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Prediction of caspase-3 inhibitory activity of 1,3-dioxo-4-methyl-2,3-dihydro-1h-pyrrolo[3,4-c] quinolines: QSAR study

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Abstract

Neurodegenerative disorders are consequences of progressive and irreversible loss of neurons due to unwanted apoptosis which involves caspases, a group of cysteine proteases that cleave other proteins and inactivate them. Among several different groups of caspase enzymes, caspases-3 plays a key role in apoptosis and are a therapeutic target for their inhibition. In pursuit of better caspase-3 inhibitors, a quantitative structure-activity relationship (QSAR) analysis was performed on a series of 1,3-dioxo-4-methyl-2,3-dihydro-1H-pyrrolo[3,4-c] quinolines as caspase-3 inhibitors using WIN CAChe 6.1 and Medicinal Chemistry Regression Machine. The best QSAR model was selected and validated by internal and external validation method. The values of statistical data are $r = 0.955$, $F = 72.95$, $SEE = 0.397$, $q^2 = 0.885$, $S_{PRESS} = 0.44$. The present study reveals that when the conformational minimum energy is increased, and lowest unoccupied molecular orbital energy and highest occupied molecular orbital energy are decreased the biological activity can be increased. On the basis of a selected QSAR model, we designed a new series of 1,3-dioxo-4-methyl-2,3-dihydro-1H-pyrrolo[3,4-c]quinolines compounds, calculated their caspases inhibitory activity and found that the designed compounds were more potent than the existing compounds.

Keywords: *QSAR, 1,3-dioxo-4-methyl-2, 3-dihydro-1H-pyrrolo[3, 4-c] quinolines, caspases-3, inhibition*

Introduction

Neurodegenerative disorders which include Alzheimer's disease [1] and Huntington's disease [2] are major consequences of excessesive apoptosis of neurons. This abnormal apoptosis is also responsible for occurrence of brain ischemia [3], myocardial infraction [4] and liver disease [5]. Current drug treatments are only partially effective and generally work by improving the function of the neurons that are still alive, rather than influencing the underlying mechanisms leading to their death [6].

Caspases, a group of cysteine proteases that cleave their substates after aspartic acid residues are the key executioners of apoptosis [7]. Among the identified caspases, caspase 3 is of particular interest, since it appears to be very important in the progression of AD (Alzheimer's disease). Caspases can be divided into initiator caspases(caspase 2, caspase 8, caspase 9, and caspase 10) and effectors caspases based on the presence of a large prodomain at their amino-terminal region. Initiator caspases containing a long prodomain, generally act in early stages of a proteolytic cascade, whereas effector caspases, (caspase 3, caspase 6, and caspase 7) act downstream and are involved in the cleavage of specific cellular proteins [8].

The initiation of this caspase cascade reaction is regulated by caspase inhibitors. Inhibitors of caspase-3 were described as promising neuroprotectants [9]. Many of the compounds such as isatins [10], peptidealdehydes [11], homophthalimides [12], quinazolinones [9] have been reported as caspase inhibitors because of having electrophilic carbonyls that interact with target site and show inhibitory action.

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Computational chemistry has developed into an important contributor to rational drug design. Quantitative structure activity relationship (QSAR) modeling results in a quantitative correlation between chemical structure and biological activity. Senior author of the article Dr. R. K. Agrawal and his team has developed a few quantitative structure-activity relationship models to predict biological activity of different group of compounds [13]–[18]. In continuation of such efforts, in this article, we have performed QSAR analysis to explore the correlation between physicochemical and biological activity of 1,3-dioxo-4-methyl-2,3-dihydro-1H-pyrrolo [3,4-c] quinolines [19] using modeling software WIN CAChe 6.1 and statistical software Medicinal Chemistry Regression Machine.

