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Research Article

QSAR study of 1- Aminobenzyl-1H-indazole-3-carboxamide Analogues For the treatment of Hepatitis C

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ABSTRACT:
In this work quantitative structure-activity relationship (QSAR) study has been done on 1- Aminobenzyl-1H-indazole-3-carboxamide Analogues as anti-Hepatitis C drugs. Genetic algorithm (GA),artificial neural network (ANN) were used to create QSAR models. The root-mean square errors of the training set and the test set for GA models using the jack-knife method, were 0.1403, 0.1305 and R^2 = 0.86. The results obtained from this work indicate that ANN and GA models are more effective than other statistical methods and exhibit reasonable prediction capabilities.

Keywords: antiviral agents, carbetamide's, hepatitis C, QSAR

INTRODUCTION:

Hepatitis C virus (HCV) is a small (+)-RNA virus classified in the genus Hepaciviru of the family Flaviviridae.[1] Nearly 3% of theglobal population (approximately 170 million) have been infectedwith HCV, while 3–4 million are newly infected eachyear. Untreated HCV infections can progress to liver fibrosis,steatosis, cirrhosis, and even hepatocellular carcinoma.[2]Sincethe discovery of the virus in 1989[3] much effort has been made to find efficient antiviral therapies.[4]Currently, the standard of care for patients with chronic hepatitis C is a combination of pegylated interferon alpha (PEG-IFN-a) and ribavirin.[5]However, this treatment regime is only effective for 40–60% ofpeople infected with HCV genotype-1, which accounts for the majority of infections in the US, Europe, and Asia.[6] Furthermore,the low success rate and high cost associated with this treatment restrict its usage. Viral protease and polymerase inhibitorsare promising agents currently under development. In2011, two NS3A/4A protease inhibitors (boceprevir and telaprevir) were approved by the US Food and Drug Administration (FDA) for the treatment of chronic hepatitis C infection. Incombination with PEG-IFN-a and ribavirin, both boceprevir and telaprevir produce a higher cure rate and shorter periodof treatment.HCV NS5B polymerase is another attractivetarget for antiviral therapy.[7] Because of the high mutation andreplication rates of HCV, [8]it is unlikely that a preventive vaccinewill become available in the coming years, and as such,more effective anti-HCV drugs are urgently needed.Quantitative structure activity relationships (QSARs) are the most important applications of chemometrics and provide useful information for the design of new compounds acting on a specific target. Computational chemical prediction of biological

activity based on QSAR substantially increases the potential for success and decreases the time spent and resources consumed.

Computational Details

Actual half-maximal inhibitory concentration (IC_{50}) values of all compounds were selected from literature. This set contained the effective concentration activities of 27 molecules. A set of nine compounds was randomly removed from the dataset to be used as the prediction set (PSET). The log ($1/IC_{50}$) of this set spanned the entire dataset. The remaining 27 compounds were utilized as the training set (TSET).

The structure and biological data of 27 molecules were obtained from literature. The structures were then fully optimized based on the *ab initio* method using the DFT level of theory (Fig.1a,1b,1c). Dragon (version 5.5) was employed to calculate the molecular descriptors. All calculations were performed using the Gaussian 09W programs series.

The independent variables were molecular descriptors and the dependent variables were the actual half-maximal inhibitory concentration (IC_{50}) values. More than 3150 theoretical descriptors were selected and calculated. For each compound in the training sets, a correlation equation was derived using the same descriptors. The equation was then used to predict log ($1/IC_{50}$) values for the compounds from the corresponding test sets.

RESULTS AND DISCUSSION

In this work, QSAR between oral bio availabilities of some drugs and their molecular structural descriptors were investigated by using linear and nonlinear techniques. After calculations of descriptors, the different methods were performed on the remaining descriptors to select the most important of them.

Statistical parameters of the different QSAR models are shown in Table 1. The descriptors selected using the methods described above were used to construct linear and nonlinear models using GA - Jack-nife (Fig.2) (Table 2,3). A value of 0 indicated that the corresponding feature was not selected and a value of 1 indicated that the feature was selected. Considering experimental error, the overall prediction for log ($1/IC_{50}$) was satisfactory. As can be seen in this table, there is correlation between some descriptors.

The results summarized above led to a study that targeted further optimization of the inhibitory activity by varyingaroyl substituents at the 3'-amino group. As anticipated, the compounds of this series showed improved bioactivity. In particular, the analogues with an aroyl group substituted in the para position (e.g., 13, 16, 19, 20 and 21) exhibited significantly increased activity compared with Unsubstituted derivative 2 (IC_{50}=0.125 mm).

