Pharmaceutical sciences, 2014, 20, 122-129

http://pharm-sci.tbzmed.ac.ir

A Review of QSAR Studies to Predict Activity of ACE Peptide Inhibitors

Reyhaneh Jahangiri[1], Somaieh Soltani[2*], Abolfazl Barzegar[1]

[1]Research Institute for Fundamental Sciences (RIFS), University of Tabriz, Tabriz, Iran.

[2]Drug Applied Research Center and Pharmacy faculty, Tabriz University of Medical Sciences, Tabriz, Iran.

ARTICLEINFO

Article Type:
Review Article

Article History:
Received: 18 October 2014
Accepted: 1 December 2014

Keywords:
ACE inhibitor
Peptide
QSAR
Review

ABSTRACT

Background: Inhibition of angiotensin converting enzyme (i.e inhibition of cleaving angiotensin I to the potent vasoconstrictor angiotensin II) leads to the treatment and reduce the risk of cardiovascular diseases. Peptides (synthetic - natural) with ACE inhibitory activity were studied continuously during the last decades and resulting data were applied by medicinal chemists to design and develop new drugs. Their structure and activity/property relationships were studied during these years and different QSAR models were developed which assisted researchers and manufactures to reduce the cost of experiments. Developed models were reviewed in the present paper according to the applied dataset, descriptors, feature selection methods, model development and validation methods. The selected descriptors for different datasets and models were compared and discussed according to the experimental findings.

Introduction

The most frequently reported causes of the occurrence and development of hypertension and atherosclerosis relates to the problems in renin–angiotensin system (RAS)[1] and one of the main aspects of current strategies to reduce the risk of cardiovascular events is its pharmacological inhibition.[1]

The important role of the angiotensin converting enzyme (ACE) as a part of RAS in maintaining human blood dynamic balance was determined after the discovery of the production of angiotensin II from the cleavage of angiotensin I by ACE in 1956.[2] Its main activity is catalyzing the activation of Angiotensin I by converting it to the vasoconstrictive octapeptide (Angiotensin II).[3] The cloning of ACE revealed that this enzyme consists of two independent catalytic domains (i.e. N and C domains, figure 1).[4] Excessive activity of ACE leads to an increased rate of vasoconstriction and development of high blood pressure. The inhibition of ACE would lead to the reduction of angiotensin II production and consequent decrease of the blood pressure.

