Quantitative Structure-Activity Relationship Studies on Matrix Metalloproteinase Inhibitors: Hydroxamic Acid Analogs

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Abstract: A quantitative structure-activity relationship study has been conducted on two different series of acyclic hydroxamic acid analogs acting as matrix metalloproteinase (MMP) inhibitors. The results suggest that in a few cases, the hydrophobic property of the molecules is the major governing factor. However, in some cases, the polarizability of the molecules is shown to be dominant. The two enzymes, MMP-9 and MMP-13, are shown to behave in a similar fashion with any group of inhibitors.

Key Words: Hydroxamic acid analogs, matrix metalloproteinase inhibitors, quantitative structure-activity relationship.

INTRODUCTION

The extracellular matrix (ECM) plays a critical role in the structure and integrity of various tissue types in higher vertebrates [1,2]. The ECM have all kinds of structural proteins such as basement-membrane and interstitial collagens, fibronectin, laminin and aggrecan [3,4]. These physiologically important structural proteins are degraded by a large family of zinc endopeptidases known as matrix metalloproteinases (MMPs) during normal tissue remodeling process, such as pregnancy, wound healing, apoptosis and angiogenesis [5-7]. However, overexpression and activation of these MMPs result in tissue degradation, leading to a wide array of disease processes, such as osteoarthritis [8,9], rheumatoid arthritis [10-12], tumor metastatis [13-15], multiple sclerosis [16-18], congestive heart failure [19,20], chronic obstructive pulmonary disease (COPD) [21-24], and a host of others.

The MMPs of current therapeutic interest are collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), gelatinase A (MMP-2), gelatinase B (MMP-9), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), matrilysin (MMP-7), membrane-type MMPs (MT1-MMP like MMP-14), metalloelastase (MMP-12) and aggrecanase. The selective inhibition of MMP-13 [25] and aggrecanase [26] over MMP-1 may have therapeutic benefit in osteoarthritis without causing musculoskeletal syndrome (MSS) side effects. The MMP-2 and MT1-MMP have a role in angiogenesis and human tumors [27] and similarly, MMP-3 and MMP-9 play their role in invasive mesenchymal like tumors [28-30]. Therefore, the specific inhibition of the MMP-2, -3, -9 and MT1-MMP is supposed to be the valuable targets for cancer treatment. Likewise, the inhibition of other MMPs is also of great value to develop drugs against many diseases.

Like MMPs, there is another enzyme known as TACE (TNF-α converting enzyme, TNF: tumor necrosis factor), which has gained equal importance. Its catalytic site is quite similar to that of MMPs [31]. It is involved in catalysis of a crucial physiological reaction, i.e., processing of membrane-bound form of pro-tumor necrosis factor α (TNF-α), a 26 kDa propeptide on the cell surface of 17 kDa soluble form of mature TNF-α [32,33].The shedding of this mature TNF-α is responsible for triggering several inflammatory events in the body. However, when over produced, it initiates a cascade of other agents including interleukin-1 and interleukin-6 that have been linked to several diseases including rheumatoid arthritis (RA) [34], Crohn's diseases [35] and psoriasis [36].

Recently, we have carried out several quantitative structure-activity relationship (QSAR) studies on MMP inhibitors [37-44] to understand the inhibition mechanism of different MMPs, which could be utilized to rationalize the development of specific inhibitors of these enzymes. In this connection, we report QSAR studies on some important series of MMP inhibitors that belong to the class of hydroxamic acid analogs.

The requirements for molecules to be effective MMP inhibitor are: (1) the presence of a functional group, such as carboxylic group (COOH), hydroxamic group (CONHOH), and sulfhydryl group (SH), that may be able to chelate the active site Zn^{2+} ion of the enzyme (such a group is referred to as zinc binding group, ZBG); (2) at least one functional group capable of hydrogen bonding with the enzyme backbone; and (3) one or more side chains which can have effective van der Waals interactions with the enzyme subsites. Since these requirements can be satisfied by a variety of different structural classes of MMPIs, several groups of compounds have been investigated by a number of methods [1,4] including substrate-based design, structure based design, and combinatorial chemistry.

