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A quantitative structure-activity relationship study on matrix metalloproteinase inhibitors: Piperidine sulfonamide aryl hydroxamic acid analogs

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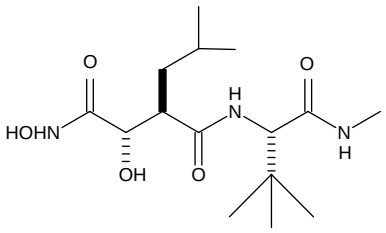
Abstract

A quantitative structure-activity relationship (QSAR) study has been made on a series of piperidine sulfonamide aryl hydroxamic acid analogs acting as matrix metalloproteinase (MMP) inhibitors. The inhibitory potencies of the compounds against two MMPs, MMP-2 and MMP-13, are found to be significantly correlated with the hydrophobic properties of the molecules, suggesting that in both enzymes the hydrophobic interaction is playing a dominant role.

Keywords: *Quantitative structure-activity relationship (QSAR), matrix metalloproteinase (MMP), inhibitors, piperidine sulfonamide aryl hydroxamic acids*

Introduction

Matrix metalloproteinases (MMPs) are a large family of zinc endopeptidases that are able to degrade and remodel elements of the extracellular matrix (ECM) [1,2]. An imbalance caused by overexpression and activation of these MMPs results 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 [14,15], chronic obstructive pulmonary disease (COPD) [16–19] and a host of others. Therefore, a study of the inhibition of MMPs has become of great interest and recently led to the development of some potent inhibitors such as marimastat (**1**), Ro-32-3555 (**2**), CGS-27023A (**3**) and AG-3340 (**4**).



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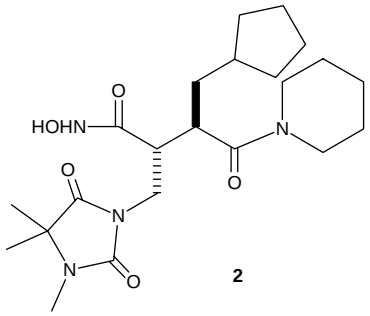

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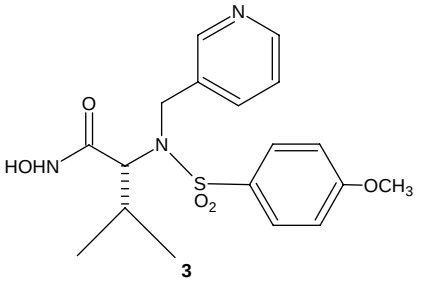

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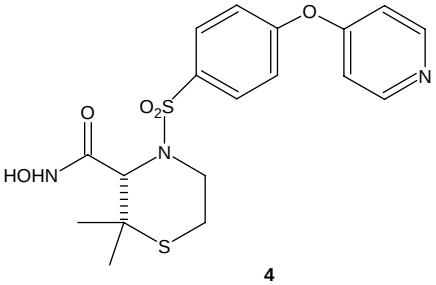

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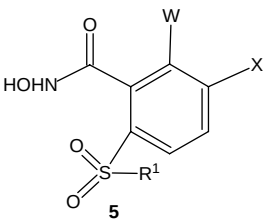
Recently around 25 mammalian zinc-containing enzymes have been isolated, of which many are of current therapeutic interest, e.g., the selective inhibition of MMP-13 [20] and aggrecanase [21] may have therapeutic benefit in osteoarthritis without causing any side effects, and the inhibition of MMP-2 may be valuable for preventing tumor metastasis [22].

In order to provide a rationale to the design of inhibitors of such an important class of enzymes, QSAR studies on their existing inhibitors became of paramount importance. In the present communication, in continuation of our previous studies, we report a QSAR study on some specific piperidine sulfonamide aryl hydroxamic acid analogs, an important class of MMP inhibitors.

Materials and methods

The compounds for the study here have been taken from Barta et al. [23,24]. These compounds are piperidine sulfonamide aryl hydroxamic acid analogs (**5**). In two consecutive studies, Barta et al. in fact reported studies on two different series, **6** and **7**, which structurally were not different from each other and could be represented by the general structure **5**. This allowed us to make a detailed study on the effect of structural variation.



