Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 1975–1981

BIOORGANIC & MEDICINAL CHEMISTRY

A Quantitative Structure–Activity Relationship Study of Hydroxamate Matrix Metalloproteinase Inhibitors Derived from Funtionalized 4-Aminoprolines

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Received 30 September 2002; accepted 28 January 2003

Abstract—A quantitative structure–activity relationship (QSAR) study has been made on the inhibitions of some matrix metalloproteinases (MMPs) by functionalized 4-aminoproline based hydroxamates. Attempts have been made to correlate the inhibition potencies of these hydroxamates with Kier's first-order valence molecular connectivity index ($^1\chi^v$) of substituents and electrotopological state (E-state) indices of some atoms. The correlations obtained for the inhibitions of all the enzymes studied, i.e. MMP-1, MMP-2, MMP-3, MMP-7, and MMP-13, were not so uniform, but suggested that in almost all the cases the substituents at the amide nitrogen may be conducive to the activity, though the whole amide group may be sterically unfavourable. Similarly, in most of the cases, the substituens at the phenyl moiety have been found to be beneficial to the inhibition potency and in many cases an electronic role of SO_2 group of the sulfonylphenyl moiety has been indicated.

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 have been implicated in tissue remodeling at various stages of human development, wound healing, and disease. However, an imbalance caused by over expression 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 metastasis,[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.

Currently, there are 17 known human MMP enzymes, all sharing significant sequence homology. 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-typ-1-MMP (MT1-MMP), and aggrecanase. Although the researchers started taking interest in the development of MMP inhibitors since the early 1980s, the three-dimensional crystal and solution structures of the inhibitors bound to some of the MMPs, for example MMP-1, 3, 7, 8 and MT1-MMP, have come only recentally (since 1994),[17] and this structural data has greatly accelerated the inhibitors development. There are now numerous reviews available on the development of MMP inhibitors.[1,2,17–20]

A number of the MMP inhibitors (MMPIs) have progressed into clinical trials for the cancer, rheumatoid arthritis, and osteoarthritis. The vast majority of them have been hydroxamic acids, such as marimastat (**1**) which is a broad-spectrum inhibitor and was the first to enter the clinical trials for the cancer treatment.[21] However, the progression through these trials has been hampered due to the musculoskeletal syndrome (MSS) which manifests itself as musculoskeletal pain after a few weeks of treatment. This is thought to be due to the inhibition of MMP-1. Consequently, attempts have been directed towards designing the MMPs that do not affect the activity of MMP-1. With this point of view, Natchus et al.[22] recently reported a few series of hydroxamates, as listed in Tables 1–4, derived from functionalized 4-aminoprolines.

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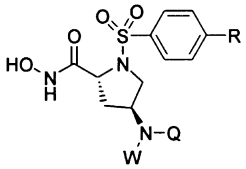
doi:10.1016/S0968-0896(03)00069-5

Table 1. A series of substituted amines and different structural variables



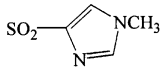
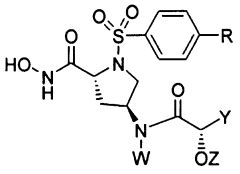
No.	Q	W	R	$^1\chi^v_N$	$^1\chi^v_R$	S_S
1	H	H	OCH_3	0.000	0.612	−5.304
2	H	H	O^{n}Bu	0.000	2.200	−5.340
3	$(CH_2)_2CH_3$	H	OCH_3	1.561	0.612	−5.321
4	$(CH_2)_2Ph$	H	OCH_3	2.961	0.612	−5.399
5	SO_2CH_3	H	OCH_3	2.836	0.612	−5.545
6	SO_2CH_3	H	O^{n}Bu	2.836	2.200	−5.601
7	SO_2CH_3	H	O-4-Pyr	2.836	2.169	−5.673
8	SO_2CH_3	CH_3	OCH_3	3.219	0.612	−5.569
9	SO_2CH_3	CH_2-3-Pyr	OCH_3	5.202	0.612	−5.677
10	SO_2CH_3	$CH_2CH_2CH_3$	OCH_3	4.295	0.612	−5.602
11	SO_2-*p*-$C_6H_4OCH_3$	H	OCH_3	4.658	0.612	−5.676
12		H	O^{n}Bu	3.958	2.200	−5.694
13	CO-*p*-Ph-Ph	H	OCH_3	4.686	0.612	−5.599
14	$CONHCH_3$	H	OCH_3	1.204	0.612	−5.480
15	CO^{i}Pr	CH_2-3-Pyr	OCH_3	4.301	0.612	−5.613
16	$COCH_2OCH_3$	H	O^{n}Pr	1.505	1.700	−5.529
17	$COCH_2OCH_3$	H	O^{n}Bu	1.505	2.200	−5.539

