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Quantum and Structural Molecular Fragment models used to predict anti-inflammatory activity

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Research

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ABSTRACT

In this paper, we predict the anti-inflammatory activity of a series of 26 structures of N-arylanthranilic acid. So, Quantitatve Structure-Activity Relationship (QSAR) method remains the focus of many studies aimed at modeling and prediction of physicochemical properties or biological activities of molecule. Two models were used: quantum model and Structural Molecular Fragment (SMF) model. In the first model, semi-empirical (AM1) approach was used to calculate the quantum chemical descriptors using GAUSSIAN 09 package and the others chemical descriptors were calculated with chemaxon package. In the second model, Structural Molecular Fragment were generated by I.S.I.D.A (In *Silico* Design and Data Analysis). Our two models were built by using a Multiple Linear Regression Analysis (MLR). The concluded QSAR models reflected that the drugs activity was mainly attributed to quantum chemical descriptors with the statistical analysis of multiple R-squared equal to 0.9898 v. s 0.9077 for the Structural Molecular Fragment developed in I.S.I.D.A.

Keywords: N-arylanthranilic acids, anti-inflammatory activity, quantum descriptors, Structural Molecular Fragment.

1. INTRODUCTION

Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) are still the most prescribed drugs worldwide for the treatment of inflammatory diseases like rheumatoid arthritis, osteoarthritis, orthopedic injuries, post-operative pain, acute myalgias etc. [1, 2]. N-arylanthranilic acids belong to the category of NSAIDS. They are amino isosteres of salicylates and are also known as fenemates. Important molecules of this class include mefenamic acid, flufenamic acid and meclofenamic acid. Fenemates act by blocking the metabolism of arachidonic acid by the enzyme cyclooxygenase (COX), one of the key enzymes in the arachidonic acid cascade [3-5]. This enzyme bis-oxygenates arachidonic acid to prostaglandine G2, which is subsequently degraded to vasoactive and inflammatory mediators such as prostanglandins (PGS), prostacyclin (PGI2), and thromboxane-A2[6]. Some fenemates also inhibit arachidonic acid lipoxygenase resulting in decreased synthesis of leukotrines, known mediators involved in inflammatory process [7]. Studies suggest that flufenamic and tolfenamic acids suppress proliferation of human peripheral blood lymphocytes by a mechanism, which involves inhibition of Ca^{2+} influx and is not related to inhibition of prostanoid synthesis [8].

Quantitative structure-activity and structure property relationship (QSAR/QSPR) studies are unquestionably of great importance in modern chemistry and biochemistry [9]. The concept of QSAR/QSPR is to transform searches for compounds with desired properties using chemical intuition and experience into a mathematically quantified and computerized form [10]. Once a correlation between structure and activity/property is found, any number of compounds, including those not yet synthesized, can be readily screened on the computer to select structures with the properties desired [11, 12]. It is then possible to select the most promising compounds to synthesize and test in the laboratory. Thus, the QSAR/QSPR approach conserves resource and accelerates the process of development of new molecules for use as drugs, materials, additives, or for any other purpose [13-16].

In the present study, relationship of chemical quantum and structural molecular fragment with anti-inflammatory activity of N-arylanthranilic acids derivatives has been investigated and suitable models developed for the prediction of anti-inflammatory activity.

2. MATERIALS AND METHODS

In this study, we used the following materials: gaussian09 [17], chemaxon [18], ISIDA/QSPR [19-37], R [38] and data set of the 26 anthranilic acids molecule belonging to a group of NSAIDs were taken from the literature with their experimental activities (table.1) [39].

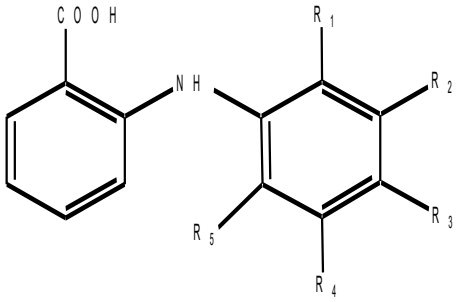


Figure 1. chemical structure of anthranilic acid

Table 1. A dataset of 26 N-arylanthranilic acids with anti-inlammatory activity [22]

