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QSAR and molecular docking study on the biological activity of levofloxacin and thiodiazole histone deacetylase inhibitors

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ABSTRACT

Using quantitative structure-activity relationship (QSAR) and molecular docking to study the interaction between levofloxacin and thiadiazole histone deacetylase inhibitors. The molecular electrical distance vector (MEDV) and multiple linear regression (MLR) were used to study the relationship between the structure and activity of compounds. The three equations obtained by multiple linear regression, their R^2 = 0.976, 0.985 and 0.976, and their R_{cv}^2 = 0.949, 0.977 and 0.932. The structures that affect HDAC1 and HDAC6 activity are -O- and -S-, and the structures that affect HDAC2 are -C- and -N-. Finally, molecular docking is used to study the binding of receptors and drug molecules to provide guidance for future drug design.

1. Introduction

Research [1] have shown that tumor generation and growth are closely related to gene-level lesions. In cells, histone acetyltransferases (HATs) and histone deacetylases (HDACs) are two key enzymes that regulate gene transcription and expression [2]. Overexpression of HDACs in cancer cells makes the original genes in Deacetylation of histones during transcription and expression enhances the ability of histones to bind to DNA, prevents other molecules from binding to DNA, prevents gene transcription, and leads to tumorigenesis [3]. In particular, HDAC1, HDAC2, and HDAC6 are overexpressed in tumor cells [4-8]. Histone deacetylation inhibitors (HDACi) can inhibit HDACs in tumor cells [9-12], so HDACi It has become a research focus of antitumor drugs at home and abroad. It is of great significance to study the structure-activity relationship and binding principle of these inhibitors.

In this experiment, the quantitative structure-activity relationship (QSAR) of drugs was studied by using electrical distance vector (MEDV) [13-15] and multiple linear regression (MLR), and then the interaction between HDACi and HDACs was analyzed using molecular docking Research, which provides a favorable basis for future research and development of anti-tumor drugs.

2. Materials and Methods

2.1. The compounds studied and their biological activities

The compounds studied here are a series of HDACs inhibitors with inhibitory activity on HDAC1, HDAC2 and HDAC6. The parent structures of these compounds [16] are shown in Figure 1. Their biological activity data on HDACs is IC_{50}, and the drug concentration results in 50% inhibition of HDACs in units of μmol • dm^{-3}. Their inhibitory activities (IC_{50}) on HDAC1, HDAC2, and HDAC6 are expressed as H_1, H_2, and H_6 in turn. The biological activity (H_i) of 18 HDACs inhibitors and vorinostat [16] are shown in Table 1.

2.2. Statistical regression analysis

A QSAR model was established with IC_{50} value as the dependent variable and electrical distance vector as the independent variable. The value of the electrical distance vector can be seen in Table 2. Regression analysis is generally performed using multiple linear regression (MLR), partial least squares (PLS), and

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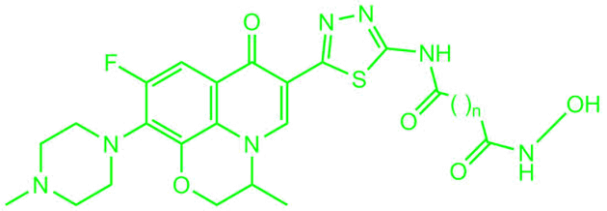
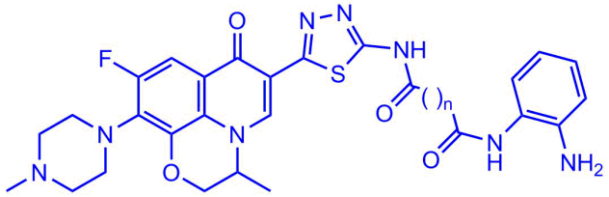
optimal variable subset regression (LBR). By using the Fischer statistic (F-test) to eliminate unimportant descriptors when entering new descriptors, stepwise regression can help identify the most important descriptors for the antitumor activity of the title compound.

