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A QSAR study of sesquiterpene lactones from *Inula falconeri* as potent anti-inflammatory agents

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ABSTRACT

Sesquiterpene lactones from Inula falconeri possess diverse biological activities i.e., anticancer, antibacterial, hepaprotective, cytotoxic, and anti-inflammatory activity. In this work we calculated quantum chemical, thermo dynamical and topological descriptors of 16 training compounds and three different QSAR models between the experimental anti-inflammatory activity and calculated molecular descriptors have been constructed. The significance of these models is verified on the basis of correlation (R), standard deviation of the regression (S), Fischer F test and quality factor (Q). These QSAR models may be used to find out the activity of the designed compounds.

Key words: QSAR, *Inula falconeri*, Sesquiterpene lactones

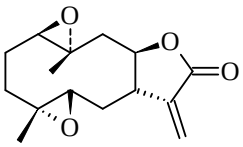
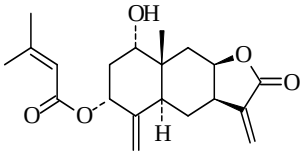
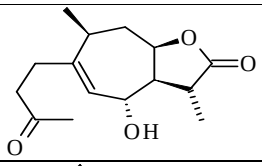
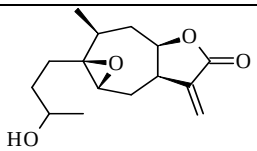
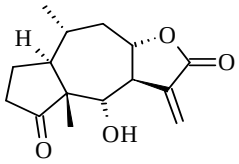
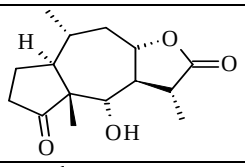
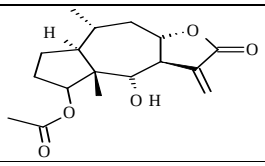
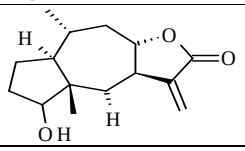
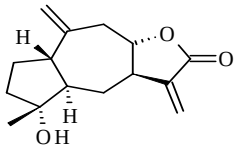
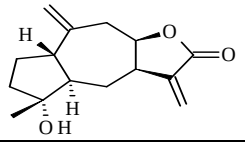
INTRODUCTION

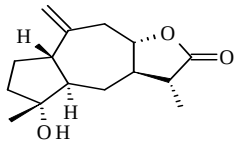
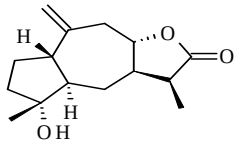
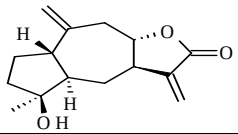
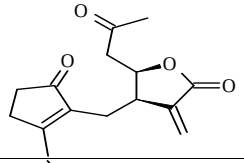
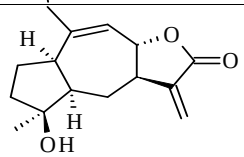
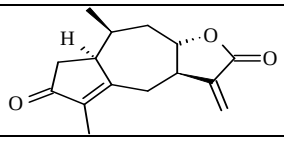
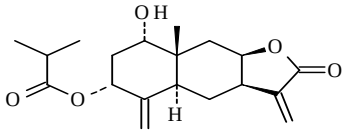
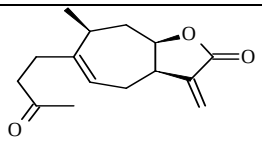
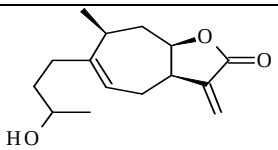
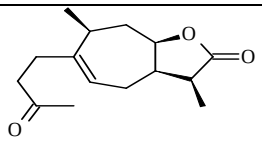
Sesquiterpenes, a class of terpenoids with a skeleton of 15 carbons, occur as hydrocarbons or in oxygenated forms such as alcohols, ketones, aldehydes, acids, and lactones. Among them sesquiterpene lactones are of special interest because of their biological and pharmacological activities. Sesquiterpene lactones constitute a large and diverse group of biologically active plant chemicals that possess anti-inflammatory and antitumor activity [1]. A number of plants from the Inula genus have rich source of sesquiterpenoids and is famous for its diverse biological activities i.e., anticancer, antibacterial, hepaprotective, cytotoxic, and anti-inflammatory activity [2]. Aim of the present study is to build QSAR models using multiple regression method, to explore the correlations between the experimental anti-inflammatory activity and calculated molecular descriptors of 16 sesquiterpene lactones from *Inula falconeri*.