Mol	R_1	R_2	R_3	R_4	R_5	MED[a]	A_{exp}
1	Cl	H	CF_3	H	Cl	0.8	3.699
2	CH_3	$SO_2N(CH_3)_2$	H	H	CH_3	0.5	3.903
3	CH_3	NH_2	H	H	Cl	6.2	2.809
4	CH_3	CH_3	H	H	Cl	12.5	2.505
5	Cl	Cl	H	H	CH_3	0.8	3.699
6	Cl	H	C_2H_5	H	Cl	0.8	3.699
7	Cl	H	Cl	Cl	H	400	1.000
8	Cl	Cl	Cl	H	H	200	1.301
9	Cl	H	Cl	H	Cl	100	1.602
10	NH_2	CH_3	H	H	CH_3	25	2.204
11	CH_3	CH_3	H	H	CH_3	6.2	2.809
12	Cl	CH_3	H	H	CH_3	3.1	3.110
13	CH_3	Cl	H	CH_3	H	1.6	3.397
14	CH_3	C_2H_5	H	H	CH_3	1.6	3.397
15	CH_3	NH_2	H	H	Cl	1.3	3.488
16	CH_3	SO_2CH_3	H	H	CH_3	0.6	3.823
17	Cl	$N(CH_3)_2$	H	H	Cl	0.6	3.823
18	CH_3	$SOCH_3$	H	H	CH_3	0.5	3.903
19	Cl	Cl	Cl	H	CH_3	12.5	2.505
20	CH_3	CH_3	H	CH_3	CH_3	100	1.602
21	Cl	Cl	Cl	H	Cl	12.5	2.505
22	Cl	CH_3	Cl	H	Cl	12.5	2.505
23	Cl	Cl	Cl	Cl	H	100	1.602
24	Cl	Cl	H	Cl	Cl	1.6	3.397
25	Cl	Cl	Cl	Cl	Cl	25	2.204
26	CH_3	CH_3	Cl	CH_3	Cl	100	1.602

The biological activity A was calculated from the minimal effective dose (MED mg/kgbody) by formula: A= log(4000/MED)

To perform our two models, we are using Multiple Linear Regression Analysis (MLR). The first model used quantum descriptors; 23 quantum chemical descriptors were computed with Gaussian 09**.** The semi-empirical AM1 method was employed for the calculation of this descriptors (Table 2). Chemaxon software with Marvin suite is a chemically intelligent desktop toolkit built to help us draw, edit, publish, render, import and export chemical structures and as well as allowing us to convert between various chemical and graphical file formats. Software R provides a wide variety of statistical (linear and nonlinear modeling, classical statistical test) and graphical techniques.

Heuristic method was applied to the whole dataset of the N-arylanthranilic acids, a pre-selection of descriptors occurs. Descriptors unavailable for some compounds are discarded altogether with the invariant descriptors and descriptors that correlate poorly. Additional descriptors are discarded when high inter-correlations between them are found. The remaining descriptors are then ranked according to their correlation coefficients.

Table 2. calculated quantum chemical descriptors of anthranilic acids (1-26)

N°	D1Q	D2Q	D3Q	D4Q	D5Q	D6Q	D7Q	D8Q	D9Q	D10Q	D11Q
1	0.493	-0.406	-0.333	-0.0551	135.969	59.388	128.307	-72.059	4.213	295.11	127.847
2	2.699	-0.962	-0.328	-0.0523	230.036	63.712	119.385	-142.96	9.243	294.226	193.816
3	0.342	-0.425	-0.319	-0.0447	164.348	50.858	110.53	-96.746	4.449	282.365	121.626
4	0.339	-0.427	-0.317	-0.0442	170.92	50.31	108.883	-101.92	3.723	280.574	125.987
5	0.34	-0.418	-0.324	-0.0493	147.951	51.347	112.229	-84.355	5.692	278.86	139.435
6	0.349	-0.414	-0.321	-0.0461	166.363	54.902	117.558	-96.687	4.446	303.441	133.932
7	0.348	-0.413	-0.329	-0.0541	125.019	52.595	118.413	-66.195	4.168	317.732	123.078
8	0.347	-0.414	-0.329	-0.0539	125.036	52.512	119.138	-66.049	5.466	316.384	125.412
9	0.356	-0.41	-0.329	-0.0516	124.947	52.541	117.487	-66.344	3.909	307.437	121.546
10	0.324	-0.44	-0.314	-0.0473	187.972	51.667	110.257	-114.12	4.545	279.002	133.142
11	0.321	-0.437	-0.309	-0.0426	194.558	51.102	108.792	-119.27	4.06	281.88	131.881
12	0.333	-0.423	-0.316	-0.0443	170.813	50.452	108.398	-101.95	4.934	276.803	133.681
13	0.33	-0.431	-0.318	-0.0473	170.813	50.639	110.432	-101.51	4.722	290.707	130.305
14	0.321	-0.437	-0.309	-0.0424	213.235	54.404	111.756	-132.31	4.096	293.214	136.805
15	0.341	-0.425	-0.318	-0.0442	199.994	54.129	110.232	-122.94	4.376	301.779	141.254
16	0.322	-0.431	-0.33	-0.0703	200.408	65.452	126.23	-119.75	9.888	315.169	170.596
17	0.352	-0.412	-0.323	-0.0466	177.581	57.27	120.913	-104.18	5	296.863	150.625
18	0.329	-0.429	-0.319	-0.0492	197.361	59.424	119.83	-118.91	5.339	320.036	169.783
19	0.345	-0.415	-0.327	-0.0532	142.744	54.694	117.589	-79.367	5.688	320.386	135.133
20	0.32	-0.437	-0.308	-0.0418	212.605	52.923	108.295	-132.6	4.3	295.67	131.93
21	0.361	-0.406	-0.333	-0.0547	119.751	55.822	122.084	-61.531	4.511	319.511	139.307
22	0.356	-0.41	-0.327	-0.0505	142.958	54.877	117.877	-79.205	3.678	315.923	132.628
23	0.353	-0.41	-0.334	-0.0564	119.827	55.909	123.598	-61.256	4.917	327.476	141.484
24	0.362	-0.405	-0.333	-0.0542	119.734	55.87	122.284	-61.475	3.886	294.038	157.987
25	0.365	-0.403	-0.336	-0.0575	114.566	59.123	127.225	-56.607	4.222	330.366	158.156
26	0.344	-0.425	-0.318	-0.0475	184.058	57.825	119.32	-109.27	3.379	327.114	137.322

