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Quantitative Structure-Activity Relationship Studies on Matrix Metalloproteinase Inhibitors: Piperazine, Piperidine and Diazepine Hydroxamic Acid Analogs

[1]S.P. Gupta and [2]S. Kumaran
[1]Department of Chemistry, [2]Department of Pharmacy,
Birla Institute of Technology and Science, Pilani-333031, India

Abstract: A quantitative structure-activity relationship study has been made on four different series of piperazine, piperidine and diazepine hydroxamic acid analogs acting as matrix metalloproteinase (MMP) inhibitors. The results suggest that in most of the cases the hydrophobic property of the molecules plays a major role in the inhibition of the enzymes MMP-1, MMP-9, MMP-13 and TACE. In many cases, MMP-9 and MMP-13 are shown to behave in a similar fashion with the different group of inhibitors.

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

Introduction

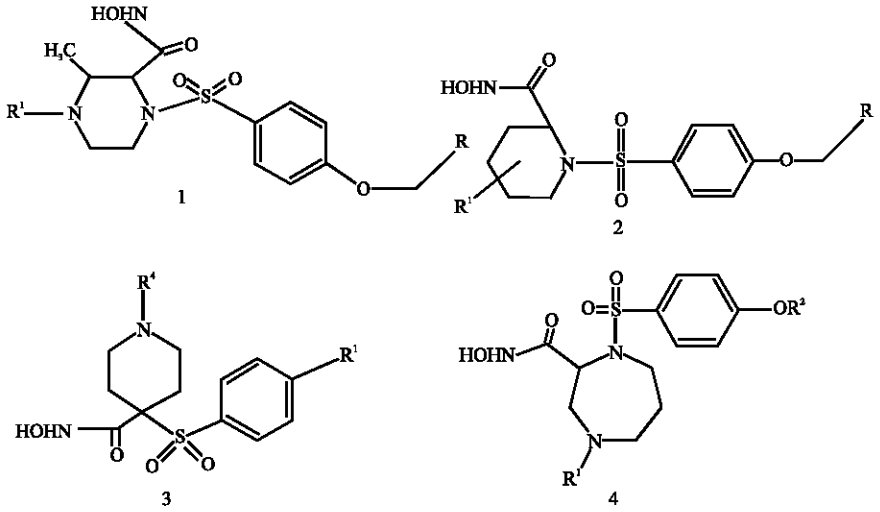
In the recent years, the study of the inhibition of matrix metalloproteinases (MMPs) has become of great interest, resulting into development of broad spectrum MMP inhibitors, like marimastat, batimastat and a few others. It is because the hyperactivity of MMPs results in tissue degradation and a wide array of disease processes, such as osteoarthritis (Cawston, 1996; Blaser *et al*., 1996), rheumatoid arthritis (O'Byrne *et al*.,1995; Doughty *et al*., 1997; Brewster *et al*., 1998), tumor metastasis (Wojtowicz-Praga *et al*., 1997; Bramhall, 1997; Brown, 1997), multiple sclerosis (Yong *et al*., 1998; Matyszak and Perry, 1996), congestive heart failure (Coker *et al*., 1998; Spinale *et al*., 1999; Tyagi, 1998), chronic obstructive pulmonary disease (COPD) (Burnett *et al*., 1988; Finlay *et al*., 1997; Ohno *et al*., 1997; Palmgren *et al*., 1992) and a host of others. Otherwise, it is well known that MMPs are a family of zinc-containing endopeptidases that collectively are able to cleave most of the structural components of extracellular matrix (ECM) like membrane collagen, fibronectin, laminin, versican, elastin, aggrecan, perlecan, tenascin, fibrinogen and proteoglycans (Murphy *et al*., 2002; Leung *et al*., 2000; Babine and Bender, 1997). The cleavages of these structural components are essential during the normal physiological and physiopathological events such as embryonic development, blastocyst implantation, nerve growth, ovulation, morphogenesis, angiogenesis, tissue resorption, wound healing, bone remodeling, apoptosis, cancer invasion and metastasis, arthritis, atherosclerosis, aneurysm, skin ulceration, corneal ulceration, gastric ulcer and liver fibrosis (Whittaker *et al*.,1999; Nagase, 1997; Nagase and Woessner, 1999; Bottomley *et al*., 1998; Dioszegi *et al*., 1995; Johnson *et al*., 1998). About 28 types of MMPs have been so far discovered and some of the recent development in the inhibitors of these MMPs has been recently reviewed by Supuran and Scozzafava (2002).

However, the clinical experiences of the inhibitors developed so far show intolerable side effects of musculoskeletal syndrome (MSS), which is due to the undesirable inhibition of some family members of MMP, e.g., MMP-1 (Rudek *et al*., 2002). Therefore, recently the efforts have been made

Corresponding Author: S.P. Gupta, Department of Chemistry, Birla Institute of Technology and Science, Pilani-333031, India

to selectively inhibit the MMPs to develop molecules for specific diseases. The selective inhibition of MMP-13 (Mitchel *et al*., 1996) and aggrecanase (Lohmander *et al*., 1993) over MMP-1 may have therapeutic benefit in osteoarthritis without causing MSS side effects. Similarly, the inhibition of MMP-9 may be valuable for preventing tumor metastasis (Yip *et al*., 1999; Nelson *et al*., 2000).