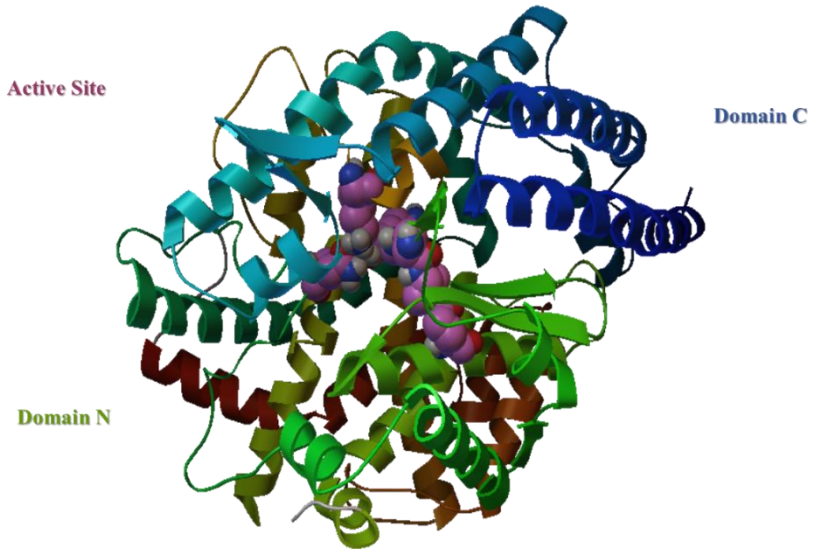
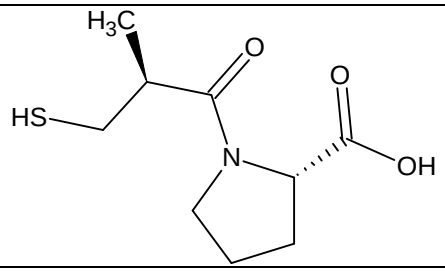
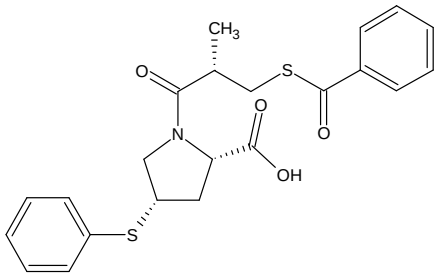
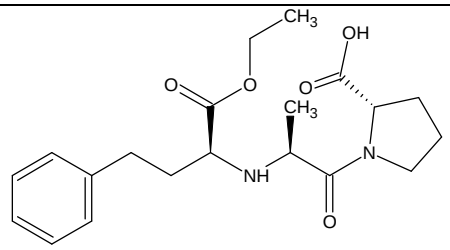
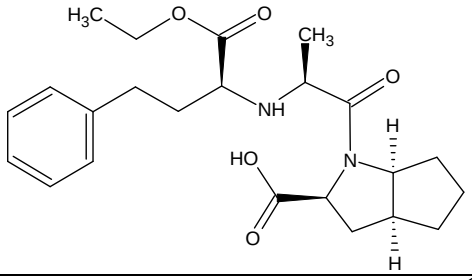
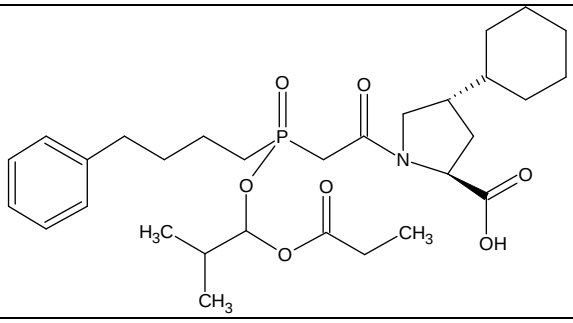


Figure 1. Crystal structure of ACE illustrated by autodock 4.2 (pdb code: 1O86).

***Corresponding Author:** Somaieh Soltani, Drug Applied Research Center and Pharmacy faculty, Tabriz university of medical sciences, Tabriz, Iran. Tel:(+98) 41-33377459 ,Fax:(+98) 41-33344798, Email:soltanisomaieh@gmail.com.

The discovery of captopril [5,6] based on a product from snake venom in 1975, represented a major breakthrough in the treatment of cardio-vascular diseases as the prototype of orally active angiotensin-converting enzyme inhibitors (ACEIs). Synthetic ACE inhibitors such as captopril, enalapril, lisinopril, and ramipril are currently used in the treatment of hypertension in human[7] (Table 1) and their structure–activity relationship are studied to clarify their mode of action: i.e. as competitive, noncompetitive, or uncompetitive inhibitors.[7]

Table 1. Examples of synthetic peptide antihypertensive drug[8].

Drug Name	Molecular structure	IC_{50}	Tissue
Captopril		13.0	Aorta
		8.8	Brain
		7.7	Heart
Zofenopril		1.6	Aorta
		0.8	Brain
		0.8	Heart
Enalapril		9.0	Aorta
		3.6	Brain
		2.6	Heart
Ramipril		0.6	Aorta
		0.6	Brain
		0.7	Heart
Fosinopril		2.9	Aorta
		2.4	Brain
		3.4	Heart

Development of selective ACE inhibitor peptides [8] with lower side effects (cough and angioedema due to interaction with the carboxypeptidase A) and higher potency necessitate the study of the natural [9]and synthetic peptides. Researchers tried to isolate ACE inhibitor peptides from natural sources (e.g. marine [9,10,] plant[11,12] animal,[13,14] and food)[15] and study their physicochemical and pharmacological properties.

Following the development and extraction of a vast number of peptides, prediction of their applicability for different therapeutic aims (e.g. ACE inhibitory activity itself or as an indicator for bioactivity) leads to the development of different quantitative structure activity relationship (QSAR) models. By the increasing of different modeling methods (by the application of various descriptors and modelling methods), selection of the appropriate method will be crucial for save the time and resources. This review will summarize the developed models according to the applied descriptor type, descriptor selection method, modeling method and validity of the developed models. In addition the models will compare according to their prediction capability.

