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QSAR study of flavonoids analogues as *in vivo* anticancer BCRP inhibition bio-activity

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Abstract: QSAR is among the most extensively used computational methodology for analogue-based design. A molecular modeling strategy using flavonoids analogue recently reported in the literature was designed. A multiple linear regression (MLR) model using stepwise method is based on 24 molecules has been developed for the prediction of the EC_{50} of some anticancer drugs using these quantum chemical descriptors, the most important class in modeling these series of compounds followed by constitutional, topological and physicochemical descriptors derived from e-dragon . The accuracy of the proposed MLR model was illustrated using the following evaluation techniques: cross-validation, and Y-randomisation. The results obtained showed the excellent prediction ability and stability of the proposed model in the prediction of anticancer BCRP inhibition bio-activity of flavonoids analogues found satisfactory and could be used for the designing a similar group of anticancer drugs.
Keywords: QSAR, MLR, Flavonoids Analogues, Quantum chemical descriptors, Anticancer drugs.

Introduction

Quantitative structure–activity relationship (QSAR) can aid in identifying functional groups with their various structural parameters used to increase the bioactivity leads designing new structures with the variation in enhanced bioactivity depends on changes in chemical structure[1-3]. The use of graph theoretical approaches to describe the chemical structure of organic compounds has accomplished more and more relevance along the later years. Since the early times in which such formalism was used to predict simple properties on simple molecules, up to the design- for instance- of novel lead anticancer drugs, a significant progress was achieved and a long path has been covered. In order to outline the particular QSAR techniques used with this methodology, descriptors will be defined before explaining the modeling tools applied with them. Diverse statistical and molecular techniques will be sketched. The inverse problem of finding compounds with desired activity and properties has also attracted attention. Such an inverse-QSAR formulation directly focuses on the goal of drug design, i.e., discovery of active compounds with good pharmacokinetic and other properties[1-8].

Cancer is one of the most formidable afflictions in the world. Although cancer mortality is second to heart disorders, the first is steadily increasing, while the latter is leveling off. Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age. Cancer causes about 13% of all deaths. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents [9-13]. Flavonoids such as chrysin, nbiochanin A and apigenin a very low micromolar concentration is capable of producing 50% (EC_{50}) of the maximum increase in mitoxantrone (MX) inhibitor

substrate accumulation (interaction) with breast cancer resistance protein (BCRP), helping the multi-drug resistance (MDR) mechanism of over expressing cancer cells[14-17].

Materials And Methods

Data set

The biological data used in this study were anticancer activity, EC_{50}, of a set of twenty four flavonoids analogue derivatives. The data set of 24 flavonoids analogue used for the QSAR models in this study were taken from the published work of Mihai V. Putz, Luciana Ienciu and Adrain Chiriac and his coworkers [18]. The range of $-\log_{10}$ (EC_{50}[μM]) values was 2.25-7.14 μM, more than two orders of magnitude between the most and least potent derivative used as dependent variable in our model. The structural features, biological activity and predicted biological activity with residuals of these compounds are listed in Table 1.

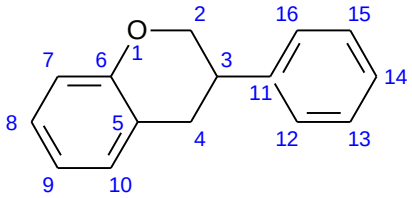


Fig 1: Parent structure of flavonoids

Calculation of descriptors

It is important to note that quantum chemical descriptor, Constitutional descriptors and topological descriptors are based solely on chemical structure. The calculated topological indices treat the structure of the compound as a graph, with atoms as vertices and covalent bonds as edges. The number of different descriptors reaches thousand in some leading commercial tools. Having at hand powerful methods for automatically selecting the informative features, one may be tempted to leave the descriptor selection process entirely to algorithmic techniques. Quantum-chemical descriptors and molecular modeling techniques enable the definition of a large number of molecular and local quantities characterizing the reactivity, shape and binding properties of a complete molecule as well as of molecular fragments and substituents. Because of the large well-defined physical information content encoded in many theoretical descriptors, their use in the design of a QSAR study presents two main advantages: (a) the compounds and their various fragments and substituents can be directly characterized on the basis of their molecular structure only; and (b) the proposed mechanism of action can be directly accounted for in terms of the chemical reactivity of the compounds under study. Constitutional descriptors capture properties of the molecule that are related to elements constituting its structure. These descriptors are fast and easy to compute. The reason is that whereas the conventional physical and geometrical descriptors are structure-related, topological indices are just an algebraic description of the structure itself. Thus, one can go backward and forward between structure and property, predicting properties for molecules and vice versa. the molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment [19-39].