Table 2: (continued) calculated quantum chemical descriptors of anthranilic acids (1-26)

	Q12Q	D13Q	D14Q	D15Q	D16Q	D17Q	D18Q	D19Q	D20Q	D21Q	D22Q	D23Q
1	124.929	-1.311	-1.652	-3.646	0.139	7.191	0.194	-0.194	0.136	182.629	28473.499	17.749
2	166.065	2.787	0.618	-8.791	0.138	7.263	0.190	-0.190	0.131	218.036	13638.764	85.433
3	128.524	-2.464	1.692	-3.295	0.137	7.287	0.182	-0.182	0.121	177.505	24775.831	19.794
4	129.211	-1.933	0.44	-3.151	0.136	7.331	0.181	-0.181	0.120	178.591	23409.146	13.861
5	120.605	0.481	3.857	-4.158	0.137	7.293	0.186	-0.186	0.127	179.633	22419.272	32.399
6	130.877	-2.456	1.549	-3.366	0.137	7.283	0.183	-0.183	0.122	189.417	29260.484	19.767
7	115.183	-0.704	-1.171	-3.937	0.138	7.273	0.192	-0.192	0.133	185.331	39489.304	17.372
8	112.254	-1.46	-1.457	-5.062	0.137	7.282	0.191	-0.191	0.133	184.683	39156.247	29.877
9	115.767	0.082	-1.651	-3.542	0.138	7.220	0.190	-0.190	0.130	181.583	35663.125	15.280
10	120.36	-0.48	0.251	4.518	0.134	7.485	0.181	-0.181	0.122	177.501	23302.902	20.657
11	124.914	1.525	0.291	-3.751	0.133	7.499	0.176	-0.176	0.116	179.558	23593.282	16.484
12	126.315	-1.464	2.502	-3.992	0.136	7.362	0.180	-0.180	0.119	178.933	21592.401	24.344
13	126.763	-0.247	2.403	-4.057	0.135	7.385	0.183	-0.183	0.123	182.592	26309.491	22.297
14	135.063	-1.466	0.621	-3.773	0.133	7.504	0.176	-0.176	0.116	188.361	24739.274	16.777
15	144.089	-2.25	1.795	-3.295	0.137	7.302	0.181	-0.181	0.120	195.707	25321.224	19.149
16	157.461	4.881	1.649	-8.439	0.130	7.699	0.200	-0.200	0.154	214.409	22972.847	97.773
17	138.271	-1.976	3.081	-3.405	0.138	7.245	0.185	-0.185	0.124	195.253	23344.798	25.000
18	136.104	0.2	4.833	-2.259	0.135	7.421	0.184	-0.184	0.126	208.641	28770.610	28.505
19	120.823	1.522	3.577	-4.152	0.137	7.317	0.190	-0.190	0.132	192.114	37174.421	32.353
20	141.262	2.054	-1.694	-3.376	0.133	7.524	0.175	-0.175	0.115	189.621	25369.852	18.490
21	115.935	1.116	2.53	-3.563	0.139	7.191	0.194	-0.194	0.135	191.584	37231.460	20.349
22	122.702	-0.3	1.347	-3.409	0.138	7.241	0.189	-0.189	0.129	190.418	35514.969	13.528
23	115.943	-1.673	-2.543	-3.861	0.139	7.210	0.195	-0.195	0.137	194.968	39995.788	24.177
24	116.463	0.062	1.88	-3.401	0.139	7.184	0.193	-0.193	0.134	189.496	25883.499	15.101
25	116.199	-1.403	-1.871	-3.514	0.139	7.169	0.197	-0.197	0.139	201.574	38642.089	17.825
26	135.721	-0.465	0.563	-3.298	0.135	7.383	0.183	-0.183	0.123	200.052	36327.423	11.418