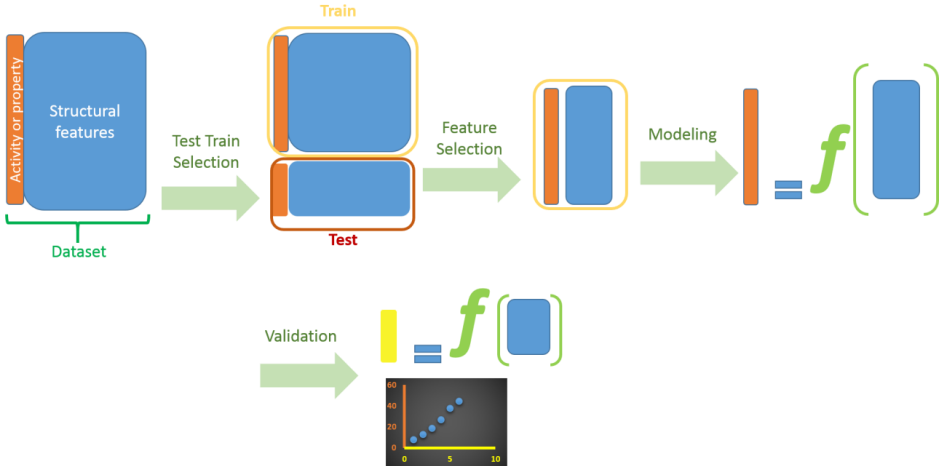


Figure 2. Common Workflow for a QSAR method development.

Overview of QSAR studies of the peptide ACE inhibitors

According to our bibliography (Scopus from 2000-2014 (April first week)) using different keywords, a number of studies have been published in which the non-English papers were not considered. The review was constructed on the bases of a routine QSAR workflow (Figure 2).[16,17] The applied databases, molecular descriptors, feature selection methods, developed models, validation parameters, prediction capability and selected descriptors are reviewed and presented via tables, graphs and figures.

Databases

Applied data for construction a QSAR method have crucial rule in the validity of the developed model. The dataset suitable size (higher statistical validity) and quality (wider applicability domain and lesser gaps) will provide more information about the studied activity and development of more predictive models will be possible. Reviewing of the published studies showed that most of them obtained the needed data from literature or databases. Some databases which have been used frequently for QSAR model construction for peptides are summarized in Table 2. These databases include amino acids along with 2-14 or higher peptides. Di and tri-peptides are studied more frequently than oligopeptides. The origin of these peptides varying from synthetic sources to planet, microorganisms, marines, milk, egg, etc.

Table 2. Available online databases for peptide ACE inhibitors.

Database/Dataset Name	Web address	Available Peptide
ACEpepDB	http://www.cftri.com/pepdb/index.php	865
BIOPEP	http://www.uwm.edu.pl/biochemia/index.php/en/biopep	556
EROPMoscow	http://erop.inbi.ras.ru	313
PepBank	http://pepbank.mgh.harvard.edu	19,792
PeptideDB	http://www.peptides.be/	20,027

Developed QSAR models

Applied linear and nonlinear models

The linear regression models (i.e. multiple linear regression (MLR), ordinary least squares (OLS), principal component regression (PCR), partial least squares (PLS)) and nonlinear models (e.g. artificial neural networks (ANNs)) are among the most frequently applied modeling methods. While methods such as support vector machines (SVM) have been used recently (Table 3).[18-36]

.

Table 3. Developed QSAR models along with the validated parameters.

