Structure–Activity Relationship Study of 6-*O*-Methylerythromycin 9-*O*-Substituted Oxime Derivatives[1)]

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Research Center, Taisho Pharmaceutical Co.,Ltd.,[a] Yoshino-cho, Ohmiya, Saitama 330, Japan and School of Pharmaceutical Sciences, Kitasato University,[b] Shirokane 5-chome, Minato-ku, Tokyo 108, Japan.
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In order to develop new-generation macrolide antibiotics active against erythromycin (EM)-resistant strains, a series of 6-*O*-methyl EM 9-*O*-substituted oxime derivatives was synthesized and evaluated for antibacterial activity against EM-resistant (*S. aureus* J-109) and susceptible (*S. aureus* 209P) strains. To understand how substituents affect the biological activity, the quantitative structure–activity relationships (QSAR) was analyzed using the Hansch–Fujita method. With the EM-resistant strain, the positive coefficient for log *P* may indicate that higher hydrophobicity of molecules is favorable for antibacterial activity. The negative coefficients of the Sterimol parameters *L*, B_1, and B_5 may indicate that long, bulky substituents are unfavorable. With the EM-susceptible strain, the negative coefficient for log *P* may indicate that hydrophilicity is important for antibacterial activity. A short substituent is also required to improve the activity. Based on the QSAR model, a derivative (87) having an anthracenylmethyl moiety was synthesized to reinforce and confirm the correlation. The activity of 87 against the EM-resistant strain was significant. In QSARs of 6-*O*-methyl EM-A 9-*O*-substituted oxime derivatives, the difference of the contribution of log *P* to the antibacterial activity between EM-resistant and susceptible strains was clearly recognized.

Keywords 6-*O*-methylerythromycin; antibacterial activity; structure–activity relationship; Hansch–Fujita method

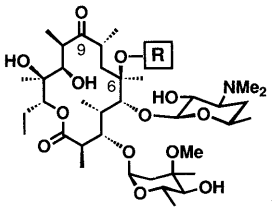
Erythromycin A (EM I) is one of the most important macrolide antibiotics for treatment of infections caused by gram-positive bacteria and *Mycoplasma* sp. A series of *O*-alkylated derivatives of EM was synthesized and their biological properties were evaluated.[2-4)] Among them, 6-*O*-methylerythromycin A (CAM, clarithromycin, II) exhibited the most potent *in vitro* and *in vivo* antibacterial activities.[5)] CAM has the same antibacterial spectrum as EM and is active against aerobic gram-positive bacteria, some gram-negative bacteria, anaerobic bacteria, *Mycoplasma*, and *Chlamydia*. The activity of CAM against clinical isolates was 1 to 16 times higher than that of EM. CAM was 6 to 15 times superior to EM against systemic infections due to gram-positive bacteria in mice. CAM also showed higher therapeutic potency than EM against respiratory tract infections caused by *S. pneumoniae* and *H. influenzae*.

However, CAM shows no activity against EM-resistant strains of *Staphylococcus aureus*. So, in order to develop a new macrolide antibiotic effective against EM-resistant strains, we focused our attention on several CAM derivatives.

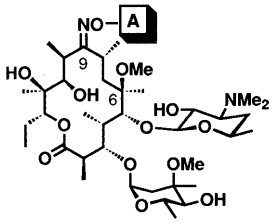
(*E*)-6-*O*-Methylerythromycin A 9-*O*-substituted oxime derivatives[6)] (III) were synthesized and evaluated using the EM-resistant strain, *Staphylococcus aureus* J-109, and the susceptible strain, *Staphylococcus aureus* 209P. Table I shows the antibacterial activity of typical derivatives. EM and CAM showed potent activity against the susceptible strain, but did not show activity against the resistant strain. The antibacterial activity of the methyl-substituted compound was similar to that of EM and CAM. Cycloalkyl and benzyl derivatives showed remarkable potency against the EM-resistant strain, but these derivatives were a little less potent than CAM and EM against the susceptible strain. These results prompted us to attempt a quantitative structure–activity analysis.

This paper describes the analysis of the quantitative structure–activity relationships (QSAR) of (*E*)-6-*O*-methylerythromycin 9-*O*-substituted oxime derivatives (86 compounds) against the EM-resistant strain and EM-susceptible strain using the Hansch–Fujita method, and the design and synthesis of a 9-*O*-substituted oxime derivative based on the results of this analysis.

