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QSAR study for the prediction of Half Maximal Inhibitory Concentration of Compounds structurally similar to Glycerol

[Gliserole Yapısal Olarak Benzeyen Bileşiklerin Yarı Maksimal İnhibisyon Konsantrasyonlarının QSAR Çalışması İle Tahmini]*

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ABSTRACT

Aim: To develop Quantitative structure-activity relationship (QSAR) models for biological activity of half maximal inhibitory concentration for structurally similar compounds to GLYCEROL as inhibitors for Parkinson's disease causing targets.

Introduction: QSAR is the procedure by which chemical structure is quantitatively associated with a well defined process, such as biological activity or chemical reactivity. Parkinson's disease is a degenerative disorder of the central nervous system that frequently damage the sufferer's motor skills and speech. Application of glycerin poultice to the flexor digitorum profundus in the middle phalanx of the little finger improves motor disturbance in Parkinson Disease.

Methods: Quantitative structure activity relationship (QSAR) study has been developed for compounds structurally similar to GLYCEROL as inhibitors for Parkinson's disease causing targets using Stepwise (multi-parametric) Linear Regression.

Results: QSAR models for biological activity of half maximal inhibitory concentration were created with 100 training compounds, 52 test compounds and 15 different descriptors. The predictive capability of the QSAR models were evaluated by r^2 , $q^2_{LMO(TestSet)}$, $q^2_{LOO(TestSet)}$, $q^2_{BOOT(TestSet)}$. The various external validation shows that, $q^2_{LMO(TestSet)}$, $q^2_{LOO(TestSet)}$ and $q^2_{BOOT(TestSet)}$ are 0.905793936, 0.7530978 and 0.884057051 respectively.

Conclusion: The above results demonstrate the high robustness and real predictive power of IC50 model. (LMO-Leave many out, LOO-Leave one out, BOOT- bootstrapping)

Key Words: Parkinson's disease, glycerol like compound, linear regression, QSAR.

ÖZET

Amaç: Parkinson hastalığına sebep olan hedeflerin inhibitörü olarak Gliserole yapısal benzerlik gösteren bileşiklerin biyolojik aktivitesi için yarı maksimum inhibisyon konsantrasyonlarının kantitatif yapı-aktivite ilişkisi ile modellenmesi.

Giris: Kantitatif yapı-aktivite ilişkisi kimyasal yapının kantitatif olarak biyolojik aktivite veya kimyasal reaktivite gibi iyi tanımlanmmiş bir proses ile ilişkilendirilmesidir. Parkinson hastalığı kişinin motor hareketleri ile konuşmasını etkileyen dejeneratif bir merkezi sinir sistem hastalığıdır. Parkinson hastalığında küçük parmağın orta kemiği fleksor digitorum profundusa uygulanan kıvamlı gliserin motor bozuklukları iyleştirmektedir.

Metod: Parkinson hastalığına sebep olan hedeflerin inhibitörü olarak gliserole yapısal benzerlik gösteren bileşikler için kademeli (çok parametreli) lineer regresyon analizinin kullanıldığı kantitatif yapı aktivite ilişkisi QSAR) çalışması geliştirildi.

Sonuç: 100 alıştırma bileşiği, 52 test bileşiği ve 12 farklı tanımlayıcı ile yarı maksimal inhibisyon konsantrasyonu QSAR modeli geliştirildi. Kantitatif yapı-aktivite ilişkisi modellerinin öngörü kapasiteleri r^2, $q^2_{LMO(TestSet)}$, $q^2_{LOO(TestSet)}$, $q^2_{BOOT(TestSet)}$ ile değerlendirilmiştir. Farklı dış validasyonlar sırasıyla $q^2_{LMO(TestSet)} = 0.905793936$, $q^2_{LOO(TestSet)} = 0.7530978$ and $q^2_{BOOT(TestSet)} = 0.884057051$ değerleri vermektedir. (LMO- birçoğunu dışarıda bırak, LOO- birini dışarıda bırak, BOOT- başlatma)

Yorum: Bu sonuçlar IC50 modelinin yüksek kuvvet ve gerçek öngörü gücünü göstermektedir.