EXPERIMENTAL SECTION

A total of 20 sesquiterpene lactones from *Inula falconeri* with anti-inflammatory activities via the inhibition of NO production in RAW264.7 macrophages published from the literature [3] were used for the QSAR studies. The initial structures of 20 compounds used in this study were generated by ChemSketch [4]. The biological property of this data set is reported as IC_{50} (μM) values and this value was changed to the logarithmic scale [log IC_{50}]. Structural details of the 20 compounds and their biological activity are listed in Table 1. It is found that HOMO energy (EH), LUMO energy (EL), dipole moment (μ), SIC (Structural Information Content), CIC (Complementary Information Content), entropy (S) and χ (electronegativity) can better represent the biological activity of the selected compounds.

Table 1: structural feature of sesquiterpene lactones from *Inula falconeri* with anti-inflammatory activity

Comp no	Structure	IC_{50} (µM)
1		6.40
2		4.70
3		21.90
4*		18.90
5		2.18
6		20.3
7		2.05
8		9.89
9*		9.64
10		3.94

11		41.2
12*		19.53
13		7.30
14		15.82
15		5.94
16		12.86
17		9.12
18*		7.14
19		5.48
20		64.9

**indicates test set compounds*

The quantum chemical properties (EH, EL, μ) of the studied molecules have been determined by DFT/B3LYP calculation and the basis set 6-31G* was used [5]. All quantum chemical calculations were performed with the Firefly [6].

The average information content is defined on the basis of the Shannon information theory and is calculated as follows [7, 8]:

$$IC = -\sum_{i=1}^{n} p_i \log_2^{p_i} \quad (p_i = n_i/n)$$

Where n_i is the number of atoms in the i^{th} class and n is a total number of atoms in the molecule. The division of atoms into different classes depends upon the coordination sphere that one has taken into account. This leads to the indices of different order k. The information content (IC) is equal to average information content multiplied by the total number of atoms. Other information content indices (SIC-structural IC, CIC-complementary IC) are defined as follows [9].

$$SIC^k = IC^k / \log_2^D$$
$$CIC^k = \log_2^n - IC^k$$

Entropy (S) at 298K of different compounds was calculated using semi-empirical PM6 method by Mopac [10]. Electronegativity (χ) is derived from the DFT framework and is defined as [11]:

$\chi_{\text{koopmans}} = (EH+EL)/2$

Multiple linear regression (MLR) analysis was used to build up QSAR models. Different combinations of parameters were tried to develop these models. Statistical qualities of MLR equations were judged by square of the correlation coefficient (R^2), standard deviation of the regression (S), Fischer statistics (F) and quality factor (Q) [12,13]. The graph theoretical descriptors such as SIC, CIC, and MLR were computed using program written by us in Fortran-77.

RESULTS AND DISCUSSION

The data set of 20 compounds was divided into two groups. The training sets constitute 16 compounds (1,2,3,5,6,7,8,10,11,13,14,15,16,17,19,20) and the remaining 4 compounds (4,9,12,18) are part of the test sets. The list of the descriptors of training and test compounds are presented in Table 2.

Table 2: SIC_1, CIC_1, quantum chemical descriptors, entropy at 298 K and electronegativity of 20 inhibitors

Comp no.	SIC_1	CIC_1	EH (eV)	EL (eV)	μ (debye)	S (cal/M-K)	χ (eV)
1	0.4763	2.7679	-6.9988	-1.2300	5.0057	128.2796	-4.1144
2	0.4984	2.8454	-6.8734	-1.3660	3.0454	155.3138	-4.1197
3	0.4878	2.7440	-6.5416	-0.6721	4.0324	136.5074	-3.6069
4	0.4947	2.7072	-6.8600	-1.2436	4.7691	133.2406	-4.0518
5	0.5332	2.4672	-6.8328	-1.2000	5.5484	124.8293	-4.0164
6	0.4822	2.7744	-6.8165	-1.0776	5.4920	127.5972	-3.9471
7	0.4905	2.8057	-7.1375	-1.3878	3.4364	158.2125	-4.2627
8	0.4880	2.7248	-6.9171	-1.1429	5.5290	137.8948	-4.0300
9	0.5113	2.5649	-6.8872	-1.2762	4.5649	120.9682	-4.0817
10	0.5113	2.5649	-6.7702	-1.2218	4.7782	120.7365	-3.9960
11	0.4821	2.7560	-6.7838	0.1633	4.7946	123.1420	-3.3103
12	0.4821	2.7560	-6.7838	0.1633	4.7946	123.1214	-3.3103
13	0.5113	2.5649	-6.7484	-1.2789	4.2564	120.7273	-4.0137
14	0.4990	2.6100	-6.1498	-1.1592	5.0376	133.1585	-3.6545
15	0.5275	2.4795	-6.6423	-1.1320	6.3539	121.6708	-3.8872
16	0.4986	2.5923	-6.4110	-1.4123	3.7251	121.2161	-3.9117
17	0.4679	3.0480	-6.9716	-1.3442	3.9610	151.9919	-4.1579
18	0.4863	2.6958	-6.4763	-1.2599	3.2386	144.7034	-3.8681
19	0..5165	2.5729	-6.4409	-1.1973	3.9615	130.7239	-3.8191
20	0.4604	2.8716	-6.4437	-0.6095	3.1041	130.2655	-3.5266

