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Original article

Carbonic anhydrase inhibitors – Part 57: Quantum chemical QSAR of a group of 1,3,4-thiadiazole- and 1,3,4-thiadiazoline disulfonamides with carbonic anhydrase inhibitory properties

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Abstract – Quantum chemical QSAR expressions for 20 1,3,4-thiadiazole disulfonamide and 20 1,3,4-thiadiazoline disulfonamide inhibitors of carbonic anhydrase, for the isozymes CA I, CA II and CA IV have been developed on the basis of AM1 calculations. As in many previous studies, charges on the atoms of the sulfonamide moiety are of central importance, as is also the electric field in the neighborhood of the primary sulfonamide group. Also as in previous studies, the polarizability of the molecule is implicated in an anisotropic manner. A new feature is correlation with the solvation energy of the molecule, calculated by the COSMO continuum model. © Elsevier, Paris

carbonic anhydrase inhibitors / charge / dipole moment / QSAR / quantum chemical / solvation energy

1. Introduction

1,3,4-Thiadiazole-2-sulfonamide and 2-sulfonamido-δ^2-1,3,4-thiadiazoline derivatives played a critical role for the development of several important classes of pharmacological agents [1–7], such as the diuretics with saluretic action [8, 9], benzothiadiazine [10] and high-ceiling diuretics [11], or the antiglaucoma drugs with carbonic anhydrase (CA) inhibitory action among others [12, 13]. The prototype of all these drugs was constituted by acetazolamide **A**, the first non-mercurial diuretic [2, 8], used for more than 45 years in clinical medicine as diuretic [8], antiglaucoma [8, 12], antiepileptic [14] and antiulcer compound [15]. It is still used nowadays, mainly as a diagnostic tool in NMR imaging [16, 17], and in many physiological studies [18–20]. The major biological action of acetazolamide and related heterocyclic/aromatic sulfonamides is connected with the powerful inhibition of the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1), of which at least eight isozymes are presently known in higher vertebrates [6–8, 12].

Many structural variants were derived using acetazolamide **A** as lead molecule, such as 5-aryl/alkyl-sulfonylamido-1,3,4-thiadiazole-2-sulfonamides **B**, **C** [21, 22] (of which benzolamide **B** is the most important representative [23], whereas other derivatives of this series, of type **C**, might be used for developing diagnostic tools in PET (positron emission tomography) [22]. Methazolamide **D** [24], was subsequently developed as it possesses completely different pharmacological properties as compared to acetazolamide. Methazolamide is more lipid soluble as compared to the previously mentioned sulfonamides and in consequence its administration mode and dosage are different [24]; it also penetrates much more easily through the blood–brain barrier, it thus being possible to use it in the treatment of epilepsy, for example [14].

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Abbreviations: AM1, Austin Model 1; CA, Carbonic Anhydrase; COSMO, Conductive Shielding Model; ESP, Electrostatic Potential; HOMO, Highest Occupied Molecular Orbital; LUMO, Lowest Unoccupied Molecular Orbital; MLR, Multiple Linear Regression; PCA, Principal Components Analysis; QSAR, Quantitative Structure–Activity Relationships

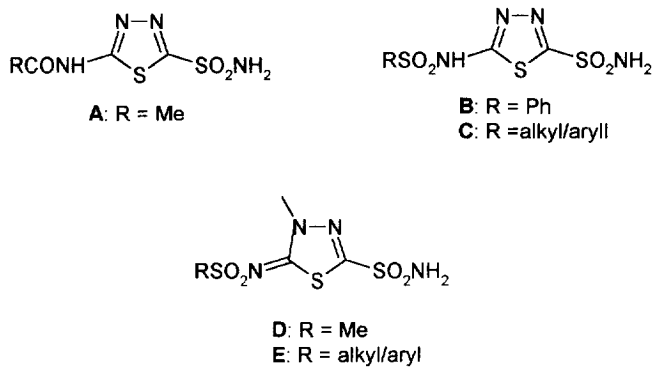


Figure 1. Structures A–E.

Recently a large number of sulfonylamido-1,3,4-thiadiazole-2-sulfonamide derivatives of type **C** and the corresponding thiadiazolines of type **E** have been reported by this group [22], in the search of diagnostic tools with applications in PET. These compounds behaved as very powerful inhibitors of several physiologically relevant CA isozymes, such as CA I, II and IV. It appeared thus of importance to try to rationalize the biological activity in this class of CA inhibitors by means of QSAR models, for at least two reasons: (i) in order to try to explain the important differences in affinity for the sulfonamide inhibitors between the above mentioned isozymes, and whence the possibility to design isozyme-specific inhibitors; and (ii) in order to predict, based on such QSAR calculations the structure of more selective and stronger inhibitors for this type of applications (PET), since the previously investigated compounds although acting as strong inhibitors, led to low radio-yields due to problems of introducing the positron emitting isotope in their molecule (^{18}F in the above-mentioned case) [22] *(figure 1)*.

