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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 3847–3854

QSAR analysis of some 5-amino-2-mercapto-1,3,4-thiadiazole based inhibitors of matrix metalloproteinases and bacterial collagenase

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Received 27 October 2005; revised 19 March 2006; accepted 7 April 2006
Available online 8 May 2006

Abstract—A quantitative structure–activity relationship (QSAR) study has been performed on 5-amino-2-mercapto-1,3,4-thiadiazole based inhibitors of matrix metalloproteinases (MMPs) and a bacterial collagenase known as *Clostridium histolyticum* collagenase (ChC) to understand the structural features influencing the affinity of these inhibitors towards the enzyme. The compounds in the selected series were characterized by topological and fragmental descriptors calculated using QuaSAR module of molecular operating environment (MOE). An indicator variable was also assigned to account for the presence of amide function in vicinity of sulfonamide group in the parent structure. Correlations between different inhibitory activities and calculated predictor variables were established through stepwise multiple regression employing the method of least squares. The results of the study indicates that MMP inhibitory activity of 5-amino-2-mercapto-1,3,4-thiadiazoles can be successfully explained in terms of topology of the molecule. The obtained correlations also suggest that increase in the number of fluorine atoms in the aromatic ring will augment inhibitory activity of these molecules against all the MMPs probably by virtue of hydrogen bond interaction with some complementary groups in the active site of the enzymes. One prime requirement for better inhibition of MMPs (except for MMP-1) and ChC identified from the present study is the presence of amide function in vicinity of sulfonamide group in the parent structure as suggested by the presence of indicator variable in almost all correlations. While MMP-1 and ChC inhibitory activity of the compounds studied is shown to be dependent on Kier's first order carbon valence molecular connectivity index indicating that increase in branching and presence of heteroatoms in the molecule will improve the MMP-1 and ChC inhibitory potency of 5-amino-2-mercapto-1,3,4-thiadiazoles, correlations derived for other enzymes (MMP-2, MMP-8, MMP-9) are quite similar. In addition to the number of fluorine atoms and presence of indicator variable, MMP-2, MMP-8 and MMP-9 inhibitory activity of 5-amino-2-mercapto-1,3,4-thiadiazoles is found to be dependent on Kier's alpha modified index of third order in such a way that infer, terminally branched functions will increase the affinity of these molecules to the MMPs.

MMPs also called Matrixins are a family of structurally related zinc containing endopeptidases capable of cleaving several macromolecules of the extracellular matrix such as collagens, elastin, fibronectin, laminin, and aggrecan.[1,2] The mammalian MMP family is now known to include at least 23 enzymes. Based on their structure and substrate specificity, the human MMPs are roughly divided into five groups: collagenases, gelatinases, stromelysins, membrane-type (MT) metalloproteinases, and the others, and it is likely that other members will be discovered in the next few years.[3] These MMPs have been implicated in the tissue remodeling at various stages of human development, wound healing, and disease. Their activation and upregulation results into tissue degradation leading to a variety of diseases, some of which are cancer,[4–7] rheumatoid arthritis,[8,9] multiple sclerosis,[10,11] and congestive heart failure.[12,13] In view of such wide-ranging clinical relevance, it is no wonder that the search for clinically useful inhibitors of these enzymes has been in the focus of intensive research. Several MMP inhibitors have reached up to clinical trials and a vast majority of them are hydroxamic acid derivatives, such as batimastat (BB-94), marimastat (BB-2516), trocade (Ro 32-3555), and BAY 12-9566 (Fig. 1).[14–22]

Keywords: QSAR; MMP; MOE.
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doi:10.1016/j.bmcl.2006.04.014

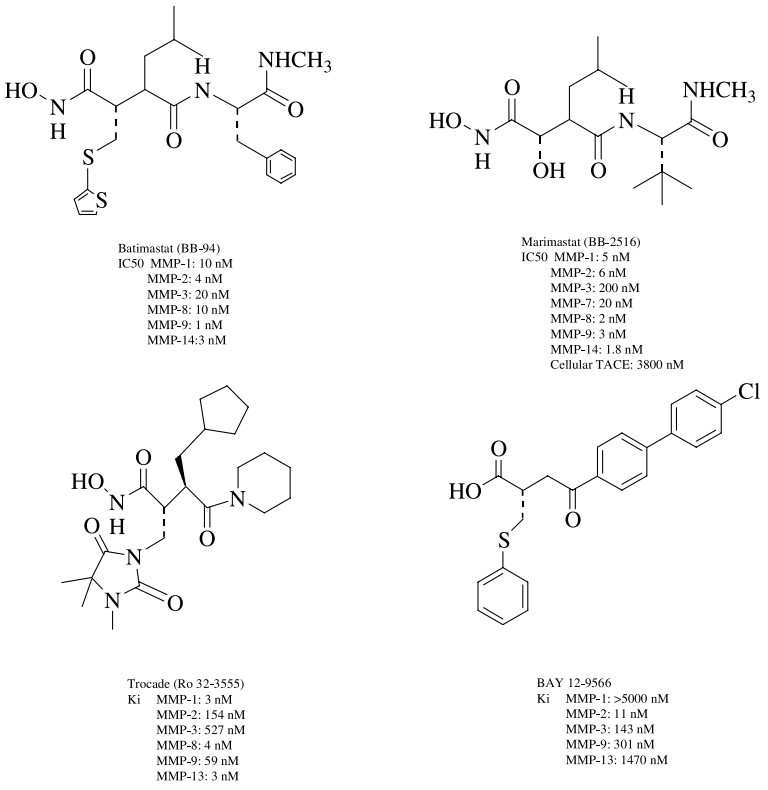


Figure 1. MMP inhibitors in clinical trials.