In the substrate-based design, which has been the principal approach for the identification of synthetic MMP inhibitors, a ZBG is attached to peptide derivatives, which mimic the sequence of collagen substrate cleavage site. Three classes of compounds have been developed: (1) compounds that have amino acid residues on both sides of ZBG, e.g., A_3-A_2-A_1-ZBG-A'_1-A'_2-A'_3; (2) compounds that

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have amino acid residues on only the right hand side of the ZBG, e.g., ZBG-A′$_1$-A′$_2$-A′$_3$ and are called right-hand side inhibitors; and (3) compounds that have amino acid residues on the left hand side of the ZBG, e.g., A′$_3$-A′$_2$-A′$_1$-ZBG and are called left-hand side inhibitors. In all these compounds, A's and A′s refer to amino acid residues which can interact with S and S′ subsites of the enzyme, respectively, as depicted in Fig. **1** for a right-hand side inhibitor, for example. The right-hand side inhibitors were reported to be potent MMP inhibitors, but corresponding left-hand side inhibitors were reported to possess only the modest inhibitory potency [1]. Thus, mainly the right-hand side inhibitors were mostly developed, although a few left-hand side inhibitors were also found to be important for drug design.

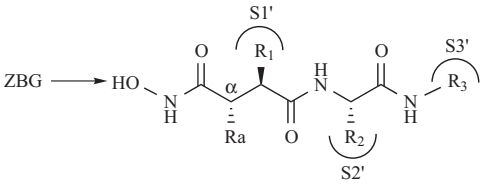


Fig. (1). A model of interaction of a right-hand side MMP inhibitor with the enzyme. R_1, R_2, and R_3 are the substituents of the amino acid residues which can be referred to as P1′, P2′ and P3′ substituents that may interact with S1′, S2′ and S3′ subsites of the enzyme.

While TACE is not a member of MMP family, its zinc-dependent endopeptidase activity (it is in fact an endopeptidase) warrants comparison in the development of MMP specific inhibitors. This is supported by the ability of many MMP inhibitors to potently inhibit TACE [45]. Despite a low sequence homology and divergent structural elements, TACE structure has excellent similarity with MMP structures and more importantly, the active site of TACE is reminiscent of the MMPs. Similar to MMPs, TACE also contains three flat substrate subsites to the left of catalytic zinc (S1, S2 and S3), and three deep subsites to the right of catalytic zinc (S1′, S2′ and S3′). However, TACE has a very interesting feature of its active sites, wherein S1′ and S3′ subsites are merged to create an L-shaped S1′ binding cleft that opens up into S3′ pocket. Both S1′ and S3′ are hydrophobic but are connected by a polar entrance. Thus, the characteristics of TACE binding pocket are unique relative to MMPs so far examined [46], and therefore, TACE is exceptionally amenable to specificity-driven structure-based design.

MATERIALS AND METHODS

The series of MMP inhibitors (**1** and **2**) taken for QSAR study have been reported by two different research groups: **1** by Martin *et al*. [47] and **2** by Levin *et al*. [48] The similarity in these two series of compounds is the presence of substituents on α-carbon of the hydroxamic acid. The analogs of both **1** and **2** are listed in Tables **1** and **2**, respectively, along with their relevant physiochemical properties that were found to be correlated with the MMP inhibition potencies. Correspondingly, Tables **3** and **4** display the inhibition potencies of these compounds with their observed as well as calculated values obtained from the correlations. In these tables, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. The most important physicochemical properties that were found to be correlated with the activities of the compounds were calculated hydrophobicity parameter (ClogP) and polarizability (Pol). The hydrophobicity parameter ClogP was calculated using www.daylight.com domain and polarizability was calculated from www.acdlabs.com domain. Some indicator variables were also used to account for the effects of some specific structural features in the compounds. These variables are defined in the text as and when they appear.