2. Calculations

The 40 compounds listed in *table I* were set up with the molecular modeling program PCMODEL [25], and optimized with the MMX molecular mechanics routine contained in PCMODEL. An effort was made to find a global minimum by the use of the dihedral driver. The coordinates so obtained were further optimized using MOPAC version 6 [26] and the AM1 Hamiltonian [27]. The polarizability was also calculated during this phase, because the MOPAC 6 method for first-order polarizabilities is much faster for large molecules than that in MOPAC 93, and the results are very similar.

The coordinates were sorted to make the first 15 atoms the common atoms for all 40 compounds, as shown in *figure 2* for a typical member, drawn using the program Schakal 92 [28]. All of the benzene-substituted derivatives were L-shaped, bent at the secondary sulfonamide, as shown. The molecule was oriented so that the midpoint of atoms 1 and 4 was at the origin, atom 4 was on the positive X axis. The midpoint of atoms 2 and 3 was in the *X–Y* plane, and the *Z* coordinate of N7 was positive. A single point calculation was run on the optimized coordinates using MOPAC 93 [29], calculating the HOMO and LUMO energies, and the ESP-based charges by the Merz–Besler method [30], all being done using the COSMO approximation [31] for a medium of dielectric constant 78.4. The solvation energy ΔH_S was calculated as the difference between the ΔH_f in solution and that in vacuum.

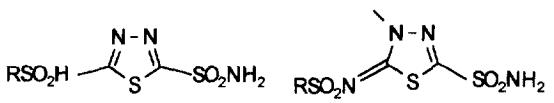
Dipole moments μ and their *X*, *Y* and *Z* components were calculated as the expectation value of the dipole moment operator. The mean of the absolute Mulliken charges of all atoms [32], the local dipole index [32] and the sum of electrophilic superdelocalizabilities were also calculated, using a program written by the authors. The surface area and volume of each molecule was calculated by the GEPOL tesselation method [33] using the program ARVOMOL [34]. An experimental value of the chloroform–aqueous buffer distribution coefficient was determined for use as a descriptor. Values of *C*Log*P* are unavailable due to missing fragments.

Statistical calculations were done with the BMDP package [35], using the All Possible Subsets algorithm [36] of Furnival and Wilson, and a principal components program written by the authors. As described previously [37], descriptors were removed from the all possible subsets calculations based on the Λ statistic [38] until equations were obtained with no significant collinearities remaining. These were reduced by dropping terms of low significance until Q^2 was maximized.

3. Results

In the following, charges of the atoms of the primary sulfonamide group will be referred to as Q_{S1}, Q_{O1}, Q_{N1} and Q_H, and the attached ring carbon as Q_{Cr1}. The corresponding values for the secondary sulfonamide group are Q_{S2}, Q_{O2}, Q_{N2} and Q_{Cr2}. The charge on the hydrogen of the secondary sulfonamide was not considered. Thus referring to *figure 2*, Q_{S1} is the charge on S6, Q_{O1} is the sum of the charges on O10 and O11, and Q_H

Table I.



C E

No.	Type	R	IC_{50} (nM)		
			HCA I	HCA II	BCA IV
1	C	Me	10	6	5
2	C	$PhCH_2$	7	5	6
3	C	4-Me-C_6H_4	5	4	3
4	C	4-F-C_6H_4	4	4	7
5	C	4-Cl-C_6H_4	4	3	5
6	C	4-Br-C_6H_4	3	2	4
7	C	4-MeO-C_6H_4	5	3	4
8	C	4-AcNH-C_6H_4	10	3	8
9	C	4-H_2N-C_6H_4	6	2	5
10	C	3-H_2N-C_6H_4	9	1	7
11	C	4-O_2N-C_6H_4	3	1	2
12	C	3-O_2N-C_6H_4	2	0.9	1
13	C	2-O_2N-C_6H_4	5	3	4
14	C	Me_2N	19	8	13
15	C	2-$HO_2CC_6H_4$	1	0.5	0.6
16	C	4-(2,4,6-Me_3Py^+)C_6H_4	18	4	10
17	C	4-(2,4,6-Ph_3Py^+)C_6H_4	360	110	320
18	C	2,4-$(O_2N)_2C_6H_3$	12	5	28
19	C	4-Cl-3-O_2N-C_6H_3	9	3	7
20	C	2,4,6-$Me_3C_6H_4$	15	9	12
21	E	Me	17	4	8
22	E	$PhCH_2$	6	8	9
23	E	4-Me-C_6H_4	5	3	3
24	E	4-F-C_6H_4	8	4	7
25	E	4-Cl-C_6H_4	8	3	5
26	E	4-Br-C_6H_4	5	2	6
27	E	4-MeO-C_6H_4	6	3	5
28	E	4-AcNH-C_6H_4	2	0.7	2
29	E	4-H_2N-C_6H_4	1	0.6	0.8
30	E	3-H_2N-C_6H_4	1	0.5	0.8
31	E	4-O_2N-C_6H_4	8	4	6
32	E	3-O_2N-C_6H_4	7	2	5
33	E	2-O_2N-C_6H_4	5	1	3
34	E	Me_2N	9	5	8
35	E	2-$HO_2CC_6H_4$	1	0.2	0.5
36	E	4-(2,4,6-Me_3Py^+)C_6H_4	17	4	12
37	E	4-(2,4,6-Ph_3Py^+)C_6H_4	455	110	180
38	E	2,4-$(O_2N)_2C_6H_3$	10	4	8
39	E	4-Cl-3-O_2N-C_6H_3	7	2	5
40	E	2,4,6-$Me_3C_6H_4$	13	7	9

