A quantitative structure–activity relationship study on some series of anthranilic acid–based matrix metalloproteinase inhibitors

ARTICLE *in* BIOORGANIC & MEDICINAL CHEMISTRY · OCTOBER 2005

Impact Factor: 2.79 · DOI: 10.1016/j.bmc.2005.05.055 · Source: PubMed

2 AUTHORS, INCLUDING:

Satya Prakash Gupta
National Institute of Technical Teachers' Tr…

164 PUBLICATIONS **1,265** CITATIONS

SEE PROFILE

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 13 (2005) 5454–5462
Bioorganic & Medicinal Chemistry

A quantitative structure–activity relationship study on some series of anthranilic acid-based matrix metalloproteinase inhibitors

S. P. Gupta[a,*] and S. Kumaran[b]

[a]*Department of Chemistry, Birla Institute of Technology and Science, Pilani 333031, India*
[b]*Department of Pharmacy, Birla Institute of Technology and Science, Pilani 333031, India*

Received 1 December 2004; revised 26 May 2005; accepted 26 May 2005
Available online 1 July 2005

Abstract—A quantitative structure–activity relationship (QSAR) study has been made on four different series of anthranilic acid-based matrix metalloproteinase (MMP) inhibitors, in which two substituted aryl rings, one bearing the hydroxamic acid moiety that binds with the zinc atom of MMPs, are joined through a bridge group of sulfonamide. The QSAR results indicate that the sulfonamide group plays a very important role in the inhibition activity of the inhibitors and that the effectiveness of this sulfonamide group can be increased by the presence at the aryl rings or at the sulfonamide nitrogen itself of nitrogen-containing or some such substituents that can increase the electronic character of the sulfonamide group. The hydrophobic character of the molecules is not found to be of any advantage; rather in most of the cases it is shown to have a detrimental effect, suggesting that MMPs provide little opportunity to the inhibitors to have a any hydrophobic interactions with them. On the other hand, polarizability of the molecules has been found to be conducive to activity in some cases. Thus the inhibition mechanism seems to predominantly involve the electronic interactions between the inhibitors and the enzymes.

1. Introduction

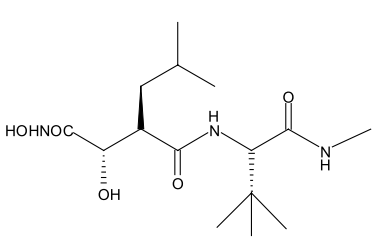
The matrix metalloproteinases (MMPs) are a family of structurally related zinc metalloproteinases that degrade and remodel structural proteins in the extracellular matrix, such as membrane collagens, aggrecan, fibronectin, and laminin.[1,2] They include over 20 zinc-containing enzymes, such as collagenases, 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 evoked great interest.

Of the known human MMP enzymes, 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 when the three-dimensional crystal and the solution structures of the inhibitors bound to some of the MMPs, for example, MMP-1, 3, 7, 8 and MT1-MMP could be studied.[17] There are now numerous reviews available on the development of MMP inhibitors.[1,2,17–20]

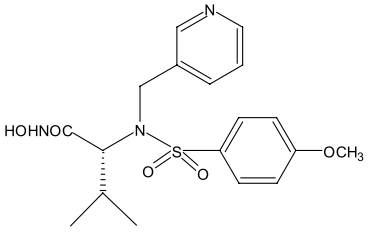
Since the researchers started taking interest in the development of MMP inhibitors, a number of compounds progressed into clinical trials for the cancer, rheumatoid arthritis, and osteoarthritis. The vast majority of them have been hydroxamic acids, such as marimastat (**1**), which is a broad-spectrum inhibitor and was the first to enter the clinical trials for the cancer treatment.[21] The discovery of sulfonamide-based hydroxamic acid inhibitors of stromelysin-1 (MMP-3), exemplified by CGS-27023A (**2**), opened a new vista in the rapidly expanding area of nonpeptide MMP inhibitors.[22] On several series of sulfonamide-based hydroxamic acid inhibitors, we recently made extensive quantitative structure–activity relationship (QSAR) studies in order to analyze the relationships between their structures and their MMP inhibition poten-

Keywords: Anthranilic acids; Matrix metalloproteinase inhibitors; QSAR studies.
* Corresponding author. Tel.:+91 1596 45073; fax:+ 91 1596 44183; e-mail: spg@bits-pilani.ac.in

0968-0896/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2005.05.055



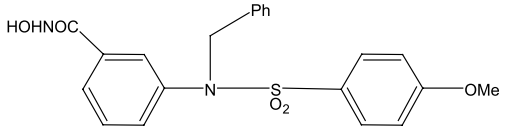
1



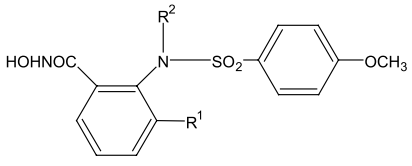
2

cies.[23–26] Sulfur atoms were found to play a very important role in the inhibition potency.

