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3D QSAR studies of *N*-4-arylacryloylpiperazin-1-yl-phenyl-oxazolidinones: A novel class of antibacterial agents☆

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Abstract—Three-dimensional QSAR studies for *N*-4-arylacryloylpiperazin-1-yl-phenyl-oxazolidinones were conducted using TSAR 3.3. The in vitro activities (MICs) of the compounds against *Staphylococcus aureus* ATCC 25923 exhibited a strong correlation with the prediction made by the model developed in the present study.

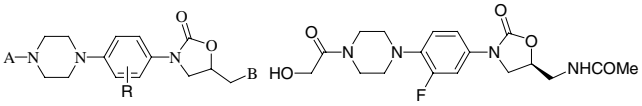
1. Introduction

Multidrug-resistant Gram-positive bacteria have continued to pose challenges to medicinal fraternity.[1] Linezolid, marketed as Zyvox®, is an oxazolidinone class of antibacterial, approved for treating mostly Gram-positive bacterial infections, especially methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), and vancomycin-resistant enterococci (VRE).[2] While much research has been aimed at the development of novel oxazolidinones, no new members of this class have achieved regulatory approval.

In the recent past, some efforts have been made to understand three-dimensional quantitative structure–activity relationships, 3D QSAR, on oxazolidinone antibacterial agents using comparative molecular field analysis (CoMFA).[3–7] During the last decade synthesis of a number of analogs of 4-piperazinylphenyloxazolidinone **1** (Fig. 1)[8] and their antibacterial activities have been reported;[9] however, only a few 3D QSAR studies have been published.

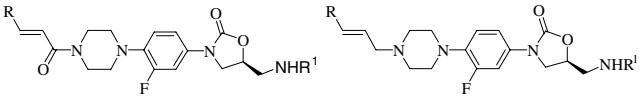
Pae et al.[3] have reported 3D QSAR on piperazinylphenyloxazolidinone **1** albeit with a small set of data. These authors have used a training set of 17 compounds with 2 reference compounds. They used CoMFA steric and electrostatic fields and clog*P* as descriptors. The r^2_{CV} (0.653; cross-validated) and conventional r^2 (0.984) from PLS and CoMFA indicated reasonable reliability of the value for predicting antibacterial activities. In the present study, we report 3D QSAR studies on several novel 4-piperazinylphenyloxazolidinones **1** and a correlation to predict the antibacterial activities with high degree of reliability.

We performed 3D-QSAR on a data set consisting of 39 antibacterials (Fig. 2) to relate the in vitro minimum inhibitory concentration (MIC) required to inhibit growth of *S. aureus* ATCC 25923 that allows the description and comparison of chemical structures without performing their direct alignment. The QSAR model was developed using multiple linear regression (MLR) and validated using an external test set of compounds.



1 Eperezolid 2

Figure 1.



3-5 6 & 7

Figure 2.

Keywords: 3D QSAR; In vitro MIC; Heat of formation; LUMO; Antibacterial agent; Arylacryloylpiperazinylphenyloxazolidinones.
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2. Data set and methodology

The structures of 39 oxazolidinone derivatives **3**–**7** (Fig. 2) synthesized by us were selected for QSAR studies (Table 1). The structures were sketched using ChemDraw Ultra 5.0 (www.cambridgesoft.com) and were exported to TSAR 3.3 software (www.accelrys.com). Three-dimensional structures of all the molecules were generated. Partial charges were derived using Charge-2 CORINA 3D package in TSAR 3.3 and their geometries were optimized using cosmic module of TSAR. The calculations were terminated, if the energy difference or the energy gradient were smaller than 1E−005 and 1E−010 kcal/mol respectively.

