American Journal of Pharmacological Sciences, 2013, Vol. 1, No. 5, 80-83
Available online at http://pubs.sciepub.com/ajps/1/5/2

DOI:10.12691/ajps-1-5-2

QSAR Study of Methionine Aminopeptidase Inhibitors as Anti-cancer Agents Using MLR Approach

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Received October 16, 2013; Revised October 21, 2013; Accepted October 22, 2013

Abstract Here Benzimidazole analogues have been used to correlate the inhibition activity with the Eccentric Connectivity index (ECI), Fragment Complexity (FC) and McGowan Volumes (MG) descriptors for studying the quantitative structure activity relationship (QSAR) against methionine aminopeptidases for the development and evaluation of anti-cancer agents. Correlation may be an adequate predictive model which can help to provide guidance in designing and subsequently yielding greatly specific compounds that may have reduced side effects and improved pharmacological activities. We have used Multiple Linear Regression (MLR) for developing QSAR model. For the validation of the developed QSAR model, statistical analysis such as cross validation test (LOO-CV), quality factor, fischers test, root mean square deviation (RMSD), variance, standard deviation etc.; have been performed and all the tests validated this QSAR model with fraction of variance r^2 = 0.8906 and LOO-CV q^2 = 0.8904.

Keywords: *QSAR, Multiple Linear Regression, benzimidazole analogues, methionine aminopeptidases (MetAPs)*

Cite This Article: Ajeet, "QSAR Study of Methionine Aminopeptidase Inhibitors as Anti-cancer Agents Using MLR Approach." *American Journal of Pharmacological Sciences* 1, no. 5 (2013): 80-83. doi: 10.12691/ajps-1-5-2.

1. Introduction

The enzyme methionine aminopeptidase (MetAP) is a dinuclear metallo-protease that removes the N-terminal methionine from proteins (nascent proteins) [1,2]. MetAPs are conserved in all life forms ranging from bacteria to humans. MetAP1 and MetAP2 are two classes of MetAPs, which differ in the presence of an internal polypeptide insertion present within the catalytic domain of MetAP2 [3]. Now a day, the target protein for the evaluation and development of anti-cancer drugs is methionine aminopeptidase which highly attract scientists as it has critical role in protein degradation, tissue repair and the enzyme plays a key role in angiogenesis.

In the present study, we developed a QSAR model on a series of benzimidazole analogues with respect to their IC_{50}. The QSAR studies are the tools with the predictive possibilities for understanding the drug design process in terms of their chemical-pharmacological activity interaction, along with it is also used in toxicology and pesticide research. QSAR studies can focus on mechanism of action of ligands with human, bacteria, virus, membranes, enzymes etc. It can also be used for the evaluation of the metabolism, absorption, distribution and excretion phenomena. The QSAR methodology comprises of computationally derived descriptors to correlate with pharmacological activities. These descriptors are principally of four types such as electronic, stearic, hydrophobic and topological indices [4]. The descriptors used for developing the QSAR model are Eccentric Connectivity index (ECI) [5], Fragment Complexity (FC) [6] and McGowan Volumes (MG) [7].

2. Materials and Method

All the bioactivity values and information about 2D structure of benzimidazole analogues were taken from literature [8]. IC_{50} is a variable that comprises the bioactivity parameter for the QSAR model. In order to calculate the 2D molecular descriptors, PaDEL descriptor software [9-17], which incorporate CDK library for descriptor calculation has been used after optimitizing the benzimidazole analogues. For the development of QSAR model, Multiple Linear Regression [4,9-17] has been employed and equation was validated through statistics.

2.1. Modeling Parameters and Structure Optimization

The 2D structure construction, energy minimization and geometry optimization of the selected benzimidazole derivatives were carried out by using ChemDraw Ultra 7.0 and Chem3D Pro 7.0. The energy minimization was carried out to minimum RMS Gradient of 0.1, with step interval of 2.0 fs and frame interval of 10 fs where fs stand for femtosecond which is a unit of time equal to 10^{-15} of a second.

2.2. Statistical Parameters

2.2.1. Fraction of Variance (r^2)

The value of fraction of variance may vary between 0 (means model without explanatory power) and 1 (means perfect model). QSAR model having $r^2 > 0.6$ will only be considered for validation [4].

2.2.2. Cross-Validation Test (q^2)

A QSAR model must have $q^2 > 0.5$ for the predictive ability [4].

Standard deviation (s): The smaller s value is always required for the predictive QSAR model.