Modeling method	Model code	Data points	Descriptors	Test dataset	Descriptor (number)	$Q^2_{(CV)}$	Descriptor inter correlation	Chance correlation	RMSE	R^2	Ref
PLS	1	168di,140 Tripeptide	Z-score	No	3	0.426	YES	NO	0.404	0.500	18
	2	58dipeptide	VHSE	No	8	0.770	YES	NO	0.48	0.770	19
	3	58dipeptide	SVWG		4	0.830			0.340	0.893	20
	4	58dipeptide	VSW	YES	9	0.835	YES	NO	0.38	0.861	21
	5	58dipeptide	V-scales	YES	3	0.783	YES	YES	0.400	0.849	22
	6	58dipeptide	SVMW	YES	11	0.885	YES	NO	0.432	0.906	23
	7	55tripeptide	SVMW	YES	11	0.931	YES	NO	0.077	0.998	23
	8	27tripeptide	Z-score	NO	3	0.649	YES	NO		0.843	24
	9	58dipeptide	SVWGM	YES	18	0.779	YES	NO	0.386	0.865	25
	10	58dipeptide	FASGAI	NO	-	0.775	YES	NO	0.456	0.796	26
	11	58dipeptide	HESH	NO	12	0.838	YES	NO	0.361	0.877	27
	12	58dipeptide	T-scales	NO	4	0.786	YES	NO	0.39	0.845	28
	13	58di dipeptide	G-scales	NO	8	0.831	YES	NO	0.37	0.870	29
	14	55 tripeptide	G-scales	NO	8	0.915	YES	NO	0.096	0.983	29
GA-PLS	15	58 dipeptide	FASGAI	NO	-	0.728	YES	NO	0.495	0.760	26
	16	58dipeptide	QTMS	YES	-	0.803	YES	NO	0.381	0.855	30
	17	55tipeptide	VTSA	NO	5	0.778	YES	NO	0.431	0.820	31
MLR	18	58dipeptide	METDV	NO	-	0.677	YES	NO	0.452	0.793	32
	19	58tripeptide	E	NO	5	0.980	YES	NO	0.062	0.991	33
	20	55tripeptide	V-scales	YES	3	0.943	YES	YES	0.130	0.967	35
OCSPLS	21	58dipeptide	V-scales	YES	3	0.817	YES	YES	0.410	0.838	22
ANN	22	58dipeptide	Z-scales	YES	3	-	YES	NO	-	0.928	35
SVM	23	58dipeptide	VTSA	NO	3	0.802	YES	NO	0.378	0.851	31
SVR	24	55tripeptide	E	NO	3	0.886	YES	NO	0.348	0.937	36

Linear models have been the basis of QSAR analysis since its beginning. They predict the activity as a linear function of molecular descriptors. In general, linear models are easily interpretable and sufficiently accurate for small datasets of similar compounds, especially when the descriptors are carefully selected for a given activity. Among the developed linear models, PLS model number 7 possessed the highest R^2 0.998 for tri-peptides, while model PLS number 6 could predict dipeptide ACEI activity more accurate than others with R^2 value of 0.906 . Model number 1 was the only general linear model which was developed using a data set of 168 di and 140 tri peptides and could predict the activity with R^2 value of 0.5.

Non-linear models extend the structure-activity relationships to non-linear functions of input descriptors. Such models may become more accurate, especially for large and diverse datasets. However, usually, they are harder to interpret. Among the developed models there are some ANN and SVM models which are developed for di or tri-peptides which were able to predict the activity more accurately than the similar linear models (Table 3. compare model number 22 and 23). Other nonlinear models were not more accurate than some of the existing linear models.

Table 4. Details of applied descriptors.

Descriptor category	Definition
Z-score	Interpreted as related to hydrophobicity (z1-score), side-chain bulk (z2-score) and electronic properties (z3- score) of amino acids calculated by principal component analysis (PCA) from a matrix consisting of 29 physicochemical variables
VHSH	Principal components score Vectors of Hydrophobic, Steric, and Electronic properties
VSW	Vector of principal component scores (VSW) for weighted holistic invariant molecular index, was derived from the principal component analysis of a matrix of 99 weighted holistic invariant molecular indices of amino acids
V-scales	Derived from a matrix of three structural variables of the natural amino acid, including van der Waal's volume, net charge index and hydrophobic parameter of side residues
HESH	A new set of descriptors, Hydrophobic, Electronic, Steric, and Hydrogen
T-scales	A new topological descriptor T-scale is derived from principal component analysis (PCA) on the collected 67 kinds of structural and topological variables of 135 amino acids.
G-scales	Eight kinds of parameters were derived from 457 kinds of physicochemical properties of the amino acid index database, which was classified into three sorts of parameters including hydrophobic, steric and electric properties.
FASGAI	Factor analysis scales of generalized amino acid information
QTMS	A new source of amino acid (AA) indices based on quantum topological molecular similarity (QTMS) descriptors
VTSA	Vector of topological and structural information for coded and non-coded amino acids
METDV	Molecular electronegativity topological distance vector
E	Quantitative multidimensional amino acids descriptors E (E1–E5)

Applied descriptors(features)

Applied descriptors could be classifies in 3 main categories: structural descriptors calculated by common software, sequence based descriptors and experimentally derived physicochemical properties. In addition 3D descriptors which are calculated using grid based methods or molecular dockings are used recently. The details of the applied descriptors are shown in Table 4.

