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QSAR studies on peptide α-ketoamides and α-ketohydroxamate derivatives as calpain I inhibitors

JESSE S. DONDAPATI[1,2], SUDHAKAR GODI[1], & AJAY P. BABU[2]

[1]*Molecular Genetics Division, Department of Human Genetics, Andhra University, Visakhapatnam, India, and* [2]*ProGene Biosciences, Institute of Bioinformatics & Research Centre, 103, Bharat Towers, Dwaraka Nagar, Visakhapatnam, India*

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Abstract

Quantitative Structure Activity Relationship (QSAR) studies were conducted on 34 peptide α-ketoamide and α-ketohydroxamate derivatives of Calpain I using multiple linear regression (MLR) procedure. The activity contributions of these compounds were determined from regression equation and the validation procedures that analyze the predictive ability of QSAR models were described. Among forty six descriptors that were considered in generating the QSAR model, three descriptors such as LogP, Heat of formation and HOMO resulted in a statistically significant model with 0.877 r^2 and 0.937 q^2 respectively. The inter-correlation between descriptors was 0.42. The proposed QSAR model indicates an increase in logP value increases hydrophobicity in order to achieve cellular permeability and an increase in heat of formation as well as decrease in HOMO energy favors better binding and activity towards development of potent calpain I inhibitors.

Keywords: *Calpain I, α-ketoamide, α-ketohydroxamate, QSAR*

Introduction

Calpains are a family of Ca^{2+} activated cytoplasmic cysteine endoproteases that are ubiquitously found in mammalian cells and participate in a variety of biological processes [1]. Calpains are of considerable therapeutic interest because of its implications in various biological processes, including integrin mediated cell migration, cytoskeletal remodeling, cell differentiation and apoptosis [2,3] as well as numerous pathological events [4]. Currently, 12 different calpains are identified in mammals, of which, two well-known ubiquitous calpains, μ-calpain (calpain I) and m-calpain (calpain II) activated at micromolar and millimolar concentrations of Ca^{2+}, are thought to play a major role in numerous diseases such as Stroke, Alzheimer's, central nervous system (CNS), spinal cord injury, brain trauma, cardiac and cerebral ischemia, muscular dystrophy, and cataracts [5]. Thus, calpain inhibition has become an important pharmacological strategy to develop novel therapies.

Calpain inhibitors are peptide substrate analogues designed by replacing the scissile amide bond with an electron-deficient center that is capable of reacting either reversibly or irreversibly with the active site thiol [9]. Reports [6–8] indicate a variety of inhibitors for calpain, where binding groups are capable of binding to the catalytic center in either irreversible or reversible manner. Irreversible inhibitors include peptidyl halo-ketones, [10,11] diazo-ketones, [6] epoxy-succinyls [12] and other derivatives. These inhibitors permanently inactivate calpain by displacing the active site cysteine thiol to form a sulfide. Reversible inhibitors include peptidyl aldehydes [13,14] and activated ketones [15,16] like α-keto-esters, α-keto-acids, and α-keto-amides. These inhibitors inactivate calpain in a transient manner by forming a reversible covalent bond (hemithioacetal or

Correspondence: A. P. Babu, ProGene Biosciences, 103, Bharat Towers, Dwaraka Nagar, Visakhapatnam 530016, India. Tel: 91 891 6671195. E-mail: ajay_pgb@progenebio.in

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hemithioketal) with the cysteine thiol [17]. However, most of these inhibitors displayed limited selectivity [9] and to enhance the potency and selectivity, peptidomimetic inhibitors were developed such as urea based [18], alpha-ketoamides [19,20], alpha-ketohydroxamates [21] and others[22,23]. α-ketoamides and α-ketohydroxamate derivatives were found to be promising inhibitors against calpain I and hence quantitative structural activity relationship studies have been carried out in order to investigate the role of various physico-chemical parameters and their quantitative contribution towards activity of compounds.

