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Quantitative Structure-activity Relationship Studies on Benzodiazepine Hydroxamic Acid Inhibitors of Matrix Metalloproteinases and Tumor Necrosis Factor-α Converting Enzyme

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Abstract: A Quantitative Structure-activity Relationship (QSAR) study has been made on the inhibitions of some Matrix Metalloproteinases (MMPs) and Tumor Necrosis Factor-α Converting Enzyme (TACE) by benzodiazepine hydroxamic acid inhibitors. It has been found that there exits an inverse parabolic relationship between the hydrophobicity (logP) and inhibition activities of compounds for certain series of inhibitors against MMP-1 and MMP-13, suggesting that inhibition mechanism of these enzymes could be allosteric. The appearance of E-state index of nitrogen atom (S_N) attached to sulfonyl group in the equations derived for MMP-9, MMP-13 and TACE reveals that there can be some electronic interaction also between the inhibitors and these enzymes.

Key words: QSAR, MMPs, TACE, benzodiazepine hydroxamic acid inhibitors

Introduction

The Matrix Metalloproteinases (MMPs) are a family of structurally related zinc metalloproteinases that degrade and remodel structural proteins in the extracellular matrix, such as membrane collagens, aggrecan, fibronectin and laminin (Leung *et al*., 2000; Babine and Bender, 1997). They include over 25 zinc-containing enzymes, such as collagenases, stromelysins, gelatinases and membrane-type MMPs and have been implicated in tissue remodeling at various stages of human development, wound healing and disease (Zucker and Vacirca, 2004). However, an imbalance caused by overexpression and activation of these MMPs result in tissue degradation, leading to a wide array of disease processes, such as osteoarthritis (Leff, 1999; Shlopov *et al*., 1997), rheumatoid arthritis (Ahrens *et al*., 1996; Blaser *et al*., 1996; Cawston, 1996), tumor metastatis (Brahmall, 1997; Lafleur *et al*., 1996; Wojtowicz-Praga *et al*., 1997), multiple sclerosis (Cuzner and Opdenakker, 1999; Yong *et al*., 1998; Matyszak and Perry, 1996), congestive heart failure (Coker *et al*., 1998; Spinale *et al*., 1999; Tyagi, 1998) and a host of others. Therefore, the study of the inhibition of MMPs has become of great interest. Their inhibition study may be of great value in designing the novel types of anticancer, anti-arthritis and other pharmacological agents useful in the management of osteoporosis, restonosis, aortic, glomerulonenephrititis, or multiple sclerosis among others. Some of the recent development in the field has been recently reviewed by Supuran and Scozzafava (2002).

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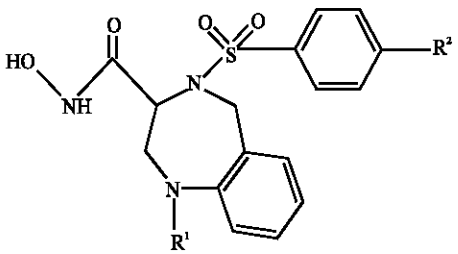
TNF-α (tumor necrosis factor-α) is a pro-inflammatory cytokine that exists in two forms, a 26 kDa membrane-bound form and a soluble non-covalently bound homotrimer of 17 kDa units. TACE sheds the 26 kDa membrane-bound TNF-α into its soluble forms whose high level leads to several inflammatory diseases including rheumatoid arthritis (RA) and Crohn's disease. It has been therefore postulated that the inhibition of TACE, reducing levels of soluble TNF-α, might offer an effective treatment of RA (Nelson and Zask, 1999; Lowe, 1998; Newton and Decicco, 1999; Konttinen *et al*., 1999). Since a variety of MMPs have been found to be over-expressed in RA synovial tissue and have been implicated in the destruction of cartilage in RA joints, the optimal MMP/TACE selectivity profile for a drug to treat rheumatoid arthritis is still to be resolved. Therefore, the study of the inhibition of TACE is also of great importance.

In the study of the enzyme inhibition, the Quantitative Structure-activity Relationship (QSAR) studies are of great value. They can throw the light on the mechanism of inhibition and point out the important active sites in the receptors. These aspects of the study become of paramount importance in the drug design. We therefore present in this research a detailed QSAR study on some MMP and TACE inhibitors using simple Hansch approach where biological activities are correlated with various physicochemical and structural parameters of the compounds.