Table 1: Molecular name of flavonoinds derivatives used in this study, their experimental and predicted activity and their residuals of best three statistical significant QSAR models for anticancer BCRP inhibition bioactivity.

Com.No.	Molecular Name	Exp. EC_{50}	QSAR Eq.02		QSAR Eq.03		QSAR Eq.04	
			Pred. EC_{50}	Residual	Pred. EC_{50}	Residual	Pred. EC_{50}	Residual
01	Silybin	3.74	3.758	-0.018	3.720	0.020	3.745	-0.005
02	Daidzein	4.24	4.776	-0.536	4.873	-0.633	4.747	-0.507
03	Naringenin	4.49	4.931	-0.441	4.682	-0.192	4.546	-0.056
04	Flavanone	4.60	4.851	-0.251	4.616	-0.016	4.563	0.037
05	7,8-Dihydroxyflavone	4.70	5.739	-1.039	5.685	-0.985	-	-
06	7-Methoxyflavanone	4.79	5.395	-0.605	5.302	-0.512	5.243	-0.453

07	Genistein	4.83	4.986	-0.156	5.048	-0.218	4.924	-0.094
08	6,2,3-7-hydroxyflavanone	4.85	4.820	0.030	4.553	0.297	4.386	0.464
09	Hesperetin	4.91	4.711	0.199	4.804	0.106	4.685	0.225
10	Chalcone	4.93	4.838	0.092	4.902	0.028	4.970	-0.040
11	Kaempferol	5.22	5.515	-0.295	5.462	-0.242	5.377	-0.157
12	4,5,7,Trimethoxyflavanone	2.25	5.485	-0.235	5.337	-0.087	5.309	-0.059
13	Flavone	5.40	5.068	0.332	5.176	0.224	5.164	0.236
14	Apigenin	5.78	4.951	0.829	5.054	0.726	-	-
15	Biochanin A	5.79	5.303	0.487	5.666	0.124	5.632	0.158
16	5,7-Dimethoxyflavone	5.85	5.968	-0.118	6.219	-0.369	6.260	-0.410
17	Galangin	5.92	6.221	-0.301	5.982	-0.062	5.981	-0.061
18	5,6,7-Trimethoxyflavone	5.96	6.007	-0.047	6.120	-0.160	6.162	-0.202
19	kaempferide	5.99	5.802	0.188	6.126	-0.136	6.151	-0.161
20	8-methylflavone	6.21	5.603	0.607	5.771	0.439	5.795	0.415
21	6,4-Dimethoxy-3-hydroxy-flavone	6.35	6.127	0.223	5.929	0.421	5.970	0.380
22	Chrysin	6.41	5.511	0.899	5.458	0.952	-	-
23	2-hydroxy-α-naphtoflavone	7.03	7.033	-0.003	6.864	0.166	6.845	0.185
24	7,8-Benzoflavone	7.14	6.981	0.159	7.032	0.108	7.037	0.103

Table 2: List of indices used in QSAR modeling and their description

No.	Abbreviation	Description	Block
1	MW	molecular weight	Constitutional indices
2	SMTIV	Schultz Molecular Topological Index by valence vertex degrees	Topological indices
3	GMTIV	Gutman Molecular Topological Index by valence vertex degrees	Topological indices
4	Xu	Xu index	Topological indices
5	Wap	all-path Wiener index	Topological indices
6	MAXDN	maximal electrotopological negative variation	Topological indices
7	BID	Balaban ID number	Walk and path counts
8	X_3	connectivity index of order 3	Connectivity indices
9	DEN	Density	Physicochemical indices

Statistical analysis

The data set was analysed using NCSS statistical software[39]. Stepwise regression analysis was used to determine the most significant descriptors. The regression coefficients were obtained by least-squares regression analysis. For each regression, the following descriptive information is provided: number of observations used in the analysis (n), correlation coefficient (r), cross-validated (R^2_{cv}), standard error of the estimate (Se), Mean of standard error of estimation (MSe), adjusted regression coefficient (R^2_{adj}) and Fisher's criterion (F). Statistical parameters were calculated subsequently for each step in the process, so the significance of the added parameter could be verified. Correspondingly, it represents the part of the variation in the observed (experimental) data that is explained by the model. Y-randomization is a tool used in validation of QSPR/QSAR models, whereby the performance of the original model in data description is compared to that of models built for permuted (randomly shuffled) response, based on the original descriptor pool and the original model building procedure.