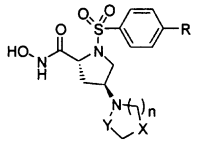
Table 2. A series of lactic acid amide derivatives and different structural variables



No.	W	Y	Z	R	$^1\chi^v_N$	$^1\chi^v_R$	S_S
18	H	CH_3	CH_2Ph	OCH_3	4.109	0.612	−5.656
19	H	CH_2Ph	CH_2Ph	OCH_3	6.204	0.612	−5.732
20	^{n}Pr	CH_3	H	OCH_3	2.657	0.612	−5.668
21	^{n}Pr	CH_2CH_2Ph	H	OCH_3	5.670	0.612	−5.744
22	H	CH_3	H	O^{n}Pr	1.578	1.700	−5.638
23	H	CH_3	H	O^{n}Bu	1.578	2.200	−5.647
24	H	^{i}Pr	H	O^{n}Bu	2.489	2.200	−5.676
25	H	CH_2-^{i}Pr	H	O^{n}Bu	2.972	2.200	−5.682

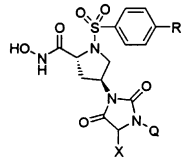
All these compounds were studied for the inhibition of five MMPs including MMP-1 to understand the structural modifications which might deliver the appropriate inhibitory profile that can slow the progress of osteoarthritis while minimizing or eliminating the occurrence of MSS through minimizing the inhibition of MMP-1. Such an understanding, however, can be had better from a quantitative structure–activity relationship (QSAR) study of these compounds. We therefore report here a QSAR study on all four series of hydroxamate inhibitors (Tables 1–4) studied by Natchus et al.[22]

Table 3. A series of MMP inhibitors containing heterocyclic scaffolds and different structural variables

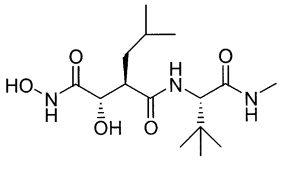


No.	*n*	Y	X	R	$^1\chi^v_N$	$^1\chi^v_R$	S_S
26	2	CH_2	CH_2	OMe	2.633	0.612	−5.561
27	2	CH_2	CH_2	O^{n}Pr	2.633	1.700	−5.587
28	2	CH_2	CH_2	^{n}Pent	2.633	2.561	−5.542
29	2	CH_2	CH_2	OPh	2.633	2.319	−5.659
30	2	CH_2	O	OMe	2.210	0.612	−5.593
31	2	CH_2	O	O^{n}Pr	2.210	1.700	−5.619
32	2	CH_2	O	O^{n}Bu	2.210	1.782	−5.628
33	2	CH_2	O	O^{n}Pent	2.210	2.561	−5.573
34	2	CH_2	O	OPh	2.210	2.319	−5.690
35	2	CH_2	SO_2	OMe	4.364	0.612	−5.707
36	2	CH_2	SO_2	O^{n}Bu	4.364	1.782	−5.743
37	1	CH_2	CH_2	O^{n}Pr	2.133	1.700	−5.571
38	1	CH_2	CH_2	O-4-C_6H_4F	2.133	2.419	−5.701
39	1	CH_2	CH_2	OPh	2.133	2.319	−5.642
40	1	SO_2	CH_2	OMe	3.729	0.612	−5.783
41	1	SO_2	CH_2	O^{n}Pr	3.729	1.700	−5.809
42	1	SO_2	CH_2	O^{n}Bu	3.729	1.782	−5.819