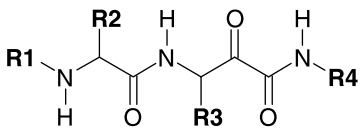
A set of 34 α-ketoamide and α-ketohydroxamate derivatives were selected for QSAR studies [19–21]. To our knowledge no attempts have been made so far to build a QSAR model on inhibitors of Calpain I. Statistically significant QSAR model was generated using multiple linear regression procedure.

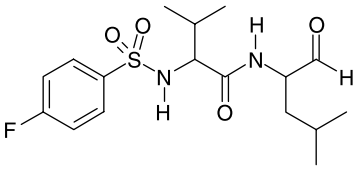
Methodology

Data set

A series of thirty four novel peptide α-ketoamide and α-ketohydroxamate biological data from the work of Y.Shirasaki et al. [19,20] and K.A.Josef et al. [21] were used in QSAR studies (Table I). The inhibitory activities of these derivatives were reported in terms of IC_{50} in μM. In order to guarantee the linear distribution of data, the enzyme inhibition was

Table I. Structures of α-ketoamide and α-ketohydroxamate derivatives and their biological data.





Compound **34**

Compound	R_1	R_2	R_3	R_4	IC_{50} (μM)
1	Py C_2H_4OCO	$(CH_3)_2CHCH_2$	Bn	*c*-Pr	0.038
2	(Py-6-Me)C_2H_4OCO	$(CH_3)_2CHCH_2$	Bn	*c*-Pr	0.031
3	(Py-5-Et)C_2H_4 OCO	$(CH_3)_2CHCH_2$	Bn	*c*-Pr	0.041
4	Cbz	$(CH_3)_2CHCH_2$	Bn	CH_3O	0.010
5	Cbz	$(CH_3)_2CHCH_2$	Bn	EtO	0.019
6	Cbz	$(CH_3)_2CHCH_2$	Bn	BnO	0.006
7	Cbz	$(CH_3)_2CHCH_2$	Bn	*t*-BuO	0.026
8	Cbz	$(CH_3)_2CHCH_2$	Bn	4Me-*c*-hexyl	0.021
9	CH_3SO_2	$BnOCH_2$	CH_3OCH_2	BnO	0.152
10	CH_3SO_2	$BnOCH_2$	Bn	BnO	0.028
11	CH_3SO_2	$BnOCH_2$	Bn	EtO	0.056
12	Cbz	$CH(CH_3)_2$	Bn	BnO	0.012
13	Cbz	$CH(CH_3)_2$	$CH_3(CH_2)_3$	BnO	0.021
14	Cbz-Leu	$(CH_3)_2CHCH_2$	Bn	CH_3O	0.020
15	Cbz-Leu	$(CH_3)_2CHCH_2$	Bn	BnO	0.017
16	PhCO	Bn	$CH_3(CH_2)_3$	EtO	0.193
17	(Ph 6 F)SO_2	$(CH_3)_2CH$	$(CH_3)_2CHCH_2$	n-Bu	0.021
18	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	Bn	Et	0.170
19	(3-THF)OCO	$(CH_3)_2CHCH_2$	Bn	Et	0.150
20	(4-THP)OCO	$(CH_3)_2CHCH_2$	Bn	Et	0.250
21	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	Bn	c-Pr	0.110
22	(3-THF)OCO	$(CH_3)_2CHCH_2$	Bn	c-Pr	0.086
23	(4-THP)OCO	$(CH_3)_2CHCH_2$	Bn	c-Pr	0.120
24	$CH_3(OC_2H_4)_2OCO$	$(CH_3)_2CHCH_2$	Bn	c-Pr	0.170
25	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	Bn	n-Pr	0.099
26	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	Bn	c-Bu	0.170
27	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	Bn	n-Bu	0.100
28	$PhCH_2OCO$	$(CH_3)_2CHCH_2$	Bn	n-Bu	0.038
29	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	Bn	CF_3CH_2	0.450
30	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	Bn	2-Indanyl	0.170
31	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	Bn	$CH_3OC_2H_4$	0.180
32	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	$PhCH_2CH_2$	Et	0.300
33	$CH_3OC_2H_4OCO$	$(CH_3)_2CHCH_2$	$PhCH_2CH_2$	c-Pr	0.180
34	–	–	–	–	0.021