RESULTS AND DISCUSSION

For the series of **1** (Table **1**), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 7.600(\pm0.334) - 0.404(\pm0.263)\text{ClogP} + 0.085(\pm0.051)(\text{ClogP})^2 + 0.935(\pm0.212)I_R + 0.388\ (\pm0.201)I_{R2}$$

$$n = 18,\ r = 0.954,\ r^2_{cv} = 0.75,\ s = 0.15,\ F_{4,13} = 32.80(5.20),\ [\text{ClogP}_m = 2.38] \quad (1)$$

MMP-2

$$\log (1/IC_{50}) = 0.648(\pm0.133)\text{Pol} + 0.496(\pm0.234)I_R + 1.088\ (\pm0.236)I_{R2} + 3.260(\pm0.633)$$

$$n = 19,\ r = 0.971,\ r^2_{cv} = 0.90,\ s = 0.19,\ F_{3,15} = 81.88(5.42) \quad (2)$$

MMP-3

$$\log (1/IC_{50}) = 0.818(\pm0.195)\text{Pol} + 0.692(\pm0.324)I_R + 1.363\ (\pm0.328)I_{R2} + 2.398(\pm0.944)$$

$$n = 19,\ r = 0.963,\ r^2_{cv} = 0.89,\ s = 0.26,\ F_{3,15} = 64.04(5.42) \quad (3)$$

MMP-8

$$\log (1/IC_{50}) = 0.425(\pm0.158)\text{Pol} + 0.783(\pm0.257)I_R + 1.045\ (\pm0.262)I_{R2} + 5.459(\pm0.762)$$

$$n = 18,\ r = 0.956,\ r^2_{cv} = 0.85,\ s = 0.20,\ F_{3,14} = 49.69(5.56) \quad (4)$$

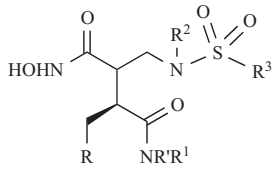
MMP-13

$$\log (1/IC_{50}) = 0.501(\pm0.212)\text{Pol} + 0.993(\pm0.424)I_R + 0.802\ (\pm0.319)I_{R2} + 4.296(\pm0.944)$$

$$n = 16,\ r = 0.947,\ r^2_{cv} = 0.72,\ s = 0.24,\ F_{3,12} = 34.55(5.95) \quad (5)$$

In these equations, n is the number of data points, r is the correlation coefficient, r^2_{cv} is the square of cross-validated correlation coefficient obtained by leave-one-out (LOO) jackknife procedure, s is the standard deviation, and F is the F-ratio between the variances of calculated and observed activities (within parenthesis the figures refer to the F-valves at 99% level). The data with ± sign within the parentheses refer to 95% confidence intervals for the coefficients of the variables as well as for the intercept.

Table 1. A Series of Acyclic Hydroxamic Acid Analogs (1) and Related Physicochemical Parameter(s)