D1Q: charge max, D2Q: charge min, D3Q: HOMO-energy, D4Q: LUMO-energy, D5Q: thermal energy, D6Q: constant volume molar heat capacity, D7Q: entropy, D8Q: partition function, D9Q: molecular dipole moment, D10Q: polarizability- α_{xx}, D11Q: polarizability- α_{yy}, D12Q: polarizability- α_{zz}, D13Q: component of dipole along inertia axe x, D14Q: component of dipole along inertia axe y, D15Q: component of dipole along inertia axe z, D16Q: absolute hardness, D17Q: inverse of hardness, D18Q: chemical potential, D19Q: electro negativity D20Q: electrophilicity index, D21Q: mean polarizability of molecule D22Q: anisotropy of polarisability, D23Q: square of molecular dipole moment.

To decide whether a model generated is good or not is commonly defined by the square coefficient of fitting model (R^2), adjusted R-squared(R^2_{adj}) and Fisher Statistic (F).

$$R^2 = \frac{SCE}{SCT} = \frac{\sum(A_i - \hat{A}_i)^2}{\sum(A_i - \bar{A})^2} \quad (1)$$

$$R^2_{adj} = 1 - (1 - R^2)\frac{N-1}{N-k} \quad (2)$$

$$F = \frac{SCE/(N-1)}{SCR/_{N-k}} \quad (3)$$

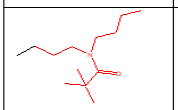
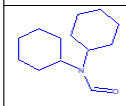
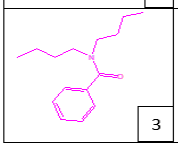
With $SCR = \sum_k^N (\hat{A}_i - \bar{A})^2 = \hat{\sigma}^2$ and N: the number of individuals, k: the variables

The second model used is Structural Molecular Fragment (SMF), this method is developed in ISIDA/QSPR, the latest is based on the splitting of a molecular graph on fragments (subgraphs), and on the calculation of their contributions to a given property Y. Two classes of fragments are used: "sequences" (I) and "augmented atoms" (II). Three sub-types of AB, A and B are defined for each class. For the fragments I, they represent sequences of atoms and bonds (AB), of atoms only (A), or of bonds only (B). Shortest or all paths from one atom to the other are used. For each type of sequences, the minimal (n_{min}) and maximal (n_{max}) number of constituted atoms must be defined. Thus, for the partitioning I (AB, n_{min} - n_{max}), I (A, n_{min} - n_{max}) and I (B, n_{min}- n_{max}), the program generates "intermediate" sequences involving n atoms ($n_{min} \leq n \leq n_{max}$). In the current version of ISIDA/QSPR, $n_{min} \geq 2$ and $n_{max} \leq 15$. The number of sequence's types of different length corresponding to $n_{min} = 2$ and $n_{max} = 15$ is equal to 105 for each of three subtypes AB, A and B, totally 315 types of sequences. QSPR modeling was performed using Multiple Linear Regression Analysis (MLR) of the ISIDA/QSPR program with combined forward and backward stepwise variable selection techniques. MLR is applied to build linear relationships between independent variables (SMF descriptors: N_i i =1, 2…) and a dependent variable (here target property Y = A)

$$A_{cal} = a_0 + \Sigma a_i N_i \quad (4)$$

where every descriptor value is associated with observed property value (A), $a_i$is descriptor contribution, and a_0 is the independent term which is omitted in a part of models see table (3). The Singular Value Decomposition method is used to fit contributions a_i and to minimize the sum of squared residuals which are squared differences between the property values calculated by the model (A_{cal}) and observed values A_{exp} in the training set. The program can generate more than 25,000 MLR models; each of them corresponds to particular type of the SMF descriptors and MLR equation (a_0= 0 or $a_0 \neq 0$) and applied variable selection technique.

