Bioorganic & Medicinal Chemistry Letters 20 (2010) 3089–3093

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

3D-QSAR study of benzene sulfonamide analogs as carbonic anhydrase II inhibitors

Kalyan K. Sethi [a,*], Saurabh M. Verma [b], Naru Prasanthi [b], Suvendu K. Sahoo [a], Rabi N. Parhi [a], P. Suresh [a]

[a] GITAM Institute of Pharmacy, GITAM University, Rushikonda, Visakhapatnam 530 045, AP, India
[b] Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi 835 215, India

ARTICLE INFO

Article history:
Received 17 December 2009
Revised 11 March 2010
Accepted 27 March 2010
Available online 2 April 2010

Keywords:
Benzene sulfonamides
Carbonic anhydrase inhibitors
3D-QSAR
CoMFA
CoMSIA

ABSTRACT

Three-dimensional quantitative structure–activity relationship (3D-QSAR) studies were performed for a series of carbonic anhydrase inhibitors using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) techniques. The large set of 37 different aromatic/heterocyclic sulfonamides carbonic anhydrase (CA, EC 4.2.1.1) inhibitors, such as CA II chosen for the present study. The conventional ligand-based 3D-QSAR studies were performed based on the low energy conformations employing database alignment rule. The ligand-based model gave q^2 values 0.538 and 0.527 and r^2 values 0.974 and 0.971 for CoMFA and CoMSIA, respectively, and the predictive ability of the model was validated. The predicted r^2 values are 0.565 and 0.502 for CoMFA and CoMSIA, respectively. Results indicate that the CoMFA and CoMSIA models could be reliable model which may be used in the design of novel carbonic anhydrase inhibitors as leads.

Several thousand different aromatic and heterocyclic sulfonamides carbonic anhydrase (CA, EC 4.2.1.1) inhibitors were synthesized in the last 50 years in the search of diverse pharmacological agents but the number of amino acid/oligopeptide derivatives among them is unexpectedly small.[1] Consequently, a large series of sulfonamides compounds were synthesized by Supuran and investigated for their inhibitory activity against physiologically relevant CA isozyme, such as CA II.[1] The synthesis involved the reaction of aromatic/heterocyclic sulfonamides containing amino, imino, hydrazine or hydroxyl groups with *N-tert*-butoxycarbonyl-γ-aminobutyric acid (Boc-GABA) in the presence of carbodimide derivatives.[2] Extending a QSAR[3–9] to drug other than those used to formulate it is always a new hypothesis, and although these extensions are often successful.

The large set of 37 sulfonamides, chosen for the present study, is presented in Figure 1, common template (Fig. 2) and Table 1. The total set of compounds was randomly divided into the training set of 29 compounds and the test set of 8 compounds (labeled with *). The three-dimensional structures of benzene sulfonamide derivatives were constructed by using SYBYL program version 7.1 on a Silicon Graphic workstation.[10] Energy minimizations were performed using the Tripos force field with a distance-dependent dielectric and conjugate gradient method.[11] The convergence criterion was 0.01 kcal/mol Å. The Gasteiger–Huckel charges were assigned.

The template molecule is most bioactive compound (KM4) in the training set was taken (Fig. 3a) were used as the reference molecule to align all the molecules using the 'DATABASE ALIGNMENT' option in SYBYL 7.1.[12] The aligned molecules are shown in Figure 3b.

Steric and electrostatic interactions were calculated using sp^3 carbon atom and a +1 charge as steric and electrostatic probes, respectively, with Tripos force field. The CoMFA grid spacing was

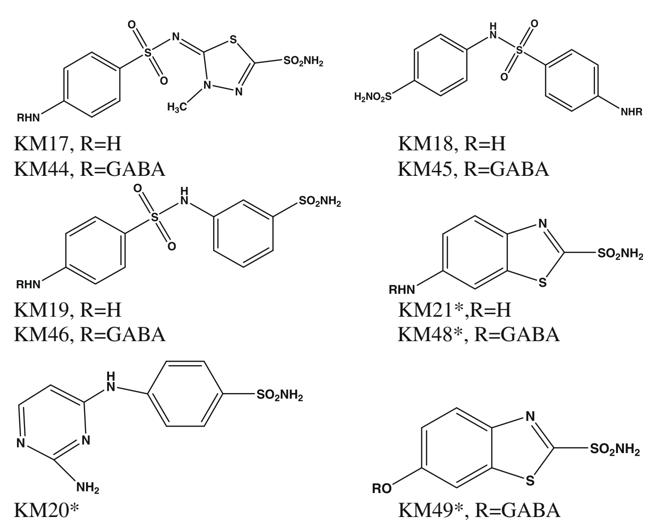

Figure 1. Structure of sulfonamides used in present data set.

* Corresponding author. Tel.: +91 9160636049/9299052717.
E-mail address: kalyansethi@gmail.com (K.K. Sethi).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.03.104

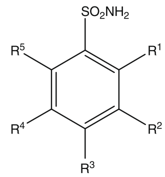

Figure 2. Common template of database molecules.

