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Modelling Vasorelaxant Activity of Some Drugs/Drug Candidates Using Artificial Neural Networks

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Abstract: Cardiovascular diseases are the most common health problems in developed and developing societies and the vasodilating agents are one of the medicinal groups to improve the life style of the patients suffering from the cardiovascular diseases. To study the quantitative structure-activity relationship of a number of pharmacological agents, the published data sets containing more than 10 vasodilating agents assessed on rat thoracic aorta, were collected from the literature. Different physico-chemical and structural descriptors of the compounds were computed using HyperChem® (12 descriptors) and Dragon software (1479 descriptors). The more suitable descriptors (Jhetv, Lop, SP20, RDF020u, RDF030m and R6m) were selected using a combination of linear regression and genetic algorithm methods. The artificial neural networks method was used for modelling -log of vasodilating activity (pEC50) using selected descriptors. The statistical analyses were performed using SPSS software and the average percentage deviation between calculated and observed values for predicted data points studied in this work was 15.0 (±18.8).

Key words: Vasorelaxant activity, Artificial neural networks, Modelling, Structural parameters

INTRODUCTION

In conventional drug discovery method usually many cycles of the structure-based design processes are employed to find a compound that binds to a specific target with a very high level of affinity. In this stage, the compound is still a long way far from being a drug on the clinical market. It still has to pass through animal and clinical trials, where factors that have not been considered, such as toxicity, bioavailability and resistance, often determine its fate. On average, it can take 15 years and 350-500 million dollars for a drug to reach the market (Berkowitz and Katzung, 2004). Therefore, any computational method(s) enabling scientists to predict a specific outcome would be invaluable and will accelerate and reduce the cost of the drug process. Different statistical approaches have been proposed to define models to identify factors that are predictive for the outcome of interest (Mecocci *et al*., 2002), such as biological activity.

Cardiovascular diseases are the main cause of death in most countries. Many scientific researches have been done to find the possible causes, mechanisms and risk factors of these diseases. One of the main problems in cardiovascular diseases is the involvement of vascular tissues through increasing tonicity or losing their capacity to relaxation. Therefore, vascular research has gained more attention and vasodilator agents would be beneficial in treating cardiovascular diseases.

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Artificial Neural Networks (ANNs) are computer algorithms meant to mimic the highly interactive processing of the human brain. Like the brain, ANNs recognize patterns, manage data and most significantly, learn from observations. These statistical-mathematical tools are able to determine the existence of a correlation between series of data and a particular outcome and when trained can predict output data once given the input (Mecocci *et al*., 2002).

Although in the past few years, ANNs have been used increasingly for the prediction of clinical outcomes (Sherriff and Ott, 2004; Jefferson *et al*., 1997), however they have not been employed in prediction of vasorelaxant effect. The aim of this study is to select suitable predictors and check the capability of ANNs for modelling the vasorelaxant activity of compounds. The accuracy of the predictions was evaluated using collected data sets from the literature.

MATERIALS AND METHODS

Experimental Data

Experimental vasorelaxant potencies of seven sets of vasodilator agents evaluated on rat thoracic aorta have been collected from the literature. The details of the collected data sets are shown in Table 1-8.

Computational Method

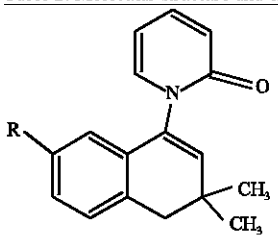
The 2D structure of each compound was drawn, converted to 3D using HyperChem 7.0 (HyperCube, 2002) and pre-minimized by Polak-Ribiere geometry optimization using MM^+ (HyperChem, 2002). The structures were found by MM^+, used as the starting point for re-minimization by Polak-Ribiere optimization using AM_1 semi-empirical and also quantum mechanical methods. The complete energy optimized molecules were used to compute molecular descriptors. From 1479 different 1D, 2D and 3D molecular descriptors calculated by Dragon software (Todeschini, 2003) including: constitutional descriptors, topological descriptors, molecular walk counts, BCUT descriptors, Galveze topological charge indices, 2D autocorrelations, charge descriptors, aromaticity indices, Randic molecular profiles, geometrical descriptors, RDF descriptors, 3D-MoRSE descriptors, WHIM descriptors, GETAWAY descriptors, functional groups, atom-centered fragments, empirical descriptors, properties descriptors with inter-correlation <0.99 were retained for further analyses. In order to select suitable descriptors (the minimum number of appropriate structural parameters for describing the biological activity) which will reduce the risk of chance correlations and over fitting to the training set, a combination of Genetic Algorithm (GA) based Partial Least Square (PLS) and Multivariate Linear Regression (MLR) were used. PLS is a well-known multivariate method, which gives a stepwise selection for a regression model and is preferable for large data sets. It extracts principle component-like latent variable from original independent variables (predictor variables) and dependent variables (response variables). GA is a simulation method based on ideas from Darwin's theory which is developed to mimic some of the processes observed in natural evolution, which is an efficient strategy to search for the global optimum solution. GA method has been successfully applied

Table 1: Summary of experimental data sets studied

Set No.	N	Serial No.	Chemical group	References
1	51	1-51	6-varied benzopyrans	Uhrig *et al.* (2002)
2	17	52-68	Furoxan	Ovchinnikov *et al.* (2003)
3	25	69-93	1,8-naphthyridine	Badawneh *et al.* (2001)
4	10	94-103	4-(cyclic amido)-2H-naphtho[1,2-b]pyrans	Chiou *et al.* (2002)
5	10	104-113	Others	Magnon *et al.* (1998)
6	11	114-124	Flavonoids	Calderone *et al.* (2004)
7	13	125-137	1,4-benzoxazines	Caliendo *et al.* (2002)