Materials and methods

The biological activities of all 25 compounds were collected from the reported series (Table I) [19]. All the twenty-five compounds were built on workspace of molecular modeling software WIN CAChe 6.1, which is a product of Fujitsu private limited, Japan. The energy minimization was done by geometry optimization of molecules using MM3 (Molecular Mechanics) followed by MOPAC-AM1 (Austin model) by using root mean square gradient of 0.1 and 0.001 respectively. The physicochemical properties were calculated on project leader file of the software. These properties were fed manually into statistical software named, Medicinal Chemistry Regression Machine (Biosoft) and a correlation matrix was made to select the parameters having very less intercorrelation and maximum correlation with activity. This was followed by multiple linear regression analysis to achieve best model.

Correlation matrix of the parameters in best model is given in Table II, observed and calculated values are shown in Table I. Internal validation was carried out by Leave one out (LOO) method using statistical software STATISTICA. The cross-validated coefficient, q^2, was calculated using the following equation:

$$q^2 = 1 - \frac{\text{PRESS}}{\sum_{i=1}^{N} (y_i - y_m)^2}$$

$$\text{PRESS} = \sum_{i=1}^{N} (y_{\text{pred},i} - y_i)^2$$

Where y_i is the activity for training set compounds, y_m is the mean observed value, corresponding to the mean of the values for each cross-validation group, and $y_{\text{pred},i}$ is the predicted activity for y_i. The LOO predicted values are shown in Table I.

In present study the calculated descriptors were conformational minimum energies (CME), Zero-order connectivity index (CI0), First-order connectivity index (CI1), Second-order connectivity index (CI2), dipole moment (DM), total energy at its current geometry after optimization of structure (TE), heat of formation at its current geometry after optimization of structure (HF), highest occupied molecular orbital energies(HOMO), lowest unoccupied molecular orbital energies(LUMO), octanol-water partition coefficient(LOGP), molar refractivity(MR), shape index order 1 (SI1), shape index order 2 (SI2), shape index order 3 (SI3), Zero-order valance connectivity index (VCI0), First-order valance connectivity index (VCI1), Second-order valance connectivity index (VCI2). (Physicochemical parameters data will be provided on request). Leave 33% out crossvalidation was also performed.

On the basis of model 5, a series of 14 compounds (Table IV) were designed with the objective of finding higher potent molecules than existing 1,3-dioxo-4-methyl-2, 3-dihydro-1H-pyrrolo [3,4-c] quinolines. The independent variables were calculated and put in model 5 to obtain predicted biological activities of all 14 compounds of the designed series (Table V). The structures of these 14 compounds have shown some relationships with the activity.

Results and discussion

In pursuit of better caspase-3 inhibitors having improved biological activity compared to the existing compounds reported [19] in series 1,3-dioxo-4-methyl-2, 3-dihydro-1H-pyrrolo [3,4-c] quinolines (Table I), a quantitative structure-activity relationship analysis was performed by using Win CAChe 6.1 and Medicinal Chemistry Regression Machine (Biosoft). Multiple linear regression analysis results five statistically significant QSAR models

$$\begin{aligned}\text{Log}(1/\text{IC}_{50}) &= 0.0688\,(\pm 0.0060)\,\text{CME} \\ &\quad - 0.3192\,(\pm 0.0789)\,\text{Log P} \\ &\quad + 2.6967\,(\pm 0.2821) \qquad (1)\end{aligned}$$

$$n = 25,\ r = 0.926,\ s = 0.496,\ F = 65.99,$$

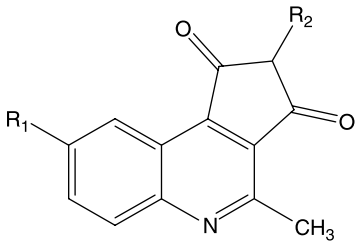
$$r^2 = 0.857,\ q^2 = 0.821,\ S_{\text{PRESS}} = 0.543$$

$$\begin{aligned}\text{Log}(1/\text{IC}_{50}) &= 0.0518\,(\pm 0.0053)\,\text{CME} \\ &\quad - 3.6813\,(\pm 0.6658)\,\text{LUMO} \\ &\quad - 5.7349\,(\pm 1.3601)\end{aligned}$$

$$n = 25,\ R = 0.946,\ s = 0.424,\ F = 94.47,$$

$$R^2 = 0.896,\ q^2 = 0.867,\ S_{\text{PRESS}} = 0.467 \qquad (2)$$

Table I. 1,3-dioxo-4-methyl-2,3-dihydro-1H-pyrrolo[3,4-c] quinolines with observed calculated and predicted biological activity data