converted to negative logarithmic values and then used for subsequent QSAR analysis. The structures were sketched using ISIS Draw 2.3 (www.mdli.com) software and the descriptors were calculated using Tsar 3.3 software (www.accelrys.com). Before the calculation of descriptors, three dimensional structures of all molecules were generated using Corina 3D package, charges were derived and the geometries optimized using cosmic module of Tsar.

Multivariate regression analysis

QSAR models were constructed based on the training set and then validated internally using leave-one-out (LOO) technique and externally by predicting the activities of validation set. The relationship between dependent variable log ($1/IC_{50}$) and the independent variables (various physicochemical and structural descriptors) was established by linear multiple regression analysis using Tsar 3.3 software. Significant descriptors were chosen based on the statistical data of analysis. Inter-correlation between these descriptors was checked for independence of the variables. Statistical quality of the generated QSAR equation was judged based on the parameters like correlation coefficient (r), explained variance (r^2), standard error of estimate (s), F-value, cross-validation r^2 (q^2) and predictive residual sum of squares (PRESS).

In our study, forty six various physico-chemical, topological and electrostatic descriptors were evaluated in terms of their efficacy to predict the activities of the investigated inhibitors. Molecular descriptors chosen for the analysis are: Molecular mass, Molecular surface area, Molecular volume, Inertia moment size (1 & 2), Ellipsoidal volume, Total lipole, Lipole components, Atom counts (O and N), Molecular refractivity, Shape indices, Molecular flexibility, 6-membered - ring and aromatic ring counts, Connectivity indices (chi and chiV types) of atoms, bonds, path, cluster and path/cluster, ADME properties and parameters such as HOMO, LUMO, surface area, heat of formation and total energy calculated using AM1 Hamiltonian and BFGS optimization in vacuum. Cross-validation was calculated using leave-one-out (LOO) technique over 2 random trials with F to leave and F to enter being 4 in F stepping to include the most significant variables in generating the QSAR model.

Predictive ability of QSAR model

Predictive ability of the generated model was estimated externally by predicting the activities of validation set. This criterion may not be sufficient for a QSAR model to be truly predictive. An additional condition for high predictive ability of QSAR model is based on external set cross-validation r^2 ($R^2_{cv,ext}$) and the regression of observed activities against predicted activities and vice versa for validation set, if the following conditions are satisfied [24,25]:

$$R^2_{cv,ext} > 0.5 \quad (1)$$

$$R^2 > 0.6 \quad (2)$$

$$(R^2 - R_0^2)/R^2 < 0.1 \text{ or } \left(R^2 - R_0'^2\right)/R^2 < 0.1 \quad (3)$$

$$0.85 \le k \le 1.15 \text{ or } 0.85 \le k' \le 1.15 \quad (4)$$

Calculations relating to $R^2_{cv,ext}$, R_0^2, slopes k of actual versus predicted and k' of predicted versus actual values are presented in detail in ref. 24.

Results and discussion

To select the most important descriptors, multivariate regression analysis was performed. The most significant descriptors are: logP, heat of formation and HOMO. The linear QSAR model from a complete set of 34 peptide α-ketoamide and α-ketohydroxamate derivatives was:

$$\log(1/IC_{50}) = +0.121 * \text{logP} + 0.003 * \text{heat of formation} - 0.895 * \text{HOMO} + 0.358 * \text{Kier ChiV3} - 7.478$$
$$r = 0.855, \quad r^2 = 0.732, \quad q^2 = 0.901, \quad F = 19.788, \quad n = 34, \quad \text{PRESS} = 1.844, \quad s = 0.252 \quad (5)$$

The data set was investigated for outliers by calculating the standard residuals. Standardized residuals greater than 2 and less than −2 are usually considered large [34]. Generally outliers have larger residuals than non-outliers. Compounds **4**, **6** and **16** (Table II) has standardized residuals 2.502, −2.004 and −2.778, respectively, and can safely be excluded from the data set. Outliers were removed in order to obtain the best statistical result [26].