(a) No. 1-6(n=1-6)



(b) No.7-12(n=1-6)



(c) No.13-18(n=1-6)

Figure 1. The basic structure of levofloxacin-HDACi conjugates

Table 1. HDACs inhibitor antitumor activity (IC_{50})

No.	n	IC_{50}(μ mol·dm^{-3})		
		H_1	H_2	H_6
1	3	6.20	14.30	5.80
2	4	2.80	11.60	2.30
3	5	1.70	7.80	1.80
4	6	1.40	5.20	1.10
5	7	2.20	7.40	1.50
6	8	4.30	8.90	3.60
7	3	0.142	0.145	0.115
8	4	0.103	0.127	0.079
9	5	0.065	0.055	0.040
10	6	0.031	0.041	0.019
11	7	0.078	0.062	0.058
12	8	0.096	0.105	0.063
13	3	0.203	0.164	0.147
14	4	0.152	0.132	0.103
15	5	0.076	0.071	0.065
16	6	0.054	0.057	0.046
17	7	0.084	0.068	0.072
18	8	0.113	0.096	0.088
19	SAHA	0.044	0.012	0.036

Table 2. Calculated electrical distance vector M_i

No.	M_{14}	M_{17}	M_{21}	M_{77}	M_{78}
1	5.84	0.00	9.28	10.33	-0.54
2	7.13	0.00	11.01	9.61	-0.50
3	8.95	0.00	12.28	9.13	-0.47
4	11.17	0.00	13.24	8.79	-0.45
5	13.67	0.00	13.98	8.54	-0.44
6	16.38	0.00	14.58	8.35	-0.43
7	5.95	0.00	9.42	6.88	-0.54
8	7.29	0.00	11.03	6.20	-0.50
9	9.16	0.00	12.22	5.74	-0.47
10	11.41	0.00	13.13	5.41	-0.46
11	13.92	0.00	13.84	5.17	-0.44
12	16.64	0.00	14.40	4.99	-0.44
13	24.88	4.28	13.39	3.22	-0.57
14	26.45	4.36	14.65	2.65	-0.52
15	28.48	4.43	15.59	2.27	-0.50
16	30.85	4.49	16.29	2.00	-0.48
17	33.47	4.54	16.84	1.81	-0.46
18	36.27	4.58	17.28	1.66	-0.45
19	32.72	0.00	12.27	4.03	0.00

In the model, verification is an important step in building a reliable and accurate model. Common statistical verification indicators are as follows:

$$V_{IF} = 1 / （1-\beta^2） \quad (1)$$

Where: β is the correlation coefficient of multiple regression between one variable and other variables in the equation. V_{IF} = 1.0 means that there is no autocorrelation between each variable; if the V_{IF} range is 1.0 to 5.0, it means that there is no obvious autocorrelation between the variables and the model is stable; when V_{IF} is greater than 5, the regression equation is unstable and must be Recheck the correlation coefficients of the variables.

In the equation of QSAR, a decision coefficient (R^2) and a cross-validated squared correlation coefficient (R_{cv}^2) are used to evaluate the quality of each regression model. The "leave-one-out" (LOO) cross-validation coefficient R_{cv}^2 is considered as an indicator of the predictive performance and stability of the QSAR model. Based on experience, equations with regression coefficients R^2> 0.80 and R_{cv}^2> 0.50 are considered reasonable. Among them, the parameter R_{cv}^2> 0.5 is used as a criterion for the robustness and prediction ability of the model, and the traditional correlation coefficient R^2 defines the goodness of fit.

Another metric used to assess model quality is standard deviation (S_D). When the ratio of the standard deviation to the range of values (the difference between the maximum and minimum values) is less than 10%,

the model is good and the prediction accuracy is acceptable.

