table 8. Comparative *in vitro* and *in vivo* activities of *E*/*Z* stereoisomer oxime derivatives.

No.	Oxime derivative **IV** R=	Oxime stereochemistry	*In vitro* activity	*In vivo* activity
II	H	*E*	0.62	0.66
III	H	Z	1.05	<0.5
13 (RU 29702)	$-CH_2-CH_2-N(C_2H_5)_2$	*E*	1.27	1.55
65	$-CH_2-CH_2-N(C_2H_5)_2$	*Z*	0.64	0.67
40 (Roxithromycin)	$-CH_2-O-CH_2-CH_2-O-CH_3$	*E*	0.51	3.84
64	$-CH_2-O-CH_2-CH_2-O-CH_3$	*Z*	0.46	1.06
ERY			1	1

those of ERY in the rat. The Cmax are several times higher than that of ERY. Whereas concentrations of all the ethers are easily detectable 7 hours after administration, ERY cannot be detected from 6 hours after administration. From a strict pharmacokinetic point of view 3 products met our objectives (**13**, **40** and **61**).

At this point, having studied 65 oxime ether derivatives of ERY, it was already possible to draw some conclusions:

- —substitution of the hydroxylic group of the oxime takes place without protection of other hydroxylic groups on the macrolide ring and sugars.
- —two classes of ethers, nitrogen- and oxygen-containing aliphatic chains, showed remarkable properties.
- —some of the nitrogen-containing oxime ether derivatives have better *in vitro* and *in vivo* activities than ERY (12/25 *in vitro* and 9/25 *in vivo*).
- —of the oxygen-containing oxime ether derivatives, only 2/24 are more active *in vitro*, while 12/24 are more active *in vivo*.
- —in experimental infection with *S. pyogenes* some nitrogen-containing oxime ether derivatives show very high activities (from 10 to 40 times more active than ERY).
- —in preliminary pharmacokinetic studies 14 ether derivatives showed clear improvement as compared to ERY.

These first statements demonstrate the importance of oxime ether substitution. Isolation of two stereoisomers of the oxime (*E* and *Z*) led us to study the influence of oxime stereochemistry on antibacterial activity. Accordingly, we prepared *Z* stereoisomers of derivatives **13** and **40**, which are especially interesting as previously shown. *In vitro* and *in vivo* activities, reported in Table 8, clearly indicate that all *Z* stereoisomers are less active.

After having considered all parameters, we selected the 5 compounds **12**, **13**, **34**, **40**, and **61** (Table 9) for in depth evaluation. Compounds **12** (RU 29065) and **13** (RU 29702) were chosen for their *in vitro* activities and their *in vivo* results in experimental streptococcal infection (mouse). Pharmacokinetic data

Table 9. Recapitulative data of selected derivatives.

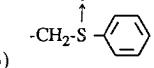
No.	Oxime ether derivative **IV** R=	*In vitro* activity MIC (μg/ml)	*In vivo* activity (mouse)		Pharmacokinetic data (rat)		
			Staphylococcal infection	Streptococcal infection	Tmax (hours)	Cmax (μg/ml)	C at 7 hours (μg/ml)
12 (RU 29065)	$-CH_2-CH_2-N(CH_3)_2$	0.126	2.36	20	2	1.9	1
13 (RU 29702)	$-CH_2-CH_2-N(C_2H_5)_2$	0.118	1.55	12	1	3.8	0.3
34 (RU 38482)	$-CH_2-O-CH_3$	0.118	2.78	5	0.5	1.60	0.15
40 (RU 28965 (Roxithromycin))	$-CH_2-O-CH_2-CH_2-OCH_3$	0.296	3.84	2.3	0.25	3.8	0.44
61 (RU 40403)		0.334	2.5	1.98	1	4.2	0.47
ERY		0.151	1	1	Not detectable	.25	Not detectable

Table 10. *In vitro* activities of selected oxime derivatives (MIC μg/ml).

Organisms	**40** (RU 28965: roxithromycin)	**12** (RU 29065)	**13** (RU 29702)	**34** (RU 38482)	**61** (RU 40403)	ERY
Gram-positive:						
Staphylococcus aureus UC1061	0.5	0.4	0.4	0.1	0.6	0.4
S. aureus UC1128	2	0.6	0.4	0.4	0.6	0.6
S. aureus 54146	1	0.4	0.4	0.2	0.6	0.4
S. aureus CO15	>40	>40	>40	>40	>40	>40
Streptococcus pyogenes group A A561	0.05	0.005	≤0.01	≤0.02	≤0.04	0.02
S. faecium 5432	0.2	0.1	0.1	0.1	0.15	0.1
S. faecalis 99F74	0.2	0.05	0.05	0.1	0.3	0.1
Gram-negative:						
Escherichia coli UC1261	200	10	10	40	>40	100
E. coli R55/123D	100	5	5	40	>40	60
Klebsiella pneumoniae 52145	100	20	15	40	>40	40
Salmonella typhimurium 420	200	10	5	40	>40	100
Pseudomonas aeruginosa 3935	>200	>40	>60	>40	>40	>200

of **13** were also attractive. Compounds **34** (RU 38482) and **61** (RU 40403) showed a good general profile. Compound **40** (RU 28965) was selected for its important differential *in vitro*/*in vivo* activity, a consequence of its remarkable pharmacokinetics. Detailed *in vitro* activities of these products against selected organisms from a selection of our screening (Table 10) show that the nitrogen containing oxime ethers **12** and **13** are relatively active against Gram-negative organisms[9]. The most active compound *in vitro* against Gram-positive organisms is **34**. However, the development of a new product is long and difficult and the two nitrogen containing ether chains **12** (RU 29065) and **13** (RU 29702) had to be abandoned due to their toxicity in semi-chronic trials in rats and dogs.

In an attempt to select the best compounds from among the final three products, RU 28965, RU

Table 11. Comparative *in vivo* activities of selected oxime derivatives.

Infecting strain	Drug	MIC (μg/ml)	$\frac{PD_{50}\,ERY}{PD_{50}\,RU}$	Infecting strain	Drug	MIC (μg/ml)	$\frac{PD_{50}\,ERY}{PD_{50}\,RU}$
Staphylococcus aureus	ERY	0.3	1	*S. pneumoniae*	ERY	0.02	1
54146	RU 28965	0.6	3.2	Type I	RU 28965	0.04	5.6
	RU 38482	0.15	2.7	69-2	RU 38482	nd	6.4
	RU 40403	0.6	3.0		RU 40403	nd	2.0
Streptococcus pyogenes	ERY	0.0025	1	*Listeria monocytogenes*	ERY	0.08	1
group A A561	RU 28965	0.0025	2.3	Orlandi	RU 28965	0.15	3.7
	RU 38482	≤0.04	5.0		RU 38482	nd	3.9
	RU 40403	≤0.04	2.0		RU 40403	nd	3.1
Streptococcus	ERY	0.02	1				
Aronson B	RU 28965	0.02	3.1				
	RU 38482	nd	3.5				
	RU 40403	nd	2.85				

nd: Not determined.

38482 and RU 40403, an extended *in vivo* study was performed in three murine experimental infections by *Streptococcus* Aronson B, *Streptococcus pneumoniae* Type I and *Listeria monocytogenes*. Comparative *in vivo* activity results (Table 11) clearly show that RU 40403 is less effective than RU 28965 and RU 38482, but more active than ERY.

RU 28965 and RU 38482 showed similar results except on *S. pyogenes* group A A561. RU 28965 was chosen for development as roxithromycin (ROX)[10,11] and RU 38482 was kept as second best back-up compound.

ROX is also the best oxime ether derivative we prepared, based on physico-chemical data.

— ROX is more stable in acidic medium than ERY†.

— The methoxy ethoxy methyl chain is very important: small changes in this chain (see derivatives **35**, **36**, **41**, **42** and **43**) lead to a decrease in the *in vivo* activity.

