A Quantitative Structure-Activity Relationship Study on Some Novel Series of Hydroxamic Acid Analogs Acting as Matrix Metalloproteinase Inhibitors

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Abstract: A quantitative structure-activity relationship study has been made on some pyranyl hydroxamic acid analogs acting as matrix metalloproteinase (MMP) inhibitors. The inhibition potencies of two different series of compounds against two MMP enzymes (MMP-1 and MMP-13) have been analyzed and found to be well correlated with hydrophobic and some indicator parameters of the substituents. In both the cases, hydrophobic parameter of substituents has been found to be a dominant factor. The results of this study led to discuss the selectivity of the compounds for MMP-13 over MMP-1.

Key Words: Quantitative structure-activity relationship, matrix metalloproteinase inhibitors, pyranyl hydroxamic acid analogs.

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 [1,2]. 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. 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 [3,4], rheumatoid arthritis [5-7], tumor metastatis [8-10], multiple sclerosis [11-13], congestive heart failure [14-16], and a host of others. Therefore, the study of the inhibition of MMPs has become of great interest.

Of all the human MMPs so far known, the ones of current therapeutic interest are fibroblast collagenase (MMP-1), neutrophil collagenase (MMP-8), collagenase (MMP-13), gelatinase A (MMP-2), gelatinase B (MMP-9), stromelysin -1 (MMP-3), stromelysin-2 (MMP-10), matrilysin (MMP -7), membrane-type-1-MMP (MT1-MMP), and aggrecanase. Although the development of MMP inhibitors started since the early 1980s, it has been greatly accelerated only recently, as the three-dimensional crystal and the solution structures of the inhibitors bound to some of the MMPs, e. g., MMP-1, 3, 7, 8 and MT1-MMP could be studied just a few years ago [17]. There are now numerous reviews available on the development of MMP inhibitors [1,2,17-20].

From the day the researchers started taking interest in the development of MMP inhibitors, a number of compounds progressed into clinical trials for cancer, rheumatoid arthritis, and osteoarthritis. This aroused further interest in the study of the inhibition of MMPs leading to the development of broad spectrum MMP inhibitors, like marimastat, Ro-32-3555, CGS-27023A and AG-3340 (Fig. (**1**)). However, the clinical experiences of these compounds show intolerable side effects of musculoskeletal syndrome (MSS) which is due to the undesirable inhibition of MMP-1 [21]. Consequently, efforts have been made to investigate selective inhibitors of MMPs to develop drugs for specific diseases. The selective inhibition of MMP-13 [22] and aggrecanase [23] over MMP-1 may have therapeutic benefits in osteoarthritis without causing MSS side effects.

Most of these broad spectrum inhibitors belong to different classes of aryl hydroxamates. Several research groups used the structure based design to modify these broad spectrum inhibitors to find compounds that are more selective for aggrecanase and MMP-13 and that could be exploited for the safe, long term treatment of cancer, osteoarthritis and rheumatoid arthritis. Recently, two novel series of aryl hydroxamates (**1** and **2**) have been reported [24,25] that contain mostly a pyran-type of ring in the back bone attached directly to the carbonyl carbon of the hydroxamic acid moiety. In order to investigate the physicochemical properties of these molecules and to explore the mechanism of the inhibition of different MMPs, which could be exploited to develop more specific and selective inhibitors, we attempted a QSAR study on them.

MATERIALS AND METHODS

The two novel series of hydoxamates **1** and **2** were taken from Reiter *et al*. [24] and Noe *et al.* [25], respectively. The two series differ in that in **1** the pyran-type ring is attached to the aryl ring through a sulfonamide bridge group (-NH-SO_2-), while in **2** it is attached to the aryl ring through only sulfonyl group. Both the series of compounds (**1** and **2**) are listed in Tables **1** and **2**, respectively, along with their physicochemical parameters that were found to be correlated with their

