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QSAR studies for the inhibition of the transmembrane isozymes XII and XIV of human carbonic anhydrase with a series of sulfonamides

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Abstract—A diverse series of aromatic/heterocyclic sulfonamides possessing inhibitory action against the human transmembrane isoforms XII (cancer-associated) and XIV of the metalloenzyme carbonic anhydrase (CA, EC 4.2.1.1) has been used to develop QSAR models. Including all the 55 investigated sulfonamides in the calibration set, the predictive qualities of the QSAR equations were weak ($r^2 = 0.1771$, $F = 5.70$) for CA XII and good for CA XIV inhibition ($r^2 = 0.8222$, $F = 57.04$ before eliminating the outliers, and $r^2 = 0.8911$, $F = 67.07$ after eliminating them). The obtained models suggest a slightly different inhibition mechanism for the two isoforms. 3-Halogeno-4-amino-benzenesulfonamides were outliers for scaffold hopping for the inhibition of CA XIV. CA XIV inhibitory activity was proportional to the degree of molecular surface rugosity. For compounds of the type X-Ar-SO_2NH_2 and Ar′-Ar-SO_2NH_2 type, best inhibitors were detected when Ar/Ar′ incorporates a heterocyclic moiety. These studies may be helpful for the design of more specific CA XII/XIV inhibitors, since this is the first QSAR model investigating them.

1. Introduction

The carbonic anhydrases (CAs, EC 4.2.1.1) are ubiquitous metalloenzymes, present in prokaryotes and eukaryotes, being encoded by four distinct, evolutionarily unrelated gene families: the α-CAs (present in vertebrates, *Bacteria*, algae, and cytoplasm of green plants), the β-CAs (predominantly in *Bacteria*, algae, and chloroplasts of both mono- as well as dicotyledons), the γ-CAs (mainly in *Archaea* and some *Bacteria*), and the δ-CAs, present in some marine diatoms, respectively.[1–8] In mammals, 16 different α-CA isozymes or CA-related proteins (CARP) were described, with very different catalytic activity, subcellular localization, tissue distribution, and susceptibility to be inhibited by sulfonamides.[1–8] Basically, there are several cytosolic forms (CA I–III, CA VII), four membrane-bound isozymes (CA IV, CA IX, CA XII, and CA XIV), one mitochondrial form (CA V), as well as a secreted CA isozyme, CA VI. These enzymes catalyze a very simple physiological reaction, the interconversion between carbon dioxide and the bicarbonate ion (reaction 1), and are thus involved in crucial physiological processes connected with respiration and transport of CO_2/bicarbonate between metabolizing tissues and lungs, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissues/organs, biosynthetic reactions (such as gluconeogenesis, lipogenesis, and ureagenesis), bone resorption, calcification, tumorigenicity, and many other physiologic/pathologic processes.[1–8] Many of these isozymes are important targets for the design of inhibitors/activators with clinical applications.[1]

$$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+ \qquad \text{(reaction 1)}$$

In the last years, the inhibitory effects of some aromatic and heterocyclic sulfonamides have been also investigated on some of the less investigated, lately discovered isoforms, such as the tumor-associated CA XII and the related, transmembrane CA XIV.[9–11] Although there are many QSAR models for the inhibition of the ubiquitous cytosolic isoforms CA I and CA II,[12] no QSAR models

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for the inhibition of these targets, that is, CA XII and XIV, are available up to now.

2. Results and discussion

The 55 sulfonamides shown in Table 1 were included in the calibration set. The inhibitory activity (as K_I values, in the nanomolar—to micromolar range for both isozymes) reported earlier[9–11] was expressed by means of the equation $A = \log(c/K_I)$, where c was taken for both investigated isozymes as 11,000, in order to obtain A values in the range of [0,4]. Also the comparison of A values for the two studied isozymes is more suggestive.