Table 4. A series of MMP inhibitors containing hydantoin moieties and different structural variables



No.	Q	X	R	$^1\chi^v_N$	$^1\chi^v_R$	S_S
43	CH_3	H	OMe	2.196	0.612	−5.857
44	CH_3	H	OEt	2.196	1.200	−5.872
45	CH_3	H	O^{n}Pr	2.196	1.200	−5.884
46	CH_3	H	O^{n}Bu	2.196	1.782	−5.893
47	CH_3	H	$OCH_2CH(CH_3)_2$	2.196	2.056	−5.901
48	CH_3	H	$OCH_2CH_2OCH_3$	2.196	1.690	−5.918
49	CH_3	H	Oph	2.196	2.319	−5.955
50	CH_3	H	O-4-Pyr	2.196	2.169	−5.965
51	H	SCH_3	O^{n}Bu	3.614	1.782	−5.865
52	H	$(CH_3)_2$	O^{n}Bu	2.829	1.782	−5.887
53	$CH_2CH{=}CH_2$	H	O^{n}Pr	2.882	1.700	−5.921
54	$CH_2CH{=}CH_2$	H	O^{n}Bu	2.882	1.782	−5.931
55	$CH_2CH{=}CH_2$	H	$OCH_2CH_2OCH_3$	2.882	1.690	−5.955
56	$CH_2CH_2CH_3$	H	O^{n}Bu	3.272	1.782	−5.915
57	$CH_2CH_2CH_3$	H	$OCH_2CH_2OCH_3$	3.272	1.690	−5.939



1 (Marimastat)

Materials and Method

As stated above, all the compounds for QSAR analysis have been taken from the communication of Natchus et

al.[22] All these compounds are listed in Tables 1–4. The observed IC_{50} (in log terms) reported in Tables 5–8 refer to the molar concentration of the compound leading to 50% inhibition of the binding of the MMPs with the fluorogenic substrate Mca-Pro-Leu-Gly-Leu-DPa-Ala-Arg-NH_2 at a concentration of 4 μM at 25 °C.

The attempt has been made to correlate the inhibition activities of the compounds with Kier's first-order valence molecular connectivity index ($^1\chi^v$) of substituents/molecules[23] and the electrotopological state (E-state) indices (S_i) of the atoms.[24,25] The $^1\chi^v$ signifies the degree of branching, connectivity of atoms, and the unsaturation in the molecule, and in a number of cases it has been found to be significantly correlated with the hydrophobic property of the molecules.[23] Similarly, E-state index (S_i) of an atom is a measure of the availability of the π and lone pair electrons on the atom. The more electronegative atoms or groups have a richer content of π and lone pair electrons, giving rise to a higher calculated value of S_i. The regression analysis has been performed using a self-generated QSAR software.

Table 5. Observed and calculated MMP inhibition potencies of compounds of Table 1

No.	log (1/K_i)									
	MMP-1		MMP-2		MMP-3		MMP-7		MMP-13	
	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
		eq 6		eq 7		eq 8		eq 9		eq 10
1	6.60	6.60	8.22	8.37	7.64	7.77	5.37	5.44	8.30	8.33
2	6.42	6.15	—	8.37	8.10	7.88	—	5.37	—	8.93
3	6.82	6.60	—	8.68	7.06	7.17	5.66	5.68	8.30	8.43
4	6.25	6.60	9.00	8.97	7.24	7.01	5.85	5.78	9.00[e]	8.52
5	6.59	6.60	8.70	8.94	7.38	7.47	5.57	5.49	8.70	8.52
6	5.89	6.15	9.10	8.94	7.80	7.63	5.41	5.38	9.16	9.12
7	6.35	6.15	—	8.94	7.66	7.85	—	5.25	9.10	9.11
8	7.72	7.35	—	9.02	8.22	8.12	6.28[d]	5.51	9.30	9.08
9	7.13	7.35	8.70[b]	9.42	8.22	8.29	5.57	5.66	9.00	9.21
10	7.48	7.35	9.10	9.24	8.00	8.09	6.04[d]	5.65	9.10	9.15
11	6.46	6.60	8.52[b]	9.31	7.44	7.63	5.52	5.56	8.70	8.64
12	6.16	6.15	—	9.17	8.22[c]	7.72	—	5.40	—	9.19
13	—	6.60	—	9.32	6.40[c]	7.39	—	5.71	—	8.63
14	5.51[a]	6.60	—	8.61	6.52[c]	7.76	—	5.32	7.57[e]	8.41
15	5.57[a]	7.35	8.66[b]	9.24	8.00	8.12	—	5.61	7.77[e]	9.14
16	6.30	6.29	—	8.67	7.52	7.80	—	5.28	8.52	8.84
17	5.92	6.15	—	8.67	7.85	7.83	5.31	5.27	9.16	9.03