In the design and development of drugs, quantitative structure-activity relationship (QSAR) study has been of great value. Therefore, the present study reports a QSAR study on some novel series of piperazine (1), piperidine (2 and 3) and diazepine (4) hydroxamic acid analogs, so as to investigate the physicochemical properties of these molecules which can make them selective for given enzyme and also to explore the mechanism of drug-receptor interactions, which could give a rationale to develop more specific and selective inhibitors.



These compounds have also been studied for the inhibition of TNF-α (tumor necrosis factor-α), which is also a zinc-containing endopeptidase that has gained equal importance. Its catalytic site is quite similar to that of MMPs (Maskos *et al*., 1998) and is involved in catalysis of a crucial physiological reaction, i.e., processing of membrane-bound form of protumor necrosis factor α (TNF-α), a 26 kDa propeptide on cell surface, to 17 kDa soluble form of mature TNF-α (Black and White, 1998; Moss *et al*., 2001). The release of this mature form of TNF-α from cell surface is responsible for causing several inflammatory events in the body leading to several diseases including rheumatoid arthritis (RA) (Feldmann and Maini, 2001), Crohn's disease (Van Assche and Rutgeerts, 2000) and psoriasis (Kristensen *et al*., 1993). 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.

Materials and Methods

The series of MMP inhibitors taken for QSAR study have been reported by the different research groups: 1 and 2 by Letavic *et al*. (2002, 2003), 3 by Venkatesan *et al*. (2003) and 4 by Levin *et al*. (1998). The derivatives of all 1-4 are listed in Tables 1-4, respectively, along with their relevant

physiochemical properties that were found to be correlated with the MMP inhibition potencies. Tables 5-8 display the inhibition potencies of compounds of Tables 1-4, respectively, 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 physicochemical parameters found to be useful in this QSAR study are the calculated hydrophobicity parameter (ClogP) and polarizability (Pol) of the whole molecules and the hydrophobic constant π of the substituents. The hydrophobicity parameter ClogP was calculated using www.daylight.com domain and polarizability was calculated from www.acdlabs.com domain. The π values of substituents are taken from the literature (Hansch and Leo, 1970). 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 piperazine hydroxamic acid analogs 1 (Table 1), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 0.965\ (\pm 0.473)\ ClogP - 0.173\ (\pm 0.073)\ (ClogP)^2 - 1.008(\pm 0.288)I_{1,H} + 4.593(\pm 0.714)$$

$$n = 13,\ r = 0.947,\ r^2_{cv} = 0.67,\ s = 0.16,\ F_{3,9} = 26.16(6.99),\ ClogP_o = 2.79 \quad (1)$$

TACE

$$\log (1/IC_{50}) = 8.888(\pm 0.300) - 0.299(\pm 0.086)\ ClogP$$

$$n = 14,\ r = 0.909,\ r^2_{cv} = 0.72,\ s = 0.16,\ F_{1,12} = 57.35(9.33) \quad (2)$$

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.

Equations 1 and 2 represent very significant correlations and suggest that the MMP-1 inhibition by this series of compounds will largely depend upon the hydrophobicity of the molecules. But since dependence of the potency of the compounds on the hydrophobic parameters ClogP is parabolic, the potency is optimized with an optimum value of ClogP equal to 2.79. For TACE inhibition, however, the potency of the compounds is shown to have a negative relation with the hydrophobicity of the molecules (Eq. 2). For MMP-1 inhibition, a negative effect is shown by $R^1 = H$, as described by $I_{1,H}$ parameter in Eq. 1. It means that a replacement of this hydrogen by any comparatively bulky group will be conducive to the activity, which may be because of some hydrophobic interaction of the group with any specific hydrophobic pocket of the receptor.

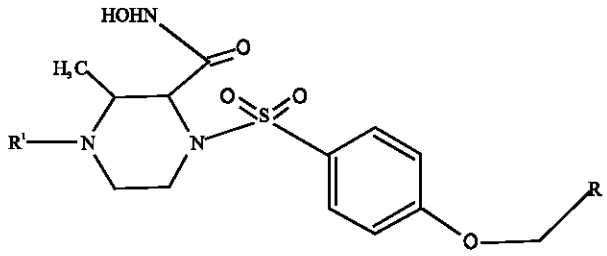
For the series of piperidine hydroxamic acid analogs 2 (Table 2), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 0.527(\pm 0.234)\pi_{X,R} + 0.289(\pm 0.212)I_{R1} + 4.846(\pm 0.128)$$

$$n = 15,\ r = 0.844,\ r^2_{cv} = 0.58,\ s = 0.17,\ F_{2,12} = 14.90(6.93) \quad (3)$$

Table 1: A series of piperazine hydroxamic acid analogs (1) and related physicochemical parameter(s)