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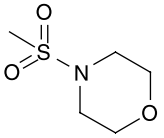
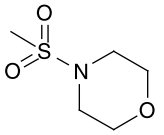
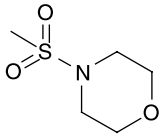
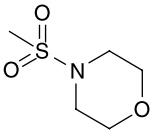
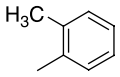
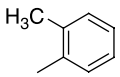
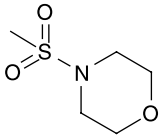
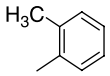
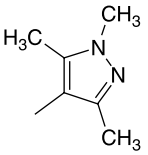
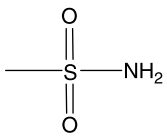
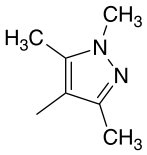
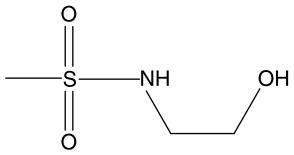
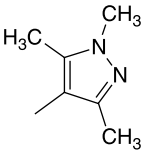
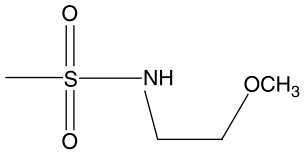
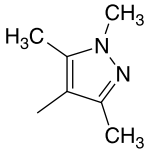
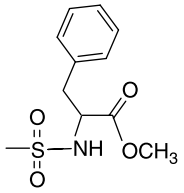
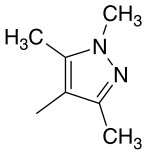
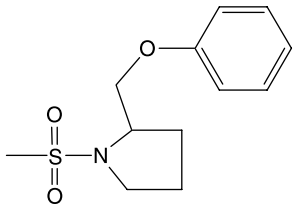
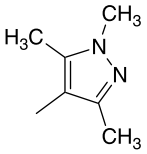
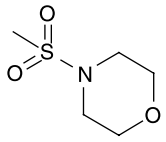
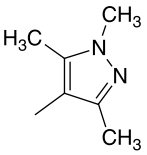
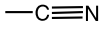
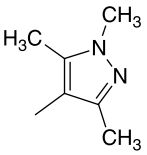
			Log (1/IC_{50}) (μM)		
Comp. No.	R_1	R_2	Obs.	Cal.	Predicted activity by LOO method
1	F	H	−1.798	−0.960	−0.895
2	Br	H	−1.569	−1.093	−1.031
3		H	0.678	0.867	0.958
4	H	CH_3	−0.803	−0.992	−1.189
5	Br	CH_3	−0.199	−0.637	−0.618
6		CH_3	1.357	1.325	1.477
7	H	$CH_2CO_2CH_3$	−0.667	−0.747	−0.951
8	F	$CH_2CO_2CH_3$	−0.398	−0.264	−0.325
9	Br	$CH_2CO_2CH_3$	0.337	−0.394	−0.432
10		$CH_2CO_2CH_3$	1.796	1.524	1.544
11	H	$CH_2CH_2CO_2CH_3$	−1.367	−1.040	−1.160
12	F	$CH_2CH_2CO_2CH_3$	−0.740	−0.604	−0.654
13	Br	$CH_2CH_2CO_2CH_3$	−0.033	−0.737	−0.804
14		$CH_2CH_2CO_2CH_3$	1.432	1.158	1.155
15	H		−0.909	−0.681	−0.321
16	Br		−0.405	−0.331	0.118
17			1.824	1.609	1.850
18	Br		0.444	0.548	0.708