The statistical significance of the model was verified by *t*-test. If the absolute value of all variables *t* in the validation model is greater than the standard *t* value ($t_{\alpha/2}$) at a certain confidence level α, it means that the model passes the *t*-test and has significant statistical significance. Akaike information criterion (A_{IC}; Eq. 2; the model that produces the smallest A_{IC} value is considered the most useful) and Kubinyi function (F_{IT}; Eq.3; the best model will present the highest value of this function) to determine whether a variable should be included in the model. That is, when adding additional variables, if the value of the Akaike information criterion decreases and the value of the Kubinyi function increases, the introduction of this new variable is reasonable.

$$A_{IC} = RSS \times \frac{f+b}{(f-b)^2} \quad (2)$$

$$F_{IT} = \frac{R^2(f-b-1)}{(f+b^2)(1-R^2)} \quad (3)$$

Where: *RSS* is the sum of squared residuals, *f* is the number of compounds included in the model, *b* is the number of variables included in the model, and R^2 is the square of the correlation coefficient.

3. Results and discussion

According to the balance principle of physical chemistry, there is a logarithmic relationship between the change of free energy and concentration. Therefore, their inhibitory activities (H_i) on HDAC1, HDAC2 and HDAC6 should be taken as negative logarithms ($pH_i = -\log H_i$) for modeling. The corresponding pHi is shown in Table 3.

3.1 QSAR equation of the pH_i

The electrical distance vector (M_i) and antitumor activity of HDACs inhibitors were input into MINITAB14.0 statistical analysis software, and the best subset of regression was used to select the best combination of variables to establish the best QSAR model. Tables 4, 5, and 6.

Where: R^2、R_{adj}^2、R_{cv}^2、S_D、S_{CV}、F、A_{IC}、F_{IT} are the judgment coefficients, corrected judgment coefficients (to eliminate the influence of the number of independent variables and sample capacity on the judgment coefficients), the judgment coefficients of the one-by-one elimination method, and the estimation standards Error, estimated standard error of the leave-one-out method, Fisher statistics, Akaike information criterion, and Kubinyi function. Table 3 shows the QSAR models for pH_1 and M_i.

Table 3. Experimental and calculated values of antitumor activity (pH_i) of HDACs inhibitors

No.	R	n	pH_1			pH_2			pH_6		
			exp.	cal.	err.	exp.	cal.	err.	exp.	cal.	err.
1	OH	3	5.21	5.21	0	4.84	4.83	0.01	5.24	5.28	-0.04
2	OH	4	5.55	5.55	0	4.94	4.99	-0.06	5.64	5.63	0.01
3	OH	5	5.77	5.7	0.07	5.11	5.08	0.02	5.74	5.78	-0.03
4	OH	6	5.85	5.72	0.14	5.28	5.14	0.14	5.96	5.79	0.16
5	OH	7	5.66	5.65	0.01	5.13	5.17	-0.04	5.82	5.72	0.1
6	OH	8	5.37	5.53	-0.16	5.05	5.2	-0.15	5.44	5.59	-0.15
7	NHOH	3	5.85	6.8	0.05	6.84	6.82	0.02	6.94	6.94	0
8	NHOH	4	6.99	7.11	-0.12	6.9	6.98	-0.09	7.1	7.27	-0.17
9	NHOH	5	7.19	7.24	-0.05	7.26	7.07	0.19	7.4	7.4	0
10	NHOH	6	7.51	7.25	0.26	7.39	7.13	0.26	7.72	7.41	0.32
11	NHOH	7	7.11	7.18	-0.07	7.21	7.16	0.04	7.24	7.33	-0.09
12	NHOH	8	7.02	7.06	-0.04	6.98	7.19	-0.21	7.2	7.19	0.01
13	—	3	6.69	6.79	-0.1	6.79	6.88	-0.1	6.83	6.9	-0.07
14	—	4	6.82	7.04	-0.22	6.88	7	-0.12	6.99	7.16	-0.17
15	—	5	7.12	7.13	-0.01	7.15	7.06	0.09	7.19	7.24	-0.06
16	—	6	7.27	7.1	0.17	7.24	7.09	0.15	7.34	7.21	0.12
17	—	7	7.08	7.01	0.07	7.17	7.1	0.06	7.14	7.11	0.03
18	—	8	6.95	6.87	0.08	7.02	7.11	-0.09	7.06	6.95	0.1
19	SAHA		7.36	7.4	-0.04	7.92	8.06	-0.14	7.44	7.5	-0.06