Molecular descriptors were calculated with TSAR 3.3. The descriptors were obtained for the entire molecule. TSAR affords calculation of the following descriptors: molecular surface area and volume, moments of inertia, ellipsoidal volume, verloop parameters, dipole moments, lipole moments, molecular mass, Wiener index, molecular connectivity indices, molecular shape indices, electrotopological state indices, log *P*, number of defined atoms (carbon, nitrogen, etc.), rings (aromatic and aliphatic), and groups (methyl, hydroxyl, etc.). Vamp which is a semiempirical molecular orbital package in TSAR 3.3 was used to calculate the electrostatic properties like total energy, electronic energy, nuclear repulsion energy, accessible surface area, atomic charge, mean polarizability, heat of formation, HOMO and LUMO eigenvalues, ionization potential, total dipole, polarizability, and dipole components and perform structure optimizations in vacuo using default parameters using Hamiltonian method like PM3.

Descriptors with the same values for all the compounds **3**–**7** (Table 1) were discarded. Pairwise correlation analysis of the remaining descriptors was performed. For each pair of descriptors, the correlation coefficient was higher than 0.65. Regression was built using descriptor subsets containing only one of these highly correlated descriptors. The descriptors and their characteristics are given in Table 2.

3. Training and test set

The data set was randomly divided into a training set and a test set of 28 and 11, respectively. The test set included compounds **3a**, **3b**, **3h**, **3s**, **3v**, **4a**, **4b**, **4f**, **5f**, **5i**, and **6** (Table 1). All the other compounds were included in the training set.

4. QSAR model development and validation

To develop QSAR models, stepwise MLR analysis with leave-one-out (LOO) cross-validation was applied to the training set. *F*-to-enter[11] and *F*-to-leave[11] values were both 4. Model with the number of descriptors less than 5, cross-validation r^2_{CV} greater than 0.6, *F*-ratio higher than 20, and correlation coefficient *R* higher than 0.8

Table 1. In vitro (MIC) values of novel oxazolidinones **3**–**7** against Gram-positive *Staphylococcus aureus* ATCC 25923

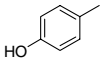
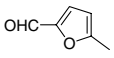
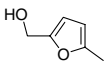
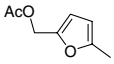
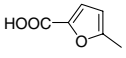
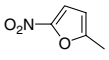
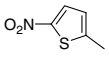
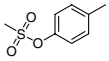
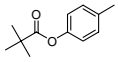
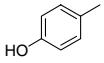
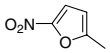
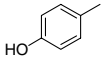
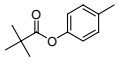
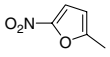
Compound	R	R[1]	MIC[a] (μg/mL)
3a		COMe	4
3b		COMe	2
3c		COMe	2
3d		COMe	1
3e		COMe	2
3f		COMe	2
3g		COMe	2
3h		COMe	2
3i		COMe	2
3j		COMe	1
3k		COMe	2
3l		COMe	4
3m		COMe	4
3n		COMe	4
3o		COMe	8
3p		COMe	>16
3q		COMe	0.25
3r		COMe	0.25
3s		COMe	>16
3t		COMe	8
3u		COMe	16

Table 1 (*continued*)

Compound	R	R^1	MIC[a] (μg/mL)
3v		COMe	>16
4a		CSMe	0.25
4b		CSMe	2
4d		CSMe	0.25
4f		CSMe	0.5
4i		CSMe	0.5
4k		CSMe	0.5
4q		CSMe	0.25
5a		$CSNH_2$	1
5b		$CSNH_2$	1
5d		$CSNH_2$	0.5
5f		$CSNH_2$	1
5i		$CSNH_2$	4
5k		$CSNH_2$	0.25
5v		$CSNH_2$	>16
6		COMe	4
7		COMe	2
2			4

[a] MIC, minimum inhibitory concentration for inhibition of the organism shown in μg/mL was determined as per NCCLS guidelines.[10]

between the predicted and the experimental antibacterial activities was validated using compounds of the test set.

In the beginning, the training and the test data set consisted of 28 and 11 compounds, respectively. The QSAR model with a high statistical significance is represented by Eq. 1:

$$\log(1/C) = 0.006919662 \times X1 - 0.72196823 \times X2 - 0.034151886 \times X3 + 0.0004945533 \times X4 + 4.8290181, \quad (1)$$

where $X1$ is heat of formation; $X2$ is LUMO; $X3$ is polarization YY; and $X4$ is Octupole XYZ component and the statistical parameters for above Eq. 1 are, s value = 0.202528; $F = 48.1599$; regression coefficient $r = 0.945167$; $r^2 = 0.893341$; cross-validation, $r^2_{CV} = 0.799722$, predictive sum of squares PRESS = 1.77147.

