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Research Article

Qsar Study of Coumarin Derivatives as Anti-inflammatory Agents

Shailja Sachan[1], Vikash Pandey[2*] and Santosh Tiwari[2]

1. Department of Chemistry, Govt. M.S.G. College, Rewa, (M.P.)
2. Department of Chemistry, A.P.S. University, Rewa, (M.P.)

Abstract

Quantitative structure activity/property relationship analysis of 12 coumarin derivative showing spectrum anti-inflammatory activity which was performed by multiple linear regression method. The physicochemical descriptor and topological descriptor are used as independent variable while pMIC is used as dependent variable, made using largest correlation coefficient (r^2 =0.87) obtained. The validation procedure indicated excellent quality of derived QSAR/QSPR.

Key Words: QSAR, Antifungal, Heterocyclic

Introduction

During the past two decades an increasing number of quantitative structure-activity/property relationship (QSAR/ QSPR) models have been using theoretical molecular descriptors for predicting biomedical, toxicological, and technological properties of chemicals.[1-7] QSARs/QSPRs are mathematical models that seek to predict complicated physicochemical/ biological properties of chemicals from their simpler experimental or calculated properties.[8] The main problem with the use of experimental data as independent variables in QSARs is that they are not available for the majority of chemical structures, real or hypothetical.

Inflammation is a complex phenomenon involving interrelationships humoral and cellular reactions through a number of inflammatory mediators. It is a usual symptom covering different pathologies, and there are still many questions to be answered in order to understand the inflammatory process as well as a need for better-tolerated and more efficient nonsteroidal anti-inflammatory drugs. In the pathways of the inflammatory process, the implication of free radicals is particularly important.

It has also been reported. that anti-inflammatory drugs may be effective in the prevention of free radical-mediated damage.[9] Coumarins have been reported to have multiple biological activities.[10] They have been used to treat such diverse ailments as cancer, burns, brucellosis, and cardiovascular and rheumatic diseases.[11] The coumarin molecule has been shown to possess unique anti-edema and anti- inflammatory activities. Thus, coumarin derivatives could be particularly effective in the treatment of all high protein edemas.[12-14]

***Corresponding Author**

E-mail: santoshsonu_2007@rediffmail.com
Mob. 910.893.1703

Coumarin is a benzopyrone and a naturally occurring constituent of many plants and essential oils, including tonka beens, sweet clover, woodru, oil of cassia and lavender. The presence of phenolic hydroxyl and carboxylic acid groups on the coumarin nucleus has been considered necessary for anti-inflammatory activtity. The coumarins are extremely variable in structure and due to the various substitutions in the basic structural form their biological activity is influenced. As a result, a lot of biological parameters should be evaluated to increase our understanding of the mechanisms by which these coumarins act and a careful structure-property/activity-relationship study of coumarins should be conducted.

Among the multivariate analysis used in the cheminformatics, the principal component analysis (PCA) and cluster analysis (CA) have been most widely used methods. Accordingly, in this study MLR and PCA is used for building an efficient model in order to evaluate the relationship between physicochemical and topological descriptor with bioactivity of anti-inflammatory coumarins.

Material and Methods

The data set of 12 coumarins and coumarin derivatives selected on the basis of anti-inflammatory activity. Anti-inflammatory activity of compounds from table.1 that were screened by the well dilution method has been taken from the literature.[15] Authors encountered problems related to reporting of anti-inflammatory activity according to the C log p30 which disabled the analysis of data set with adequate care.

Preliminary results have shown that coumarins posses considerable anti-inflammatory activity. Ten attributes have been generated for the description of selected coumarin derivatives that includes (Table.2); formula weight, molar refractivity, molar volume, parachor, index of refraction, surface density, polarizability, molecular index and nominal mass, etc. Calculation of quantum chemical descriptor was proceded by molecular geometry optimization based on the PM3 semiempirical approach. Both semiempirical and regular calculations were carried out by ACD LAB 11.02 were included in the pool that makes better understanding of structure-function activity of coumarin anti-inflammatory activity.