Table I – *continued*

Comp. No.	R_1	R_2	Log $(1/IC_{50})$ (μM)		
			Obs.	Cal.	Predicted activity by LOO method
19			1.481	1.610	1.488
20			1.699	2.062	1.990
21			1.678	2.043	2.024
22			1.638	1.333	1.401
23			1.260	1.714	1.314
24			2.398	2.479	2.461
25			1.796	1.137	1.126

Obs – Observed biological activity, Cal – Calculated biological activity, LOO – Leave one out.

Table II. Correlation matrix, variance inflation factor of the physico-chemical parameters and biological activity.

Variables	Log $(1/IC_{50})$	CME	HOMO	LUMO	VIF*
Log $(1/IC_{50})$	1				
CME	0.866	1			2.404
HOMO	0.060	0.445	1		2.577
LUMO	−0.670	−0.364	0.437	1	2.383

*VIF – Variance inflation factor.

$$\begin{aligned}\text{Log}(1/IC_{50}) = {} & 0.0575\,(\pm 0.0074)\,\text{CME} \\ & - 0.1240\,(\pm 0.1134)\,\text{DM} \\ & - 4.0142\,(\pm 0.7194)\,\text{LUMO} \\ & - 5.9506\,(\pm 1.3684)\end{aligned} \tag{3}$$

$$n = 25,\ R = 0.949,\ s = 0.42,\ F = 63.94,$$
$$R^2 = 0.901,\ q^2 = 0.867,\ S_{PRESS} = 0.47$$

$$\begin{aligned}\text{Log}(1/IC_{50}) = {} & 0.0537\,(\pm 0.0099)\,\text{CME} \\ & - 3.7375\,(\pm 0.7228)\,\text{LUMO} \\ & - 0.0018\,(\pm 0.0077)\,\text{MR} \\ & + (-5.6422 \pm 1.4473)\end{aligned} \tag{4}$$

$$n = 25,\ R = 0.947,\ s = 0.43,\ F = 60.28,$$
$$R^2 = 0.896,\ q^2 = 0.849,\ S_{PRESS} = 0.49$$

$$\begin{aligned}\text{Log}(1/IC_{50}) = {} & 0.0622\,(\pm 0.0072)\,\text{CME} \\ & - 1.2489\,(\pm 0.623)\,\text{HOMO} \\ & - 2.3886\,(\pm 0.898)\,\text{LUMO} \\ & - 14.9946\,(\pm 4.792)\end{aligned} \tag{5}$$

$$n = 25,\ R = 0.955,\ s = 0.397,\ F = 72.95,$$
$$R^2 = 0.912,\ q^2 = 0.885,\ S_{PRESS} = 0.44$$

Where IC_{50} = molar concentration of drug required to 50% inhibition of enzyme caspase-3, n = No. of data points, r = correlation coefficient, s = Standard Error of Regression, F-ratio = F-ratio between variances of calculated and observed value, q^2 = cross validated r^2.

Out of above five models, model 5 was selected as the best model on the basis of high q^2 values.

Model 5 reveals that in order to increase biological activity we need to decrease HOMO, LUMO energies values and increase CME values. The selected model was externally validated by randomly making training set of 20 compounds and test set of 5 compounds (**6, 7, 13, 18** and **20**) (Table III). QSAR was performed for training set and a model 6 was developed. This model was used to predict the biological activities of test set of compounds.

Table III. Observed and calculated activities for training set and predicted activities for test set compounds.

