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QSAR Studies of Flavonoids Derivatives for Antioxidant and Antimicrobial Activity

Sharma Mukesh[1]*, Ahuja Dharmendra[2]

[1] Research Scholar, Faculty of Pharmaceutical Sciences Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

[2] Professor, Faculty of Pharmaceutical Sciences Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

ABSTRACT

The biological activity and the molecular structures are the two main aspects for the QSAR study of a specific compound, which leads to generate a new chemical moiety. The Quantitative Structure Activity Relationship (QSAR) paradigm is based on the assumption that there is an underlying relationship between the molecular structure and biological activity. Physico-chemical properties were calculated employing the modeling software Win CAChe 6.1. The calculated descriptors were conformational minimum energies (CME) , HOMO energy, LUMO energy, heat of formation (HF), ionization potential (IP), molar refractivity(MR), Shape Index (basic kappa, order 1) (SI1), log P, electron affinity (EA), solvent accessible surface area (SAS). In random selection, 18 compounds were in training set and 10 in test set. Subsequently with the stepwise multiple linear regression analysis was carried out to achieve the best models. The equation generated was validated. The selected QSAR model showed correlation coefficient R^2 0.7609, and cross-validated squared correlation coefficient Q^2 of 0.5041 for antioxidant activity ANOVA of predicted value for Variance were found as 0.063638, 201.73 and 0.112396 for group -1.51851, 86.27 and -8.151 respectively. Source of Variation for between and within group i.e. SS value 40522.91 df value 2, MS value 20261.45 F value 301.0527 and p-value 1.01E-17. The HOMO-LUMO range were 73.149 to 84.775, Molar refractivity range was observed -7.409 to -8.84, Predicted value range was -2.52559 to -2.98191 for compound V1 to V5 and R1, R2. The result of study indicated that C5 [1-(2- hydroxyphenyl)-5-phenylpenta-2,4-dien-1-one]; is only inactive against *Streptococcus mutans*. All 3-hydroxyflavone derivatives exhibited their MIC to be in range of 250-125 µg/ml., 2,3-dihydroflavan-3-ol derivatives exhibited their MIC to be in range of 1000- 500 µg/ml. The chalcone derivatives exhibited their MIC to be at 250µg/ml.

Keywords: QSAR, *Streptococcus mutans,* Win CAChe 6.1 and antioxidant activity

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***Address for Correspondence:**

Sharma Mukesh, Research Scholar, Faculty of Pharmaceutical Sciences Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

INTRODUCTION:

Drug discovery is the extremely time consuming and expensive processes. With rapidly increasing costs, diminishing resources, more intense public scrutiny, greater government regulations, and higher expectations, this hit and- miss approach is not effective on economical and efficiency basis. The combined application of molecular graphics, computational pharmaceutical chemistry and biological data studies are comes in the field of computer added drug design (CADD). These advance computer based techniques are helpful for the achieving to long-term goal for a medical analyst: the prediction of pharmacological activity prior to extensive chemical synthesis and biological data testing.

The biological activity and the molecular structures are the two main aspects for the QSAR study of a specific compound, which leads to generate a new chemical moiety. The Quantitative Structure Activity Relationship (QSAR) paradigm is based on the assumption that there is an underlying relationship between the molecular structure and biological activity. On the basis of this assumption QSAR study establish a correlation between various molecular properties of a series of molecular compound with their well known biological activity.

The antioxidant effects of flavonoids lead to many effective and observable pharmacological responses as cardio-vascular, antithrombogenic, antitumor, anti-inflammatory, antidiarrheal, antiviral, antiplaque etc. Flavonoides are the well known biological response. They have the ability of

modification to the metabolic reaction and activity of body to allergic molecules, viruses and carcinogens. Thus, goal of this work is to syntheses flavonoids starting from commonly available raw materials and its evaluation for antioxidant and antibacterial activity.