— The *E* stereochemistry of the oxime is also essential.

— X-Ray analysis of ROX[12] shows that the oxime ether chain is folded above the molecule and NMR analysis that the conformation in solution is very similar to that of the solid state[13]. The position of the oxime ether chain above the plane leads to a globular structure for ROX with respect to ERY. Such modifications of the physico-chemical characteristics have consequences on cytochrome P-450 binding and can explain why ROX does not interact with hepatic mono-oxygenase *in vitro* or *in vivo*[14].

— In physiological conditions (37°C, pH 7.40) the octanal-water partition coefficient of ROX (P=408, Log P=2.61) indicates a more lipophilic character than ERY (P=50, Log P=1.70)[15], which can be linked with its tissue penetration[16].

Experimental

In Vitro and *In Vivo* Studies, Serum/Plasma Level Determinations and Acute Systemic Infection Studies

The *in vitro* activity in the tables is the ratio of the geometric mean of ERY/geometric mean of the ether oxime derivative MICs of 7 selected sensitive microorganisms (3 Staphylococci and 4 Streptococci) read after incubation at 35°C for 24 hours and measured by standard broth or agar dilution methods. The *in vivo* activity is expressed as the ratio of the PD_{50} of ERY/PD_{50} of the ether oxime derivative. To

† Acid stability of roxithromycin (ROX): A comparative study of ROX and ERY was performed at 30~35°C in pH 2.6 citrate - phosphate buffer. After 2 hours' incubation, ERY was unstable with only 16% of the compound remaining, whereas ROX was relatively stable with 65% remaining (Fig. 3). In pH 4.2 acetic acid - acetate buffer ROX was completely stable for 1 hour unlike ERY, which was labile with 33% of the compound remaining. In artificial gastric juice (2 g NaCl, 7 ml HCl conc, H_2O for 1 liter→pH 1.35), the cladinose part of ROX was completely cleaved in 3 hours at 25°C.

determine the PD_{50}, we used albino mice (Charles River CD_1) with an average weight of 21 g, infection was produced by a 0.5-ml intraperitoneal injection of an overnight culture of the challenging organisms suitably diluted in physiological saline. The test antibiotics were suspended in 0.5 ml of water and then orally administered to groups of 10 mice (for each dose of macrolide) 1 hour, 5 hours and 24 hours after the bacterial challenge. The mice were observed for 7 to 10 days. The PD_{50}s given in the tables relate to experimental infection induced by *S. aureus* 54146.

Serum levels were determined in male Sprague Dawley SPF rats (200 g), after a single oral dose of 20 mg/kg. Blood samples were taken by cardiac puncture from two rats each time. Determination of antibiotic levels was carried out by using a microbiological assay and *Micrococcus luteus* 5345 as the test strain.

Determination of acid stability was measured in pH 2.6 citrate-phosphate buffer (0.1 M) at 30~35°C with a starting concentration of 200 μg/ml. Samples were removed at intervals over a period of 2 hours, the pH adjusted to neutral and the amount of compound remaining dosed by reverse phase HPLC (Bondapak C_{18}; solvent acetonitrile-methanol-0.2 M ammonium acetate-water (4.5:1:1:3.5)).

MP's were determined on a Kofler hot plate. Spectral data were recorded on the following spectrometers: NMR, Brücher WM, WP or WH: Ms, MAT-311A or ZAB-HFQ. For the NMR chemical shifts are given in ppm from tetramethylsilane as an internal standard. Elemental analysis results were within ±0.4% of the claculated values.

Chemistry

1) Ether Oxime Derivatives Starting from ERY and *O*-Alkylhydroxylamine

General Method

(*E*)-9-[*O*-(2-Ethoxyethyl)oxime] of ERY **42**: 1.4 ml of triethylamine and then 2.8 g of *O*-(2-ethoxyethyl)hydroxylamine hydrochloride were added to a solution of 3.7 g of ERY in 25 ml of dry methanol and the mixture was stirred under an inert atmosphere at room temperature for 96 hours. This solution was poured into 12 ml of 28% ammonium hydroxide in 50 ml of water and the resulting mixture was cooled in an ice-water bath. The mixture was filtered and the recovered product was washed with water and taken up in methylene chloride. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness to obtain 3.83 g of the raw product. The latter was chromatographed over silica gel and eluted with a benzene-triethylamine mixture (15:1) to obtain 1.9 g of 9-[*O*-(2-ethoxyethyl)oxime] of ERY with a specific rotation of $[\alpha]_D^{20}$ −73°±3° (*c* 0.6, $CHCl_3$). Yield 46% (amorphous). EI-MS *m/z* 820 (M^+, $C_{41}H_{76}N_2O_{14}$=820). ^1H NMR (60 MHz, $CDCl_3$). δ 2.30 (s, $N(CH_3)_2$), 1.50 (s, 6-CH_3).

Products **1** and **7** were prepared by a similar method replacing triethylamine by calcium carbonate.

(*E*)-9-[*O*-(2-Methyloxime)] of ERY (**1**): The crude product was purified by chromatography over silica gel with a chloroform-triethylamine mixture (9:1). $[\alpha]_D^{20}$ −74° (*c* 1, EtOH). Yield 22% (amorphous). EI-MS *m/z* 762 (M^+, $C_{38}H_{70}N_2O_{13}$=762). ^1H NMR (60 MHz, $CDCl_3$). δ 3.83 (s, N−OCH_3), 3.33 (s, 4″-OCH_3).

(*E*)-9-[*O*-[2-(4-Chlorophenoxy)ethyloxime]] of ERY (**7**): The crude product was purified by chromatography over silica gel with a chloroform-triethylamine mixture (9:1). $[\alpha]_D^{20}$ −79° (*c* 1, EtOH). Yield 22.5% (amorphous). EI-MS *m/z* 902 (M^+, $C_{45}H_{75}ClN_2O_{14}$=902.5). ^1H NMR (60 MHz, $CDCl_3$) δ 7.4, 7.25, 7.01, 6.86 (Ar-H), 4.33 (m, N−O−CH_2−O−).

2) Ether Oxime Derivatives Starting from Oxime of ERY and Alkylhalide

Preparation of ERY Oximes

a) *E* Oxime Configuration (Major Isomer): To a solution of 500 g of ERY in 1 liter of methanol was added 237 ml of triethylamine and 237 g of hydroxylamine hydrochloride. The mixture was refluxed for 24 hours. A complete dissolution was observed after 30 minutes of reaction and the progressive crystallization of ERY oxime hydrochloride took place 15 minutes later. The mixture was cooled at 0±2°C for 1 hour. Crystals were separated, washed 3 times with 250 ml cooled methanol.

To a stirred suspension of ERY oxime hydrochloride in 1.63 liters methanol was added at 20°C, 326 ml of concentrated NH_4OH (20%). After 30 minutes of stirring 326 ml of water were added to the solution. The mixture remains clear and to initiate the crystallization some crystals of ERY oxime were added. To the crystallized mixture 1.435 liters of water was added to give 372.3 g of *E* isomer. MP 170°C. $[\alpha]_D^{20}$ −70°

(*c* 1, EtOH). TLC (SiO_2, benzene - chloroform - triethylamine, (5 : 4 : 1)). Rf 0.26

b) *Z* Oxime Configuration (Minor Isomer): To a solution of 1.2 ml of 2 N NaOH and 2.7 ml of methanol was added 0.88 g of *E* ERY oxime. The mixture was kept 6 hours at 25°C and overnight at 0±5°C. The mixture was evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water and dried, and the solvent was removed to give 0.8 g of crude product. Crystallization from a mixture acetone - methylene chloride (3 : 4) gave 0.495 g of *Z* isomer. MP 170°C $[\alpha]_D^{20}$ −69° (*c* 1, EtOH). TLC (SiO_2, benzene - chloroform - triethylamine, (5 : 4 : 1)). Rf 0.16.