QSAR of (*E*)-6-*O*-Methylerythromycin A 9-*O*-Substituted Oxime Derivatives (86 Compounds) The compounds analyzed by the Hansch–Fujita method[7)] are listed in Table II along with structural descriptors and antibacterial activities. In the parametrization of structural features for this analysis, we investigated physicochemical parameters generally used in QSAR studies and several indicator variables. These parameters were effective for deriving good regression equations, formulated as Eqs. 1—6 (Table III). In these equations, log *P*



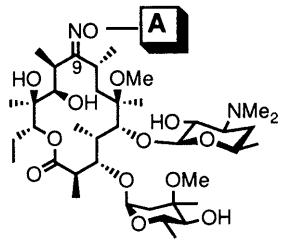
I (erythromycin) ; R=H
II (clarithromycin) ; R=CH_3

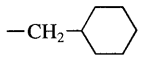
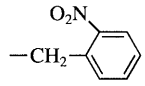
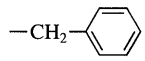
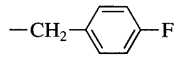
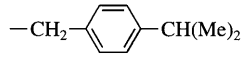
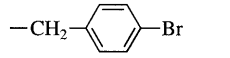
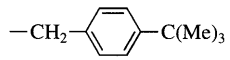


III

Chart 1

TABLE I. Antibacterial Activity of Typical 6-*O*-Methylerythromycin 9-*O*-Substituted Oxime Derivatives



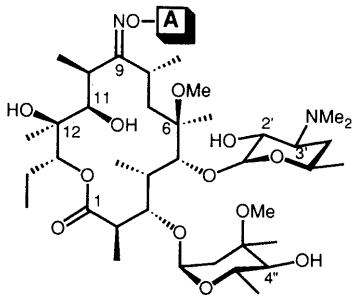
A	Resistant strain *S. aureus* J-109	Susceptible strain *S. aureus* 209P-JC
$-(CH_2)_{15}-Me$	>100	>100
$-CH_3$	>100	0.05
	50	0.78
	25	1.56
	100	0.39
	50	0.78
	25	0.78
	12.5	3.13
	12.5	0.78
	6.25	3.13
EM	>1600	0.10
CAM	>1600	0.10

(partition coefficient in octanol/water) is the hydrophobic constant calculated by the method of Moriguchi *et al.*[8] L, B_1 and B_5 are the Sterimol parameters[9]: L is the length of the substituent along the axis of the bond between the substituent and the parent molecule, and B_1 and B_5 are the smallest and the largest widths of the substituent, respectively. D_1—D_4 are the indicator variables described in the footnote in Table III. Table IV shows the correlation matrix for colinearity between the variables used in Eqs. 1—6, indicating that there seems no statistical objection to using these variables at the same time.

With the EM-resistant strain, Eqs. 1—3 (Table III) suggest that higher hydrophobicity of molecules is favorable for the activity. The negative coefficients of L and B_5 may indicate that the steric influence of long and bulky substituents reduces the activity. As for indicator variables, the positive coefficients for D_1 and D_3 indicate that the presence of a hydrocarbon moiety (substituted or condensed), or *m* (or *p*)- chloro (or bromo) substituent, in the benzene ring of benzyl group is favorable. The negative coefficient for D_2 may indicate that the presence of a chloro (or bromo) group at the *ortho* position in the benzene ring of benzyl group decreases the activity. Equation 3 seems to be a good QSAR model with a high R value; 0.86 in calculation and 0.82 in prediction.

With the EM-susceptible strain, in Eqs. 4—6 (Table III), the negative coefficient for $\log P$ may indicate that hydrophilicity is important for the activity; this is in remarkable contrast to the EM-resistant strain. Moreover, judging from the t-value in Eqs. 1—6, $\log P$ is the most significant of all the structural parameters. A short substituent is required to improve the activity. The negative coefficient for D_4 may indicate that the presence of a methyl or trifluoromethyl group at the ortho position in the benzene ring of the benzyl group decreases the activity. Equation 6 seems to be a reasonable QSAR model with $R=0.87$ in calculation and $R=0.84$ in prediction.