EXPERIMENTAL WORK:

Selection of training and test set:

QSAR models are used largely to screen chemical databases and/or virtual chemical libraries for potentially biological active molecules. These developments highlight the importance of rigorous model validation to ensure that the models have both the ability to explain the difference in the biological activity (internal validation) and the acceptable anticipate power e.g. external validation. For model validation the dataset is required to be divided into test set for making the QSAR model and test set for screening its predictive power. For any QSAR model, it is of very importance that the training set selected to calibrate the model exhibits a well-balanced distribution and contains representative molecules.

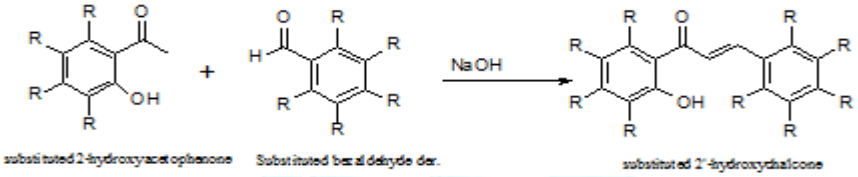
Evaluation of the Model:

The numbers of statistical methods are available for evaluation of the significance of the model, these methods are;

1. **n** number of molecules (> 20 molecules)
2. **k** number of descriptors in a model (statistically n/5 descriptors in a model)
3. **df** degree of freedom (n-k-1) (higher is better)
4. **r2** coefficient of determination (> 0.7)
5. **q2** cross-validated r2 (>0.5)
6. **pred_r2** r2 for external test set (>0.5)
7. **SEE** standard error of estimate (smaller is better)
8. **F-test** F-test for statistical significance of the
9. **F_prob**. Alpha error probability (smaller is better)
10. **Zscore** Z score calculated by the randomization test (higher is better)
11. **best_ran_q2** highest q2 value in the randomization test (as low as compared to q2)
12. **best_ran_r2** highest r2 value in the randomization test (as low as compared to r2) alpha test (<0.01)statistical significance parameter by randomization

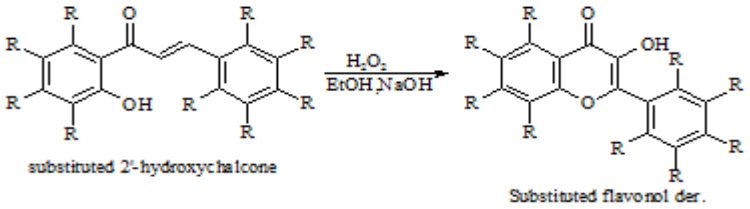
Interpretation of Model:

Multiple regressions are largely used method for construction of QSAR model. It is very easy to interpret a regression procedure modal, which contribution of each descriptor could be seen by the magnitude and sign of its regression coefficient. A descriptor coefficient magnitude shows its relative contribution w.r.t other descriptors and sign indicates whether it is directly (positive) or inversely (negative) proportional to the activity.



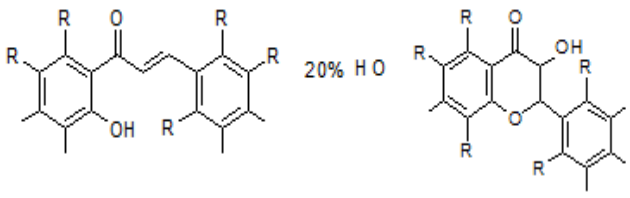
Procedure:

2.5 mmol of the benzaldehyde derivative and 2.5 mmol of the acetophenone derivative were measured accurately and placed in a mortar. To this added 3 pellets of NaOH (7.5 mmole). Mixture was ground for about 5–10 min. The mixture was turned yellow and pasty after a few times of grinding. Grinding was continued until the mixture turn into a solid mass and the solid became powdery. 10 mL of water added to the mortar at the last minute of the grinding period. Product was mixed properly with the water, using the spatula solid product was dislodged from the mortar's wall and filtered.



Procedure:

To a mixture of chalcone [0.01mole] in ethyl alcohol [85ml] was added 20 present aqueous sodium hydroxide [10ml] with continues mixing, thereafter by careful addition of hydrogen peroxide [18ml] 20% solution over a period of 0.5hr.The reaction mixture was mixing by continues stir for 3 hrs. at 300c temperature and then put it onto crushed ice containing 5M Hydrochloric acid. The precipitate then filtered. It washed with water and then dried in hot oven. The dried powder was crystallized from chloroform: methyl alcohol [9:1].