The virtual building of the molecules **1**–**55** and the geometry optimization were done by using the molecular mechanics program PCModel.[13] The more rigorous geometry optimization was subsequently performed by using Mopac[14] with the following sequence of keywords: 'am1 pulay gnorm = 0.01 shift = 50 geo-ok camp-king mmok bonds vectors'. Based on output files created by Mopac, PRECLAV[15–17] has been employed to calculate for each of the 55 molecules around 400 whole molecule descriptors, specific to this program. Separately, by using DRAGON,[18] for each sulfonamide **1**–**55** were calculated around 1400 descriptors, specific to this last program. Statistical calculations used for obtaining the QSAR equations were done again with PRECLAV, as reported earlier.[19]

Each descriptor set was used to calculate multilinear QSAR equations of type (1):

$$A = c_0 + \sum_{i=2}^{k} c_i \cdot D_i \qquad (1)$$

where:

A represents a dependent property (here the inhibitory activity defined above)
c_0 is the free term (intercept)
c_i are descriptor coefficients (weighting factors)
D_i represent significant descriptors
k is the number of descriptors in a set

Coefficients c_i were calculated by using the Ordinary Least Square Method.[19] Thousands of equations of type (1) were thus calculated. With each such equation values of the inhibitory activity A were calculated, which were compared to the observed activity. The agreement between the calculated/observed inhibitory activity was measured using the cross-validation function Q, specific to the employed program,[15] which possesses values in the interval $[-1, 1]$. By increasing the number of descriptors k, the quality Q of the equations increases, reaches a maximum, and then decreases. For predictions, the equation with the highest quality was used, the descriptors present in this equation being called 'predictors'. For each predictor the utility function U was calculated, which is again specific to the employed program.[15] The values of U were then normalized, the least one becoming 0, the highest one 1000. Useful predictors were correlated better with A and weaker with other predictors as compared to less useful predictors. Each useful predictor describes rather correctly the variation of the inhibitory activity and in the same time something different from what other descriptors describe. Outlier molecules were detected by COIN (Combined Outlier Index),[20] in a classical enough manner, by comparing the estimated error of the inhibitory activities with the standard error of value estimation and comparison of the estimation error in the rank of activity values with the error of the rank estimation.

We applied the PRECLAV algorithm in three QSAR studies by using the set of CA XII/XIV inhibitors **1**–**55**. The quality of the obtained equations is reflected by the value of the Q function and also by values of some usual statistical functions.

2.1. QSAR study #1

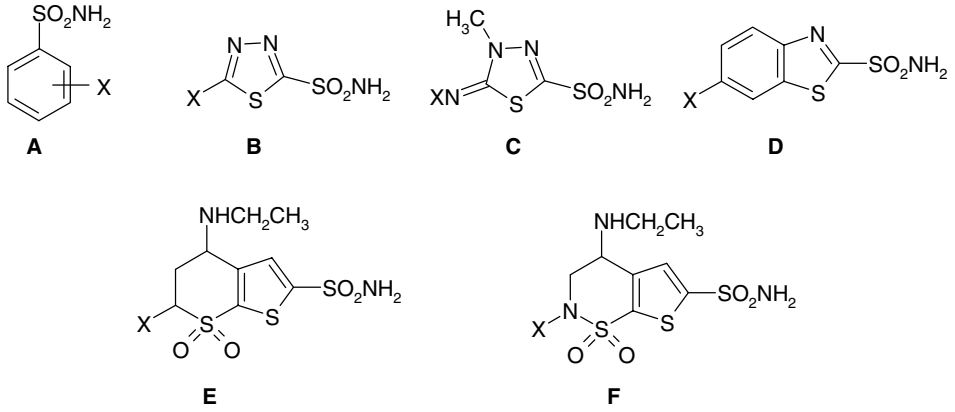
Dependent property: CA inhibitory activity against hCA XII (Table 1, column 4)
Number of molecules in the calibration set: 55
Number of significant descriptors: 7
Type (1) QSAR used for prediction:

$c_0 = 2.8945$
$c_1 = -0.9392$
D_1 is the complementary information content—neighborhood symmetry[21] of 3-order
$c_2 = 12.371$
D_2 is the average valence connectivity index[22] χ^{-5}

Standard error of values s_{value}: 0.6370
Standard error of ranks s_{rank}: 16.9411
Pearson square correlation r^2: 0.1771
Fisher function F: 5.70
Pearson cross-validated square correlation r^2_{CV}: 0.1088
Kendall rank correlation K: 0.2970
Kendall cross-validated rank correlation K_{CV} 0.2310
Quality Q: 0.2226
Number of outliers: 2

The values of almost 1800 descriptors were calculated, but the number of descriptors identified as significant was quite low. The predictive quality of QSAR #1 equation was rather weak. This may be due to the fact that the calibration set is rather non-homogeneous, including many types of aromatic/heterocyclic sulfonamides, possessing an inhibition mechanism which may be slightly different between them (see discussion later in the text). In addition, the Pearson, Spearman, and Kendall correlations between the inhibitory activity against isozyme XII and isozyme XIV are very low (for 49 molecules $r^2 = 0.1574$, $\rho^2 = 0.1932$, and $\tau^2 = 0.1157$). This also suggests that many molecules from Table 1 inhibit the two isozymes by diverse mechanisms. A scatter-plot of this QSAR model is shown in Figure 1.