[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.
[e]Not included in the derivation of eq 10.

Table 6. Observed and calculated inhibition potencies of compounds of Table 2

No	log (1/K_i)									
	MMP-1		MMP-2		MMP-3		MMP-7		MMP-13	
	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
		eq 6		eq 7		eq 8		eq 9		eq 10
18	6.85	6.60	9.52	9.20	8.16[c]	7.60	—	5.91	—	8.60
19	6.62	6.60	9.70	9.63	8.00	7.87	—	6.13	8.70	8.74
20	7.06	7.35	9.15	8.91	8.70	8.53	5.07[d]	5.63	9.00	9.04
21	6.58[a]	7.35	9.22	9.52	7.92[c]	8.46	—	6.02	9.30	9.24
22	6.85[a]	6.29	—	8.69	8.10	8.09	5.46	5.50	9.00	8.85
23	5.92	6.15	—	8.69	8.00	8.12	5.38	5.48	9.05	9.04
24	6.57[a]	6.15	—	8.87	8.10	7.94	5.77	5.59	9.10	9.09
25	6.36	6.15	—	8.97	8.00	7.84	5.62	5.66	9.05	9.13

[a–e]See footnotes of Table 5.

Table 7. Observed and calculated MMP inhibition potencies of compounds of Table 3

No.	log (1/K_i)									
	MMP-1		MMP-2		MMP-3		MMP-7		MMP-13	
	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
		eq 11		eq 12		eq 13		eq 14		eq 15
26	6.55	7.00	8.22	8.16	7.32[b]	8.06	5.13	5.23	9.00	9.17
27	6.68	6.39	—	8.21	8.05	8.07	6.21[c]	5.29	9.40	9.19
28	5.70[a]	9.40	—	8.12	7.92	8.07	5.01[c]	6.46	9.05	9.16
29	7.77	7.68	—	8.35	8.10	8.07	6.22	6.21	—	9.25
30	6.66	6.82	8.22	8.32	7.85	8.12	—	5.07	—	9.09
31	6.31	6.21	—	8.37	8.16	8.12	4.78	5.13	9.00	9.11
32	6.04	6.30	8.40	8.39	8.30	8.12	5.27	5.22	9.22	9.12
33	5.70[a]	9.22	—	8.28	7.92	8.12	5.13[c]	6.30	9.16	9.07
34	7.72	7.50	—	8.51	8.16	8.12	6.15	6.05	—	9.17
35	6.52	6.17	—	8.07	7.64	7.83	5.15	5.36	9.00	9.03
36	—	5.65	8.15	8.14	7.92	7.83	5.47	5.51	9.05	9.06
37	6.51	6.48	—	8.29	8.10	8.13	5.06	4.99	9.00	9.05
38	7.70	7.85	—	8.54	8.40	8.13	6.07	6.20	—	9.15
39	7.72	7.78	—	8.43	8.30	8.13	6.10	5.91	—	9.10
40	7.38	7.18	—	8.36	7.89	7.92	5.85	5.74	9.40	9.32
41	7.00	6.57	—	8.41	8.10	7.92	6.08	5.80	—	9.33
42	6.64	6.66	—	8.43	7.89	7.92	6.17	5.89	—	9.34

[a]Not included in the derivation of eq 11.
[b]Not included in the derivation of eq 13.
[c]Not included in the derivation of eq 14.

