vol 1 July-September 2003, 13- 20 http//www.idecefyn.com.ar ISSN 1666-888X

Optimized Calculation on the Inhibition of Carbonic Anhydrase Isozymes I and II by some Phenyl and Pyridyl Substituted Sulfanilamide Schiff's Bases

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Abstract

Previous linear calculations on the inhibition of carbonic anhydrase isozymes I and II by some phenyl and pyridyl substituted sulfanilamide Schiff's bases are improved resorting to high-order fitting polynomials. Statistical parameters associated with the regression equations show a better predictive power for these new equations, which reveal the need to employ more general analytical fitting equations when dealing with this sort of Quantitative Structure Activity Relationships.

Keywords: QSAR theory – Carbonic anhydrase isozymes – Phenyl and pyridyl substituted sulfanilamide Schiff's bases.

Running title: Schiff's base inhibitors

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vol 1 July-September 2003, 13- 20 http//www.idecefyn.com.ar ISSN 1666-888X

Introduction

Supuran and Clare have described a set of sulfanilamide Schiff's bases with carbonic anhydrase (CA) inhibitory properties, and published quantum Quantitative Structure-Activity Relationships (QSAR) for them on the basis of applying quantum mechanical molecular descriptors (17). After that, they have found a set of suitable quantum chemical descriptors, the so-called frontier orbital phase angles, which are highly useful in correlating the activities of benzene derivatives (2). Although originally derived as a mere numerical procedure using the coefficients of the six p_z atomic orbitals on the benzene ring carbon atoms (where the z-axis is normal to the ring.), it was later shown to be directly related to the orientation of the nodes in the π orbitals on the benzene ring (3). Although the first publication related the hallucinogenic activity of phenylalkylamines to these new molecular descriptors, it was later shown that the activity of some serine protease inhibitors could also be correlated with these descriptors (18). A recent publication has extended this treatment to carbon anhydrase inhibitors (19) and these authors consider it is applicable whenever a pharmacophore demands an aromatic group, and the series of molecules in question can be considered as derived from benzene. Thus, they reanalyzed the data of reference (17) and showed that the correlation could be ameliorated using these new descriptors.

These authors presented the best six linear regression equations for 27 CA inhibitors (see equations 1-6 in Ref. 19) to relate the logarithm of the inhibitory concentrations (*i.e.* the concentration producing 50% inhibition of the enzyme) of the compounds against CA isozymes I and II against to the calculated descriptors (see Table 2 in Ref. 19). The analysis of statistical parameters related to these optimal linear equations shows that there is room for improving the predictions. In fact, the largest correlation coefficient is r = 0.889 (Eq.6 in Ref. 19), while the lowest one is equal to 0.683 (Eq. 2 in Ref. 19).

Thus, the present contribution presents the results on higher order polynomial calculations which improve previous results and so yields better predictive equations through the simple expedient of resorting to fitting equations computed at orders larger than one. The paper is organized as follows: next section deals with a brief sketch of the calculation scheme and some previous antecedents. Then we present numerical results and discuss them, making suitable comparisons with previous published data. Finally, we give the conclusions on the proposed procedure and the evident advantages in resorting to this rather simple and direct method.

Calculation method

Multivariate regression analysis is one of the oldest, if not the oldest, data reduction technique that continues to be used in QSAR and Quantitative Structure-Property Relationship (QSPR) studies. Typically in such studies, after selecting the compounds and the property or activity to be analyzed, one considers selection of potentially useful descriptors. The major classes of descriptors used in QSAR and QSPR are physicochemical (such as log P, index of refraction, Hammet σ values, Taft's steric constant E_s), graph theoretical (for example, Wiener number, Hosoya's Z index, connectivity index $^1\chi$, Balaban's J index) and quantum mechanical (such as, HOMO – LUNO gap, bond orders, electronic charges). It is clear that in each case a different model for the molecular structure under investigation is considered. Consequently, different results could be expected for the same structure-activity (property) study.

While each of these three major methods applied to QSAR/QSPR has its advantages which the respective proponents tend to overestimate, each of them has deficiencies that tend to be overlooked. In addition, multivariate regression analysis has some limitations as a data reduction technique, particularly in the manner in which it is often practiced (12). One special point to be taken into account is that although a rather satisfactory fitting equation could be found, it does not necessarily implies a direct cause-effect between the property or activity under study and the chosen independent variables (i.e. molecular descriptors).