Compds	R	R^1	ClogP	$I_{1,H}$
1	C_6H_5	H	2.470	1
2	C_6H_4-2-CH_3	H	2.910	1
3	C_6H_4-2-CH_3	(O)CCH_3	2.580	0
4	C_6H_4-2-CH_2CH_3	(O)CCH_3	3.110	0
5	C_6H_3-3,5-$(F)_2$	(O)CCH_3	2.420	0
6	C_6H_4-4-F	(O)CCH_3	2.280	0
7	C_6H_3-2-CH_3,3-F	(O)CCH_3	2.730	0
8	C_6H_4-2-CF_3	(O)CCH_3	3.020	0
9	4-isoquinoline	(O)CCH_3	1.810	0
10	4-quinoline	(O)CCH_3	2.020	0
11	3-(2-CH_3)-pyridyl	(O)CCH_3	1.090	0
12	C_6H_4-2-CH_3	SO_2CH_3	2.980	0
13	C_6H_4-2-CH_3	$SO_2C_6H_4$-4-CH_3	5.120	0
14	C_6H_4-2-CH_3	CH_3	3.390	0
15	C_6H_4-2-CH_3	$CH_2C_6H_5$	5.220	0
16	C_6H_4-2-CH_3	(O)$CNHC_6H_5$	4.170	0
17	C_6H_4-2-CH_3	(O)$COCH_3$	3.670	0
18	C_6H_4-2-CH_3	(O)CNH-iPr	3.790	0
19	C_6H_4-2-CH_3	(O)$COCH_2CH_3$	4.200	0

TACE

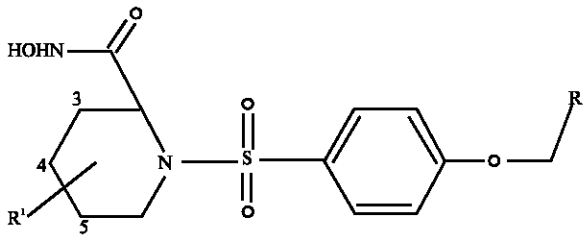
$$\log (1/IC_{50}) = 0.692(\pm0.197)\pi_{X,R} - 0.519(\pm0.132)(\pi_{X,R})^2 + 0.164(\pm0.130)I_{R1} + 0.351(\pm0.227)I_{R,Ph} + 0.181(\pm0.145)I_o + 7.667(\pm0.107)$$

$$n = 23,\ r = 0.909,\ r^2_{cv} = 0.72,\ s = 0.14,\ F_{5,17} = 16.21(4.34),\ (\pi_{X,R})_{opt} = 0.67 \quad (4)$$

For this group of compounds, the MMP-1 inhibition is shown to be primarily governed by only the hydrophobic property of the X-substituents present in the R-moiety of OCH_2R group of the aryl ring (Eq. 3). These substituents therefore seem to have specific hydrophobic interactions with the receptors. The additional factor to be favorable to the MMP-1 inhibition is the substitution of an OH group at the 5-position of piperidine ring (R^1 = 5-OH). The same at the 4-position would be less effective. This comparative effect of OH is described in Eq. 3 by the indicator variable I_{R1} with a value of 1 for R^1 = 5-OH and zero for R^1 = 4-OH.

R^1 = 5-OH is shown to be favorable to the TACE inhibition also (Eq. 4). The hydrophobic property of X-substituents in R is also shown to be conducive to TACE inhibition, however till only $\pi_{X,R}$ attains an optimum value of 0.67. Two additional parameters, $I_{R,Ph}$ and I_o describe the advantageous role of two discrete features of the molecules. $I_{R,Ph}$ stands with a value of 1 for R = C_6H_5 (i. e. unsubstituted phenyl moiety) and I_o stands with a value of 1 for 2-X (i.e., 2-position substituents at phenyl ring). Thus, de facto, an unsubstituted or a 2-substituted phenyl is indicated to be of additional advantage, but it is hard to explain as to how they would produce additional effects as compared to a 3-or 4-substituted phenyl.

Table 2: A series of piperidine hydroxamic acid analogs (2) and related physicochemical parameter(s)



Compd	R^1	R	$\pi_{X,R}$	I_{R1}	$I_{R,Ph}$	I_o
1	4-OH	C_6H_5	0.000	0	1	0
2	4-OH	C_6H_4-4-F	0.140	0	0	0
3	4-OH	C_6H_4-3-F	0.140	0	0	0
4	4-OH	C_6H_4-2-F	0.140	0	0	1
5	4-OH	C_6H_4-4-Cl	0.710	0	0	0
6	4-OH	C_6H_4-3-Cl	0.710	0	0	0
7	4-OH	C_6H_4-2-Cl	0.710	0	0	1
8	4-OH	C_6H_4-4-CH_3	0.560	0	0	0
9	4-OH	C_6H_4-3-CH_3	0.560	0	0	0
10	4-OH	C_6H_4-2-CH_3	0.560	0	0	1
11	4-OH	C_6H_4-3-OCH_3	-0.020	0	0	0
12	4-OH	C_6H_4-2-OCH_3	-0.020	0	0	1
13	4-OH	C_6H_4-2-CF_3	0.100	0	0	1
14	4-OH	C_6H_4-4-CN	-0.570	0	0	0
15	4-OH	C_6H_4-3-CN	-0.570	0	0	0
16	4-OH	C_6H_4-2-C_6H_5	1.960	0	0	1
17	5-OH	C_6H_5	0.000	1	1	0
18	5-OH	C_6H_4-4-CF_3	0.100	1	0	0
19	5-OH	C_6H_4-3-CF_3	0.100	1	0	0
20	5-OH	C_6H_4-2-CF_3	0.100	1	0	1
21	5-OH	C_6H_4-3-CN	-0.570	1	0	0
22	5-OH	C_6H_4-2-CN	-0.570	1	0	1
23	5-OH	C_6H_4-2-CH_3	0.560	1	0	1
24	5-OH	C_6H_4-2-CH_2CH_3	1.020	1	0	1
25	5-OH	C_6H_4-2-$CH(CH_3)_2$	1.530	1	0	1
26	5-OH	1-naphthyl	0.000	1	0	0
27	5-OH	C_6H_4-2-I	1.120	1	0	1