Procedure:

A mixture of powdered 2-hydroxychalcone (0.45 mmol) and aq. Sodium hydroxide solution (8 N, 1.0 ml) and a 30% H_2O_2 solution (0.25 g) was mixed with continues stirring at room temperature for 2 hours. The raw product was filtered off. It was washed with water. The product was dried in a desiccator to give flavanol and recrystallization of the crude product from methyl alcohol.

Characterization of Final Compounds:

The identification & characterization of the prepared compounds were performed on the basis of their physiochemical and spectral data. Such as thin layer chromatography (TLC), melting point (MP), UV-visible analysis(UV), infrared spectroscopy (IR) and Nuclear Magnetic resonance method (^{1}H NMR).

RESULT AND DISCUSSION:

Physico-chemical properties were calculated employing the modeling software Win CAChe 6.1. The calculated descriptors were conformational minimum energies(CME) , HOMO energy, LUMO energy, heat of formation (HF), ionization potential (IP), molar refractivity(MR), Shape Index (basic kappa, order 1) (SI1), log P, electron affinity (EA), solvent accessible surface area (SAS). The above properties served as source data for the statistical software and a correlation matrix was prepared to select the parameters with a very low inter-correlation and maximum correlation with the studied compounds anti- oxidant activity. In random selection, 18 compounds were in training set and 10 in test set. Subsequently with the stepwise multiple linear regression analysis was carried out to achieve the best models.

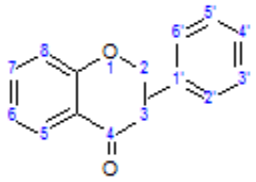


Table 1: Substitution pattern of the series of flavonoids examined for their antiradical activity

Compound	RSAexp. /%	R3	R5	R7	R8	R2'	R3'	R4'	R'5	C2=C3
Morin	96.5	OH	OH	OH	H	OH	H	OH	H	+
Taxifolin	94.8	OH	OH	OH	H	H	OH	OH	H	-
Kaempferol	93.5	OH	OH	OH	H	H	H	OH	H	+
Fustin	91.9	OH	H	OH	H	H	OH	OH	H	-
Galangin	91.8	OH	OH	OH	H	H	H	H	H	+
Rutin	90.9	Ogl	OH	OH	H	H	OH	OH	H	+
Quercetin	89.8	OH	OH	OH	H	H	OH	OH	H	+
luteolin 7-gl	87.6	H	OH	Ogl	H	H	OH	OH	H	+
quercetin 3,7,-digl	86.8	Ogl	OH	Ogl	H	H	OH	OH	H	+
laricytrin	84.6	OH	OH	OH	H	H	OH	OH	OMe	+
laricetrin-3'-gl	83.8	OH	OH	OH	H	H	Ogl	OH	OMe	+
robinetin	82.3	OH	H	OH	H	H	OH	OH	OH	+
fisetin	79	OH	H	OH	H	H	OH	OH	H	+
myricetin	72.8	OH	OH	OH	H	H	OH	OH	OH	+
kaempferol	70.6	Ogl	OH	Ogl	H	H	H	OH	H	+
Apigenin-7-gl	34.8	H	OH	Ogl	H	H	H	OH	H	+
hesperetin	30	H	OH	OH	H	H	OH	OMe	H	-
vitexin	21	H	OH	OH	Ogl	H	H	OH	H	+
3,5,7,3',4',5'-hexamethoxyflavone	12.6	OMe	OMe	OMe	H	H	OMe	OMe	OMe	+
naringenin	6.3	H	OH	OH	H	H	H	OH	H	-
Naringin	4.7	H	OH	Ogl	H	H	H	OH	H	-
7-hydroxyflavone	2.8	H	H	OH	H	H	H	H	H	+
Flavanone	2.6	H	H	H	H	H	H	H	H	-
Flavones	1.5	H	H	H	H	H	H	H	H	+
Chrysin	1.1	H	OH	OH	H	H	H	H	H	+
Apigenin	0.7	H	OH	OH	H	H	H	OH	H	+
8-methoxyflavone	0.7	H	H	H	OMe	H	H	H	H	+
5-hydroxyflavone	0.6	H	OH	H	H	H	H	H	H	+

