Research Article

YO2D QSAR Analysis on 8-Biarylchromen-4-one Inhibitors of the DNA Dependent Protein Kinase (DNA-PK)

Srushti P. Shah*, Rajesh B. Patil and Sanjay D. Sawant

Sinhgad Technical Education Society's, Smt. Kashibai Navale College of Pharmacy, Kondhwa (Bk), Pune, Maharashtra, India

Abstract

A two dimensional quantitative structure activity relationship (2D-QSAR) study was performed on 8-biarylchromen-4-one analogues as anti-cancer agents. This study was performed on 48 compounds; using random and manual data selection methods by the division of the data set into training and test set. Multiple linear regression analysis was used along with stepwise variable selection method to derive QSAR models which were further validated for statistical significance. The most significant model has squared correlation coefficient (r^2), cross validated correlation coefficient (CV_ r^2) and predictive correlation coefficient (pred_r^2) 0.9511, 0.9998 and 0.9511 respectively. The QSAR model indicates that the descriptors like VAMPp, JGI7, BEHm1, Mor13u, Mor17e, contributing 21.8%, 22.47%, 22.029%, 21.64%, 22.13% respectively and the other descriptors contributes in the range 2.76 – 12.7%. Negative coefficient value of BEHm1, RDFO40e, Mor21m and G3m indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity. Positive coefficient value of other descriptors indicated that higher value leads to good inhibitory activity while lower value leads to reduced inhibitory activity.

Keywords: 2D-QSAR, Biaryl chromenone, anticancer, DNA dependent protein kinase (DNA-PK).

INTRODUCTION

Oxygen containing heterocycles are abundantly found in nature[1]. Chromen-4-ones are naturally occurring compounds possessing diverse biological and pharmacological activities. Many synthetic analogues of chromen-4-ones have been evaluated for their anticancer[2-4], anticonvulsant[5], antihistaminic[6], antimicrobial[7], antioxidant[8], anti-HIV[9] activities. Cancer is one of the most serious threats to human beings. In recent years, there has been a growing interest in search of anti-cancer substances with high efficacy, low toxicity and minimum side effects. Some flavonoids are reported to have carcinogenic benzo[α]pyrene metabolism inhibitory activity[10], cytotoxicity of TNF- α (tumor necrosis factor- α)[11] augmenting activity, tyrosinase inhibitory activity[12], aromatase inhibitory activity[13] and inhibition of estradiol induced DNA synthesis[14]. For more effective and safer anticancer agents , attempts were made to synthesize chromenes containing 8-(biphenyl-3-yl) group as it is well known that the introduction of phenyl motif into organic molecules offers more alternative region for binding to ATP-binding domain of the kinase. The introduction of the aromatic ring provides potent and selective DNA-PK inhibitory activity in the treatment of cancer[15]. 2-Morpholine containing chromen-4-ones were found to be less potent but more selective inhibitor of DNA-PK. In order to enhance the biological activity, distal and proximal aromatic rings containing chromen-4-ones along with morpholine substitution were synthesized by Marine Desage-El Murr et al[15] and were reported to possess considerably enhanced anticancer activity. Quantitative structure activity relationship (QSAR) is an accepted means for establishing quantitative relationship between biological activity and descriptors representing physicochemical properties of the compounds using statistical methods[16] and it help to precisely predict the biological activities of newly designed analogues[17]. In a view to further refine and

set precise structure activity relationship, we decided to establish quantitative relationship between physiochemical properties and biological activities of these reported 8-biarylchromen-4-one derivatives[15].

MATERIALS AND METHODS

QSAR analysis and statistical analysis were carried out by using various freeware available online[18 – 21] and some descriptors were computed by using various freewares and TSAR 3.3 from Oxford Molecular Limited.

Data Set

In the present study a data set 8-biaryl chromen-4-one derivatives (48 molecules) has been taken from the literature[15] for QSAR studies. The reported IC_{50} values (µM) were convereted to the log IC_{50} values. The structures of these derivatives with their reported IC_{50} and log IC_{50} values are given in Table 1. Structures were drawn using the 2D Marvin sketch application and converted to 3D structures. Structures were optimized by energy minimization and geometry optimization was done using Universal Force Field method with 10000 as maximum number of cycles, 0.01 as convergence criteria (root mean square gradient) and 1.0 as constant (medium's dielectric constant which is 1 for in vacuum optimization) in dielectric properties. The default values of 20.0 and 10.0 Kcal/mol were used for electrostatic and steric energy cutoff. The selected dataset were aligned by using most active molecules 15b, 15c, 5i, 5j, 4. The aligned molecules are shown in Figure 1.