Feature selection methods

Feature selection dimension reduction is one of the most important part of a QSAR method development procedure. Appropriate set of features or feature combination will prevent over fitting. Application of suitable feature selection/dimension reduction method will lead to the development of an applicable model.

Table 3 shows the applied feature selection/dimension reduction methods in the reviewed studies. According to the table most of the studies applied PLS as a dimension reduction method, while some of them are used GA-PLS method.

Validation of the developed methods

Validation of QSAR models is one the most important part of the model development. Our review showed that most of the studies validated the developed methods according to the test set prediction capability and leave one out cross validation results. Y-randomization, leave many out, applicability domain were not studied for most of the models. It seems that the future models would need to be validated according to the guidelines in order to be applicable for drug discovery studies.

Selected descriptors

Regulska et. al. [37] reviewed the structure activity relationship of ACEIs and concluded the minimal obligatory requirements which is needed for the inhibitor to interact with the active site of ACE as:

- The terminal carboxyl to facilitate the ionic interactions with the cationic site
- A hydrogen bond acceptor (e.g. carbonyl of amidic nature)
- The ionisable functional group to coordinate with the Zn^{2+} ion

-

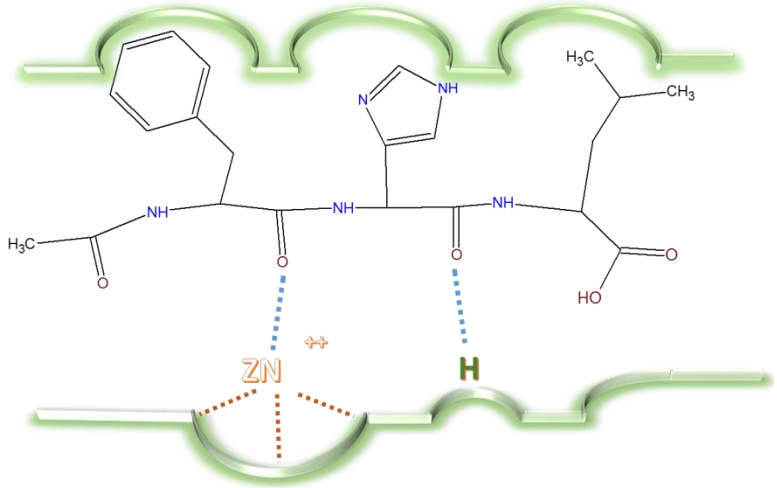


Figure 3. Scheme of ACE active site, interacted with angiotensin (I).

They also listed a number of auxiliary features which are responsible for potency enhancement of available ACEIs that could be summarized as additional ionisable groups or hydrophobic moieties for further interaction. Figure 3 shows a schematic SAR of ACEIs.

According to Table 4, the applied descriptors are including hydrophobic, topologic and electronic variables or a combination of different descriptors, and a correlation was found between ACE inhibition and structural properties related to hydrophobicity, positive charge and molecular volume of the amino acids at the C-terminal region covering the two last amino acids for peptides containing up to six amino acid residues.[38]

Conclusion

Prediction of peptides bioactivity can help to identify natural proteins containing encrypted peptides of potential biological effect. Developing of reliable QSAR models would help the researchers to predict the available peptides activity and to predict the possible modifications which will improve the activity of peptides. These models could be used in high-throughput screening studies if they are developed based on a reliable database. This review indicates that most of the available models are developed based on a small dataset and most of them are not validated. The availability of online datasets would help the researchers to use more diver's datasets and develop more reliable methods.