Table 1. Structure and inhibitory activity (observed vs calculated) for sulfonamides **1**–**55** from the calibration sets used to develop QSAR models



Compound	See structure above	Substituent X	Observed activity		Calculated activity		
			hCA XII	hCA XIV	hCA XII QSAR #1	hCA XIV QSAR #2	hCA XIV QSAR #3
1	A	2-NH_2	4.112	0.228	3.006	0.002	−0.161
2	A	4-NH_2	2.473	0.309	2.710	0.519	0.592
3	A	4-$NHNH_2$	3.000	0.880	2.738	0.354	0.508
4	A	4-CH_3	3.786	—	2.701	—	—
5	A	4-CH_2NH_2	4.564	0.536	2.731	0.437	0.640
6	A	4-$(CH_2)_2NH_2$	3.536	0.579	2.763	0.763	0.850
7	A	3-F, 4-NH_2	4.000	1.786	3.031	1.845	1.659
8	A	3-Cl, 4-NH_2	3.550	2.719	3.167	1.863	—
9	A	3-Br, 4-NH_2	2.740	2.865	3.315	2.375	2.172
10	A	3-I, 4-NH_2	3.000	2.144	3.414	2.612	2.392
11	A	3-SO_2NH_2, 4-NH_2, 6-CF_3	2.388	1.209	2.503	1.207	1.173
12	A	3-SO_2NH_2, 4-NH_2, 6-Cl	2.398	1.286	2.743	1.061	1.361
13	B	NH_2	2.523	1.594	3.271	2.098	1.713
14	C	H	3.439	1.652	3.203	1.591	1.374
15	B	$NHSO_2$–C_6H_4-4-NH_2	2.112	2.927	3.069	2.923	2.944
16	A	4-(CH_2–$NHSO_2$–C_6H_4-4-NH_2)	3.497	—	2.702	—	—
17	A	4-(CH_2CH_2–$NHSO_2$–C_6H_4-4-NH_2)	3.388	2.161	2.737	1.721	1.703
18	A	4-NH-(2-NH_2-Pyrimidin-4-yl)	3.510	2.092	2.787	1.302	—
19	D	OH	3.473	2.360	3.288	2.195	2.013
20	B	C_6H_4-2-Cl	2.485	—	3.207	—	—
21	A	4-CH_2OH	1.699	0.457	2.788	0.445	0.464
22	A	4-CH_2CH_2OH	2.301	0.529	2.800	0.670	0.533
23	A	4-COOH	2.510	1.149	2.776	0.590	—
24	A	2-$NHNH_2$	2.278	—	3.019	—	—
25	B	$NHCOCH_3$	3.286	2.429	3.117	2.437	2.652
26	C	$COCH_3$	3.510	2.408	2.986	2.031	2.334
27	D	OCH_2CH_3	2.699	2.643	3.075	2.745	2.634
28	A	3-SO_2NH_2, 4-Cl, 5-Cl	2.342	1.504	2.465	1.351	1.582
29	E	CH_3	3.497	2.610	3.423	2.083	2.104
30	F	$(CH_2)_3OCH_3$	3.564	2.661	3.278	2.196	2.175
31	B	$NHSO_2C_6H_5$	3.497	2.523	3.041	2.953	2.901
32	A	3-$CONHCH_2$-(*N*-Methyl-pyrrolidin-2-yl), 4-OCH_3	3.450	—	2.870	—	—
33	A	4-SO_2NH-(3-Cl-Indol-7-yl)	3.510	—	2.803	—	—
34	A	3-NH_2	1.944	0.360	3.117	0.627	0.348
35	A	4-$NHCOCH_3$	2.351	0.418	2.697	0.733	0.630
36	A	4-$NHCOCF_3$	2.550	0.886	2.622	1.230	1.144
37	A	4-$NHCOCH_2CH_3$	2.293	0.473	2.699	0.876	0.695
38	A	4-$NHCO(CH_2)_2CH_3$	2.112	0.670	2.702	1.073	0.884
39	A	4-$NHCOCH(CH_3)_2$	1.902	0.661	2.416	1.019	0.869
40	A	4-$NHCO(CH_2)_3CH_3$	1.874	0.680	2.729	1.021	0.791
41	A	4-$NHCOC(CH_3)_3$	1.645	0.618	2.039	1.147	1.016
42	A	4-$NHCOC_6H_5$	2.719	0.913	2.589	1.106	0.964
43	A	4-$NHSO_2CH_3$	2.523	0.944	2.759	1.101	1.055