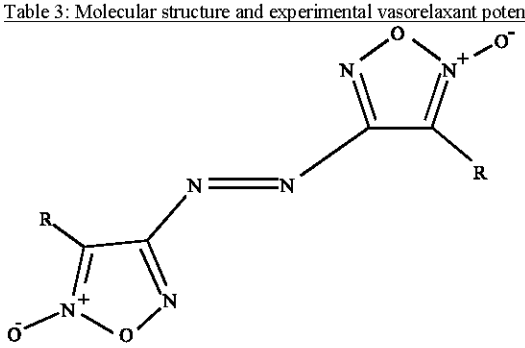
N: No. of data points

Table 2: Molecular structure and experimental vasorelaxant potency of 6-varied benzopyrans

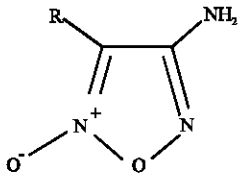


Serial No.	R	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
1	H	1.73	0.64	0.10	1.93	4.25	0.41	5.43
2	CO-CH_3	1.79	0.89	0.66	2.17	5.02	0.39	7.37
3	CO-C_2H_5	1.79	1.07	1.97	2.46	2.27	0.40	6.63
4	CO-C_6H_{11}	1.52	0.58	2.58	4.55	7.93	0.39	6.33
5	CO-Ph	1.56	0.58	5.05	2.28	7.75	0.39	6.61
6	CO-pOH-Ph	1.80	0.89	0.72	3.29	5.87	0.46	6.65
7	CO-3-furyl	1.56	0.60	4.27	1.79	7.73	0.41	6.49
8	CO-3-thienyl	1.55	0.62	7.22	2.62	7.61	0.37	6.40
9	CO-pOCH_3-Ph	1.51	0.77	8.43	4.21	7.46	0.35	6.15
10	CO-pNO_2-Ph	1.51	0.79	8.50	2.50	2.98	0.35	6.20
11	CO-oF-Ph	1.56	0.62	5.16	2.25	5.24	0.35	7.08
12	CO-oNO_2-Ph	1.86	1.24	3.84	2.76	3.92	0.49	6.17
13	CO-oCH_3-Ph	1.59	0.62	5.32	2.70	5.48	0.32	6.83
14	CO-oCF_3-Ph	1.54	0.80	4.04	2.47	10.10	0.47	6.76
15	CHO	1.77	0.87	0.28	2.54	4.66	0.43	6.91
16	C(=NOH)-NH_2	1.75	1.07	2.02	3.50	6.54	0.39	5.99
17	CH=$C(CN)_2$	1.82	1.47	4.02	1.96	6.46	0.45	6.95
18	N-2,5-(CH_3)2-pyrrolyl	1.48	0.64	2.28	2.77	7.47	0.33	7.27
19	CO-o,o'-F-Ph	1.56	0.64	5.28	2.14	5.08	0.37	6.97
20	CN	1.79	0.87	0.58	1.68	4.51	0.45	7.67
21	Br	1.18	0.56	1.79	4.19	7.38	0.46	7.84
22	CF_3	1.27	0.53	4.48	4.23	6.14	0.37	7.61
23	Pyridyl	1.28	0.57	3.87	2.39	8.86	0.41	6.68
24	CS-NH_2	1.60	1.07	1.05	2.31	4.42	0.41	6.21
25	OCONH-Ph	1.25	0.57	6.68	3.21	5.16	0.36	5.30
26	OCH_2-Ph	1.23	0.56	4.63	3.95	8.80	0.39	4.73
27	OCO-Ph	1.59	1.07	1.89	4.25	2.27	0.48	5.20
28	OCO-CH_3	1.58	1.07	2.68	5.13	2.29	0.45	5.60
29	OCH_2-o,o'F-Ph	1.51	1.22	3.57	5.56	4.19	0.52	5.27
30	OCH_2-CO-Ph	1.28	1.32	1.37	11.63	3.40	0.33	5.05
31	OSO_3-	1.94	1.19	0.00	3.37	4.92	0.00	4.82
32	OSO_2F	1.60	1.07	2.68	5.08	2.81	0.42	7.95
33	OSO_2CF_3	1.60	1.07	1.82	2.27	8.16	0.51	6.53
34	OSO_2Ph	1.26	0.59	7.12	3.34	11.22	0.35	7.63
35	OSO_2CH_3	1.79	1.24	1.23	3.87	6.97	0.47	6.60
36	OSO_2NH_2	1.44	0.59	1.91	4.18	7.96	0.58	4.50
37	OSO_2Cl	1.83	0.90	0.74	1.74	5.42	0.49	7.09
38	OCH_2SO_2Ph	1.82	1.07	1.24	3.94	8.29	0.45	7.42
39	SO_2NH-C_2H_5	1.49	0.61	2.49	3.39	6.89	0.53	7.25
40	SO_2NH-CH_2-Ph	1.49	0.62	3.23	6.75	8.25	0.47	6.28
41	SO_2NH_2	1.78	1.23	3.99	3.50	6.75	0.44	7.16
42	SO_2N-$(CH_3)_2$	1.82	1.07	1.10	3.86	7.18	0.47	7.79
43	SO_2NH-Ph	1.64	0.62	3.46	2.30	7.11	0.46	8.51
44	SO_2N-$(CH_2CH_2)_2$-O	1.81	0.90	0.72	1.69	3.75	0.55	7.07
45	SO_2NH-$CH(CH_3)_2$	1.57	0.79	4.97	3.52	8.06	0.41	6.17
46	SO_2-NH-CH_3	1.73	0.68	0.12	2.14	2.04	0.45	7.75
47	SO_2-Ph	1.69	0.87	0.50	3.76	4.46	0.39	7.76
48	SO_2F	1.77	0.68	0.14	1.95	3.67	0.71	8.32
49	SO_2N_3	1.71	0.90	0.68	1.91	6.27	0.51	7.79
50	OH	1.58	0.55	3.46	3.01	6.12	0.38	5.44
51	OCH_3	1.54	0.60	4.02	2.55	8.22	0.39	6.65