Table 12. NMR of *E* and *Z* ERY oximes.

	Major isomer (*E*)	Minor isomer (*Z*)
H-8	3.78 (m)	2.9 (m)
H-10	2.70 (q)	2.8 (q)
C-8	25.5	35.8 (d)
C-10	32.8 (d)	34.2
^2J ^{15}N-C-8	0	11
^2J ^{15}N-C-10	7.5	0

Stereochemistry of Oxime Isomers

The oxime stereochemistry was determined by NMR using proton and ^{13}C chemical shifts and ^{15}N-^{13}C coupling constants. All NMR measurements were performed on $CDCl_3$ solution using a Bruker WM 250 spectrometer. Chemical shifts are in ppm from internal tetramethylsilane, coupling constants in hertz. Isotopically labeled ERY oximes were synthesised from 95% ^{15}N enriched hydroxylamine chlorhydrate. ^2J ^{15}N-^{13}C were determined from proton decoupled ^{13}C spectra.

^{1}H and ^{13}C Chemical Shifts

Chemical shifts were assigned to carbons and protons neighboring the oxime group by single frequency decoupling measurements. Results are shown in Table 12. In the major oxime isomer H-8 is clearly deshielded and appears well separated from other protons; C-8 is shielded. Both displacements suggest an *E* configuration for this oxime (the oxime-OH being close to H-8 and C-8).

^{15}N-^{13}C Coupling Constants

According to literature[17], in simple oximes these coupling constants are in the range from 7 to 12 Hz for carbons *anti* and from 0 to 2 Hz for carbons *syn* to the oxime-OH. Values found in ERY oximes show that OH is *syn* to C-8 in the major oxime isomer (*E*) and *syn* to C-10 in the minor isomer (*Z*).

General Methods

(*E*)-9-[*O*-(2-Methoxyethoxy)methyloxime] of ERY (**40**): A mixture of 1.89 g of the oxime of ERY, 25 ml of acetone, 1 g of sodium bicarbonate and 0.36 ml of (methoxyethoxy)methyl chloride was refluxed under an inert atmosphere for 75 hours during which another 0.35 ml of (methoxyethoxy)methyl chloride was added once. The mixture was vacuum filtered and the filtrate evaporated to dryness. An aqueous sodium bicarbonate solution was added to the mixture which was then extracted with ether. The organic phase was dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a benzene - triethylamine mixture (9 : 1) yielded 1.72 g of 9-[*O*-(2-methoxyethoxy)methyloxime] of ERY with a specific rotation of $[\alpha]_D^{20}$ −77.5°±2° (*c* 0.45, $CHCl_3$) and an Rf 0.2 (silica support, benzene - triethylamine eluant (9 : 1)). Yield 81.4%. MP 128.5°C. EI-MS *m/z* 836 (M^+, $C_{41}H_{76}N_2O_{15}$=836). ^{1}H NMR (60 MHz, $CDCl_3$). δ 5.18 (N−O−CH_2−O), 3.41 (s, OCH_3).

(*E*)-9-[*O*-(2-Bromoethyl)oxime] of ERY (**2**): 0.75 g of sodium hydride was added to a mixture of 5.62 g of the oxime of ERY and 100 ml of ethyl ether and after the evolution of gas ceased, 15 ml of 1,2-dibromoethane were added. The mixture was refluxed for 16 hours and was then cooled to 20°C and 0.75 g of sodium hydride was added. The mixture was refluxed for another 6 hours and after cooling it to about 0°C, 100 ml of methylene chloride were added. 3 ml of acetic acid were then added dropwise while stirring the mixture, which was returned to room temperature before being poured into 50 ml of water containing 4 ml of 28% ammonium hydroxide. The aqueous phase was extracted with methylene chloride and the combined organic phases were washed with water, dried and evaporated to dryness. The residue was chromatographed over silica gel and eluted with a methylene chloride - triethylamine mixture (25 : 0.5) to obtain 4.78 g of 9-[*O*-(2-bromoethyl)oxime] of ERY with a specific rotation of $[\alpha]_D^{20}$ −87°±2.5° (*c*

0.5, EtOH). Yield 74.4%. MP 200°C. EI-MS *m/z* 854 (M^+, $C_{39}H_{71}BrN_2O_{13}$=854.9). ^1H NMR (90 MHz, $CDCl_3$). δ 4.27 (m, N-O-CH_2-), 3.47 (m, CH_2-Br).

These two basic methods were adapted according to the reactivity of alkyl halide and the solubility of reagents, thus in some cases we used sodium carbonate as a base and THF, DMF and hexamethylphosphotriamide (HMPT) as solvents.

(*E*)-9-[*O*-(2-Propenyl)oxime] of ERY (**3**): Alkyl halide=allylbromide, base used=sodium hydride, solvent=ethyl ether-DMF (10:1), purification by chromatography=SiO_2 in chloroform-triethylamine (9:1). $[\alpha]_D^{20}$ −68° (*c* 0.5, $CHCl_3$). MP 131°C. Yield 70%. MS *m/z* 789 (M^+, $C_{40}H_{72}N_2O_{13}$=789). ^1H NMR (90 MHz, $CDCl_3$). δ 6.22, 5.76 (m, -CH=C).

(*E*)-9-[*O*-(2-Chloro-2-propenyl)oxime] of ERY (**4**): Alkyl halide=2,3-dichloro 1-propene, base=sodium hydride, solvent=HMPT, crystallization in *n*-pentane. $[\alpha]_D^{20}$ −64° (*c* 1, $CHCl_3$). MP 146°C. Yield 60.5%, MS *m/z* 822 (M^+, $C_{40}H_{71}ClN_2O_{13}$=823). ^1H NMR (60 MHz, $CDCl_3$). δ 5.45 (=CH_2), 4.6 (N-O-CH_2-).

(*E*)-9-[*O*-([4-Chlorophenoxy]methyl)oxime] of ERY (**5**): Alkyl halide=4-chlorophenoxymethyl chloride, base=sodium hydride, solvent=ethyl ether-HMPT (10:1), crystallization in *n*-pentane. $[\alpha]_D^{20}$ −64.5° (*c* 0.5, EtOH). MP 90°C. Yield 35.6%. MS *m/z* 889$^+$ (M, $C_{44}H_{73}ClN_2O_{14}$=889.5). ^1H NMR (90 MHz, $CDCl_3$). δ 7.33~7.24 (Ar-H, *o*-O-CH_2-), 7.02~6.92 (Ar-H, *m*-O-CH_2-), 5.74, 5.66, 5.63, 5.55 (N-O-CH_2-O).

(*E*)-9-[*O*-(Phenylmethoxy)methyloxime] of ERY (**6**): Alkyl halide=phenylmethoxymethyl chloride, base=sodium bicarbonate, solvent=acetone, chromatographic separation (SiO_2, benzene-triethylamine (9:1)) then recrystallization in *n*-hexane. $[\alpha]_D^{20}$ −74° (*c* 0.25, EtOH). MP 120°C. Yield 54.5%. EI-MS *m/z* 867 (M^+, $C_{45}H_{76}N_2O_{14}$=869). ^1H NMR (90 MHz, $CDCl_3$). δ 7.34 (Ar), 5.32, 5.24, 5.21, 5.13 (N-O-CH_2-O), 4.67 (Ar-CH_2-O).

(*E*)-9-[*O*-(3-Methoxy-1,2,4-thiadiazol-5-yl)oxime] of ERY (**8**): Alkyl halide=3-methoxy-5-chloro 1,2,4-thiadiazol, base=sodium hydride, solvent=HMPT, chromatographic purification (SiO_2, toluene-chloroform-triethylamine (6:4:1)) and recrystallization in isopropylether. $[\alpha]_D^{20}$ −103° (*c* 1, $CHCl_3$). MP 240~242°C. Yield 21.6%. MS *m/z* 862 (M^+, $C_{40}H_{70}N_4O_{14}S$=863). ^1H NMR (90 MHz, $CDCl_3$). δ 4.01 (s, ).