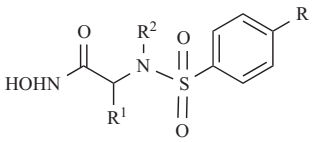


Compd	R	NR'R[1]	R[3]	R[2]	ClogP	Pol	I_R	I_{R2}
1	iPr	piperidinyl	CH_3	CH_3	0.933	3.810	0	1
2	iPr	piperidinyl	CH_2CH_3	CH_3	1.462	4.000	0	1
3	iPr	piperidinyl	C_6H_4-4-OCH_3	CH_3	2.815	4.860	0	1
4	iPr	piperidinyl	dansyl	CH_3	4.214	5.820	0	1
5	iPr	$N(CH_3)_2$	CH_3	CH_3	0.044	3.340	0	1
6	c-pentyl	piperidinyl	CH_3	CH_3	1.038	3.910	1	1
7	c-pentyl	piperidinyl	CH_2CH_3	CH_3	1.567	4.090	1	1
8	c-pentyl	piperidinyl	C_6H_4-4-OCH_3	CH_3	3.449	5.140	1	1
9	c-pentyl	piperidinyl	dansyl	CH_3	4.848	6.110	1	1
10	c-pentyl	piperidinyl	naphthalyl	CH_3	3.925	5.400	1	1
11	c-pentyl	piperidinyl	CH_3	n-propyl	2.096	4.280	1	0
12	c-pentyl	piperidinyl	CH_3	c-pentyl	2.510	4.560	1	0
13	c-pentyl	piperidinyl	CH_3	c-propyl	1.622	4.190	1	0
14	c-pentyl	piperidinyl	CH_3	iPr	1.876	4.280	1	0
15	c-pentyl	piperidinyl	iPr	CH_3	1.876	4.280	1	1
16	c-pentyl	piperidinyl	C_6H_4-4-Cl	CH_3	3.464	4.900	1	1
17	c-pentyl	piperidinyl	$N(CH_3)_2$	CH_3	1.017	4.250	1	1
18	c-pentyl	piperidinyl	CF_3	CH_3	2.147	3.920	1	1
19	c-pentyl	morpholinyl	CH_3	CH_3	0.244	3.790	1	1
20	c-pentyl	morpholinyl	C_6H_4-4-OCH_3	CH_3	2.126	4.840	1	1

All the above equations exhibit very significant correlations and present very interesting results. Equation 1 indicates that the inhibition potency of the compounds against MMP-1 will be largely controlled by the hydrophobic property of the molecules. It is shown that the activity will initially decrease with the increase in the ClogP value and then after ClogP attains a minimum value ($ClogP_m$ = 2.38), the value of ClogP where the activity becomes minimum, the activity will start increasing with the increase in the ClogP value.

Equations 2-5 obtained for four different MMP enzymes, MMP-2, MMP-3, MMP-8, and MMP-13, astonishingly express very parallel correlations, indicating that the inhibitions of all these four enzymes are primarily governed by the polarizability of the molecules. In all the Eqs. 2-5, the coefficients of polarizability factor (Pol) are almost identical. In all these equations and also in Eq. 1, however, there are two indicator variables I_R and I_{R2}, which have been used for R- and R^2- substituents, respectively. I_R = 1 for R = c-pentyl, otherwise it is zero, similarly I_{R2} = 1 for $R^2 = CH_3$, otherwise it is zero. Now it is noticed that in all the five equations, both of these indicator variables have positive coefficients, indicating that a cyclopentyl group at R-position and a methyl group at R^2- position will be more conducive to the activity than any other group present at these positions (Table **1**). It is also observed that the magnitude of the coefficient of each of these variables in Eqs 2-5 is almost identical, hence each of the two structural features described by these variables, just like polarizability, produce almost equal effects on the inhibition of the four MMPs of Eqs 2-5. Almost equal effect is described of cyclopentyl group at R-position in MMP-1 inhibition (Eq. 1), but a slightly poor effect is shown of CH_3 group at R^2-position because of a very small coefficient of I_{R2}. A better effect of c-pentyl group at R-position than an isopropyl group at this position (the only other substituent studied at this position) in all the

Table 2. A Series of Acyclic Hydroxamic Acid Analogs (2) and Related Physicochemical Parameter(s)