The definition of descriptors based on the model used in the present study is indicated in Table 2. Heat of formation descriptor in the QSAR model indicates conformational stability and this may favor better binding and better activity at the molecular level. LUMO, an electronic parameter, measures electrophilicity of the molecule and it is negatively correlated with the activity. Polarization component relates negatively with the activity, whereas an octupole component relates positively with the biological activity. Octupole is the first-order derivative with respect to the derivative of field gradient in x, y or z direction. The overall biological activity will depend on the combined effect of the four descriptors.

The values of descriptors for all the training as well as the test set are summarized in Table 3 derived from Eq. 1.

The estimated activity of the molecule against *S. aureus* ATCC 25923 of the training set and test set is summarized in Tables 4 and 5, respectively.

All the compounds included in the training set showed negative heat of formation as well as negative value for LUMO, whereas polarization was always a positive value. On the other hand, octupole value could be positive or negative, which is a parameter for antibacterial activity. The correlation between the observed and the predicted antibacterial activities for Eq. 1 is shown in Figure 3.

From Eq. 1, it is clear that log ($1/C$) will depend heavily on heat of formation (HOF) and LUMO. On the other hand, the value of polarization and octupole really does not affect the outcome of Eq. 1. Thus, if we assume that log ($1/C$) will be dependent on HOF and LUMO, it is clear from Table 3 that if HOF is relatively high (less −ve value) and LUMO is relatively low (highly −ve value), the given compound shows a very high antibacterial activity, that is, log ($1/C$) is high. However, the two factors together play a critical role. Thus, molecules that show high heats of formation but low LUMO should show good antibacterial activity. This assumption is clearly verified in the test set (Table 5).

We plotted coefficient × heat of formation versus coefficient × LUMO for all the compounds as shown in Figure 4.

Table 2. Descriptors included in the model

Descriptor	Coefficient[a]	Jacknife SE[b]	Covariance SE[c]	*t*-value[d]	*t*-probability[e]
Heat of formation (X1)	0.0069197	0.000762	0.000638	10.847	1.61E−10
LUMO (X2)	−0.72197	0.15224	0.11291	−6.3939	1.59E−06
Polarization YY (X3)	−0.034152	0.010649	0.007421	−4.6021	0.000125
Octupole XYZ component (X4)	0.00049455	0.00018	0.000157	3.144	0.004546
Constant (C)	4.829	0.66639			

[a] The regression coefficient for each variable in the equation.
[b] An estimate of the standard error on each regression coefficient derived from a jack-knife procedure on the final regression model.
[c] Gives an estimate of the standard error on each regression coefficient derived from the covariance matrix.
[d] Measures the significance of each variable included in the final model.
[e] Statistical significance for *t*-values.

Table 3. Descriptor calculations for *N*-4-arylacryloylpiperazin-1-yl-phenyl-oxazolidinones **3**–**7**