Comp. No.	Obs.	Cal.	Pred.
1	−1.798	−1.203	–
2	−1.569	−1.261	–
3	0.678	0.856	–
4	−0.803	−1.195	–
5	−0.199	−0.658	–
6*	1.357	–	1.496
7*	−0.667	–	−0.960
8	−0.398	−0.396	–
9	0.337	−0.447	–
10	1.796	1.627	–
11	−1.367	−1.291	–
12	−0.740	−0.779	–
13*	−0.033	–	−0.821
14	1.432	1.193	–
15	−0.909	−0.458	–
16	−0.405	0.067	–
17	1.824	1.916	–
18*	0.444	–	0.727
19	1.481	1.531	–
20*	1.699	–	2.043
21	1.678	2.074	–
22	1.638	1.494	–
23	1.260	1.262	–
24	2.398	2.583	–
25	1.796	1.217	–

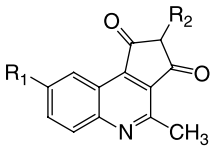
Obs – Observed biological activity, Cal – Calculated biological activity, Pred – Predicted biological activity, * - Test set compounds

$$\begin{aligned}\text{Log}(1/IC_{50}) = {} & 0.068\,(\pm 0.008)\,\text{CME} \\ & - 1.450\,(\pm 0.659)\,\text{HOMO} \\ & - 2.172\,(\pm 0.990)\,\text{LUMO} \\ & - 16.389\,(\pm 5.105)\end{aligned} \tag{6}$$

$$n = 20,\ r = 0.962,\ s = 0.398,$$
$$F = 66.29,\ r^2 = 0.926$$

The observed and estimated values of biological activities with residuals and predicted activities of test set of compounds are given in Table III. Observed and predicted biological activity for test set of compounds show that the prediction ability of this model is good. Leave 33% out crossvalidation was also performed to confirm the predictivity of the selected model

Table IV. The new designed series of compounds based on model 5



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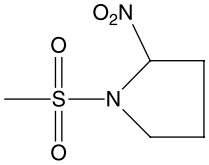
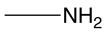
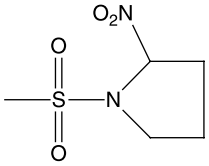
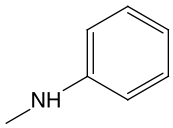
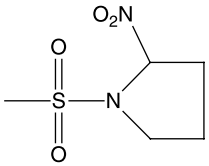
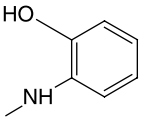
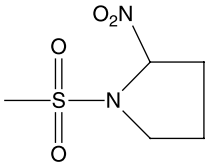
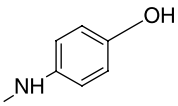
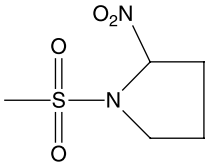
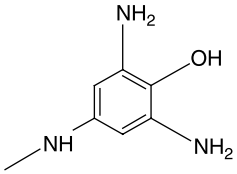
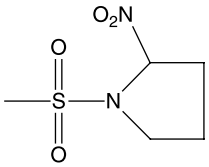
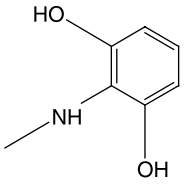
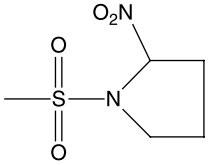
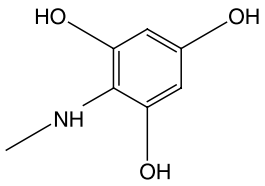
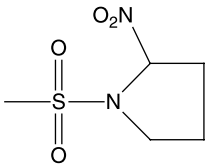
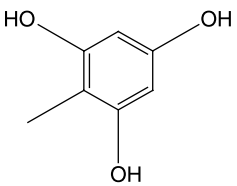
Comp. No.	R_1	R_2
1		
2		
3		
4		
5		
6		
7		
8		