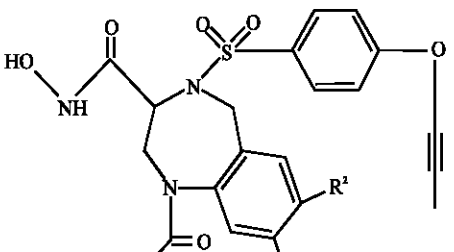
Materials and Methods

Nelson *et al*. (2002) and Levin *et al*. (2004) recently reported two different series of benzodiazepine hydroxamic acid inhibitors (1 and 2) with their inhibition potencies against MMP-1, MMP-9, MMP-13 and TACE. The reported present study is a (QSAR) study on these two series in order to find physicochemical and structural properties of the compounds that govern their activity.

The series 1 reported by Nelson *et al*. (2002) and series 2 reported by Levin *et al*. (2004) are listed in Table 1 and 2, respectively, along with the physicochemical parameters of the compounds that were found to be correlated with their MMP/TACE inhibition potencies. Their inhibition potencies, observed as well as calculated from correlations obtained, are listed in Table 3 and 4, respectively. In these Table 3 and 4, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. The parameters that were found to play important roles were calculated hydrophobicity (ClogP) and E-State index (S) of nitrogen atom attached to sulfonyl group. The logP was calculated using www.daylight.com software freely available at Internet. The E-state index is calculated as follows (Kier and Hall, 1992, 1999).

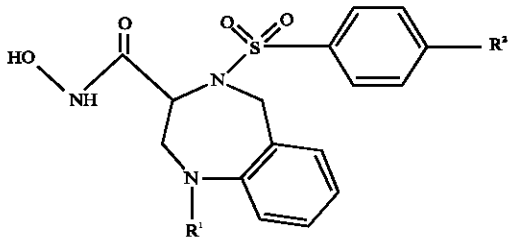


1



2

Table 1: A series of benzodiazepine hydroxamic acid inhibitors (1) and related physiochemical parameters



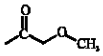
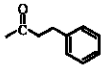
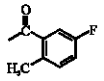
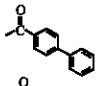
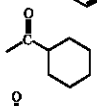
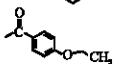
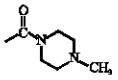
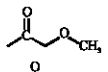
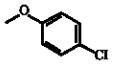
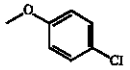
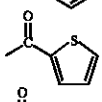
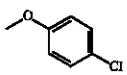
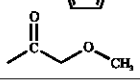
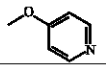
Compound	R^1	R^2	logP	S_N	$I_{R1\text{-}A}$	$I_{R2\text{-}CC}$	I_{AC}
1		—OCH_3	1.370	-19.266	0	0	0
2		—OCH_3	1.297	-23.512	0	0	0
3		—OCH_3	2.595	-18.936	1	0	0
4		—OCH_3	1.954	-17.596	0	0	1
5		—OCH_3	2.372	-18.769	1	0	0
6		—OCH_3	1.424	-20.266	0	0	0
7		—OCH_3	3.467	-17.936	1	0	0
8		—OCH_3	3.313	-24.276	1	0	0
9		—OCH_3	4.483	-18.276	1	0	0
10		—OCH_3	3.401	-16.436	0	0	1
11		—OCH_3	3.344	-19.606	1	0	0
12		—OCH_3	2.555	-16.766	0	0	1
13			1.424	-21.717	0	0	0
14			2.595	-20.387	1	0	0
15			1.424	-22.498	1	0	0
16			1.424	-20.936	0	0	0

Table 1: Continued

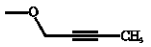
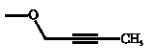
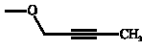
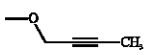
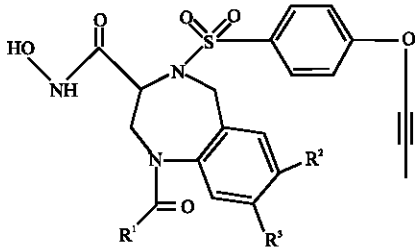
Compd	R^1	R^2	logP	S_N	$I_{R1\text{-}A}$	$I_{R2\text{-}CC}$	I_{AC}
17			2.499	-19.766	0	1	0
18			2.426	-24.012	0	1	0
19			3.724	-19.436	1	1	0
20			3.083	-18.096	0	1	1