Descriptors used in the QSAR analysis

Numbers of physicochemical, topological, constitutional, alignment and atom type independent descriptors were calculated using www.vcclab.org interface, molinspiration.org interface and TSAR software after optimization or minimization of the energy of the data set molecules. Total 180 descriptors were computed and used in the statistical model development. By using various data reduction methods like Principal Component Analysis (PCA) the descriptors contributing to the biological activity were only used in the development of statistically significant model. Some of the descriptors used while developing final models are given in Table 2.

Data selection

The data generated was standardized by manual data selection method and standardization by mean and standard deviation. Stepping was carried out during stepwise multiple regression analysis which include cross validation calculations. Stepping was carried out either by forward stepping method or by backward stepping method. Cross validation calculations were carried out by leave out one row method or leave out group of rows method. Two to ten random trials were carried out to arrive at the best model. The results of the cross validation were used to help detect over fitting and other potential problems with the final regression equation. Principal component analysis was carried out to help detect the descriptors contributing to the biological activity. Non contributing descriptors were eliminated while generating the final model.

RESULTS AND DISCUSSION

Selected data set of 48, 8-biarylchromen-4-one derivatives was subjected to stepwise multiple regression analysis method for model building. Data set was manually subjected to cross validation analysis by leave out one row method or leave out group of rows method with different number of random trials. Thus in leave out one row cross validation method each row was automatically selected as test set data and in leave out group of rows alternate numbers of groups are randomly selected as test set data. The statistically significant models obtained are shown in Table 3. Model 1 was found to be most significant. The results of stepwise multiple linear regression analysis are shown in Table 4. The contribution of each descriptor in model 1

is shown in Figure 2. Result of the observed and predicted biological activity for the compounds for the Model 1 is shown in Table 5. The plot of observed vs. predicted activity for model 1 is shown in Figure 3.

Interpretation of the Model 1 (most significant)

Among the three significant models generated (Table 3), model 1 is the most significant one as it is having the highest cross validated correlation coefficient value (CV_r^2 : 0.9998). The regression model (Model 1) has standard error (s: 0.1375) which explains predictive ability with standard error of 0.1375 units. The squared correlation coefficient (r^2: 0.9511) is in close agreement with cross validated correlation coefficient which explains the better the predictive power. The residual sum of squares (RSS: 0.5869) is the variance in the residuals which is not accounted in the regression method. The predictive sum of square values (PRESS: 0.00132) for the Model 1 are much smaller than other models and also it is much smaller than total sum of square value (12.041) which explains Model 1 generated is reasonable. The predictive squared coefficient ($pred\_r^2$) for the model is 0.9511 which explains true predictive ability of model. Various descriptors contributing in Model 1 are VAMP (polarization xy, quadpole xz, heat of formation, octapole xy), HOMA, JG17, Mor13u and Mor17e, RDF040e, Mor30u, Mor32u, Mor21m, BEHmI. VAMP is electrostatic parameter and signifies various properties like polarization, quadpole, heat of formation, octapole. HOMA is the Harmonic Oscillatory Model of Aromaticity, Mor13u is the 3D Morse signal 13, Mor17e is the Morse signal 17, Mor30u and Mor21m are the morse signal 30 and 21 respectively, JGI7, is the topological charge index and signifies mean topological charge index of order 7, G3m is 3rd component symmetry directional WHIM index which is weighted by atomic masses, BEHmI is the highest eigen value number of Burden matrix. In the QSAR model 1, the negative coefficient value of BEHm1 which is the highest eigen value number of burden matrix, indicate that lower value leads to better inhibitory activity whereas higher value leads to decreased activity. Positive coefficient value of $VAMP_{f/p/o/q}$ indicate that higher values lead to good activity while lower value leads to reduced activity. Negative coefficient value of RDF040e [Radial Distribution Function - 4.0 / weighted by atomic Sanderson electronegativities] signifies contribution of each atom to the overall electronegativity of a molecule and Mor21m and G3m show inverse relation to biological activity where as positive coefficient value of other descriptors viz. $VAMP_f$, HOMA [Harmonic Oscillator Model of Aromaticity], JGI7 [topological charge index and signifies mean topological charge index of order 7], Mor30u [MoRSE signal- 30/unweighted] and Mor17e[3D-MoRSE - signal 17 / weighted by atomic Sanderson electronegativities] show direct relationship with biological activity. Thus molecular connectivity, molecule shape as a function of the number of atoms, distance parameter, molecular walk and path count and mean topological charge parameter are decisive in conferring DNA-PK inhibitory activity to the compounds.