In addition to MMPs there are also some other enzymes, which can degrade ECM, such as bacterial collagenases. One such bacterial collagenase known as *Clostridium histolyticum* collagenase (ChC),[23] which belongs to the family of M-31 metalloproteinase family, is capable of hydrolyzing triple helical region of collagen under physiological conditions as well as many synthetic peptides. MMPs and ChC, though relatively different, are considered to act through same mechanism of action in the hydrolysis of proteins and synthetic substrates.

Most of the MMP inhibitors reported until now incorporate hydroxamic acid function as zinc binding group (ZBG) because it provides most potent inhibitory activity against MMP but such inhibitors show some noteworthy shortcomings, as these inhibitors are rapidly metabolized and show poor selectivity toward different MMPs. Additionally these inhibitors show poor bioavailability. Recently, Scozzafava and Supuran[24] reported a series of 5-amino-2-mercapto-1,3,4-thiadiazole derivatives as inhibitors of four MMPs (MMP-1, MMP-2, MMP-8, and MMP-9) and ChC. These inhibitors are non-hydroxamates and thus may overcome the aforementioned shortcomings of hydroxamate inhibitors. With the view of progression of design and development of such inhibitors of MMPs, a quantitative structure–activity relationship (QSAR) study has been performed in order to relate MMP inhibitory activity of these non-hydroxamic acid inhibitors to their molecular structures. Although structure based design has been used primarily in the design of new MMP inhibitors, there are several examples where the indirect approaches such as QSAR have been utilized in search of more potent analogues.[25–27] QSAR analysis will provide structural insight into the mechanism of action of these inhibitors, which is of utmost importance in the design of new analogues by modification of structure of parent compound.

The QSAR study has been performed on a series of compounds incorporating 5-amino-2-mercapto-1,3,4-thiadiazoles as zinc binding function, reported by Scozzafava and Supuran. The biological activities of these 27 compounds were expressed in terms of enzyme inhibition constants (K_i). These K_i values were obtained by Scozzafava and Supuran from Easson–Stedman plots, using a linear regression program, from at least three different assays. All the K_i values of the compounds were reported in terms of micromolar (μM) concentration. For correlation purposes, reported K_i values were converted to their molar units and subsequently to free energy related negative logarithmic state, that is, log ($1/K_i$). All the computational studies were performed on Compaq (Pentium-IV) computer using the software Molecular Operating Environment (MOE version 2005.04). Molecules were sketched using builder module of MOE. Various 2D descriptors, for which neither energy minimization nor alignment is required, were calculated for built structures of the molecules, using QuaSAR module of MOE. A large number of descriptors were generated by the MOE (Table 1). The descriptor pool was reduced by eliminating out the descriptors with constant and near constant values. Further reduction in the descriptor pool

Table 1. Classification and description of the calculated molecular descriptors

Functional families of the descriptors	Descriptor: definition
Physical properties	apol: sum of the atomic polarizabilities bpol: sum of the absolute value of the difference between atomic polarizabilities of all bonded atoms in the molecule mr: molecular refractivity Weight: molecular weight TPSA: topological polar surface area log *P*(O/W): log of the octanol/water partition coefficient
Atom counts and bond counts	a_aro: number of aromatic atoms a_nN: number of nitrogen atoms a_nO: number of oxygen atoms a_nF: number of fluorine atoms a_nS: number of sulfur atoms a_nCl: number of chlorine atoms a_nBr: number of bromine atoms b_1rotN: number of rotatable single bonds b_ar: number of aromatic bonds b_ singlet: number of single bonds b_double: number of double bonds b_triple: number of triple bonds
Kier and Hall connectivity indices and Kier shape indices	${}^{0}\chi$: atomic connectivity index (order 0) ${}^{0}\chi_{c}$: carbon connectivity index (order 0) ${}^{1}\chi$: atomic connectivity index (order 1) ${}^{1}\chi_{c}$: carbon connectivity index (order 1) ${}^{0}\chi^{V}$: atomic valence connectivity index (order 0) ${}^{0}\chi_{c}^{V}$: carbon valence connectivity index (order 0) ${}^{1}\chi^{V}$: atomic valence connectivity index (order 1) ${}^{1}\chi_{c}^{V}$: carbon valence connectivity index (order 1) ${}^{1}K$: first kappa shape index ${}^{2}K$: second kappa shape index ${}^{3}K$: third kappa shape index ${}^{1}K_{\alpha}$: first alpha modified shape index ${}^{2}K_{\alpha}$: second alpha modified shape index ${}^{3}K_{\alpha}$: third alpha modified shape index KierFlex: Kier molecular flexibility index
Adjacency and distance matrix descriptors	balabanJ: Balaban's connectivity topological index petitjeanSC: Petitjean graph shape coefficient weinerPath: Wiener path number weinerPol: Wiener polarity number zagreb: Zagreb index