For the series of another piperidine hydroxamic acid analogs 3 (Table 3), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 0.532(\pm0.180)\ ClogP - 0.102(\pm0.044)\ (ClogP)^2 + 0.592(\pm0.170)I_{1,OMe} + 4.984(\pm0.249)$$

$$n = 38,\ r = 0.850,\ r^2_{cv} = 0.64,\ s = 0.21,\ F_{3,34} = 28.95(4.42),\ ClogP_o = 2.61 \quad (5)$$

TACE

$$\log (1/IC_{50}) = 0.379(\pm0.282)\ ClogP - 0.064(\pm0.054)\ (ClogP)^2 - 0.306(\pm0.140)\ Pol + 0.312(\pm0.108)I_{4,benz} + 7.283(\pm0.576)$$

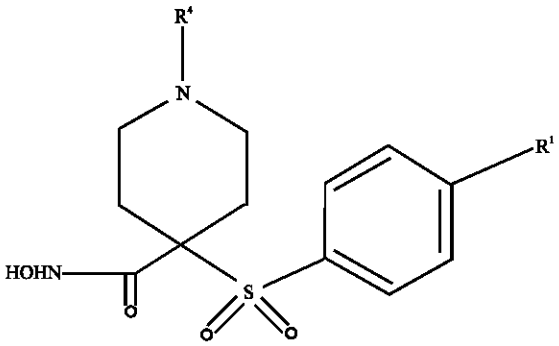
$$n = 27,\ r = 0.840,\ r^2_{cv} = 0.55,\ s = 0.11,\ F_{4,22} = 12.91(4.31),\ ClogP_o = 2.96 \quad (6)$$

MMP-9

$$\log (1/IC_{50}) = 0.909(\pm0.263)\ ClogP - 0.128(\pm0.061)(ClogP)^2 + 0.770(\pm0.285)I_{1,PhCl} + 6.686(\pm0.284)$$

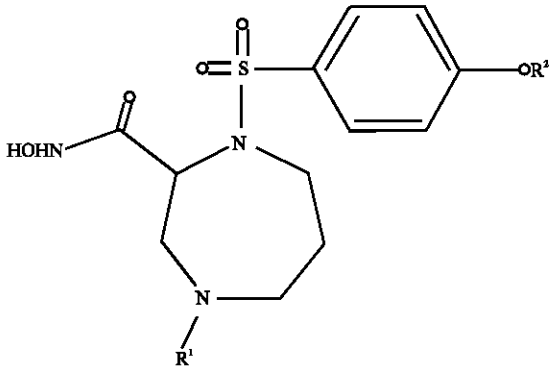
$$n = 42,\ r = 0.891,\ r^2_{cv} = 0.74,\ s = 0.31,\ F_{3,38} = 48.79(4.34),\ ClogP_o = 3.55 \quad (7)$$

Table 3: A series of piperidine hydroxamic acid analogs (3) and related physicochemical parameter(s)