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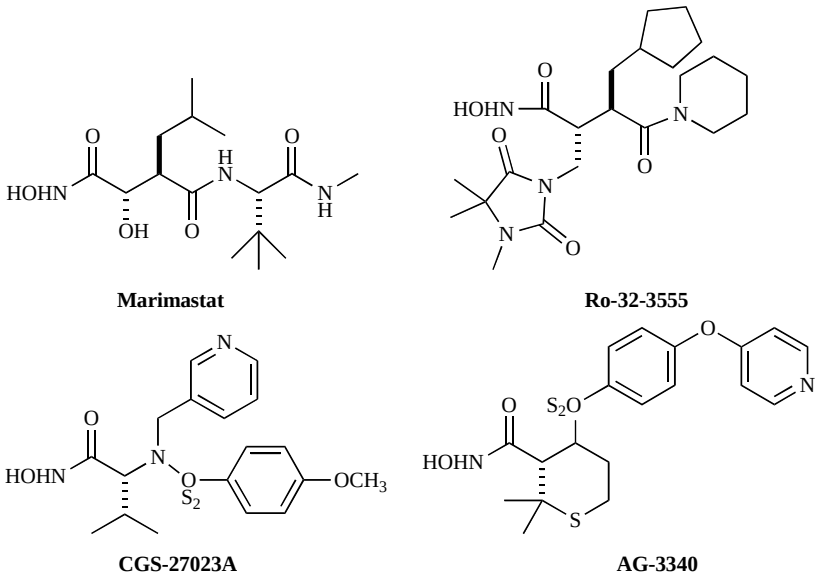


Fig. (1). Some MMP inhibitors in clinical trials.

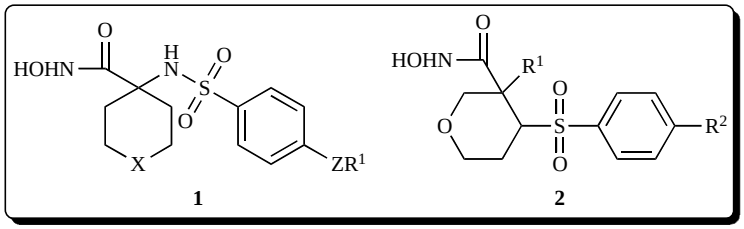
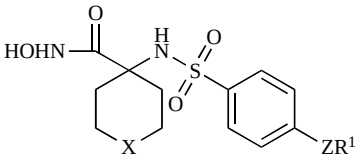


Table 1. Analogs of Series 1 and Related Physicochemical Parameter(s)

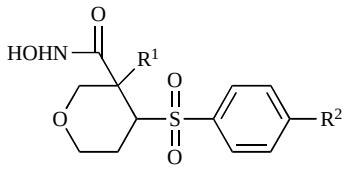


Compd	X	Z	R^1	$\pi_2(R^1)$	$\pi_{3,4}(R^1)$	$I_{1,Ph}$
1	O	O	C_6H_5	0.000	0.000	1
2	O	O	C_6H_4-2-F	0.140	0.000	1
3	O	O	C_6H_4-3-F	0.000	0.140	1
4	O	O	C_6H_4-4-F	0.000	0.140	1
5	O	O	C_6H_4-2-Cl	0.710	0.000	1
6	O	O	C_6H_4-3-Cl	0.000	0.140	1
7	O	O	C_6H_4-4-Cl	0.000	0.710	1
8	O	O	C_6H_4-4-OCH_3	0.000	-0.020	1
9	O	O	C_6H_4-4-NC	0.000	-0.570	1
10	O	O	1-naphthyl	0.000	0.000	0
11	O	O	2-naphthyl	0.000	0.000	0
12	O	O	$CH_2C_6H_5$	0.000	0.000	0

(Table 1. Contd….)

Compd	X	Z	R^1	$\pi_2(R^1)$	$\pi_{3,4}(R^1)$	$I_{1,Ph}$
13	O	O	$CH_2C_6H_4$-2-F	0.140	0.000	0
14	O	O	$CH_2C_6H_4$-3-F	0.000	0.140	0
15	O	O	$CH_2C_6H_4$-4-F	0.000	0.140	0
16	O	O	2-pyridyl	0.000	0.000	0
17	O	O	3-pyridyl	0.000	0.000	0
18	O	O	4-pyridyl	0.000	0.000	0
19	O	O	2-pyridyl-5-F	0.000	0.140	0
20	O	O	2-pyridyl-5-Cl	0.000	0.710	0
21	O	S	C_6H_4-4-F	0.000	0.140	1
22	O	-	C_6H_4-4-F	0.000	0.140	1
23	S	O	C_6H_4-4-F	0.000	0.140	1
24	SO_2	O	C_6H_4-4-F	0.000	0.140	1

Table 2. Analogs of Series 2 and Related Physicochemical Parameter(s)