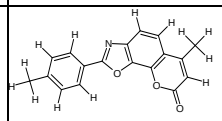
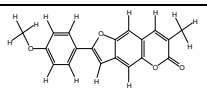
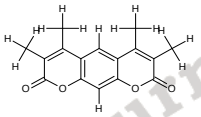
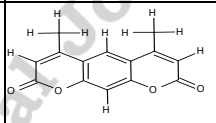
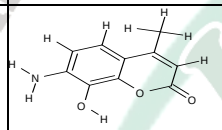
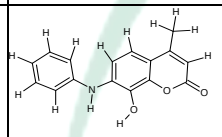
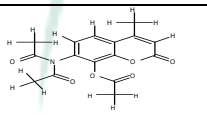
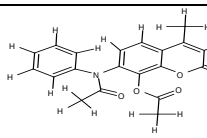
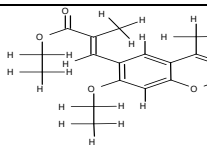
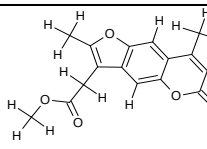
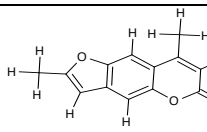
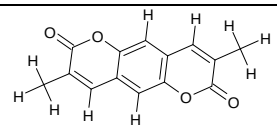
Number	Compound	Clog p30
1		3.86
2		4.49
3		2.58
4		1.68
5		1.33
6		3.68
7		3.73
8		4.76
9		4.07
10		2.21
11		2.97
12		1.68

Table: 1 Structure and bioactivity of studied coumarins

The physicochemical and topological descriptors were used as the inputs, while C log P_{30} was the output of the present MLR. Model validation process provides a reasonable mean for understanding and approach to molecular design and action mechanism analysis. Applied primary validation methods involved the use of random number generators as a part of the learning process. Accuracy has been selected for evaluation of predictive performance of a single validation process, while a correlation coefficient of accuracies obtained was established as a measure of learning stability. Also cross validation was applied by leave-n-out method.

Results

The results of this paper are based on investigation and analysis of collected or calculated data of several coumarin structural descriptors. The MLR was performed to build a powerful model for prediction of lead and template anti-inflammatory coumarins. To rationalize the substituent variations of the coumarin derivatives to provide insight for the future endeavors. These models were identified in MLR by successively incrementing the filter-3 with increasing number of descriptors (per equation). For this the optimum r-bar value of the preceding level model has been used as the new threshold of filter-3 for the next generation. The highest significant models in three and four descriptors are given below.

$$C \log P_{30} = -1.955 = 0.5357\ POL + 0.0383\ {}^{1}X^{v} - 3.057\ FW$$

n =12, MSE^2 = 0.4807, R^2 =0.8783, R^2A = 0.8326, F-Ratio = 19.2370,

These and all follow up regression equations, the values given in the parentheses are the standard errors of the regression coefficients. The r^2 And Y (sd) is the mean random squared multiple correlation coefficient of the regressions in the activity (Y) randomization study with its standard deviation from 100 simulations. In the randomization study (100 simulations per model), none of the identified models has shown any chance correlation. The Se Test is the standard error of estimation for the test set activity values. The signs of the regression coefficients suggest the direction of influence of explanatory variables in the models.

Com. No.	$^1X^v$	FW	MR	MV	PC	IR	ST	POL	MI	NM
1	7.09	291.3007	82.12	226.7	607.9	1.644	51.6	32.55	291.0895	291
2	5.597	306.312	85.88	241.2	632.7	1.63	47.3	34.04	306.089	306
3	6.38	270.2799	72.09	216.6	551.2	1.579	41.8	28.58	270.089	270
4	5.535	242.2268	62.68	180.7	478.5	1.61	49.1	24.85	242.0579	242
5	4.1	191.1834	50.58	135.7	385.1	1.667	64.7	20.05	191.058	191
6	6.615	267.2793	75.72	199.5	557.5	1.683	60.9	30.02	267.0895	267
7	5.29	317.29	79.45	237.9	640.9	1.582	52.6	31.49	317.0899	317
8	8.1	351.3527	94.55	271	729.5	1.615	52.5	37.48	351.1107	351
9	7.21	316.3484	87.18	269.3	688.6	1.560	42.7	34.56	316.1311	316
10	6.2	286.2794	75.39	221	584.3	1.597	48.8	29.88	286.0841	286
11	5.08	214.2167	59.43	168.2	440.3	1.624	46.9	23.56	214.0629	214
12	5.534	242.2268	62.68	180.7	478.5	1.61	49.1	24.85	242.0579	242

$$C \log P_{30} = -1.9550 + 0.5357\ POL - 0.0383\ MI - 0.3748\ {}^1X^V$$

n =12 MSE^2 =0.4806 R^2 = 0.8783 R^2A = 0.8326 F-Ratio = 19.2360

The descriptor $^1X^V$, MI, has shown negative influence on the activity. Thus, suggesting that a lower value of MI and $^1X^V$ connectivity index would be favorable to the activity.From the positive sign of regression coefficient of descriptor POL, the sum of topological distance.