Compd	R^1	R^4	ClogP	Pol	$I_{1,OMe}$	$I_{1,PhCl}$	I_{4benz}
1	$-OCH_3$	$CH_2C_6H_5$	1.260	4.210	1	0	1
2	$-OCH_3$	$CH_2C_6H_4$-3-OCH_3	1.179	4.460	1	0	1
3	$-OCH_3$	$CH_2C_6H_3$-3,4-$(Cl)_2$	2.566	4.590	1	0	1
4	$-OCH_3$	$CH_2C_6H_4$-4-CH_3	1.759	4.390	1	0	1
5	$-OCH_3$	2-CH_2-naphthyl	2.434	4.910	1	0	0
6	$-OCH_3$	4-CH_2-biphenyl	3.148	5.190	1	0	0
7	$-OCH_3$	Isoprene	1.510	3.940	1	0	0
8	$-OCH_3$	$CH_2C_6H_4$-4-Br	2.123	4.520	1	0	1
9	$-OCH_3$	3-Phenyl propyl	1.780	4.580	1	0	0
10	$-OCH_3$	tBu	0.539	3.780	1	0	0
11	$-OCH_3$	nBu	1.059	3.780	1	0	0
12	$-OCH_3$	Cyclo octyl	2.361	4.430	1	0	0
13	$-OCH_3$	CH_2CH_3	0.001	3.410	1	0	0
14	$-OCH_3$	iPr	0.140	3.600	1	0	0
15	$-OCH_3$	CH_3	-0.698	3.230	1	0	0
16	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_5$	2.847	4.760	0	0	1
17	$-OCH_3$	$CH_2C_6H_4$-4-F	1.403	4.220	1	0	1
18	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-4-F	2.990	4.770	0	0	1
19	$-OCH_3$	$CH_2C_6H_4$-4-OCH_3	1.179	4.460	1	0	1
20	$-OCH_3$	$CH_2CH_2C_6H_4$-4-OCH_3	1.490	4.650	1	0	0
21	$-OCH_3$	2-Phenyl ethyl	1.400	4.390	1	0	0
22	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-4-OCH_3	2.766	5.010	0	0	1
23	$-OCH_3$	3-Phenyloxy propyl	1.650	4.645	1	0	0
24	$-OCH_2CH_2CH_2CH_3$	3-Phenyloxy propyl	3.230	5.200	0	0	0
25	$-OCH_3$	2-Phenyloxy propyl	1.360	4.460	1	0	0
26	$-OCH_2CH_2CH_2CH_3$	2-Phenyloxy propyl	2.940	5.010	0	0	0
27	$-OCH_3$	$CH_2C_6H_4$-4-$O(CH_2)_2$-piperidinyl	2.513	5.640	1	0	1
28	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-4-$O(CH_2)_2$-piperidinyl	4.100	6.190	0	0	1
29	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-3-$O(CH_2)_2$-morpholinyl	2.886	6.070	0	0	1
30	$-OCH_2CH_2CH_2CH_3$	CH_3	0.889	3.780	0	0	0
31	$-OCH_2CH_2CH_2CH_3$	CH_2CH_3	1.418	3.970	0	0	0
32	$-OCH_2CH_2CH_2CH_3$	nBu	2.476	4.330	0	0	0
33	$-OC_6H_4$-4-Cl	CH_3	1.938	4.220	0	1	0
34	$-OC_6H_4$-4-Cl	CH_2CH_3	2.467	4.400	0	1	0
35	$-OC_6H_4$-4-Cl	nBu	3.525	4.770	0	1	0
36	$-OC_6H_4$-4-Cl	$CH_2C_6H_5$	3.726	5.200	0	1	1
37	$-OC_6H_4$-4-Cl	H	1.492	4.010	0	1	0
38	$-OCH_2CH_2CH(CH_3)_2$	$CH_2C_6H_5$	3.246	4.940	0	0	1
39	$-OCH_2CH(CH_3)_2$	$CH_2C_6H_5$	3.775	5.130	0	0	1
40	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-3-OCH_3	2.766	5.010	0	0	1
41	$-OCH_3$	$CH_2C_6H_4$-2-thiazolyl	3.004	5.120	1	0	1
42	$-OCH_3$	$CH_2C_6H_4$-2-pyridyl	1.861	5.100	1	0	1
43	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_3$-3,4-$(Cl)_2$	2.847	4.760	0	0	1
44	$-OCH_2C_6H_5$	$CH_2C_6H_5$	3.028	5.190	0	0	1
45	$-OCH_2C_6H_4$-4-Cl	$CH_2C_6H_4$-4-CH_3	4.240	5.570	0	0	1
46	-2-furyl	$CH_2C_6H_5$	2.189	4.640	0	0	1
47	$-OC_6H_4$-4-Cl	$CH_2C_6H_4$-4-OCH_3	3.645	5.450	0	1	1

Table 4: A series of diazepine hydroxamic acid analogs (4) and related physicochemical parameter(s)



Compd	R^1	R^2	ClogP	$I_{1,COPh}$
1	$-CH_2C_6H_5$	CH_3	2.430	0
2	$-C(O)C_6H_5$	CH_3	1.220	1
3	$-C(O)C_6H_5$	C_6H_5	3.150	1
4	$-C(O)C_6H_4$-4-OCF_3	CH_3	2.550	0
5	$-C(O)C_6H_4$-2-C_6H_5	CH_3	3.110	0
6	$-C(O)CH_2NHBOC$	CH_3	1.600	0
7	$-C(O)CH_2NH_2$-HCl	CH_3	-0.690	0
8	-C(O)tBu	CH_3	0.790	0
9	-C(O)OtBu	CH_3	2.130	0
10	-H-HCl	CH_3	0.160	0
11	$-C(O)NHC_6H_5$	CH_3	1.260	0
12	$-C(O)NH(S)$-$CH_2CH_2C_6H_5$	CH_3	3.530	0

Table 5: Observed and calculated MMP and TACE inhibition potencies of compounds of Table 1. Observed activities have been taken from Letavic *et al.* (2003).

	$\log(1/IC_{50})$, MMP-1			$\log(1/IC_{50})$, TACE		
Compd	Obs	Calcd Eq. 1	Loo	Obs	Calcd Eq. 2	Loo
1	4.92	4.91	4.91	7.60[b]	8.15	-
2	4.92	4.93	4.94	7.72[b]	8.02	-
3	5.80	5.93	5.95	8.22	8.12	8.10
4	5.17[a]	5.92	-	8.15	7.96	7.94
5	5.42[a]	5.92	-	8.22	8.16	8.16
6	5.77	5.89	5.92	8.22	8.21	8.20
7	5.72	5.94	5.98	8.15	8.07	8.06
8	5.00[a]	5.93	-	7.96	7.99	7.99
9	5.19[a]	5.77	-	-	8.35	-
10	6.08	5.84	5.78	-	8.28	-
11	5.47	5.44	5.33	8.30	8.56	8.71
12	5.89	5.93	5.94	8.22	8.00	7.98
13	-	5.00	-	7.49	7.36	7.31
14	-	5.88	-	7.51[b]	7.87	-
15	4.77	4.91	5.40	7.17	7.33	7.39
16	5.66	5.61	5.59	7.59	7.64	7.65
17	5.82	5.80	5.80	7.85	7.79	7.79
18	5.85	5.76	5.75	7.47	7.75	7.78
19	5.82	5.59	5.55	7.55	7.63	7.64