Correlation Analysis

Pearson's correlation coefficients may serve as a preliminary filter for discarding inter-correlated descriptors. This can be done by e.g. creating clusters of descriptors having correlation coefficients higher than certain threshold and retaining only one, randomly chosen member of each cluster. Table 3 describes correlation coefficient between the chosen descriptors and anticancer bioactivity. Firstly, the descriptors were checked for

constant or near constant values and those detected were removed from the original data matrix. Then, the correlation of descriptors with each other's and with the activity data was determined. Among the collinear descriptors detected (r > 0.8), one of them that had the highest correlation with activity was retained and the rest were omitted. Recent studies have shown that both yield small prediction error in numerous QSAR applications. Given the complexity of these methods, one may be tempted to treat them as black boxes[41-47].

Table 3: Correlation matrix between the used descriptors in QSAR modeling

	EC50	MW	DEN	SMTIV	GMTIV	Xu	Wap	MAXDN	BID	X_3
EC50	1.0000									
MW	-0.1952	1.0000								
DEN	-0.1869	0.3693	1.0000							
SMTIV	-0.3216	0.9602	0.3238	1.0000						
GMTIV	-0.3476	0.9536	0.3782	0.9977	1.0000					
Xu	-0.1724	0.9964	0.3155	0.9640	0.9540	1.0000				
Wap	-0.2956	0.8747	0.2113	0.9650	0.9595	0.8907	1.0000			
MAXDN	-0.2207	0.7128	0.7941	0.7197	0.7528	0.6791	0.6200	1.0000		
BID	-0.0978	0.9913	0.3697	0.9242	0.9148	0.9892	0.8363	0.6811	1.0000	
X_3	-0.1331	0.9808	0.3679	0.9519	0.9447	0.9816	0.9023	0.6967	0.9814	1.0000

Result And Discussion

In the first step, separate stepwise selection-based MLR analysis were performed using different types of descriptors, and then, an MLR equation was obtained utilizing the pool of all calculated descriptors. The resulted QSAR models from different types of descriptors for the compounds (24 molecules) are listed in Table 2-3. Based on the results of the above analysis, the QSAR equation with the largest cross-validation coefficient was obtained for 24 compounds are given in table 3. Among the several models, one of the best models was selected from each cell line and the results are summarized in Table 3. The best QSAR model has characters of large F, small Se, R and R^2_{cv} values close to 1. The QSAR study leads to the development of statistically significant model, which allows understanding of the molecular properties/features that play an important role in governing the variation in activities. Usually, the chemoinformatic methods underlying QSAR analysis are in constant advancement. Well-established techniques continue to be used, providing successful results especially in small, homogeneous datasets consisting of compounds relating to a single mode of action [49-51].

QSAR/QSPR models no. 1,2 and 03 indicate that the anticancer BCRP inhibition bio-activity of flavonoids increase with the magnitude of X_3, Wap, Xu, MAXDN, BID while Gutman Molecular Topological Index by valence vertex degrees (GMTIV), molecular weight (MW), Density show negative contribution with the anticancer BCRP inhibition bio-activity.

The X_3 represents the accessibility of a bond to encounter another bond in intermolecular interactions, as the reciprocal of the vertex degree δ is the fraction of the total number of non-hydrogen sigma electrons contributing to each bond formed with a particular atom [52-69]. This interpretation places emphasis on the possibility of bimolecular encounters among molecules, reflecting the collective influence of the accessibilities of the bond in each molecule to other molecules in its immediate environment.