A total number of 8 models, sharing 3 descriptors among them, were obtained through MLR. All these 3 descriptors along with their brief meaning, average regression coefficients and total incidence are listed in Table **5.2,** which will serve as a measure of their estimate across these models. The given below are some five-descriptor models for the activity. These models have accounted for up to 87 percent variance in the observed activities.

The results of the QSAR study give rise to QSAR models with good predictive ability for anti-inflammatory activity. Linear regression for the total data set of 12 coumarin derivative in the present study with the anti-inflammatory activity demonstrated that the physicochemical (Polarizability and Molecular Index) and topological descriptor Second order connectivity Index appears to be the governing factors for the anti-inflammatory potency for synthesized coumarin derivatives.

Table 3: correlation Matrix of the descriptor used in model

	C log P_{30}	$^1X^v$	FW	MR	PC	POL	MI
Clog P_{30}	1.0000						
$^1X^v$	0.6568	1.0000					
FW	0.8121	0.7663	1.0000				
MR	0.8886	0.8215	0.9730	1.0000			
PC	0.8467	0.7967	0.9912	0.9862	1.0000		
POL	0.8885	0.8216	0.9731	0.9999	0.9862	1.0000	
MI	0.8121	0.7662	1.0000	0.9730	0.9912	0.9731	1.0000

Table -4: The resulted QSAR models obtained by different regression methods and their calibration statistic

Parameter	Ai	Intercept	M.S.E.^{2}	R^2	AR^2	F-Ratio	T value
MR	A1 = 0.0383	-2.855	0.5650	0.7896	0.7686	37.5340	-2.903
PC	A1 = 0.0383	-2.3352	0.6556	0.7160	0.6886	25.3000	
POL	A1 = 0.2026	-2.8558	0.5650	0.7890	0.7684	37.4870	
FW, MR	A1= 0.0383 A2 =0.1670	-2.4070	0.5170	0.8415	0.8063	23.895	-2.570
NM, MR	A1 = 0.0383 A2 =0.1672	-2.4073	0.517	0.8415	0.8063	23.895	-2.570
POL, FW	A1 = 0.4221 A2 = 0.0383	-2.4092	0.5174	0.8413	0.8061	23.859	-2.570
POL, FW, $^1X^v$	A1 = 0.5357 A2 = -0.3745 A3 = 0.0383	-1.9550	0.4807	0.8783	0.8326	19.237	-2.129
POL, MI, FW	A1 = 0.5535 A2 = 30.3573 A3 =-30.3755	-2.3665	0.5054	0.8654	0.8149	17.147	-2.583
POL, MI, $^1X^v$	A1 = 0.5356 A2 = -3.058 A3 = -0.3748	-1.9552	0.4806	0.8783	0.8326	19.2370	-2.129

F = F- Ratio, M.S.E. ^{2} = Root of Mean square error,
AR^2 = Adjusted R^2, R^2 = Multiple Correlation coefficient,

The results of the QSAR study give rise to QSAR models with good predictive ability for anti-inflammatory activity. Linear regression for the total data set of 12 coumarin derivative in the present study with the anti-inflammatory activity demonstrated that the physicochemical (Polarizability and Molecular Index) and topological descriptor Second order connectivity Index appears to be the governing factors for the anti-inflammatory potency for synthesized coumarin derivatives.