is the sum of the charges on H14 and H15 and Q_{Cr1} is the charge on C4. The charges on N2 and N3 are Q_{Nr1} and Q_{Nr2} respectively. The charge on S5 was never significant.

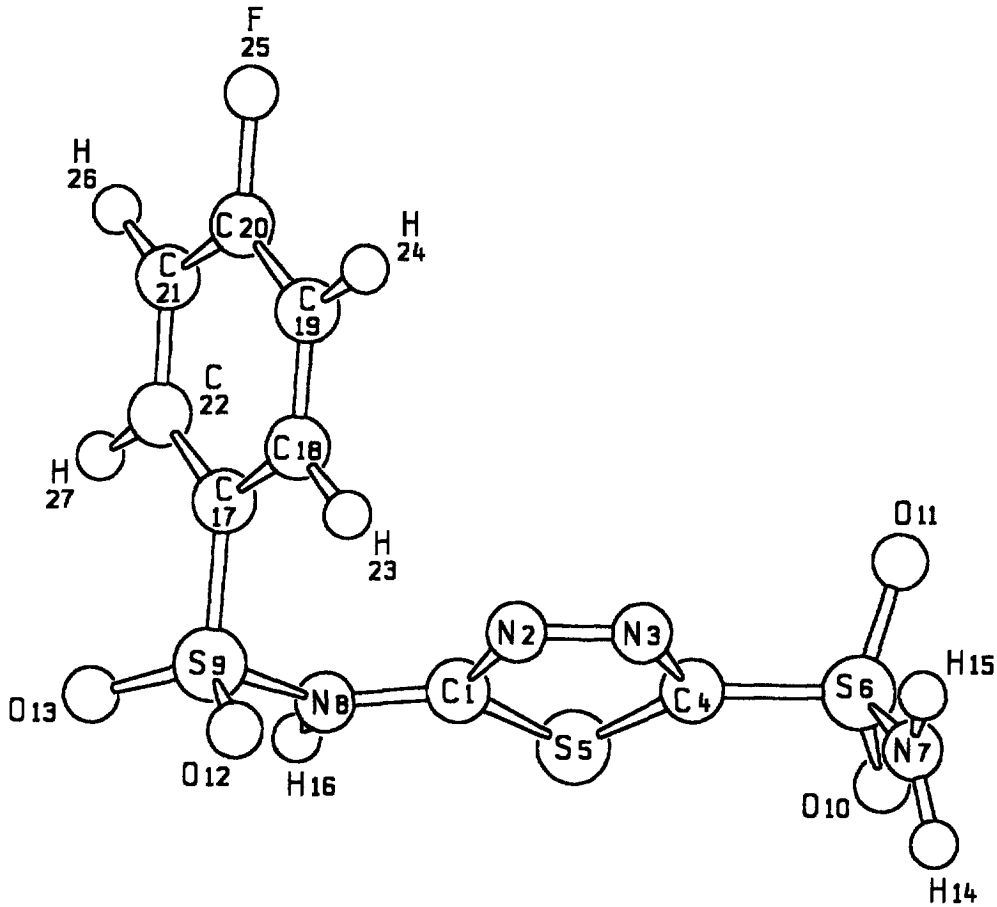


Figure 2. Compound 4 showing atom numbering and optimized geometry.

3.1. CA I

3.1.1. All compounds

The best equation found by the procedure described above was:

$$\text{Log IC}_{50} = C_1\,\Pi_{xx} + C_2\,\Pi_{zz} + C_3\,Q_{\text{Nr2}} + C_4\,Q_{\text{S1}} + C_5\,Q_{\text{S2}} + C_6\,\mu_x + C_7 \quad (1)$$

	1	2	3	4	5	6	7
C_i	9.29×10^{-3}	-5.72×10^{-3}	−13.04	17.07	1.560	6.90×10^{-2}	−50.83
σ	1.38×10^{-3}	2.31×10^{-3}	2.87	4.59	0.790	1.82×10^{-2}	12.29
α	0.00000	0.01863	0.00007	0.00075	0.05677	0.00062	0.00023

$N = 40$, $R^2 = 0.753$, $Q^2 = 0.628$, $s = 0.289$, $F = 16.78$, $\Lambda = 2.87$