Compd	R	R^1	R^2	ClogP	I_{CC}	$I_{1,pyr}$	$I_{1,NH}$	$I_{2,H}$
1	OCH_2CCCH_3	H	H	0.861	1	0	0	1
2	OCH_2CCCH_3	H	CH_3	1.277	1	0	0	0
3	OCH_2CCCH_3	H	CH_2-3-pyridyl	1.484	1	0	0	0
4	OCH_2CCCH_3	CH_3	H	1.170	1	0	0	1
5	OCH_2CCCH_3	CH_3	CH_3	1.586	1	0	0	0
6	OCH_2CCCH_3	iPr	H	2.098	1	0	0	1
7	OCH_2CCCH_3	iPr	CH_3	2.514	1	0	0	0
8	OCH_2CCCH_3	tBu	H	2.497	1	0	0	1
9	OCH_2CCCH_3	$(CH_3)_2$	H	1.479	1	0	0	1
10	OCH_2CCCH_3	$CH(CH_3)OH$	H	0.467	1	0	0	1
11	OCH_2CCCH_3	CH_2SCH_2-3-pyridyl	H	1.969	1	1	0	1
12	OCH_2CCCH_3	CH_2SCH_2-3-pyridyl	CH_3	2.430	1	1	0	0
13	OCH_2CCCH_3	$C(CH_3)_2SCH_2$-3-pyridyl	H	2.677	1	1	0	1
14	OCH_2CCCH_3	$C(CH_3)_2SCH_2$-3-pyridyl	CH_3	3.138	1	1	0	0
15	OCH_2CCCH_3	C_6H_4-4-$O(CH_2)_2NHCH_3$	H	2.021	1	0	1	1
16	OCH_2CCCH_3	C_6H_4-4-$O(CH_2)_2NHCH_3$	CH_3	2.431	1	0	1	0
17	$NHCH_2CCH$	H	CH_3	1.778	0	0	0	0
18	SCH_2CCCH_3	H	CH_3	2.927	0	0	0	0
19	CH_2CH_2CN	H	CH_3	0.700	0	0	0	0

cases, however, can be attributed to its cyclic nature that might have better steric interaction. Similarly, a better effect of a CH_3 group at R^2-position than any other group at this position can be attributed to its small size, which may have better steric fit in the active site than any other group. The R^2-substituents may interact with the S1′ subsite of the enzyme (Fig. **1**). Through a molecular modeling study for the binding of inhibitors with MMP-1, Tsai and Lin [49] have observed that this S1′ is a relatively small one and its depth is defined by Arg 214 at the bottom of the pocket. Thus it appears that R^2-position may be capable of accommodating only a substituent of the size of CH_3 and this could be the reason that a CH_3 group at R^2-position gives better results than any bigger group. Since this CH_3 at R^2-position is conducive not only for MMP1 but also for other enzymes treated, it can be said that in other enzymes also the S1′ subsite may be as small as in MMP-1.

In MMP-1 inhibition, only highly hydrophobic molecules are shown to be beneficial. It means that only highly hydrophobic molecules may be able to access the hydrophobic regions in the enzyme. In other MMPs (MMP-2, MMP-3, MMP-8, and MMP-13), the inhibitor molecules seem to have effective contacts with the polar regions of the enzyme molecules.

For the series of **2** (Table **2**), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 6.869(\pm0.975) - 1.367(\pm1.068)\text{ClogP} + 0.551(\pm0.283)(\text{ClogP})^2 - 0.673(\pm0.464)I_{1,NH} - 0.785(\pm0.315)I_{2,H}$$

$n = 15$, $r = 0.961$, $r^2_{cv} = 0.86$, $s = 0.27$, $F_{4,10} = 30.28(5.99)$, $[\text{ClogP}_m = 1.24]$

(6)

MMP-9

$$\log (1/IC_{50}) = 0.612(\pm0.222)\text{ClogP} + 1.363(\pm0.499)I_{CC} - 0.940(\pm0.337)I_{2,H} + 4.946(\pm0.682)$$

Table 3. Observed and Calculated MMP Inhibition Potencies of Compounds of Table 1. Observed Activities Have Been Taken from Reference [47]