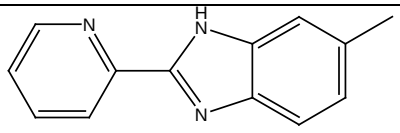
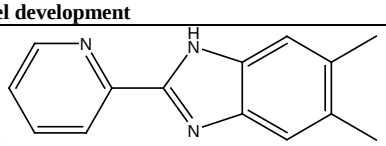
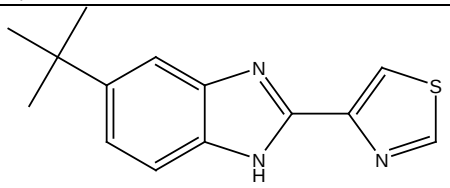
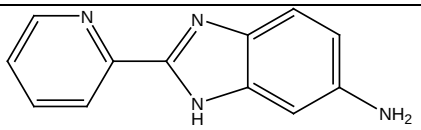
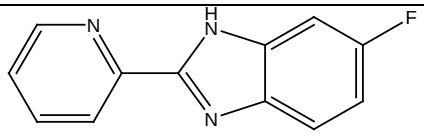
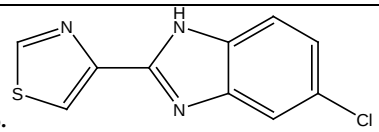
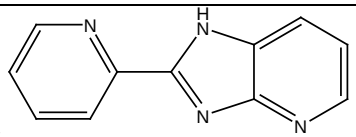
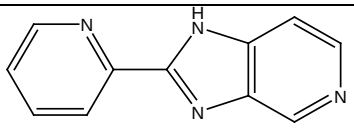
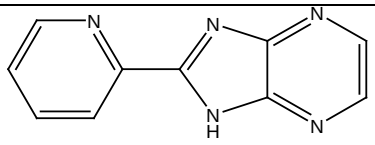
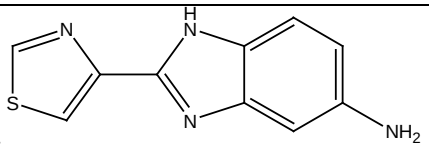
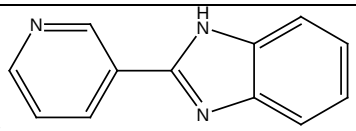
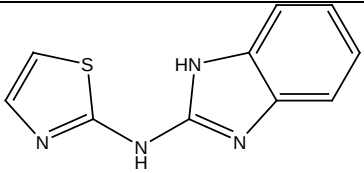
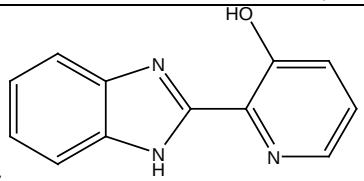
2.2.3. r^2-$q^2 < 0.3$

The difference between r^2 and q^2 should never be exceeding by 0.3. A large difference suggests the following: presence of outliers, over-fitted model, and presence of irrelevant variables in data [4].

Table 1. Descriptors used to derive QSAR equation along with bioactivities

SN.	Training set	IC_{50}			Descriptors used		
		Obs.	Pred.	Diff.	ECI	FC	MG
1	5-Methyl-2-pyridin-2-yl-1(3)H-benzoimidazole	2.086	2.348	-0.262	208	466.04	1.537
2	5,6-Dimethyl-2-pyridin-2-yl-1H-benzoimidazole	2.433	1.856	0.577	261	752.03	1.753
3	5-tert-Butyl-2-thiazol-4-yl-1H-benzimidazole	3.906	4.08	-0.174	277	919.04	1.96
4	2-Pyridin-2-yl-3H-benzoimidazol-5-ylamine	0.967	1.269	-0.302	244	544.04	1.571
5	6-Fluoro-2-pyridin-2-yl-1H-benzoimidazole	1.511	1.239	0.272	244	436.04	1.489
6	5-Chlor-2-thiazol-4-yl-1H-benzimidazol	5.153	5.038	0.115	208	319.05	1.519
7	2-Pyridin-2-yl-1H-imidazo[4,5-b] pyridine	0.105	0.312	-0.207	211	415.04	1.43
8	2-Pyridin-2-yl-1H-imidazo[4,5-c] pyridine	0.55	0.312	0.238	211	415.04	1.43
9	2-Pyridin-2-yl-1H-imidazo[4,5-b] pyrazine	0.24	0.187	0.053	211	366.05	1.389
10	5-Amino-2-thiazol-4-yl-1H- benzimidazole	3.39	2.267	1.123	208	415.05	1.496
11	2-Pyridin-3yl-1H-benzoimidazol	0.54	0.422	0.118	211	466.03	1.472
12	(1H-Benzimidazol-2-yl)- thiazol-2-yl-amin	1.343	2.186	-0.843	216	415.05	1.496
13	2-(1H-Benzoimidazol-2-yl)-pyridin-3-ol	0.777	1.479	-0.702	224	489.04	1.53

Table 2. Chemical Structures used for model development

1. 	**2.** 
3. 	**4.** 
5. 	**6.** 
7. 	**8.** 
9. 	**10.** 
11. 	**12.** 
13. 	

2.2.4. Quality Factor (Q)

Quality factor is calculated by equation Q=r/s where r is variance and s is standard deviation. Over fitting and chance correlation, due to excess number of descriptors, can be detected by Q value. Positive value for this QSAR model suggests its high predictive power and lack of over fitting.[4]

2.2.5. Fischer Statistics (F)

The F value of QSAR model was compared with their literature value at 95% level.