(*E*)-9-[*O*-(2-Dimethylamino)ethyloxime] of ERY (**12**): Alkyl halide=dimethylaminochloroethane (hydrochloride), base/solvent=sodium bicarbonate or sodium carbonate-acetone or sodium hydride-ethyl ether-HMPT (3:1), crystallization in acetone. $[\alpha]_D^{20}$ −76.5° (*c* 0.5, EtOH) and −86.4°, (*c* 1, $CHCl_3$). EI-MS *m/z* 820 (M^+, $C_{41}H_{77}N_3O_{13}$=820). ^1H NMR (90 MHz, $CDCl_3$), 2.27, 2.21 ($N(CH_3)_2$).

(*E*)-9-[*O*-(2-Diethylamino)ethyloxime] of ERY (**13**): Alkyl halide=diethylaminochloroethane (hydrochloride), base=sodium carbonate, solvent=THF, crystallization in isopropyl alcohol. $[\alpha]_D^{20}$ −85° (*c* 1, EtOH). MP 205°C. Yield 88%. EI-MS 848 (M^+, $C_{43}H_{81}N_3O_{13}$=848). ^1H NMR (250 MHz, $CDCl_3$). δ 4.13 (-N-O-CH_2-), 2.61 ($N<^{CH_2-}_{CH_2-}$).

(*E*)-9-[*O*-(Bis(1-methylethyl)amino)ethyloxime] of ERY (**14**): Alkyl halide=diisopropylaminochloroethane (hydrochloride), base=sodium bicarbonate, solvent=THF, chromatographic purification (SiO_2, methylene chloride-triethylamine (19:1)) recrystallization in ethanol-water (10:6). $[\alpha]_D^{20}$ −73° (*c* 0.5, EtOH). MP 125°C. Yield 66.6%. FD-MS *m/z* 877 (M^+, $C_{45}H_{85}N_3O_{13}$=876). ^1H NMR (60 MHz, $CDCl_3$) δ 4.1, 3.98, 3.86 (N-O-CH_2-), 2.83 (-$\overset{C}{\underset{C}{CH}}$), 1.06, 0.95 (-$C(CH_3)_2$).

(*E*)-9-[*O*-(2(Morpholin-4-yl)ethyl)oxime] of ERY (**15**): Alkyl halide=β-chloroethyl morpholine, base=sodium carbonate, solvent=acetone, crystallization in ethyl ether. $[\alpha]_D^{20}$ −73°5 (*c* 0.5, EtOH). MP 232°C. Yield 61.5%. EI-MS *m/z* 861 (M^+, $C_{43}H_{79}N_3O_{14}$=862). ^1H NMR (90 MHz, $CDCl_3$). δ 4.11, 3.77 ($O<^{CH_2-}_{CH_2-}$), 3.05, 2.44 ($N<^{CH_2-}_{CH_2-}$).

(*E*)-9-[*O*-(2(Piperidin-1-yl)ethyl)oxime] of ERY (**16**): Alkyl halide=β-chloroethyl *N*-piperidine, base=sodium carbonate, solvent=acetone, chromatographic purification (SiO_2, benzene-chloroform-

triethylamine (5:4:1)). $[\alpha]_D^{20}$ −78° (*c* 0.6, EtOH). MP 204°C. Yield 66%. EI-MS *m/z* 860 (M^+, $C_{44}H_{81}N_3O_{13}$=860). ^{1}H NMR (90 MHz, $CDCl_3$). δ 4.87, 4.83 (d, 1″-H), 4.46, 4.38 (d, 1′-H), 2.28 (s, $-N(CH_3)_2$).

(*E*)-9-[*O*-(2(Pyrrolidin-1-yl)ethyl)oxime] of ERY (**17**): Alkyl halide=β-chloroethyl *N*-pyrrolidine (hydrochloride), base=sodium carbonate, solvent=acetone, crystallization in acetone-water (1:1). $[\alpha]_D^{20}$ −83° (*c* 1, EtOH). MP 135°C. Yield 68%. FD-MS *m/z* 845 (M^+, $C_{43}H_{79}N_3O_{13}$=846). ^{1}H NMR (90 MHz, $CDCl_3$). δ 3.32 (s, $-OCH_3$), 2.28 (s, $-N(CH_3)_2$).

(*E*)-9-[*O*-(2-Diethyloxydo)aminoethyloxime] of ERY (**20**): Alkyl halide=β-chloroethyl *N*(diethyl) (oxydo), base=sodium carbonate, solvent=THF, chromatographic purification (SiO_2, benzene-chloroform-triethyl amine (55:35:10)). $[\alpha]_D^{20}$ −72° (*c* 0.5, EtOH). MP 136°C. Yield 42.6%. EI-MS *m/z* 864 (M^+, $C_{43}H_{81}N_3O_{14}$=864). ^{1}H NMR (250 MHz, $CDCl_3$). δ 4.20 (t, $-N-O-CH_2-$), 3.92 (m, $O-C-CH_2-N$), 2.75 (m, $\underset{\underset{O}{\downarrow}}{N}-CH_2-$).

(*E*)-9-[*O*-(2-Diethylamino)-1-methylethyl)oxime] of ERY (**21**): Alkyl halide=2-chloro-1-dimethylamino propane, base=sodium carbonate, solvent=acetone, crystallization in acetone-water (1:1) stereoisomer mixture. $[\alpha]_D^{20}$ −96° (*c* 0.75, EtOH). Yield 91.4%. EI-MS *m/z* 833 (M^+, $C_{42}H_{79}N_3O_{13}$=834). ^{1}H NMR (60 MHz, $CDCl_3$). δ 3.33 (s, OCH_3), 2.19 ($N(CH_3)_2$), 0.86, 0.75 ($H_3C-\underset{\underset{H}{|}}{\overset{\overset{C}{|}}{C}}-C$).

(*E*)-9-[*O*-(2-Diethylamino)-1-methylethyl)oxime] of ERY (**22**): Alkyl halide=1-diethylamino 2-chloro propane (hydrochloride), base=sodium carbonate, solvent=acetone, crystallization in acetone-water (1:1.5). $[\alpha]_D^{20}$ −84° (*c* 0.75, EtOH) stereoisomer mixture. Yield 82.5%. EI/FD-MS *m/z* 861 (M^+, $C_{44}H_{83}N_3O_{13}$=862). ^{1}H NMR (60 MHz, $CDCl_3$). δ 3.35 (s, OCH_3) 2.78, 2.66, 2.55, 2.41 (m, $N-(CH_2-C)_2$), 2.31 (s, $N(CH_3)_2$).

(*E*)-9-[*O*-(2-Diethylamino)-1,1-dimethylethyl)oxime] of ERY (**23**): Alkyl halide=2-chloro-2-methyl-1-diethylamino propane (hydrochloride), base=sodium carbonate, solvent=acetone, crystallization in acetone-water (2:1). $[\alpha]_D^{20}$ −68.5° (*c* 0.5, EtOH). Yield 78.7%. MP 166°C. FD-MS *m/z* 876 (M^+, $C_{45}H_{85}N_3O_{13}$=876). ^{1}H NMR (250 MHz, $CDCl_3$). δ 3.31 (s, OCH_3), 2.4, 2.7 (m, $N-CH_2-$), 1.24 (s, CH_3-C-).

(*E*)-9-[*O*-(3-Diethylamino)propyloxime] of ERY (**24**): Alkyl halide=1-chlorodiethylamino propane (hydrochloride), base=sodium carbonate, solvent=acetone, crystallization in acetone-hexane (1:15). $[\alpha]_D^{20}$ −70° (*c* 1, $CHCl_3$). MP 155°C. Yield 31%. EI-MS *m/z* 835 (M^+, $C_{42}H_{79}N_3O_{13}$=834). ^{1}H NMR (60 MHz, $CDCl_3$). δ 4.15, 4.05, 3.95 (m, $-N-O-CH_2-$), 3.31 (s, $-OCH_3$).