Table 2: A series of benzodiazepine hydroxamic acid inhibitors (2) and related physiochemical parameters



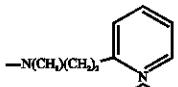
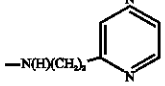
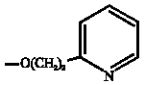
Compd	R_1	R_2	R_3	logP	S_N	$I_{R1\text{-}A}$	$I_{R2\text{-}H}$
1	—CH_3	—H	—H	2.499	-19.106	0	0
2	—CH_2OCH_3	—H	—H	2.499	-23.606	0	0
3		—H	—H	2.900	-20.276	1	0
4		—H	—H	2.623	-19.776	1	0
5		—H	—H	1.668	-20.776	1	0
6	—CH_3	—$N(CH_3)_2$	—H	2.664	-19.106	0	1
7	—CH_3	—$N[(CH_2)_2]_2O$	—H	1.955	-18.606	0	1
8	—CH_3	—$N[(CH_2)_2]_2NH_3$	—H	2.397	-17.106	0	1
9	—CH_3		—H	3.264	-18.776	0	1
10	—CH_3		—H	2.598	-19.276	0	1
11	—CH_3		—H	4.515	-19.276	0	1
12	—CH_3	—H	—CH_2OH	1.461	-21.606	0	0
13	—CH_3	—H	—CH_2NHCH_3	1.867	-19.106	0	0
14	—CH_3	—H	—$CH_2N(CH_3)_2$	2.333	-18.606	0	0
15	—CH_3	—H	—$CH_2N[(CH_2)]_2NH$	2.232	-17.606	0	0
16	—CH_3	—H	—$CH_2NHCOCH_3$	1.307	-23.776	0	0
17	—CH_3	—H	—$CONHCH_3$	1.518	-24.276	0	0

Table 3: Observed and calculated MMP and TACE inhibition potencies of compounds of Table 1

	log (1/IC_{50})											
	MMP-1			TACE			MMP-9			MMP-13		
	Obsd[a]	Calcd	Loo	Obsd[a]	Calcd	Loo	Obsd[a]	Calcd	Loo	Obsd[a]	Calcd	Loo
Compd		Eq. 6			Eq. 7			Eq. 8			Eq. 9	
1	7.74	7.48	7.35	6.99	6.96	6.95	8.85	8.88	8.88	9.00	8.98	8.97
2	6.80[b]	7.57	-	6.98	6.97	6.97	8.10	8.38	8.45	8.52	8.49	8.49
3	7.80	7.49	7.43	7.02	6.80	6.78	9.22	8.92	8.87	9.40	9.02	8.95
4	6.77	6.85	6.86	7.16	6.88	6.85	8.40	8.28	8.20	8.52	8.34	8.22
5	7.70	7.64	7.62	7.89[c]	6.83	-	9.00	8.94	8.93	9.00	9.04	9.05
6	7.47	7.41	7.39	7.02	6.96	6.94	8.70	8.76	8.77	8.70	8.87	8.88
7	6.28[b]	7.18	-	6.68	6.68	6.68	7.74[d]	9.03	-	7.59[e]	9.14	-
8	7.26	7.20	7.19	6.57	6.70	6.72	8.40	8.29	8.24	8.70	8.40	8.24
9	7.28	7.31	7.43	6.70	6.55	6.46	9.15	9.00	8.96	9.40	9.10	9.02
10	6.33	6.06	5.94	6.50	6.69	6.72	7.89	8.42	8.74	8.15	8.47	8.68
11	7.62	7.20	7.13	6.80	6.70	6.68	8.70	8.84	8.86	8.70	8.94	8.97
12	5.30[b]	6.40	-	6.09[c]	6.80	-	6.73[d]	9.17	-	6.50[e]	9.28	-
13	7.21	7.41	7.49	6.80	6.96	6.98	8.70	8.59	8.58	8.70	8.70	8.71
14	7.23	7.49	7.55	6.28[c]	6.80	-	8.70	8.75	8.75	8.70	8.85	8.87
15	7.46	7.64	7.68	6.60	6.83	6.85	8.70	8.50	8.46	8.40	8.61	8.64
16	6.12[b]	7.41	-	6.80	6.96	6.98	8.70	8.68	8.68	8.70	8.79	8.80
17	6.08	6.43	6.51	7.80	7.74	7.72	6.64[d]	7.67	-	7.11[e]	8.05	-
18	6.59	6.48	6.45	7.70	7.75	7.77	7.02	7.17	7.29	7.46	7.55	7.63
19	6.78	7.16	7.24	7.23	7.58	7.72	7.45	7.71	7.95	8.02	8.08	8.13
20	6.08	6.14	6.17	8.00	7.66	7.55	7.48	7.07	6.63	7.54	7.40	7.23