Anahtar Kelimeler: Parkinson hastalığı, gliserole benzer bileşik, lineer regresyon, QSAR

Introduction

Quantitative structure-activity relationship (QSAR) describes how a known biological activity can differ as a function of molecular descriptors derived from the chemical structure of a set of molecules. Many physiological activities of a molecule can be associated to their composition and structure. Molecular descriptors, which are numerical depictions of the molecular structures, are used for performing QSAR analysis. GLYCEROL (CID 753) represents the most important class of biologically active compounds as inhibitors (1) of Parkinson's disease causing targets. Parkinson's disease is a neurodegenerative disease and it is caused by degeneration of neurons (2) within the brain (3,4). The application of glycerin (5) poultice to the flexor digitorum profundus in the middle phalanx of the little finger (GFML) improves motor disturbance in Parkinson Disease (PD). Parkinson's disease (6) patients are treated domperidone (20 mg by mouth three times a day) to prevent nausea and apomorphine (1-3 mg by subcutaneous injection), apomorphine in glycerol (10-30 mg sublingually) or their usual levodopa regimen. Yang B et al. (7) examined the functional consequence of aquaporin (AQP) expression in mitochondria by measurement of water and glycerol permeabilities in mitochondrial membrane preparations from rat brain, liver, and kidney and from wild-type versus knock-out mice deficient in AQPs -1, -4, or -8. Osmotic water permeability, measured by stopped-flow light scattering, was similar in all mitochondrial preparations. The half maximal inhibitory concentration (IC50) is the concentration of an inhibitor that is necessary for 50-percent inhibition of an enzyme in vitro. In the literature, a number of QSAR (8-21) studies were developed. In the present study, QSAR Studies have been carried out for GLYCEROL and its structurally similar compounds with (>90%). We have developed the QSAR model for GLYCEROL and its structurally similar compounds with (>90%) using stepwise (multivariate) linear regression method by the Poly analyst (22) software.

Methods

Data Set

Training set of 100 compounds and test set of 52 compounds structurally similar to GLYCEROL which is available in Parkinson's disease causing targets collected from pubchem (23). Table 1 shows the different regression summary of IC50 model Training Set.

Molecular Descriptors

Theoretical molecular descriptors are calculated using QikProp (24) program (Schrodinger, 2008a). The following descriptors are procured into consideration for developing the model. 1. Molecular Weight (MW), 2. Hydrophobic Solvent Accessibile Surface Area (HAS), 3. Hydrophilic Solvent Accessibile Surface Area (HLSA), 4. Molecular Volume (MV), 5. Donor - Hydrogen Bonds (DHB), 6. Acceptor - Hydrogen Bonds (AHB) 7. log P for octanol/water (Log P), 8. log S for aqueous solubility (AS), 9. Half maximal inhibitory concentration (IC50), 10. Ionization Potential (IP), 11. Electron Affinity (EA), 12. Human Oral Absorption (HOA), 13. vdW Polar SA (PSA), 13. Ring Atom (RingA), 14. Skin Permuability (SP).

Stepwise (Multivariate) Linear Regression methods

PolyAnalyst (22) is used to develop the model using stepwise (multi-parametric) linear regression algorithm. It automatically determines the most influencing attributes by considering subsets of the attributes selected, and then includes the most significant attributes in the final analysis. The process of creating the regression model is incremental in polyanalyst. At first, only one-dimensional models are endeavored. The most accurate model is picked up. After that, all two-dimensional models produced by adding a new attribute to the first model are experimented. Again the best model is choosed and supplemented by a new attribute. All the considered regresion models must pass a test based on the value of Fisher statistics (25) of all their regression coefficients. If a term has the value of F-ratio less than a specified threshold, this term is removed from the model. Thus, the process of adding new terms stops either when all attributes are included in the model or when no new term can be added without violating the F-ratio criterion. The above process permits PolyAnalyst to find all influential attributes, but at the same time, it includes in the model only those attributes which do not correlate significantly with each other. If two powerful correlating attributes were tried in the same model, they both would have low values of F-ratio, and the second attribute is removed. Randomized testing is used in PolyAnalyst. While PolyAnalyst searches for the best regression model fitting the explored dataset, it solves the same problem also for several randomized datasets. Randomized datasets are prepared from the original dataset using