The most significant descriptors selected are X4A, RDF120m, Mor20m, Mor24m, Mor19v, Mor20v andHATS1m. Average connectivity index, topological charge index, weighted by atomic masses and atomic van der waals volumes were important descriptors in this study.

CONCLUSION

In the present study ,GA, ANN, were used as nonlinear models to their calculated molecular descriptors. The calculated statistical parameters of these models revealed that ANN was better than others which mean that there are some nonlinear relations between selected molecular descriptors and their structures.ANN was successfully used to develop a QSAR model for 1- Aminobenzyl-1H-indazole-3-carboxamide Analogues that provided the best results in comparison with other methods. This attempt to correlate log ($1/IC_{50}$) with theoretically calculated molecular descriptors led to a relatively successful QSAR model that relates these derivatives.

Conflict of Interest: The authors have no conflict of interest.

ACKNOWLEDGMENTS

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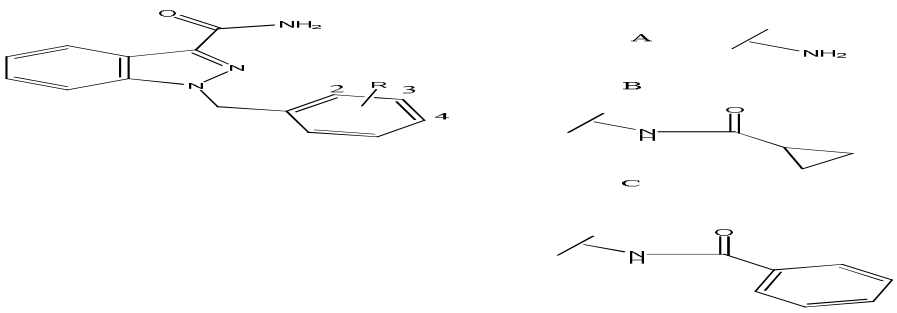

Fig.1a. Structures of molecules used for QSAR model building

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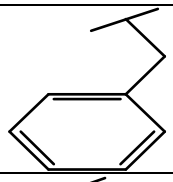
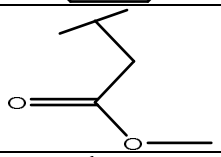
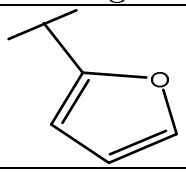
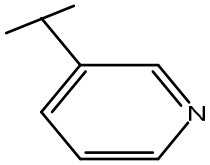
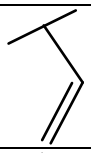
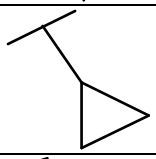
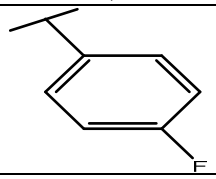
1	3A
2	3C
25	2A
26	2B
27	2C

COMP	**R1**	**R2**
3	H	
4	H	
5	H	

6	H	
7	H	
23	Ph	
24	CH3COOMe	

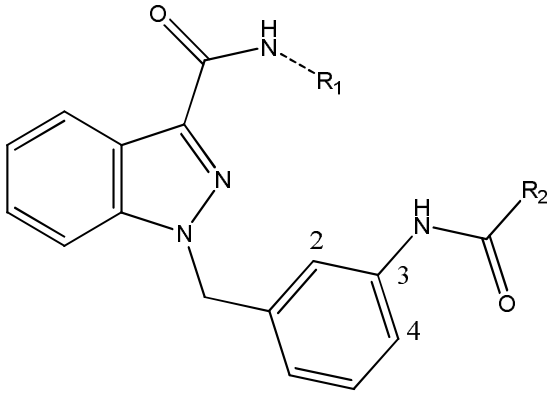
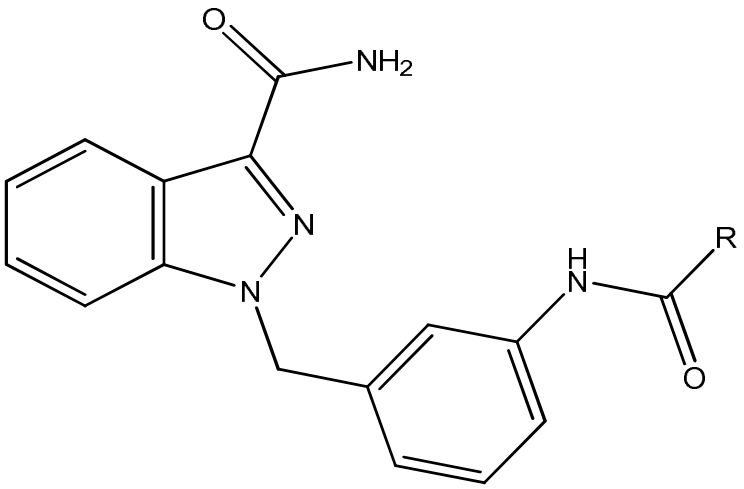
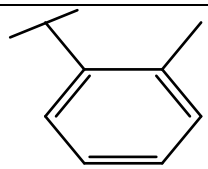
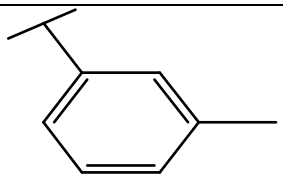
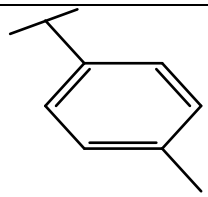
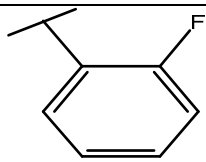
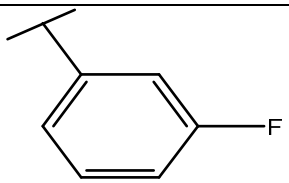
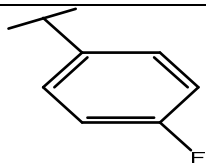
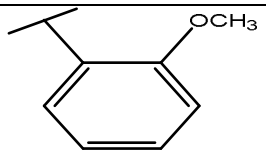
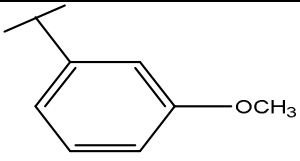