Compd	R^1	R^2	$\pi_2(R^2)$	$\pi_4(R^2)$	I_1	$I_{2,OPh}$
1	OH	$OCH_2C_6H_4$-2-CH_3	0.560	0.000	0	0
2	OH	$OCH_2C_6H_4$-3-CH_3	0.000	0.000	0	0
3	OH	$OCH_2C_6H_4$-4-CH_3	0.000	0.560	0	0
4	OH	$OCH_2C_6H_4$-2-Cl	0.710	0.000	0	0
5	OH	$OCH_2C_6H_4$-3-Cl	0.000	0.000	0	0
6	OH	$OCH_2C_6H_4$-4-Cl	0.000	0.710	0	0
7	OH	$OCH_2C_6H_4$-2-CF_3	0.100	0.000	0	0
8	OH	$OCH_2C_6H_3$-2,3-$(Cl)_2$	0.710	0.000	0	0
9	OH	$OCH_2C_6H_3$-2,4-$(Cl)_2$	0.710	0.710	0	0
10	OH	$OCH_2C_6H_3$-2,5-$(Cl)_2$	0.710	0.000	0	0
11	OH	$OCH_2C_6H_3$-2,6-$(Cl)_2$	0.710	0.000	0	0
12	OH	$OCH_2C_6H_3$-2,4-$(CH_3)_2$	0.560	0.560	0	0
13	OH	$OCH_2C_6H_3$-2,5-$(CH_3)_2$	0.560	0.000	0	0
14	OH	$OCH_2C_6H_3$-2,6-$(CH_3)_2$	0.560	0.000	0	0
15	OH	OC_6H_4-2-CH_3	0.560	0.000	0	1
16	OH	OC_6H_4-3-CH_3	0.000	0.000	0	1
17	OH	OC_6H_4-4-CH_3	0.000	0.560	0	1

(Table 2. Contd….)

Compd	R^1	R^2	$\pi_2(R^2)$	$\pi_4(R^2)$	I_1	$I_{2,OPh}$
18	OH	C_6H_4-2-CH_3	0.560	0.000	0	0
19	OH	C_6H_4-3-CH_3	0.000	0.000	0	0
20	OH	C_6H_4-4-CH_3	0.000	0.560	0	0
21	OCH_3	$OCH_2C_6H_4$-2-Cl	0.710	0.000	1	0
22	OCH_3	$OCH_2C_6H_3$-2,4-$(Cl)_2$	0.710	0.710	1	0

MMP inhibition potencies. The inhibition potencies of these compounds against two enzymes, MMP-1 and MMP-13, are listed in Tables **3** and **4**. In these Tables, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. The physicochemical parameter found to be useful in this QSAR study was only the hydrophobic constant π of the substituents. The values of π were taken from the literature [26]. Some indicator variables were also used to account for the effects of some specific structural features of the compounds. These variables are defined in the text as and when they appear.

RESULTS AND DISCUSSION

For the compounds of series **1** (Table **1**), the correlations obtained were:

MMP-1

$$\log (1/IC_{50}) = 0.935(\pm0.219)I_{1,Ph} + 0.961(\pm0.429)\pi_{3,4}(R^1) + 5.128(\pm0.162)$$

$$n = 20,\ r = 0.924,\ r^2_{cv} = 0.79,\ s = 0.23,\ F_{2,17} = 49.42(6.11) \quad (1)$$

MMP-13

$$\log (1/IC_{50}) = 0.962(\pm0.265)I_{1,Ph} - 1.163(\pm0.840)\pi_2(R^1) + 7.948(\pm0.193)$$

$$n = 20,\ r = 0.884,\ r^2_{cv} = 0.69,\ s = 0.27,\ F_{2,17} = 30.30(6.11) \quad (2)$$

In these equations, n is the number of data points, r is the correlation coefficient, r^2_{cv} is square of the 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 (the figures within parenthesis refer to the F-values 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 constant of the equation.

In equation (1), $\pi_{3,4}(R^1)$ refers to the hydrophobic constant of 3- or 4- position substituent in R^1-moiety in ZR^1 group. Similarly in equation (2), $\pi_2(R^1)$ refers to the hydrophobic constant of a 2-position substituent in R^1. In both equations (1) and (2), $I_{1,Ph}$ is an indicator variable used for an R^1-moiety which is a substituted or unsubstituted phenyl group. For such a group $I_{1,Ph}$ is equal to 1 and for others it is zero. Now a positive coefficient of this variable in both the equations suggests that for both MMP-1 as well as MMP-13 inhibitions a substituted or unsubstituted phenyl R^1-moiety would be preferred to any other kind of R^1-moiety. Further, for MMP-1 inhibition, equation (1) indicates that if substituted phenyl group has a hydrophobic susbtituent at 3- or 4-position, the group will have an enhanced effect. Since $\pi_{3,4}$ has been defined for 3- or 4- position substituent at any kind of ring, the hydrophobic nature of such substituents at any ring, e.g. even at pyridyl ring (compds 19 and 20, Table **1**), will have a positive effect on the activity of the compounds. It can, therefore, be assumed that 3- or 4- position substituents might be involved in some hydrophobic interaction with the enzymes and that this interaction may have an optimium effect with a phenyl group. In this case (i.e.,MMP-1), however, 2-position substituents were not found to produce any effect. On the other hand, in the case of MMP-13 inhibition, the hydrophobic 2-position substituents are shown to be deterimental to the activity of the compounds (equation (2)) and the 3,4- position substituents are found to have no effect.