Table 8. Observed and calculated inhibition potencies of compounds of Table 4

No.	log (1/K_i)									
	MMP-1		MMP-2		MMP-3		MMP-7		MMP-13	
	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
		eq 11		eq 12		eq 13		eq 14		eq 15
43	6.70	6.76	—	8.84	8.10	8.12	5.75	5.54	9.30	9.30
44	6.24	5.88	—	8.87	7.48[c]	8.12	5.13	5.36	8.40[e]	9.31
45	6.59[a]	5.81	—	8.89	8.05	8.12	5.59	5.38	9.52	9.32
46	6.04	6.24	—	8.91	8.70[c]	8.12	5.80	5.69	9.52	9.33
47	6.52	6.85	—	8.92	8.52[c]	8.12	5.64	6.02	8.55[e]	9.33
48	5.75	5.94	9.00	8.96	7.59	7.56	5.04	4.73	8.36	8.47
49	7.68	7.44	—	9.03	8.22	8.12	6.51	6.52	—	9.37
50	6.22[a]	6.85	—	9.05	7.96	8.12	5.13[d]	6.30	9.15	9.38
51	6.13	6.40	7.31[b]	8.55	7.38[c]	7.93	6.07	5.99	—	9.40
52	6.11	6.27	8.70	8.76	8.52[c]	8.04	6.35	5.97	—	9.46
53	6.46[a]	5.94	9.10	8.82	7.96	8.03	5.59	5.98	9.40	9.49
54	6.32	6.02	—	8.83	8.16	8.03	6.00	6.07	9.40	9.50
55	5.54	5.73	8.70	8.88	7.34	7.47	4.96	5.10	8.70	8.65
56	6.24	6.12	9.40[b]	8.72	8.00	7.98	5.92	6.10	9.52	9.49
57	5.60	5.82	8.70	8.77	7.52	7.42	4.96	5.13	8.70	8.64

[a–e]Not included in the derivation of eqs 11–15, respectively.

Calculation of $^1\chi^v$ and S_i

$^1\chi^v$ is calculated according to the equation:

$$^1\chi^v = \Sigma\left(\delta_i^v \delta_j^v\right)^{-1/2} \quad (1)$$

where δ_i^v and δ_j^v are the vertex connectivity indices of atoms i and j, respectively, and the summation extends to all bonded pairs of non-hydrogenic atoms in the group or molecule. For the second and third rows of atoms, a unified definition of δ^v, as expressed by eq 2, was given.[26] In this equation, Z_i^v is the number of valence electrons of atom i, h_i is the number of hydrogen atoms attached to it, and Z_i is its atomic number.

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

To calculate the E-state of an atom i (S_i), we first define the intrinsic state of that atom, I_i, as

$$I_i = \left(\delta_i^v + 1\right)/\delta_i \quad (3)$$

where δ_i is the σ electron count on the atom i. Then a factor ΔI_i is defined as

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

where n refers to the number of atoms in the path i to j including both i and j.[24] I_i and ΔI_i are then used to find the value of S_i according to the equation

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

Now, using these procedures, the values of $^1\chi^v$ and S_i were calculated for the series of compounds treated. All calculations were made manually.

Results and Discussion

If we look at Tables 1 and 2, we find that the two series of compounds differ only with respect to the nature of Q moiety attached to the nitrogen of the amide group present at the 4-position. In Table 2, all the compounds have Q that contains carbonyl group, while a very few compounds in Table 1 have Q that contains carbonyl group. The Q in most of the cases in Table 1 has sulfonyl group. We have calculated $^1\chi^v$ for the whole 4-amide group in both the series ($^1\chi_N^v$) and that of R-substituent of the phenyl ring ($^1\chi_R^v$). Both the series were then combined and the following correlations were obtained for the inhibition of the various MMPs with the use of activity data as given in Tables 5 and 6.