was done by ousting the descriptors that are highly degenerate and the descriptors that were showing very low correlation with inhibitory activity. The remaining fragmental and topological descriptors were taken into account for the reported analysis. An indicator variable was assigned for the presence of amide function in vicinity of sulfonamide group in the title compounds. The series of compounds along with the descriptors used in the selected regressions are given in the Table 2. Data set generated so was subjected to statistical analyses. Stepwise multiple regression analysis was used as statistical tool, with the help of our inhouse statistical program VALSTAT.

Correlations between different inhibitory activities and calculated predictor variables were established through stepwise multiple regression using the method of least squares. Statistically significant QSARs generated for different inhibitory activity data were as follows:

MMP-1

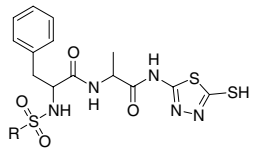
$$\begin{aligned}\log(1/K_{\mathrm{i}}) = {} & [4.39725(\pm 1.03418)] \\ & + {}^{1}\chi_{\mathrm{c}}^{\mathrm{V}}[-0.207152(\pm 0.0851363)] \\ & + {}^{3}K_{\alpha}[0.201545(\pm 0.0927689)] \\ & + \mathrm{a\_nF}[0.0832763(\pm 0.0471238)]\end{aligned}$$

$$\begin{aligned}& N = 27,\ r = 0.913,\ r^2 = 0.834,\ \mathrm{SEE} = 0.122, \\ & F = 38.645(F_{3,23} = 4.765),\ \mathrm{chance} =< 0.001, \\ & q^2 = 0.734,\ S_{\mathrm{PRESS}} = 0.154,\ S_{\mathrm{DEP}} = 0.142. \end{aligned} \quad (1)$$

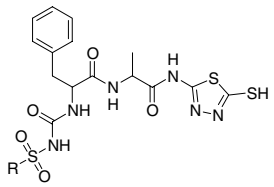
MMP-2

$$\begin{aligned}\log(1/K_{\mathrm{i}}) = {} & [2.92822(\pm 0.860004)] \\ & + {}^{3}K_{\alpha}[0.255415(\pm 0.122169)] \\ & + \mathrm{a\_nF}[0.110207(\pm 0.0556175)] \\ & + I[0.357692(\pm 0.191531)]\end{aligned}$$

Table 2. Structural variation in 5-amino-2-mercapto-1,3,4-thiadiazole derivatives along with descriptors involved in QSAR models



Compound 1 to 22



Compound 23 to 27

Compound	R	I	a_nF	$^{1}\chi_{c}^{V}$	$^{3}K_{\alpha}$
1	C_6H_5–	0	0	5.737	6.684
2	$C_6H_5CH_2$–	0	0	6.091	7.702
3	4-F–C_6H_4–	0	1	5.648	6.883
4	4-Cl–C_6H_4–	0	0	5.648	7.263
5	4-Br–C_6H_4–	0	0	5.648	7.508
6	4-I–C_6H_4–	0	0	5.648	7.725
7	4-CH_3–C_6H_4–	0	0	6.148	6.925
8	4-NO_2–C_6H_4–	0	0	5.648	7.181
9	3-NO_2–C_6H_4–	0	0	5.648	7.181
10	2-NO_2–C_6H_4–	0	0	5.654	6.955
11	4-AcNH–C_6H_4–	0	0	6.148	7.956
12	C_6F_5–	0	5	5.327	6.481
13	3-CF_3–C_6H_4–	0	3	5.898	7.555
14	2,5-Cl_2–C_6H_4–	0	0	5.565	7.614
15	4-OCH_3–C_6H_4–	0	0	5.648	7.184
16	2,4,6-$(CH_3)_3$-C_6H_2–	0	0	6.981	6.969
17	1-Naphthyl	0	0	7.148	6.289
18	2-Naphthyl	0	0	7.143	6.475
19	5-$(CH_3)_2$N-1-naphthyl	0	0	7.065	6.831
20	2-Thienyl	0	0	4.783	6.631
21	Quinoline-8-yl	0	0	6.526	6.265
22	Camphor-10-yl	0	0	7.993	5.781
23	C_6H_5–	1	0	5.737	7.698
24	4-F–C_6H_4–	1	1	5.648	7.912
25	4-Cl–C_6H_4–	1	0	5.648	8.309
26	4-CH_3–C_6H_4–	1	0	6.148	7.956
27	2-CH_3–C_6H_4–	1	0	6.154	7.706

$$N = 27,\ r = 0.893,\ r^2 = 0.797,\ \mathrm{SEE} = 0.152,$$
$$F = 30.175(F_{3,23} = 4.765),\ \mathrm{chance} =< 0.001,$$
$$q^2 = 0.682,\ S_{\mathrm{PRESS}} = 0.189,\ S_{\mathrm{DEP}} = 0.175. \quad (2)$$