The new QSAR model was generated by dividing the set as 26 molecule training and a 5 molecule validation set (Table II) based on hierarchical clustering after rejecting outliers from the data set. Cross-validation was calculated using leave-one-out (LOO) technique over 2 random trials with F to leave and F to enter being 4 in F stepping to include the most significant variables in generating the QSAR model. The observed, calculated and predicted values of whole molecules are presented in Table II. The statistically significant QSAR model for training set was given below.

$$\log(1/IC_{50}) = +0.146 * \text{logP} + 0.004 * \text{heat of formation} - 1.338 * \text{HOMO} - 11.036$$
$$r = 0.936, \quad r^2 = 0.877, \quad q^2 = 0.937, \quad F = 52.152, \quad n = 26, \quad \text{PRESS} = 0.623, \quad s = 0.168 \quad (6)$$

Comparison between Equations (5) and (6) justifies the removal of outliers from the data set, where a

Table II. Observed logarithmic data, calculated and standard residuals (Equation 5) and training and validation sets (Equation 6) of peptide α-ketoamide and α-ketohydroxamate derivatives.

Compound	Observed log (1/IC_{50})	Calculated [a] log (1/IC_{50})	Std [b] Res.	Training Set [c] log (1/IC_{50})	Validation Set [d] log (1/IC_{50})	LogP	Heat of formation	HOMO
1	1.420	1.421	−0.004	1.576		2.956	−124.715	−9.519
2⋆	1.508	1.417	0.385	–	1.497	3.141	−129.979	−9.457
3⋆	1.387	1.518	−0.554	–	1.632	3.820	−138.495	−9.513
4#	2.000	1.409	2.502	–	–	3.227	−153.749	−9.620
5	1.721	1.543	0.753	1.813		3.570	−160.309	−9.748
6#	1.222	1.696	−2.004	–	–	5.004	−124.366	−9.548
7	1.585	1.815	−0.974	1.610		4.061	−168.683	−9.570
8	1.677	1.656	0.089	1.717		5.143	−183.664	−9.582
9	0.818	1.061	−1.027	1.004		0.400	−203.922	−9.634
10	1.552	1.436	0.493	1.399		2.593	−133.827	−9.457
11	1.251	1.110	0.597	1.038		1.159	−168.530	−9.459
12⋆	1.920	1.676	1.033		1.944	4.680	−115.880	−9.576
13	1.677	1.404	1.156	1.632		4.255	−165.223	−9.554
14	1.699	1.465	0.990	1.398		3.884	−209.865	−9.569
15	1.769	1.795	−0.108	1.756		5.660	−182.350	−9.550
16#	0.714	1.371	−2.778	–	–	3.146	−118.302	−9.635
17	1.677	1.690	−0.053	1.666		2.686	−240.704	−10.002
18⋆	0.769	0.704	0.276	–	0.726	1.357	−237.612	−9.435
19	0.823	0.724	0.419	0.694		1.302	−233.655	−9.403
20	0.602	0.799	−0.832	0.807		1.354	−242.707	−9.512
21	0.958	0.931	0.115	0.974		1.411	−202.501	−9.497
22⋆	1.065	0.937	0.543	–	0.920	1.356	−200.136	−9.455
23	0.920	0.950	−0.126	0.941		1.408	−208.159	−9.492
24	0.769	0.760	0.037	0.741		1.246	−249.576	−9.498
25	1.004	0.805	0.842	0.863		1.826	−243.316	−9.505
26	0.769	0.907	−0.586	0.932		1.807	−221.547	−9.486
27	1.000	0.802	0.836	0.848		2.222	−249.580	−9.471
28	1.420	1.291	0.546	1.421		4.163	−176.094	−9.443
29	0.346	0.532	−0.785	0.405		1.990	−390.116	−9.634
30	0.769	1.073	−1.285	1.019		3.095	−205.864	−9.358
31	0.744	0.529	0.909	0.498		0.850	−278.951	−9.457
32	0.522	0.752	−0.974	0.787		1.753	−244.559	−9.460
33	0.744	0.915	−0.724	0.939		1.807	−210.012	−9.453
34	1.678	1.609	0.293	1.596		2.148	−189.735	−9.839