Compound	Heat of formation	0.006919662 × heat of formation	LUMO	0.72196823 × LUMO	Polarization YY	Octupole xyz
3a	−133.431	−0.8894	−0.83613	−0.6037	62.0362	−192.959
3b	−178.186	−1.1877	−0.79324	−0.5727	64.3487	192.574
3c	−178.258	−1.1882	−0.87611	−0.6325	62.4797	−90.519
3d	−122.886	−0.8191	−1.21269	−0.8755	64.5067	−21.912
3e	−125.284	−0.8351	−1.00035	−0.7222	62.9192	−119.022
3f	−159.744	−1.0648	−0.85782	−0.6193	59.6859	375.224
3g	−161.318	−1.0752	−0.64928	−0.4688	60.7604	133.153
3h	−130.924	−0.8727	−0.62513	−0.4513	61.0953	236.936
3i	−125.391	−0.8358	−1.15646	−0.8349	64.0023	−384.049
3j	−125.498	−0.8365	−1.0773	−0.7778	64.1002	42.817
3k	−115.998	−0.7732	−0.62269	−0.4496	63.5625	−66.395
3l	−168.64	−1.1241	−0.82628	−0.5965	61.3	−152.28
3m	−191.132	−1.274	−1.24423	−0.8983	64.0397	138.643
3n	−204.073	−1.3602	−0.83036	−0.5995	64.0579	287.405
3o	−246.568	−1.6435	−0.96664	−0.6979	59.7308	−349.294
3p	−246.616	−1.6438	−1.33472	−0.9636	60.5341	−452.041
3q	−164.123	−1.0939	−1.79968	−1.2993	62.0214	102.718
3r	−127.101	−0.8472	−2.17754	−1.5721	64.6719	−102.234
3s	−219.126	−1.4606	−1.25657	−0.9072	65.5749	−200.154
3t	−246.637	−1.6439	−0.97309	−0.7025	62.6516	−13.896
3u	−221.839	−1.4786	−0.85757	−0.6191	59.2606	25.61
3v	−227.925	−1.5192	−0.91759	−0.6625	80.0716	−311.221
4a	−62.7008	−0.4179	−1.03184	−0.7450	65.118	407.146
4b	−108.103	−0.7206	−1.02931	−0.7431	64.5089	455.334
4d	−52.8378	−0.3522	−1.18516	−0.8556	65.0254	−170.998
4f	−88.6499	−0.5909	−1.0619	−0.7667	62.067	−154.475
4i	−55.4126	−0.3693	−1.13322	−0.8181	64.9131	53.224
4k	−45.8714	−0.3058	−1.04218	−0.7524	68.2142	202.853
4q	−94.6545	−0.6309	−1.80353	−1.3021	60.0437	176.295
5a	−58.6057	−0.3906	−0.86536	−0.6248	65.7018	205.86
5b	−104.002	−0.6932	−0.86857	−0.6271	65.0974	226.469
5d	−48.8215	−0.3254	−1.15567	−0.8344	65.7246	−136.197
5f	−84.6378	−0.5641	−0.90901	−0.6563	62.6384	−117.024
5i	−50.5512	−0.3369	−1.11066	−0.8019	67.6833	−361.832
5k	−45.0351	−0.3002	−0.90636	−0.6544	55.4737	140.358
5v	−153.076	−1.0203	−0.88376	−0.6380	85.5222	409.321
6	−122.746	−0.8182	−0.51003	−0.3682	60.3459	−72.532
7	−130.646	−0.8708	−1.3797	−0.9961	57.369	−928.236
2	−220.346	−1.4687	−0.60012	−0.4333	49.6036	−23.766

In Figure 4, it is observed that the activity of the compounds increases when LUMO is lower, whereas the heat of formation is higher (as shown in Fig. 4). Thus, the compounds, which are having lower HOF, become less and less active. Similarly, compounds having lowest LUMO are most active and the activity decreases as LUMO increases.

Based on the present model, we have calculated that phenyloxazolidinones containing substitutions such as CF_3, $COCF_3$, SO_2CH_3, and $SOCHF_2$ have a very low HOF (large −ve) and high LUMO (high −ve value). Therefore, we predict such compounds to show poor antibacterial activity, based on predicted log (1/*C*).

Table 4. The comparison between the experimental and the predicted antibacterial activities for the training set