(*E*)-9-[*O*-(Cyanomethyl)oxime] of ERY (**27**): Alkyl halide=acetonitrile chloride, base=sodium hydride, solvent=acetone, chromatographic purification (SiO_2, ethyl ether-triethylamine (85:15)) and crystallization in *n*-hexane. $[\alpha]_D^{20}$ −74.5° (*c* 0.6, $CHCl_3$). Yield 57%. MP 140°C. MS *m/z* 787 (M^+, $C_{39}H_{69}N_3O_{13}$=788). ^{1}H NMR (90 MHz, $CDCl_3$). δ 4.93, 4.88 (d, 1″-H), 4.7 ($O-CH_2-CN$), 4.46, 4.38 (d, 1′-H).

(*E*)-9-[*O*-(2-Cyanoethyl)oxime] of ERY (**28**): Alkyl halide=bromopropionitrile, base=sodium hydride, solvent=HMPT, chromatographic purification (SiO_2, chloroform-triethylamine (95:5)) and crystallization in *n*-pentane. $[\alpha]_D^{20}$ −77.5° (*c* 1, $CHCl_3$). Yield 39%. MP 210°C. MS *m/z* 801 (M^+, $C_{40}H_{71}N_3O_{13}$=802). ^{1}H NMR (60 MHz, $CDCl_3$). δ 4.35, 4.25, 4.15 (m, $N-O-CH_2-$), 3.31 (s, $-OCH_3$), 2.76, 2.66, 2.56 (m, $-CH_2-CN$).

(*E*)-9-[*O*-(Methoxymethyl)oxime] of ERY (**34**): Alkyl halide=methoxymethyl chloride, base=sodium hydride, solvent=ethyl ether, crystallization in acetone-water (1:1). $[\alpha]_D^{20}$ −82° (*c* 0.5, EtOH). Yield 61.5%. MP 145°C. EI-MS *m/z* 792 (M^+, $C_{39}H_{72}N_2O_{14}$=793). ^{1}H NMR (90 MHz, $CDCl_3$). δ 5.18, 5.11, 5.07, 5.00 (m, $N-O-CH_2-O$), 3.44 (s, $-C-OCH_3$), 3.32 (s, $-OCH_3$).

(*E*)-9-[*O*-(Ethoxymethyl)oxime] of ERY (**35**): Alkyl halide=ethoxymethyl chloride, base=sodium hydride, solvent=HMPT, chromatographic separation (SiO_2, toluene-chloroform-triethylamine (6:4:1)). $[\alpha]_D^{20}$ −78° (*c* 1, $CHCl_3$). Yield 48%. MP 123°C. MS *m/z* 806 (M^+, $C_{40}H_{74}N_2O_{14}$=807). ^{1}H NMR (90 MHz, $CDCl_3$). δ 5.23, 5.16, 5.12, 5.05 ($N-O-CH_2-O$), 3.32 (s, OCH_3).

(*E*)-9-[*O*-(Propoxymethyl)oxime] of ERY (**36**): Alkyl halide=propoxymethyl chloride, base=sodium hydride, solvent=ethyl ether-DMF (1:2), chromatographic separation (SiO_2, benzene-chloroform-

triethylamine (55:35:10)). $[\alpha]_D^{20}$ −81.5° (*c* 0.75, EtOH). Yield 40%. MP 110°C. FD-MS *m/z* 821 (M^+, $C_{41}H_{76}N_2O_{14}$=821). ^{1}H NMR (250 MHz, $CDCl_3$). δ 5.16 (d), 5.07 (a) (N−O−CH_2−O), 3.52 (−O−CH_2−).

(*E*)-9-[*O*-((2-Chloroethoxy)methyl)oxime] of ERY (**38**): Alkyl halide=(2-chloroethoxy)methyl chloride, base=sodium hydride, solvent=ethyl ether, crystallization in ethanol-water (1:9). $[\alpha]_D^{20}$ −78.5° (*c* 0.5, $CHCl_3$). Yield 88.7%. MP 129°C. MS *m/z* 840 (M^+, $C_{40}H_{73}ClN_2O_{14}$=841.5). ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.32, 5.24, 5.19, 5.11 (N−O−CH_2−O), 3.32 (s, −OCH_3), 2.28 (s, $N(CH_3)_2$).

(*E*)-9-[*O*-((2-Methylpropoxy)methyl)oxime] of ERY (**39**): Alkyl halide=(2-methylpropoxy)methyl chloride, base=sodium bicarbonate, solvent=acetone, chromatographic purification (SiO_2, benzene-triethylamine (15:1)). $[\alpha]_D^{20}$ −79.5° (*c* 0.5, EtOH). Yield 61.5% EI/FD-MS *m/z* 834 (M^+, $C_{42}H_{78}N_2Q_{14}$=835). ^{1}H NMR (90 MHz, $CDCl_3$). δ 5.23~5.00 (O−CH_2−O), 3.31 (s, −OCH_3).

(*E*)-9-[*O*-((2-Ethoxyethoxy)methyl)oxime] of ERY (**41**): Alkyl halide=1-chloromethoxy-2-ethoxy ethane, base=sodium bicarbonate, solvent=acetone, chromatographic purification (SiO_2, benzene-triethylamine (9:1)). $[\alpha]_D^{20}$ −79° (*c* 0.7, EtOH). Yield 80%. EI-MS *m/z* 850 (M^+, $C_{42}H_{78}N_2O_{15}$=851). ^{1}H NMR (60 MHz, $CDCl_3$). δ 5.2 (N−O−CH_2−O), 3.32 (s, −OCH_3).

(*E*)-9-[*O*-(2-(2-Hydroxyethoxy)ethyl)oxime] of ERY (**43**): Alkyl halide=2-(2-chloroethoxy)ethanol, base=sodium hydride, solvent=HMPT, chromatographic purification (SiO_2, toluene-triethylamine (9:1)). $[\alpha]_D^{20}$ −83.5° (*c* 1, $CHCl_3$). Yield 36%. MP 132°C. MS *m/z* 836 (M^+, $C_{41}H_{76}N_2O_{15}$=837). ^{1}H NMR (60 MHz, $CDCl_3$). δ 4.33~3.00 (m, −O−CH_2−CH_2−O−CH_2−CH_2−O−), 3.33 (s, −OCH_3), 2.32 (s, $N(CH_3)_2$).

(*E*)-9-[*O*-(Oxinarylmethyl)oxime] of ERY (**44**): Alkyl halide=epibromhydrin, base=sodium hydride, solvent=DMF, chromatographic purification (SiO_2, chloroform-triethylamine (9:1)). $[\alpha]_D^{20}$ −79° (*c* 0.5, $CHCl_3$). Yield 22.4%. MP 154°C. MS *m/z* 804 (M^+, $C_{40}H_{72}N_2O_{14}$=804). ^{1}H NMR (60 MHz, $CDCl_3$). δ 3.33 (s, −OCH_3), 2.3 (s, $N(CH_3)_2$).

(*E*)-9-[*O*-(1,3-Dioxolan-2-yl)methyloxime] of ERY (**45**): Alkyl halide=2-(2-bromomethyl)-1,3-dioxolanne, base=sodium hydride, solvent=ethyl ether-DMF (10:1), chromatographic purification (SiO_2, toluene-triethylamine (9:1)). $[\alpha]_D^{20}$ −67.5° (*c* 1, $CHCl_3$). Yield 36.7%. MP 208°C. MS *m/z* 834 (M^+, $C_{41}H_{74}N_2O_{15}$=834). ^{1}H NMR (90 MHz, $CDCl_3$). δ 4.91~4.86 (d, 1″-H), 4.45~4.37 (d, 1′-H), 2.28 (s, $N(CH_3)_2$).