Table 4 shows that with the increase in the number of independent variables in the model, except for R^2, the other statistical indicators have turned in the ternary equation, where R_{adj}^2, R_{cv}^2, F_{IT}, F have maximum values, and A_{IC}, S_D, S_{CV} have minimum values . So choose the best ternary QSAR model:

pH_1 = 12.061(±0.311) – 0.086(±0.006)M_{14} – 0.461(±0.021) M_{77} + 2.900(±0.455) M_{78} (4)

f = 19, R^2=0.976, R_{adj}^2= 0.971, F =201.833, S_D = 0.128

R_{cv}^2 = 0.949, S_{CV} = 0.187

Table 5 shows that with the increase in the number of independent variables in the model, except for R^2 and Radj2, the other statistical indicators have turned in the ternary equation. Among them, R_{cv}^2, F_{IT}, and F have maximum values, and A_{IC}, S_D, S_{CV} have minimum values . So choose the best ternary QSAR model:

pH_2 = 12.243(±0.347) – 0.346(±0.028)M_{17} – 0.149(±0.022) M_{21} – 0.584(±0.021) M_{77} (5)

f = 19, R^2=0.985, R_{adj}^2= 0.982, F =319.745, S_D = 0.139

R_{cv}^2 = 0.977, S_{CV} = 0.171

Table 5 shows that the changes of all statistical indicators are the same as those in Table 3. Therefore, the best ternary QSAR model is selected:

pH_6 = 12.463(±0.323) – 0.092(±0.006)M_{14} – 0.485(±0.022) M_{77} +3.000(±0.306) M_{78} (6)

f = 19, R^2=0.976, R_{adj}^2= 0.971, F =200.751, S_D = 0.133

R_{cv}^2 = 0.932, S_{CV} = 0.224

Using QSAR equations (4), (5), and (6), we can predict the antitumor activity pH_1, pH_2, and pH_6. Their predicted values are shown in Table 3 as pH_1 (cal.), pH_2 (cal.) and pH_6 (cal.).