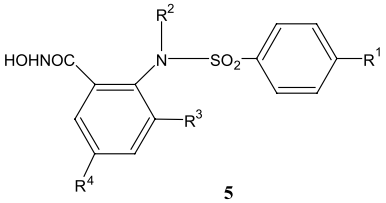
All the sulfonylated hydroxamic acids are, however, derived from α-amino acids, with a single carbon linking the sulfonamide nitrogen and the zinc chelating hydroxamic acid moiety. Some authors, therefore, became interested in studying if novel, potent MMP inhibitors could be made by using an aromatic ring as the linker between the sulfonamide nitrogen and the hydroxamic acid moiety as exemplified by **3**. Levin et al.[27–30] recently reported several series of such compounds with their inhibition potencies against many important MMPs. The following four anthranilic acid-based series (**4**–**7**) were reported by these authors with their inhibition potencies against MMP-1, MMP-9, MMP-13, and TACE (TNF-α converting enzyme). 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 noncovalently bound homotrimer of 17 kDa units. TACE sheds the 26 kDa membrane-bound TNF-α into its soluble forms whose high levels lead 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.[31–34] 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 RA is still to be resolved.



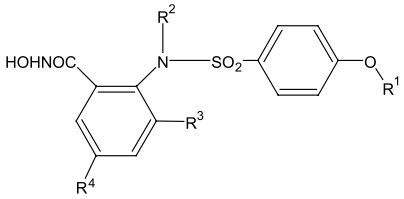
3



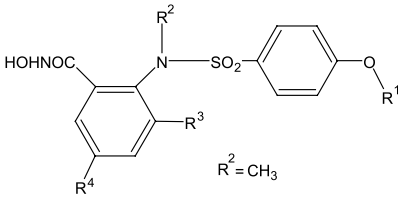
4



5



6



7

In this article, we report a QSAR study on all the four series of MMP inhibitors (**4**–**7**) reported by Levin et al. to describe the relationship between the structure of the compounds and their MMP/TACE inhibition potencies in a quantitative manner.

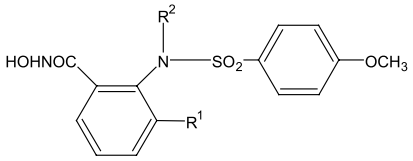
2. Materials and methods

All the four different series of anthranic acid-based MMP inhibitors (**4**–**7**) reported by Levin et al. are listed in Tables 1–4, respectively, along with the physicochemical parameters that were found to be correlated with their MMP inhibition potencies. Their inhibition potencies—the observed ones as well as those calculated from the correlations obtained—are listed in Tables 5–8, respectively. In these tables, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. The most relevant physicochemical parameter that has been found to be relevant in most of the cases is hydrophobic parameter, log *P*, of the molecules. It was calculated using www.daylight.com software freely available at internet. Many other parameters were also calculated and used but they were rarely of any use. However, many indicator variables were used that described the specific roles of some structural features present in the molecules. These parameters are defined as and when they appear in the correlations.

3. Results and discussion

For the compounds of Table 1, the excellent correlations were obtained between the inhibition potencies against all the three MMPs, MMP-1, MMP-9 and MMP-13, as mentioned in Table 5, and the hydrophobicity of the molecule (Eqs. 1–3).

Table 1. Analogs of **4** and their related physicochemical parameters



Compound	R^1	R^2	log *P*
1	H	CH_2Ph	1.681
2	CH_3	CH_2Ph	1.840
3	CH_3	CH_2-3-Py	0.343
4	OCH_3	CH_2Ph	1.711
5	Cl	CH_2Ph	1.784
6	NO_2	CH_2Ph	0.939
7	$N(CH_3)_2$	CH_2Ph	1.905
8	CF_3	CH_2Ph	1.670
9	$OCH_2CONHOH$	CH_2Ph	−0.120
10	$OC(CH_3)_2CONHOH$	CH_2Ph	0.498
11	CO_2CH_3	CH_2-3-Py	0.187

MMP-1

$$\log(1/IC_{50}) = 7.286(\pm0.331) - 2.473(\pm1.279)\log P + 1.098(\pm0.683)(\log P)^2$$

$$n = 7, r = 0.960, r^2_{cv} = 0.80, s = 0.18,$$

$$F_{1,4} = 23.53(21.20), [\log P_o = 1.13]$$

Outliers 2, 10 (1)

MMP-9

$$\log(1/IC_{50}) = 8.525(\pm0.193) - 0.576(\pm0.147)\log P$$

$$n = 10, r = 0.954, r^2_{cv} = 0.86, s = 0.15,$$

$$F_{1,8} = 81.56(11.26)$$

Outlier 1 (2)