2.3. Model Validation

The QSAR model validation was carried with statistical analysis.

3. Results and Discussion

From the data in Table 1, QSAR equation has been developed. The chemical structures of data set are given in Table 2.

$$\text{Derived model-IC}_{50} = (-30.27919) - 0.0103899(\text{ECI}) - 0.0219303(\text{FC}) + 29.27613(\text{MG}) \quad (1)$$

3.1. Validation of QSAR Model

A quantitative assessment of model robustness has been performed through model validation. All the statistical results of model validation have been given in Table 3.

Table 3. Results of statistical validation

n/p (>=4)	r^2	q^2	$r^2 - q^2 < 0.3$	s	Q	RMSD	Variance	F
4.33	0.8906	0.8904	0.0002	1.48	0.63	0.1374	0.3549	24.39

n= no. of molecules taken for modeling, p= no. of descriptors used, s= standard deviation, Q=quality factor.

The QSAR model has been developed with a data set of 13 molecules, with n/p ratio of 4.33, fraction of variation of 0.8906 which represent an accuracy of 89%, leave one out cross validation with 0.8904, r^2Adj = 0.8541, quality factor value Q = 0.63 and fishers F value of 24.39.

According to the developed QSAR model, the benzimidazole analogues must have negative ECI as well as FC values for enhanced inhibition activity. Moving towards the effects of the MG on the bioactivity of derivatives of benzimidazole analogues, the developed QSAR model suggest that a positive MG will definitely be favourable to the activity, as discussed by Verma and Hansch (2010) [4]. A comparison (multiple linear regression plots) of observed values and predicted values of IC_{50} for benzimidazole analogues used for development of QSAR equation is shown in Figure 1 and multiple linear graph is shown in Figure 2 for studying the comparative pattern of observed and predicted bioactivity, which is found to be very similar.

The developed QSAR model also suggests that the substitutions at the two fused rings of benzimidazole at various positions results in the improved activities or better bioactivity values. The suggested substitutions are -CH_3, -NH_2, isopropyl group, -OH, -Cl, -F at ortho-, meta- and para- positions. A deep interpretation of the derivatives along with the model interpretation also pretends to go for the two substitutions simultaneously at meta- and para- positions for the improved and potent bioactivity values.

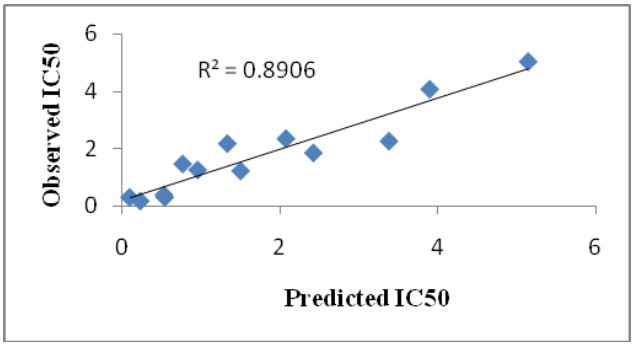


Figure 1. Multiple linear regression plot for QSAR study

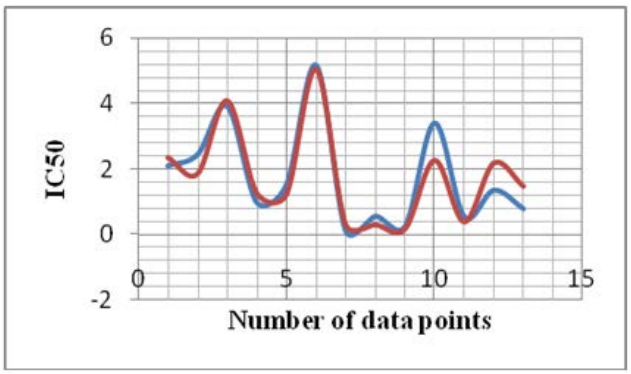


Figure 2. Multiple linear graph between Number of data points and bioactivities (Blue color series- observed bioactivity values, Magenta color series- predicted bioactivity values)

4. Conclusion

With deluged data of QSAR studies of benzimidazole analogues, for the development of anti-cancer drugs we could draw the following conclusions. On the basis of discussion given earlier we could conclude that benzimidazole analogues must have negative eccentric connectivity index as well as fragment complexity values for enhanced inhibition activity. Talking about the effects of the McGowan volume on the bioactivity of derivatives of benzimidazole analogues, the developed QSAR model suggests that a positive McGowan volume will definitely be favourable to the activity.

So for developing the novel benzimidazoles on the basis of ECI, FC and MG we have to select such groups or substituents which increase the McGowan volume of the novel molecules and simultaneously decrease the eccentric connectivity index and fragment complexity of the molecule and we can evaluate the novel molecules by calculating their IC_{50} values on the basis of the derived QSAR equation. The suggested substitutions are -CH_3, -NH_2, isopropyl group, -OH, -Cl, -F at ortho-, meta- and para- positions and two substitutions simultaneously at meta- and para- positions for the improved and potent bioactivity values.

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