CONCLUSION

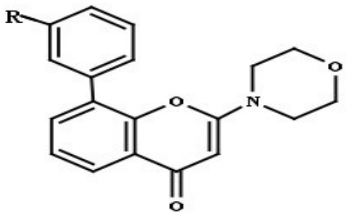
Two dimensional quantitative structure activity relationship (2D-QSAR) studies by means of stepwise multiple linear regression method was performed on a series of 8-Biarylchromen-4-one derivatives as DNA-PK inhibitory agents. Statistically significant QSAR models were generated. Among them most significant model (Model 1) has squared correlation coefficient (r^2), cross validated correlation coefficient (CV_r^2) and predictive squared correlation coefficient ($pred\_r^2$) 0.9511, 0.99998 and 0.00132 respectively. The QSAR model indicates that the descriptors VAMP, JGI7, HOMA, Mor13u ,G3m, BEHm1, Mor17e contributing to DNA-PK inhibitory activity. The negative coefficient value of BEHm1, RDF040e, Mor21m, G3m on the biological activity indicated that lower value leads to better DNA-PK

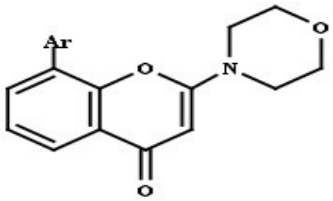
inhibitory activity whereas higher value leads to decrease activity. Positive coefficient value of VAMP, JGI7, HOMA, Mor13u, Mor30u, Mor17e indicates that higher value leads to better DNA-PK inhibitory activity whereas lower value leads to decrease activity.

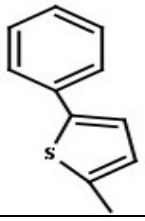
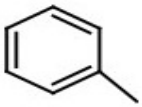
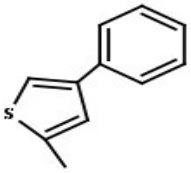
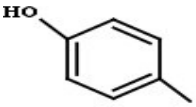
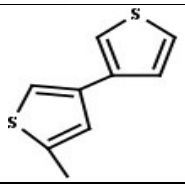
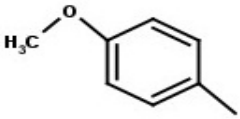
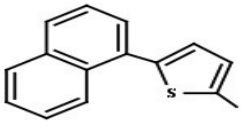
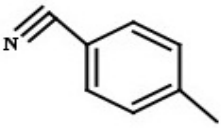
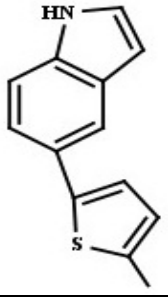
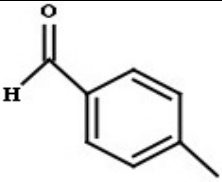
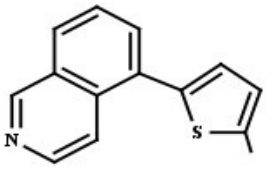
ACKNOWLEDGEMENT