MMP-13

$$\log(1/IC_{50}) = 8.699(\pm0.302) - 1.240(\pm0.247)\log P$$

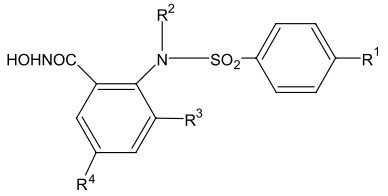
$$n = 9, r = 0.976, r^2_{cv} = 0.92, s = 0.23,$$

$$F_{1,7} = 140.93(12.25)$$

Outlier 2 (3)

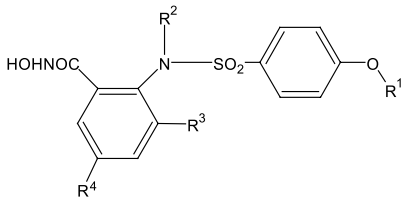
In Eqs. (1)–(3), n is the number of data points, r is the correlation coefficient, r^2_{cv} is the square of cross-validated correlation coefficient obtained by leave-one-out jackknife procedure, s is the standard deviation, and F is the F-ratio between the variances of calculated and observed activities (within parenthesis the figure refers to the F value 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.

Table 2. Analogs of **5** and their related physicochemical parameters



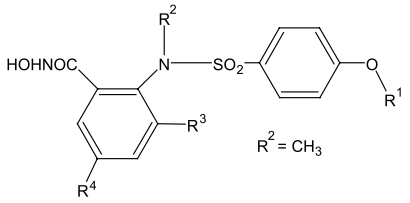
Compound	R^1	R^2	R^3	R^4	log *P*	I_1	I_2	I_3	I_4	$I_{4,Br}$
1	OCH_3	CH_2-3-Py	CH_3	H	0.343	0	1	0	0	0
2	OCH_3	CH_2-3-Py	CH_3	Br	1.426	0	1	0	0	1
3	OCH_3	CH_2-3-Py	CH_3	CH_3	0.842	0	1	0	0	0
4	OCH_3	CH_2-3-Py	CH_3	Ph	2.231	0	1	0	1	0
5	OCH_3	CH_2-3-Py	CH_3	Ph-4-CF_3	3.191	0	1	0	1	0
6	OCH_3	CH_2-3-Py	CH_3	2-Naphthyl	3.405	0	1	0	1	0
7	OCH_3	CH_2-Ph	CH_3	CH_2NEt_2	2.732	0	0	0	0	0
8	OCH_3	CH_2-3-Py	CH_3	$N(CH_3)_2$	0.567	0	1	0	0	0
9	OCH_3	CH_2-3-Py	Ph	CH_3	2.111	0	1	1	0	0
10	OCH_3	CH_2-3-Py	2-Furyl	CH_3	0.285	0	1	1	0	0
11	OEt	CH_2-Ph	CH_3	CH_3	2.868	0	0	0	0	0
12	O-*n*-Bu	CH_2-Ph	CH_3	CH_3	3.926	0	0	0	0	0
13	OCH_2Ph	CH_2-Ph	CH_3	CH_3	4.107	1	0	0	0	0
14	$O(CH_2)_2Ph$	CH_2-Ph	CH_3	CH_3	4.436	0	0	0	0	0
15	Oph	CH_2-Ph	CH_3	CH_3	4.268	0	0	0	0	0
16	OPh-4-*t*Bu	CH_3	CH_3	Br	4.910	0	0	0	0	1
17	O-4-Py	CH_3	CH_3	H	0.504	0	0	0	0	0
18	O-4-Py	CH_3	H	H	0.345	0	0	0	0	0
19	SPh	CH_3	CH_3	CH_3	2.840	0	0	0	0	0
20	OPh-4-OCH_3	CH_2-3-Py	CH_3	H	2.031	0	1	0	0	0
21	Ph-3,4-(-OCH_2O-)	CH_2-3-Py	CH_3	H	2.050	0	1	0	0	0
22	OCH_2Ph	CH_2-Ph	CH_3	Br	3.194	1	0	0	0	1
23	OCH_2Ph	CH_3	CH_3	Br	3.452	1	0	0	0	1
24	OCH_2-3-Thienyl	CH_3	CH_3	Br	3.098	0	0	0	0	1
25	OCH_2-2-Thiazolyl	CH_3	CH_3	Br	1.796	0	0	0	0	1
26	OCH_2-3-Py	CH_3	CH_3	Br	1.955	0	0	0	0	1