[a]Not included in the derivation of Eq. 1, [b]Not included in the derivation of Eq. 2

MMP-13

$$\log (1/IC_{50}) = 0.726(\pm0.192)\ ClogP - 0.141(\pm0.045)(ClogP)^2 - 0.265(\pm0.177)I_{1,OMe} + 8.000(\pm0.265)$$

$$n = 41,\ r = 0.850,\ r^2_{cv} = 0.63,\ s = 0.23,\ F_{3,37} = 31.90(4.36),\ ClogP_0 = 2.57 \quad (8)$$

Table 6: Observed and calculated MMP and TACE inhibition potencies of compounds of Table 2. Observed activities have been taken from Letavic *et al.* (2002)

	log ($1/IC_{50}$)					
	MMP-1			TACE		
Compd	Obs	Calcd Eq. 3	Loo	Obs	Calcd Eq. 4	Loo
1	5.10	4.85	4.82	8.05	8.02	7.98
2	-	4.92	-	7.85	7.75	7.74
3	4.80	4.92	4.93	7.68	7.75	7.76
4	4.92	4.92	4.92	7.17[b]	7.93	-
5	5.20	5.22	5.23	8.15	7.90	7.85
6	5.19	5.22	5.23	8.00	7.90	7.88
7	4.54[a]	5.22	-	7.44[b]	8.08	-
8	4.52[a]	5.14	-	7.70	7.89	7.92
9	5.05	5.14	5.16	7.74	7.89	7.91
10	5.30	5.14	5.11	8.22	8.07	8.03
11	4.62	4.84	4.86	7.57	7.65	7.67
12	5.66[a]	4.84	-	7.85	7.83	7.83
13	-	4.84	-	7.80	7.91	7.95
14	4.52	4.55	4.56	7.60[b]	7.10	-
15	4.64	4.55	4.51	7.82[b]	7.89	-
16	-	5.88	-	7.17	7.21	7.34
17	4.52[a]	5.14	-	8.15	8.18	8.22
18	5.43	5.19	5.13	8.00	7.90	7.87
19	5.24	5.19	5.18	7.82	7.90	7.91
20	4.82	5.19	5.28	8.30	8.08	8.03
21	-	4.83	-	7.31	7.27	7.23
22	4.82	4.84	4.84	7.41	7.45	7.48
23	5.52	5.43	5.39	8.10	8.24	8.27
24	-	5.67	-	8.00	8.18	8.22
25	-	5.94	-	7.96	7.86	7.81
26	-	5.14	-	7.80	7.83	7.84
27	-	5.73	-	8.15	8.14	8.13

[a]Not included in the derivation of Eq. 3, [b]Not included in the derivation of Eq. 4

It is to be noted that as for piperidine hydroxamic acids 2, for piperidine hydroxamic acids 3 also MMP-1 and TACE inhibitions are controlled by the hydrophobic property of the molecules (Eq. 5 and 6). In this case, however, there exists a better similarity between the QSARs of MMP-1 and TACE. For both, there exists a parabolic dependence of the inhibition potency of the compounds on ClogP and for both the optimum value of ClogP ($ClogP_o$) is almost same. However, for the TACE inhibition, the polarizability of the molecules is also found to play a role and, as obvious from Eq. 6, it is producing an adverse effect. It is of course in line with the fact that polarizability will always play an opposite role to that of hydrophobicity.

For the series of 3, the hydrophobicity of the molecules is shown to govern also the activity of the compounds studied against two other MMPs, MMP-9 and MMP-13 (Eq. 7 and 8). The parabolic dependence of the activity on ClogP in these two cases also leads to suggest that in the inhibition of all the four MMPs here, the hydrophobicity of the molecules plays almost an identical role. However, in all the cases, there are some indicator variables describing the positive or negative effect of some typical substituents. In the case of MMP-1 and MMP-13 (Eq. 5 and 8), the variable $I_{1,OMe}$ describes the effect of a methoxy group substituted at the aryl ring (R^1 = OMe). It has a value of 1 for R^1 = OMe and zero for R^1 being any other substitutent. Now while a positive coefficient of $I_{1,OMe}$ in Eq. 5 indicates a favorable role of an OMe group at R^1-position in MMP-1 inhibition, for MMP-13 inhibition a negative coefficient of it in Eq. 8 indicates a detrimental effect of OMe. The one possible reason of this difference may be the size of this substitutent. The methoxy substitutent is the smallest one among all R^1-substituents. A favorable role of it, as compared to other substituents, in MMP-1 may be due to its optimum steric fit with the receptor site in this enzyme and its comparative unfavorable role in MMP-13 may be due to its insufficiently small size to have any interaction with the receptor site in this enzyme.