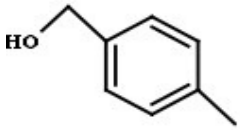
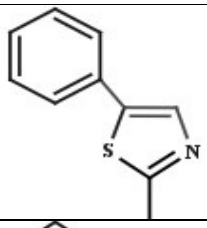
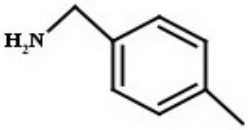
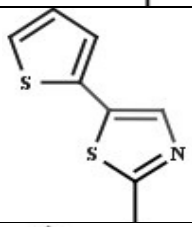
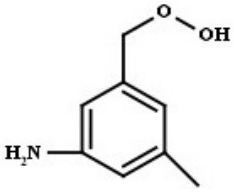
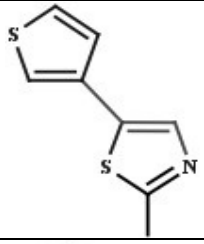
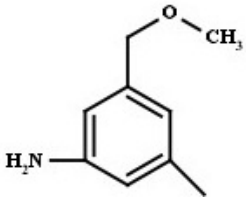
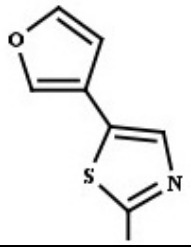
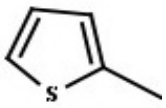
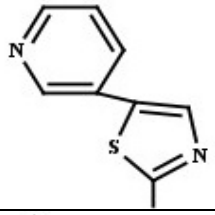
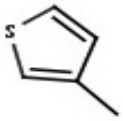
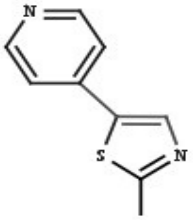
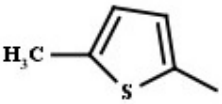
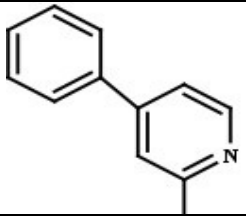
Authors express their gratitude to Prof. M. N. Navale, Founder President, Sinhgad Technical Education Society, Pune for providing the necessary facilities during the course of this research work.

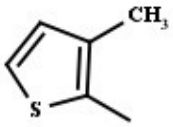
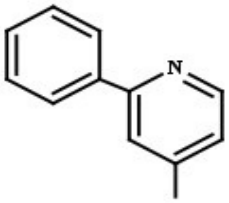
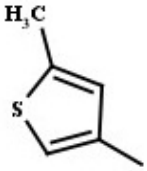
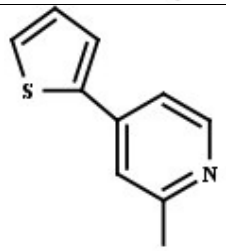
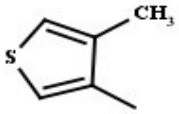
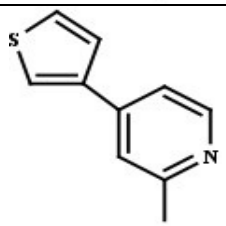
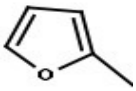
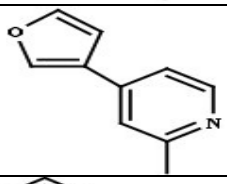
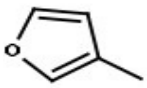
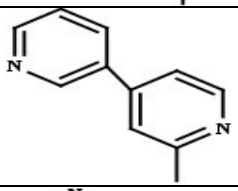
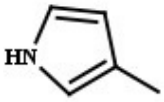
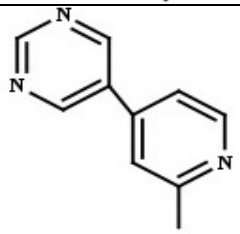
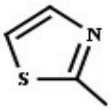
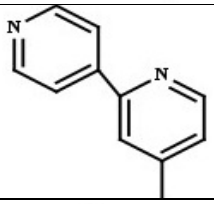
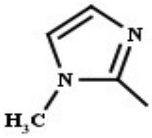
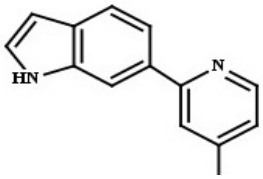
Table 1: General structures of 8-biarylchromen-4-one derivatives and their biological activities





Comp.	R	IC_{50}	Log IC_{50}	Comp	Ar	IC_{50}	Log IC_{50}
1	H	1.6	0.20	15 a		0.40	-0.39
4		0.18	-0.74	15b		0.09	-1.04
5a		0.14	-0.85	15c		0.09	-1.04
5b		0.83	-0.08	15d		2.46	0.39
5c		1.48	0.17	15e		0.34	-0.46
5d		1.10	0.04	15f		0.71	-0.14

5e		1.0	0	15g		0.37	-0.43
5f		1.9	0.27	15h		0.48	-0.31
5g		0.51	-0.29	15i		0.24	-0.56
5h		0.26	-0.58	15j		0.51	-0.61
5i		0.01	-1.74	15k		0.17	-0.29
5j		0.02	-1.69	15l		1.55	-0.76
5k		1.07	0.02	15m		0.67	0.19