Clearly, simple regression involving only a single descriptor restricts regression analysis considerably. Many correlations, particularly when involving molecules of different size, need not be linear. But even if we have molecules of the same or similar size, a quadratic regression may result in a better description of the relationship than a simple linear model. In general, one should test single descriptor regression for quadratic dependence and, if warranted, for higher polynomial relationships or other functional dependence.

Some previous results on studying multivariate higher order relationships to analyze several physical chemistry properties and biological activities has shown the convenience of resorting to higher-order equations in order to get suitable fitting equations giving satisfactory predictions (1,4-11,13-16,21)

We have chosen the same molecular set comprising 27 molecules as described in Ref. 5 and identical molecular descriptors to calculate log C_{iI} and log C_{iII} in order to be able to perform a comparison analysis between present results and those previously published. They are displayed in **Tables 1** and **2**, respectively.

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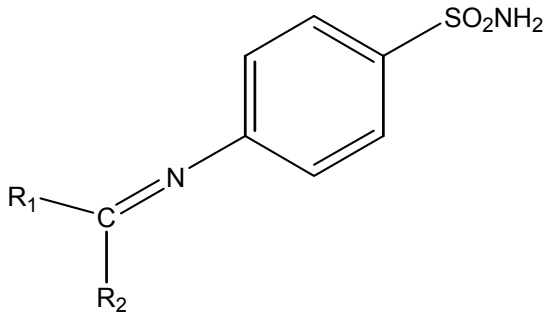
Table 1. Structures and IC_{50} for CA I and CA II of the CA inhibitors.



No.	R_1	R_2	C_i *CA I* (x 10^6 *M)*	C_i *CA II* (x 10^8 *M)*
1	Phenyl	H	18	27
2	2-Hydroxyphenyl	H	35	41
3	2-Nitrophenyl	H	9	21
4	4-Chlorophenyl	H	25	28
5	4-Hydroxyphenyl	H	14	19
6	4-Methoxyphenyl	H	13	19
7	4-Dimethylaminophenyl	H	10	8
8	4-Nitrophenyl	H	13	5
9	4-Cyanophenyl	H	4	11
10	3-Methoxy-4-hydroxyphenyl	H	5	8
11	3,4-Dimethoxyphenyl	H	7	3
12	3-Methoxy-4-acetoxyphenyl	H	3	10
13	2,3-Dihydroxy-5-formylphenyl	H	4	2
14	2-Hydroxy-3-methoxy-5-formylphenyl	H	5	3
15	3,4,5-Trimethoxyphenyl	H	5	3
16	3-Methoxy-4-hydroxy-5-bromophenyl	H	12	4
17	2-Pyridyl	H	2	9
18	3-Pyridyl	H	4	8
19	4-Pyridyl	H	4	5
20	Phenyl	Styryl	20.9	0.56
21	Phenyl	4-Methoxystyryl	19	1.50
22	Phenyl	4-Dimethylaminostryl	16	1.69
23	Phenyl	3,4,5-Trimethoxystyryl	10.7	2.35
24	4-Methoxyphenyl	3,4,5-Trimethoxystyryl	12.5	1.27
25	4-Methoxyphenyl	3-Nitrostyryl	6.3	0.95*
26	4-Aminophenyl	3,4,5-Trimethoxystyryl	10.6	0.85
27	4-Phenylphenyl	3,4,5-Trimethoxystyryl	25.0	2.48

* The value reported in Table in Ref. 19 is 0.65, but the true figure is 0.95 (Clare, B. W., personal communication).

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Table 2. Molecular descriptors in this study corresponding to the molecular set in **Table 1.**