Here N is the number of compounds, R^2 is the square of the multiple correlation coefficient, Q^2 is the same quantity based on predicted errors (the leave-one-out technique [39]), s is the standard error of estimate of the equation, F is the Fisher variance ratio, and the α are the individual statistical significance of each of the coefficients ot the equation, based on a Student's t-test. The σ_i are standard errors of the estimate for each coefficient in the equation. The diagnostic Λ is defined as

$$\Lambda = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{\lambda_i}$$

where n is the number of descriptors and the λ_i are the eigenvalues of the correlation matrix of descriptors [38]. A value of Λ greater than 5 is taken to indicate that a collinearity problem exists in the equation. E_L and ΔH_s also showed a tendency to enter the equation, both with negative sign. The dipole moment components μ_y and μ_z also appeared, but with negative sign and much smaller

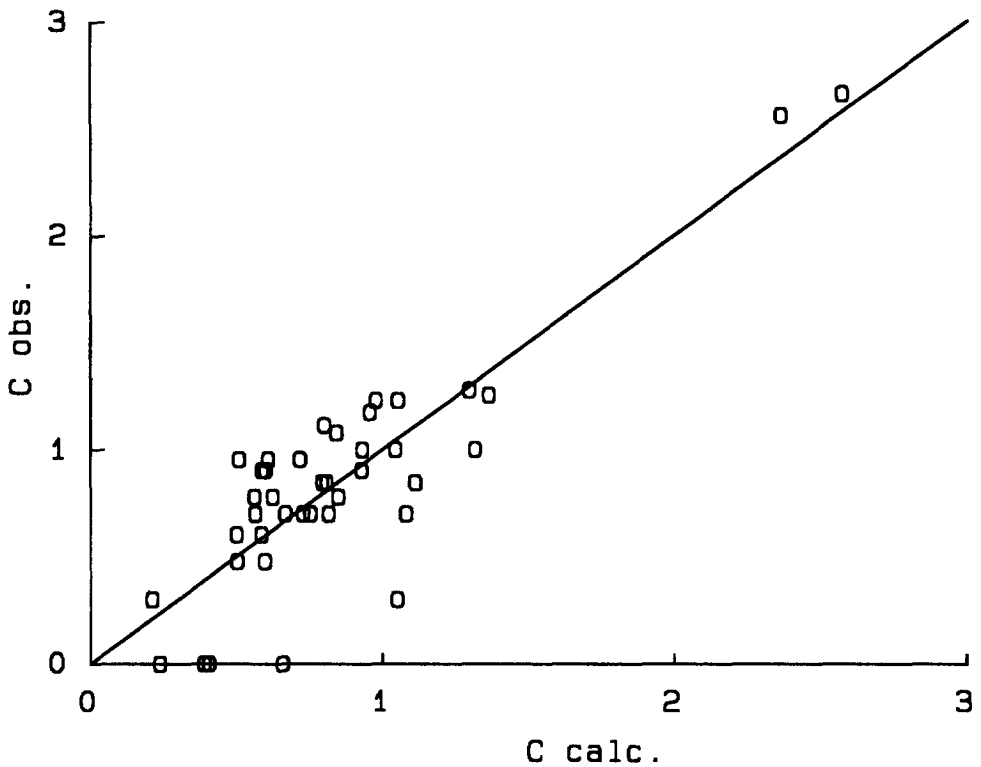


Figure 3. Fit of data to equation (1); C = Log IC_{50} CA I, all compounds.

magnitude than μ_x. A plot of the fit of equation (1) is given in *figure 3*.

3.1.2. Leaving out compounds 16, 17, 36 and 37 (the cationic compounds)

$$\text{Log } IC_{50} = C_1 \Pi_{zz} + C_2 Q_{Cr2} + C_3 \mu_x + C_4 \text{ Log } P + C_5 Q_{O1} + C_6 \quad (2)$$

	1	2	3	4	5	6
C_i	-3.68×10^{-3}	3.152	0.157	0.400	-24.62	-44.1
σ	1.44×10^{-3}	1.074	0.023	0.168	4.01	7.4
α	0.01588	0.00632	0.00000	0.02319	0.00000	0.00000

N = 36, R^2 = 0.700, Q^2 = 0.570, s = 0.201, F = 13.98, Λ = 2.41

As with the set containing all of the data, μ_y when it appeared had small magnitude and negative sign. A plot of the fit of equation (2) is given in *figure 4*.

3.1.3. Compounds 1 to 20 (the thiadiazoles)

$$\text{Log } IC_{50} = C_1 Q_{S1} + C_2 \mu_x + C_3 \mu_z + C_4 \Delta H_S + C_5 Q_{O1} + C_6 \quad (3)$$

	1	2	3	4	5	6
C_i	59.43	0.1359	-0.0300	-0.0204	98.87	27.83
σ	6.57	0.0325	0.0116	0.0073	10.30	10.39
α	0.00000	0.00093	0.02193	0.01451	0.00000	0.01800

N = 20, R^2 = 0.909, Q^2 = 0.502, s = 0.18, F = 27.94, Λ = 4.45

3.1.4. Compounds 21 to 40 (the thiadiazolines)

$$\text{Log } IC_{50} = C_1 \Pi_{yy} + C_2 Q_{S2} + C_3 E_H + C_4 E_L + C_5 \Delta H_S + C_6 Q_{O1} + C_7 Q_{O2} + C_8 \quad (4)$$