MMP-8

$$\log(1/K_i) = [2.96998(\pm 0.987275)] + I[0.413534(\pm 0.245314)] + \mathrm{a\_nF}[0.272465(\pm 0.063659)] + {}^{3}K_{\alpha}[0.242856(\pm 0.140256)]$$

$$N = 25,\ r = 0.916,\ r^2 = 0.840,\ \mathrm{SEE} = 0.170,$$
$$F = 36.846(F_{3,21} = 4.874),\ \mathrm{chance} =< 0.001,$$
$$q^2 = 0.773,\ S_{\mathrm{PRESS}} = 0.203,\ S_{\mathrm{DEP}} = 0.186. \quad (3)$$

MMP-9

$$\log(1/K_i) = [2.59183(\pm 1.56751)] + I[0.789148(\pm 0.349099)] + \mathrm{a\_nF}[0.237027(\pm 0.101373)] + {}^{3}K_{\alpha}[0.293886(\pm 0.222674)]$$

$$N = 27,\ r = 0.885,\ r^2 = 0.784,\ \mathrm{SEE} = 0.276,$$
$$F = 27.834(F_{3,23} = 4.765),\ \mathrm{chance} =< 0.001,$$
$$q^2 = 0.676,\ S_{\mathrm{PRESS}} = 0.338,\ S_{\mathrm{DEP}} = 0.312 \quad (4)$$

ChC

$$\log(1/K_i) = [6.09875(\pm 0.569215)] + I[0.574679(\pm 0.199763)] + {}^{1}\chi_{c}^{V}[-0.218646(\pm 0.0929326)]$$

$$N = 25,\ r = 0.858,\ r^2 = 0.736,\ \mathrm{SEE} = 0.156,$$
$$F = 30.805(F_{2,22} = 6.81),\ \mathrm{chance} =< 0.001,$$
$$q^2 = 0.626,\ S_{\mathrm{PRESS}} = 0.185,\ S_{\mathrm{DEP}} = 0.174 \quad (5)$$

In the above QSAR models N is the number of data points, r is correlation coefficient, r^2 is squared correlation coefficient which when multiplied by 100 gives explained variance in biological activity, SEE is standard error of estimate, F represents Fischer ratio between the variances of calculated and observed activities, figures given in parentheses that follow calculated F value are tabulated F value, and the values in parentheses within the model with ± sign are standard error associated with the regression coefficients, q^2 is cross validated squared correlation coefficient, and S_{PRESS} and S_{DEP} correspond to standard deviation based on predicted residual sum of squares and standard deviation of error of prediction, respectively. The Z score method was adopted for the detection of outliers. Z Score can be defined as absolute difference between the value of the model and the activity field, divided by the square root of the mean square error of the data set. Any compound which shows a value of Z score higher than 2.5, during generation of a particular QSAR model, is considered as outlier (Table 3).

All the QSAR models are significant at 99% level as shown by their Fischer ratio values, which exceed the tabulated values by a large margin as desired for a meaningful correlation. Each QSAR model can explain more than 75% of the total variance ($r^2 > 0.75$) in the MMP inhibitory activity exhibited by 5-amino-2-mercapto-1,3,4-thiadiazole derivatives, the highest and lowest r^2 values of 0.84 and 0.78 were recorded for inhibition of MMP-8 and MMP-9, respectively Eqs. 3 and 4. Accuracy in the analysis is shown by low values of standard error of estimate. Absence of collinearity is confirmed by calculation of intercorrelation matrix for the predictor variables used in the models (Table 4). Intercorrelation coefficients, so obtained, indicate non-dependency of the descriptors on each other.

It is very much evident from the obtained correlations that the MMP inhibitory activity of 5-amino-2-mercapto-1,3,4-thiadiazoles can be successfully explained in terms of topology of the molecule. The observation also stems from the fact that topological indices appear predominantly in all the regressions generated for describing MMP inhibitory activity of 5-amino-2-mercapto-1,3,4-thiadiazoles.