Table 1 (*continued*)

Compound	See structure above	Substituent X	Observed activity		Calculated activity		
			hCA XII	hCA XIV	hCA XII QSAR #1	hCA XIV QSAR #2	hCA XIV QSAR #3
44	A	4-$NHSO_2C_6H_5$	2.209	1.071	2.594	1.581	1.466
45	A	4-$NHSO_2C_6H_4$-(4-$NHCOCH_3$)	2.161	1.097	2.456	1.561	1.477
46	A	4-$CH_2NHSO_2C_6H_5$	2.122	1.374	2.631	1.573	1.431
47	A	4-$CH_2NHCSNHC_6H_5$	2.786	1.667	2.706	1.619	1.435
48	A	4-$(CH_2)_2NHCSNHC_6H_5$	2.661	1.734	2.720	1.640	1.591
49	A	4-$(CH_2)_2NHCONHC_6H_5$	2.927	1.626	2.696	1.434	1.403
50	A	4-$(CH_2)_2NHCSNHC_6H_4$-(4-SO_2NH_2)	2.144	2.112	2.408	1.897	1.969
51	A	4-$(CH_2)_2NHCONHC_6H_4$-(4-SO_2NH_2)	2.927	2.144	2.349	1.743	1.733
52	A	3-$NHCONHC_6H_5$	3.041	0.880	2.495	1.013	0.907
53	A	3-SO_2NH_2, 4-$NHCONHC_6H_5$, 6-Cl	1.500	1.408	2.617	1.358	1.392
54	B	$NHSO_2C_6H_4$-4Br	3.523	2.927	3.211	3.407	3.551
55	B	$NHSO_2C_6H_4$-4NO_2	3.762	3.041	3.019	2.817	2.922

2.2. QSAR study #2

Dependent property: Inhibitory activity against hCA XIV (Table 1, column 5)
Number of molecules in calibration set: 49
Number of significant descriptors: 264
Type (1) QSAR used for prediction:

$c_0 = -1.0387$
$c_1 = 1.7577$
D_1 is R autocorrelation of lag 3 weighted by atomic masses[23,24]
$c_2 = 0.7655$
D_2 is M (Moran) autocorrelation of lag 5 weighted by atomic Sanderson electronegativities[25]
$c_3 = 0.0301$
D_3 is variation coefficient of distances to geometric center computed for H and halogen atoms
$c_4 = 1.3187$
D_4 is 100·average Fukui electrophilic reaction index for N atoms

Standard error of values s_{value}: 0.3600
Standard error of ranks s_{rank}: 5.4199
Pearson square correlation r^2: 0.8222
Fisher function F: 52.04
Pearson cross-validated square correlation r^2_{CV}: 0.7770
Kendall rank correlation K: 0.7738
Kendall cross-validated rank correlation K_{CV}: 0.7602
Quality Q: 0.6981
Number of outliers: 3

The lowest correlation with activity *A* was computed for predictor D_4 ($r^2 = 0.0854$). The highest intercorrelation between predictors was computed for the pair D_3, D_4 ($r^2 = 0.1386$).

The predictive quality of QSAR #2 is good. The outlier sulfonamides in the group of inhibitors shown in Table 1 are **8**, **18**, and **23**. Probably **18** and **23** are outliers due to their particular structures, as they incorporate a pyrimidine ring and a COOH moiety, respectively, and these functionalities are not present in other molecules investigated here. Only 8% of the molecules of Table 1 showed more potent CA XIV inhibitory activity as compared to **8**. Molecules **9**, **15**, **54**, and **55**, which are stronger CA XIV inhibitors than **8**, are not in fact outliers. Thus, **8** probably represents a potential outlier for lead hopping, that is, allows to identify molecules that belong to different chemical series but which could form the same interactions with the enzyme,[26,27] being thus a possible starting point to develop novel classes of potent CA XIV inhibitors. A scatter-plot of QSAR #2 is shown in Figure 2.