TABLE II. Antibacterial Activity of Typical 6-*O*-Methylerythromycin 9-*O*-Substituted Oxime Derivatives



No.	A	*S. aureus* J-109		*S. aureus* 209P		Substituent A							
		$-\log MIC^{a)}$ (obs.)	$-\log MIC^{b)}$ (calc.)	$-\log MIC^{a)}$ (obs.)	$-\log MIC^{c)}$ (calc.)	$\log P^{d)}$	$L^{e)}$	$B_1^{e)}$	$B_5^{e)}$	$D_1^{f)}$	$D_2^{g)}$	$D_3^{h)}$	$D_4^{i)}$
1[j]	$-CH_3$	3.89	4.09	7.19	6.91	−0.26	2.87	1.52	2.04	0	0	0	0
2	$-CH_2CH_3$	3.90	4.07	6.60	6.72	0.09	4.11	1.52	3.17	0	0	0	0
3	$-CH_2C\equiv CH$	3.90	4.05	6.60	6.66	0.33	3.99	1.52	4.49	0	0	0	0
4	$-CH_2C\equiv N$	3.90	3.77	6.90	7.01	−0.86	3.99	1.52	4.12	0	0	0	0
5	$-CH_2CH=CH_2$	3.91	4.07	6.31	6.58	0.33	5.11	1.52	3.78	0	0	0	0
6	$-CH_2CH_2CH_3$	3.91	4.12	6.32	6.56	0.43	4.92	1.52	3.49	0	0	0	0

TABLE II. (continued)

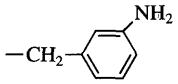
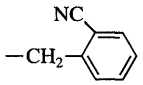
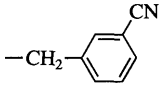
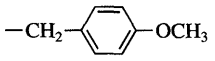
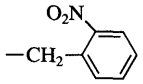
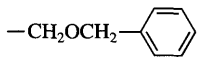
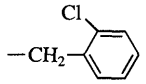
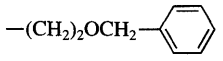
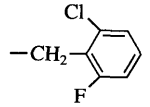
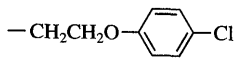
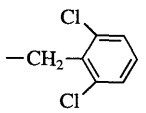
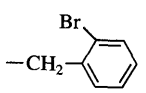
No.	A	*S. aureus* J-109		*S. aureus* 209P		Substituent A							
		$-\log MIC^{a)}$ (obs.)	$-\log MIC^{b)}$ (calc.)	$-\log MIC^{a)}$ (obs.)	$-\log MIC^{c)}$ (calc.)	$\log P^{d)}$	$L^{e)}$	$B_1^{e)}$	$B_5^{e)}$	$D_1^{f)}$	$D_2^{g)}$	$D_3^{h)}$	$D_4^{i)}$
7	$-CH(CH_3)_2$	3.91	4.10	6.61	6.62	0.43	4.11	1.90	3.17	0	0	0	0
8	$-CH_2CH_2NH_2$	3.91	3.82	6.91	6.92	−0.76	4.83	1.52	3.42	0	0	0	0
9	$-CH_2OCH_3$	3.91	4.04	6.61	6.67	0.08	4.78	1.52	3.40	0	0	0	0
10	$-CH_2CH_2CH_2CH_3$	3.91	4.11	6.02	6.37	0.78	6.17	1.52	4.54	0	0	0	0
11	$-CH_2CH_2CH_2OH$	3.91	3.83	6.32	6.73	−0.41	6.02	1.52	4.15	0	0	0	0
12	$-CH_2CH=C(CH_3)CH_3$	3.92	4.15	6.33	6.28	1.02	6.39	1.52	4.82	0	0	0	0
13	$-C(CH_3)_2COCH_3$	3.92	3.82	6.62	6.72	−0.07	4.78	2.54	3.40	0	0	0	0
14	$-CH_2CH(CH_3)NCH_3$	3.92	3.89	6.92	6.62	−0.07	6.07	1.52	4.47	0	0	0	0
15	$-CH(CH_3)OCH_2CH_3$	3.92	4.05	6.33	6.38	0.77	6.01	1.90	4.45	0	0	0	0
16	$-CH_2CH(OCH_3)CH_3$	3.93	3.89	6.34	6.63	−0.08	6.03	1.52	4.44	0	0	0	0
17	$-CH_2OCH_2CH_2OCH_3$	3.93	3.76	6.63	6.49	−0.08	7.91	1.52	5.78	0	0	0	0
18	$-CH(CH_3)CH_2CH_3$	3.94	4.12	6.04	6.13	1.45	6.82	1.90	5.75	0	0	0	0
19	$-(CH_2)_6OH$	3.94	3.88	6.35	6.22	0.62	8.90	1.52	6.29	0	0	0	0
20		3.94	4.09	6.35	6.41	0.95	4.92	1.52	6.07	0	0	0	0
21		3.94	4.16	6.35	6.36	1.19	4.62	1.52	6.02	0	0	0	0
22		3.94	4.07	6.35	6.36	1.19	4.73	1.52	7.37	0	0	0	0
23		3.95	4.04	6.05	6.29	1.29	5.27	1.52	7.95	0	0	0	0
24		3.95	4.21	6.36	6.18	1.39	6.28	1.71	4.90	0	0	0	0
25		3.95	4.19	6.36	6.04	1.85	6.49	1.52	7.39	0	0	0	0
26		3.95	3.88	6.06	6.09	2.14	4.62	1.52	6.02	0	1	0	0
27		3.95	4.14	6.36	5.91	1.35	10.25	1.52	4.72	0	0	0	0
28	$-(CH_2)_6OCOCH_3$	3.96	3.86	5.76	5.90	1.20	10.90	1.52	8.03	0	0	0	0
29		3.96	4.00	6.07	5.95	2.60	4.62	1.52	6.02	0	1	0	0
30		3.96	4.10	6.07	5.96	1.92	7.25	1.52	8.77	0	0	0	0
31		3.97	4.05	5.77	5.90	2.77	4.62	1.52	6.02	0	1	0	0
32		3.97	3.92	6.06	6.04	2.31	4.62	1.52	6.02	0	1	0	0