Table 3. *Z* Score values of compounds in the QSAR models

Compound	Model 1 (MMP-1)	Model 2 (MMP-2)	Model 3 (MMP-8)	Model 4 (MMP-9)	Model 5 (ChC)
1	0.890	0.766	0.166	1.030	−0.135
2	−0.594	−0.698	−1.496	−0.228	−0.305
3	0.206	−0.189	−1.063	0.008	−1.245
4	0.069	0.088	0.068	0.375	−1.103
5	−1.056	−0.155	−0.593	−0.465	−0.454
6	−0.931	−0.925	−0.784	−0.452	−0.065
7	0.030	0.012	−0.086	0.275	0.465
8	1.307	1.112	1.795	0.163	0.149
9	0.615	1.112	1.080	0.163	0.382
10	−0.787	0.836	0.693	0.839	−0.257
11	1.108	0.957	0.901	0.268	0.277
12	0.256	0.611	0.587	0.065	2.457
13	−0.542	−1.614	−0.625	−0.856	1.585
14	−0.504	0.892	1.424	−0.230	−0.388
15	−1.069	−0.129	−0.098	−0.097	−0.065
16	1.102	−0.621	−0.379	−0.394	1.322
17	−0.762	−0.637	−0.624	−0.322	−0.535
18	−0.701	−0.706	−1.229	−0.844	−0.932
19	−2.187	−1.929	−1.947	−1.148	−1.255
20	0.971	1.853	2.137	1.768	−0.049
21	−1.551	−0.991	−0.518	−0.332	−1.527
22	2.227	0.358	0.594	0.412	1.680
23	−0.341	0.343	0.301	−0.944	0.696
24	0.138	1.978	2.619	2.231	2.703
25	0.858	−0.073	3.482	2.212	3.396
26	0.846	−1.145	−0.093	−1.609	0.461
27	0.401	−1.103	−0.207	−1.888	−1.157

The best correlation for modeling MMP-1 inhibition by 5-amino-2-mercapto-1,3,4-thiadiazoles comprises of two topological descriptors, Kier's first order carbon valence molecular connectivity index[28] ($^1\chi_c^V$) and Kier's alpha modified index of third order.[29] The topological descriptor, $^1\chi_c^V$, encodes information regarding degree of branching, cyclization, heteroatom content, and heteroatom position in the molecule and is calculated as follows:

$$^1\chi_c^V = \sum(\delta_i^v \delta_j^v)^{-1/2}, \quad (6)$$

where δ_i^v and δ_j^v are the vertex connectivity indices of carbon atoms i and j, respectively, and the summation extends to all bonded pairs of non-hydrogen carbon atoms in the group or molecule. For second and third rows of atoms, Kier[30] gave a unified definition of δ^v, as expressed by Eq. 7. In this equation, Z_i^v is the number of valence electrons of atom i, h_i is the number of hydrogen atoms attached to it, and Z_i is its atomic number.

$$\delta_i^v = (Z_i^v - h_i)/(Z_i - Z_i^v - 1). \quad (7)$$

The value of the δ_i^v increases with branching and with increases in the number of heteroatoms in the molecule. Thus, the negative coefficient of the descriptor $^1\chi_c^V$ in Eq. 1 implies that increase in branching and presence of heteroatoms in the molecule will improve the MMP-1 inhibitory potency of 5-amino-2-mercapto-1,3,4-thiadiazoles. The distance matrix based Kier α modified shape index of order three ($^3K_\alpha$) was derived from ^{3}K shape index, a descriptor based on the counts of three-path (^{3}P) fragments. The ^{3}K index was modified to account for the different shape contribution of non-sp^3 carbon atoms, through addition of an α-modifier by Kier. $^3K_\alpha$ have two solutions in terms of the total number of atoms in the molecule, depending upon whether *A*, which represents the total number of vertices in the graph, is even or odd. It is calculated as:

$$^3K_\alpha = \frac{(A+\alpha-3)(A+\alpha-2)^2}{(^3P_i+\alpha)^2}, \quad \text{(if A is even)}, \quad (8)$$

$$^3K_\alpha = \frac{(A+\alpha-1)(A+\alpha-3)^2}{(^3P_i+\alpha)^2}, \quad \text{(if A is odd)}, \quad (9)$$

where ^3P_i refers to the intermediate count of three path fragments, which lay at or within the boundaries of minimum and maximum values of ^3P, that is, $^3P_{min} \leqslant {}^3P_i \leqslant {}^3P_{max}$.

The α modifier is calculated as the sum of the ratio of radii of all heteroatoms or carbon of another valence state (r_x) relative to the sp^3 carbon atom ($r^3_{C\ sp}$):

$$\alpha = \sum[(r_x/r^3_{C\ sp}) - 1]. \quad (10)$$

$^3K_\alpha$ index encodes the information about the specific kind of branching in the molecule as it varies when the branching occurs in the middle (centrality) or at the ends (non-centrality) of a long chain fragment. The value of the descriptor increases when branching is located in the extremity of the molecular graph. Thus, the positive coefficient of the $^3K_\alpha$ in the Eq. 1 indicates that terminally branched functions will increase the affinity of 5-amino-2-mercapto-1,3,4-thiadiazoles to the MMP-1. Furthermore, the positive coefficient of the fragmental descriptor a_nF in the equation suggests that the MMP-1 inhibitory potency of the 5-amino-2-mercapto-1,3,4-thiadiazoles increases with the increase in the number of fluorine atoms in the molecule. This may be due

Table 4. Correlation matrix for intercorrelation between structural descriptors and their correlation to enzyme affinity data