5l		0.36	-0.44	15n		1.26	-0.17
5m		1.13	0.05	15o		0.30	0.10
5n		0.64	-0.19	15p		1.24	-0.52
5o		0.38	-0.42	15q		2.37	0.09
5p		0.27	-0.56	15r		1.41	0.37
5q		1.82	0.26	15s		1.75	0.14
5r		0.49	-0.30	15t		0.61	0.24
5s		3.01	0.47	15u		4.45	-0.21

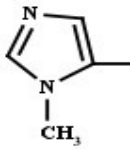
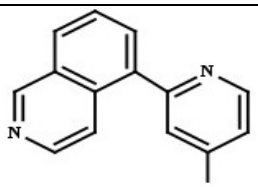
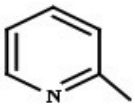
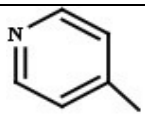
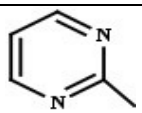
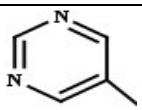
5t		1.23	0.08	15v		4.45	0.64
5u		0.88	-0.05				
5v		0.51	-0.29				
5w		3.05	0.48				
5x		1.57	0.19				

Table 2: Descriptors calculated for QSAR studies

Physicochemical Descriptors	Constitutional Descriptors	Topological descriptors	Other categories of Descriptors
Molecular Mass Molecular Surface area Molecular Volume Log P Molecular Refractivity Kier Chi (atom/ bond/path/path-cluster/cluster) index of order 0-6 Kier Chi V (atom/ bond/path/path-cluster/cluster) index of order 0-6 Kappa 1-3 index KAlpha 1-3 index Shape flexibility index Rotatable bonds Randic Topologic index Wiener Topologic index Sum of E-state indices VAMP (total enery, electronic enery, Nuclear energy, surface area, mean polarizability) Ui: Unsaturation index Hy: hydrophilic factor MLOGP: Moriguchi octanol-water partition coeff. (logP) ALOGP: Ghose-Crippen octanol-water partition coeff.	Sv: sum of atomic van der Waals volumes (scaled on Carbon atom) Se: sum of atomic Sanderson electronegativities (scaled on Carbon atom) Sp: sum of atomic polarizabilities (scaled on Carbon atom) Ss: sum of Kier-Hall electrotopological states Mv: mean atomic van der Waals volume (scaled on Carbon atom) Me:mean atomic Sanderson electronegativity (scaled on Carbon atom) ARR: aromatic ratio nCIC: number of rings nDB: number of double bonds nH: number of Hydrogen atoms nC: number of Carbon atoms nR06: number of 6-membered rings ATS: Broto-Moreau autocorrelation of a topological structure weighted by atomic masses MATS: Moran autocorrelation weighted by atomic masses	ZM: Zagreb index Qindex: Quadratic index VDA: average vertex distance degree MSD: mean square distance index (Balaban) SMTI: Schultz Molecular Topological Index (MTI) RHyDp reciprocal hyper-distance-path index Wap: all-path Wiener index ICR: radial centric information index ZM: Zagreb index Qindex: Quadratic index SNar: Narumi simple topological index (log) HNar: Narumi harmonic topological index GNar: Narumi geometric topological index Xt: Total structure connectivity index Dz: Pogliani index Ram: ramification index Pol: polarity number	Walk and path counts Connectivity indices Information indices 2D autocorrelations Edge adjacency indices BCUT descriptors Topological charge indices Eigenvalue-based indices Randic molecular profiles Geometrical descriptors Radial Distribution Function descriptors 3D-MoRSE descriptors WHIM descriptors GETAWAY descriptors Functional group counts Atom-centred fragments Charge descriptors

Table 3: Statistically significant models generated

Sr. no	Equation
1	Log IC_{50} = 0.16010001(VAMPf) + 0.29997486 (VAMPp) + 0.16129853 (VAMPq) + 0.097510524 (VAMPo) - 0.30308869 (BEHm1)+ 0.30919218 (JGI7) + 0.16949072 (HOMA) - 0.1062862 (RDF040e) + 0.29776576 (Mor13u) + 0.038027551(Mor30u) + 0.13426135(Mor32u) - 0.11958265 (Mor21m) + 0.3044937 (Mor17e) - 0.17483312 (G3m) + 0.10743423 (G2e) - 0.21400511 Cross validated leaving out one row randomly over 2 random trials; Correlation limit of 0.8 applied; 15 steps to generate final model.
2	Log IC_{50} = 0.29213947 (VAMPp) + 0.10010359 (VAMPq) + 0.28811699 (JGI7) + 0.28213149 (HOMA) + 0.45684105 (Mor13u) + 0.22540605 (Mor17e) - 0.16542196 (G3m) + 0.14870359 (Dv) - 0.16512288 (ALOGP2) - 0.21400511 Cross validated leaving out one row randomly over 2 random trials; Correlation limit of 0.9 applied; 11 steps to generate final model.
3	Log IC_{50} = 0.15601125 (VAMPf) + 0.25615302 (VAMPp) + 0.1328395 (VAMPq) - 0.2568053 (BEHm1) + 0.31707504 (JGI7) + 0.2052466 (HOMA) + 0.33348823 (Mor13u) + 0.27589878 (Mor17e) - 0.11906573 (G3m) - 0.21400511 Cross validated leaving out one row randomly over 2 random trials; Correlation limit of 0.9 applied; 11 steps to generate final model