TABLE II. (continued)

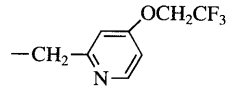
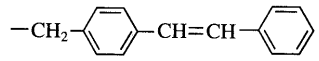
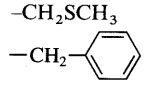
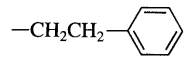
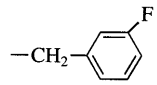
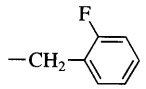
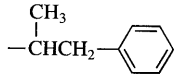
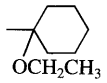
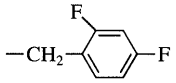
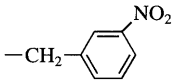
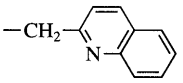
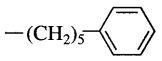
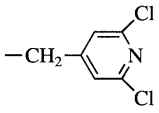
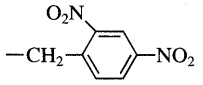
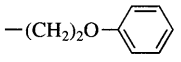
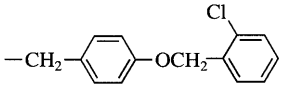
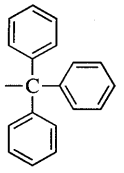
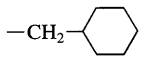
No.	A	*S. aureus* J-109		*S. aureus* 209P		Substituent A							
		$-\log MIC^{a)}$ (obs.)	$-\log MIC^{b)}$ (calc.)	$-\log MIC^{a)}$ (obs.)	$-\log MIC^{c)}$ (calc.)	$\log P^{d)}$	$L^{e)}$	$B_1^{e)}$	$B_5^{e)}$	$D_1^{f)}$	$D_2^{g)}$	$D_3^{h)}$	$D_4^{i)}$
33		3.98	3.93	6.39	6.34	0.96	5.88	1.52	8.18	0	0	0	0
34		3.98	4.37	4.88	5.34	3.87	8.01	1.52	12.15	0	0	0	0
35	$-(CH_2)_{15}CH_3$	4.00	4.29	4.00	4.27	4.91	18.49	1.52	13.17	0	0	0	0
36	$-CH_2SCH_3$	4.22	4.02	6.61	6.03	0.09	5.37	1.52	3.53	0	0	0	0
37		4.23	4.25	6.04	6.27	1.51	4.62	1.52	6.02	0	0	0	0
38		4.24	4.40	6.05	5.90	1.86	8.33	1.52	3.58	0	0	0	0
39		4.24	4.37	6.05	6.14	1.97	4.62	1.52	6.02	0	0	0	0
40		4.24	4.37	6.35	6.14	1.97	4.62	1.52	6.02	0	0	0	0
41		4.25	4.42	6.05	5.80	2.20	8.33	1.90	3.58	0	0	0	0
42		4.25	4.11	6.06	6.08	1.77	6.17	2.98	4.45	0	0	0	0
43		4.25	4.45	6.36	6.00	2.42	4.70	1.52	6.59	0	0	0	0
44		4.25	4.15	6.65	6.28	1.45	4.70	1.52	7.14	0	0	0	0
45		4.26	4.09	6.66	6.22	1.50	5.31	1.52	8.07	0	0	0	0
46		4.26	4.31	5.46	5.57	2.89	8.73	1.52	8.92	0	0	0	0
47		4.27	4.05	6.66	6.31	1.20	5.29	1.52	7.44	0	0	0	0
48		4.27	4.26	6.08	6.10	1.33	7.66	1.77	3.11	0	0	0	0
49		4.28	4.12	6.09	5.90	2.09	7.45	1.52	9.06	0	0	0	0
50		4.30	4.33	5.20	5.37	3.69	8.32	1.52	11.88	0	0	0	0
51		4.30	4.46	6.11	5.39	4.53	4.62	4.78	6.02	0	0	0	0
52		4.54	4.22	5.74	6.19	1.43	6.09	1.52	5.42	0	0	0	0