	MMP-1	MMP-2	MMP-8	MMP-9	ChC	*I*	a_nF	$^1\chi_c^V$	$^3K_\alpha$
MMP-1	1.000								
MMP-2	0.852	1.000							
MMP-8	0.727	0.908	1.000						
MMP-9	0.766	0.928	0.978	1.000					
ChC	0.667	0.895	0.951	0.962	1.000				
I	0.372	0.710	0.673	0.714	0.785	1.000			
a_nF	0.406	0.303	0.440	0.398	0.208	−0.074	1.000		
$^1\chi_c^V$	−0.799	−0.598	−0.440	−0.501	−0.419	−0.121	−0.237	1.000	
$^3K_\alpha$	0.652	0.722	0.563	0.604	0.603	0.582	−0.102	−0.468	1.000

to participation of fluorine atom in the hydrogen bond interaction with the complementary sites in the active site of MMPs. The importance of fluorine atoms substituted in the aryl ring has also been suggested through similar findings by Kumar and Gupta.[26]

The best regressions for MMP-2, MMP-8, and MMP-9 inhibitory activities of 5-amino-2-mercapto-1,3,4-thiadiazoles Eqs. 2–4 comprised of the same set as descriptors used for characterizing MMP-1 inhibition except for the topological descriptor $^{1}\chi^{V}$, which is replaced by indicator variable *I*. The positive coefficient of I in all these regressions reveals that presence of an amide function in vicinity of sulfonamide moiety in 5-amino-2-mercapto-1,3,4-thiadiazoles analogues contributes to the tight binding of these molecules to the active site of the enzyme. These parallel correlations also highlight the similar mode of binding of inhibitor molecules to the active site of the enzymes.

The last regression Eq. 5 derived for ChC inhibition of 5-amino-2-mercapto-1,3,4-thiadiazoles correlates the ChC inhibition of these molecules with the indicator variable *I*, and the Kier's first order carbon valence molecular connectivity index ($^{1}\chi_{c}^{V}$). The equation suggests that presence of amide function, decrease in branching, and introduction of heteroatoms in the substituents molecule will be conducive for ChC inhibitory activity.

It was found that two compounds, viz. 4-flurophenylsulfonyluriedo (compound **24**) and 4-chlorophenylsulfonyluriedo (compound **25**) analogues of 5-amino-2-mercapto-1,3,4-thiadiazole, behaved as outlier in the QSAR modeling of MMP-8 and ChC inhibition. It was interesting to observe that the compounds with the same pattern of substitution among sulfonamides were quietly fitting into the derived models, which demonstrate that the presence of sulfonyluriedo group may be a factor behind the outlying pattern of these compounds. Moreover, the outlying behavior of these compounds may also be attributed to the fact that they exhibit higher potency than the compounds with the same pattern of substitution among sulfonamide derivatives in the series and this phenomenon could not described in terms of any of the descriptors present in Eqs. 3 and 5.

Summarizing the above discussion, it may be concluded that a fair idea about drug–enzyme geometric fit can be achieved by using the descriptors $^{1}\chi^{V}$, $^{3}K_{\alpha}$, number of fluorine atoms, and indicator variable representing the sulfonyluriedo moiety. The sign of the regression coefficient of the topological descriptors $^{1}\chi^{V}$ and $^{3}K_{\alpha}$ in model 1 is particularly interesting as the topological descriptor $^{1}\chi^{V}$ advocates for the increase in branching and increase in heteroatom content in the molecule for MMP-1 inhibitory potency whereas the descriptor $^{3}K_{\alpha}$ stress on the importance of branching at the extremal part of the

Table 5. Observed and predicted activity values for MMP and ChC inhibition calculated by using the QSAR models