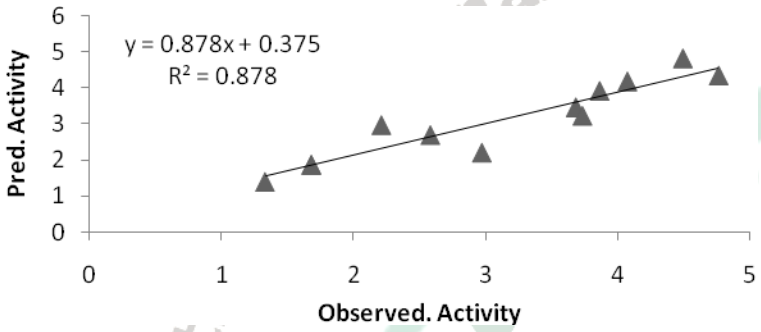


Table 5: Observed and Predicted Value of Inhibitory activity of Anti-inflammatory Agents

Row	Obs.	Pre.	Res.
1	3.860	3.922	-0.062
2	4.490	4.821	-0.331
3	2.580	2.703	-0.123
4	1.680	1.879	-0.199
5	1.330	1.406	-0.076
6	3.680	3.468	0.212
7	3.730	3.233	0.497
8	4.760	4.349	0.411
9	4.070	4.187	-0.117
10	2.210	2.978	-0.768
11	2.970	2.215	0.755
12	1.680	1.880	-0.200

References

1) Gute, B. D., Basak, S. C., , *SAR QSAR EnViron. Res*., *7*(1997) 117-131.
2) Basak, S. C., Grunwald, G. D., *Chemosphere.*, *31*(1995) 2529-2546.
3) Basak, S. C., Grunwald, G. D., In *Proceeding of XVI International Cancer Congress*., (1995) 413-416.
4) Basak, S. C., Devillers, J., Balaban, A. T., Eds., Gordon & Breach Science Publishers., The Netherlands, (1999) 563-593.
5) Basak, S. C., Grunwald, G. D., Gute, B. D., Balasubramanian, K., Opitz, D., *J. Chem. Inf. Comput. Sci*., *40*(2000) 885-890.
6) Basak, S. C., Gute, B. D., Grunwald, G. D., *J. Chem. Inf. Comput. Sci., 37*(1997*)* 651-655.
7) Basak, S. C., Gute, B. D., Ghatak, S., *J. Chem. Inf. Comput. Sci*., *39*(1999) 255-260.
8) Hansch, C., Leo, A., American Chemical Society: Washington, DC, (1995) .
9) Gute, B. D., Basak, S. C., , *SAR QSAR EnViron. Res*., *7*(1997) 117-131.
10) Basak, S. C., Grunwald, G. D., *Chemosphere.*, *31*(1995) 2529-2546.
11) Basak, S. C., Grunwald, G. D., In *Proceeding of XVI International Cancer Congress*., (1995) 413-416.
12) Basak, S. C., Devillers, J., Balaban, A. T., Eds., Gordon & Breach Science Publishers., The Netherlands, (1999) 563-593.
13) Basak, S. C., Grunwald, G. D., Gute, B. D., Balasubramanian, K., Opitz, D., *J. Chem. Inf. Comput. Sci*., *40*(2000) 885-890.
14) Basak, S. C., Gute, B. D., Grunwald, G. D., *J. Chem. Inf. Comput. Sci., 37*(1997*)* 651-655.
15) Basak, S. C., Gute, B. D., Ghatak, S., *J. Chem. Inf. Comput. Sci*., *39*(1999) 255-260.
16) Hansch, C., Leo, A., American Chemical Society: Washington, DC, (1995) .
17) Hiller, P. L., Hodd, K. O., Wilson, R. L., *Chem.-Biol. Interact., 47*(1983)293-305.
18) Egan, D., O'Kennedy, E., Moran, E., Cox, D., Prosser, E., Thornes, R. D., *Drug. Metab. Rev., 22(*1990)503-529.
19) Murray, R. D. H., Mendez, I., Brawn, S. A., *The Natural Coumarins*; Wiley: New York, (1982).
20) Piller, N. B., *Br. J. Exp. Pathol.,56*(1975)554-559.
21) Piller, N. B., Casley-Smith, J. R., *Br. J. Exp. Pathol., 56* (1975) 439-445.
22) Fylaktakidou, K., Hadjipavlou-Litina, D., Litinas, K., Nicolaides., *Cur. Pharm. Des., 30*(2004) 3813-3833.
23) Kontogiorgis, C., Hadjipavlou, D.,J. of Enzyme Inhibi. And Med. Chem.,18(1)(2010)63-69.