[a]Taken from Nelson *et al.*(2002). [b]Not included in the derivation of Eq. 6. [c]Not included in the derivation of Eq. 7. [d]Not included in the derivation of Eq. 8., [e]Not included in the derivation of Eq. 9

Table 4: Observed and calculated MMP and TACE inhibition potencies of compounds of TABLE 2

	log (1/IC_{50})								
	MMP-1			MMP-13			TACE		
	Obsd[a]	Calcd	Loo	Obsd[a]	Calcd	Loo	Obsd[a]	Calcd	Loo
Compd		Eq. 10			Eq. 11			Eq. 12	
1	6.08	6.08	6.08	7.11	7.34	7.38	7.80	7.80	7.80
2	6.07	6.12	6.13	7.01	6.96	6.86	7.09	7.43	7.53
3	6.90	6.88	6.84	8.15[c]	7.15	-	7.48	6.82	7.11
4	6.62	6.61	6.61	7.72[c]	7.25	-	7.05	7.23	7.39
5	6.45	6.48	6.53	7.70	7.66	7.65	7.16	7.27	7.20
6	6.17	6.20	6.22	7.77[c]	7.29	-	6.71	7.19	6.88
7	5.90	5.95	5.96	7.48	7.64	7.67	6.89	6.83	6.87
8	6.07	6.03	6.01	7.68	7.53	7.49	7.04	6.87	6.98
9	-	6.95	-	7.28	7.23	7.22	6.92	6.99	6.84
10	-	6.15	-	7.33	7.29	7.28	7.31[d]	6.82	-
11	-	10.06	-	7.55	7.57	8.08	7.44[d]	6.85	-
12	6.30	6.170	6.12	7.70	7.75	7.78	7.92	7.59	7.54
13	6.34[b]	5.96	-	7.49	7.65	7.68	7.85	7.80	7.78
14	6.04	6.00	5.99	7.17[c]	7.45	-	7.74	7.84	7.87
15	6.32[b]	5.97	-	7.77	7.57	7.51	7.85	7.92	7.96
16	6.24	6.30	6.38	7.92	7.71	7.59	7.51	7.41	7.39
17	6.09	6.12	6.13	7.38	7.49	7.56	7.39	7.37	7.36

[a]Taken from Levin *et al.* (2004). [b]Not included in the derivation of Eq. 10. [c]Not included in the derivation of Eq. 11. [d]Not included in the derivation of Eq. 12

To calculate S_i of an atom i, one first defines the intrinsic state I_i of an atom i as

$$I_i = (\delta_i^v + 1) / \delta_i \quad (1)$$

where, δ_i is the σ electron count of the atom i and δ_i^v is the valence vertex connectivity index of the same atom, which is calculated for the second and third rows of atoms as

$$\delta_i^v = (Z_i - h_i) / (Z_i - Z_i^v - 1) \quad (2)$$

In Eq. (2), Z_i^v is the number of valence electrons of the atom i, h_i is the number of hydrogen atoms attached to it in a molecule or group and Z_i is its atomic number. For higher quantum level atoms, intrinsic state is calculated as

$$I_i = [(2/N)^2\delta_i^v + 1] / \delta_i \quad (3)$$

where, N is the principal quantum number. After calculating I_i, one calculates a factor ΔI_i for the atom i, using the equation,

$$\Delta i_i = \Sigma_{j=1} (I_i - I_j) / n^2 \quad (4)$$

where n refers to the number of the atoms in the path i to j, including both i and j. I_i and ΔI_i are then used to find the E-state index S_i of the atom i according to the equation:

$$S_i = I_i + \Delta i_i \quad (5)$$

Results and Discussion

For the compounds of Table 1, the following correlations were obtained between their inhibition activities against MMP-1, TACE, MMP-9 and MMP-13. In all these correlations, 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 jackknife procedure, s is the standard deviation and F is the F-ratio between the variances of calculated and observed activities (within parenthesis the figure refers to the F-valve 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.