Compound	log ($1/K_i$)									
	MMP-1 (Model 1)		MMP-2 (Model 2)		MMP-8 (Model 3)		MMP-9 (Model 4)		ChC (Model 5)	
	Observed activity	Predicted activity	Observed activity	Predicted activity	Observed activity	Predicted activity	Observed activity	Predicted activity	Observed activity	Predicted activity
1	4.657	4.543	4.745	4.627	4.619	4.591	4.824	4.536	4.824	4.845
2	4.619	4.693	4.795	4.909	4.602	4.874	4.795	4.864	4.721	4.769
3	4.721	4.695	4.769	4.798	4.745	4.925	4.854	4.852	4.677	4.875
4	4.698	4.690	4.795	4.783	4.745	4.733	4.824	4.720	4.698	4.874
5	4.619	4.748	4.824	4.848	4.698	4.803	4.677	4.810	4.795	4.868
6	4.677	4.792	4.769	4.921	4.721	4.865	4.745	4.879	4.854	4.864
7	4.522	4.519	4.698	4.697	4.638	4.653	4.698	4.623	4.824	4.751
8	4.824	4.664	4.921	4.753	5.000	4.697	4.745	4.699	4.886	4.862
9	4.745	4.669	4.921	4.753	4.886	4.704	4.745	4.699	4.921	4.860
10	4.537	4.635	4.824	4.698	4.769	4.653	4.854	4.624	4.824	4.865
11	4.854	4.708	5.096	4.929	5.045	4.868	5.000	4.914	4.795	4.752
12	5.045	4.938	5.222	4.908	6.000	5.641	5.698	5.637	5.301	4.896
13	4.886	4.976	4.958	5.295	5.523	5.670	5.301	5.626	5.045	4.797
14	4.721	4.783	5.000	4.857	5.045	4.792	4.769	4.836	4.824	4.886
15	4.553	4.683	4.745	4.764	4.698	4.715	4.677	4.705	4.854	4.864
16	4.481	4.339	4.619	4.713	4.602	4.665	4.537	4.645	4.769	4.547
17	4.096	4.200	4.445	4.548	4.397	4.513	4.356	4.453	4.455	4.548
18	4.143	4.235	4.481	4.593	4.346	4.564	4.275	4.517	4.397	4.559
19	4.06	4.345	4.397	4.689	4.318	4.647	4.301	4.617	4.366	4.581
20	4.854	4.676	4.886	4.601	4.921	4.553	5.000	4.504	5.045	5.055
21	4.131	4.334	4.387	4.551	4.408	4.505	4.346	4.446	4.444	4.686
22	4.161	3.748	4.455	4.385	4.468	4.335	4.397	4.248	4.602	4.218
23	4.721	4.763	5.301	5.239	5.301	5.229	5.397	5.708	5.522	5.365
24	4.92	4.903	5.698	5.337	7.000	[a]	6.523	5.779	6.698	[a]
25	5.000	4.882	5.397	5.411	6.698	[a]	6.397	5.657	6.523	[a]
26	4.824	4.713	5.155	5.359	5.301	5.323	5.301	5.825	5.397	5.294
27	4.721	4.671	5.096	5.295	5.222	5.272	5.155	5.775	5.155	5.415

[a] Compounds **24** and **25** were not considered while deriving model 3 and model 5.

molecule for MMP-1 inhibition. Given the nature of the substituents in the phenyl ring, it is more likely that the valence molecular connectivity index of first order $^{1}\chi^{V}$ characterizes the heteroatom content rather than the connectivity of substituent atoms. Thus, it may be apt to conclude that increase in the number of heteroatoms in the molecule and branching of the substituents in the phenyl ring is conducive for MMP-1 inhibition by 5-amino-2-mercapto-1,3,4-thiadiazole derivatives.

It is worth mentioning here that the descriptor a_nF, which represents the number of fluorine atoms in the molecule, appears to positively influence the binding affinity of the molecules to all the matrix metalloproteases (MMP-1, -2, -8, -9), except for bacterial collagenase ChC. However, the magnitude of contribution of descriptor a_nF differs with different MMPs as indicated by the magnitude of the regression coefficient in the generated models. The order of MMP inhibitory activity of title compounds may be given as MMP-8 > MMP-9 > MMP-2 > MMP-1. The finding suggests that increase in the number of fluorine atoms in the 5-amino-2-mercapto-1,3,4-thiadiazole derivatives will impart selectivity for MMP-8, MMP-9, and MMP-2 over MMP-l as they are more likely to be influenced by the increase in number of fluorine atoms in the molecule. Further, it is also observed from the correlations Eqs. 1–5 that presence of sulfonyluriedo moiety (indicator variable *I*) in the 5-amino-2-mercapto-1,3,4-thiadiazole derivatives seems to preferentially effect MMP-2, MMP-8, and MMP-9 inhibition whereas it has no effect on MMP-1 inhibition. The finding could be of clinical relevance as recent studies have suggested that side effects owing to non-selective MMP inhibition (collectively termed as musculoskeletal syndrome) arise from the inhibition of MMP-1 owing to its presumed role in the normal turnover of extracellular matrix in connective tissue.[31] Thus, presence of sulfonyluriedo moiety and increase in the number of fluorine atoms may impart the much-needed selectivity for MMP-2, MMP-8, and MMP-9 over MMP-1.

Although, generation of QSAR models with good statistical significance is of paramount importance, the models should also exhibit good predictive ability. The predictive ability of the models was gauged by a cross-validation procedure following a leave-one-out scheme. All the models exhibit high q^2 and low S_{PRESS} and S_{DEP}

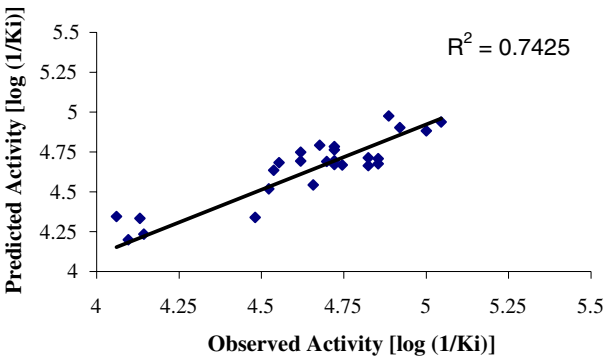


Figure 2. Graphical plot between predicted and observed activity values for model 1.