2.3. QSAR study #3

Dependent property: Inhibitory activity against hCA XIV (Table 1, column 5)

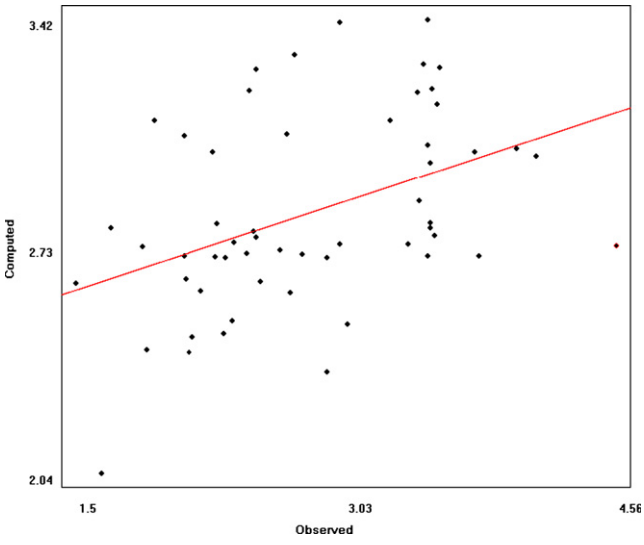


Figure 1. Scatter-plot of observed versus calculated inhibitory activity using QSAR #1.

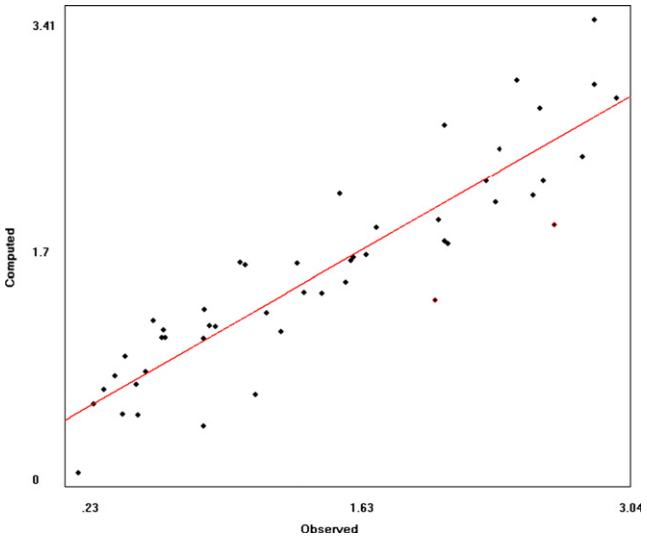


Figure 2. Scatter-plot of observed versus calculated inhibitory activity using QSAR #2 (before elimination of outliers).

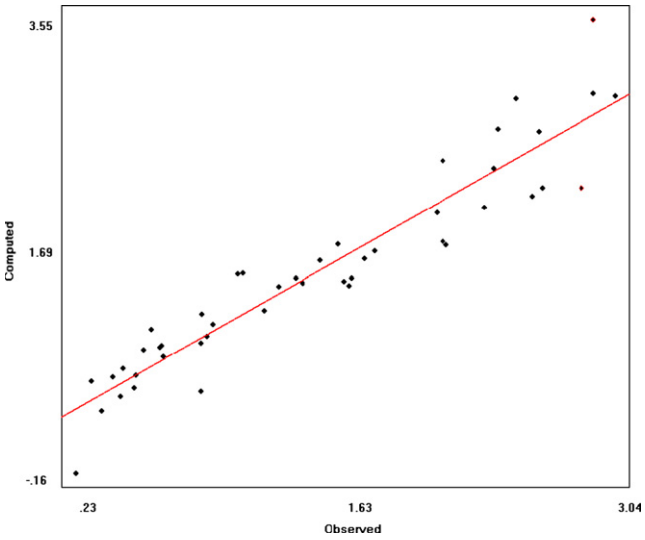


Figure 3. Scatter-plot of observed versus calculated inhibitory activity using QSAR #3 (after elimination of outliers).