The Balaban ID number indices is a very discriminating molecular descriptor and its values do not increase substantially with molecule size or number of rings [70-76]. the presence of three serious outliers compounds namely compound no. 05 (7,8-Dihydroxyflavone), 14 (Apigenin) and 22 (Chrysin) in the series of flavonoids analogue and after deleting these the statistically significant QSAR/QSPR model no.04 with

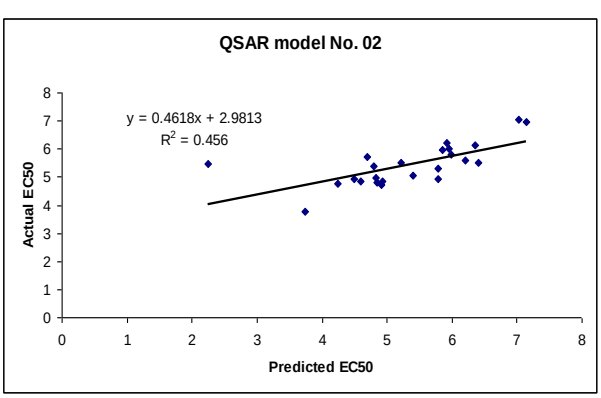
positive contribution of topological descriptors and negative contribution of physicochemical descriptors i.e. the increase in the anticancer BCRP inhibition bioactivity of flavonoids analogues undergo with the increase in the magnitude of BID and MAXDN and decreases in the magnitude of molecular weight and Density. The correlation represents the intrinsic density of the flavonoids analogue calculated as the ratio of the molecular mass and molecular volume (represents by the overlapping Vander waal atomic spheres model) of the molecule.

Table 4: Developed QSAR/QSPR models by using both chemical and topological descriptors flavonoids analogues with validated and cross-validated statistical descriptors

Model No.	QSAR/QSPR Models	n	Se	r	F	PRESS	MSe	R^2_{ADJ}	R^2cv
01	EC_{50} = 1.6249E-02+ 1.02062X_3 -1.9392E-04GMTIV	24	1.5708	0.6896	9.521	12.847	0.4306	0.4256	0.255
02	EC_{50} = -11.2346+ 0.9052Xu +1.5766E-04Wap + 2.5164MAXDN -6.0788E-04GMTIV	24	2.7088	0.8551	12.92	08.955	0.2439	0.6745	0.481
03	EC_{50} = -102.2566+ 3.0670MAXDN + 48.4727BID -0.1467MW -4.9642DEN	24	14.269	0.8772	15.85	5.1205	0.2091	0.7210	0.703
04	EC_{50} = -106.0590 + 3.5035MAXDN + 50.3744BID -0.1529MW -5.8422DEN	21	9.447	0.9524	38.98	2.092	0.090	0.883	0.86

n = no. of compounds, Se= standard error of estimation, r= correlation coefficient, F= fischer criterion, PRESS= Predicted Residual Sum of Squares, MSe= Mean of Standard error of estimation, R^2_{adj}= adjusted regression coefficient, R^2_{cv}= cross validated regression coefficient

QSAR model no.01 to 04 and the used topological and physicochemical descriptor describes that in flavonoids analogue metabolization operation started on the same planer configuration of molecule. Methoxylation of oxygens in position 10 , 08 and 14.Direct hydroxylation in position 10, 08 and 14 position resulting the metabolization of molecule 13 (flavone) in molecule 03 (naringenin). While on hydroxylation on the indicated position 09, 08, 16 and 15 turing the molecule no.8 into 03 on by reverse hydroxylation in 16 and 15 with direct hydroxylation of position 4 and with movement from ortho 9 to para 10 of hydroxyl group on ring A respecting pattern molecule in figure1.



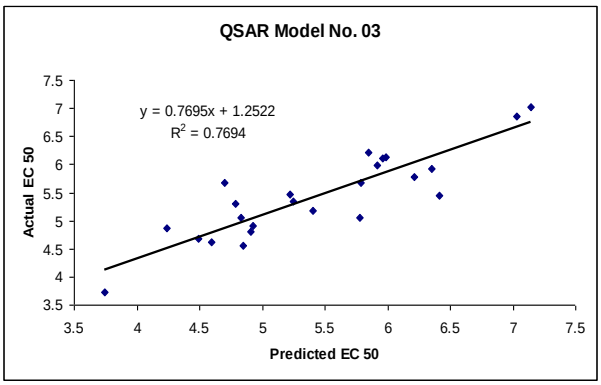


Fig 2: Graph between the predicted anticancer BARP inhibition bioactivity of flavonoids ananlogue of developed QSAR model no.02 and 03 against actual anticancer BCRP inhibition bioactivity