Among the generated QSAR models; three models were finally selected. Model summary of three best models with predicted log IC_{50} are given below:

Model1
Log IC_{50}=13.208046 + 0.8186EH +0.4259LH +0.0630μ +(-13.1295)SIC_1 + (-0.0223)CIC_1

N=16, R=0.96, R^2=0.92, F=23, S=0.40, Q=2.40

Model 2
Log IC_{50} = 4.2297+ (-0.3389)EL + (1.8210)χ + (1.2849)CIC_1
N=16, R=0.91, R^2=0.83, F=19.53, S=0.39, Q=2.33

Model 3
Log IC_{50}= 4.2297 + -0.9710S + 0.9800χ + (-12.3293)SIC_1
N=16, R=0.95, R^2=0.90, F=36, S=0.40, Q=2.38

By using model number 1, 2 and 3 the predicted log IC_{50} values of 16 training inhibitors are presented in Table 3 together with experimental log $IC_{50.}$ The model 3 with the R=0.95, R^2=0.90, F=36, S=0.40, Q=2.38 turns out to be the best fit model.

Table 3: List of experimental and predicted logIC_{50} of 16 training compounds

Comp no.	Experimental logIC_{50}	Predicted logIC_{50} (by model 1)	Predicted logIC_{50} (by Model 2)	Predicted logIC_{50} (by Model 3)
1	0.8062	0.9550	0.7107	1.0209
2	0.6721	0.5844	0.8467	0.5576
3	1.3404	1.3551	1.4151	1.3161
5	0.3385	0.3975	0.4926	0.4419
6	1.3075	1.1222	0.9721	1.1173
7	0.3118	0.4881	0.5427	0.4969
8	0.9952	0.9393	0.7795	0.8892
10	0.5955	0.6763	0.6627	0.7643
11	1.6149	1.6356	1.6875	1.7771
13	0.8633	0.6370	0.6498	0.7470
14	1.1992	1.3877	1.3213	1.1555
15	0.7738	0.7077	0.7207	0.6637
16	1.1092	0.9890	0.9160	0.9996
17	0.9600	0.9668	1.0301	0.9172
19	0.7388	0.8364	0.9868	0.7963
20	1.8122	1.7603	1.7041	1.7780

Using the model number 3, we calculated the theoretical log IC_{50} of the test set (R=0.53) which appeared in Table 4. The correlation graph of training compounds between experimental log IC_{50} and predicted log IC_{50} (by model 3) are presented in Fig. 1.

Table 4: List of experimental and predicted pIC_{50} of 4 test compounds

Comp no.	Experimental logIC_{50}	Predicted logIC_{50} (by Model 3)
4	1.2765	0.9156
9	0.9841	0.6785
12	1.2907	1.7772
18	0.8537	1.0220

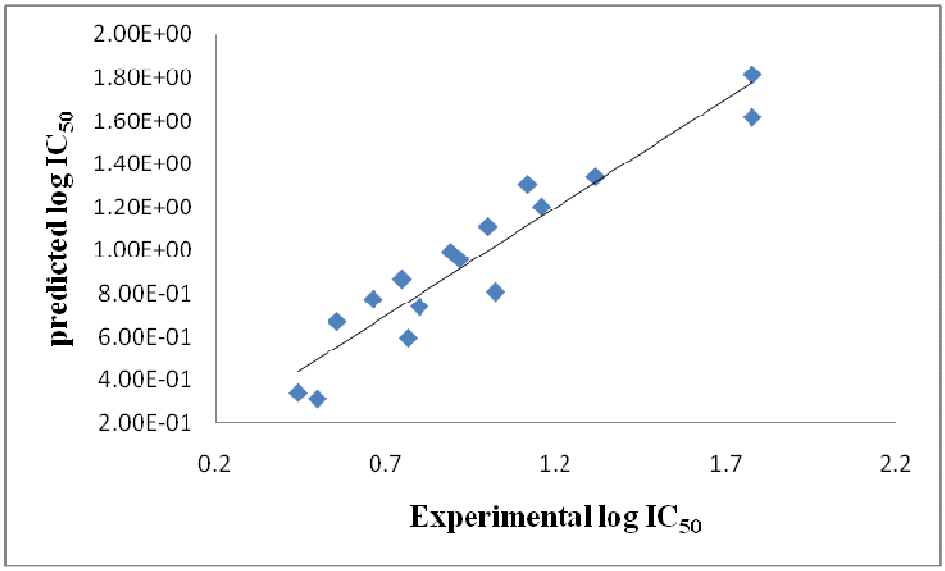


Figure 1: A plot between the predicted and the experimental activities for the 16 training compounds using model 3.
This QSAR study has been carried out different descriptor like first order SIC, first order CIC, HOMO energy, LUMO energy, dipole moment, entropy and electro negativity. These QSAR models may be used to find out the activity of the designed compounds

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