Experimental values as RSA, radical scavenging activity (percents) were taken from ref. 26, gl: glycosyl

Table 2: physic-chemical parameters of flavonoids

Flavonoids	Log (1/Activity)	eA	HF	HOMO	IP	Log P	LUMO	MR	SI1	CME	SAS
3,5,7,3',4',5'-Hexamethoxyflavone	-1.1	0.76	-206.16	-8.82	8.82	0.19	-0.76	105.74	23.66	-206.16	398.7
5-hydroxyflavone	0.22	0.75	-33.54	-9.13	9.13	2.03	-0.75	68.67	13.01	-33.54	252.7
7-hydroxyflavone	-0.44	0.87	-37.80	-9.34	9.34	2.03	-0.87	68.67	13.01	-37.80	255.0
8-methoxyflavone	0.15	0.78	-27.74	-8.98	8.98	2.07	-0.78	73.43	13.96	-27.74	272.5
Naringin	-0.67	0.29	- 567.09	-9.12	9.12	0.09	-0.29	133.73	32.40	-567.09	520.9
Apigenin Glucoside	-1.54	0.89	-360.20	-9.08	9.08	0.00	-0.89	104.49	24.14	-360.20	406.7
Apigenin	0.15	0.78	-123.03	-9.05	9.05	1.47	-0.78	72.05	14.92	-123.03	273.1
Chrysin	-0.04	0.78	-78.45	-9.23	9.23	1.75	-0.78	70.36	13.96	-78.45	262.7
Fisetin	-1.89	0.98	-154.49	-8.74	8.74	0.56	-0.98	73.73	15.88	-154.49	280.7
Flavanone	-0.41	0.41	-16.59	-9.30	9.30	2.84	-0.41	65.35	12.06	-16.59	243.4
Flavones	-0.17	0.85	6.90	-9.27	9.27	2.32	-0.85	66.97	12.06	6.90	244.7
Fustin	-1.96	0.51	-184.42	-9.09	9.09	1.56	-0.51	71.77	15.88	-184.42	281.8
Galangin	-1.96	0.79	-111.31	-8.85	8.85	0.85	-0.79	72.04	14.92	-111.31	268.7
Hesperitin	-1.47	0.36	-181.60	-8.84	8.84	1.74	-0.36	76.89	16.84	-181.60	298.5
Kaempferol dirhamnose	-1.84	0.82	-532.89	-8.94	8.94	-2.96	-0.82	134.13	32.40	-532.89	517.8
kaempferol	-1.97	0.79	-155.60	-8.71	8.71	0.56	-0.79	73.73	15.88	-155.60	278.8
laricetrin 3-O-glucoside	-1.92	1.01	-497.00	-8.75	8.75	-1.72	-1.01	114.68	28.02	-497.00	443.2
Laricytrin	-1.93	0.86	-225.57	-8.69	8.69	0.03	-0.86	81.89	18.78	-225.57	314.6
luteoline glucoside	-1.94	0.87	-395.90	-8.91	8.91	-0.28	-0.87	106.18	25.10	-395.90	413.1
Morin	-1.98	0.68	-195.33	-8.53	8.53	0.28	-0.68	75.43	16.84	-195.33	285.8
Myricetin	-1.86	0.95	-235.10	-8.79	8.79	-0.01	-0.95	77.12	17.81	-235.10	296.7
Naringenin	-0.80	0.35	-147.57	-9.24	9.24	1.99	-0.35	70.43	14.92	-147.57	270.8
Quercetin Diglucoside	-1.94	1.74	-559.06	-7.84	7.84	-4.41	-1.74	130.08	34.34	-559.06	517.5
Quercetin	-1.95	0.88	-195.45	-8.68	8.68	0.28	-0.88	75.43	16.84	-195.45	288.5
Robenitin	-1.92	1.04	-194.10	-8.85	8.85	0.28	-1.04	75.43	16.84	-194.10	289.1
Rutin	-1.96	0.48	-617.39	-9.00	9.00	-4.53	-0.48	137.27	34.34	-617.39	513.6
Taxifolin	-1.98	0.43	-225.85	-9.05	9.05	1.27	-0.43	73.46	16.84	-225.85	290.2
Vitaexine	-1.32	0.92	-399.67	-9.01	9.01	-0.28	-0.92	106.18	25.10	-399.67	398.6