Table 3. Example of ISIDA Model

Molecule ↓ SMF(Ni) →	The contribution matrix M_{ij}					A_{cal}
	$N_{C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}C}$	$N_{C\text{-}C\text{-}C\text{-}N\text{-}C\text{-}C}$	$N_{C=O}$	$N_{C\text{-}C\text{-}C\text{-}N}$	$N_{C\text{-}N\text{-}C\text{-}C=O}$	
 1	0	1	10	5	0	-0.222
 2	0	8	1	4	0	0.973
 3	0	4	1	2	4	-0.056

e.g.: ISIDA Model for molecule 1	$A_{cal,1} = -0.36 \times N_{C-C-C-N-C-C} + 0.29 \times N_{C=O} + 0.12 \times N_{C-N-C-C=O}$

To validate consensus model, the external 5-fold cross validation (5-CV) was applied. [40-42] ISIDA, implicitly keeps every 5th compound in the test set, the initial set was randomly split into 5 subsets, each of which was iteratively ignored at the training stage, to serve as internal validation set while the four others formed, together, the learning set. For each of these 5 splitting schemes, models were built followed by prediction calculations on the corresponding validation set. Finally, all values calculated for five test sets are merged into one file to analyse overall linear correlations between experimental and predicted property. One can use Determination Coefficient (R^2) (1), Root Mean Squared Error (RMSE) or Mean Average Error (MAE), to estimate the quality of the linear correlation between predicted (A_{pred}) and experimental (A_{exp}) data for n compounds. Formulas for the statistical parameters are formulated below.

Root –Mean Square Error

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=n}^{n}(A_{pred,i} - A_{exp,i})^2} \quad (5)$$

Mean Average Error

$$MAE = \frac{1}{n}\sum_{i=1}^{n}\left|A_{pred,i} - A_{exp,i}\right| \quad (6)$$

ISIDA calculates a Consensus Model (CM) combining the information issued from several models. At the first step, hundreds of models are built using different initial pools of descriptors corresponding to different fragmentation types.

The contributions of a_i are calculated by minimizing a functional

$$U(a_i) = \sum_{i=1}^{n} W_i (A_{exp,i} - A_{cal,i})^2 \quad (7)$$

where n is the number of the compounds in the training set, wi the weight accounting for the accuracy of the experimental data, A_{exp} and A_{calc} are, respectively, experimental and calculated.

Linear equations (4) are obtained by the contribution matrix M_{ij}

$$M_{ij} = molecule(row) \times fragment(column) \quad (8)$$

3. RESULTS AND DISCUSSION

3.1. Quantum model

With quantum-chemical descriptors, 18 descriptors were evicted in the reached model which are listed in table 1 while their numerical values are in equation A_{cal} (9).

$$A_{cal} = -134.3 + 0.211D_{1Q} - 12.73D_{2Q} + 175\,D_{3Q} + 1771D_{4Q} + 0.06162D_{5Q} + 0.28\,D_{6Q} - 0.151\,D_{7Q} + 0.101D_{8Q} + 1.5D_{9Q} + 0.712D_{10Q} - 0.2927\,D_{11Q} - 0.435D_{12Q} - 0.171\,D_{13Q} + 0.111\,D_{14Q} - 0.152D_{15Q} + 4.58D_{17Q} + 1451D_{20Q} - 0.157D_{23Q} \quad (9)$$

$$R^2 = 0.9898, \quad F - statistic = 30.79, \quad R^2adj = 0.9577, \quad N = 26.$$

Table 4. A dataset of 26 N-arylanthranilic acids with calculated anti-inflammatory activity

Mol	R_1	R_2	R_3	R_4	R_5	MED[a]	A_{exp}	A_{cal}	A_{exp}- A_{exp}
1	Cl	H	CF_3	H	Cl	0.8	3.699	3.725	-0.026
2	CH_3	$SO_2N(CH_3)_2$	H	H	CH_3	0.5	3.903	3.902	0.001
3	CH_3	NH_2	H	H	Cl	6.2	2.809	2.863	-0.054
4	CH_3	CH_3	H	H	Cl	12.5	2.505	2.546	-0.041
5	Cl	Cl	H	H	CH_3	0.8	3.699	3.525	0.174
6	Cl	H	C_2H_5	H	Cl	0.8	3.699	3.529	0.170
7	Cl	H	Cl	Cl	H	400	1.000	0.919	0.081
8	Cl	Cl	Cl	H	H	200	1.301	1.404	-0.103
9	Cl	H	Cl	H	Cl	100	1.602	1.747	-0.145
10	NH_2	CH_3	H	H	CH_3	25	2.204	2.180	0.024
11	CH_3	CH_3	H	H	CH_3	6.2	2.809	2.755	0.054
12	Cl	CH_3	H	H	CH_3	3.1	3.110	3.291	-0.181
13	CH_3	Cl	H	CH_3	H	1.6	3.397	3.369	0.028
14	CH_3	C_2H_5	H	H	CH_3	1.6	3.397	3.351	0.046
15	CH_3	NH_2	H	H	Cl	1.3	3.488	3.455	0.033
16	CH_3	SO_2CH_3	H	H	CH_3	0.6	3.823	3.829	-0.006
17	Cl	$N(CH_3)_2$	H	H	Cl	0.6	3.823	3.822	0.001
18	CH_3	$SOCH_3$	H	H	CH_3	0.5	3.903	4.078	-0.175
19	Cl	Cl	Cl	H	CH_3	12.5	2.505	2.389	0.116
20	CH_3	CH_3	H	CH_3	CH_3	100	1.602	1.611	-0.009
21	Cl	Cl	Cl	H	Cl	12.5	2.505	2.613	-0.108
22	Cl	CH_3	Cl	H	Cl	12.5	2.505	2.505	0.000
23	Cl	Cl	Cl	Cl	H	100	1.602	1.607	-0.005
24	Cl	Cl	H	Cl	Cl	1.6	3.397	3.397	0.000
25	Cl	Cl	Cl	Cl	Cl	25	2.204	2.091	0.113
26	CH_3	CH_3	Cl	CH_3	Cl	100	1.602	1.588	0.014