MMP-1

$$\log (1/IC_{50}) = 1.123(\pm0.347)I_{R1\text{-}A} - 1.929(\pm0.972)\text{ClogP} + 0.259(\pm0.170)(\text{ClogP})^2 + 9.635(\pm1.276)$$
$$n = 16,\ r = 0.911,\ r^2_{cv} = 0.72,\ s = 0.27,\ F_{3,12} = 19.55(5.95),\ \text{ClogP}_o = 3.72 \quad (6)$$

TACE

$$\log (1/IC_{50}) = 0.930(\pm0.251)I_{R2\text{-}CC} - 0.133(\pm0.112)\text{ClogP} + 7.143(\pm0.299)$$
$$n = 17,\ r = 0.906,\ r^2_{cv} = 0.71,\ s = 0.20,\ F_{2,14} = 31.97(6.51) \quad (7)$$

MMP-9

$$\log (1/IC_{50}) = 0.119(\pm 0.074)S_N - 1.149(\pm 0.355)I_{R2\text{-}CC} - 0.798(\pm 0.440)I_{AC} + 11.169(\pm 1.535)$$
$$n = 17,\ r = 0.932,\ r^2_{cv} = 0.65,\ s = 0.25,\ F_{3,14} = 28.47(5.56) \quad (8)$$

MMP-13

$$\log (1/IC_{50}) = 0.115(\pm 0.065)S_N - 0.885(\pm 0.314)I_{R2\text{-}CC} - 0.834(\pm 0.390)I_{AC} + 11.205(\pm 1.361)$$
$$n = 17,\ r = 0.927,\ r^2_{cv} = 0.73,\ s = 0.23,\ F_{3,14} = 26.34(5.56) \quad (9)$$

Equation 6 shows the existence of parabolic relationship (inverted parabola) between logP and the inhibitory activities of the compounds for the MMP-1, suggesting that activity would initially decrease with increase in logP and then would start increasing after the logP reaches an optimum value ($ClogP_o = 3.72$) (it should in fact be called the worst value in case of inverted parabola).

The additional parameter $I_{R1\text{-}A}$ in Eq. 6 is an indicator variable that accounts for the effect of some substituent in series 1. This stands, with a value of unity, for an R^1-substituent that has an aromatic moiety. The positive coefficient of it suggests that for MMP-1 inhibition the presence of an aromatic group at R^1 position would be beneficial for the compounds.

Equation 7 for TACE inhibition shows a linear negative dependence of activity on logP of the compounds. In this equation, the indicator variable $I_{R2\text{-}CC}$ stands, with a value of unity, for an acetylene-derived R^2-substituent and with its positive coefficient indicates that such a substituent may have a beneficial effect on the TACE inhibition.

Equation 8 and 9 obtained for MMP-9 and MMP-13 inhibitions exhibit parallel correlations, indicating an increase in inhibition activity of the compounds with an increase in the value of S_N, the E-state index of the nitrogen atom attached to sulfonyl group. The E-state index of an atom is the measure of the availability of π electrons and/or lone pair of electrons on the atom. Thus, the nitrogen atom can be assumed to be involved in some charge-transfer interaction with the receptors. This is in very good agreement with our previous QSAR studies on MMPs (Kumar and Gupta, 2003; Gupta *et al*., 2003a,b; Gupta and Kumaran, 2003). However, for MMP-9 and MMP-13, acetylene-derived R^2-substituents are shown to be detrimental to the activity, which is totally adverse to TACE inhibition. The presence in both Eqs. 8 and 9 with a negative coefficient of another indicator variable I_{AC}, that stands with a value of unity for an R^1-substituent containing an aliphatic ring, indicates that such an R^1-substituent will also not be conducive to the activity of the compounds against MMP-9 and MMP-13. As Eq. 8 and 9 are exactly parallel to each other, it can be suggested that both MMP-9 and MMP-13 might involve the similar mechanism of inhibition by these compounds.