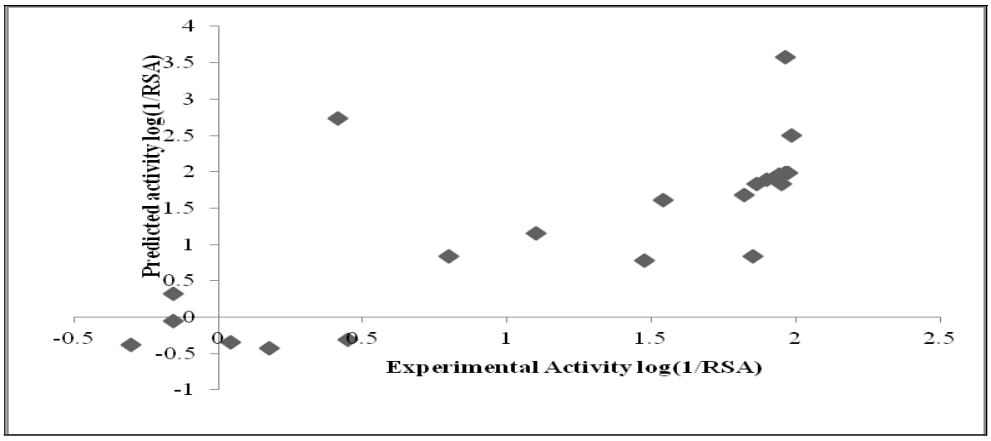


Figure 1: Experimental *vs* predicted

Table 3: ANOVA of predicted value

Groups	Count	Sum	Average	Variance
-1.51851	9	-14.6228	-1.62475	0.063638
86.27	9	694.379	77.15322	201.73
-8.151	9	-72.489	-8.05433	0.112396

Source of Variation	SS	df	MS	F	p-value	F-crit
Between Groups	40522.91	2	20261.45	301.0527	1.01E-17	3.402826
Within Groups	1615.248	24	67.30202			
Total	42138.16	26				

Table 4: predicted activity of synthesized compounds

Comp. code	HOMO-LUMO	Molar refractivity	Prediction
V1	68.652	-7.927	-2.79822
V2	75.115	-7.769	-2.76108
V3	83.08	-7.43	-2.52559
V4	84.775	-7.409	-2.62972
V5	78.97	-7.595	-2.67344
R1	66.685	-8.841	-2.98191
R2	73.149	-8.778	-2.87362

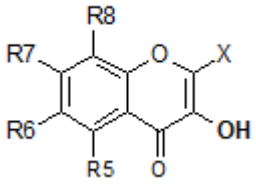


Figure 2: General structure of 3-hydroxy flavonoid derivatives

Table 5: Different substitution of synthesized compounds

Compound code	COMPOUND NAME	SU BSTITUENTS				
		X	R 5	R 6	R 7	R 8
V 1	3-hydroxy-2-phenyl-4H-chromen-4- one	2 - Hydroxyphenyl	H	H	H	H
V 2	3-hydroxy-2-(4-methoxyphenyl)- 4H-chromen-4-one	4 - Isopropylphenyl	H	H	H	H
V 3	3-hydroxy-2-*p*-tolyl-4*H*-chromen-4- one	4 - Methylphenyl	H	H	H	H
V 4	3,7-dihydroxy-2-(2-hydroxyphenyl)- 4H-chromen-4-one	2 - Hydroxyphenyl	H	H	OH	H
V 5	3,7-dihydroxy-2-(4-isopropylphenyl)- 4H-chromen-4-one	4 - Isopropylphenyl	H	H	OH	H
V 6	3,7-dihydroxy-2-*p*-tolyl-4*H*-chromen- 4-one	4 - Methylphenyl	H	H	OH	H