Number of molecules in the calibration set: 46 (outliers identified with QSAR #2 were eliminated)
Number of significant descriptors: 285
Type (1) QSAR used for prediction:

$c_0 = -1.6753$
$c_1 = 1.7750$
D_1 is R autocorrelation of lag 3 weighted by atomic masses[23,24] ($U = 1000$)
$c_2 = 0.7240$
D_2 is 100·maximum Fukui electrophilic reaction index for N atoms ($U = 610$)
$c_3 = 0.7974$
D_3 is M (Moran) autocorrelation of lag 5 weighted by atomic Sanderson electronegativities[25] ($U = 439$)
$c_4 = 0.0343$
D_4 is variation coefficient of distances to geometric center computed for H and halogen atoms ($U = 816$)
$c_5 = 9.0602$
D_5 is mean topological charge index of order 5[28] ($U = 227$)

Standard error of values s_{value}: 0.2827
Standard error of ranks s_{rank}: 3.6818
Pearson square correlation r^2: 0.8911
Fisher function F: 67.07
Pearson cross-validated square correlation r^2_{CV}: 0.8567
Kendall rank correlation K: 0.8454
Kendall cross-validated rank correlation K_{CV}: 0.8242
Quality Q: 0.7346
Number of outliers: 0

The lowest correlation with activity A was computed for predictor D_5 ($r^2 = 0.1316$). The highest intercorrelation between predictors was computed for the pair D_3, D_5 ($r^2 = 0.2826$). The predictive quality of QSAR #3 is good and the number of outliers is 0. However, molecule **9** is a border limit outlier by applying the used criteria.

With a pronounced inhibitory activity against CA XIV, sulfonamide **9** is yet another possible outlier for lead hopping (see above). A scatter-plot using QSAR #3 (after elimination of outliers) is shown in Figure 3.

Considering now the physical meaning of the predictors with high utility ($U > 500$) and the signs of the coefficients present in QSAR #3 we conclude the following: (i) CA XIV inhibitory activity for the set of compounds used in these models is proportional to the degree of rugosity of the molecular surface (i.e., a physico-chemical parameter describing the degree of ruggedness/unevenness of the molecular surface); (ii) in derivatives of the types X-Ar-SO_2NH_2 and Ar′-Ar-SO_2NH_2, best inhibitors are those incorporating a heterocyclic moiety.

3. Conclusions

The set of investigated sulfonamides as CA XII/CA XIV inhibitors was quite heterogeneous, including several classes of aromatic/heterocyclic derivatives. The obtained results suggest that some of these derivatives may show slightly different inhibition mechanisms against the investigated CA isoforms. It is in fact known[29,30] that at least two steps are needed for a sulfonamide inhibitor to bind within the enzyme active site (as mainly investigated for the cytosolic ubiquitous isoform CA II): (i) a hydrophobic interaction (recognition) between the inhibitor scaffold and the enzyme active site cavity; and (ii) deprotonation of the sulfonamide moiety, with subsequent coordination to the Zn(II) ion within the active site. The sum of the two steps leads (in favorable cases) to very strong interactions between the inhibitor and the amino acid residues lining the enzyme active site, and as thus, to low nanomolar CA inhibitors.[29] It is not clear whether for all known isozymes, including CA XII and XIV which were less investigated up to now as compared to CA II, the recognition events are the same as those mentioned above. It is also rather unclear whether the deprotonation of the

SO_2NH_2 moiety takes place in solution, outside the active site cavity (case in which the hydrophobic recognition event (i) should in fact involve an anionic species) or this deprotonation occurs only after the binding of a neutral sulfonamide molecule to the enzyme active site by means of weak, hydrophobic interactions. If such events are diverse for different isozymes, this might in fact be reflected by the results of these QSAR models developed here, but such hypotheses should be tested in the future. Interestingly, the 3-X-4-amino-benzenesulfonamides (X = Cl, Br) included in these studies were detected as outliers for scaffold/lead hopping for the inhibition of CA XIV and may be thus used to develop novel inhibitors of this isozyme, presumably with some selectivity against it. Furthermore, in derivatives of the types X-Ar-SO_2NH_2 and Ar′-Ar-SO_2NH_2, best inhibitors were those incorporating a heterocyclic moiety.

4. Experimental

4.1. Inhibition constants

All the inhibition constants were reported earlier as K_I values for the physiologic reaction catalyzed by this enzyme, that is, CO_2 hydration to bicarbonate, by means of a stopped-flow assay technique.[9–11]

4.2. Calculations of descriptors

The programs Mopac93, PRECLAV, and DRAGON[14–18] have been used to calculate the descriptors as mentioned in Section 2.

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