The dataset N-arylanthranilic acids (1-26), the model shows the best correlation with R^2=0.989 (Figure 2)

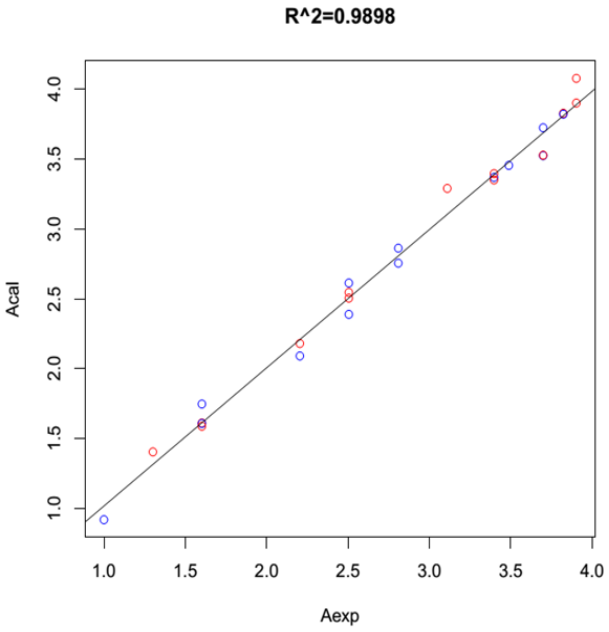


Figure 2. The plot A_{cal} v.s A_{exp}

3.2. Structural Molecular Fragment (SMF) model

ISIDA generates 582 predefined fragments **(**SMF**)**, but among these 582 fragments, 24 contributed to build our model. The contribution matrix M_{ij}(8)

$$M_{ij} = 26 \times 24$$

$$M_{ij} = molecule(row) \times SMF(column)$$

1	1	2	2	1	0	3	3	6	0	0	1	0	0	0	1	0	1	0	0	0	0	0	0
1	2	2	2	1	0	2	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
1	1	2	3	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0
1	1	1	2	1	1	1	0	0	1	0	1	0	1	0	0	0	0	0	1	0	0	0	0
1	1	2	2	1	0	1	0	0	0	0	2	1	0	0	1	0	0	1	0	0	0	0	0
1	1	1	2	1	0	2	0	0	0	0	2	0	1	0	1	0	0	0	1	0	0	1	0
1	1	1	2	1	0	0	0	0	0	0	3	0	0	1	1	0	0	1	0	1	0	0	0
1	1	1	2	1	0	0	0	0	0	0	3	1	0	1	1	0	0	1	0	0	0	0	0
1	1	1	2	1	0	0	0	0	0	0	3	0	0	1	1	0	0	0	1	0	0	0	0
1	1	3	3	1	2	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
1	1	2	2	1	1	3	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	
1	1	2	2	1	1	2	0	0	1	0	1	0	0	0	1	0	0	0	0	1	0	0	
1	1	1	2	1	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	
1	1	2	2	1	1	4	0	0	1	0	0	0	2	0	0	0	0	0	0	1	0	0	
1	4	2	3	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	
1	1	2	2	1	0	2	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
1	4	1	3	1	0	0	0	0	0	0	2	0	0	0	1	0	0	0	3	0	0	0	0
1	1	2	2	1	0	2	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
1	1	2	2	1	0	1	0	0	0	0	3	1	0	1	1	0	0	1	0	0	0	0	
1	1	2	2	1	1	4	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	
1	1	1	2	1	0	0	0	0	0	0	4	1	0	1	1	0	0	1	1	0	0	0	
1	1	1	2	1	1	1	0	0	1	0	4	0	0	1	1	0	1	0	1	0	0	0	
1	1	1	2	1	0	0	0	0	0	0	4	1	0	1	1	0	0	2	0	1	0	0	
1	1	1	2	1	0	0	0	0	0	0	4	1	0	0	1	0	0	1	1	1	0	0	
1	1	1	2	1	0	0	0	0	0	0	5	1	0	1	1	0	0	2	1	1	0	0	
1	1	1	2	1	1	2	0	0	0	1	4	0	1	1	0	0	1	0	1	0	0	0	