VAMPf- Heat of formation; **VAMPp**- Polarization XY; **VAMPq**- Quadpole XZ; **VAMPo**- Octupole XXZ; **BEHm1**- Highest eigen value n 1 of Burden matrix; **JGI7** – Mean topological charge index of order 7 ; **HOMA**- Harmonic Oscillator Model of Aromaticity; **RDF040e**- Radial Distribution Function – 4.0 / weighted by atomic Sanderson electronegativities; **Mor13u**- 3D MoRSE signal- 13/ unweighted; **Mor30u**- 3D MoRSE signal- 30/unweighted; **Mor32u-** 3D MoRSE signal- 32/ unweighted; **Mor21m**- 3D-MoRSE - signal 21 / weighted by atomic masses; **Mor17e**- 3D-MoRSE - signal 17 / weighted by atomic Sanderson electronegativities; **G3m**- 3rd component symmetry directional WHIM index / Weighted by atomic masses; **G2e**- 2nd component symmetry directional WHIM index / weighted by atomic Sanderson electro negativities; **Dv**- D total accessibility index / weighted by atomic Van Der Waal`s volume; **ALOGP2**- Squared Ghose-Crippen octanol-water partition coeff. (logP^2)

Table 4: Result of stepwise multiple linear regression analysis

Model no.	Stepwise Multiple linear regression								
	Total sum of squares	s	f	r	r^2	CV_r^2	RSS	PRESS	Pred. r^2
1	12.014	0.1375	40.23	0.9752	0.9511	0.9998	0.5869	0.00132	0.9511
2	12.014	0.1934	31.57	0.9406	0.8847	0.9344	1.3840	0.7880	
3	12.041	0.1861	34.39	0.9451	0.8932	0.9998	1.2827	0.0020	

S: standard error; F: a value derived from sum of squares and degrees of freedom;
r: correlation coefficient; r^2: squared correlation coefficient, CV_r^2: cross validated correlation coefficient;
RSS: Residual sum of squares; PRESS: Predictive sum of squares, Pred r^2: Predicted r^2.

Table 5: Observed and predicted activity for Model 1

Compound	Observed activity	Predicted activity
1	0.2041	0.14096
4	-0.7447	-0.60707
5a	-0.8538	-0.85566
5b	-0.0809	-0.054972
5c	0.1702	0.18189
5d	0.0413	0.034595
5e	0	-0.078614
5f	0.2787	0.28092
5g	-0.2924	-0.19754
5h	-0.585	-0.67618
5i	-1.7447	-1.5947
5j	-1.6989	-1.6247
5k	0.02938	-0.12987
5l	-0.4436	-0.25064
5m	0.05307	0.032568
5n	-0.1938	-0.19848
5o	-0.42021	-0.35851
5p	-0.5689	-0.52893
5q	0.26007	0.024506
5r	-0.3098	-0.58955
5s	0.4785	0.36224
5t	0.0899	0.15478
5u	-0.05551	-0.004875
5v	-0.2924	-0.14379
5w	0.48429	0.68572
5x	0.1958	-0.11092
15a	-0.3979	-0.46888
15b	-1.0458	-1.0569
15c	-1.0458	-1.0364
15d	0.3909	0.49436
15e	-0.46852	-0.46393
15f	-0.1487	-0.11166
15g	-0.43179	-0.44869
15h	-0.3187	-0.31895
15i	-0.5686	-0.5236
15j	-0.6197	-0.67132
15k	-0.2924	-0.19889
15l	0.19033	0.060137
15m	-0.17392	-0.24148
15n	0.10037	0.048106
15o	-0.52287	-0.59393
15p	0.09342	0.2353
15q	0.37474	0.36723
15r	0.14921	0.35164
15s	0.24303	0.29026
15t	-0.21467	-0.2195
15u	0.64836	0.55561
15v	-0.3979	-0.46888