Acknowledgement

The authors would like to thank the Drug design laboratory of Tabriz Pharmacy faculty for providing the needed software and hardware for this study.

References

1. Paulis L, Unger T. Novel therapeutic targets for hypertension. *Nat Rev Cardiol* 2010;7:431-441.
2. Thind GS. Angiotensin converting enzyme inhibitors: comparative structure, pharmacokinetics, and pharmacodynamics. *Cardiovasc Drugs Ther* 1990;4:199-206.
3. Phillips M, Ea S. B. Kimura. *Levels of angiotensin and molecular biology of the tissue renin angiotensin and molecular biology of the tissue renin angiotensin systems Regul Pept* 1993;43:1-20.
4. Soubrier F, Alhenc-Gelas F, Hubert C, Allegrini J, John M, Tregear G, et al. Two putative active centers in human angiotensin I-converting enzyme revealed by molecular cloning. *PNAS* 1988;85:9386-9390.

5. Smith CG, Vane JR. The Discovery of Captopril. *The FASEB J* 2003;17:788-789.
6. D. W. Cushman MaO. History of the design of captopril and related inhibitors of angiotensin converting enzyme. *Hypertension* 1991;17:589-592.
7. Jao C-L, Huang S-L, Hsu K-C. Angiotensin I-converting enzyme inhibitory peptides: Inhibition mode, bioavailability, and antihypertensive effects. *BioMedicine* 2012;2:130-136.
8. Tzakos AG, Gerothanassis IP. Domain-selective ligand-binding modes and atomic level pharmacophore refinement in angiotensin I converting enzyme (ACE) inhibitors. *Chembiochem* 2005;6:1089-1103.
9. He HL, Liu D, Ma CB. Review on the angiotensin-I-converting enzyme (ACE) inhibitor peptides from marine proteins. *Appl Biochem Biotechnol* 2013;169:738-749.
10. Sheih I, Fang TJ, Wu T-K. Isolation and characterisation of a novel angiotensin I-converting enzyme (ACE) inhibitory peptide from the algae protein waste. *Food Chem* 2009;115:279-284.
11. Jimsheena VK, Gowda LR. Arachin derived peptides as selective angiotensin I-converting enzyme (ACE) inhibitors: structure-activity relationship. *Peptides* 2010;31:1165-1176.
12. Kumar R, AK, RS, AB. Pharmacological review on Natural ACE inhibitors. *Scholars Res Libr* 2010;2:273-293.
13. Tanzadehpanah H, Asoodeh A, Saberi MR, Chamani J. Identification of a novel angiotensin-I converting enzyme inhibitory peptide from ostrich egg white and studying its interactions with the enzyme. *Innov Food Sci Emerg Technol* 2013;18:212-219.
14. Vercruysse L, Van Camp J, Smagghe G. ACE inhibitory peptides derived from enzymatic hydrolysates of animal muscle protein: a review. *J Agric Food Chem* 2005;53:8106-8115.
15. De Leo F, Panarese S, Gallerani R, Ceci LR. Angiotensin converting enzyme (ACE) inhibitory peptides: production and implementation of functional food. *Curr Pharm Des* 2009;15:3622-3643.
16. Soltani S, Abolhasani H, Zarghi A, Jouyban A. QSAR analysis of diaryl COX-2 inhibitors: comparison of feature selection and train-test data selection methods. *Eur J Med Chem* 2010;45:2753-2760.
17. Soltani S, Haghaei H, Shayanfar A, Vallipour J, Asadpour Zeynali K, Jouyban A. QSBR Study of Bitter Taste of Peptides: Application of GA-PLS in Combination with MLR, SVM, and ANN Approaches. *BioMed Res Int* 2013;2013:13.
18. Wu J, Aluko RE, Nakai S. Structural Requirements of Angiotensin I-Converting Enzyme Inhibitory Peptides: Quantitative Structure-Activity Relationship Modeling of Peptides Containing 4-10 Amino Acid Residues. *QSAR Comb Sci* 2006;25:873-880.
19. Mei H, Liao ZH, Zhou Y, Li SZ. A new set of amino acid descriptors and its application in peptide QSARs. *Biopolymers* 2005;80:775-786.