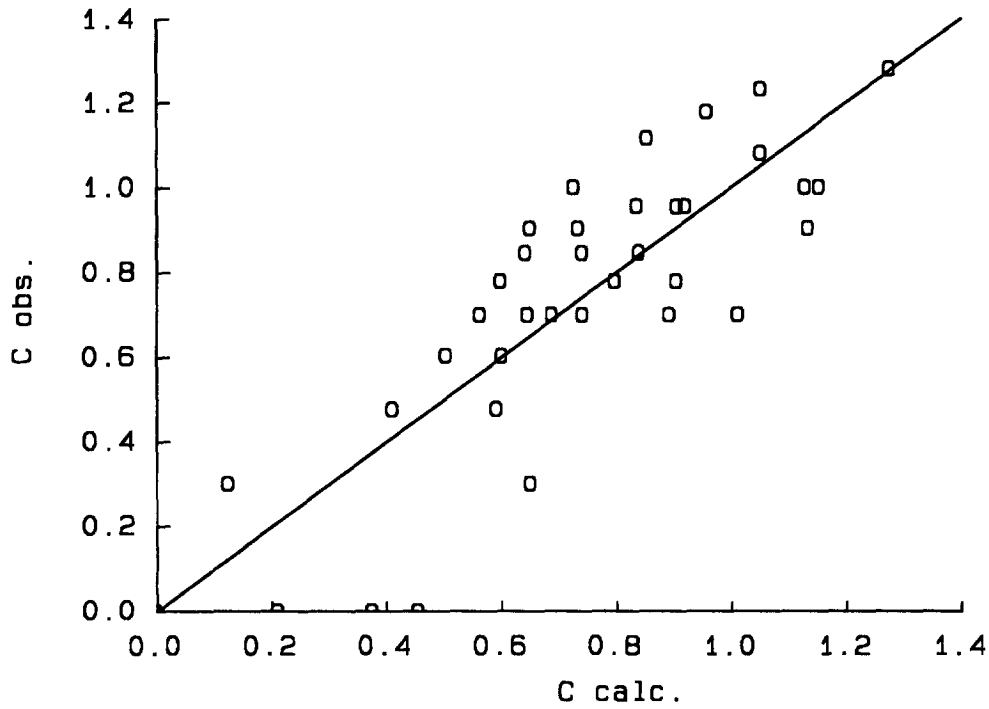


Figure 4. Fit of data to equation (2); C = Log IC_{50} CA I, ionic compounds deleted.

	1	2	3	4	5	6	7	8
C_i	8.47×10^{-3}	-5.871	-1.787	-1.575	0.0501	-82.31	-16.36	-182.6
σ	1.43×10^{-3}	1.791	0.367	0.329	0.0100	17.76	4.16	32.8
α	0.00007	0.00659	0.00038	0.00044	0.00031	0.00058	0.00198	0.00012

$N = 20$, $R^2 = 0.917$, $Q^2 = 0.712$, $s = 0.21$, $F = 18.92$, $\Lambda = 4.54$

3.2. CA II

3.2.1. All compounds

$$\text{Log IC}_{50} = C_1 \Pi_{xx} + C_2 Q_{Cr1} + C_3 Q_{S1} + C_4 E_H + C_5 \mu_x + C_6 \mu_z + C_7 \Delta H_S + C_8 \quad (5)$$

	1	2	3	4	5	6	7	8
C_i	8.92×10^{-3}	-6.68	18.97	-0.736	0.0667	-0.0417	0.0275	-64.15
σ	1.20×10^{-3}	1.56	4.94	0.266	0.0211	0.0160	0.0081	14.45
α	0.00000	0.00016	0.00056	0.00945	0.00345	0.01339	0.00178	0.00010

$N = 40$, $R^2 = 0.719$, $Q^2 = 0.475$, $s = 0.304$, $F = 11.70$, $\Lambda = 2.47$

The dipole momentcomponents again tended to enter, μ_x with positive sign and μ_y and μ_z with negative sign and smaller magnitude. The components of the polarizability tensor, Π_{yy} and Π_{zz} also tended to appear, the former with a positive sign and the latter negative.

3.2.2. Leaving out compounds 16, 17, 36 and 37

$$\text{Log IC}_{50} = C_1 Q_{Cr1} + C_2 Q_{S1} + C_3 E_H + C_4 \mu_x + C_{5\mu} + C_6 \text{Log } P + C_7 \Delta H_S + C_8 \quad (6)$$

	1	2	3	4	5	6	7	8
C_i	-7.05	13.19	-0.677	0.126	-0.0421	0.298	0.0302	-46.52
σ	1.07	4.35	0.140	0.016	0.0144	0.133	0.0083	11.93
α	0.00000	0.00520	0.00004	0.00000	0.00697	0.03277	0.00106	0.00055

$N = 36$, $R^2 = 0.876$, $Q^2 = 0.777$, $s = 0.152$, $F = 28.66$, $\Lambda = 2.60$

The dipole moment μ and its components entered some of the equations, the magnitude and the components μ_y and μ_z with a negative sign, andthe component μ_x with a positive sign and larger value. A plot of the fit to equation (6) is given in *figure 5*.