Fig.1b . Structures of molecules used for QSAR model building



COMP	R
8	
9	
10	
11	
12	
13	
14	
15	

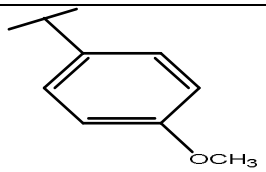
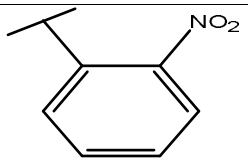
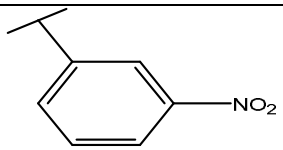
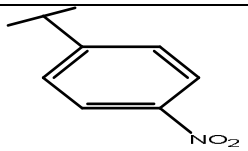
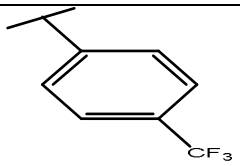
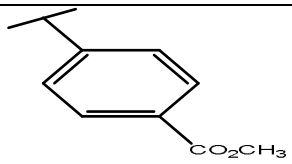
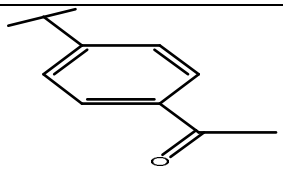
16	
17	
18	
19	
20	
21	
22	

Fig.1c. Structures of molecules used for QSAR model building

Table 1: The Statistical parameters of GA and ANN models**.**

Method	RMSE test	RMSE train	R	R square
GA-ANN	0.4901	0.2065	0.99941	-
Jack-nife	0.1403	0.1305	-	0.8610