(*E*)-9-[*O*-(2,2-Dimethoxyethyl)oxime] of ERY (**46**): Alkyl halide=bromoacetaldehyde dimethylether, base=sodium hydride, solvent=ethyl ether-HMPT (1:1), chromatographic purification (SiO_2, toluene-triethylamine (9:1)) and recrystallization in *n*-pentane. $[\alpha]_D^{20}$ −80° (*c* 0.6, $CHCl_3$). Yield 57%. MP 1) 146°C, 2) 186°C. MS *m/z* 836 (M^+, $C_{41}H_{76}N_2O_{15}$=836). ^{1}H NMR (90 MHz, $CDCl_3$). δ 3.42~3.41 ($C(OCH_3)_2$), 2.28 (s, $N(CH_3)_2$).

(*E*)-9-[*O*-(2-Diethoxy)ethyloxime] of ERY (**47**): Alkyl halide=bromoacetal diethyl ether, base=sodium hydride, solvent=ethyl ether-HMPT (5:18), chromatographic purification (SiO_2, benzene-chloroform-triethylamine (7:2:1)). $[\alpha]_D^{20}$ −75.5° (*c* 0.65, EtOH). Yield 26%. EI/FD-MS *m/z* 864 (M^+, $C_{43}H_{80}N_2O_{15}$=864). ^{1}H NMR (90 MHz, $CDCl_3$). δ 4.72, 4.00 (), 3.77, 3.33 (−O−CH_2−C−), 3.32 (s, OCH_3).

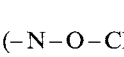
(*E*)-9-[*O*-(1,3-Dioxolan-2-yl)ethyloxime] of ERY (**48**): Alkyl halide=2-(2-bromoethyl)-1,3-dioxolanne, base=sodium hydride, solvent=DMF, chromatographic purification (SiO_2, methylene chloride-methanol-aq ammonia (95:10:1)). $[\alpha]_D^{20}$ −77° (*c* 1, EtOH). Yield 35%. EI/FD-MS *m/z* 848 (M^+, $C_{42}H_{76}N_2O_{15}$=848). ^{1}H NMR (250 MHz, $CDCl_3$). δ 4.57 (t, ), 4.18 (t, N−O−CH_2−), 3.32 (s, OCH_3).

(*E*)-9-[*O*-(2-(1,1-Dimethylethoxy)-2-oxoethyl)oxime] of ERY (**49**): Alkyl halide=*tert*-butyl monochloracetate, base=sodium hydride, solvent=ethyl ether-DMF (10:1), chromatographic purification (SiO_2, toluene-triethylamine (9:1)). $[\alpha]_D^{20}$ −71.5° (*c* 1, $CHCl_3$). Yield 52%. MP 214°C. MS *m/z* 862 (M^+, $C_{43}H_{78}N_2O_{15}$=862). ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.46 (−O−CH_2−CO_2), 3.33 (s, OCH_3) 1.5 (s, *tert*-butyl).

(*E*)-9-[*O*-(2-Ethoxy-2-oxoethyl)oxime] of ERY (**50**): Alkyl halide=ethylbromacetate, base=sodium hydride, solvent=ethyl ether, chromatographic purification (SiO_2, methylene chloride-triethylamine (9:1)).

$[\alpha]_D^{20}$ −80° (*c* 0.8, EtOH). Yield 41%. MP 130°C. FD-MS *m/z* 834 (M^+, $C_{41}H_{74}N_2O_{15}$=834). ^{1}H NMR (90 MHz, $CDCl_3$). δ 4.64 (N−O−CH_2), 4.5, 4.16 (CO_2−CH_2−C), 3.34 (s, OCH_3).

(*E*)-9-[*O*-(3,3-Dimethyl-2-oxo-butyl)oxime] of ERY (**52**): Alkyl halide=bromopinacolone, base=sodium hydride, solvent=HMPT, chromatographic purification (SiO_2, toluene-chloroform-triethylamine (6:4:1)). $[\alpha]_D^{20}$ −63.5° (*c* 1, $CHCl_3$). Yield 14%. MP 146°C. MS *m/z* 846 (M^+, $C_{43}H_{78}N_2O_{14}$=846). ^{1}H NMR (90 MHz, $CDCl_3$). δ 4.88 (−O−CH_2−C(=O)), 1.17 (s, *tert*-butyl).

(*E*)-9-[*O*-(3-(2-methyl-1,3-dioxolanne-2-yl)propyl)oxime] of ERY (**54**): Alkyl halide=3-(2-methyl-1,3-dioxolanne-2-yl)propyl bromide, base=sodium hydride, solvent=DMF-ethyl ether (4:1), crystallization in ethanol-water (1:1). $[\alpha]_D^{20}$ −80.5° (*c* 0.6, EtOH). Yield 73.5%. MP 159°C. FD-MS *m/z* 876 (M^+, $C_{44}H_{80}N_2O_{15}$=876). ^{1}H NMR (250 MHz, $CDCl_3$). δ 4.21, 3.92 (−N−O−CH_2− and ), 1.32 (s, −C−CH_3).

(*E*)-9-[3-(2-Hydroxyethyloxy)-2-hydroxypropyl)oxime] of ERY (**57**): Alkyl halide=6-chloro-3-oxa hexane-1,5-diol, base=sodium hydride, solvent=ethyl ether, chromatographic purification (SiO_2, methylene chloride-triethylamine (9:1)). $[\alpha]_D^{20}$ −81° (*c* 0.5, EtOH). Yield 30%. EI-MS *m/z* 866 (M^+, $C_{42}H_{78}N_2O_{16}$=866). ^{1}H NMR (250 MHz, $CDCl_3$). δ 4.20 3.95 (N−O−CH_2− and −CH−OH), 3.80, 3.40 (CH_2O of the chain).

(*E*)-9-[*O*-(Methylthio)methyloxime] of ERY (**58**): Alkyl halide=dimethylsulfure chloride, base=sodium hydride, solvent=ethyl ether, chromatographic purification (SiO_2, toluene-triethylamine (9:1)). $[\alpha]_D^{20}$ −75.5° (*c* 0.45, $CHCl_3$). Yield 29%. MP 132°C. MS *m/z* 808 (M^+, $C_{39}H_{72}N_2O_{13}S$=808). ^{1}H NMR (90 MHz, $CDCl_3$). δ 5.14 (N−O−CH_2−S−), 3.33 (s, OCH_3), 2.24 (s, −S−CH_3).

(*E*)-9-[*O*-(Methylsulfinylmethyl)oxime] of ERY (**59**): Alkyl halide=chloromethylmethyl sulfoxide, base=sodium hydride, solvent=ethyl ether, chromatographic purification (SiO_2, chloroform-triethylamine (19:1)). $[\alpha]_D^{20}$ −78° (*c* 0.6, EtOH). Yield 35.3%. MP 170°C. FD-MS *m/z* 824 (M^+, $C_{39}H_{72}N_2O_{14}S$=824). ^{1}H NMR (250 MHz, $CDCl_3$). δ 5.1, 4.7 (O−CH_2), 2.64, 2.57 (H_3C−S(=O)−) diastereoisomeric mixture.

(*E*)-9-[*O*-(Phenylthio)methyloxime] of ERY (**60**): Alkyl halide=chloromethylphenyl sulfide, base=sodium hydride, solvent=ethyl ether-HMPT (1:1), chromatographic purification (SiO_2, chloroform-triethylamine (9:1)). $[\alpha]_D^{20}$ −2.5° (*c* 0.5, $CHCl_3$). Yield 68%. MP 198°C. MS *m/z* 870 (M^+, $C_{44}H_{74}N_2O_{13}S$=870). ^{1}H NMR (60 MHz, $CDCl_3$). δ 7.5 (Ar-H), 5.65, 5.46, 5.39, 5.2 (N−O−CH_2−S), 3.31 (OCH_3).