*Molecule**	*$-Q_N$ (e)*	*$-\mu_x$ (D) #*	*μ(D) #*	*D_1 (e)*	*log P*	*pK_1*	*Φ_H (°)*	*Φ_L (°)*
1	1.1912	6.143	8.444	0.8013	1.23	10.50	89.2	45.5
2	1.1931	7.893	9.746	0.8330	0.56	10.62	47.8	17.5
3	1.1841	7.259	11.515	0.8249	0.97	10.39	113.1	82.2
4	1.1905	4.535	7.475	0.7947	1.94	10.47	90.6	15.6
5	1.1915	6.011	9.211	0.8335	0.56	10.62	91.2	44.7
6	1.1879	6.196	7.859	0.7632	1.14	10.50	87.9	44.7
7	1.1856	7.651	9.739	0.7056	1.42	10.62	88.8	44.7
8	1.1890	-1.762	6.458	0.8224	0.97	10.39	0.8	44.9
9	1.1916	0.880	6.174	0.7685	0.66	10.41	2.0	45.0
10	1.1944	5.241	8.769	0.7405	0.41	10.66	70.3	41.5
11	1.1860	5.235	7.246	0.6896	0.68	10.53	66.1	19.1
12	1.1933	6.215	10.473	0.7114	0.12	10.50	122.1	11.5
13	1.1942	3.975	7.651	0.7974	0.12	10.67	169.9	14.8
14	1.1935	4.596	8.128	0.7377	0.36	10.60	169.9	14.3
15	1.1870	3.086	7.526	0.6492	0.12	10.57	86.8	14.4
16	1.1855	3.547	7.475	0.7473	1.20	10.63	67.9	19.6
17	1.1779	6.349	7.935	0.8291	-0.27	9.96	65.2	14.8
18	1.1716	4.606	5.664	0.8425	-0.27	10.02	105.1	15.1
19	1.1755	2.392	4.208	0.8274	-0.27	10.02	179.4	14.1
20	1.1684	6.130	6.702	0.6013	4.27	10.05	104.6	45.5
21	1.1701	6.247	7.199	0.5876	4.19	10.00	113.2	45.4
22	1.1698	8.736	9.281	0.5647	4.47	10.09	104.9	45.4
23	1.1793	2.895	3.452	0.5363	3.16	10.10	114.7	14.5
24	1.1769	2.042	2.742	0.5344	3.16	10.12	92.4	43.9
25	1.1842	-0.641	6.611	0.6193	4.01	10.03	91.0	16.2
26	1.1714	2.104	2.351	0.5665	2.09	10.20	89.5	15.8
27	1.1730	2.864	3.443	0.4730	5.05	10.10	90.1	15.1

***** Numbering as in Table 1.

[#] Columns 3 and 4 in Table III of Ref. 19 are transposed each other (Clare, B. W., personal communication).

We have made a complete regression analysis resorting to first, second, …., fifth relationships in several independent variables as computed in Ref. 5 for the most significant fitting equations 2, 4-6. Computations were carried out by means of the Mathematica® software (20).

Results and discussion

We present in Tables 3-6 the statistical parameters for first up to fifth-order fitting polynomials for regression equations 2, 4-6 of Ref. 19. The calculated equations have the following general form

$$\log C_{iII} = f(Q_N, \mu_x, D_1, a) \quad \textbf{(1)}$$

$$\log C_{iII} = f(Q_N, D_1, \cos 2\varphi_H, a) \quad \textbf{(2)}$$

$$\log C_{iII} = f(Q_N, D_1, \cos 2\varphi_H, \sin 2\varphi_H, a) \quad \textbf{(3)}$$

$$\log C_{iI} = f(\mu_x, \mu, D_1, \log P, pK_1, a) \quad \textbf{(4)}$$

where: C_{iI} and C_{iII} are IC_{50} for CA I and II, respectively (the concentration that produces 50% inhibition of the enzyme, allowing for the uncatalyzed rate); Q_N is the ESP-based charge on sulfonamide N (e); ESP is the electrostatic potential; μ_x is the X-component of ESP-based dipole moment (Debye). The origin is at the center of the sulfanilamide benzene ring, the 1-carbon of this ring on the positive X axis; μ is the magnitude of ESP-based dipole moment (Debye); D_1 is the local dipole index (e/bond); log P is the lipophilicity; pK_1 is the pK_a of the sulfonamide N; φ_H is the HOMO node angle (°); HOMO is the highest occupied molecular orbital; and a is the independent term in the polynomial relationships 1-4.

Fitting polynomials in several variables do not present cross terms, so that, for example, second-order general equation 1 has the algebraic structure

$$\log C_{iII} = AQ_N + B(Q_N)^2 + C\mu_x + D(\mu_x)^2 + ED_1 + F(D1)^2 + a$$

Complete listings of adjusting coefficients in polynomial equations 1-4 are disposable upon request to one of us (E. A. C.).

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Table 3. Statistical parameters corresponding to Eq.(1) [Eq.(2) in Ref. 19].