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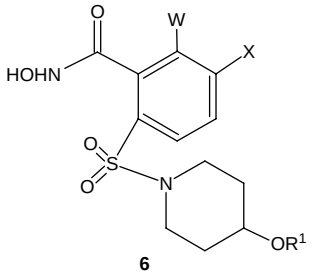

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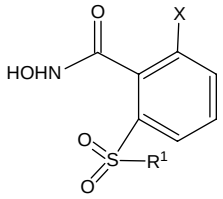

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The complete series comprising **5** is listed in Table I along with their physicochemical properties that were found relevant in formulating a QSAR for them. The most important physicochemical property that was found to be correlated with their activities was the calculated hydrophobicity parameter ClogP, obtained using the software on www.daylight.com. We tried to use several other properties, but they were found to be of no consequence. Rather, some indicator variables were found to be useful which could account for the effects of some specific structural features of the compounds. These indicator variables are defined in the text as and when they appear. Table II lists the inhibition potencies of the compounds – observed as well as calculated from the correlations obtained – against two very important MMPs, MMP-2 and MMP-13 studied by Barta et al. [23,24]. In this Table, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzymes.

Results and discussion

The QSARs obtained for the piperidine sulfonamide aryl hydroxamic acid analogs (**5**) were as follows:

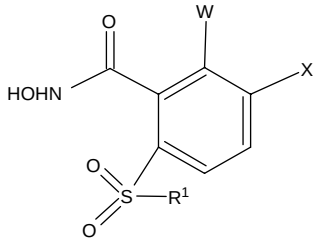
MMP-2

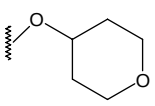
$$\log(1/IC_{50}) = 3.528(\pm 2.400)\text{ClogP} - 0.894(\pm 0.592)(\text{ClogP})^2 + 1.975(\pm 0.458)I_1 - 1.352(\pm 0.711)I_{1N} + 3.860(\pm 2.162)$$

$$n = 22, r^2 = 0.916, r^2_{cv} = 0.82, s = 0.42,$$

$$F_{4,17} = 46.66(4.67), [\text{ClogP}_o = 1.97] \quad (1)$$

Table I. A series of piperidine sulfonamide aryl hydroxamic acid analogs (**5**) and related physicochemical parameter(s)



Compd	W	X	R^1	ClogP	I_1	I_{1N}
1	OCH_3	OCH_3	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.520	1	0
2	OCH_3	OCH_3	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-O-CF_3$	2.590	1	0
3	OCH_3	OCH_3	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-2-O-CH_3$	1.130	0	0
4	OCH_3	OCH_3	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-3-O-CH_3$	1.480	0	0
5	OCH_3	OCH_3	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-O-CH_3$	1.480	1	0
6	OCH_3	OCH_3	$-(N[(CH_2)_2]_2CH)-O-C_6H_5$	1.390	0	0
7	OCH_3	OCH_3	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-Cl$	2.250	1	0
8	OCH_3	OCH_3	$-(N[(CH_2)_2]_2CH)-O-$piperonyl	1.430	0	0
9	$-OCH_2O-$		$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.970	1	0
10	$-OCH_2O-$		$-(N[(CH_2)_2]_2CH)-O-$piperonyl	1.810	0	0
11	$-OCH_2CH_2O-$		$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.930	1	0
12	F	H	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.670	1	0
13	Cl	H	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.820	1	0
14	$O(CH_2)_2-O-CH_3$	H	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.780	1	0
15		H	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.520	1	0
16	OCH_3	H	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.390	1	0
17	H	H	$-(N[(CH_2)_2]_2CH)-CH_2-C_6H_5$	2.940	0	0
18	H	H	$-(N[(CH_2)_2]_2CH)-C_6H_5$	2.410	0	0
19	H	H	$-(N[(CH_2)_2]_2CH)-O-CH_2-C_6H_4-4-CF_3$	2.360	0	0
20	H	H	$-NH-C_6H_4-O-C_6H_5$	2.400	0	1
21	H	H	$-(N[(CH_2)_3]CH_2)-NH-C(O)-C_6H_4-4-OCH_3$	1.080	0	1
22	H	H	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.870	1	0
23	H	H	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-OCF_3$	2.940	1	0
24	H	H	$-(N[(CH_2)_3]CH_2)-O-C_6H_4-4-CF_3$	2.930	0	0
25	H	H	$-(N[(CH_2)_2]_2N)-C(O)-C_6H_5$	0.922	0	0
26	H	H	$-(N[(CH_2)_2]_2CH)-O-C_6H_4-4-CF_3$	2.670	1	0

MMP-13

$$\log(1/IC_{50}) = 5.485(\pm 2.130)\text{ClogP} - 1.334(\pm 0.519)(\text{ClogP})^2 + 1.866(\pm 0.406)I_1 + 1.280(\pm 1.945) \quad (2)$$

$$n = 22,\ r^2 = 0.910,\ r^2_{cv} = 0.86,\ s = 0.38,$$

$$F_{4,17} = 60.61(4.67),\ [\text{ClogP}_o = 2.05]$$

In these equations, n is the number of data points, r^2 is the square of 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 parentheses the figures 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 intercept.