Table 3. Analogs of **6** and their related physicochemical parameters



Compound	R^1	R^2	R^3	R^4	log *P*	Pol	I_1	I_2	I_3	$I_{4,Br}$
1	CH_3	CH_2-3-Py	CH_3	H	0.343	4.450	0	1	0	0
2	CH_3	CH_2-3-Py	CH_3	Br	1.426	4.750	0	1	0	1
3	CH_3	CH_2-Ph-4-Cl	CH_3	H	2.553	4.730	0	1	0	0
4	CH_3	CH_2Ph-4- $O(CH_2)_2NC_5H_{10}$	CH_3	H	3.092	5.960	0	1	0	0
5	CH_3	CH_2Ph-4- $O(CH_2)_2NC_5H_{10}$	CH_3	Br	4.175	6.270	0	1	0	1
6	CH_3	CH_2Ph-4- $CH_2N(CH_3)_2$	CH_3	H	1.674	5.240	0	1	0	0
7	CH_3	CH_2Ph-4- $N[(CH_2)_2]_2NCH_3$	CH_3	H	1.738	5.680	0	1	0	0
8	CH_3	$CH_2CCCH_2NEt_2$	CH_3	H	1.954	4.920	0	1	0	0
9	CH_3	$CH_2CCCH_2NEt_2$	CH_3	Br	3.037	5.220	0	1	0	1
10	CH_3	$CH_2CCCH_2N[(CH_2)_2]_2NCH_3$	CH_3	Br	1.199	5.480	0	1	0	1
11	CH_3	CH_3	CH_2NEt_2	H	0.465	4.440	0	0	0	0
12	CH_3	CH_3	$CH_2N[(CH_2)_2]_2O$	H	−0.680	4.430	0	0	0	0
13	CH_3	CH_3	CH_2ProCH_3	H	−0.002	4.800	0	0	0	0
14	CH_3	CH_3	CH_2Im	H	−0.814	4.320	0	0	0	0
15	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	H	−0.238	4.700	0	0	1	0
16	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	Br	0.845	5.000	0	0	1	1
17	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NPh$	Br	2.395	5.800	0	0	0	1
18	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NBoc$	Br	2.376	5.820	0	0	0	1
19	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	Ph-4-OCF_3	2.714	5.950	0	0	1	0
20	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	2-Naphthyl	2.824	6.380	0	0	1	0
21	Ph-4-Cl	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	H	2.523	5.690	1	0	1	0
22	Ph-4-Cl	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	Br	3.606	5.990	1	0	1	1

Table 4. Analogs of **7** and their related physicochemical parameters



Compound	R^1	R^3	R^4	log *P*	Pol	$I_{1,CC}$	$I_{1,N}$	$I_{4,Br}$
1	CH_3	CH_3	Br	1.155	3.860	0	0	1
2	CH_3	$CH_2[(CH_2)_2]_2NCH_3$	Br	0.833	4.850	0	0	1
3	CH_2-3-C_5H_4N	CH_3	Br	1.426	4.750	0	0	1
4	$(CH_2)_3CH_3$	CH_3	Br	2.722	4.410	0	0	1
5	CH_2CCH	CH_3	Br	1.755	4.140	1	0	1
6	$CH(CH_3)CCH$	CH_3	Br	2.064	4.330	1	0	1
7	CH_2CCCH_3	CH_3	Br	2.284	4.330	1	0	1
8	$CH_2CCCH_2CH_3$	CH_3	Br	2.284	4.520	1	0	1
9	$CH_2CC(CH_2)_2CH_3$	CH_3	Br	3.342	4.700	1	0	1
10	$CH_2CC(CH_2)_3CH_3$	CH_3	Br	3.871	4.890	1	0	1
11	CH_2CCPh	CH_3	Br	2.873	5.130	1	0	1
12	CH_2CCCH_2OH	CH_3	Br	1.197	4.400	1	0	1
13	$CH_2CCCH_2OCH_3$	CH_3	Br	1.913	4.590	1	0	1
14	$CH_2CCCH_2NHCH_3$	CH_3	Br	1.443	4.660	1	1	1
15	$CH_2CCCH_2NH(CH_2)_3N(CH_3)_2$	CH_3	Br	2.200	5.550	1	1	1
16	$CH_2CCCH_2N(CH_2CH_3)_2$	CH_3	Br	3.037	5.220	1	1	1
17	CH_2CCCH_3	CH_3	H	1.201	4.030	1	0	0
18	CH_2CCCH_3	H	H	1.042	3.850	1	0	0
19	CH_2CCCH_3	$CH_2[(CH_2)_2]_2NCH_3$	Br	1.686	5.130	1	0	1
20	CH_2CCCH_3	$CH_2[(CH_2)_2]_2NCH_3$	Ph	2.491	5.810	1	0	0

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

Compound	log (1/IC_{50})								
	MMP-1			MMP-9			MMP-13		
	Obsd	Calcd Eq. 1	Loo	Obsd	Calcd Eq. 2	Loo	Obsd	Calcd Eq. 3	Loo
1	6.19	6.24	6.25	6.19[b]	7.56	—	6.26	6.61	6.71
2	6.94[a]	6.45	—	7.64	7.47	7.42	7.30[c]	6.42	—
3	6.84	6.57	6.43	8.30	8.33	8.34	8.10	8.27	8.32
4	6.28	6.27	6.27	7.64	7.54	7.52	6.86	6.58	6.50
5	6.40	6.37	6.35	7.51	7.50	7.49	—	6.49	—
6	6.69	5.93	—	7.89	7.97	8.00	7.38	7.53	7.55
7	—	6.56	—	7.19	7.43	7.50	6.27	6.34	6.36
8	—	6.22	—	7.57	7.56	7.56	6.87	6.63	6.56
9	7.62	7.60	7.45	8.70	8.61	8.54	9.00	8.85	8.76
10	6.22[a]	6.33	6.44	8.40	8.23	8.21	8.22	8.08	8.06
11	6. 68	6.87	6.93	8.22	8.42	8.48	8.40	8.47	8.49

Observed activities have been taken from Ref. 27
[a] Not included in the derivation of Eq. 1.
[b] Not included in the derivation of Eq. 2.
[c] Not included in the derivation of Eq. 3.