⋆ Validation set molecules. # Outliers. [a] Calculated values from Equation (5). [b] Standardized residuals from Equation (5). [c] Calculated values from Equation (6). [d] Predicted values from Equation (6).

remarkable increase in statistical parameter values such as r, r^2, q^2 and F-test (0.85 vs. 0.93, 0.73 vs. 0.87, 0.90 vs. 0.93 and 19.78 vs. 52.15 for Equations (5) and (6), respectively) were obtained.

Equation (6) accounts for the significant correlation of descriptors with biological activity and displayed good internal predictivity as shown by q^2 value of 0.937 and was able to explain 87.7% variance of inhibitory activities of α-ketoamide and α-ketohydroxamate derivatives. The predictive residual sum of squares and the standard error of estimate are 0.623 and 0.168, respectively. Observed verses predicted values are shown graphically in Figure 1 which displays the predictive ability of Equation (6) when applied on validation set molecules.

Inter-correlation between significant descriptors utilized in Equation (6) was presented in Table-III, where, it is clear that the descriptors are not highly correlated.

A brief explanation of the descriptors that were utilized to generate the statistical QSAR model:

Log P is a measure of hydrophobicity/lipophilicity and describes the distribution of a compound between organic (usually octanol) and water phase. A value of Log P $>$ 0 indicates greater solubility in the organic

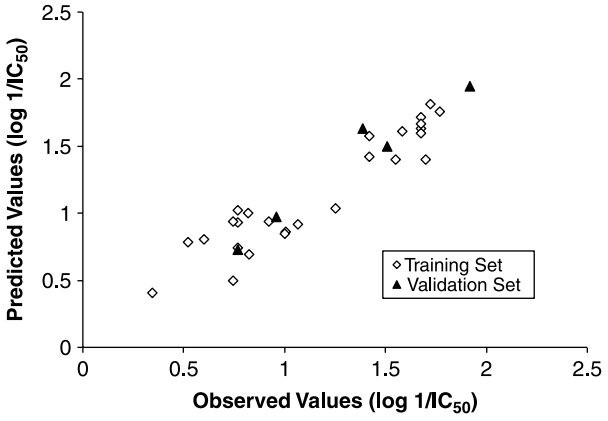


Figure 1. Observed and predicted values of molecules in training and validation set.

Table III. Correlation matrix of the three descriptors.

	LogP	Heat of formation	HOMO
LogP	1		
Heat of formation	0.416	1	
HOMO	−0.161	0.047	1

phase whereas Log P < 0 indicates greater solubility in the aqueous phase.

Enthalpies or heat of formation is an important variable used to explore reactivities and/or equilibria and is a measure of the relative thermal or conformational stability of a molecule [27,28].

Molecular Orbital (MO) surfaces represent the various stable electronic distributions of a molecule. According to Frontier Orbital theory, the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) are crucial in predicting the reactivity of a species. HOMO is the outermost orbital containing the electron and LUMO is the first orbital that does not contain an electron. Molecules with high HOMOs can donate electrons with ease and are hence relatively reactive, compared to molecules with low HOMOs. Thus HOMO measures the nucleophilicity of a molecule.