In Table **1**, a slight variation is shown in the heteroatom X in the pyran ring and in the Z-moiety attached to the aryl ring. Our QSAR analysis did not show any effect of these variations.

The above two equations, thus, suggest that a selective inhibition of MMP-13 can be achieved by controlling the hydrophobic properties of the substituents in the R^1-moiety. If no substituents are taken at 3- and 4- positions and, instead of lipophilic susbtituents, hydrophilic substituents (with negative π value) are taken at the 2-position, the compounds will be more effective against MMP-13 than against MMP-1.

For the compounds of series **2** (Table **2**), the correlations obtained were:

MMP-1

$$\log (1/IC_{50}) = 4.843(\pm0.202) - 4.207(\pm3.357)\pi_4(R^2) + 8.113(\pm5.153)[\pi_4(R^2)]^2 + 1.806(\pm0.413)I_{2,OPh}$$

$$n = 12,\ r = 0.971,\ r^2_{cv} = 0.87,\ s = 0.22,\ F_{3,8} = 43.21(7.59),\ [\pi_4(R^2)]_{opt} = 0.26 \quad (3)$$

MMP-13

$$\log (1/IC_{50}) = 0.772(\pm0.625)\pi_4(R^2) - 12.768(\pm4.248)\pi_2(R^2) + 16.953(\pm6.207)[\pi_2(R^2)]^2 - 1.088(\pm0.692)I_1 + 8.715(\pm0.326)$$

$$n = 18,\ r = 0.926,\ r^2_{cv} = 0.68,\ s = 0.38,\ F_{4,13} = 19.60(5.20),\ [\pi_2(R^2)]_{opt} = 0.38 \quad (4)$$

In this series, the variations are shown not only in the substituents at the aryl ring (R^2) but also in the substituents at the pyran ring (R^1). In the above equations, $\pi_x(R^2)$ means the hydrophobic constant for the substituent at the x-position (x = 1,2,3,---) in the aryl ring of R^2-substituent. Thus equation

Table 3. Observed and Calculated MMP Inhibition Potencies of Compounds of Table 1. Observed Activities have been Taken from Ref. [24]

Compound	log (1/IC_{50})					
	MMP-1			MMP-13		
	Obsd	Calcd, eq 1	Loo	Obsd	Calcd, eq 2	Loo
1	6.31	6.06	6.06	8.82	8.91	8.92
2	6.74[a]	6.06	-	9.19	8.75	8.70
3	5.96	6.20	6.23	9.25	8.91	8.87
4	6.38	6.20	6.18	9.12	8.91	8.89
5	5.77	6.06	6.10	8.01	8.09	9.12
6	5.41[a]	6.20	-	8.34[b]	8.91	-
7	6.49	6.75	6.92	8.92	8.91	8.91
8	6.11	6.04	6.04	9.06	8.91	8.89
9	5.32	5.51	5.66	8.77	8.91	8.93
10	5.31	5.13	5.11	6.68[b]	7.95	-
11	5.41	5.13	5.09	8.30	7.95	7.90
12	5.27	5.13	5.11	8.19	7.95	7.92
13	5.02	5.13	5.14	7.72	7.79	7.96
14	5.06	5.26	5.29	7.62	7.95	7.99
15	5.19	5.26	5.27	7.96	7.95	7.95
16	4.92	5.13	5.15	7.89	7.95	7.96
17	6.26[a]	5.13	-	7.60	7.95	7.99
18	4.92	5.13	5.15	8.24	7.95	7.91
19	5.42	5.26	5.25	7.85	7.95	7.96
20	5.85	5.81	5.79	8.82[b]	7.95	-
21	5.23[a]	6.20	-	8.34[b]	8.91	-
22	6.70	6.20	6.14	8.36	8.91	8.97
23	6.12	6.20	6.21	8.82	8.91	8.92
24	6.26	6.20	6.19	8.70	8.91	8.93

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

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

(3) suggests that, for MMP-1 inhibition, the inhibition potency of the compounds will initially decrease with the increase in hydrophobic property of 4-position substituent but after the optimum value of $\pi_4(R^2)$, which is equal to 0.26, it will start increasing. However, for MMP-13, equation (4) indicates that such a hydrophobic effect would be produced by 2-position substituent and not by 4-position substituent. The 4-position substituents will have simply a linear hydrophobic effect.