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

Compound	log (1/IC_{50})											
	MMP-1			MMP-9			MMP-13			TACE		
	Obsd	Calcd Eq. 4	Loo	Obsd	Calcd Eq. 5	Loo	Obsd	Calcd Eq. 6	Loo	Obsd	Calcd Eq. 7	Loo
1	6.84	6.93	6.97	8.30	8.25	8.23	8.10	7.84	7.79	6.64	7.10	7.28
2	6.91	6.73	6.70	7.62	7.96	7.99	7.70	7.64	7.63	7.37	7.56	7.62
3	6.88	6.84	6.83	7.82	8.11	8.16	7.96	7.75	7.72	7.15	7.02	6.99
4	6.71	6.57	6.56	8.52	8.93	9.15	8.40	8.83	9.06	7.19	6.79	6.75
5	6.27	6.39	6.40	9.00	8.67	8.51	8.70	8.65	8.63	6.53	6.64	6.65
6	6.13	6.35	6.38	8.70	8.62	8.58	9.00	8.61	8.42	6.71	6.60	6.59
7	5.98	6.48	6.53	8.30	7.61	7.55	6.95	7.40	7.44	—	6.71	—
8	7.13	6.89	6.82	8.70	8.19	8.09	7.41	7.80	7.86	6.20[d]	7.06	—
9	6.99	7.19	7.42	8.15	7.78	7.75	8.52	8.59	8.63	6.88	6.81	6.80
10	7.74	7.54	7.31	8.10	8.26	8.30	9.00	8.93	8.85	7.21	7.11	7.07
11	6.54	6.45	6.44	—	7.58	—	7.62	7.37	7.35	6.76	6.69	6.68
12	—	5.23	—	6.84	7.30	7.39	6.86	7.18	7.24	6.42	6.52	6.53
13	—	5.19	—	6.26	6.01	5.88	6.02	6.09	6.13	6.37	6.49	6.51
14	6.13	6.15	6.15	7.34[b]	7.16	—	7.12	7.08	7.07	6.33	6.43	6.46
15	6.42	6.18	6.11	8.40	7.16	7.11	8.22[c]	6.04	—	—	6.46	—
16	——	5.04	—	6.90	7.04	7.10	7.36	7.00	6.85	—	6.99	—
17	5.49	5.88	6.18	8.15[b]	8.20	—	8.40	7.81	7.91	—	7.07	—
18	—	5.91	—	6.82	8.20	8.21	7.42	7.84	7.92	—	7.10	—
19	5.88	5.43	5.19	8.10[b]	7.58	—	8.5[c]	6.30	—	6.14[d]	6.69	—
20	5.64[a]	6.61	—	6.82	7.59	7.53	7.74	7.53	7.51	—	6.82	—
21	—	6.61	—	—	7.79	—	7.59	7.52	7.52	—	6.82	—
22	—	5.37	—	5.46	6.25	6.65	5.76	6.26	6.52	6.55[d]	7.27	—
23	—	5.32	—	6.72[b]	7.42	—	6.79	6.21	5.93	7.24	7.23	7.22
24	5.33	5.38	5.41	6.63	6.18	5.91	6.85	7.33	7.38	7.25	7.29	7.30
25	—	5.63	—	6.02	7.52	7.62	6.18[c]	6.49	—	7.64	7.50	7.46
26	—	5.60	—	—	7.82	—	—	6.46	—	7.55	7.47	7.45

Observed activities have been taken from Ref. 28.
[a] Not included in the derivation of Eq. 4.
[b] Not included in the derivation of Eq. 5.
[c] Not included in the derivation of Eq. 6.
[d] Not included in the derivation of Eq. 7.

The correlations expressed by Eqs. (1)–(3) exhibit that highly hydrophobic molecules will not be favored. Therefore, it suggests that probably MMPs do not possess hydrophobic sites to interact with the molecules. The high r^2_{cv} value (>0.60) in each equation suggests that each equation is quite significant and has very high predictive value. Tables also give the predicted values from leave-one-out equations that are in very good agreement with the observed values.