Table 3: Molecular structure and experimental vasorelaxant potency of Furoxan



Serial No.	R	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
52	CH_3	1.36	0.75	3.16	1.64	2.83	0.24	6.82
53	C_6H_5	1.23	0.47	7.27	1.59	7.36	0.27	6.30
54	$CONH_2$	1.52	1.07	3.76	2.97	10.92	0.23	6.59
55	$CONHCH_3$	1.54	1.34	6.21	4.99	10.53	0.25	6.82
56	CONHnPr	1.54	1.81	12.90	4.76	10.78	0.31	7.38
57	CONHnBu	1.53	2.01	14.44	5.57	12.31	0.31	7.00
58	CONH-cyclohexyl	1.07	0.53	9.67	6.66	14.95	0.53	7.24
59	CO-piperidyl	1.10	0.55	7.67	5.57	9.06	0.54	6.40
60	$CONH(CH_2)_2OH$	1.52	1.81	11.06	7.58	12.04	0.41	6.59
61		1.98	2.11	0.73	2.88	1.89	0.66	7.66



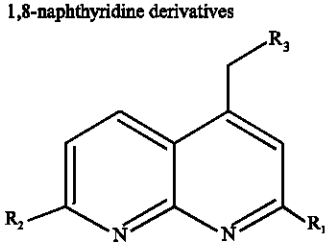
62	$CONH_2$	1.60	1.07	2.69	5.08	3.10	0.41	4.82
63	$CONHCH_3$	1.95	1.47	0.00	4.23	4.79	0.07	4.96
64	CONHnPr	1.89	1.95	0.46	4.28	4.76	0.14	5.23
65	CONHnBu	1.86	2.15	1.18	4.64	5.12	0.15	5.26
66	CONH-cyclohexyl	1.50	0.70	0.31	4.95	7.82	0.29	5.51
67	CO-piperidyl	1.56	0.73	0.05	4.76	6.10	0.28	4.10
68	$CONH(CH_2)_2OH$	1.85	1.95	0.36	5.33	4.75	0.17	5.11

to feature selection in QSAR analyses (Tang and Li, 2002). Moreover, an approach combining GA with PLS (GA-PLS) has been proposed for variable selection in QSAR studies (Daren, 2001). Here, we employed GA-PLS method of Leardi using MATLAB software (Demuth and Beale, 2000) to select the variables significantly contributing to the prediction of activity (Leardi and Lupianez, 1998; Leardi, 2000).

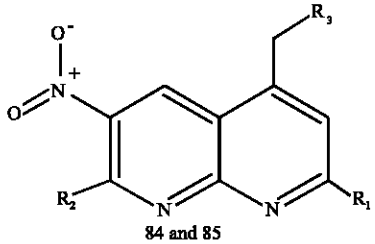
Before using GA-PLS method, the highly correlated descriptors were excluded and the remained (517 Dragon and 12 HyperChem descriptors) were used as input data to a combination of GA-PLS and stepwise multiple linear regression methods. More than 20 dragon descriptors selected using GA-PLS and 12 HyperChem descriptors were studied using stepwise multiple linear regression and cross correlation procedure in order to investigate their inter correlation. The descriptors showed higher correlation with experimental values and lower intercorrelation with each other have been selected as suitable predictors. The selected descriptors were: Jhetv (Balaban-type index from van-der Wals weighted distance matrix topological descriptors), Lop (Lopping centric index topological descriptors), SP20 (shape profile No. 20 Randic molecular profiles), RDF020u (Radial Distribution Function-2.0/unweighted RDF descriptors), RDF030m (Radial Distribution Function 2.5/weighted by atomic masses RDF descriptors) and R6m (R autocorrelation of lag 6/weighted by atomic masses GETAWAY descriptors). The numerical values of the selected descriptors are listed in Table 2-8.

Table 4: Molecular structure and experimental vasorelaxant potency of 1,8-naphthyridine derivatives