TABLE II. (continued)

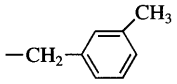
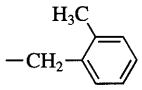
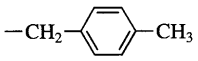
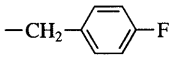
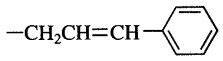
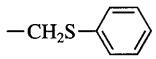
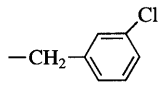
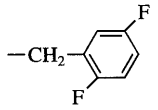
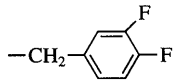
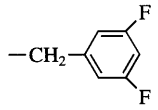
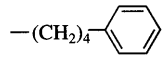
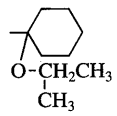
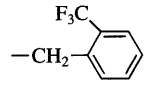
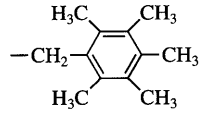
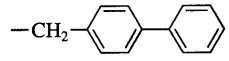
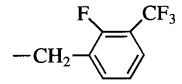
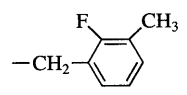
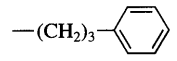
No.	A	*S. aureus* J-109		*S. aureus* 209P		Substituent A							
		$-\log MIC^{a)}$ (obs.)	$-\log MIC^{b)}$ (calc.)	$-\log MIC^{a)}$ (obs.)	$-\log MIC^{c)}$ (calc.)	$\log P^{d)}$	$L^{e)}$	$B_1^{e)}$	$B_5^{e)}$	$D_1^{f)}$	$D_2^{g)}$	$D_3^{h)}$	$D_4^{i)}$
53		4.54	4.70	6.05	6.16	1.86	4.70	1.52	6.58	1	0	0	0
54		4.54	4.74	6.35	5.76	1.86	4.62	1.52	6.02	1	0	0	1
55		4.54	4.65	6.35	6.11	1.86	5.39	1.52	7.10	1	0	0	0
56		4.54	4.33	6.05	6.13	1.97	4.70	1.52	6.59	0	0	0	0
57		4.55	4.24	6.05	5.97	2.10	6.40	1.52	7.76	0	0	0	0
58		4.55	4.37	6.06	5.89	1.80	8.67	1.52	3.60	0	0	0	0
59		4.55	4.76	6.36	6.07	2.14	4.78	1.52	6.76	0	0	1	0
60		4.55	4.49	6.06	6.01	2.42	4.62	1.52	6.02	0	0	0	0
61		4.55	4.45	6.06	6.00	2.42	4.70	1.52	6.59	0	0	0	0
62		4.55	4.49	6.06	6.01	2.42	4.62	1.52	6.02	0	0	0	0
63		4.55	4.44	5.76	5.55	2.54	10.39	1.52	4.84	0	0	0	0
64		4.56	4.30	6.06	5.87	2.49	6.17	2.98	4.45	0	0	0	0
65		4.57	4.55	4.87	5.53	2.66	4.62	1.52	6.02	0	0	0	1
66		4.57	5.01	5.17	5.31	3.23	5.39	1.52	7.10	1	0	0	1
67		4.57	4.69	5.47	5.75	3.28	4.62	1.52	6.41	0	0	0	0
68		4.58	4.58	5.78	6.03	3.11	5.21	1.52	7.12	0	0	0	0
69		4.58	4.82	5.78	5.76	2.31	4.70	1.52	6.58	1	0	0	0
70		4.85	4.28	5.75	5.92	2.20	6.67	1.52	7.47	0	0	0	0