20. Tong J, Chen Y, Liu S, Che T, Xu X. A descriptor of amino acids SVWG and its applications in peptide QSAR. *J Chemom* 2012;26:549-555.
21. Tong J, Liu S, Zhou P, Wu B, Li Z. A novel descriptor of amino acids and its application in peptide QSAR. *J Theor Biol* 2008;253:90-97.
22. Long H-X, Wang Y-Q, Lin Y, Lin Z-H. QSAR Study on ACE Inhibitors by Using OSC-PLS Algorithm. *J Chin Chem Soc* 2010;57:417-422.
23. Jianbo Tong JC, Xiameng Xu, Shuling Liu, Mim Bai. A New Descriptor For Amino Acids And Its Applications In Peptide Qsar *Revista De Chimie* 2014;65:550-555.
24. Jing P, Qian B, He Y, Zhao X, Zhang J, Zhao D, et al. Screening milk-derived antihypertensive peptides using quantitative structure activity relationship (QSAR) modelling and in vitro/in vivo studies on their bioactivity. *Int Dairy J* 2014;35:95-101.
25. Jian-Bo Tong JC, Shu-Ling Liu and Min Bai. QSAR study of peptide drugs based on a new descriptor of amino acids - SVWGM. *JIAN-BO TONG, JIA CHANG, SHU-LING LIU and MIN BAI* 2014;in press.
26. Liang G, Yang L, Kang L, Mei H, Li Z. Using multidimensional patterns of amino acid attributes for QSAR analysis of peptides. *Amino Acids* 2009;37:583-591.
27. Shu M, Mei H, Yang S, Liao L, Li Z. Structural Parameter Characterization and Bioactivity Simulation Based on Peptide Sequence. *QSAR Comb Sci* 2009;28:27-35.
28. Tian F, Zhou P, Li Z. T-scale as a novel vector of topological descriptors for amino acids and its application in QSARs of peptides. *J Mol Struct* 2007;830:106-115.
29. Wang X, Wang J, Lin Y, Ding Y, Wang Y, Cheng X, et al .QSAR study on angiotensin-converting enzyme inhibitor oligopeptides based on a novel set of sequence information descriptors. *J Mol Model* 2011;17:1599-1606.
30. Hemmateenejad B, Yousefinejad S, Mehdipour AR. Novel amino acids indices based on quantum topological molecular similarity and their application to QSAR study of peptides. *Amino Acids* 2011;40:1169-1183.
31. Li Z, Li G, Shu M, Sun J, Yang S, Mei H, et al. A novel vector of topological and structural information for amino acids and its QSAR applications for peptides and analogues. *Sci China Ser B-Chem* 2008;51:946-957.
32. Zhihua L, Yuzhang W, Xuejun Q, Yuegang Z, Bing N, Ying W. Use of a novel electrotopological descriptor for the prediction of biological activity of peptide analogues. *Lett Pept Sci* 2002;9:273-281.
33. Yin J. Prediction of ACE Inhibitor Tripeptides Activity Based on Amino Acid Descriptors(E) from

Multiple Linear Regression Model. *Int Conf Bioinform Biomed Eng* 2011. p. 1-4.
34. Lin Z-H ,Long H-X, Bo Z, Wang Y-Q, Wu Y-Z. New descriptors of amino acids and their application to peptide QSAR study. *Peptides* 2008;29:1798-1805.
35. He R, Ma H, Zhao W, Qu W, Zhao J, Luo L, et al. Modeling the QSAR of ACE-Inhibitory Peptides with ANN and Its Applied Illustration. *Int J Peptides* 2012;2012.
36. Yin J, Diao Y, Wen Z, Wang Z, Li M. Studying Peptides Biological Activities Based on Multidimensional Descriptors (E) Using Support Vector Regression. *Int J Pept Res Ther* 2010;16:21-111.
37. Regulska K, Stanisz B, Regulski M, Murias M. How to design a potent, specific, and stable angiotensin-converting enzyme inhibitor. *Drug Discovery Today* 2014;19:1731-1743.
38. Pripp AH, Isaksson T, Stepaniak L, Sørhaug T. Quantitative structure-activity relationship modelling of ACE-inhibitory peptides derived from milk proteins. *Eur Food Res Technol* 2004;219:579-583.