Equation order	r^{2+}	*F^*	*P x 10^6 #*	*Av**	$S^{2\&}$
First	0.6840	16.60	6	0.082	0.097
Second	0.8123	14.43	2	0.049	0.066
Third	0.8387	9.82	36	0.057	0.067
Fourth	0.9122	12.12	21	0.023	0.044
Fifth	0.9203	8.47	514	0.021	0.051

+ Square correlation coefficient, ^ F Ratio, # P Value,
* Average absolute deviation., & Estimated variance

Table 4. Statistical parameters corresponding to Eq. (2) [Eq. (4) in Ref. 19].

Equation Order	R^2	*F*	*P x 10^6*	*Av*	S^2
First	0.6046	11.72	73	0.103	0.121
Second	0.6723	6.84	465	0.085	0.115
Third	0.7161	4.77	2797	0.074	0.117
Fourth	0.7300	3.15	21878	0.070	0.136
Fifth	0.8663	4.75	6416	0.035	0.085

Table 5. Statistical parameters corresponding to Eq. (3) [Eq. (5) in Ref. 19].

Equation Order	R^2	*F*	*P x 10^6*	*Av*	S^2
First	0.6283	9.30	148	0.097	0.119
Second	0.6852	4.90	2468	0.082	0.123
Third	0.7226	3.04	25353	0.072	0.139
Fourth	0.7340	1.72	192413	0.069	0.187
Fifth	0.8700	2.01	197574	0.033	0.152

Table 6. Statistical parameters corresponding to Eq. (4) [Eq. (6) in Ref. 19].

Equation Order	r^2	*F*	*P x 10^6*	*Av*	S^2
First	0.7901	15.81	2	0.018	0.026
Second	0.8689	10.60	26	0.013	0.022
Third	0.9406	11.61	114	0.006	0.014
Fourth	0.9519	5.93	17673	0.005	0.021
Fifth	0.9814	2.11	502616	0.002	0.049

Although first order equations were calculated previously by Supuran and Clare **[5]** we have included statistical parameters into Tables 3-6 since there are some minor disagreements between both set of results (see second line in Tables 3-6 and statistical parameters adjoined to equations 2, 4-6 in Reference 19).

The analysis of data presented in Tables 3-6 shows that results improved markedly when polynomial order increases (see specially second and fifth columns in Tables 3-6). Particularly noticeable are predictions derived from Eq.(4), where average absolute deviation decreases by a factor 9 when passing from first to fifth order fitting polynomial. However, remaining equations also improved at a large extent when resorting to higher-order polynomials.

In order to appreciate in a better way the results we present in Tables 7 and 8 some predicted values in order to compare them with experimental data and the

degree of improvement when resorting to higher order fitting polynomials.

Table 7. Experimental and predicted values of log C_{iI} (Eq.1)

Molecule	*- log C_{iII} (exper.)*	*- log C_{iII} (first order)*	*- log C_{iII} (second order)*	*- log C_{iII} (third order)*	*- log C_{iII} (fourth order)*	*- log C_{iII} (fifth order)*
1	6.569	6.854	6.781	6.736	6.510	6.567
2	6.387	6.634	6.441	6.477	6.507	6.480
3	6.678	6.849	6.592	6.579	6.718	6.727
4	6.553	6.983	6.952	6.847	6.757	6.821
5	6.721	6.778	6.581	6.586	6.507	6.492
6	6.721	7.001	6.986	6.899	6.734	6.721
7	7.097	7.091	7.105	7.072	7.035	6.972
8	7.301	7.334	7.313	7.309	7.353	7.305
9	6.959	7.256	7.406	7.236	7.058	7.016
10	7.097	7.004	7.191	7.310	7.447	7.434
11	7.523	7.274	7.341	7.333	7.377	7.378
12	7.000	7.033	7.195	7.289	7.141	7.104
13	7.699	6.947	7.015	7.058	7.304	7.375
14	7.523	7.067	7.244	7.282	7.310	7.289
15	7.523	7.490	7.570	7.524	7.625	7.673
16	7.398	7.247	7.306	7.178	7.363	7.325
17	7.046	7.003	6.832	6.973	6.966	7.021
18	7.097	7.188	7.215	7.241	7.238	7.166
19	7.301	7.296	7.287	7.314	7.322	7.359
20	8.252	7.738	8.106	8.020	8.295	8.267
21	7.824	7.735	7.959	8.034	7.796	7.836
22	7.772	7.641	7.734	7.667	7.729	7.765
23	7.629	7.911	7.641	7.746	7.874	7.820
24	7.896	8.010	7.806	7.913	7.831	7.765
25	8.187	7.863	7.963	8.048	8.084	8.174
26	8.071	8.023	8.186	8.214	7.972	7.966
27	7.606	8.177	7.683	7.543	7.572	7.602
Average absolute deviation	-	***0.082***	***0.049***	***0.057***	***0.023***	***0.021***

Evidently, results improve markedly when passing from linear relationships to high-order fitting polynomials and average absolute deviations are rather low.