Table 5. Structural Molecular Fragment (SMF) with contributions a_i

24 SMF			a_i
1	C-C=O	SMF_1	-0.398275
2	C-N-C	SMF_2	0.204297
3	C-C-C-N	SMF_3	1.236656
4	C=C-C-N	SMF_4	-0.493310
5	C-C-C-O	SMF_5	1.447280
6	C-C-C=C-N	SMF_6	-0.731878
7	C-C-C=C-C	SMF_7	-0.338618
8	C-C=C-C-F	SMF_8	-0.887086
9	C-C=C-C-C-F	SMF_9	0.597106
10	C-C-C=C-N-C-C-C-O	SMF_{10}	1.220001
11	C-C=C-C-N-C=C-C-C-F	SMF_{11}	0.675218
12	Cl-C=C-C	SMF_{12}	-0.325778
13	Cl-C-C=C-N-C-C-C-O	SMF_{13}	1.365737
14	C-C-C-C	SMF_{14}	0.857632
15	Cl-C-C=C-C-N-C-C=C-C	SMF_{15}	-0.402841
16	Cl-C=C-N-C-C-C-O	SMF_{16}	0.916635
17	S-C-C-C	SMF_{17}	1.015195
18	Cl-C-C-C	SMF_{18}	0.453626
19	Cl-C-C-Cl	SMF_{19}	-0.470649
20	Cl-C-C-N-C	SMF_{20}	0.718064
21	Cl-C=C-C=C-Cl	SMF_{21}	0.620912
22	C-C-C=C-C-C	SMF_{22}	-0.378501
23	C-C-C-C=C-C-N	SMF_{23}	0.845447
24	S-C-C=C-C-C	SMF_{24}	0.794212

From the contribution matrix and table (5), we will express the predicted activity as a linear function of Structural Molecular Fragment. Here we have 26 equations, so one for each molecule. Let express the linear equation of molecule number 1.

$$A_{cal,1} = -0.398 \times SMF_1 + 0.204 \times SMF_2 + 1.236 \times SMF_3 - 0.493 \times SMF_4 + 1.447 \times SMF_5 - 0.338 \times SMF_7 - 0.887 \times SMF_8 + 0.597 \times SMF_9 - 0.325 \times SMF_{12} + 0.916 \times SMF_{16} + 0.453 \times SMF_{18} \quad (10)$$

$$A_{cal,1} = 3.690000$$

The predicted activity of all these molecules is confined in table (6) below:

Table 6. A dataset of 26 N-arylanthranilic acids with calculated anti-inflammatory activity

Mol	R1	R2	R3	R4	R5	MED	A_{EXP}	A_{CAL}	A_{EXP}- A_{CAL}
1	Cl	H	CF_3	H	Cl	0.8	3.699	3.699000	-0.000000
2	CH_3	$SO_2N(CH_3)_2$	H	H	CH_3	0.5	3.903	4.076463	-0.176463
3	CH_3	NH_2	H	H	Cl	6.2	2.809	2.638972	0.161028
4	CH_3	CH_3	H	H	Cl	12.5	2.505	2.902764	-0.402764
5	Cl	Cl	H	H	CH_3	0.8	3.699	3.561545	0.128455
6	Cl	H	C_2H_5	H	Cl	0.8	3.699	3.512326	0.177674
7	Cl	H	Cl	Cl	H	400	1.000	1.190064	-0.190064
8	Cl	Cl	Cl	H	H	200	1.301	1.934889	-0.634889
9	Cl	H	Cl	H	Cl	100	1.602	1.757864	-0.157864
10	NH_2	CH_3	H	H	CH_3	25	2.204	2.183851	0.016149
11	CH_3	CH_3	H	H	CH_3	6.2	2.808	2.691396	0.108604
12	Cl	CH_3	H	H	CH_3	3.1	3.110	3.216865	-0.106865
13	CH_3	Cl	H	CH_3	H	1.6	3.390000	2.996924	0.393076
14	CH_3	C_2H_5	H	H	CH_3	1.6	3.397	3.210410	0.179590
15	CH_3	NH_2	H	H	Cl	1.3	3.488	3.251863	0.228137
16	CH_3	SO_2CH_3	H	H	CH_3	0.6	3.823	3.872166	-0.052166
17	Cl	$N(CH_3)_2$	H	H	Cl	0.6	3.823	4.042193	-0.222193
18	CH_3	$SOCH_3$	H	H	CH_3	0.5	3.903	3.872166	0.027834
19	Cl	Cl	Cl	H	CH_3	12.5	2.505	2.832926	-0.332926
20	CH_3	CH_3	H	CH_3	CH_3	100	1.602	2.352778	-0.752778
21	Cl	Cl	Cl	H	Cl	12.5	2.505	2.327175	0.172825
22	Cl	CH_3	Cl	H	Cl	12.5	2.505	2.035218	0.464782
23	Cl	Cl	Cl	Cl	H	100	1.602	1.759374	-0.159374
24	Cl	Cl	H	Cl	Cl	1.6	3.397	3.350928	0.039072
25	Cl	Cl	Cl	Cl	Cl	25	2.204	2.151661	0.048339
26	CH_3	CH_3	Cl	CH_3	Cl	100	1.602	1.637597	-0.037597

