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3D QSAR STUDIES ON NEW OXAZOLIDINONE ANTIBACTERIAL AGENTS BY COMPARATIVE MOLECULAR FIELD ANALYSIS

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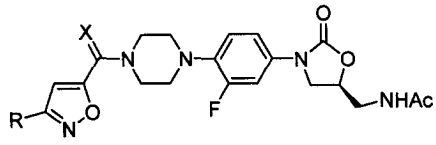
Abstract: Three-dimensional QSAR studies for two series of new oxazolidinone antibacterial agents were conducted using the comparative molecular field analysis (CoMFA). *In vitro* activities (MICs) of the compounds against methicillin-resistant *Staphylococcus aureus* 88 (MRSA 88) exhibited a strong correlation with their steric, electrostatic factors and lipophilicities.

Introduction: Correlating the physicochemical properties of compounds to their biological activities is believed to provide a powerful tool in designing new drugs. It hopefully will minimize the number of compounds that synthetic chemists should prepare and the time needed to discover new drug candidates. We have been interested in oxazolidinone antibiotics which have excellent activities against multi-resistant pathogens such as strains of *Staphylococcus*, *Streptococcus* and *Enterococcus* species.[1,2] The extensive studies on the syntheses of oxazolidinone antibacterial agents and their structure-activity relationship (SAR) have been reported,[3] but no example on quantitative structure-activity relationship (QSAR) could be found. Here we wish to report 3D QSAR studies on two series of new oxazolidinone antibacterial agents (**1** and **2**), which were syntheisized[4] in our lab, by using the comparative molecular field analysis (CoMFA).[5]



1 : X = H_2 R = H, alkyl, alkoxy, aryl,
2 : X = O heterocyclyl, halogen

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Molecular 3D structure building: Structures of entire sets of oxazolidinone analogs were built using SYBYL 6.5[6] molecular modeling software. The structural energy minimization was performed using the standard Tripos molecular mechanics force field and Gasteiger-Huckel charge, with a 0.005 kcal/mol energy gradient convergence criterion on Silicon Graphics IRIS Indigo II R4000 computer system. Low energy conformation was searched by both systematic and random conformational search. All of the structures generated were aligned into 3D lattice box by fitting with oxazolidinone having phenyl group as a common structure.

PLS and CoMFA analysis: The CoMFA study was performed using SYBYL 6.5/CoMFA routine. An sp^3 carbon atom with a +1.0 charge was selected as a probe for the calculation of the steric and electrostatic field. Values of the steric and electrostatic energies were truncated at 30 kcal/mol. For each of the alignment sets, the steric and Coulombic energy fields were individually calculated at each lattice interaction of regularly spaced grid of 2 Å units in all x, y and z directions. The partial least squares (PLS) method was used for fitting the 3D structural features and their biological activities.

Results and Discussion: A training set composed of 17 compounds synthesized and 2 reference compounds[1] was chosen as the model of our 3D QSAR studies (Table 1). The CoMFA and ClogP were used as descriptors, and the activities against methicillin-resistant *Staphylococcus aureus* 88 (MRSA 88) as a dependent column. Good cross-validated r^2 (0.653) and conventional r^2 (0.984) values by the PLS and CoMFA analysis indicated this method a considerably reliable one for predicting the antibacterial activities of a series of oxazolidinone antibacterial agents. The contributions of steric and electrostatic fields were 0.550 and 0.284, respectively, and that of lipophilicity was 0.165. The results of the CoMFA analysis are summarized in Table 1, and their actual and predicted activities are shown in Table 2 and Figure 1. The 3D QSAR derived from CoMFA study showed that MICs of the compounds in the training set correlated well with their steric, electrostatic fields and lipophilicities. In this case the steric field was the most contributing factor (0.550) for their activities. The major steric and electrostatic features of the QSAR are illustrated in Fig. 2 as three-dimensional solid surfaces. In the steric CoMFA map shown in colors of green and yellow, the large green colored part around the substituent group of template molecule **2h** indicated that a sterically bulky group at that position could result in the enhancement of the antibacterial activity. In the electrostatic CoMFA map, the red color of isoxazole moiety showed that more electronegative groups at that region could confer better activities.