1,8-naphthyridine derivatives



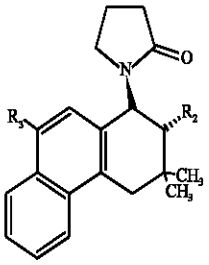
All except 84 and 85



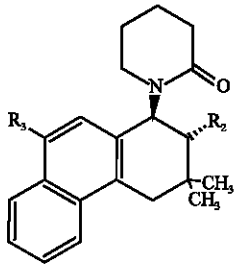
84 and 85

Serial No.	R1	R2	R3	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
69	CEP	CEP	NH_2	1.10	1.28	10.28	12.43	5.46	0.25	4.44
70	CEP	CEP	NHAc	1.14	1.38	15.19	13.50	8.37	0.22	3.02
71	CEP	OH	NH_2	1.28	1.20	0.63	10.13	3.39	0.35	3.13
72	FP	OH	NH_2	1.43	0.82	0.35	10.02	3.70	0.33	3.59
73	CEP	OH	NHAc	1.29	1.36	10.64	8.06	6.17	0.31	4.03
74	CEP	Cl	NHAc	1.30	1.36	9.76	8.32	6.92	0.39	3.73
75	PIP	CEP	NHAc	1.17	1.01	8.82	10.14	5.27	0.23	4.60
76	CEP	SH	NH_2	1.30	1.20	0.80	9.55	3.26	0.43	3.78
77	CEP	H	NH_2	1.25	1.17	8.61	8.28	2.46	0.21	4.68
78	CEP	OH	OH	1.28	1.20	0.75	9.05	3.42	0.37	3.53
79	CEP	Cl	Cl	1.37	1.20	9.67	9.09	4.09	0.62	3.10
80	CEP	OCH_3	OCH_3	1.33	0.61	5.59	6.91	4.71	0.45	5.05
81	CEP	H	NHAc	1.26	1.35	2.06	10.51	4.18	0.31	6.92
82	PIP	PIP	OH	1.33	0.38	2.99	7.71	6.38	0.28	4.52
83	CEP	PIP	OH	1.16	1.01	8.65	9.79	6.35	0.29	5.29
84	PIP	PIP	OH	1.36	0.70	4.36	8.76	5.93	0.32	5.45
85	CEP	PIP	OH	1.22	1.14	8.54	9.98	5.30	0.31	5.51
86	CEP	PIP	OCH_3	1.16	1.08	10.10	11.35	6.08	0.26	4.34
87	CEP	CEP	Cl	1.11	1.28	8.35	12.22	6.20	0.37	4.67
88	PIPZ	PIP	NH_2	1.33	0.38	3.81	11.07	5.20	0.24	4.95
89	PIPZ	H	NH_2	1.50	0.46	3.80	9.18	2.76	0.22	4.68
90	PIPZ	OCH_3	OCH_3	1.46	0.86	5.47	10.35	2.62	0.24	3.75
91	PIPZ	OCH_3	NH_2	1.51	0.76	3.73	10.24	2.66	0.25	4.15
92	PIPZ	PIP	OH	1.32	0.38	3.42	10.82	5.88	0.29	5.84
93	PIPZ	PIP	OCH_3	1.30	0.56	4.48	12.10	5.51	0.25	5.19

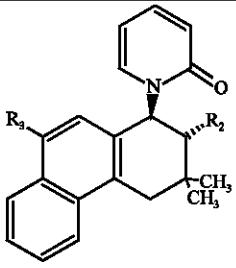
Table 5: Molecular structure and experimental vasorelaxant potency of 4-(cyclic amido)-2H-naphtho[1,2-b]pyrans



94, 95, 101, 103



96, 97



98, 99, 102

Serial No.	R2	R3	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
94	NO_2	OH	1.60	0.85	2.32	4.88	10.51	0.54	6.59
95	CN	OH	1.64	0.84	2.35	4.41	9.11	0.49	5.63
96	NO_2	OH	1.59	0.83	2.71	5.78	10.79	0.54	6.66
97	CN	OH	1.63	0.82	2.88	5.28	9.46	0.49	6.13
98	NO_2	OH	1.61	0.83	2.80	5.89	10.65	0.56	6.41
99	CN	OH	1.65	0.82	2.60	3.97	7.89	0.52	5.88
100	CN	Δ3,4	1.66	0.81	2.57	2.62	5.73	0.45	5.99
101	CN	Δ3,4	1.67	0.80	2.93	2.07	5.09	0.48	6.47
102	CN	H	1.62	0.81	2.29	3.20	5.71	0.45	5.40
103	---	---	1.74	0.91	0.64	4.36	8.93	0.46	7.19

Table 6: Molecular structure and experimental vasorelaxant potency of miscellaneous compounds

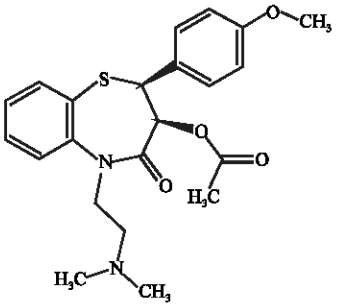
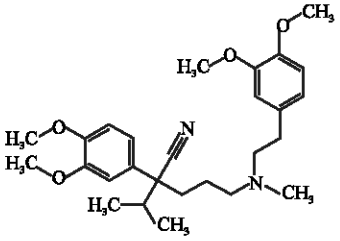
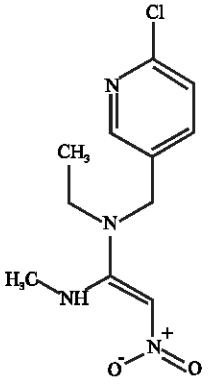
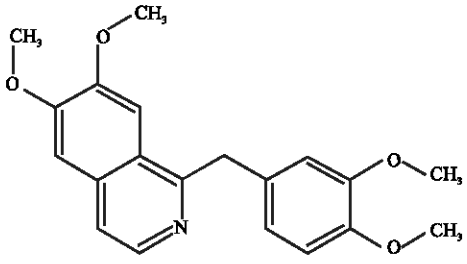
Serial No.	Brand name	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
104	 Diltiazem	1.69	1.41	4.29	8.63	10.58	0.46	6.97
105	 Verapamil	1.75	1.10	13.35	14.18	7.08	0.26	7.20
106	 Nitemdipoine	2.06	1.63	3.52	5.62	3.45	0.47	8.15
107	 Papaverine	1.66	1.03	5.98	10.70	2.71	0.30	6.39