Both Equations (1) and (2) are seen to express highly significant correlations between the inhibitory potencies and the hydrophobic properties of the molecules. Both equations are almost parallel and exhibit parabolic correlation in ClogP with an optimum ClogP value equal to 1.97 for MMP-2 (Equation (1)) and 2.05 for MMP-13 (Equation (2)), which are almost identical. This similarity between the two equations leads to suggest that the two enzymes (MMP-2 and MMP-13) interact with this series of

Table II. Observed and calculated MMP inhibitory potencies of compounds in Table 1. Observed activities have been taken from Ref. [23,24].

	log ($1/IC_{50}$)					
	MMP-2			MMP-13		
Compd	Obsd	Calcd, Equation 1	Loo	Obsd	Calcd, Equation 2	Loo
1	8.62	9.05	9.10	8.57	8.43	8.41
2	9.10	8.98	8.96	8.43	8.33	8.32
3	6.48	6.71	6.79	5.60	5.75	5.78
4	7.92	7.12	6.88	6.60	6.44	6.40
5	8.74	9.10	9.24	7.85	8.30	8.47
6	8.96[a]	7.04	–	8.17[b]	6.29	–
7	9.52	9.25	9.18	8.82	8.67	8.64
8	9.00[a]	7.08	–	7.89[b]	6.36	–
9	8.52	8.43	8.41	7.74	7.59	7.55
10	8.96[a]	7.32	–	7.72	6.79	6.50
11	8.85	8.50	8.44	8.11	7.68	7.61
12	8.48	8.88	8.91	7.92	8.21	8.23
13	8.72	8.67	8.67	7.83	7.93	7.94
14	9.00	8.73	8.71	8.37	8.01	7.97
15	8.96	9.05	9.06	8.66	8.43	8.40
16	7.68[a]	8.88	–	6.96[b]	8.21	–
17	6.83	6.50	6.37	6.00	5.79	5.70
18	7.15	7.17	7.17	6.28[b]	6.70	–
19	7.46	7.21	7.12	6.05	6.68	6.80
20	5.46	5.82	6.42	5.05	6.73	6.94
21	5.64	5.27	4.68	5.66	5.62	5.60
22	8.89	8.60	8.56	7.55	7.82	7.85
23	8.70	8.48	8.44	7.48	7.66	7.69
24	5.74	6.52	6.84	5.70	5.82	5.86
25	6.00	6.35	6.66	5.17	5.18	5.18
26	8.48	8.88	8.91	7.91	8.21	8.23

[a] Not included in the derivation of Equation (1); [b] Not included in the derivation of Equation (2).

compounds in a similar manner and that both predominantly involve the hydrophobic interaction. However, since in both the cases, the correlation is parabolic in ClogP, highly hydrophobic molecules may not be conducive to the inhibitory potencies. Since these inhibition potencies have been measured *in vitro*, where there is no intervening hydrophobic-lipophilic barrier, the decrease in the activity with the increase in ClogP value after the optimum value may be attributed to the steric effects of the molecules, which could arise from the misfit of the molecules with the receptor sites.

In both Equations (1) and (2), there is one common indicator variable I_1 which has been used for an R^1-substituent which is a 4-substituted phenoxy piperidinyl group. For this R^1-substituent, I_1 is equal to 1 and for others it is zero. Now almost identical positive coefficient of this variable in both the equations suggests that the presence of such an R^1-substituent is equally conducive to both MMP-2 and MMP-13 inhibition. The only difference between MMP-2 and MMP-13 inhibition is accounted for by the presence of an additional parameter I_{1N} in Equation (1). This parameter has been used for an R^1-substituent that contains an NH moiety (compounds **20** and **21**). The presence of this parameter with a negative coefficient in Equation (1) suggests that an R^1-group with an NH moiety will be detrimental to the potency of the compound against MMP-2. This NH moiety can act as a hydrogen bond donor group, and the corresponding active site in the receptor may also probably be a hydrogen bond donor, requiring a hydrogen bond acceptor in the molecule, so that this NH would be undesirable. The absence of I_{1N} in Equation (2) indicates that such a hydrogen bonding site may not be present in MMP-13. Both Equations (1) and (2) represent highly significant correlations and have very high predictive ability, as in both the value of r^2_{cv} is greater than 0.6. However, in the derivation of both the equations, some compounds were not included because of their aberrant behavior. In Equation (1), such compounds were **6**, **8**, **10** and **16** and in Equation (2) they were **6**, **8**, **16** and **18**. Compounds **6**, **8** and **16** are common in both equations. It means that these three compounds must be behaving in a quite different manner to the other compounds with both enzymes. Another reason may be that the experimental results are in error, or that there has been metabolism. The reasons for compound **10** behaving as an outlier in Equation (1) and for compound **18** in Equation (2) are not obvious.

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