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

Compound	log (1/IC_{50})											
	MMP-1			MMP-9			MMP-13			TACE		
	Obsd	Calcd Eq. 9	Loo	Obsd	Calcd Eq. 10	Loo	Obsd	Calcd Eq. 11	Loo	Obsd	Calcd Eq. 8	Loo
1	6.84	6.78	6.76	8.30	8.10	8.07	8.10	7.78	7.73	6.64	6.73	6.74
2	6.48[a]	6.95	—	8.15	8.05	8.04	7.74	7.91	7.92	6.45[d]	7.39	—
3	6.41	6.64	6.70	8.10	8.17	8.18	7.74	7.90	7.91	6.19	6.51	6.57
4	6.75	6.61	6.56	8.15	8.28	8.30	7.25[c]	8.40	—	6.56	6.46	6.43
5	7.46[a]	6.78	—	8.70	8.61	8.46	8.52	8.53	8.53	6.97	7.11	7.16
6	6.67	6.70	6.70	8.52[b]	8.06	—	7.96	8.11	8.12	6.61	6.60	6.60
7	6.85	6.69	6.67	8.15	8.07	8.05	7.70[c]	8.29	—	6.84	6.59	6.57
8	6.33[a]	6.68	—	7.96	8.09	8.10	7.72	7.98	8.00	6.66	6.57	6.56
9	6.82	6.85	6.86	7.85[b]	8.27	—	8.15	8.10	8.09	7.44	7.23	7.19
10	6.89	6.96	7.00	8.00	8.05	8.06	8.22	8.21	8.20	7.59	7.41	7.37
11	6.13	6.14	6.15	8.10	8.09	8.08	7.08[c]	7.78	—	6.68	6.72	6.73
12	6.22	6.21	6.21	8.30	8.28	8.27	7.85	7.77	7.76	6.76	6.84	6.85
13	6.29	6.17	6.14	8.30	8.14	8.12	8.22	7.93	7.90	6.70	6.77	6.78
14	6.11	6.22	6.26	8.00	8.31	8.49	7.37	7.73	7.80	6.80	6.85	6.86
15	6.51	6.50	6.50	9.00	8.88	8.82	7.92	7.89	7.88	6.81	6.79	6.79
16	6.71	6.67	6.64	8.70	8.75	8.77	8.30	8.01	7.99	7.59	7.45	7.40
17	6.35	6.26	6.21	8.52[b]	8.14	—	8.52	8.34	8.31	7.06	7.29	7.33
18	6.17	6.26	6.30	8.15	8.14	8.14	8.22	8.34	8.36	7.20	7.29	7.31
19	6.13	6.32	6.43	8.70	8.89	8.93	8.40	8.40	8.40	6.68	6.50	6.46
20	6.46	6.31	6.22	8.70	8.91	8.96	8.52	8.57	8.59	7.31[d]	6.48	—
21	6.81	6.87	6.95	9.00	8.86	8.82	9.10	9.06	9.03	6.91[d]	6.51	—
22	7.09	7.03	6.96	9.30	9.11	9.02	9.15	9.19	9.22	7.10	7.17	7.18

Observed activities have been taken from Ref. 29.
[a] Not included in the derivation of Eq. 9.
[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. 8.

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

Compound	log (1/IC_{50})											
	MMP-1			MMP-9			MMP-13			TACE		
	Obsd	Calcd Eq. 15	Loo	Obsd	Calcd Eq. 12	Loo	Obsd	Calcd Eq. 13	Loo	Obsd	Calcd Eq. 14	Loo
1	6.94	6.59	6.41	7.96	7.86	7.78	7.68	7.85	7.94	7.49	7.56	7.58
2	6.71	6.78	6.85	8.70	8.35	8.11	8.30	7.95	7.73	7.59	7.65	7.67
3	—	6.43	—	—	8.31	—	—	7.76	—	7.55	7.48	7.46
4	5.60	5.65	5.66	7.68	8.13	8.36	7.17	7.35	7.50	7.17	7.11	7.08
5	6.95[a]	6.23	—	7.82[b]	6.91	—	7.28	6.77	6.70	7.96	7.88	7.87
6	5.81	6.05	6.08	6.34	6.29	6.27	6.36	6.67	6.70	6.91[d]	7.79	—
7	5.79	5.91	5.93	6.52	6.29	6.24	6.81	6.60	6.57	7.80	7.73	7.72
8	5.91	5.91	5.92	6.10	6.38	6.42	6.54	6.60	6.60	7.92	7.73	7.70
9	5.63	5.28	5.09	6.63	6.47	6.45	6.45	6.26	6.20	7.33	7.43	7.45
10	—	4.97	—	6.41	6.57	6.59	6.15	6.09	6.05	7.47	7.28	7.18
11	5.42	5.56	5.60	6.07	6.69	6.79	6.49	6.41	6.40	7.18	7.56	7.62
12	5.49[a]	6.56	—	6.32	6.32	6.32	7.08	6.95	6.91	8.15	8.04	8.00
13	5.11[a]	6.14	—	6.41	6.42	6.42	6.63	6.72	6.73	7.96	7.83	7.81
14	—	6.42	—	6.19	5.64	5.25	6.59	6.33	6.17	7.24	7.08	6.87
15	—	5.96	—	5.92	6.09	6.20	6.04	6.09	6.12	7.54[d]	6.86	—
16	—	5.47	—	5.55	5.93	6.12	5.62	5.82	5.96	6.46	6.62	6.83
17	—	6.56	—	—	6.14	—	6.38	6.94	7.08	7.55	7.61	7.64
18	—	6.65	—	—	6.05	—	—	7.00	—	7.57	7.65	7.70
19	5.78[a]	6.27	—	6.78	6.69	6.67	6.60	6.79	6.81	7.60	7.90	7.95
20	5.72	5.79	5.80	7.55	7.03	6.57	7.33[c]	6.53	—	7.38	7.24	7.14