Table 7: Observed and calculated MMP and TACE inhibition potencies of compounds of Table 3. Observed activities have been taken from Venkatesan *et al.* (2003)

	log (1/IC_{50})											
	MMP-1			TACE			MMP-9			MMP-13		
Compd	Obs	Calcd Eq. 5	Loo	Obs	Calcd Eq. 6	Loo	Obs	Calcd Eq. 7	Loo	Obs	Calcd Eq. 8	Loo
1	6.31	6.08	6.07	6.64	6.68	6.69	8.00	7.63	7.61	8.70	8.43	8.41
2	6.28	6.06	6.05	6.67	6.59	6.57	8.05	7.58	7.56	8.70	8.39	8.38
3	6.35	6.27	6.26	6.94	6.75	6.70	8.22	8.18	8.18	8.70	8.67	8.67
4	6.31	6.19	6.19	6.65	6.72	6.73	7.77	7.89	7.90	8.70	8.57	8.57
5	6.43	6.26	6.25	6.77[b]	6.32	-	8.30	8.14	8.14	8.70	8.67	8.66
6	5.88	6.23	6.29	6.21	6.26	6.27	7.89	8.28	8.31	8.52	8.62	8.63
7	5.86	6.15	6.16	-	6.50	-	7.41	7.77	7.79	8.15	8.51	8.53
8	6.22	6.24	6.24	-	6.73	-	8.00	8.04	8.04	8.70	8.64	8.63
9	5.71[a]	6.20	-	6.30	6.35	6.36	7.89	7.90	7.90	7.96[d]	8.58	-
10	-	5.83	-	-	6.31	-	6.19[c]	7.14	-	6.83[d]	8.09	-
11	-	6.02	-	-	6.46	-	6.34[c]	7.51	-	7.42[d]	8.35	-
12	5.58	5.58	5.61	-	6.47	-	6.86[c]	8.12	-	7.54[d]	8.66	-
13	5.43	5.65	5.70	-	6.24	-	6.44	6.68	6.75	7.48	7.73	7.80
14	5.35[a]	6.26	-	-	6.23	-	6.43	6.81	6.88	7.47	7.83	7.90
15	5.29	5.16	4.99	-	6.00	-	6.32	5.98	5.59	7.36	7.16	6.93
16	5.62	5.67	5.67	6.81	6.70	6.68	8.40	8.24	8.23	9.00	8.92	8.91
17	6.18	6.12	6.12	6.60	6.71	6.73	7.80	7.71	7.71	8.70	8.48	8.46
18	5.33	5.66	5.68	-	6.70	-	7.72	8.26	8.29	8.30[d]	8.91	-
19	6.19	6.06	6.05	6.71	6.59	6.57	7.92	7.58	7.56	8.70	8.39	8.38
20	6.18	6.14	6.14	-	6.28	-	7.47	7.76	7.77	8.70	8.50	8.49
21	5.88	6.12	6.13	6.33	6.34	6.35	7.35	7.71	7.73	8.05	8.47	8.50
22	5.58	5.67	5.68	6.68	6.62	6.61	8.52	8.22	8.21	9.00	8.93	8.92
23	5.92	6.17	6.19	-	6.31	-	7.36	7.84	7.86	8.40	8.55	8.56
24	5.42	5.63	5.65	6.20	6.25	6.26	8.30	8.29	8.29	9.00	8.87	8.87
25	6.20	6.11	6.10	6.53	6.31	6.27	7.59	7.68	7.69	8.52	8.46	8.46
26	5.54	5.66	5.67	6.57[b]	6.31	-	8.30	8.25	8.25	8.70	8.91	8.93
27	6.41	6.26	6.25	6.41	6.42	6.42	8.52	8.16	8.15	8.52	8.67	8.68
28	5.71	5.44	5.36	6.24	6.18	6.15	8.70	8.27	8.16	9.00	8.60	8.51
29	5.66	5.67	5.67	6.30	6.30	6.30	8.70	8.25	8.22	8.70	8.92	8.93
30	5.47	5.38	5.36	6.23	6.41	6.51	8.00[c]	7.39	-	8.70	8.53	8.50
31	5.15	5.53	5.59	-	6.48	-	7.37	7.72	7.74	8.70	8.74	8.75
32	-	5.68	-	6.06	6.49	6.47	7.55[c]	8.15	-	8.70	8.93	8.95
33	5.85	5.63	5.61	6.57	6.49	6.51	8.70	8.74	8.75	8.70	8.87	8.90
34	5.76	5.67	5.67	6.38	6.37	6.32	9.00	8.92	8.90	9.00	8.93	8.93
35	5.97	5.59	5.55	6.52	6.53	6.53	9.00	9.07	9.09	9.00	8.80	8.79
36	6.10[a]	5.55	-	6.52[b]	6.66	-	9.00	9.07	9.08	9.00	8.74	8.73
37	5.90	5.55	5.50	6.07[b]	6.11	-	8.70	8.53	8.48	8.70	8.77	8.78
38	5.59	5.63	5.64	6.25	6.62	6.63	8.40	8.29	8.29	8.70	8.87	8.88
39	5.50	5.53	5.53	-	6.54	-	7.85	8.30	8.35	8.30	8.73	8.78
40	5.82	5.67	5.66	6.57	6.59	6.60	8.52	8.22	8.21	9.00	8.93	8.92
41	6.27	6.25	6.24	6.56	6.52	6.51	7.96	8.26	8.28	8.52	8.64	8.66
42	6.37	6.21	6.20	6.53	6.57	6.58	8.22	7.93	7.92	8.70	8.60	8.59
43	5.44	5.67	5.68	-	6.62	-	7.70	8.24	8.26	8.30[d]	8.92	-
44	7.40[a]	5.66	-	6.38[b]	6.57	-	8.52	8.27	8.26	9.00	8.90	8.90
45	5.32	5.40	5.43	6.38	6.35	6.34	8.22	8.24	8.25	8.22	8.54	8.64
46	7.40[a]	5.66	-	6.38[b]	6.70	-	8.52	8.06	8.04	9.00	8.91	8.90
47	6.31[a]	5.57	-	6.31	6.46	6.48	9.00	9.07	9.09	9.00	8.77	8.74