Table 6: Continued

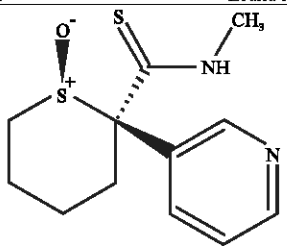
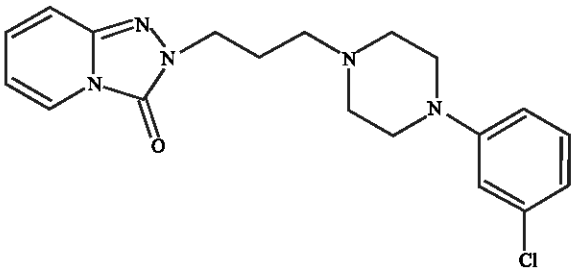
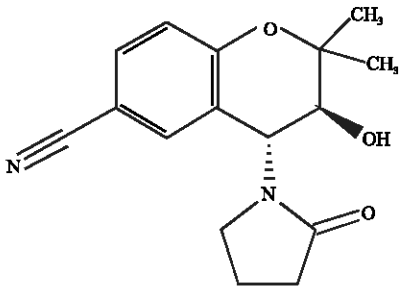
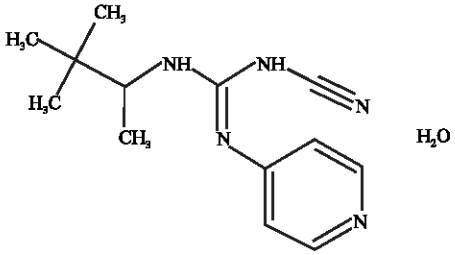
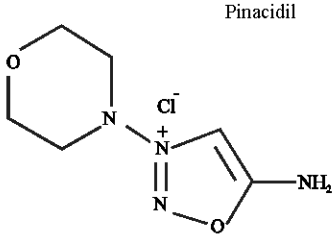
Serial No.		Brand name	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
108		Aprikalim	2.31	1.16	0.02	6.05	8.46	0.31	6.70
109		Bimakalim	2.03	0.87	0.86	2.31	4.40	0.43	7.81
110		Levcromakalim	1.85	0.91	0.68	2.36	6.71	0.46	6.98
111		Pinacidil	2.20	2.14	0.96	6.29	4.39	0.33	6.79
112		Linsidomine	1.22	0.60	0.03	7.22	2.52	0.13	7.06

Table 6: Continued

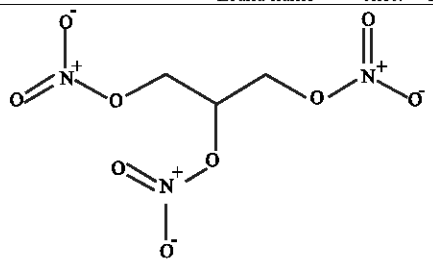
Serial No.	Brand name	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
								
113	Nitroglycerin	1.98	2.11	0.73	2.88	1.89	0.66	8.07

Table 7: Molecular structure and experimental vasorelaxant potency of flavonoid derivatives

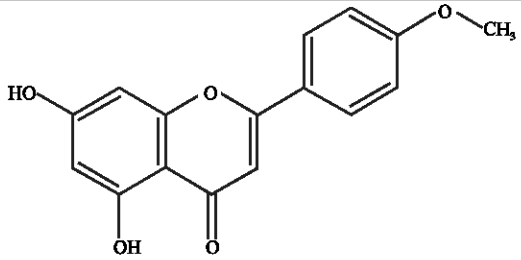
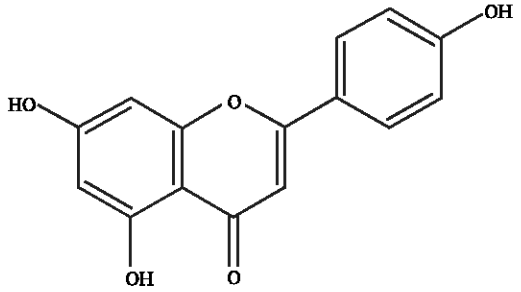
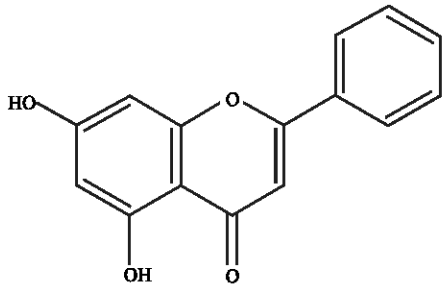
Serial No.	Brand name	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
								