Observed activities have been taken from Ref. 30.
[a] Not included in the derivation of Eq. 15.
[b] Not included in the derivation of Eq. 12.
[c] Not included in the derivation of Eq. 13.
[d] Not included in the derivation of Eq. 14.

In each correlation, as mentioned below each equation, there have been certain outliers. We could not find any obvious reasons in any case to explain their aberrant behaviors.

For the compounds of Table 2 also, we could not find any positive role of the lipophilicity of the molecules (Eqs. 4–7). However, some specific substituents were found to be favorable to the activity as indicated by some indicator parameters. The indicator parameters used are I_1, I_2, I_3, I_4, and $I_{4,\ Br}$.

MMP-1

$$\log(1/IC_{50}) = 1.020(\pm0.396)I_2 + 0.596(\pm0.487)I_3 - 0.192(\pm0.118)\log P + 5.979(\pm0.432)$$
$$n = 16, r = 0.919, r^2_{cv} = 0.67, s = 0.28, F_{3,12} = 21.86(5.95)$$
Outlier 20 (4)

MMP-9

$$\log(1/IC_{50}) = 8.336(\pm0.492) - 0.265(\pm0.183)\log P - 1.241(\pm0.725)I_1 + 1.183(\pm0.691)I_4$$
$$n = 19, r = 0.882, r^2_{cv} = 0.64, s = 0.50,$$
$$F_{3,15} = 17.47(5.42)$$
Outliers 14, 17, 19, 23 (5)

MMP-13

$$\log(1/IC_{50}) = 7.902(\pm0.366) - 0.184(\pm0.138)\log P - 1.051(\pm0.552)I_1 + 1.079(\pm0.626)I_3 + 1.341(\pm0.527)I_4$$
$$n = 22, r = 0.919, r^2_{cv} = 0.75, s = 0.38,$$
$$F_{4,17} = 23.06(4.67)$$
Outliers 15, 19, 25 (6)

TACE

$$\log(1/IC_{50}) = 0.637(\pm0.229)I_{4,Br} - 0.163(\pm0.084)\log P + 7.156(\pm0.248)$$
$$n = 16, r = 0.898, r^2_{cv} = 0.69, s = 0.20,$$
$$F_{2,13} = 27.14(6.70)$$
Outliers 8, 19, 22 (7)

I_1 stands for R^1-substituents and has a value of unity for $R^1 = OCH_2Ph$ and zero for others, I_2 stands for R^2-substituents and has a values of unity for $R^2 = CH_2$-3-pyridyl group and zero for others, I_3 stands for R^3-substiutents and is equal to 1 for R^3 = an aromatic substituent and zero otherwise, similarly I_4, which stands for R^4-substituents also has a value of unity for R^4 = an aromatic moiety and zero for others. The specific effect of bromine at R^4 is, however, described by a parameter $I_{4,Br}$. Now as obvious from Eqs. 5 and 6, the positive coefficients of I_4 suggest that aromatic substituents at R^4-position will be favorable to the inhibition potency of the compounds against MMP-9 and MMP-13. However, the bromine seems to be better than any other substituent at this position for the inhibition of TACE (Eq. 7). This difference can be obviously attributed to the structural difference in the enzymes. The positive coefficients of I_3 in Eqs. 4 and 6 also suggest that aromatic substituents at that ring (ring attached to nitrogen) will favor the activity of compounds against MMP-1 as well as MMP-13. This favorable effect of aromatic substituents at R^3 and R^4-positions may be attributed to their ability to be in the plane of the ring. The positive coefficient of I_2 in Eq. 4 indicates that a substituent like CH_2-3-pyridyl will be beneficial to the inhibition of MMP-1. The beneficial role of this substituent may be obviously due to the presence of a nitrogen atom with a lone pair of electrons. This lone pair of electrons at the nitrogen may either participate in some electronic interaction with the receptor or might affect the electronic property of the nitrogen of sulfonamide group, whose electronic character has been shown in many studies[23–26] to be very crucial for MMP inhibitions.

The role of bromine in TACE inhibition is consistently observed in the case of the compounds of Table 3 also (Eq. 8). Eq. 8, which has been obtained for the compounds of Table 3 for TACE inhibition, is exactly parallel to Eq. 7. In the case of these compounds, bromine is found to be favorable for MMP-1 inhibition also (Eq. 9).