Compd	log (1/IC_{50})														
	MMP-1			MMP-2			MMP-3			MMP-8			MMP-13		
	Obsd	Calcd	Loo	Obsd	Calcd	Loo	Obsd	Calcd	Loo	Obsd	Calcd	Loo	Obsd	Calcd	Loo
		Eq. 1			Eq. 2			Eq. 3			Eq. 4			Eq. 5	
1	7.22	7.30	7.30	5.00[b]	5.73	-	5.40	5.51	5.57	7.00	7.08	7.12	-	6.20	-
2	7.30	7.19	7.13	5.70	5.85	5.91	5.70	5.67	5.66	7.00	7.16	7.23	-	6.30	-
3	7.10	7.13	7.16	6.22	6.41	6.48	6.40	6.37	6.36	7.70	7.53	7.47	7.00	6.73	6.34
4	8.22[a]	7.41	-	7.10	7.03	6.98	7.22	7.16	7.11	8.00	7.93	7.88	-	7.21	-
5	6.00[a]	7.58	-	5.70	5.42	5.24	-	5.13	-	5.40[c]	6.88	-	5.70	5.97	6.36
6	8.22	8.21	8.20	6.05	6.29	6.33	6.70	6.29	6.22	6.70[c]	7.90	-	6.40[d]	7.25	-
7	8.22	8.11	8.09	6.22	6.41	6.43	6.40	6.43	6.44	8.00	7.98	7.98	7.40	7.34	7.33
8	8.00	8.15	8.17	7.22	7.09	7.07	7.22	7.30	7.31	8.52	8.43	8.42	7.70	7.86	7.89
9	8.70	8.57	8.18	7.70	7.72	7.72	8.15	8.09	8.05	8.70	8.84	8.92	8.10	8.35	8.54
10	8.22	8.25	8.26	7.30	7.26	7.25	7.30	7.51	7.55	8.40	8.54	8.56	8.10	7.99	7.97
11	7.52	7.67	7.72	5.52	5.44	5.42	5.22	5.23	5.23	7.05	7.02	7.01	6.70	6.63	6.61
12	7.70	7.67	7.65	5.52	5.63	5.66	5.00	5.46	5.62	6.70	7.13	7.29	6.70	6.77	6.80
13	8.00	7.72	7.61	5.70	5.39	5.28	5.70	5.16	4.97	7.40	6.98	6.84	7.00	6.59	6.44
14	7.52	7.69	7.74	5.15	5.44	5.54	5.15	5.23	5.26	7.00	7.02	7.02	6.22	6.63	6.77
15	8.30	8.07	8.03	6.40	6.53	6.55	6.52	6.59	6.60	8.05	8.06	8.07	7.40	7.43	7.44
16	8.05	8.15	8.17	7.00	6.93	6.92	7.52	7.10	7.05	8.40	8.33	8.32	8.00	7.74	7.71
17	8.22	8.21	8.21	6.52	6.51	6.51	6.40	6.57	6.59	8.00	8.05	8.06	7.40	7.42	7.42
18	8.05	8.06	8.06	6.30	6.30	6.29	6.10	6.30	6.33	8.00	7.91	7.89	7.40	7.25	7.22
19	8.30	8.44	8.62	6.40	6.21	6.17	6.10	6.19	6.21	7.70	7.85	7.89	7.10	7.19	7.22
20	8.00	8.06	8.07	7.02	6.89	6.88	7.00	7.05	7.06	8.52	8.30	8.28	7.70	7.71	7.71

[a]Not included in the derivation of Eq. 1.

[b]Not included in the derivation of Eq. 2.

[c]Not included in the derivation of Eq. 4.

[d]Not included in the derivation of Eq. 5.