(*E*)-9-[*O*-(Phenylsufinyl)methyloxime] of ERY (**61**): Alkyl halide=iodomethylphenyl sulfoxide, base=sodium hydride, solvent=HMPT, chromatographic purification (SiO_2, chloroform-triethylamine (21:1)). $[\alpha]_D^{20}$ −71° (*c* 0.6, EtOH). Yield 64%. FD-MS *m/z* 886 (M^+, $C_{44}H_{74}N_2O_{14}S$=886). ^{1}H NMR (90 MHz, $CDCl_3$). δ 7.7, 7.5 (Ar-H), 4.98, 4.97, 4.87, 4.72 (CH_2O), 3.31 (s, −OCH_3), 2.23 (s, $N(CH_3)_2$).

(*E*)-9-[*O*-(4-Chlorophenylthio)methyloxime] of ERY (**62**): Alkyl halide=4-chlorophenylthiomethyl chloride, base=sodium hydride, solvent=ethyl ether-HMPT (10:1), chromatographic purification (SiO_2, toluene-triethylamine (9:1)). $[\alpha]_D^{20}$ −32.5° (*c* 0.8, $CHCl_3$). Yield 22%. MP 126°C. MS *m/z* 904 (M^+, $C_{44}H_{73}ClN_2O_{13}S$=904.5). ^{1}H NMR (60 MHz, $CDCl_3$). δ 5.41 (N−O−CH_2−), 3.33 (s, −OCH_3).

(*E*)-9-[*O*-(3-Ethylthio-2-hydroxypropyl)oxime] of ERY (**63**): Alkyl halide=3-ethylthio-2-hydroxypropyl chloride, base=sodium hydride, solvent=ethyl ether-HMPT (1:1), chromatographic purification (SiO_2, chloroform-triethylamine (9:1)). $[\alpha]_D^{20}$ −76.5° (*c* 0.8, $CHCl_3$). Yield 8%. MP 142°C. MS *m/z* 866 (M^+, $C_{42}H_{78}N_2O_{14}S$=866). ^{1}H NMR (60 MHz, $CDCl_3$). δ 3.33 (s, −OCH_3), 2.91, 2.00 (−CH_2−S).

(*Z*)-9-[*O*-(2-Methoxyethoxy)methyloxime] of ERY (**64**): Alkyl halide=methoxyethoxymethyl chloride, base=sodium bicarbonate, solvent=acetone, chromatographic purification (SiO_2, benzene-chloroform-triethylamine (5:4:1)). $[\alpha]_D^{20}$ −52° (*c* 0.5, EtOH). Yield 37%. FD-MS *m/z* 836 (M^+, $C_{41}H_{76}N_2O_{15}$=836). ^{1}H NMR (250 MHz, $CDCl_3$). δ 5.19, 5.09 (N−O−CH_2−), 3.77, 3.57 (O−CH_2−CH_2−O), 3.39 (s, −OCH_3), 3.1, 2.8 (m, H-8 and H-10).

(*Z*)-9-[*O*-(2-Diethylamino)ethyloxime] of ERY (**65**): Alkyl halide=diethylaminoethyl chloride hydrochloride, base=sodium carbonate, solvent=THF, chromatographic purification (SiO_2, methylene chloride-triethylamine (15:1)). $[\alpha]_D^{20}$ −52° (*c* 0.5, EtOH). Yield 30%. EI/FD-MS *m/z* 847 (M^+,

$C_{43}H_{81}N_3O_{13}$=847). ^{1}H NMR (250 MHz, $CDCl_3$). δ 4.07 (m, N-OCH_2-), 2.7, 2.56 (m, -CH_2-N), 2.28 (s, -$N(CH_3)_2$).

3) Ether Oxime Derivatives Starting from Reactive Halogenated Ether Oximes of ERY

The halogenated ether oximes of ERY, compound **2** (*E*)-9-[*O*-(2-bromoethyl)oxime] and compound **38** (*E*)-9-[*O*-[(2-chloroethoxy)methyl]oxime] were used as starting material to obtain mainly nitrogenous ethers.

General Methods

a) Starting from (*E*)-9-[*O*-(2-Bromoethyl)oxime] of ERY (**2**)

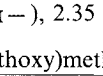
(*E*)-9-[*O*-(2-Methylethylamino)ethyloxime] of ERY (**11**): A mixture of 2.58 g of (*E*)-9-[*O*-(2-bromoethyl)oxime] of ERY and 12 ml of isopropylamine was stirred under an inert atomosphere at room temperature for 15 hours and the mixture was then poured into 600 ml of water. The mixture was filtered and the recovered product was washed with water and dried to obtain 2.29 g of raw product. The latter was chromatographed over silica gel and was eluted with a methylene chloride-triethylamine mixture (25:0.5) to obtain 1.60 g of 9-[*O*-(2-isopropylaminoethyl)oxime] of ERY with a specific rotation of $[\alpha]_D^{20}$ -78.5° (*c* 0.5, EtOH). Yield 63.9% (amorphous). EI-MS *m/z* 834 (M^+, $C_{42}H_{79}N_3O_{13}$=833). ^{1}H NMR (90 MHz, $CDCl_3$). δ 3.32 (s, 4″-OCH_3), 2.25 (s, $N(CH_3)_2$).

The following ether derivatives were prepared according to this method.

(*E*)-9-[*O*-(2-Aminoethyloxime)] of ERY (**9**): Exchange in NH_3, purification by chromatography over silica gel with a chloroform-triethylamine mixture (15:1). $[\alpha]_D^{20}$ -76° (*c* 0.8, EtOH). Yield 40% (amorphous). EI-MS *m/z* 791 (M^+, $C_{39}H_{73}N_3O_{13}$=791). ^{1}H NMR (90 MHz, $CDCl_3$). δ 4.08 (m, N-O-CH_2-), 2.94 (m, -CH_2-N).

(*E*)-9-[*O*-(2-Ethylaminoethyloxime)] of ERY (**10**): Substitution in ethylamine, purification by chromatography over silica gel with a methylene chloride-triethylamine mixture (50:1). $[\alpha]_D^{20}$ -82° (*c* 1, EtOH). Yield 79.6% (amorphous). EI-MS *m/z* 819 (M^+, $C_{41}H_{77}N_3O_{13}$=819). ^{1}H NMR (90 MHz, $CDCl_3$). δ 2.65 (m, N-CH_2-).

(*E*)-9-[*O*-(2-Piperazinylethyloxime)] of ERY (**18**): Substitution in piperazine, purification by chromatography over silica gel with a chloroform-triethylamine mixture (15:1). $[\alpha]_D^{20}$ -84° (*c* 0.6, EtOH). Yield 35.9% (amorphous). FD-MS *m/z* 860 (M^+, $C_{43}H_{80}N_4O_{13}$=860). ^{1}H NMR (250 MHz, $CDCl_3$). δ 4.16 (m, N-O-CH_2-), 2.3~2.5 (m, ), 2.20~2.82 (m, CH_2-N).