Table 1. The regression summary of IC50 model

Model	r^2	$q^2_{LMO(TestSet)}$	$q^2_{LOO(TestSet)}$	$q^2_{BOOT(TestSet)}$	Significance Index	Standard deviation	Standard error	Training Set(Min)	Training Set(Max)
IC50	0.8818	0.905793936	0.7530978	0.884057051	60.28	0.481	0.3439	-6.53	-1.054

the random permutation of the target attribute values for various records. Thus, all the values of independent and target variables remain the same, but the relation between independent and dependent attributes is broken. Only if an accuracy obtained for the real data is much higher than for any randomized data then the created regression model can be considered as reliable and significant. Otherwise, the system conclude that it do not have enough data to create a reliable model. The degree of certainty that the discovered model is not merely a result of a random statistic fluctuation in the data is expressed by Significance. Randomized testing was done by the poly analyst software which is not visible to the user. For example, in IC50 model, the influential attributes are HAS, MV, DHB, PSA, and RingA. The best equation is produced by the system based on correlation coefficient, square of correlation coefficient r^2. The square of correlation coefficient r^2 value is given in the bracket as follow: for IC50 (0.8818). The present calculated r^2 values are closer to 1.0, which is a clear evidence for the best fit regression. In addition to that, PolyAnalyst performs careful significance testing on the result, comparing its significance with other models generated. q^2 is calculated using the following formula. yi is the actual experimental activity,

$$q^2 = 1 - \sum (\dot{y} - y\hat{i})^2 / \sum (\dot{y} - y\bar{i})^2 \quad (1)$$

Where, $y\bar{i}$ the average actual experimental activity and $y\hat{i}$ the predicted activity of compound i computed by the predicted model. The robustness and internal predictivity of the models was evaluated by both leave-one-out cross validation ($q^2_{LOO(TestSet)}$) and leave-many-out cross validation ($q^2_{LMO(TestSet)}$). The in-house computer programs created in Java programming to do the following cross validation techniques: Leave-some-out, Leave-one-out and Bootstrapping. In Leave-many-out, the data set was splitted into the sequence of ten set of compounds (2,7,12,17,22,27,32,37,42,47) and the cross validation was performed. The average of q^2_{LMO} was calculated as follows: IC50(0.905793936). Leave-one-out cross validation is as follows:

1. Assign Total Compound n=52, Compound i=1
2. Leave Compound i
3. Calculate q^2_i
4. i=i+1
5. Repeat step 2 to 5 till i<=50
6. Find the average of $q^2_{i=1..n}$

$q^2_{LOO(TestSet)}$ for IC50 is 0.7530978. Bootstrap cross validation is computed as follows:

1. Generate n random number R_i within the range of 1 to 52 where i=1..n
2. i=1
3. Remove R_i Compounds
4. Calculate q^2_i
5. i=i+1
6. Repeat step 3 to 5 till i<=n
7. Find the average of $q^2_{i=1..n}$

The average of q^2_{BOOT} was calculated as follows: IC50(0.884057051).

Results and Discussion

Table 3 describes the observed and predicted value of IC50 model. The studied data set comprises a total of 100 training compounds and 52 test compounds structurally highly similar (>90% similarity) to that of GLYCEROL as inhibitors for Parkinson's disease causing proteins. Few different compounds in the training and test set compounds were not shown in the table 3, since the properties which we took for the compounds are same. The objective of this study is to propose a stepwise multivariate linear QSAR models for IC50 prediction applicable to the GLYCEROL structurally similar compounds. Several QSAR equations for training set of 100 compounds were obtained using different F-ratio value. From those equations, the best QSAR equation is generated with a selected F-ratio cut off value greater than 5, which resulted in five descriptors for IC50 model. The IC50 provides the good statistical measures such as correlation coefficient, standard deviation and standard error as 0.8818 , 0.481 and 0.3439 respectively (Table 1). The External test set data allows the verification of the proposed models by statistical validation like $q^2_{LMO(TestSet)}$, $q^2_{LOO(TestSet)}$ and $q^2_{BOOT(TestSet)}$. The statistical external validation was performed by checking the models with 52 compounds, which did not participate to the model development. The various external validation shows that, $q^2_{LMO(TestSet)}$, $q^2_{LOO(TestSet)}$ and $q^2_{BOOT(TestSet)}$ are 0.905793936, 0.7530978 and 0.884057051 respectively, which demonstrates the high robustness and real predictive power of IC50 model. Thus the following equations (2) has good performance in prediction of the test set compounds. Individual model descriptions are documented below.