MMP-1

$$\log(1/IC_{50}) = 6.775(\pm0.268) - 0.286(\pm0.166)^1\chi_R^v + 0.748(\pm0.309)I_W$$
$$n = 19,\ \ r = 0.901,\ \ R_A^2 = 0.79,$$
$$r_{cv}^2 = 0.63,\ \ s = 0.23,\ \ F_{2,16} = 34.71(6.23) \quad (6)$$

MMP-2

$$\log(1/IC_{50}) = 8.369(\pm0.414) + 0.202 \times (\pm0.106)^1\chi_N^v$$
$$n = 9,\ \ r = 0.863,\ \ R_A^2 = 0.71,$$
$$r_{cv}^2 = 0.56,\ \ s = 0.23,\ \ F_{1,7} = 20.46(12.25) \quad (7)$$

MMP-3

$$\log(1/IC_{50}) = -0.501(\pm0.206)^1\chi_N^v + 0.050(\pm0.029) \times \left(^1\chi_N^v\right)^2 + 0.656(\pm0.218)I_W - 2.946 \times (\pm0.945)S_S - 7.850(\pm5.066)$$
$$n = 20,\ \ r = 0.916,\ \ R_A^2 = 0.80,$$
$$r_{cv}^2 = 0.65,\ \ s = 0.18,\ \ F_{4,15} = 19.58(4.89) \quad (8)$$

MMP-7

$$\log(1/IC_{50}) = 0.175(\pm0.084)^1\chi_N^v + 1.863 \times (\pm0.982)S_S + 0.405(\pm0.234)I_W + 15.319(\pm5.224)$$
$$n = 12,\ \ r = 0.866,\ \ R_A^2 = 0.66,$$
$$r_{cv}^2 = 0.47,\ \ s = 0.10,\ \ F_{3,8} = 8.01(7.59) \quad (9)$$

MMP-13

$$log(1/IC_{50}) = 8.098(\pm0.269) + 0.065(\pm0.054)^1\chi_N^v + 0.379(\pm0.124)^1\chi_R^v + 0.535 \times (\pm0.211)I_W$$
$$n = 18,\ \ r = 0.900,\ \ R_A^2 = 0.77,$$
$$r_{cv}^2 = 0.72,\ \ s = 0.15,\ \ F_{3,14} = 19.87(5.56) \quad (10)$$

In these correlations, an indicator variable I_W has been used for W-substituent. If W = H, $I_W = 0$, otherwise $I_W = 1$. In each equation, n refers to the number of data points, r is the correlation coefficient, s is the standard deviation, F is the F-ratio between the variances of calculated and the observed activities, and the figures within parentheses with ± sign are 95% confidence intervals. R_A^2 is the adjusted value of r^2 defined as $R_A^2 = r^2(1-1/F)$. R_A^2 is also known as explained variance (EV), which, when multi-

plied by 100, gives what per cent of the variance in activity can be accounted for by the equation. The r^2_{cv} is the square of cross-validated correlation coefficient obtained from leave-one-out jacknife procedure. This gives the predictive ability of the equation. Its value equal to or greater than 0.60 indicates a good predictive ability of the equation.

Now the presence of I_W with positive coefficient in all the equations, except in eq 7, suggests that the presence of a substituent at the amide nitrogen would be beneficial to the activity. It is also to be noted that in all the equations I_W has almost equal weightage indicating that all the enzymes, except MMP-2, might have identical active site to accommodate the W-substituent. However, the whole amide group does not appear to behave identically with all the enzymes. In MMP-2, MMP-7 and MMP-13 (eqs. 7, 9 and 10), its connectivity index ($^1\chi^v_N$) appears to have always a positive effect on the inhibition, but in MMP-3 (eq 8), its initial effect is detrimental till it attains a value of 5.01, which is quite high. Thus a large amide group does not seem to be preferred by MMP-3. In MMP-1, it was not found to have any effect (eq 6). As far as the substituent R at the phenyl ring is concerned, its connectivity index $^1\chi^v_R$ is found to produce a detrimental effect on the inhibition of MMP-1 (eq 6) but a beneficial effect on MMP-13 inhibition (eq 10). On the inhibition of other enzymes, $^1\chi^v_R$ was found to have no effect.