Compound	Experimental MIC (μg/mL)	Experimental log (1/*C*)	Predicted log (1/*C*)	Predicted MIC (μg/mL)	Residual = experimental log (1/*C*) − predicted log (1/*C*)
3c	2	2.3825	2.0495	4.3059	0.3330
3d	1	2.6745	2.6404	1.0817	0.0341
3e	2	2.3735	2.4766	1.5770	−0.1032
3f	2	2.3584	2.4901	1.4768	−0.1317
3g	2	2.3584	2.1723	3.0703	0.1862
3i	2	2.3688	2.4206	1.7753	−0.0518
3j	1	2.6698	2.5704	1.2572	0.0994
3k	2	2.4028	2.2723	2.7009	0.1305
3l	4	2.0706	2.0898	3.8264	−0.0193
3m	4	2.0833	2.2862	2.5066	−0.2030
3n	4	2.0851	1.9708	5.2035	0.1142
3o	8	1.8200	1.6081	13.0331	0.2120
3p	16	1.4953	1.7952	8.0203	−0.2999
3q	0.25	3.3024	2.9253	0.5956	0.3770
3r	0.25	3.3160	3.2624	0.2829	0.0536
3t	8	1.8456	1.6784	11.7577	0.1672
3u	16	1.4936	1.9019	6.2490	−0.4083
4d	0.25	3.2911	3.0137	0.4734	0.2773
4i	0.5	2.9855	3.0732	0.4086	−0.0876
4k	0.5	3.0184	3.0347	0.4816	−0.0163
4q	0.25	3.3160	3.5127	0.1589	−0.1967
5a	1	2.6845	2.9062	0.6002	−0.2217
5b	1	2.6986	2.6252	1.1841	0.0734
5d	0.5	2.9909	3.0136	0.4746	−0.0227
5k	0.25	3.3318	3.3466	0.2416	−0.0149
5v	16	1.5621	1.6895	11.9319	−0.1274
7	2	2.3870	2.5028	1.5319	−0.1158
2	4	1.9939	2.0318	3.6664	−0.0378

C, concentration expressed in mM/L of the drug molecule required for inhibition of 90% growth of *S. aureus* ATCC 25923.

Table 5. The comparison between the experimental and the predicted antibacterial activities for the test set

Compound	Experimental MIC (μg/mL)	Experimental log (1/*C*)	Predicted log (1/*C*)	Predicted MIC (μg/mL)	Residual = experimental log (1/*C*) − predicted log (1/*C*)
3a	4	2.0669	2.2953	2.3638	−0.2285
3b	2	2.3825	2.0663	4.1421	0.3162
3h	2	2.3575	2.4051	1.7926	−0.0476
3s	16	1.4971	1.8815	6.6027	−0.3844
3v	16	1.5492	1.0258	53.3993	0.5234
4a	0.25	3.2857	3.1176	0.3682	0.1681
4b	2	2.3967	2.8462	0.7105	−0.4495
4f	0.5	2.9755	2.7862	0.7733	0.1894
5f	1	2.6754	2.7025	0.9394	−0.0272
5i	4	2.0833	2.7906	0.7848	−0.7073
6	4	2.0439	2.2511	2.4824	−0.2072

C, Concentration expressed in mM/L of the drug molecules required for inhibition of 90% growth of *S. aureus* ATCC 25923.

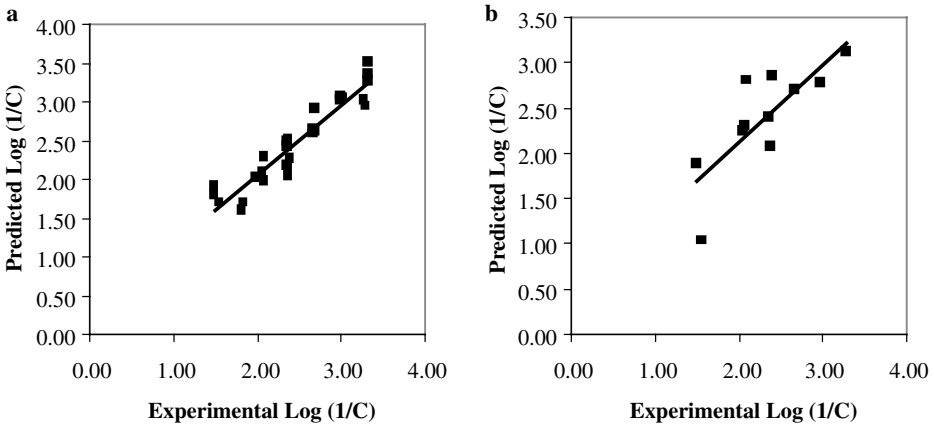


Figure 3. (a) Prediction of antibacterial activity for training set compounds against *Staphylococcus aureus* ATCC 25923 using Eq. 1. (b) Prediction of antibacterial activity for test set compounds against *Staphylococcus aureus* ATCC 25923 using Eq. 1.