Fig.2: Plot of output versus target data using GA method

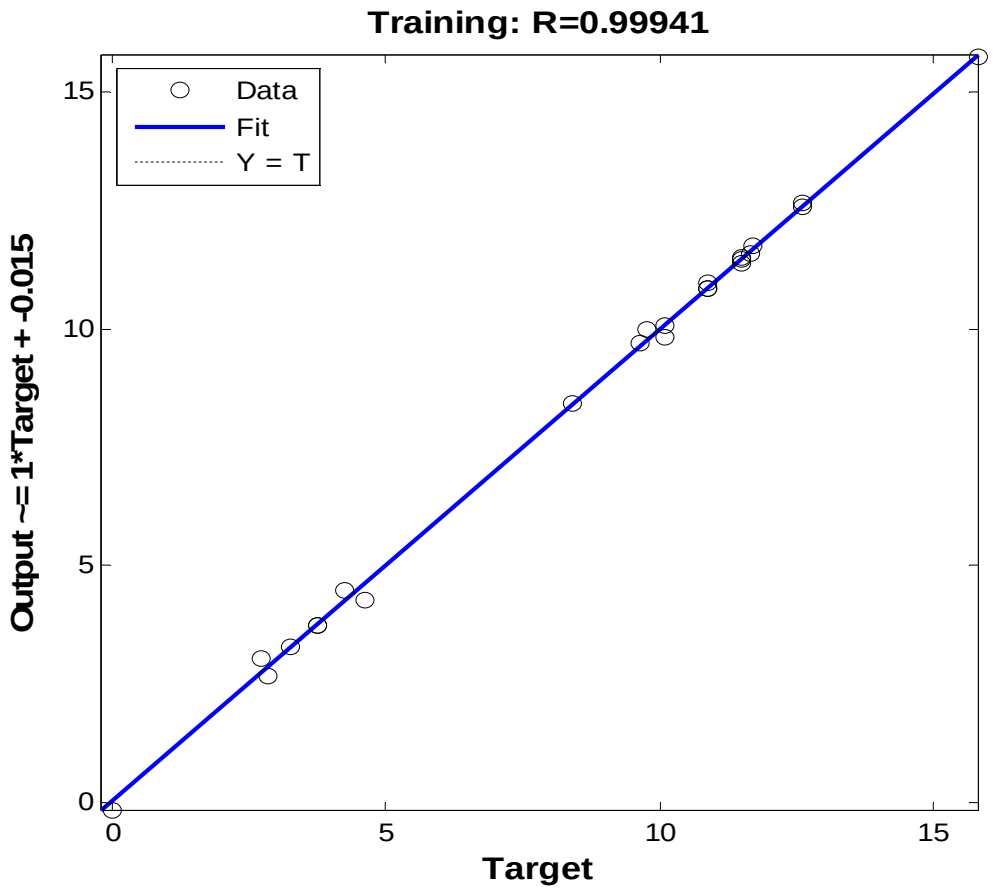


Table 2: The result of GA

Descriptor symbol	Descriptor group	Meaning
X4A	It is among the connectivity indices.	The symbol X4A corresponds to: Average connectivity index Chi-4.
RDF120m	It is among the RDF Descriptors.	The symbol RDF120m corresponds to: Radial Distribution Function -12.0 /weighted by atomic masses.
Mor20m	It is among the 3D-MoRSE Descriptors.	The Symbol Mor20m corresponds to: 3D-MoRSE-signal 20 /weighted by atomic masses.
Mor24m	It is among the 3D-MoRSE Descriptors.	The Symbol Mor24m corresponds to: 3D-MoRSE-signal 24 /weighted by atomic masses.
Mor19v	It is among the 3D-MoRSE Descriptors.	The Symbol Mor19v corresponds to: 3D-MoRSE-signal 19 /weighted by atomic van der waals.
Mor20v	It is among the 3D-MoRSE Descriptors.	The Symbol Mor19v corresponds to: 3D-MoRSE-signal 19 /weighted by atomic van der waals volumes.
HATS1m	It is among the GETAWAY Descriptors	The symbol HATS1m corresponds to: leverage – weighted autocorrelation of lag 1/ weighted by atomic masses.

Table 3: Volumes descriptors for GA

Molecule	**Descriptor symbol**						
NO.	X4A	RDF120m	Mor20m	Mor24m	Mor19v	Mor20v	HATS1m
1	.11	.00	.65	.25	.24	.80	.09
2	.12	2.57	1.02	.57	.62	1.28	.09
3	.12	.16	.98	.63	.56	1.18	.09
4	.12	1.16	.56	.33	.50	.75	.09
5	.11	2.66	.86	.62	.40	.91	.11
6	.12	1.96	1.02	.52	.37	1.13	.10
7	.11	.03	.61	.46	.44	.80	.09
8	.12	1.43	.49	.37	.93	.73	.07
9	.11	2.69	1.10	.48	.63	1.37	.09
10	.11	2.93	1.02	.55	.64	1.27	.08
11	.12	.67	1.19	.43	.54	1.38	.10
12	.11	1.67	1.05	.42	.42	1.23	.10
13	.11	3.04	1.20	.58	.43	1.35	.11
14	.11	.79	.73	.63	.86	.87	.08
15	.11	2.29	1.25	.46	.55	1.41	.09
16	.12	1.29	1.16	.78	.73	1.32	.09
17	.11	1.85	.50	.35	.50	.77	.10
18	.11	3.66	1.14	.45	.49	1.41	.12
19	.12	.92	.97	.79	.59	1.20	.14
20	.11	4.13	1.33	.59	.52	1.40	.13
21	.12	3.94	1.17	.72	.67	1.37	.10
22	.12	.89	2.14	.36	.79	1.41	.11
23	.11	2.16	1.16	.42	.58	1.40	.07
24	.11	2.34	1.05	.79	.61	1.29	.10
25	.11	.00	.61	.34	.31	.69	.10
26	.11	.00	.58	.49	.54	.66	.09
27	.11	.59	1.10	.39	.42	1.10	.09