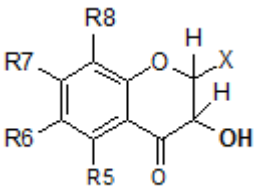


Figure 3: General structure of 2, 3-dihydroxy flavan-3-ol derivatives

Table 5: Different substitution of 2, 3-dihydroxy flavan-3-ol derivatives

Compound Code	Compound Name	Substituents				
		X	R 5	R 6	R 7	R 8
R1	3-hydroxy-2-phenyl-2,3-dihydro- 4H-chromen-4-one	2 - Hydroxyphenyl	H	H	H	H
R2	2,3 -dihydro-3-hydroxy-2-(4-isopropylphenyl)chromen-4-one	4 - Isopropylphenyl	H	H	H	H
R3	2,3-dihydro-3-hydroxy-2-p- tolylchromen-4-one	4 - Methylphenyl	H	H	H	H
R4	2,3-dihydro-3,7-dihydroxy-2-(2-hydroxyphenyl)chromen-4-one	2 - Hydroxyphenyl	H	H	OH	H
R5	2,3-dihydro-3,7-dihydroxy-2-(4-isopropylphenyl)chromen-4-one	4 - Isopropylphenyl	H	H	OH	H
R6	3, 7-dihydroxy-*p*-tolylchromen-4- one	4 - Methylphenyl	H	H	OH	H

Minimum inhibitory concentration:

On observation of positive results of antimicrobial activity, the MICs of synthesized compounds were determined by tube dilution method. Studies indicated the requirement of inhibitory concentration in order "chalcone derivatives > 2,3-dihydroflavan-3-ol derivatives > 3-hydroxyflavone derivatives. The result of study indicated that C5 [1-(2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-one]; is only inactive against *Streptococcus mutans*. All 3-hydroxyflavone derivatives exhibited their MIC to be in range of 250-125 µg/ml., 2,3-dihydroflavan-3-ol derivatives exhibited their MIC to be in range of 1000- 500 µg/ml. The chalcone derivatives exhibited their MIC to be at 250 µg/ml.

Table 6: MIC of flavonoid derivatives with *Streptococcus mutans*

Compound code	% Transmittance			
	1000 µg/ml	**500 µg/ml**	**250 µg/ml**	**125 µg/ml**
J1	37	34	**30**	17
J2	24	26	**29**	16
J3	18	**27**	17	19
J4	33	35	**28**	19
J5	30	31	29	**26**
J6	31	39	**34**	27
V1	30	37	**41**	25
V2	27	33	30	**27**
V3	32	34	**36**	12
V4	33	36	**25**	15
V5	33	35	**28**	19
V6	32	33	30	**28**
R1	30	39	**35**	27
R2	**47**	24	21	25
R3	**34**	15	18	15
R4	58	**43**	23	27
R5	44	**48**	32	30
R6	**53**	16	13	18