An E-state index S_S is found to be important only in the case of MMP-3 and MMP-7 inhibitions (eqs 8 and 9), but its coefficients have sign opposite to each other in these two cases. The S_S refers to the availability of π or lone pair electrons on the sulfur atom. Its negative coefficient in eq 8 suggests that an increase in the value of S_S would decrease the activity. One may assume that sulfur atom might be facing some negatively charged site in MMP-3, thus undergoing a charge–charge repulsive interaction. However, its positive coefficient in eq 9 leads to assume that in the case of MMP-7 it may not be sulfur atom but the two oxygen atoms attached to it that might have the opportunity to form the hydrogen bonds with the receptor. It has been pointed out in many studies that SO_2 of the inhibitor may be involved in strong hydrogen bonding with amino acid residues from the active site cleft of the enzyme. In SO_2, sulfur itself may not participate in the hydrogen bondings, but it can enhance the participation of the two oxygen atoms by donating them a major share of the lone pairs of electrons, now forming the coordinate bonds. This leads to the development of partial negative charges on the oxygen atoms, to the extent they attract the lone pairs of sulfur, and this makes them capable of forming the hydrogen bonds. The strength of hydrogen bonds will depend on the partial negative charges developed on them. An attempt was made to account for the effect of an SO_2 group vis-à-vis a carbonyl group present in the Q moiety of the amide group, but nothing specific came out.

A similar correlation analysis was performed on the two series as listed in Tables 3 and 4. In these series the amide moiety forms a cyclic structure that has a carbonyl group on both sides of the nitrogen in series of Table 4 but not in the series of Table 3. For a combine of Tables 3 and 4, the following correlations were obtained with the use of activity data as given in Tables 7 and 8.

MMP-1

$$\begin{aligned}\log(1/IC_{50}) &= -4.721(\pm1.093)^1\chi^v_R + 1.858 \\ &\times (\pm0.387)\left(^1\chi^v_R\right)^2 + 5.678 \\ &\times (\pm2.511)S_S + 1.444(\pm0.712)I_Y \\ &+ 42.213(\pm14.811) \\ n &= 26,\quad r = 0.933,\quad R^2_A = 0.85, \\ r^2_{cv} &= 0.78,\quad s = 0.27, F_{4,21} = 35.36(4.37)\end{aligned} \tag{11}$$

MMP-2

$$\begin{aligned}\log(1/IC_{50}) &= -1.965(\pm0.823)\ S_s - 0.217 \\ &\times (\pm0.195)^1\chi^v_N - 2.195(\pm4.679) \\ n &= 9,\quad r = 0.926,\quad R^2_A = 0.81, \\ r^2_{cv} &= 0.76,\quad s = 0.15, \\ F_{2,6} &= 18.18(10.92)\end{aligned} \tag{12}$$

MMP-3

$$\begin{aligned}\log(1/IC_{50}) &= 7.864(\pm0.278) - 0.137(\pm0.080)^1\chi^v_N \\ &+ 0.561(\pm0.177)I_R \\ n &= 26,\quad r = 0.843, \\ R^2_A &= 0.69,\quad r^2_{cv} = 0.63,\quad s = 0.14, \\ F_{2,23} &= 28.27(5.66)\end{aligned} \tag{13}$$

MMP-7

$$\begin{aligned}\log(1/IC_{50}) &= 1.843(\pm1.541)^1\chi^v_N - 0.274(\pm0.247) \\ &\times \left(^1\chi^v_N\right)^2 - 1.709(\pm1.025)1\chi^v_R + 0.743 \\ &\times (\pm0.348)\left(^1\chi^v_R\right)^2 - 1.811(\pm0.931)Ss \\ &+ 0.928(\pm0.346)I_R - 7.950(\pm5.200) \\ n &= 27,\quad r = 0.903,\quad R^2_A = 0.76, \\ r^2_{cv} &= 0.68,\quad s = 0.25,\quad F_{6,20} = 14.71(3.87)\end{aligned} \tag{14}$$

MMP-13

$$\begin{aligned}\log(1/IC_{50}) &= 1.158(\pm0.964)^1\chi^v_N - 0.187(\pm0.151) \\ &\times \left(^1\chi^v_N\right)^2 - 0.799(\pm0.487)Ss + 0.871 \\ &\times (\pm0.213)I_R + 2.102(\pm3.042) \\ n &= 20,\quad r = 0.915,\quad R^2_A = 0.79, \\ r^2_{cv} &= 0.73,\quad s = 0.14,\quad F_{4,15} = 19.38(4.89)\end{aligned} \tag{15}$$