In equation (3), however, there is an indicator parameter $I_{2,OPh}$, which has been used with a value of 1 for an R^2-substituent which is a substituted or unsubstituted phenoxy group. This is almost equivalent to $I_{1,Ph}$ in equation (1) if we consider the whole ZR^1 group in **1**. Thus, like $I_{1,Ph}$ in equation (1), the positive coefficient of $I_{2,OPh}$ in equation (3) also suggests that for MMP-1 inhibition a substituted or unsubstituted phenoxy group at the aryl ring would be advantageous to the potency of the compounds of series 2 also as compa-

Table 4. Observed and Calculated MMP Inhibition Potencies of Compounds of Table 2. Observed Activities have been Taken from Ref. [25]

Compd	log (1/IC_{50})					
	MMP-1			MMP-13		
	Obsd	Calcd, eq 3	Loo	Obsd	Calcd, eq 4	Loo
1	4.92	4.84	4.83	7.68[b]	6.88	-
2	4.66	4.84	4.88	8.30	8.71	8.80
3	5.27	5.03	4.87	8.89	9.15	9.20
4	5.55[a]	4.84	-	8.57	8.19	8.06
5	5.10	4.84	4.80	8.62	8.71	8.74
6	5.85	5.95	6.04	9.06	9.26	9.33
7	-	4.84	-	7.55	7.61	7.63
8	4.89	4.84	4.84	7.82	8.19	8.33
9	6.04	5.95	5.85	9.02	8.74	8.56
10	4.57	4.84	4.89	7.89	8.19	8.31
11	-	4.84	-	-	8.20	-
12	4.72	5.03	5.25	7.77	7.32	7.02
13	-	4.84	-	6.52	6.89	7.04
14	-	4.84	-	-	6.88	-
15	5.33[a]	6.65	-	8.01[b]	6.88	-
16	6.57	6.65	6.78	8.96	8.71	8.67
17	6.92	6.84	6.70	9.00	9.15	9.18
18	5.00	4.84	4.81	6.85	6.89	6.90
19	-	4.84	-	9.37	8.71	8.58
20	-	4.84	-	9.41	9.15	9.10
21	-	4.81	-	7.42	7.10	6.68
22	-	5.95	-	7.34	7.65	8.09

[a]Not included in the derivation of eq 3.

[b]Not included in the derivation of eq 4.

red to any other group. Other group is mostly benzoxy group, which is slightly flexible as compared to the phenoxy group, and this flexibility of benzoxy group might be responsible for its inferior effect.

However, $I_{2,OPh}$ does not appear in equation (4), suggesting that phenoxy substituents have to play no role for MMP-13 inhibition. On the other hand, another indicator variable, I_1, has appeared, which stands for $R^1 = OCH_3$. Its value is 1 for $R^1 = OCH_3$ and zero for $R^1 = OH$. A negative coefficient of it suggests that as compared to OH group, a methoxy group at R^1 will not be advantageous. This might be due to any steric effect produced by it, or its inability to form any hydrogen bond with the receptor, which might be possible with the OH group.

As discussed above, we find that there are some variations in the effect of substituents at the aryl moiety in R^2-group in **2** and in equivalent ZR^1-group in **1**. The reason of this may be the diffference in the bridge groups present in the two between their pyran and the aryl rings.

However, as for compounds of Table **1**, equations (3) and (4) suggest that for the series of compounds of Table **2** also a selectivity can be provided for MMP-13 by controlling the hydrophobic properties of the R^2-substituents. If the hydrophobic property of 4-position substituent is kept very low

(less than 0.26), it would not be beneficial to MMP-1 inhibition but would be conducive to MMP-13 inhibition. Further, the activity of compounds against MMP-13 versus MMP-1 can be increased by increasing the hydrophobic property of 2-position substituent.

However, all the above conclusions drawn for either series are based on limited number of data points. Therefore, an extension of these series is required for detailed study. The present QSAR study would be of great value for further synthesis of active compounds.

All equations (1) to (4) exhibit very significant correlations and have very good predictive value, as all of them have r^2_{cv} values 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 behaviours. 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 assumed may be the experimental error, or the conformational behavior of the enzymes, or the metabolism.

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