For the compounds of Table 2, the following correlations were obtained.

MMP-1

$$\log (1/IC_{50}) = 0.444(\pm 0.108)I_{R1\text{-}A} - 2.740(\pm 0.968)ClogP + 0.672(\pm 0.235)(ClogP)^2 + 8.734(\pm 0.950)$$
$$n = 12,\ r = 0.981,\ r^2_{cv} = 0.91,\ s = 0.06,\ F_{3,8} = 69.69(7.59),\ ClogP_o = 2.04 \quad (10)$$

MMP-13

$$\log (1/IC_{50}) = 0.079(\pm 0.055)S_N - 1.519(\pm 0.747)ClogP + 0.234(\pm 0.125)(ClogP)^2 + 11.190\ (\pm 1.861)$$
$$n = 13,\ r = 0.853,\ r^2_{cv} = 0.20,\ s = 0.16,\ F_{3,9} = 8.01(6.99),\ ClogP_o = 3.25 \quad (11)$$

TACE

$$\log (1/IC_{50}) = 0.082(\pm 0.056)S_N - 0.470(\pm 0.280)I_{R1\text{-}A} - 0.965(\pm 0.290)I_{R2\text{-}H} + 9.369\ (\pm 1.191)$$
$$n = 15,\ r = 0.914,\ r^2_{cv} = 0.71,\ s = 0.19,\ F_{3,11} = 18.60(6.22) \quad (12)$$

Equation 10 and 11 obtained for MMP-1 and MMP-13, respectively, show that there exists a parabolic correlation (inverted parabola) between logP and inhibition activities of these compounds. The $ClogP_o$ values for MMP-1 and MMP-13 are 2.04 and 3.25, respectively. The indicator variable $I_{R1\text{-}A}$ in Eq. 10 has the same meaning as in Eq. 6. Its positive coefficient in Eq. 10 suggests that, as in the series of 1, the presence of an R^1-substituent with an aromatic moiety will also be beneficial to the inhibition potency of series 2 for MMP-1. Equation 6 and 10 are exactly parallel to each other suggesting a similar mode of inhibition of MMP-1 by both the series of compounds. For MMP-13, there occurs an electronic term, E-state index (S) of nitrogen atom attached to sulfonyl group, along with the hydrophobic parameter logP (Eq. 11). The positive coefficient of this term (S_N) suggests the possibility of a charge-transfer interaction with the enzyme through nitrogen atom. For TACE inhibition, the S_N is found to be the primary factor governing the activity (Eq. 12). There are, however, two indicator parameters in Eq. 12, $I_{R1\text{-}A}$ and $I_{R2\text{-}H}$. While $I_{R1\text{-}A}$ has the same meaning as in Eq. 6 and 10, $I_{R2\text{-}H}$ stands, with a value of unity, for an R^2-substituent other than H and has a value of zero for H. The negative coefficient of $I_{R1\text{-}A}$ suggests that the presence of an R^1-substituent with an aromatic moiety will be detrimental to the TACE inhibition and similarly the negative coefficient of $I_{R2\text{-}H}$ suggests that any substituent other than hydrogen at R^2-position will be detrimental to TACE inhibition. It shows that the bulky substituents at both R^1 and R^2 position may create some steric hinderance in TACE inhibition.

In deriving Eq. 6-12, some compounds as shown in Table 3 and 4 were excluded as they were found to be misfit in the correlations. However, no apparent reasons could be found to explain this behavior. All the equations (Eq. 6-12), except Eq. 11, were found to have high predictive power as indicated by the high r^2_{cv} value in each case. Equation 11 has an r^2_{cv} equal to 0.20 indicating poor predictive ability.

In our QSAR analysis on the benzodiazepine hydroxamic acid derivatives we could easily find two prominent features expressed by Eq. 6-12. The first is the existence of inverse parabolic relationship with logP of inhibition activities of both the series 1 and 2 against MMP-1 and of series 2 against MMP-13. This suggests that the mechanism of inhibition of these enzymes could be allosteric. The second is the appearance of E-state index of nitrogen atom (S_N) attached to sulfonyl group for the inhibitions of MMP-9 and MMP-13 by series 1 and the inhibitions of MMP-13 and TACE by series 2, which shows that the inhibitions of these enzymes may involve electronically the nitrogen atom, depending upon their conformational orientation.

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