From these correlations, the E-state index S_S is found to be important in the inhibition of all the enzymes but the MMP-3. Its positive coefficient in MMP-1 (eq 11) suggests, as already discussed in connection to eq 9, a possible involvement of oxygen atoms of SO_2 group in the hydrogen bonding with the receptor. In other cases, its negative coefficient indicates the charge–charge repulsive interaction of the sulfur atom with the receptors. The cyclic amide groups in these series appears to have predominantly detrimental effect either for all values of $^1\chi^v_N$ as in MMP-2 (eq 12) and MMP-3 (eq 13) or after an optimum value of $^1\chi^v_N$ as in MMP-7 (eq 14) and MMP-13 (eq 15). For both MMP-7 and MMP-13, the $(^1\chi^v_N)_{opt}$ is almost same, i.e., 3.363 and 3.096, respectively. This detrimental effect of amide groups may be due to their steric roles. The MMP-1 inhibition, however, was not found to be affected by the amide groups. This was also the case for MMP-1 inhibition in the series of Tables 1 and 2.

As far the effect of phenyl ring substituents R is concerned, they are again found to have negative effect on MMP-1 and MMP-7 (eq 11) and (eq 14) but only to an optimum value of $^1\chi^v_R$ equal to 1.270 and 1.150, respectively, beyond which they may be beneficial. Both values are essentially identical. In deriving eqs 11–15 some indicator parameters have also been used. In eq 11, I_Y is equal to zero for $Y = CH_2$ and unity for $Y = SO_2$ or CO and I_R in eqs 13–15 is for R-substituents. It has been given a value of one for all R-substituents except $R = OCH_2CH_2OCH_3$ for which it zero. Now its positive coefficient in all three equations suggests that except a substituent of the type $OCH_2CH_2OCH_3$, all other R-substituents at the phenyl ring would be beneficial to the inhibition potency of the compounds against MMP-3, MMP-7 and MMP-13. $OCH_2CH_2OCH_3$ is a lengthy substituent as compared to others and hence its disadvantageous role can be attributed to its length. All other substituents, which are mainly alkoxy groups, have their $^1\chi^v_R$ value higher enough than the optimum value of $^1\chi^v_R$ (1.150–1.270) to be advantageous to the activity. The exception is only OCH_3 group.

The variable I_Y in eq 11 has the positive coefficient suggesting that SO_2 or CO moiety adjacent to nitrogen in amide group may be preferred to a CH_2 moiety. These groups may probably form the hydrogen bonds with the receptor. In deriving some of the equations, a few outliers were excluded as given in the footnotes of Tables 5–8. No specific reasons could be found for the aberrant behaviors of these outliers.

Conclusion

Now the overall picture that has emerged from this study is that the acyclic and cyclic amide groups present at the 4-position of the five-membered cyclic ring in each series of the compounds listed in Tables 1–4 have entirely different effects on the inhibitory activity of the compounds. While the acyclic amide present in compounds of Tables 1 and 2 are found to produce positive effects in the inhibition of most of the MMPs (eqs 7, 9 and 10), the cyclic amide groups in the compounds of Tables 3 and 4 have been found to produce mostly adverse effects (eqs 12–15). However, in the case of MMP-1 inhibition, neither the acylic amide group nor cyclic amide group could be found to produce any effect (eqs 6 and 11). Thus MMP-1 appears to be structurally quite different from other MMPs. In other MMPs, the acyclic amide group might have proper orientation towards the active sites of the enzyme and the cyclic ones might produce steric hindrance, which, of course, in some cases, as in MMP-7 and MMP-13, may be effective only after a particular value of $^1\chi^v_N$ (eqs 14 and 15). The proper orientation of the acyclic amide groups and their interaction with the active sites in the enzyme may be probably the reason that a substituent W at the nitrogen is found to be conductive to the activity.

The R-substituents of the phenyl ring have not been found to play any uniform role, but mostly they have advantageous effects. Finally, the involvement of the sulfonyl group (SO_2) through it sulfur atom or both oxygen atoms in some electronic interactions with the enzymes in most of the cases has been indicated.

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