Table 4. Stepwise regression results of pH_1 and M_i

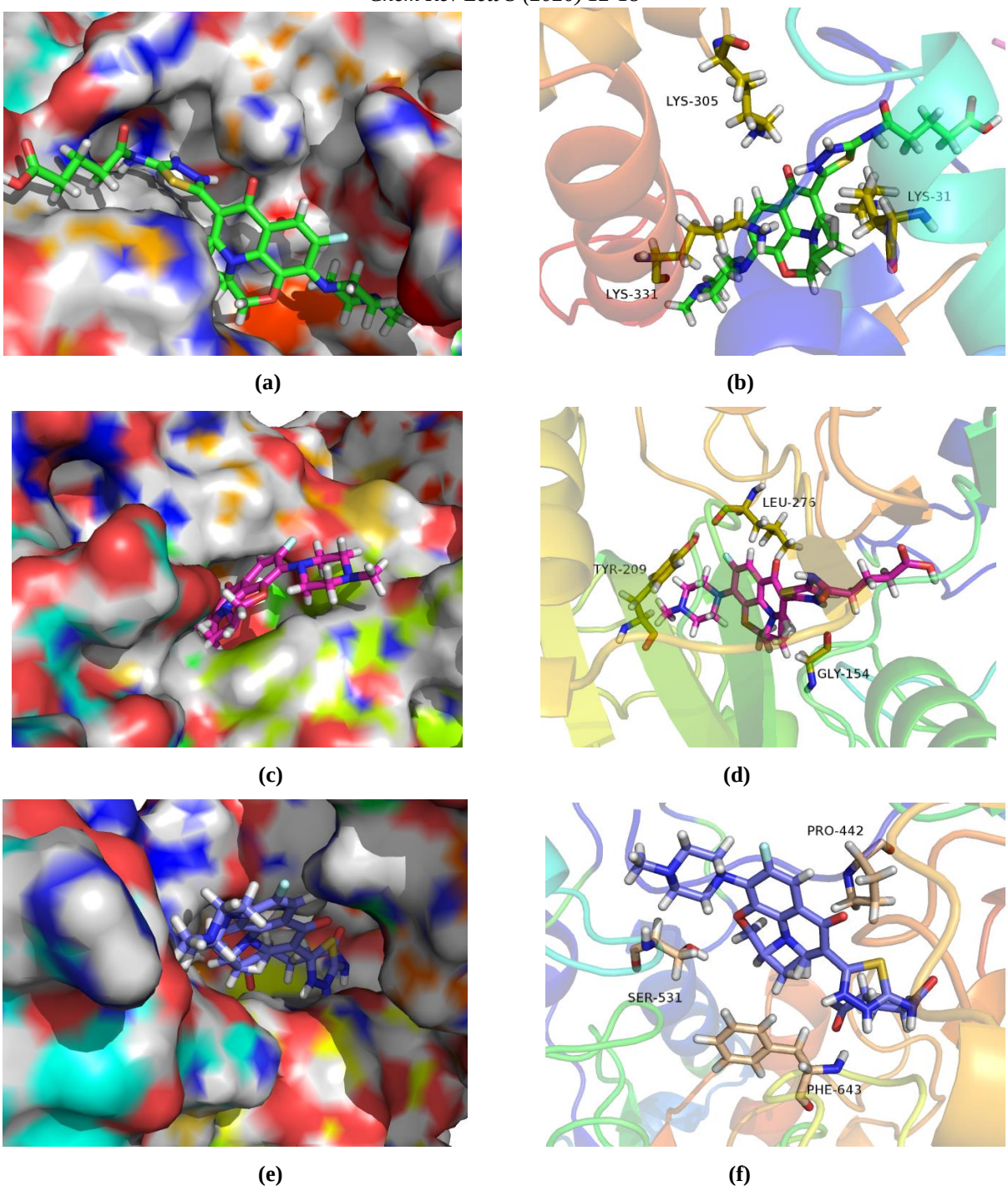
No.	R^2	R_{adj}^2	R_{cv}^2	A_{IC}	F_{IT}	S_D	S_{CV}	F	Variables
1	0.651	0.631	0.581	0.264	1.586	0.457	0.502	31.744	M_{77}
2	0.899	0.886	0.864	0.101	6.192	0.254	0.295	70.825	M_{77}, M_{17}
3	**0.976**	**0.971**	**0.949**	**0.045**	**21.786**	**0.128**	**0.187**	**201.833**	**M_{77}, M_{14}, M_{78}**
4	0.976	0.969	0.877	0.128	16.267	0.133	0.300	141.285	M_{77}, M_{14}, M_{78}, M_{17}

Table 5. Stepwise regression results of pH_2 and M_i

No.	R^2	R_{adj}^2	R_{cv}^2	A_{IC}	F_{IT}	S_D	S_{CV}	F	Variables
1	0.691	0.673	0.630	0.432	1.901	0.585	0.642	38.070	M_{77}
2	0.936	0.928	0.914	0.119	10.174	0.274	0.319	117.197	M_{77}, M_{17}
3	**0.985**	**0.982**	**0.977**	**0.038**	**35.179**	**0.139**	**0.171**	**319.745**	**M_{77}, M_{17}, M_{21}**
4	0.987	0.984	0.938	0.121	30.369	0.130	0.290	275.840	M_{77}, M_{14}, M_{21}, M_{17}