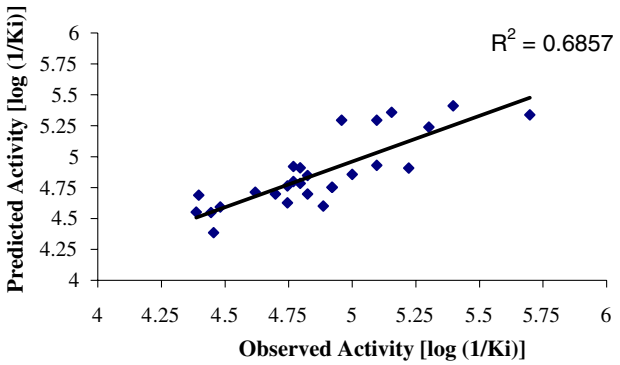


Figure 3. Graphical plot between predicted and observed activity values for model 2.

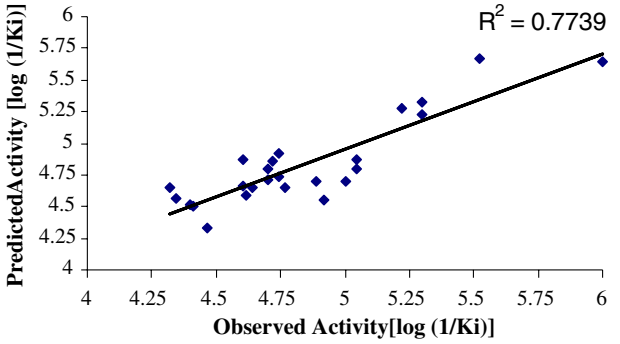


Figure 4. Graphical plot between predicted and observed activity values for model 3.

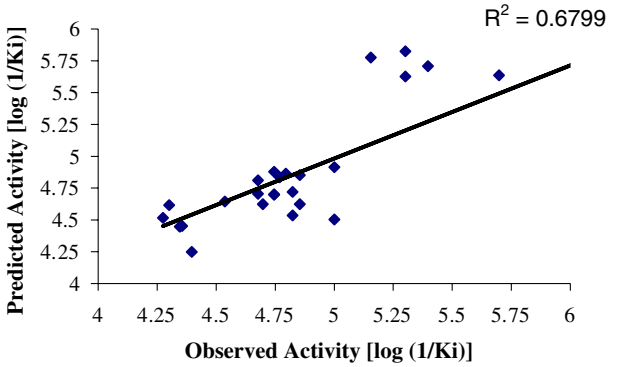


Figure 5. Graphical plot between predicted and observed activity values for model 4.

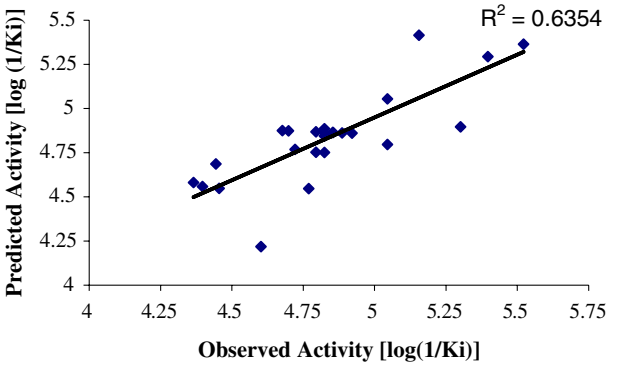


Figure 6. Graphical plot between predicted and observed activity values for model 5.

values reflecting their good predictive potential and the best being recorded for model 3 (MMP-8). Furthermore, a comparison was made between the experimental activity values and predicted activity values calculated by using the obtained models in Table 5 and graphical representation of the same are depicted in Figures 2–6. This comparison together with the graphical plot provides ample evidence for the good predictive potential of the models generated for modeling MMP inhibitory activity of thiadiazoles.

The present study gives rise to quantitative models to be capable of good prediction of MMP inhibition by 5-amino-2-mercapto-1,3,4-thiadiazole derivatives. In addition to good predictivity, the analysis of the regression models also gives an insight into the characteristic features of the inhibitor molecules that influences the binding affinity for the MMPs. The results of the QSAR study suggest a possibility that the increase of fluorine atoms increases inhibitory potency of thiadiazole derivatives against respective MMPs with preferential order as MMP-8 > MMP-9 > MMP-2 > MMP-1. Furthermore, branching at the molecular terminus is found to enhance the inhibitory potency of the 5-amino-2-mercapto-1,3,4-thiadiazole derivatives against all the MMPs, except for bacterial collagenase ChC, whereas increase in the overall branching and in the heteroatoms content in the molecule is found to be beneficial for MMP-1 and ChC inhibition. Additionally, incorporation of sulfonyluriedo moiety in the molecules spares MMP-1 while inhibiting other MMPs, a finding that might be of significance for designing MMP inhibitors with lesser side effects.

Acknowledgments

The authors gratefully acknowledge Prof. Lemont B. Kier, Emeritus Faculty of Medicinal Chemistry, Virginia Commonwealth University, for providing reprints of his research publications. The authors wish to thank TATA ELXSI for providing molecular modeling software MOE for the present research work. The authors also wish to thank honorable referees for their contribution toward betterment of this research paper.

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