TABLE II. (continued)

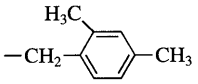
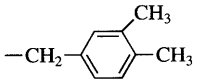
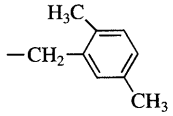
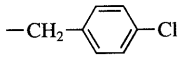
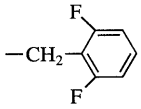
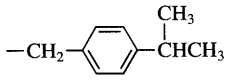
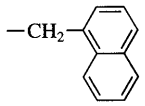
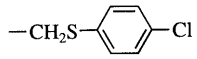
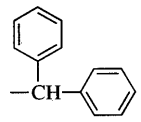
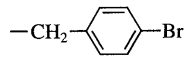
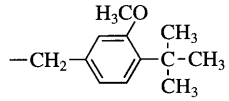
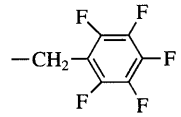
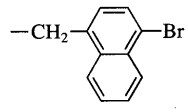
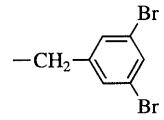
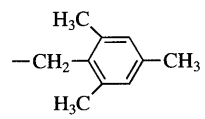
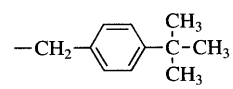
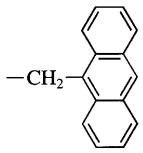
No.	A	*S. aureus* J-109		*S. aureus* 209P		Substituent A							
		$-\log MIC^{a)}$ (obs.)	$-\log MIC^{b)}$ (calc.)	$-\log MIC^{a)}$ (obs.)	$-\log MIC^{c)}$ (calc.)	$\log P^{d)}$	$L^{e)}$	$B_1^{e)}$	$B_5^{e)}$	$D_1^{f)}$	$D_2^{g)}$	$D_3^{h)}$	$D_4^{i)}$
71		4.85	4.74	5.75	5.61	2.20	5.39	1.52	7.10	1	0	0	1
72		4.85	4.74	5.75	6.01	2.20	5.39	1.52	7.10	1	0	0	0
73		4.85	4.78	5.75	5.64	2.20	5.00	1.52	6.59	1	0	0	1
74		4.85	4.70	6.06	6.04	2.14	5.29	1.52	7.44	0	0	1	0
75		4.85	4.49	6.06	6.01	2.42	4.62	1.52	6.02	0	0	0	0
76		4.86	4.73	5.46	5.83	2.54	6.50	1.52	8.10	1	0	0	0
77		4.86	4.90	5.76	5.93	2.69	4.62	1.52	6.93	1	0	0	0
78		4.87	4.50	6.07	5.61	2.42	10.12	1.52	3.60	0	0	0	0
79		4.87	4.61	5.78	5.72	3.28	5.15	2.01	6.02	0	0	0	0
80		4.87	4.72	6.08	5.97	2.31	5.49	1.52	7.73	0	0	1	0
81		4.88	4.76	5.48	5.79	2.67	6.59	1.52	8.11	1	0	0	0
82		4.88	4.73	5.78	5.68	3.51	4.70	1.52	6.59	0	0	0	0
83		4.90	4.96	5.50	5.71	3.21	5.49	1.52	7.73	1	0	0	0
84		4.91	4.99	5.51	5.78	3.11	4.95	1.52	7.04	0	0	1	0
85		5.16	4.83	5.46	5.51	2.54	5.39	1.52	7.10	1	0	0	1
86		5.16	4.80	5.46	5.73	2.89	6.50	1.52	8.41	1	0	0	0

TABLE II. (continued)