$n = 17$, $r = 0.944$, $r^2_{cv} = 0.80$, $s = 0.29$, $F_{3,13} = 35.32(5.74)$

(7)

MMP-13

$\log (1/IC_{50}) = 0.644(\pm0.251)ClogP + 1.270(\pm0.556)I_{CC} + 5.085(\pm0.777)$

$n = 15$, $r = 0.890$, $r^2_{cv} = 0.68$, $s = 0.33$, $F_{2,12} = 22.90(6.93)$

(8)

TACE

$\log (1/IC_{50}) = 0.895(\pm0.492)ClogP - 0.368(\pm0.143)(ClogP)^2 + 0.525(\pm0.222)I_{1,pyr} + 7.708(\pm0.396)$

$n = 17$, $r = 0.910$, $r^2_{cv} = 0.71$, $s = 0.15$, $F_{3,13} = 20.89(5.74)$, $[ClogP_o = 1.22]$

(9)

Now for this series of compounds also, Eq. 6 suggests that the hydrophobic property of the molecules will play a dominant role in MMP-1 inhibition. Since, like Eq. 1, Eq. 6 is also parabolic, the potency of the compounds will initially decrease and then after a minimum value of ClogP ($ClogP_m = 1.24$) will start increasing as ClogP value increases. The two indicator variables $I_{1,NH}$ and $I_{2,H}$ in Eq. 6, however, indicate the unwanted effects of two structural features in the molecule. The variable $I_{1,NH}$ presents a value of unity for an

Table 4. Observed and Calculated MMP Inhibition Potencies of Compounds of Table 2. Observed Activities Have Been Taken from Reference [48]

Compd	log (1/IC_{50})											
	MMP-1			MMP-9			MMP-13			TACE		
	Obsd	Calcd	Loo	Obsd	Calcd	Loo	Obsd	Calcd	Loo	Obsd	Calcd	Loo
		Eq. 6			Eq. 7			Eq. 8			Eq. 9	
1	-	4.91	-	6.12	5.90	5.84	6.73	6.91	6.95	8.30	8.21	8.19
2	5.72	6.02	6.13	6.51	7.09	7.27	7.00	7.18	7.20	8.15	8.25	8.27
3	5.94	6.06	6.09	7.40	7.22	7.17	7.70	7.31	7.27	8.15	8.23	8.29
4	5.39	5.24	5.21	6.10	6.08	6.08	6.71	7.11	7.17	8.40	8.25	8.23
5	6.48	6.09	5.96	7.17	7.28	7.30	7.55	7.38	7.36	8.30	8.21	8.19
6	5.53	5.64	5.67	7.38[b]	6.65	-	7.74	7.71	7.70	8.00	7.97	7.96
7	6.59	6.92	6.99	7.96	7.85	7.82	7.42	7.97	8.06	7.82	7.64	7.59
8	6.06	6.11	6.12	6.65	6.89	6.97	7.39[c]	7.96	-	7.77	7.65	7.62
9	5.00	5.27	5.33	5.86	6.27	6.25	6.40[c]	7.31	-	7.89[d]	8.23	-
10	5.61	5.56	5.34	6.11	5.65	5.45	7.07	6.66	6.47	8.00	8.05	8.09
11	5.72	5.53	5.49	6.80	6.57	6.58	7.55	7.62	7.63	8.52	8.57	8.58
12	7.21	6.80	6.71	7.85	7.79	7.78	8.30	7.92	7.87	8.22	8.24	8.17
13	6.32	6.37	6.40	6.89	7.00	7.04	8.10	8.08	8.07	8.22	8.00	8.00
14	8.05	8.00	7.93	8.40	8.23	8.16	8.70	8.38	8.25	7.27	7.42	7.62
15	5.00	4.90	4.76	6.46	6.60	6.63	6.84[c]	7.66	-	7.74	8.02	8.05
16	6.03	6.13	6.26	7.96	7.79	7.77	7.57	7.92	7.97	7.59	7.71	7.74
17	-	3.65	-	5.82	6.04	6.29	6.12	6.23	6.36	8.10	8.14	8.14
18	5.31[a]	2.08	-	6.95	6.74	6.48	7.08	6.97	6.84	7.85[d]	7.17	-
19	-	5.13	-	7.13[b]	5.37	-	6.68[c]	5.54	-	8.15	8.16	8.16

[a]Not included in the derivation of Eq. 6.