114	Acacetin	1.65	0.87	5.63	5.69	3.65	0.19	4.99
								
115	Apigenin	1.72	0.68	4.35	4.09	3.62	0.27	5.02
								
116	Chrysin	1.75	0.64	2.27	3.05	3.63	0.26	4.80

Table 7: Continued

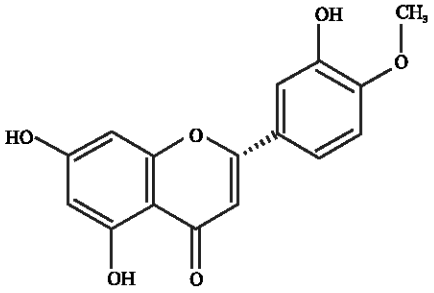
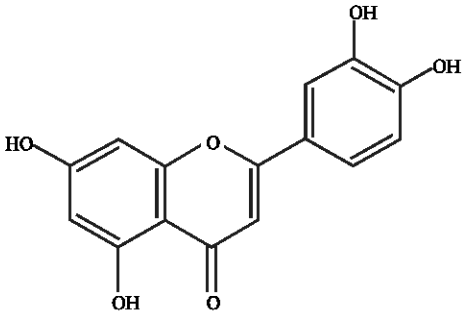
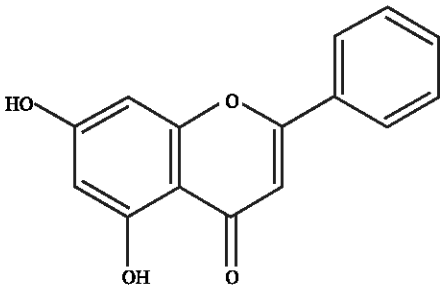
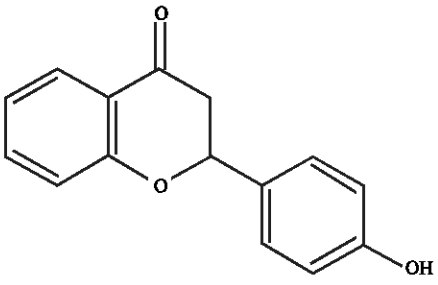
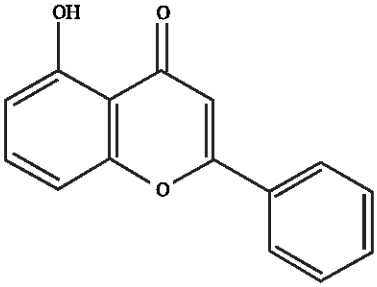
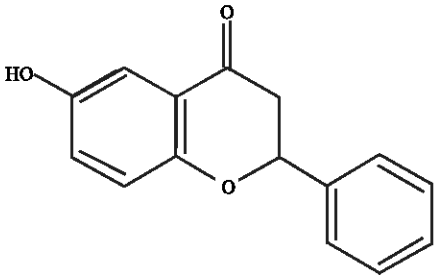
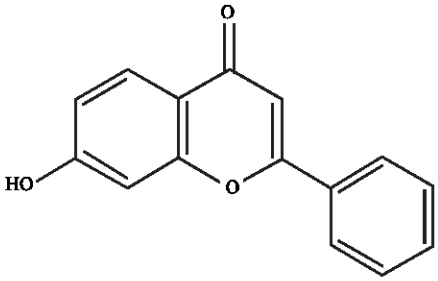
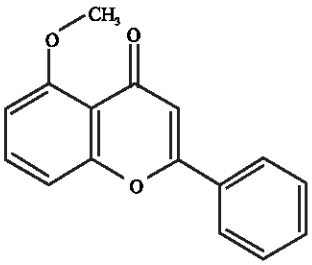
Serial No.	Brand name	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
117	 Hesperetin	1.59	0.89	5.72	6.06	3.47	0.25	4.86
118	 Luteolin	1.71	0.70	4.67	3.78	3.60	0.29	4.97
119	 Pinocembrin	1.68	0.64	2.29	3.84	3.27	0.25	4.80
120	 4'-hydroxyflavanone	1.59	0.58	3.35	2.39	1.45	0.21	4.76

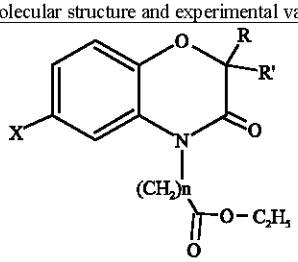
Table 7: Continued

Serial No.		Brand name	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
121		5-hydroxyflavone	1.75	0.58	1.86	2.85	3.68	0.21	4.41
122		6-hydroxyflavanone	1.66	0.79	2.67	3.21	4.58	0.21	4.43
123		7-hydroxyflavone	1.62	0.58	3.42	2.37	1.44	0.20	4.87
124		5-methoxyflavone	1.67	0.58	2.01	1.60	1.93	0.28	4.38

ANN Calculations

All the ANNs calculations were carried out using Matlab mathematical software (Demuth and Beale, 2000), with artificial neural network toolbox for windows running on a personal computer (Pentium III 640 MHz). The networks were generated by using the calculated molecular descriptors

Table 8: Molecular structure and experimental vasorelaxant potency of 1, 4-benzoxazines



Serial No.	X	n	R = R'	Jhetv	Lop	SP20	RDF020u	RDF030m	R6m	pEC50
125	4,5-dihydro-1,3-thiazole	2	H	1.45	1.56	2.29	5.99	5.20	0.37	4.46
126	Cl	2	CH_3	1.74	1.77	1.75	4.24	2.38	0.40	4.09
127	4,5-dihydro-1,3-thiazole	2	CH_3	1.52	1.58	3.27	4.83	6.28	0.33	4.11
128	Cl	3	H	1.59	1.98	1.98	5.43	2.11	0.41	4.15
129	NO_2	3	H	1.61	2.02	5.46	5.67	2.79	0.35	4.32
130	CN	3	H	1.64	2.03	5.11	5.36	2.27	0.29	4.20
131	4,5-dihydro-1,3-thiazole	3	H	1.41	1.71	4.13	6.43	6.24	0.36	4.49
132	H	3	CH_3	1.63	1.96	4.19	4.35	2.74	0.21	4.23
133	CH_3	3	CH_3	1.68	1.93	5.76	4.45	2.70	0.23	4.28
134	Cl	3	CH_3	1.68	1.93	6.20	4.02	2.79	0.36	4.57
135	NO_2	3	CH_3	1.70	1.96	7.42	4.52	2.80	0.28	4.14
136	CN	3	CH_3	1.73	1.99	8.13	5.17	3.69	0.28	4.70
137	4,5-dihydro-1,3-thiazole	3	CH_3	1.48	1.72	6.87	5.83	5.14	0.28	4.72