[a]Not included in the derivation of Eq. 5, [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

In Eq. 7, $I_{1,PhCl}$ stands with a value of unity for $R^1 = OC_6H_4$-4-Cl. A positive coefficient of it exhibits a favorable role of this substituent for MMP-9 inhibition. Here the chlorine may be expected to have some electronic interaction with the receptor. Similarly, in Eq. 6 $I_{4,benz}$ describes a conducive role of a substituted or unsubstituted benzyl present at the piperidine nitrogen (R^4-substituent). This variable has a value of 1 for $R^4 = CH_2C_6H_4$-X and zero for any other R^4-substituent.

For the series of diazepine hydroxamic acid analogs 4 (Table 4), the QSARs obtained were as follows:

Table 8: Observed and calculated MMP inhibition potencies of compounds of Table 4. Observed activities have been taken from Levin *et al.* (1998)

	log(1/IC_{50}), MMP-9			log(1/IC_{50}), MMP-13		
Compd	Obs	Calcd Eq. 9	Loo	Obs	Calcd Eq. 10	Loo
1	7.51[a]	7.22	-	7.19[b]	7.57	-
2	8.70	8.48	8.21	8.66	8.61	8.55
3	8.92	9.14	9.41	8.89	8.93	9.00
4	8.40	8.08	8.02	8.21	8.00	7.96
5	8.48	8.27	8.20	8.34	8.10	8.02
6	7.64	7.76	7.78	7.80	7.84	7.85
7	6.80	6.99	7.15	7.34	7.45	7.60
8	8.32[a]	7.22	-	7.96	7.70	7.65
9	8.04	7.94	7.92	7.59	7.93	7.98
10	7.22	7.27	7.29	8.29[b]	7.57	-
11	7.74	7.65	7.63	7.77	7.78	7.79
12	8.04	8.41	8.59	7.98	8.17	8.26

[a]Not included in the derivation of Eq. 9, [b]Not included in the derivation of Eq. 10

MMP-9

$$\log (1/IC_{50}) = 0.339(\pm 0.148)\ ClogP + 0.853(\pm 0.479)I_{1,COPh} + 7.217(\pm 0.329)$$
$$n = 10,\ r = 0.942,\ r^2_{cv} = 0.70,\ s = 0.25,\ F_{2,7} = 27.51(9.55) \quad (9)$$

MMP-13

$$\log (1/IC_{50}) = 0.168(\pm 0.135)\ ClogP + 0.834(\pm 0.415)I_{1,COPh} + 7.574(\pm 0.304)$$
$$n = 10,\ r = 0.914,\ r^2_{cv} = 0.71,\ s = 0.22,\ F_{2,7} = 17.75(9.55) \quad (10)$$

For most of the cases, the correlation obtained for MMP-9 and MMP-13 have been found to be parallel. We observe the same for the series of 4, too (Eq. 9 and 10). Equation 9 and 10 clearly exhibit that for both these MMPs, the hydrophobicity of the molecules of this series of compounds will be a dominant factor and that a benzoyl group at the diazepine nitrogen ($R^1 = C(O)C_6H_5$) would be an additional advantage as described by the indicator variable $I_{1,COPh}$. The hydrophobicity of the molecules will obviously lead to a hydrophobic interaction of the molecules with the enzymes and the benzoyl group at the nitrogen may have some optimum polar interaction with some sites of the receptor.

Equations 1-10 exhibit very significant correlations, devoid of any mutual correlation among the parameters used in any equation, and have very good predictive value as judged from their r^2_{cv} values. However, in deriving these equations, some compounds as indicated in the foot-notes of the Tables 5-8 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 behaviour of each compound. In such situations, the only reason that can be assigned is the experimental error, or the conformational behavior of the enzymes.

Conclusions

This study suggests that for piperazine, piperidine and diazepine hydroxamic acid analogs, the hydrophobic property of the molecules plays a major role in the inhibition of the enzymes studied: MMP-1, MMP-9, MMP-13 and TACE. Therefore, one can assume that the nature of enzyme-ligand interaction is predominantly hydrophobic. In most of the cases, the QSARs for MMP-9 and MMP-13 have been found to be quite similar, hence in those cases the compounds are supposed to interact with these enzymes in a similar fashion.

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