Conclusions

Usually, QSAR/QSPR adopt a first-order polynomial form when predictive equations relating biological activities and physical chemistry properties with molecular descriptors are developed. However, from a formal point of view there is not any restrictions to employ more general mathematical formulations (12). One obvious way to generalize first-order multivariate formulae is to adjust data to higher-order fitting polynomials, and this resource has shown to be really effective to ameliorate the predictive power of simple linear equations(1,4-11,13-16,21). This paper has dealt with previous results on the data on the inhibition of carbonic anhydrase isozymes I and II by some phenyl and pyridyl substituted sulfanilamide Schiff's bases where activity can be better explained by considering the directions of the nodes in π-like near frontier orbitals in the molecules (19). The analysis of the former modeling equations showed us there was room for studying some possible improvements through the employment of higher-order fitting polynomials, so that this study presented these multivariate equations for the same molecular set as chosen before(19). Comparison of the statistical parameters associated with the previous and present regression equations shows clearly the superior quality of the latter ones and these findings are in line with some formerly published results and demonstrates the convenience of resorting to these more general polynomial forms in the QSAR analysis.

A possible further step in this regard is to analyze the employment of more general mathematical forms in the fitting predictive equations in such a way to choose arbitrary functions of the independent variables instead of the variables themselves. Research in this line is under development and results will be published elsewhere in the forthcoming future.

Table 8. Experimental and predicted values of log C_{iI} (Eq. 4)

Molecule	*log C_{iI} (exper.)*	*log C_{iI} (first order)*	*log C_{iI} (second order)*	*log C_{iI} (third order)*	*log C_{iI} (fourth order)*	*log C_{iI} (fifth order)*
1	4.745	4.817	4.759	4.780	4.751	4.714
2	4.456	4.819	4.717	4.571	4.610	4.526
3	5.046	5.131	5.025	5.025	5.038	5.042
4	4.602	4.613	4.637	6.641	4.631	4.607
5	4.854	4.871	4.869	4.723	4.711	4.809
6	4.886	4.857	4.813	4.866	4.867	4.990
7	5.000	4.919	4.902	4.939	4.931	4.919
8	4.886	5.155	4.946	4.941	4.920	4.879
9	5.398	5.203	5.169	5.305	5.390	5.370
10	5.301	5.134	5.252	5.415	5.430	5.384
11	5.155	5.163	5.142	5.033	5.053	5.117
12	5.523	5.554	5.544	5.548	5.536	5.543
13	5.398	5.021	5.154	5.220	5.273	5.354
14	5.301	5.185	5.261	5.295	5.253	5.211
15	5.301	5.557	5.553	5.396	5.381	5.342
16	4.921	4.874	5.006	5.066	5.005	4.963
17	5.699	5.593	5.599	5.656	5.701	5.689
18	5.398	5.382	5.398	5.414	5.383	5.405
19	5.398	5.407	5.505	5.467	5.417	5.399
20	4.680	4.654	4.797	4.655	4.689	4.684
21	4.721	4.747	4.828	4.802	4.820	4.705
22	4.796	4.759	4.655	4.785	4.742	4.791
23	4.971	4.989	4.911	4.959	4.938	4.977
24	4.903	4.956	4.890	4.897	4.927	4.893
25	5.201	5.086	5.211	5.146	5.146	5.219
26	4.975	5.078	5.000	4.961	4.966	4.979
27	4.602	4.592	4.573	4.608	4.606	4.604
Average absolute deviation	**-**	***0.018***	***0.013***	***0.006***	***0.005***	***0.002***

Acknowledgments

Authors thank very much Prof. Clare some personal correspondence dealing with numerical data published previously in Ref. 5 and also he valuable comments and suggestions of referees, which have been really useful to improve the final version of this article.

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