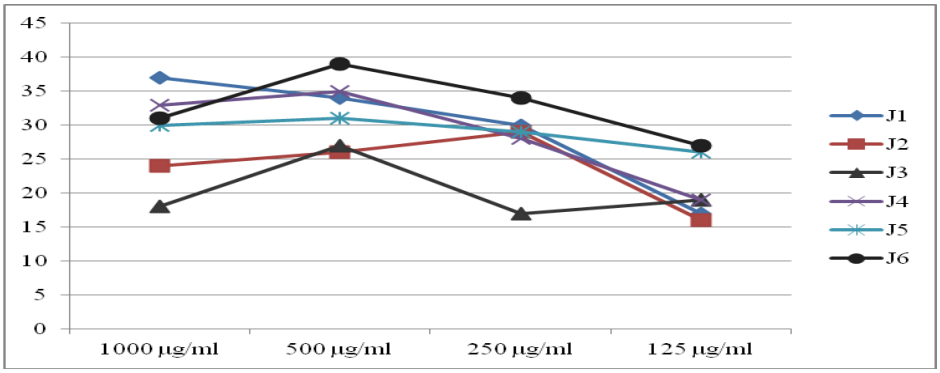


Figure 4: MIC of 2-hydroxy Chalcone derivatives

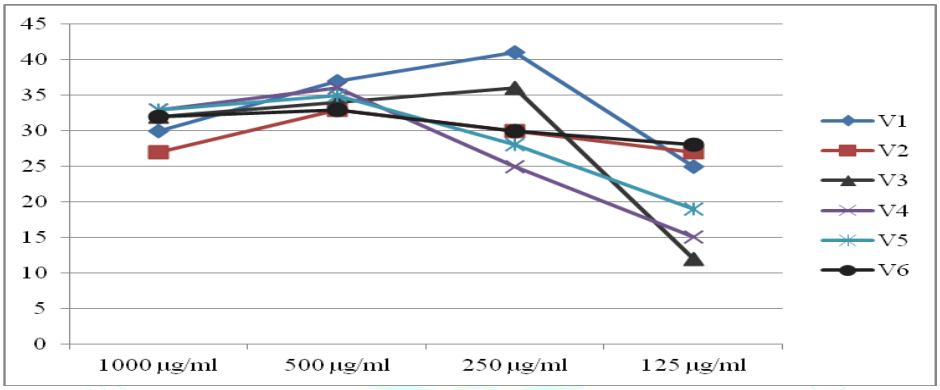


Figure 5: MIC of 3-hydroxy flavone derivatives

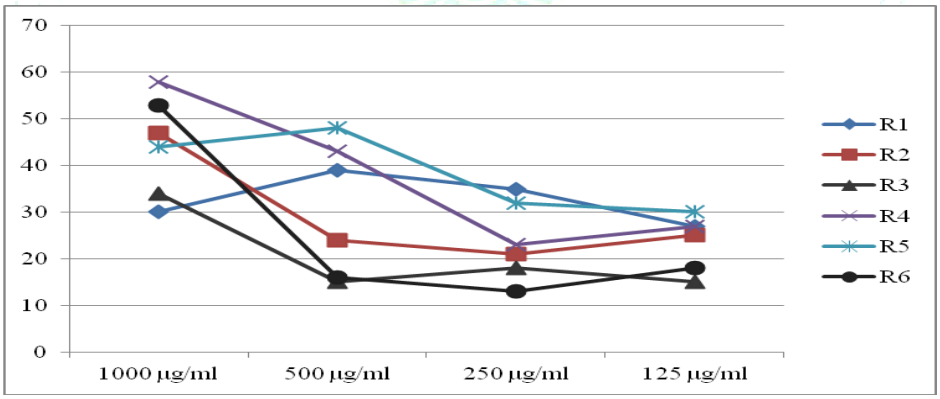


Figure 6: MIC of 2, 3-dihydroxy flavan-3-ol derivatives

CONCLUSION:

A QSAR study was performed on a series of flavonoids using WIN CAChe 6.1 and Vlife MDS 3.5 to explore the physico-chemical parameters responsible for their antioxidant activity. The equation generated was validated. The selected QSAR model showed correlation coefficient R^2 0.7609, and cross-validated squared correlation coefficient Q^2 of 0.5041 for antioxidant activity. The developed model indicated that positive dependence of molar refractivity & HOMO-LUMO gap on the antioxidant activity of flavonoids. The newly synthesized flavonoid derivatives were screened for antioxidant, antimicrobial activity. The results of pharmacological screenings are satisfactory. Most of the derivatives have shown comparable antioxidant activity in relation to standard Ascorbic acid. These derivatives were found to have inhibitory effect against *Streptococcus mutans*. The result of antimicrobial study against microorganism *Streptococcus mutans* shows flavonoid derivatives possess antibacterial activity.

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