The generated QSAR model (Equation 6) indicates that a high value of HOMO energy contributes negatively to the activity. An electron-donating substituent, such as hydroxy, or methoxy group, on the ring increases the energy of the HOMO orbital. For instance, a lone pair of electrons on oxygen atom of methoxy group delocalizes into the π space of benzene ring, thereby increasing the energy of HOMO. Electron-withdrawing substituents, such as halogens, lower the energy of HOMO. An electronegative halogen removes electron density from the σ space of benzene ring, thereby decreasing the energy of HOMO [29]. Thus, designing analogs with electron-withdrawing substituents should improve activity.

On the other hand, a high value of Log P and heat of formation represents a positive contribution to the activity. Log P is known to be an important parameter for absorption, permeability and *in vivo* distribution of organic compounds [30,31]. Therefore, according to Equation 6, an increase in logP value increases hydrophobicity on molecules that would favor cellular permeability. Heat of formation indicates conformational stability and an increase in enthalpies of the molecules favors better binding and activity at the molecular level.

The proposed whole molecule QSAR model Equation (6) illustrated the predictive ability of Equations (1–4) and depicted graphically in Figure 2.

$$R^2_{cv,ext} = 0.910 \quad R^2 = 0.949 \quad \left(R^2 - R_0^2\right)/R^2 = 0.0004$$
$$\text{or } \left(R^2 - R_0'^2\right)/R^2 = 0.005$$
$$k = 0.97 \text{ and } k' = 1.04$$

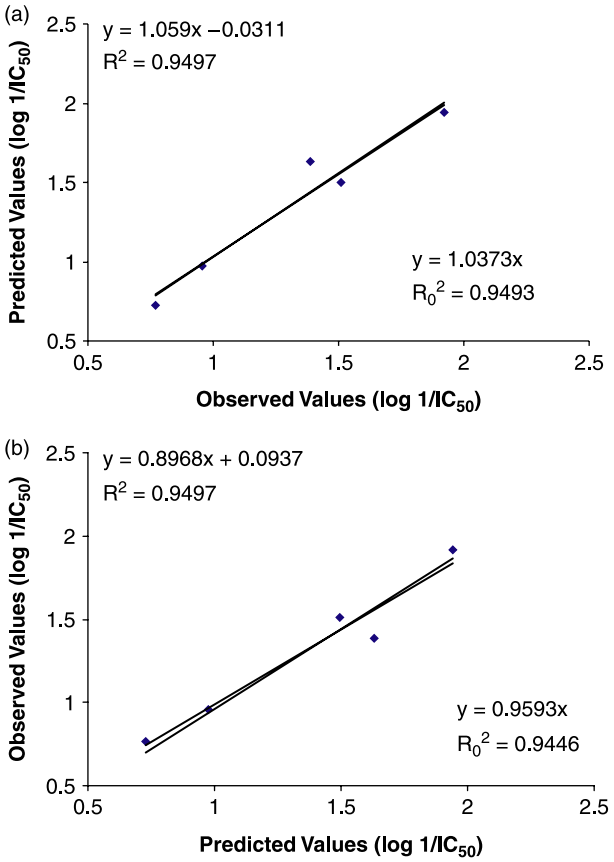


Figure 2. Regression plot between (a) observed vs. predicted values and (b) predicted vs. observed values of compounds from validation set justifying the predictive ability of QSAR model Equation (6).

Conclusion

The generated whole molecule QSAR model demonstrates a promising method and indicates the importance of logP value to increase hydrophobicity in order to achieve cellular permeability and an increase in heat of formation and a decrease in HOMO energy favors better binding and activity towards development of potent calpain I inhibitors. The predictive ability (Equations 1–4) of QSAR model illustrated the accuracy and robustness of Equation 6 on validation set. Therefore, considering the contributions of these descriptors (HOMO, heat of formation and logP) on α-ketoamide and α-ketohydroxamate derivatives would help in designing novel compounds.

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