IC50 model

The proposed model is based on the five descriptors HAS, MV, DHB, PSA and RingA (2). The Graph of experimental verses the predicted values for the present IC50 model is displayed in Fig. 1. The training compound in this study shows the range of RingA between 5 to 24, However, the range of HAS is between 56.905 and 385.661 with high F-ratio (>31). The regression coefficient of RingA is calculated to be positive as 0.241326. This shows the increase in the above properties supports towards inhibitory activity of IC50. Hence, one out of five selected descriptors influences the predicted IC50 values positively. On the other hand, HAS (-0.0138722), MV (-0.00737868), DHB (-0.223657) and PSA (-0.0183267) are correlated negatively to the affinity. Table 2 depicts the regression coefficient, mean and F-ratio of various parameter which were involved to build the QSAR model of IC50. Table 1 describes the q2 LMO (Test Set), q2 LOO (Test Set) and q2 BOOT (Test Set) values of IC50

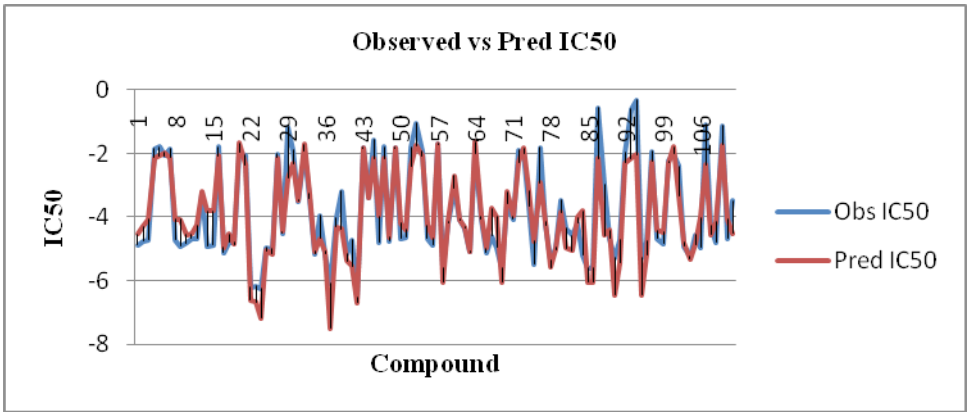

Fig. 1 Observed vs Predicted IC50 for Training and Test Set

Table 2. Training Set Parameter of IC50 Model

name	coef.	std dev.	F-Ratio
HAS	-0.01387	0.002476	31.38
MV	-0.007379	0.002305	10.25
DHB	-0.2237	0.06972	10.29
PSA	-0.01833	0.006969	6.915
RingA	0.2413	0.02916	68.5

Table 3. Observed vs Predicted Values of IC50 Model

Compound No	Obs IC50	Pred IC50
1	-4.867	-4.53474
2	-4.744	-4.29558
3	-4.725	-4.06627
4	-1.856	-2.13912
6	-1.783	-2.08346
7	-2.066	-1.97602
9	-1.856	-2.13912
11	-4.725	-4.06627
12	-4.902	-4.06962
18	-4.81	-4.55048
19	-4.678	-4.53553
20	-4.654	-4.2478
22	-3.235	-3.19742
23	-4.905	-3.82121
24	-4.886	-3.8008
25	-1.783	-2.08346
29	-5.13	-4.9537
31	-4.797	-4.53293
32	-4.791	-4.86696
33	-1.971	-1.6845
34	-2.064	-2.37155
35	-6.218	-6.61679
36	-6.15	-6.67556
39	-6.239	-7.17395

Table 3. Continued

40	-4.938	-5.06073
41	-4.977	-5.17121
45	-2.015	-2.14015
46	-4.497	-4.46473
47	-1.146	-2.77995
48	-1.897	-2.31328
49	-3.512	-3.47582
50	-1.942	-1.71904
54	-3.422	-3.27169
55	-5.143	-5.08071
56	-3.959	-4.67523
58	-5.143	-5.08071
62	-6.08	-7.50303
63	-4.004	-4.31691
64	-3.163	-4.37223
65	-5.149	-5.3764
66	-4.711	-5.5371
67	-6.53	-6.6937
68	-1.79	-1.82636
69	-3.384	-3.39485
71	-1.562	-2.1564
72	-4.804	-3.97716
73	-1.786	-2.16315
74	-4.746	-4.63528
75	-1.79	-1.82636
77	-4.688	-4.18984
79	-4.617	-4.39002
80	-1.794	-2.41488
81	-1.054	-1.76084
82	-1.912	-2.0946
83	-4.654	-4.24785
84	-4.857	-4.65984