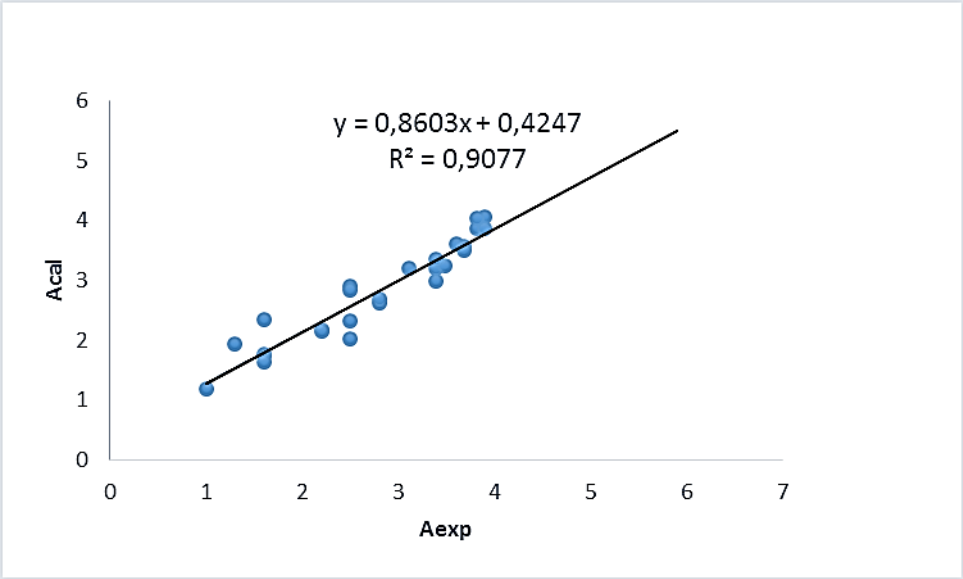


Figure 3. The plot A_{cal} *v.s* A_{exp}

The quantum model give a squared correlation coefficient (R^2=0.9898), a Root Mean Square Error (RMSE=0.090), an adjusted R-squared (R^2adj= 0.9577) and Mean Average Error (MAE= 0.065), also The ISIDA model give a squared correlation coefficient (R^2= 0.9077), a Root Mean Square Error (RMSE= 0.277), an adjusted R-squared (R^2adj= 0.8351) and Mean Average Error (MAE=0.206). See table (7)

Table 7. The results of QSAR analysis by MLR for Quantum model and ISIDA model for the compounds in series 1-26

	MLR Equation	n	R^2	R^2adj	MAE	RMSE
Quantum model	Equation (9)	26	0.9898	0.9577	0.065	0.090
ISIDA model	Equation (10)	26	0.9077	0.8351	0.206	0.277

4. CONCLUSION

The QSAR studies were conducted with a series of 26 structures of N-arylanthranilic acid and some useful predictive molecular models were obtained. The physicochemical descriptors were found to have an important role in the determining of the activity. To test the robustness of these models, we evaluate the coefficient of correlation, R^2, which defines the degree of dependence between theoretical and experimental variables. Two models were studied, quantum model and Structural Molecular Fragment (SMF) model. The two models present a good coefficient correlation, 0.989 and 0.907 respectively. Among the two QSAR models (quantum and ISIDA), results of quantum analysis showed significant predictive power. But the advantages of Structural Molecular Fragment model are the power of fragment descriptors originates from their universality, very high computational efficacy, simplicity of interpretation, as well as their high diversity and versatility.

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