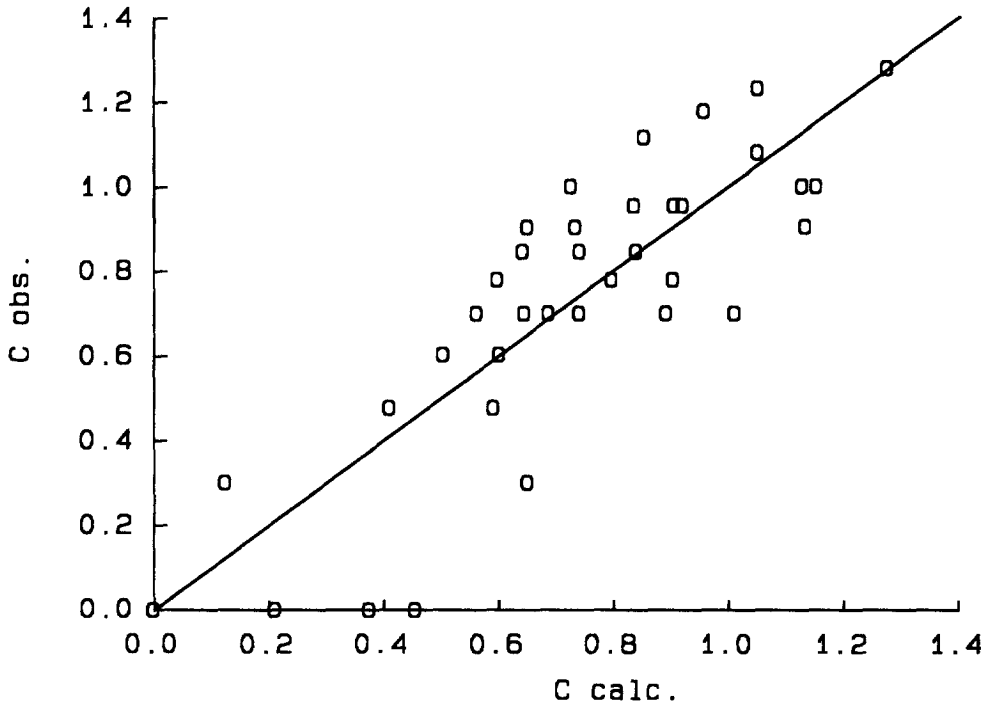


Figure 5. Fit of data to equation (6); C = Log IC_{50} CA II, ionic compounds deleted.

3.2.3. Compounds 1 to 20

$$\text{Log } IC_{50} = C_1 Q_{S1} + C_2 E_H + C_3 \mu_x + C_4 \mu_z + C_5 \Delta H_S + C_6 Q_{O1} + C_7 \quad (7)$$

	1	2	3	4	5	6	7
C_i	63.34	−0.696	0.1346	−0.0504	0.0406	104.7	22.46
σ	6.97	0.204	0.0345	0.0135	0.0077	10.6	11.49
α	0.00000	0.00474	0.00181	0.00254	0.00016	0.00000	0.07243

$N = 20$, $R^2 = 0.902$, $Q^2 = 0.156$, $s = 0.18$, $F = 19.93$, $\Lambda = 4.24$

3.2.4. Compounds 21 to 40

No statistically valid equation was obtained.

3.3. CA IV

3.3.1. All compounds

$$\text{Log } IC_{50} = C_1 \Pi_{xx} + C_2 Q_{Cr1} + C_3 Q_{S1} + C_4 \mu_x + C_5 \quad (8)$$

	1	2	3	4	5
C_i	7.31×10^{-3}	−5.570	11.46	0.0602	−37.16
σ	9.65×10^{-4}	1.431	4.90	0.0201	13.68
α	0.00000	0.00043	0.02523	0.00492	0.01022

$N = 40$, $R^2 = 0.632$, $Q^2 = 0.444$, $s = 0.34$, $F = 15.07$, $\Lambda = 1.48$

The component of the polarizability tensor Π_{zz}, when it appeared, did so with a negative sign.