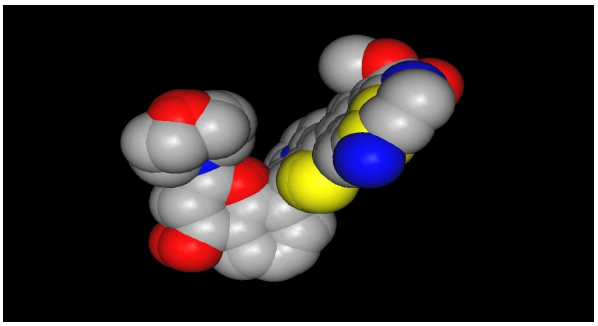
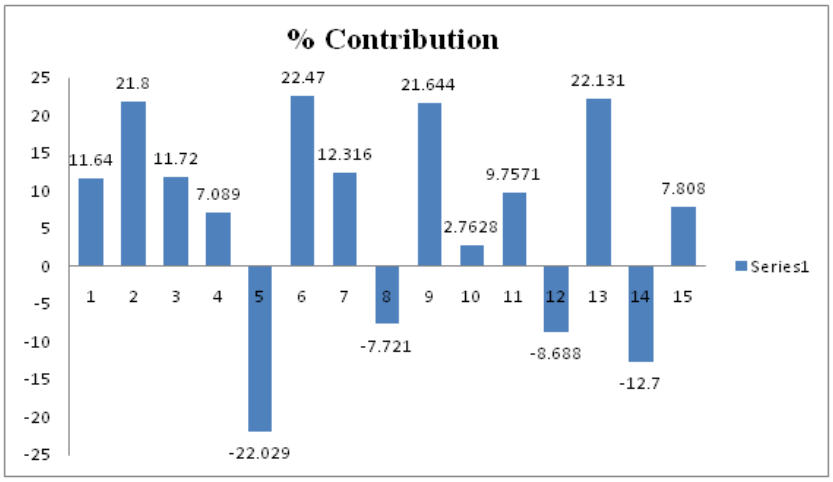


Fig. 1: Aligned molecules by space fill model



1. VAMPf , 2. VAMPp, 3. VAMPq, 4. VAMPo, 5. BEHm1, 6. JGI7, 7. HOMA, 8. RDF040E, 9. Mor13u, 10. Mor30u, 11. Mor32u, 12. Mor21m, 13. Mor17e, 14. G3m, 15. G2e

Fig. 2: Contribution chart for model 1 showing contribution of different descriptors

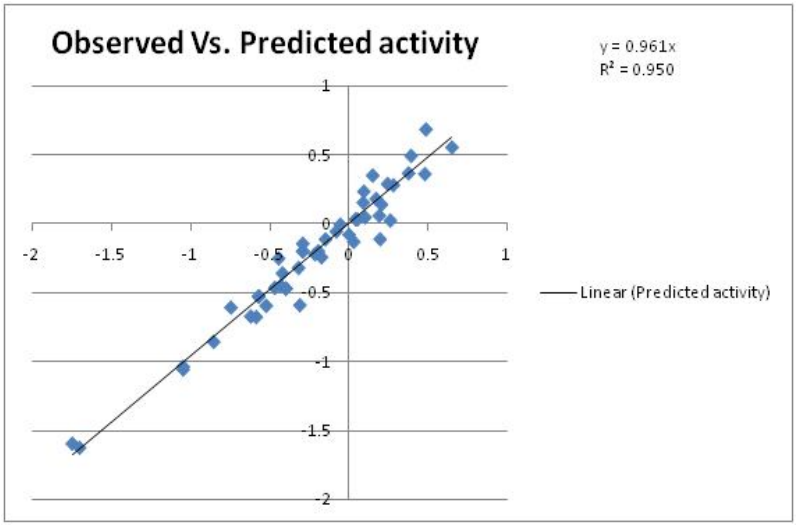


Fig. 3: Graph between actual and predicted biological activity for Model 1

REFERENCES

1. Maegawa H, Obata T and Shibata T. A new antidiabetic agent (JTT-501) rapidly stimulates glucose disposal rates by enhancing insulin signal transduction in skeletal muscle. Diabetologia. 1999; 42(2):151-159.
2. Garg HG and Singh PP. New compounds: Potential antidiabetics IV: 1-(2,4-dinitrophenyl)-3,5-diphenyl-4-arylazopyrazoles and 1-carbamoyl-3,5-diphenyl-4-arylazopyrazoles. Journal of Pharmaceutical Sciences. 1970; 59 (6): 876–877.