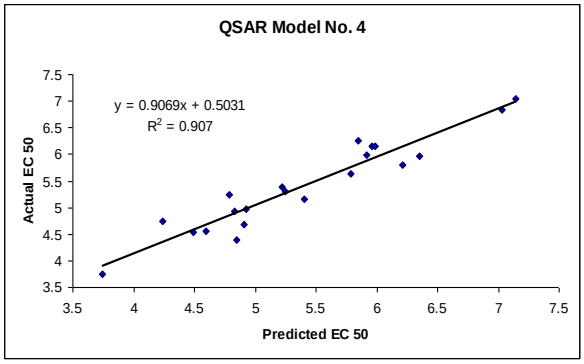


Fig 3: Graph between the predicted anticancer BARP inhibition bioactivity of flavonoids analogue of developed QSAR model no. 04 against actual anticancer BCRP inhibition bioactivity

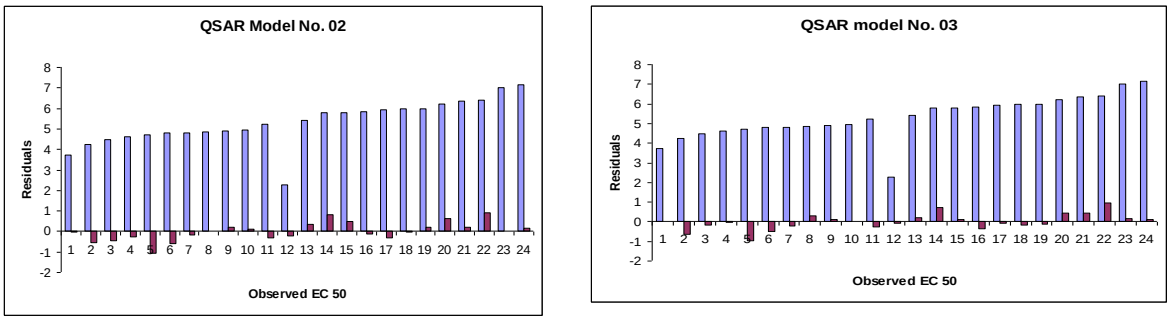


Fig 4: Graph between observed EC_{50} and Residuals of developed QSAR model no.02 and 03.

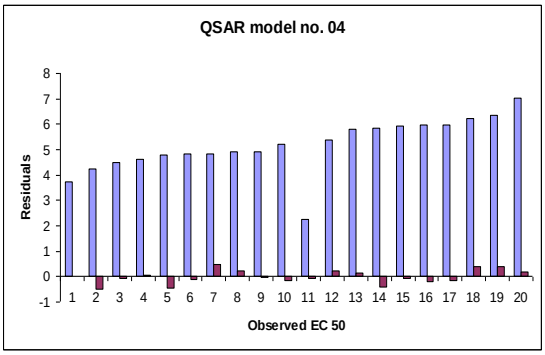


Fig 5: Graph between observed EC_{50} and Residuals of developed QSAR model no.04

Conclusion

The present study affirms the position 8, 14 respecting the pattern molecule in figure1 as the most suitable ones for producing an increase in BCRP inhibition activity. The position no.7 may present adverse drug interactions. The present QSAR study may allow interpretetation inter-conversion of concerned molecules towards receptor binding since belonging to the same class of analogs, while they certainly undertaking such transformation during their interaction with macromolecules, proteins and enzymes present on cellular walls or with in vivo environment. All potential interconversion of employed molecules involved in correlation as well as for establishing their quantum metabolization complete map. Combined with the increased complexity of the inspected datasets, this makes the QSAR analysis a challenging endeavor. The graph between actual anticancer BCRP inhibition bioactivity of flavonoids analogue and predicted anticancer BCRP inhibition bioactivity of statistically significant developed QSAR/QSPR model . the QSAR studies can offer important insights into designing high activity compounds prior to synthesis. Based on the established model, as well as the law of polarity alternation and the idea of polarity interference, new compounds with higher predicted anticancer

BCRP inhibition bio-activity have been theoretically designed, and they are expected to be confirmed experimentally.

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