No.	A	*S. aureus* J-109		*S. aureus* 209P		Substituent A							
		$-\log MIC^{a)}$ (obs.)	$-\log MIC^{b)}$ (calc.)	$-\log MIC^{a)}$ (obs.)	$-\log MIC^{c)}$ (calc.)	$\log P^{d)}$	$L^{e)}$	$B_1{}^{e)}$	$B_5{}^{e)}$	$D_1{}^{f)}$	$D_2{}^{g)}$	$D_3{}^{h)}$	$D_4{}^{i)}$
87		5.18	5.15	5.48	5.60	3.87	4.62	1.52	6.93	1	0	0	0

a) *MIC* in mol/l. *b*) From Eq. 3. *c*) From Eq. 6. *d*) Simple method of calculating octanol/water partition coefficient by I. Moriguchi *et al.*, 1992. *e*) Sterimol program. *f*) Alkylbenzyl or naphthylmethyl. *g*) *o*-Chloro (or bromo) benzyl. *h*) *m*- (or *p*-) Chloro (or bromo) benzyl. *i*) *o*-Methyl (or trifluoromethyl) benzyl. *j*) See ref. 15.

TABLE III. Hansch Analysis of Antibacterial Activities

Eq. No.	$n^{a)}=86$	$R^{b)}$	$S^{c)}$	$R^{d)}$ (pred)
	EM resistant (*S. aureus* J-109)			
1)	$-\log C=0.19\log P+3.97$ ($t=6.72^{e)}$)	0.59	0.31	0.55
3)	$-\log C=0.19\log P-0.04L+0.37D_1{}^{f)}-0.50D_2{}^{g)}+4.17$ (7.95) (3.08) (5.00) (3.96)	0.79	0.24	0.75
3)	$-\log C=0.26\log P-0.03L-0.18B_1-0.07B_5+0.40D_1-0.53D_2+0.40D_3{}^{h)}+4.64$ (9.24) (2.29) (3.13) (4.14) (6.13) (4.86) (3.75)	0.86	0.20	0.82
	EM susceptible (*S. aureus* 209P)			
4)	$-\log C=-0.34\log P+6.67$ (12.21)	0.80	0.30	0.78
5)	$-\log C=-0.31\log P-0.06L+6.70$ (11.86) (4.47)	0.84	0.27	0.82
6)	$-\log C=-0.29\log P-0.07L-0.41D_4{}^{i)}+7.05$ (11.79) (5.36) (3.73)	0.87	0.25	0.84

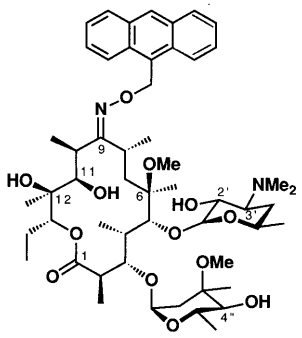
a) Number of compounds. *b*) Correlation coefficient. *c*) Standard error of estimate. *d*) Correlation coefficient for prediction (leave-one-out). *e*) *t*-value. *f*) D_1: hydrocarbon moiety substituted or condensed in the benzene ring of benzyl. *g*) D_2: *o*-chloro (or bromo) benzyl. *h*) D_3: *m*-(or *p*)-chloro (or bromo) benzyl. *i*) D_4: *o*-methyl (or trifluoromethyl) benzyl.

TABLE IV. Correlation Matrix for Colinearity between Variables Used in Eqs. 1—6

	$\log P$	L	B_1	B_5	D_1	D_2	D_3	D_4
$\log P$	1							
L	0.26	1						
B_1	0.18	−0.06	1					
B_5	0.65	0.35	−0.17	1				
D_1	0.25	−0.12	−0.12	0.23	1			
D_2	0.13	−0.14	−0.06	−0.02	−0.10	1		
D_3	0.12	−0.09	−0.06	0.12	−0.10	−0.05	1	
D_4	0.20	−0.12						1

The validity and predictive power of the parameter sets were investigated by the leave-one-out technique,[10] which reconstructed the QSAR model by removing each compound once and predicted the removed compound. The actual estimation of the leave-one-out prediction was done based on the predicted sum of squares using the algorithm of Okuno *et al.*[11] The reliability of the QSAR models (Eqs. 3, 5, 6) was good in prediction.

Design, Synthesis and Assay of New Derivatives Based on the QSAR models (Eqs. 1—3) for the EM-resistant strain, an anthracene derivative (**87**) was designed and synthesized to confirm and reinforce the correlation.