Table 9: The details of the experimental and predicted pEC50 of prediction set for all data sets, the individual relative deviation (IRD) and Average Relative Deviation (ARD) values

Serial No.	Set No.	Experimental	Predicted	IRD
1	1	5.43	6.07	11.7
4	1	6.33	6.27	0.9
7	1	6.49	6.85	5.5
10	1	6.20	6.24	0.6
13	1	6.83	6.32	7.4
16	1	5.99	6.77	13.0
19	1	6.97	6.43	7.7
22	1	7.61	5.73	24.7
26	1	4.73	6.15	30.1
29	1	5.27	6.16	16.9
32	1	7.95	5.66	28.9
35	1	6.60	7.00	6.1
38	1	7.42	7.14	3.8
41	1	7.16	7.07	1.3
44	1	7.07	6.86	3.0
47	1	7.76	5.94	23.4
50	1	5.44	6.27	15.3
53	2	6.30	6.09	3.3
56	2	7.38	6.55	11.2
59	2	6.40	6.37	0.4
61	2	7.66	6.90	9.9
63	2	4.96	5.10	2.9
66	2	5.51	5.80	5.3
70	3	3.02	4.71	56.0
73	3	4.03	5.11	26.8
76	3	3.78	4.96	31.3
79	3	3.10	6.31	103.6
82	3	4.52	5.14	13.7
85	3	5.51	4.93	10.5
88	3	4.95	4.62	6.6
91	3	4.15	4.36	5.1
95	4	5.63	6.89	22.3
98	4	6.41	6.96	8.5

Table 9: Continued

Serial No.	Set No.	Experimental	Predicted	IRD
101	4	6.47	6.75	4.4
106	5	8.15	6.96	14.6
109	5	7.81	7.09	9.3
112	5	7.06	2.91	58.8
114	6	4.99	5.06	1.4
117	6	4.86	5.17	6.3
120	6	4.76	4.25	10.8
123	6	4.87	4.28	12.0
127	7	4.11	5.37	30.6
130	7	4.20	4.01	4.5
133	7	4.28	4.20	1.9
136	7	4.70	4.91	4.4
			ARD	15.0

Table 10: The details of the experimental and predicted pEC50 of prediction set for 1 data set, the Individual Relative Deviation (IRD) and Average Relative Deviation (ARD) values

Serial No.	Set No.	Experimental	Predicted	IRD
1	1	5.43	6.48	19.4
4	1	6.33	6.71	6.0
7	1	6.49	6.57	1.2
10	1	6.20	6.76	9.0
13	1	6.83	6.68	2.2
16	1	5.99	6.50	8.5
19	1	6.97	6.64	4.7
22	1	7.61	6.61	13.1
25	1	5.30	6.62	24.9
28	1	5.60	6.54	16.7
31	1	4.82	6.18	28.2
34	1	7.63	6.86	10.1
37	1	7.09	6.64	6.3
40	1	6.28	6.73	7.2
43	1	8.51	6.64	21.9
46	1	7.75	6.62	14.5
49	1	7.79	6.81	12.6
			ARD	12.2

as inputs. Vasodilating potency (pEC50) on rat aorta was the output. A 3 layer network with sigmoidal transfer function in hidden and output layers was designed by using back propagation learning algorithm. The transfer function possesses minimum and maximum values of 0 and 1, respectively. The inputs and outputs were normalized between 0.1 and 0.9, which allows the network to slightly exceed the minimum and maximum values that were given in the original data file (Despagne and Massart, 1998). The Mean Square Error (MSE) was used to identify the training process of the network and computed using:

$$MSE = \frac{1}{N}\sum_{l=1}^{N}(y - \hat{y})^2$$

where, N denotes the number of experimental data employed in the training process of the network, and are target and output values.

Statistical Analysis

To test the accuracy of the trained network, the vasorelaxant activity data was randomly divided y into ŷ two subsets, namely training (92 compounds) and prediction (45 compounds). All data points

in training subset were fitted to the network and the back-calculated activities were compared with the corresponding experimental values and the Average Relative Deviation (ARD) was computed as an accuracy criterion by:

$$ARD = \frac{100}{N}\sum\left(\frac{|Calculated - Observed|}{Observed}\right)$$

where N is the number of data points. The ARD is comparable with experimental RSD value and by this it is possible to compare the calculation error with experimental error for repeated experiments.

The individual relative deviation (IRD) was computed and summarized in Table 9 and 10 using following equation:

$$IRD = 100\ \frac{|Calculated - Observed|}{Observed}.$$

RESULTS AND DISCUSSION

The features of the network i.e., number of epochs, learning rate, momentum, transfer function and number of neurons in the hidden layer were optimized and the selected number of epochs was found to be 10000. The training process was stopped manually when the Mean Square Errors (MSE) of the prediction set remained constant after successive iteration. Since there are several local minima where the model could arrive, the algorithm ran from different starting values for initial weights to find the optimum, but nearly the same results were obtained. The training function used here was TRAINGDM, iteration rate was 0.25 and other training parameters used in this work were default values.