3.3.2. Leaving out compounds 16, 17, 36 and 37

$$\text{Log } IC_{50} = C_1 Q_{Nr1} + C_2 Q_{S1} + C_3 \mu_x + C_4 \text{ Log } P + C_5 \Delta H_{S2} + C_6 \quad (9)$$

	1	2	3	4	5	6
C_i	−2.798	8.447	0.1800	0.5295	0.0298	−20.11
σ	0.336	3.732	0.0230	0.1682	0.0076	10.02
α	0.00000	0.03103	0.00000	0.00371	0.00047	0.05375

$N = 36$, $R^2 = 0.769$, $Q^2 = 0.646$, $s = 0.20$, $F = 20.05$, $\Lambda = 1.99$

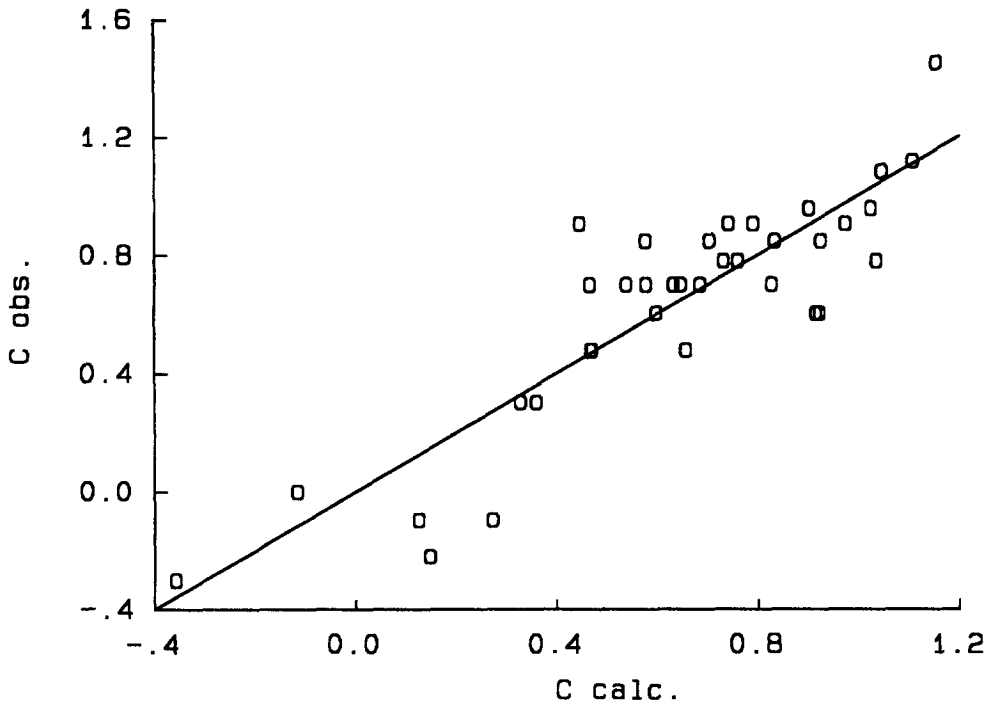


Figure 6. Fit of data to equation (9); C = Log IC_{50} CA IV, ionic compounds deleted.

The dipole moment component μ_z entered some equations with a negative sign, a small magnitude, and was not statistically significant. A plot of the fit to equation (9) is given in *figure 6*.

3.3.3. Compounds 1 to 20

$$\text{Log IC}_{50} = C_1 \Pi_{xx} + C_2 Q_{N1} + C_3 \mu_x + C_4 \quad (10)$$

	1	2	3	4
C_i	7.36×10^{-3}	-18.90	0.1228	-22.29
σ	1.04×10^{-3}	6.72	0.0452	7.78
α	0.00000	0.01260	0.01525	0.01124

$N = 20$, $R^2 = 0.760$, $Q^2 = 0.340$, $s = 0.29$, $F = 16.8$, $\Lambda = 1.14$

3.3.4. Compounds 21 to 40

$$\text{Log IC}_{50} = C_1 \Pi_{yy} + C_2 E_H + C_3 \mu_x + C_4 Q_{O1} + C_5 \quad (11)$$

	1	2	3	4	5
C_i	7.29×10^{-3}	-1.628	0.0977	-105.4	-208.9
σ	1.22×10^{-3}	0.384	0.0226	21.5	40.1
α	0.00003	0.00072	0.00062	0.00019	0.00011

$N = 20$, $R^2 = 0.822$, $Q^2 = 0.358$, $s = 0.25$, $F = 17.23$, $\Lambda = 1.96$

The procedure of repeated stepwise regression on each dependent variable data set, wit the dependent variable randomly reassigned, was applied in order to estimate the statistical validity of the results with respect to chance correlation in variable selection [40, 41]. For each data set, a stepwise regression was done according to Efroymson's algorithm with F-to-enter and F-to-leave both set at 3.0. A set of 10^4 regressions was carried out on the same data, with the dependent variable randomly reassigned, allowing only the number of variables to enter as entered the actual regression. The statistical significance was calculated was calculated from the distribution of the correlation coefficient. The results are presented in *table II*. It will be seen that there is satisfactory statistical significance for the full data set with all three isozymes. The results for the set with the first 20 compounds only are also satisfactory, but those for the second 20 are

Table II. Statistical significance estimates from multiple stepwise regressions on data sets with the dependent variable randomly reassigned.

	CA I	CA II	CA IV
All compounds	9.7×10^{-4}	1.3×10^{-3}	2.6×10^{-3}
First 20 compounds	2.3×10^{-5}	7.5×10^{-4}	5.0×10^{-4}
Last 20 compounds	0.036	0.236	0.063

barely acceptable for CA I and unsatisfactory for CA II and CA IV. With these three data sets 20 compounds is insufficient to safeguard against chance correlation of the type described by Topliss et al. [42, 43].