Table 1. Summary of CoMFA-PLS results of the training set.

Opt. No. of components	4
Probe atom	C(sp^3, +1)
Cross-validated r^2	0.653
Standard error of estimate	0.073
Conventional r^2	0.984
F values (n1 = 3, n2 = 15)	219.943

Relative contributions	
ClogP	0.165
CoMFA (steric)	0.550
CoMFA (electrostatic)	0.284

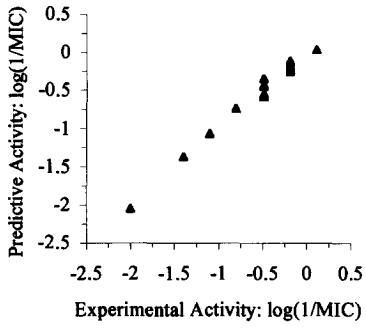


Fig. 1. Experimental *vs.* predicted activities

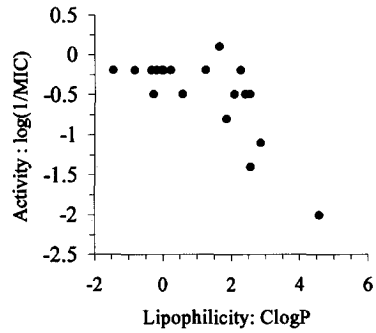
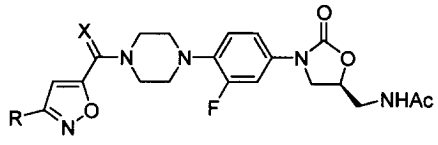


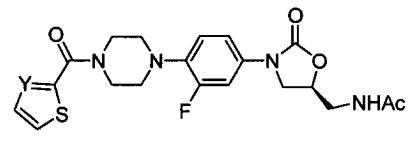
Fig. 3. Relationship between lipophilicity and *in vitro* activity against MRSA 88

Fig. 2. CoMFA contour maps from PLS analysis. Sterically favored/or disfavored areas are shown in green/or yellow color. Electronegative potential favored/or disfavored areas are depicted in red/or blue.

Regarding the lipophilicity (ClogP), the activity was increased with decreasing ClogP in the positive region, but in the negative region it was static (Fig. 3). According to the 3D QSAR studies, the thiophenyl substituent of the most active compound in the training set, **2h**, was replaced either by carbamoyl, hydroxyl or carboxyl group to lower ClogP, or by thiazole or thiadiazole group to lower ClogP and keep similar steric hindrance at the same time. Thus, we designed and synthesized[4] 14 compounds as a test set. Their antibacterial activities were



1, X = H_2
2, X = O



5, Y = C
6, Y = N

<Compounds listed in Table 2 and 3>

Table 2. Actual and predicted activities [log (1/MIC)] of training set.