87

	MIC (μg/ml)
S. aureus J-109	6.25
S. aureus 209P	3.13

Chart 2

Compound **87** was prepared from (*E*)-6-*O*-methylerythromycin A 9-oxime and evaluated for antibacterial activity against both the resistant (*S. aureus* J-109) and susceptible (*S. aureus* 209P) strains.

Against the EM-resistant strain, **87** showed the most potent antibacterial activity among all the compounds.

On the other hand, the activity of **87** against the EM-susceptible strain was less potent than that of CAM. However, the agreement between the observed and predicted values was excellent in both strains as shown in Table II; the absolute errors in log *MIC* were 0.03 for the resistant strain and 0.12 for the susceptible strain. This suggests that Eqs. 3 and 6 are very reliable as QSAR models.

In the QSAR of (*E*)-6-*O*-methyl EM-A 9-*O*-substituted oxime derivatives, the opposite contribution of log *P* to the antibacterial activity between the EM-resistant and susceptible strains was clearly recognized. It was reported[12-14] that the mechanism of acquisition of EM resistance in clinical bacterial isolates involves N^6-dimethylation of adenine in 23S ribosomal RNA, which markedly reduces the affinity between EM and the ribosome. This change of hydrophobicity on the target site could explain why molecules with higher log *P* more active against the EM-resistant strain, as shown in the QSAR models (Eqs. 1—3) derived in the present study.

Experimental

Melting point was determined with a Yanaco micro melting point apparatus without correction. Infrared (IR) spectra was taken on a Perkin-Elmer 1760 FT-IR spectrometer. Mass spectra (MS) was measured on a JEOL JMS-SX 102 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on Varian VXR-300 spectrometer.

(*E*)-6-*O*-Methylerythromycin A 9-*O*-Substituted Oxime Derivatives (Compd. 1—86) Their synthesis will be described in detail elsewhere.[6]

(*E*)-6-*O*-Methylerythromycin A 9-*O*-(9-Anthracenylmethyl)Oxime (87) A solution of 6-*O*-methylerythromycin A 9-oxime[16] (5.0 g, 6.55 mmol), (9-chloromethyl)anthracene (1.93 g, 8.52 mmol) and sodium iodide (0.15 g, 1.0 mmol) in tetrahydrofuran (THF) (30 ml) was treated with 95% KOH powder (0.542 g, 9.17 mmol), with stirring at room temperature. The stirring was continued for 24 h. The reaction solvent was evaporated under reduced pressure, then the residue was suspended in water, and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was purified by silica gel column chromatography (Wako-gel C-200, eluent; MeOH/$CHCl_3$ = 1/19) to give 4.71 g of 6-*O*-methylerythromycin A 9-*O*-(9-anthracenylmethyl)oxime (**87**) as a foam. Crystallization from acetone–hexane gave **87** as yellow crystals: 2.52 g (40.3%); mp 264—266 °C. IR (KBr) 3559, 3441, 1733, 1626 cm^{-1}. MS (FAB) *m/z* 953 (MH^+). ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 8.46—8.39 (3H, m), 8.03—7.98 (2H, m), 7.56—7.43 (4H, m), 6.04, 5.99 (1H, ABq, J = 12 Hz), 5.10 (1H, dd, J = 11, 2 Hz, 13-H), 4.90 (1H, d, J = 5 Hz, 1″-H), 4.38 (1H, d, J = 7 Hz, 1′-H), 3.30 (3H, s, 3″-OCH_3), 2.88 (3H, s, 6-OCH_3), 2.31 (6H, s, 3′-$N(CH_3)_2$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm: 175.5 (C-1), 171.1 (C-9), 131.4, 131.1, 128.9, 128.4, 126.1, 125.0, 124.6 (aromatic carbon), 102.6 (C-1′), 96.1 (C-1″), 67.9 (-$\underline{C}H_2$-anthracenyl), 50.8 (6-OCH_3), 49.5 (3″-OCH_3), 40.3 (3′-$N(CH_3)_2$). *Anal.* Calcd for $C_{53}H_{80}N_2O_{13}$: C, 66.78; H, 8.46; N, 2.94. Found: C, 66.68; H, 8.55; N, 2.92.

References and Notes

1) A part of this work was presented at the 112th Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, March 1992.
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