As noted in statistical analysis section, all the experimental pEC50 data was divided into training and prediction prediction. The ANN was trained using training data set (N = 92) and then the pEC50 of the prediction set were predicted and showed in Table 9. The lowest IRD (0.4%) was observed for compound number 59 from furoxan derivatives and the highest IRD (103.6%) for compound number 79 from 1,8 naphthyridine derivatives. The ARD (±SD) for 45 predicted pEC50 values using the trained network was 15.0 (±18.8). From mechanisms of actions point of view, the predicted data possess various mechanism of actions which discussed in the literature. As examples, benzopyran derivatives bind to the potassium channel receptors and differences in pEC_{50} values are due to a variation of binding affinity, drug access to the receptor biophase (Lemoine *et al*., 1999) and preorientation of the drug in the way that it approaches the receptor (Uhrige *et al*., 2002). Other studies showed that for some furoxan derivatives NO• (free radical molecule nitric oxide or one of its bioequivalent forms) is involved in their activity (Ovchinnikov *et al*., 2003). For benzoxazine derivatives, Caliendo *et al*. (2002) hypothesized that hypothesized that different types of potassium channels are involved in their vasorelaxant activity. They concluded that the complexity of the pharmacological data, mostly results from the involvement of different receptors each to different extent in vasorelaxant activity (Caliendo *et al*., 2002). In addition we included some currently used drugs in our dataset (i.e., Diltiazem and Nitrendipine) which are calcium channel blockers (Magnon *et al*., 1998).

It is obvious that the descriptors can not deal with differences in mechanisms of actions. To exclude this differences and also the inter-laboratory variations from the calculations, a set of 51 compounds which were similar in mechanism of action and reported by a single Laboratory, was used to carry out the same calculations. In other words, 34 compounds were used as training set (the

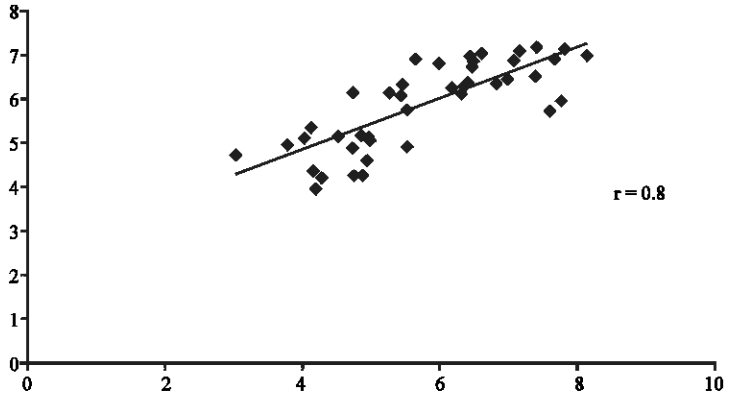


Fig. 1: The plot of the predicted vasorelaxant activity of compounds of prediction values versus experimental values

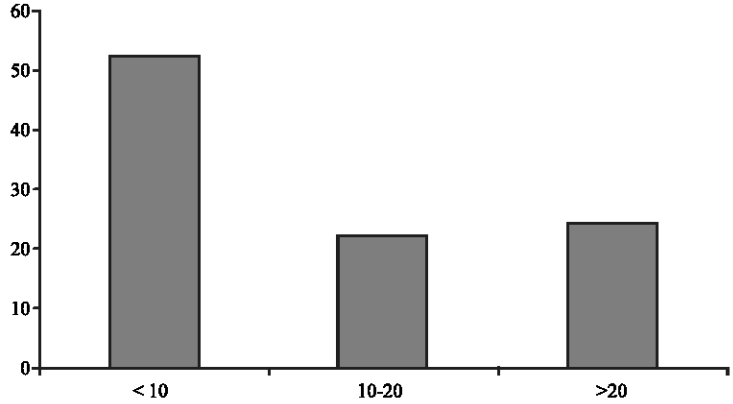


Fig. 2: The relative frequencies of IRD values sorted in three subgroups for prediction set

networks were similar in all properties except hidden layer which were 3 and iteration rate which was 0.15) and the pEC50 of the remaining 17 compounds were predicted. The results were listed in Table 10 and the IRD range was 1.2-28.2 and the ARD value was 12.2 (±7.9).

In order to evaluate the performance of the ANNs, the predicted pEC50 by the ANN was plotted against the experimental values for the prediction set (Fig. 1). It seems that this method is able to predict the requested response with acceptable error range. Although the observed correlation coefficient (R) was 0.6 but we found that omitting three outliers, i.e., compound numbers 70, 79 and 112 in Table 9, leads to better correlation (R = 0.8). These findings reveal the capability of ANN model for predicting pEC50. The IRD distribution of the predicted data was shown in Fig. 2. The IRDs are sorted in three subgroups, i.e., ≤10%, 10-20% and >20% showed that the probability of pEC50 prediction using the proposed method with IRD<10% is about 0.55 and the corresponding probability for IRD>20% is about 0.22.

CONCLUSIONS

One ANN model with 6 descriptors was used to predict the vasorelaxant potency for 137 vasorelaxant agents. This study reveals the capability of the ANNs in modelling and its

potential for use in other research areas of medical sciences. Such a prediction tool could assist medicinal chemists for designing compounds with higher vasorelaxant activities and save time and cost in drug discovery studies.

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