Table IV – *continued*

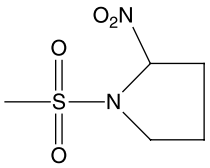
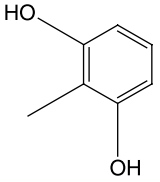
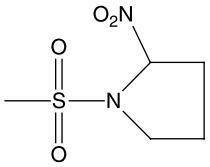
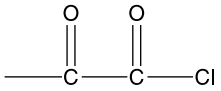
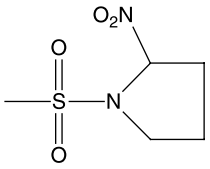
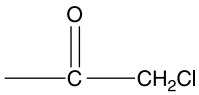
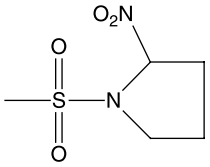
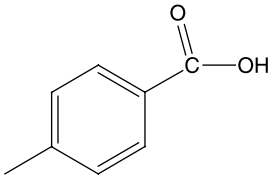
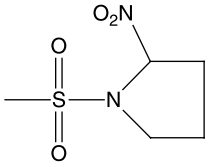
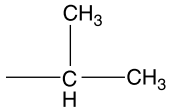
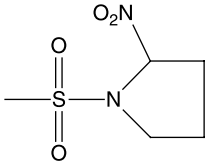
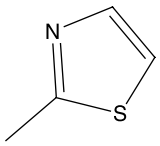
Comp. No.	R_1	R_2
9		
10		
11		
12		
13		
14		

Table V. The physico-chemical properties and predicted activities of the designed series of compounds.

Comp. No.	CME	HOMO	LUMO	Predicted activity (Log1/IC_{50})	Predicted IC_{50} (μM)
1	17.769	−9.722	−2.074	3.206	0.000622
2	32.674	−9.25	−2.226	3.907	0.000124
3	30.818	−9.111	−2.123	3.372	0.000425
4	32.319	−8.939	−2.22	3.482	0.00033
5	24.442	−8.584	−2.233	2.580	0.00263
6	33.644	−9.196	−2.151	3.721	0.00019
7	33.301	−9.151	−2.139	3.615	0.000243
8	26.28	−9.049	−2.265	3.351	0.000446
9	27.034	−9.288	−2.263	3.692	0.000203
10	21.976	−10.206	−2.494	5.076	0.000008
11	10.393	−10.161	−2.392	4.055	0.00008
12	2.689	−9.599	−2.358	2.793	0.001611
13	13.995	−10.087	−2.164	3.642	0.000228
14	8.962	−10.075	−2.237	3.489	0.000324

(Equation 7).

$$\begin{aligned}\text{Log}\,(1/IC_{50}) = {} & 0.062\,(\pm 0.009)\,\text{CME} \\ & - 1.092\,(\pm 0.906)\,\text{HOMO} \\ & - 2.486\,(\pm 1.245)\,\text{LUMO} \\ & - 13.669\,(\pm 6.933) \qquad (7)\end{aligned}$$

$q^2 = 0.879$, Average of absolute values of predicted residuals (Average Pres) = 0.187.

Equation (7), q^2 value indicates that the prediction ability of the selected model (equation 5) is good.

The selected model indicates that increase in conformational minimum energy would increase the biological activity of compound. The biological activity is increased when highest occupied molecular orbital energy and lowest unoccupied molecular orbital energy are decreased. Thus we conclude that the biological activity will be increased if substituents that bring about changes in the molecule as mentioned above are attached to it.

The presence of a 2-nitropyrrolidine-1-sulfonyl group at position R_1 and a substituted hydramine on position R_2 increases the biological activity in a greater amount than a substituted morpholine sulfonyl moiety and 2-substituted 1,3,5-trimethyl-1H-pyrazol-4yl group **(24)** which was shown to be a highly active compound in the reported series [19].

The predicted activities of newly designed series (Table V) of compounds show that they all have predicted activities ranging from $IC_{50} = 0.000008$–$0.00263\ \mu M$ whereas the reported series of 1,3-dioxo-4-methyl-2, 3-dihydro-1H-pyrrolo [3,4-c] quinolines [19] has most active compound with $IC_{50} = 0.004\ \mu M$.

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