(*E*)-9-[*O*-(2-(4-Methylpiperazinyl)ethyloxime)] of ERY (**19**): Substitution in *N*-methylpiperazine, purification by chromatography over silica gel with a methylene chloride-triethylamine mixture (19:1). $[\alpha]_D^{20}$ -81° (*c* 1, EtOH). Yield 39.7% (amorphous). EI-MS *m/z* 874 (M^+, $C_{44}H_{82}N_4O_{13}$=874). ^{1}H NMR (90 MHz, $CDCl_3$). δ 2.33~2.61 (m, ), 2.35 (m, -CH_2-N-).

b) Starting from (*E*)-9-[*O*-[(2-Chloroethoxy)methyl]oxime] of ERY (**38**)

(*E*)-9-[*O*-[(2-Dimethylaminoethoxy)methyl]oxime] of ERY (**31**): A mixture of 8.86 g of dimethylamine and 3 g of compound **38** was cooled in an ice bath and after hermetically sealing the flask, it was placed in a bath at 30~32°C. After complete dissolution, the mixture was held at 30~32°C for 74 hours and was then cooled in an ice bath. The flask was opened and the dimethylamine was removed. The residue was dried under reduced pressure to obtain 3.286 g of a white solid and 3.256 g of the latter was taken up in 100 ml of ethyl acetate containing a little ether. The mixture was washed with water 6 times and with aqueous saturated sodium chloride solution 3 times and the organic phase was dried and evaporated to dryness under reduced pressure to obtain 3.1 g of the product. 3 g of the latter and 10 ml of pentane were stirred for 2 hours and the mixture was vacuum filtered. The recovered product was washed and dried to obtain 2.79 g of 9-[*O*-[(2-dimethylaminoethoxy)methyl]oxime] of ERY melting at 162°C and having a specific rotation of $[\alpha]_D^{20}$ -78°±2° (*c* 1, $CHCl_3$). Yield 96%. MP 142~162°C. MS *m/z* 850 (M^+, $C_{42}H_{79}N_3O_{14}$=850). ^{1}H NMR (60 MHz, $CDCl_3$). δ 2.3 ($N(CH_3)_2$).

Other ether derivatives were prepared according to this method.

(*E*)-9-[*O*-((2-Aminoethoxy)methyloxime)] of ERY (**29**): Substitution in NH_3, purification by chromatography over silica gel with chloroform-triethylamine mixture (9:1). $[\alpha]_D^{20}$ -73° (*c* 1, $CHCl_3$).

MP 195°C. Yield 37%. EI-MS *m/z* 821 (M^+, $C_{40}H_{75}N_3O_{14}$=821). ^1H NMR (60 MHz, $CDCl_3$). δ 5.33, 5.21, 5.16, 4.88 (m, $-O-CH_2-O$).

(*E*)-9-[*O*-((2-Methylaminoethoxy)methyloxime)] of ERY (**30**): Substitution in methylamine, chromatographic purification (SiO_2, chloroform-triethylamine (92.5:7.5)) and crystallization in ethanol. $[\alpha]_D^{20}$ −79° (*c* 1, $CHCl_3$). MP 132°C. Yield 68%. FD-MS *m/z* 835 (M^+, $C_{41}H_{77}N_3O_{14}$=835). ^1H NMR (60 MHz, $CDCl_3$). δ 2.66 (CH_2-N), 2.46 ($N-CH_3$).

(*E*)-9-[*O*-((2-Diethylaminoethoxy)methyloxime)] of ERY (**32**): Substitution in diethylamine, chromatographic purification (SiO_2, toluene-chloroform-triethylamine (6:4:1)) and crystallization in isopropyl ether. $[\alpha]_D^{20}$ −74° (*c* 1, $CHCl_3$). MP 135°C. Yield 35%. EI-MS *m/z* 877 (M^+, $C_{44}H_{83}N_3O_{14}$=877). ^1H NMR (90 MHz, $CHCl_3$). δ 5.15 ($N-O-CH_2-O$), 2.7, 2.62, 2.54, 2.46 ($-N-(CH_2)_2-$).

(*E*)-9-[*O*-((2-Morpholin-4-yl)ethoxymethyl)oxime] of ERY (**33**): Substitution in morpholin, chromatographic purification (SiO_2, toluene-chloroform-triethylamine (6:4:1)). $[\alpha]_D^{20}$ −72° (*c* 1, $CHCl_3$). MP 130°C. Yield 64%. MS *m/z* 892 (M^+, $C_{44}H_{81}N_3O_{15}$=892). ^1H NMR (60 MHz, $CDCl_3$). δ 3.83, 3.76, 3.68 (m, ), 2.58 ().

4) Ether Oxime Derivatives Starting from the Epoxide-containing Ether Chain Derivative **44**

(*E*)-9-[*O*-(3-Dimethylamino-2-hydroxypropyl)oxime] of ERY (**25**): 2.5 g of product **44** were placed in a hermetically sealed flask cooled in an ice bath, 2.8 g of dimethylamine were rapidly added and the flask was sealed. The mixture was stirred at 20°C for 4 hours, then cooled and the flask was opened. The dimethylamine was evaporated and the residue was chromatographed over silica gel. Elution with a chloroform-triethylamine mixture (9:1) yielded after crystallization from pentane and drying 1.21 g of 9-[*O*-(3-dimethylamino-2-hydroxypropyl)oxime] of ERY melting at 144°C and having a specific rotation of $[\alpha]_D^{20}$ −84.5°±2.5° (*c* 0.6, $CHCl_3$). Yield 46%. MP 144°C. FD-MS 849 (M^+, $C_{42}H_{79}N_3O_{14}$=850). ^1H NMR (60 MHz, $CDCl_3$). δ 2.3 ($N(CH_3)_2$).

Two derivatives were prepared starting from epoxide **44**.

(*E*)-9-[*O*-((2-Hydroxy-3-[(1-methylethyl)amino]propyloxime)] of ERY (**26**): Nucleophilic agent isopropylamine, purification by chromatography (SiO_2, chloroform-triethylamine (92.5:7.5)). $[\alpha]_D^{20}$ −77° (*c* 1, $CHCl_3$). MP 158°C. Yield 44%. EI-MS *m/z* 863 (M^+, $C_{43}H_{81}N_3O_{14}$=864). ^1H NMR (60 MHz, $CDCl_3$). δ 4.98 (s, OCH_3), 3.43 (s, $N(CH_3)_2$), 1.35, 1.23, 1.06 (m, $-CH_2-C$).

(*E*)-9-[*O*-(3-Acetoxy-2-hydroxypropyl)oxime] of ERY (**56**): Nucleophilic agent potassium acetate in DMF, purification by chromatography (SiO_2, methylene chloride-methanol-aq ammonia (95:10:1)) stereoisomer mixture. $[\alpha]_D^{20}$ −76° (*c* 0.5, EtOH). Yield 20%. EI-MS *m/z* 864 (M^+, $C_{42}H_{76}N_2O_{16}$=865). ^1H NMR (250 MHz, $CDCl_3$). δ 4.15, 3.97 (m, $O-CH_2-CH-CH_2-O$), 2.10 (s, $O-CO-CH_3$).

Hydrolysis of ketal **54** with acetic acid led to ketone **53**.

(*E*)-9-[*O*-(4-Oxopentyl)oxime] of ERY, $[\alpha]_D^{20}$ −75.5° (*c* 0.5, EtOH). Yield 36% (amorphous). EI-MS *m/z* 833 (M^+, $C_{42}H_{76}N_2O_{14}$=833). ^1H NMR (250 MHz, $CDCl_3$). δ 4.03 (m, $N-O-CH_2-$), 2.52 (t, $-CO-CH_2-$), 2.18 ($S-CO-CH_3$), 1.92 (m, $C-CH_2-C$). Saponification of ester **50** by NaOH in methanol at room temperature gave acid **51**.

(*E*)-9-[*O*-(2-Hydroxy-2-oxo-ethyl)oxime] of ERY. Yield 80.8%. MP 280°C, $[\alpha]_D^{20}$ −63.5° (*c* 0.6, H_2O-TEA (95:5). FD-MS *m/z* 806 (M^+, $C_{39}H_{70}N_2O_{15}$=807). The acetate group of **56** is cleaved in NH_4OH-ethanol-H_2O to obtain diol **55** (*E*)-9-[*O*-(2,3-dihydroxypropyl)oxime] of ERY. Yield 76%. $[\alpha]_D^{20}$ −76.5° (*c* 0.8, EtOH). FD-MS *m/z* 823 (M^+, $C_{40}H_{74}N_2O_{15}$=823). ^1H NMR (250 MHz, $CDCl_3$). δ 4.0~4.2 (m, $-\underset{\underset{O}{|}}{CH}-CH_2-O-N$), 3.5~3.75 (m, $-CH_2-O-$).

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