Table 6. Stepwise regression results of pH_6 and M_i

No.	R^2	R_{adj}^2	R_{cv}^2	A_{IC}	F_{IT}	S_D	S_{CV}	F	Variables
1	0.633	0.612	0.559	0.299	1.464	0.487	0.534	29.335	M_{77}
2	0.897	0.884	0.859	0.113	6.058	0.266	0.312	69.754	M_{77}, M_{17}
3	**0.976**	**0.971**	**0.932**	**0.065**	**21.785**	**0.133**	**0.224**	**200.751**	**M_{77}, M_{14}, M_{78}**
4	0.978	0.972	0.882	0.132	17.782	0.136	0.304	144.682	M_{77}, M_{14}, M_{78}, M_{17}



(a) **(b)**

(c) **(d)**

(e) **(f)**

Figure 2. Docking diagram

3.2. Molecular docking

Molecular docking is a commonly used method for drug design. Finding a reasonable orientation and conformation allows the receptor and ligand to match optimally. The degree of binding between the receptor and the ligand is determined by the change in free energy during the binding process.

Molecular docking uses Ledock software. Compound No. 1 with the highest inhibition rate of HDAC1, HDAC2 and HDAC6 was selected for molecular docking. Their 3D structure comes from the Bioinformatics Research Cooperative Laboratory (RSCB). HDAC1 (PDBID: 5ICN), HDAC2 (PDBID: 5IWG) and HDAC6 (PDBID: 5W5K).

Before molecular docking, the small molecules and receptors of the ligand are pretreated, including deleting the original ligands in the receptor, combining non-polar hydrogen atoms, adding electric charges, and removing water molecules. The docking results of Compound 1 with HDAC1, HDAC2, and HDAC6 are listed in Table 7.

The most active compound No. 1 is connected to HDAC1 in Figure 2 (a) and Figure 2 (b). This

conformation has the lowest free energy of all conformations, and its value is -6.34 kcal / mol, so it is also the most stable conformation.

Table 7. Ledock docking results

No.	Name	ΔG_{min}(kcal/mol)
1	HDAC1	-6.34
2	HDAC2	-7.79
3	HDAC6	-6.78

The identification of compound 1 shows that the recognition region penetrates into the active pocket of HDAC1. The O atom on the naphthalene ring forms a hydrogen bond with the amino acid residues LYS-305 and LYS-331, The methyl group on the branched chain forms a hydrophobic interaction with the amino acid residue LYS-31.

The docking mode of compound 1 and HDAC2 is shown in Figure 2 (c) and Figure 2 (d). This conformation has the lowest free energy among all conformations. Its value is -7.79 kcal / mol, which is the most stable conformation. The O atom on the naphthalene ring and the N atom on the five-membered ring form hydrogen bonds with amino acid residues LEU-275 and GLY-154, respectively.

The docking mode of compound 1 and HDAC6 is shown in Figure 2 (e) and Figure 2 (f). This conformation is the lowest free energy of all conformations, and its value is -6.88 kcal / mol. The O atom on the naphthalene ring forms hydrogen bonds with the amino acid residues PRO-442 and SER-531, respectively, and the carboxyl group at the chain end forms an intermolecular hydrogen bond with PHE-643.

From the results after docking, it can be seen that during the binding process of the ligand to the receptor, hydrogen bonding can determine the position of the ligand in the active pocket. The active part of the molecule forms a hydrogen bond with the active part of the macromolecule, while the hydrophobic part of the small molecule can have a hydrophobic effect with non-polar amino acid residues in the active part of the macromolecule.

4. Conclusion

(1) According to Stepwise regression results of pH1, pH_6 and M_i, the electrical distance vectors M_{77}, M_{14}, and M_{78} are most closely related to the biological activity of HDAC1. According to Kier's study [17], the structure in the title compound that affects the activity of HDAC1 and HDAC6 is: -O- and -S-. (2) According to Stepwise regression results of pH_2 and M_i, it is shown that the electrical distance vectors M_{77}, M_{17}, and M_{21} have the greatest correlation with the biological activity of HDAC2. The structure affecting HDAC2 in the title compound is: -C- and -N-.

(3) The docking results indicate that the main factors affecting biological activity are hydrogen bonding and hydrophobic interaction.

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