Entry	R	X	MIC (μg/mL)	ClogP	CoMFA	Actual [log (1/MIC)]	Predicted [log (1/MIC)]	Residual
1a	*trans*-Styryl	H_2	25.00	2.56	109.00	-1.40	-1.366	-0.03
1b	4-Tolyl	H_2	12.50	2.86	107.00	-1.10	-1.063	-0.03
1c	4-Cyanophenyl	H_2	6.25	1.87	105.00	-0.80	-0.739	-0.06
1d	4-Fluorophenyl	H_2	3.12	2.54	102.00	-0.49	-0.544	-0.05
1e	3-Methoxyphenyl	H_2	3.12	2.39	107.00	-0.49	-0.348	0.15
1f	3,4-Dimethoxyphenyl	H_2	3.12	2.08	113.00	-0.49	-0.585	-0.09
1g	4-Phenoxyphenyl	H_2	100	4.57	123.00	-2.00	-2.048	0.05
1h	2-Pyridyl	H_2	1.56	1.25	101.00	-0.19	-0.181	0.01
1i	2-Thiophenyl	H_2	1.56	2.27	98.00	-0.19	-0.249	-0.06
2a	H	O	1.56	-0.34	82.00	-0.19	-0.117	0.08
2b	OCH_3	O	1.56	-0.04	93.00	-0.19	-0.227	-0.03
2c	OCH_2CH_2F	O	1.56	0.22	99.00	-0.19	-0.135	0.06
2d	CN	O	1.56	-0.83	84.00	-0.19	-0.214	-0.02
2e	CF_3	O	3.12	0.57	88.00	-0.49	-0.428	0.07
2f	$CONH_2$	O	1.56	-1.47	88.00	-0.19	-0.230	0.04
2g	$CH_2OCON(CH_3)_2$	O	3.12	-0.28	104.00	-0.49	-0.451	0.04
2h	2-Thiophenyl	O	0.78	1.64	93.00	0.11	0.031	-0.08
3h	Eperezolid	-	1.56	-0.20	80.00	-0.19	-0.257	-0.06
3i	Linezolid	-	1.56	0.01	68.00	-0.19	-0.241	-0.05

compared with the corresponding CoMFA-predicted values (Table 3). Comparing the activities of **2h** (Table 2) and **2p** (Table 3) with **5** and **6**, respectively, it could be found that the activities of the oxazolidinones were significantly enhanced by the isoxazole group. By introducing the isoxazole group, **2h** and **2p** gained 2- and 4-fold activity (MIC), respectively. In these cases, CoMFA analysis predicted approximately 3-fold increases in the activities (MICs) of both compounds. The actual activities of **2j** and **2k** which were synthesized to improve activities against Gram-negative strains by increasing polarity and solubility in water showed strong deviation from predicted activities. The compounds **2o**, **2p** and **2q**, which were predicted to be active, actually showed good activities [log (1/MIC)] of –0.19, 0.41 and 0.11, respectively. The activity of **2o** might be overestimated because of its low lipophilicity (-1.28). From the study of 3D QSAR and synthesis, we could find successfully the lead compound **2p** having better activity than **2h** and we analyzed the contributions of the physicochemical properties of oxazolidinone compounds on their activities and could apply successfully the results to the prediction of their *in vitro* antibacterial activities.

Table 3. Actual and predicted activities [log (1/MIC)] of compounds forming test set by CoMFA analysis

Entry	R	X	MIC (μg/mL)	ClogP	CoMFA	Actual [log (1/MIC)]	Predicted [log (1/MIC)]	Residual
1j	OCH_3	H_2	3.12	0.70	90.00	-0.49	-0.252	0.24
1k	4-Chlorophenyl	H_2	50	3.11	106.00	-1.70	-0.822	0.88
2i	CH_3	O	1.56	-0.07	86.00	-0.19	-0.088	0.11
2j	OH	O	50	-0.25	82.00	-1.70	-0.229	1.47
2k	CO_2^-	O	100	-0.32	86.00	-2.00	-1.425	0.58
2l	Br	O	0.78	0.53	84.00	0.11	-0.246	-0.35
2m	Cl	O	0.78	0.38	84.00	0.11	-0.249	-0.36
2n	$CON(CH_3)_2$	O	3.12	-1.67	97.00	-0.49	0.057	0.44
2o	CH_2OCONH_2	O	1.56	-1.28	95.00	-0.19	0.213	0.41
2p	2-Thiazolyl	O	0.39	0.35	91.00	0.41	0.144	-0.27
2q	1,2,3-Thiadiazolyl	O	0.78	0.27	88.00	0.11	0.303	0.20
2r	1,3,5-Thiadiazolyl	O	1.56	0.41	90.00	-0.19	0.053	0.25
5	2-Thiophenyl	-	1.56	1.64	87.00	-0.19	-0.449	-0.26
6	2-Thiazolyl	-	1.56	-0.11	86.00	-0.19	-0.318	-0.12

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