[b]Not included in the derivation of Eq. 7.

[c]Not included in the derivation of Eq. 8.

[d]Not included in the derivation of Eq. 9.

R^1-substitutent which has an -NH- moiety, e.g., compounds 15 and 16 (Table **2**), and for the others it is zero and the variable $I_{2,H}$ presents a value of unity for an R^2-substitutent which is only H.

The negative effect of NH in R^1 can be attributed to the fact that NH is a hydrogen bond donor moiety and it must face a site of the same nature in the receptor, depriving the latter of the opportunity to form any hydrogen bond with the molecule (we may call it a hydrogen-bond repulsive interaction). The negative effect of H at R^2 here establishes an optimum role played by a CH_3 group at this position, since for the series of **1,** Eqs 1-5 have shown that also a group larger than CH_3 at this position will not be advantageous to the inhibition potency against any MMP. Thus, it leads to the conclusion that a group of the size of CH_3 is an optimum requirement at this position (at the sulfonamide nitrogen).

The indicator variable $I_{2,H}$ is present also in Eq. 7, indicating the same preferential role of CH_3 at sulfonamide nitrogen in the inhibition of MMP-9 also as in the inhibition of MMP-1. Barring this variable, Eq.7 seems to be similar to Eq. 8 obtained for MMP-13. In both Eqs. 7 and 8, the hydrophobic property of the molecules seems to be a major governing factor. Because of the similarity of the two equations, thus, both the MMP-9 and MMP-13 appear to involve the same inhibition mechanism with a dominance of hydrophobic interaction. In both Eqs 7 and 8, there is however, an additional indicator variable I_{CC} that stands with a value of unity for a butynyloxy substituent at the aryl ring ($R = OCH_2CCCH_3$). A positive coefficient of it in both the

equations suggests that such a substitutent at the aryl ring would be of advantage for both MMP-9 and MMP-13 inhibitions. The beneficial role of this acetylene-derived linear substituent may be assumed to be due to its ability to penetrate fully into any deep hydrophobic pocket of the receptor. This deep pocket may presumably be the S3′ subsite.

The hydrophobicity of the molecule is shown to govern the inhibition of TACE also. (Eq. 9) but exactly in a reverse order of MMP-1 (Eq. 5). For both MMP-1 and TACE inhibitions, the optimum value of ClogP is almost the same, but while for the former it refers to a cut-off point from where the potency of the compounds starts decreasing, for the latter it refers to a cut-off point from where the potency starts increasing with the increase in the value of ClogP. As we have discussed in the Introduction section, both S1′ and S3′ subsites in TACE are hydrophobic, it is plausible to assume that molecules upto a certain limit of hydrophobicity might have hydrophobic interaction with S1′ or/and S3′ subsites.

An additional factor affecting the TACE inhibition is an R^1-substituent that contains a pyridyl ring. Its effect is described by the indicator variable $I_{1,pyr}$,which has a value of unity for such a substituent and is zero for others. A positive coefficient of the indicator variable in Eq. 9 suggests that such an R^1-substituent will be beneficial to TACE inhibition. It may be beneficial because of its pyridine moiety that contains a nitrogen with a lone pair of electrons, which might be involved in some electronic interactions with the active sites of the receptor. This is an important finding of QSAR which requires attention.

All Eqs. 1-9 exhibit very significant correlations and have very good predictive value, as for all of them the r^2_{cv} values are greater than 0.6. However, in deriving these equations, some compounds as indicated in the foot-notes of the Tables **3** and **4** were not included, since they exhibited aberrant behaviors. Since in different equations different compounds were excluded, it was hard to explain in each case the aberrant behavior of each compound. In such situations, the only reason that can be assigned is the experimental error or the conformational behavior of the enzymes.

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