The values of all descriptors that were found significant are given in a table, which is available over the Internet [44]. Examination of scatterplots indicated that for those variables found significant above, the variables Q_{Nr1}, Q_{Nr2}, Q_{Cr1}, Q_{O1} and Q_{O2} polarized into separated thiadiazole and thiadiazoline groups. Most variables had the cationic compounds as outliers.

4. Discussion and conclusions

It will be seen from above that the principal determinants of the activity of these drugs are charge factors, such as the charges on the atoms of the sulfonamide groups and the dipole moment, especially the X component. This is consistent with the findings of many other studies [2, 45–49]. Both the primary and to a lesser extent the secondary group are involved, and the effect is also reflected in the X component of the dipole moment. This appeared always with a positive coefficient, and was of greater magnitude when the cationic compounds were excluded. Unlike our findings in another series of sulfonamides [37], there was no striking difference between CA I and CA II.

Similarly, in the data sets with all compounds, Q_{S1} was implicated with positive sign and comparable magnitude in all three isozymes. Only the CA I activity showed dependence on Q_{S2}, and this was positive, with smaller magnitude than Q_{S1} in the data set with all compounds, but negative when only compounds 21–40 were considered. As mentioned above, this reduced series was of doubtful significance.

Examination of the fit (R^2) and predictivity (Q^2) measures for the various data sets clearly shows the benefits of having a large number of cases. For CA II there is an excellent R^2 but very poor Q^2 for the thiadiazole subset, and no satisfactory equation at all for the thiadiazoline subset. The corresponding Q^2 results for CA IV were only slightly better. For these isozymes both R^2 and Q^2 for the subset with the cationic compounds deleted were substantially better than the full data set, and much better than the thiadialoles or thiadiazolines alone. Because these four compounds were very different from the remainder, being the only charged compounds and outliers in several descriptors, it is not surprising that they were not well described.

In contrast, the thiadiazoline subset of the CA I results appears to be both well fit and well predicted. Examination of the randomization results however suggests that this may be misleading. The thiadiazole subset is well fit but poorly predicted. For CA I however, the full data set is both better fit and better predicted than the set with the cationic compounds deleted. Comparison of *figure 3* with *figure 4* shows that the quality of the fit in equation (1) is due largely to the outliers. There is thus no difference between the factors which influence the activities of the thiadiazoles and thiadiazolines, and the full data sets reflect the advantages of the larger numbers of compounds.

The coefficient of Log P is always positive for all three isozymes, consistent with our previous findings [37] and in contrast with the findings of Kakeya et al. [50, 51, 52, 53] in the study of benzenesulfonamides. It should be noted that Log P here is the experimental Log of the chloroform–buffer partition coefficient, not the calculated quantity C Log P.

The polarizability of the molecule is also implicated, in an anisotropic manner. The component Π_{xx} in implicated with positive coefficient in all three isozymes for the full data sets and several subsets. The components Π_{yy} appears with positive coefficient with CA I and CA IV in compounds 21 to 40, but Π_{zz} appears with a negative coefficient in the CA I results only. We have previously found anisotropic dependence on polarizability in a series of cationic pyridinium thiadiazole sulfonamide inhibitors of CA I [54]. It should be noted that in this and our previous work, the axes for the polarizability tensor are the inertial axes, not the defined X, Y and Z axes.

A feature of the present results is the appearance of the energy of solvation of the compound in many of the equations. We have not computed this quantity in our previous work. For CA I, the coefficient of ΔH_S is negative and of relatively low significance for compounds 1 to 20 and positive for compounds 21 to 40. For CA II the term appears always with positive coefficient in both the full data sets and the subsets, while for CA IV it appears only in the set without the cationic compounds, and with a positive coefficient. A positive coefficient for ΔH_S means that the activity of the drug increases with increasing solvation.

We consider the present an important result, since for the first time a well-known feature for the interaction of

the three CA isozymes mentioned above with the sulfonamide inhibitors is inferred by QSAR calculations. Thus, it is well established that CA II has the highest affinity for sulfonamide inhibitors, followed by CA IV and then by CA I. As seen from the above calculation, it is precisely what we obtained from the solvation energy results.

Probably the discrimination of these isozymes for this class of inhibitors is highly influenced by the ability of the inhibitor molecule in its solvated form to interact with amino acid residues from the active site. Half of the active site of all CA isozymes consists of hydrophilic amino acid residues, providing an environment favorable for the binding of a molecule which may be readily solvated. In fact, the most active sulfonamide inhibitors possess in their molecule both hydrophilic as well as hydrophobic structural elements, a right balance between the two factors being very favorable [7, 8]. Obviously, the distribution and nature of these hydrophilic amino acid residues is quite different in the three isozymes and this also explains their totally different affinity for the sulfonamide (and anion) inhibitors [55].

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