3. Lee HW, Kim BY and Ahn JB. Molcular design, synthesis, and hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione. European Journal of Medicinal Chemistry. 2005, 40(9): 862-874.
4. Sofia RD., Diamantis W and Ludwig BJ. Comparative anti-inflammatory, analgesic, and antipyretic activities of 7-chloro-3,3a-dihydro-2-methyl-2H,9H-isoxazolo-(3,2-b)(1,3)-benzoxazin-9-one and 5-chlorosalicylic acid in rats. Journal of Pharmaceutical Sciences. 1975; 64(8): 1321-1324.
5. Farghaly AM, Soliman FS and el Semary MM. Polysubstituted pyrazoles, Part 4: Synthesis, antimicrobial and antiinflammatory activity of some pyrazoles. Pharmazie, 2001; 56(1): 28-32.
6. Bennett GB, Mason RB and Alden LJ. Synthesis and antiinflammatory activity of trisubstituted pyrimidines and triazines. Journal of medicinal Chemistry. 1978, 21(7): 623-628.
7. Lee YS and Kim BH. Heterocyclic nucleoside analogues: design and synthesis of antiviral, modified nucleosides containing isoxazole heterocycles. Bioorganic Medicinal Chemistry Letters, 20; 2002; 12(10): 1395-1397.
8. Pancic F, Steinberg BA and Diana GD. Antiviral activity of Win 41258-3, a pyrazole compound, against herpes simplex virus in mouse genital infection and in guinea pig skin infection. Antimicrob Agents Chemother. 1981; 19(3): 470–476.
9. Holy A, Votruba I and Masojidkova M. 6-[2-(Phosphonomethoxy) alkoxy] pyrimidines with antiviral activity. Journal of Medicinal Chemistry. 25; 2002; 45(9): 1918-1929.
10. Liu YL, Ho DK and Cassady J. M. Isolation of potential cancer chemopreventive agents from Eriodictyon californicum. Journal of Natural Products. 1992; 55: 357-363.
11. Hebtemariam S, Flavonoids as inhibitors or enhancers of the cytotoxicity of tumor necrosis factor-alpha in L-929 tumor cells. Journal of Natural Products. 1997, 60: 775-778.
12. Kubo I, Kinst-Hori I, Chaudhuri SK, Kubo Y and Sanchez Y. Flavonols from Heterotheca inuloides: tyrosinase inhibitory activity and structural criteria. Bioorganic Medicinal Chemistry. 2000, 8: 1749.
13. Suresh CT, Leena S, Sari M and Risto SJ. Inhibition of 17-beta-Estradiol Formation by Isoflavonoids and Flavonoids in Cultured JEG-3 Cells: Search for Aromatase-Targeting Dietary Compounds. J Med Food., 1999, 2: 235.
14. Wang CF, Kurzer MS. Effects of phytoestrogens on DNA synthesis in MCF-7 cells in the presence of estradiol or growth factors. Nutr Cancer., 1998; 31: 90-100.
15. El-Murr MD, Cano C, et al. 8-Biarylchromen-4-one Inhibitors Of DNA- dependent protein kinase (DNA-PK). Bioorganic & Medicinal Chemistry Letters, 2008, 4885-4890.
16. Kiralj R and Ferreira MMC. Basic validation procedures for regression models in QSAR and QSPR studies: theory and applications. J. Braz. Chem. Soc., 2009, 20: 770-787.
17. de Melo EB, Martins JPA, Jorge TCM, Ferreira MMC. Mutivariate QSAR study on the antimutagenic activity of flavonoids against 3-NFA on Salmonella typhimurium TA98, European Journal of Medicinal Chemistry. 2010, 45: 4562-4569.
18. http://www.vcclab.org
19. Tetko IV, Gasteiger J, Todeschini R et al. Virtual computational chemistry laboratory - design and description. J. Comput. Aid. Mol. Des., 2005, 19: 453-63.
20. http://www.graphpad.com (Graphpad InStat 3 trial version)
21. http://www.molinspiration.org