Compound No	Obs IC50	Pred IC50
86	-1.702	-1.70036
87	-5.593	-6.05363
88	-4.202	-4.12997
89	-3.112	-2.70691
90	-4.071	-4.08495
91	-4.33	-4.30835
93	-5.062	-5.10822
94	-2.002	-1.6337
95	-4.071	-3.97323
97	-5.098	-4.98992
99	-4.589	-3.74346
100	-4.949	-3.98564
101*	-5.593	-6.05363
102*	-3.568	-3.19803
103*	-4.071	-3.97323
104*	-1.898	-2.28611
105*	-2.009	-1.84498
106*	-3.639	-3.17731
107*	-5.466	-4.76074
108*	-1.819	-2.93461
109*	-4.248	-4.14992
110*	-5.371	-5.58921
111*	-4.939	-5.03043
112*	-3.446	-3.84072
113*	-4.339	-4.97404
114*	-4.569	-5.06317
115*	-4.202	-4.0182
116*	-5.211	-3.8147
117*	-5.593	-6.05363
118*	-5.608	-6.05858
119*	-0.565	-2.17352
120*	-2.983	-4.57745
122*	-4.676	-4.4079
123*	-5.286	-6.4404
124*	-4.695	-5.45353
126*	-1.968	-2.30136
127*	-0.59	-2.16566
129*	-0.313	-2.0339
132*	-5.286	-6.4404
135*	-4.742	-5.18867
136*	-1.914	-2.25746
137*	-4.676	-4.4079
138*	-4.844	-4.47727
139*	-2.227	-2.30282
140*	-2.021	-1.79901
141*	-2.391	-3.33397
142*	-4.922	-4.78986
143*	-5.224	-5.31473
144*	-4.547	-4.84993
145*	-4.949	-4.00328
146*	-1.096	-2.37679
147*	-4.265	-4.55958
148*	-4.774	-4.16002
150*	-1.124	-1.74039
151*	-4.665	-4.07703
152*	-3.478	-4.52331

*Test Set

model. Since the values are greater than 5, The QSAR model may be considered.

Prediction rule:

IC50 = -0.0138722*HAS -0.00737868*MV -0.223657*DHB -0.0183267*PSA +0.241326*RingA (2)

Discussion

The proposed model IC50 (2), which are having positive values in the regression coefficient point out that the designated descriptors supplies positively to the value of IC50 (2), In other words, negative values indicate that the greater the value of the descriptors the lower value of IC50 (2). In IC50 Model, raising the RingA boost the IC50 values. Amplifying HAS, MV, DHB and PSA will dwindle the IC50 values. In IC50 model, the presence of molecular descriptors with positive coefficient in IC50 model is manifested in the compounds 104 and 105. The occurrence of molecular descriptor with negative coefficient at PSA, MV, HAS increases, the IC50 of drug compounds decreases. The presence of molecular descriptors with negative coefficient at PSA, MV and HAS increases, the IC50 of drug component decreases; this is evident in the compounds 102 and 103. In IC50 model, the presence of molecular descriptors with positive at RingA increases, the IC50 of drug component decreases; this is apparent in the compounds 104 and 105. Stepwise multivariate linear regression analysis provides constructive equation (2) that can be used to predict the IC50 of compounds based upon HAS, MV, DHB, PSA and RingA parameters. This procedure allows us to carry out a precise and reasonably fast method for fortitude of IC50 of GLYCEROL and its structurally similar compounds with (>90%) and also it predicts the IC50 values with sufficient accuracy.

Conclusion

In this study it was possible to obtain a stepwise multivariate linear regression QSAR model of IC50 for a set of one hundred compounds which are 90% structurally similar to GLYCEROL as inhibitors of Parkinson's disease causing targets. The training compound in this study shows the range of RingA between 5 to 24, However, the range of HAS is between 56.905 and 385.661 with high F-ratio (>31). IC50 model is IC50 = -0.0138722*HAS -0.00737868*MV -0.223657*DHB -0.0183267*PSA +0.241326*RingA. The various external validation shows that, $q^2_{LMO(TestSet)}$, $q^2_{LOO(TestSet)}$ and $q^2_{BOOT(TestSet)}$ are 0.905793936, 0.7530978 and 0.884057051 respectively, The LMO, LOO and BOOT cross validation techniques shows that the model is significant, robust and has good predictability. IC50 model is determined by HAS, MV, DHB, PSA and RingA. The most important parameter by considering the regression coefficients of IC50 model are as follows: RingA and HAS. In IC50 Model, raising the RingA boost the IC50 values. Amplifying HAS, MV, DHB and PSA will dwindle the IC50 values. It afforded a theory direction to synthesize some compounds with high activities. IC50 model is showing minimum deviation between observed and predicted values and also having good internal and external predictive power.

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