Table 1
Dataset molecules

Compd code	R^1	R^2	R^3	R^4	R^5
KM1	NH_2	H	H	H	H
KM2	H	NH_2	H	H	H
KM3	H	H	NH_2	H	H
KM4	H	H	$NHNH_2$	H	H
KM5	H	H	CH_2NH_2	H	H
KM6	H	H	$CH_2CH_2NH_2$	H	H
KM7	H	F	NH_2	H	H
KM8	H	Cl	NH_2	H	H
KM9	H	Br	NH_2	H	H
KM10	H	I	NH_2	H	H
KM11*	H	SO_2NH_2	Cl	Cl	NH_2
KM12	H	SO_2NH_2	NH_2	H	Cl
KM16*	H	H	CH_2CH_2OH	H	H
KM24	H	H	CH_2OH	H	H
KM25	H	H	CH_2CH_3	H	H
KM28	NH-GABA	H	H	H	H
KM29	H	NH-GABA	H	H	H
KM31	H	H	NHNH-GABA	H	H
KM32	H	H	CH_2NH-GABA	H	H
KM33	H	H	CH_2CH_2NH-GABA	H	H
KM34	H	F	NH-GABA	H	H
KM35	H	Cl	NH-GABA	H	H
KM36	H	Br	NH-GABA	H	H
KM37	H	I	NH-GABA	H	H
KM39	H	SO_2NH_2	NH-GABA	H	Cl
KM51*	H	H	CH_2O-GABA	H	H
KM52*	H	H	CH_2CH_2-GABA	H	H

GABA = $H_2NCH_2CH_2CH_2CO$–.
* Test set molecule.

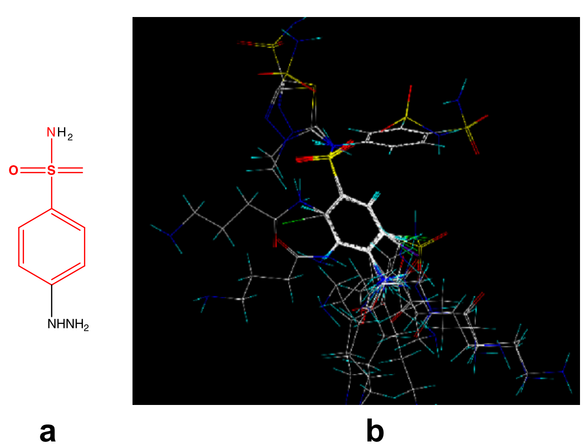

Figure 3. Alignment of the training set: a, is the common template structure (in red color) of highest bioactive molecule KM4; b, is the alignment of the training set for ligand-based model.

2.0 Å in the *x*, *y*, and *z* directions. The default value 30 Kcal/mol was set as the maximum steric and electrostatic energy cut off. Minimum-sigma (column filtering) was set to be 2.0 Kcal/mol.[13]

The CoMSIA[14] method defines five fields: steric, electrostatic, hydrophobic, H-bond donor and H-bond acceptor, which were calculated at each lattice interactions of a regularly spaced grid of 2.0 Å. A probe atom with radius 1.0 Å, +1 charge, hydrophobicity +1.0, and H-bond donor and acceptor properties of +1.0 was used to calculate steric, electrostatic, hydrophobic, and H-bond donor and acceptor fields.[15] A distance-dependent GAUSSIAN type functional form will be taken into account abrupt changes of potential energy near the molecular surface. The default value of 0.3 was used as the attenuation factor.[16]

The benzene sulfonamide ring system, found in all sulfonamide synthetic novel analogs. Such analogs have been developed that have high affinity for the human carbonic anhydrase enzyme. 3D-QSAR studies may be used for the further design of novel human carbonic anhydrase inhibitors. Lead optimization is envisaged with the help of CoMFA and CoMSIA techniques for obtaining a robust model for potent hCAII inhibitors.

CoMFA and CoMSIA are computer programs that are particularly effective in correlating the 3D structures of the molecules and their bioactivities based on statistical techniques.[17]

In order to test the predictive power of the CoMFA and CoMSIA models obtained by the training set, other eight inhibitors that were not included in the training set were used as a test set (Table 3). Table 2 summarizes the predicted results obtained from the CoMFA and CoMSIA models. The plots of predicted versus actual binding affinities for the test set inhibitors are shown in Figures 4a and b which represent models based on CoMFA and CoMSIA, respectively. By comparison of the experimentally observed and theoretically predicted pK_i values of inhibitory activity of a series of benzene sulfonamides derivatives, it can be seen that both CoMFA and CoMSIA models performed well in the prediction of the activities of the test inhibitors (Table 3). In almost all the cases, the predicted values were close to the observed pK_i values, deviating by less than small logarithm unit. Especially for KM4, both CoMFA and CoMSIA models gave ideally predictive values, both of which are less than 0.2 log units.

The predictive ability of each analysis was determined from the test set of eight compounds that were not included in the training set. These molecules were aligned in the same way as those in the training set and their activities were predicted by each PLS analysis. The predictive correlation coefficient (r^2 predicted) is defined as

$$r^2_{\text{pred}} = (\text{SD} - \text{PRESS})/\text{SD}$$

Where SD is the sum of squared deviations between the biological activities of the test set and mean activity of the training set mole-

Table 2
Summary of CoMFA and CoMSIA model results

Components	Ligand-based model	
	CoMFA	CoMSIA
		SEHDA
q^2	0.538	0.527
r^2	0.974	0.971
n	6	6
F-values	139.583	122.58
SEE	0.107	0.110
r^2 predicted	0.565	0.502
Field contribution		
Steric	2.044	0.535
Electrostatic	2.426	0.963
Hydrophobic	–	0.931
Donor	–	0.868
Accepter	–	0.652

q^2: LOO cross-validated correlation coefficient; r^2: non-cross-validated correlation coefficient; n: number of components used in the PLS analysis; SEE: standard error estimate; *F*-value: *F*-statistic for the analysis.