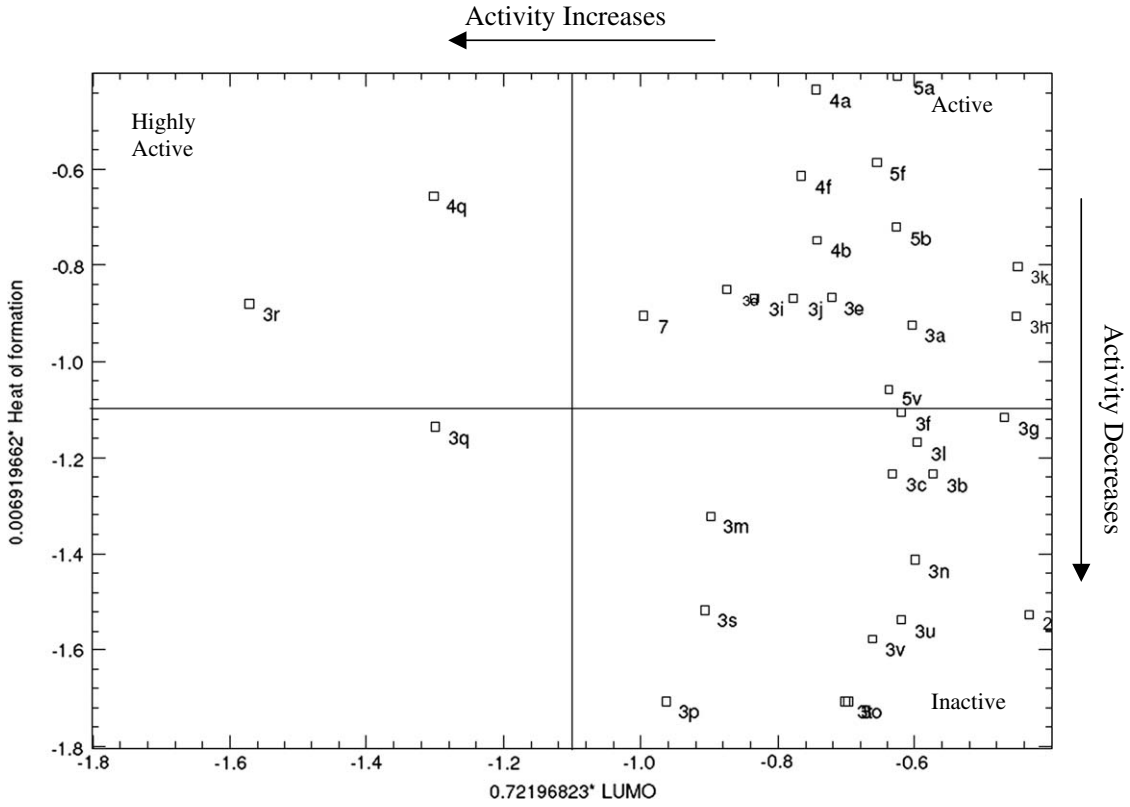


Figure 4. Plot of heat of formation versus LUMO of various training and test sets of compounds **3**–**7**.

On the other hand, substitutions like CN or NO_2 group on furan or benzene ring lead to high heat of formation (low −ve value) and low LUMO (i.e., large −ve value) and are predicted to show good antibacterial activity from Eq. 1.

Thus, the present model based on 3D QSAR gives us a reasonable prediction capability of antibacterial activity of different oxazolidinones against *S. aureus* ATCC 25923. Presently, we are studying several sets of compounds whose antibacterial activities have been reported in the literature against different strains. We are applying this model to predict the antibacterial activities of these compounds based on Eq. 1 with reasonable accuracy and will be reported later.

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