TACE

$$\log(1/IC_{50}) = 0.763(\pm0.188)I_{4,Br} - 0.100(\pm0.063)\log P + 6.767(\pm0.121)$$
$$n = 19, r = 0.907, r^2_{cv} = 0.75, s = 0.16,$$
$$F_{2,14} = 37.28(6.51)$$
Outliers 2, 20, 21 (8)

MMP-1

$$\log(1/IC_{50}) = 0.234(\pm0.147)I_{4,Br} + 0.317(\pm0.186)I_3 + 0.629(\pm0.173)I_2 + 0.534(\pm0.251)I_1 - 0.062(\pm0.060)\log P + 6.801(\pm0.150)$$
$$n = 19, r = 0.935, r^2_{cv} = 0.74, s = 0.13,$$
$$F_{5,13} = 18.15(4.86)$$
Outliers 2, 5, 8 (9)

MMP-9

$$\log(1/IC_{50}) = 0.695(\pm0.172)I_3 - 0.154(\pm0.133)\log P + 0.064(\pm0.039)(\log P)_2 + 8.143(\pm0.122)$$
$$n = 19, r = 0.931, r^2_{cv} = 0.74, s = 0.16,$$
$$F_{2,16} = 32.65(6.23), [\log P_o = 1.20]$$
Outliers 6, 9, 17 (10)

MMP-13

$$\log(1/IC_{50}) = 0.410(\pm0.158)\mathrm{Pol} + 0.773(\pm0.325)I_1 + 5.960(\pm0.824)$$
$$n = 19, r = 0.914, r^2_{cv} = 0.79, s = 0.19,$$
$$F_{2,14} = 40.71(6.51)$$
Outliers 4, 7, 11 (11)

In MMP-1 inhibition, however, there are also some other substituents that are shown to be favorable to the activity of the compounds (Eq. 9). The positive coefficient of I_3 that has been used with a value of unity for $R^3 = CH_2N[(CH_2)_2]_2NCH_3$ [(*N*-methylpiperazinyl)-methyl group] suggests that such a substituent at R^3-position will have better effect than any other substituent. The reason may be that this substituent has double nitrogens and is present at the aryl ring ortho to sulfonamide nitrogen, and because of this it might change the electronic characterstics of the latter. There are, of course, some other piperazine-derived sustituents at R^3-position, but only 4-methyl derivative ($CH_2N[(CH_2)_2]_2NCH_3$) is shown to be better. One can, therefore, assume that there can also be a size effect of R^3-substituent and that 4-methyl derivative gives an optimum size. Similarly, a nitrogen-containing R^2-substituent directly attached to sulfonamide nitrogen is shown by parameter I_2 to be more conducive than a small CH_3 group. I_2 has a value of 1 for R^2 = a nitrogen-containing group and zero for $R^2 = CH_3$. This effect of nitrogen-containing R^2-substituent is consistent with what we discussed about CH_2-3-pyridyl group in Table 2.

At R^1-position, a group like Ph-4-Cl would be preferred to a methyl group as indicated by the positive coefficient of I_1 in Eq. 9. I_1 is equal to 1 for R^1 = Ph-4-Cl and zero for $R^1 = CH_3$. This effect of Ph-4-Cl may be due to its aromatic character. If we compare this with the case of OCH_2-Ph at R^1-position in Table 2, we can conclude that there can also be a requirement of an optimum size of such aromatic moiety to be effective. The Ph-4-Cl is shown to be favorable to MMP-13 inhibition also (Eq. 13).

The (*N*-methylpiperazinyl)methyl group for which parameter I_3 has been used is found to be also conductive to the MMP-9 inhibition (Eq. 10). As usual, the hydrophobicity of the molecule is shown to have the negative effect but acquires an optimum value [$\log P_o$] = 1.20. Averse to hydrophobicity, a polarizability term (Pol) is found to control the activity of the compounds for the inhibition of MMP-13 (Pol has been calculated using www.acdlabs.com software).

In the case of the compounds of Table 4, the polarizability of the compounds has been shown to be a major factor in the inhibition of MMP-9 (Eq. 12). In addition to the polarizability, two structural features of R^1 moiety in compounds of Table 4 are found to control the activity by producing negative effect. These structural features are acetylene-derived substituents and nitrogen-containing substituents. Their effects are described by two indicator parameters, $I_{1,CC}$ and $I_{1,N}$, respectively, with a value of 1 each for these substituents and zero for others. Both these parameters are present in Eqs. 12 and 13 with negative coefficients, suggesting that acetylene-derived or a nitrogen-containing R^1-substituent will not be favorable to MMP-9 and MMP-13 inhibitions.

MMP-9

$$\log(1/IC_{50}) = 0.503(\pm0.477)\mathrm{Pol} - 1.806(\pm0.567)I_{1,CC} - 0.807(\pm0.559)I_{1,N} + 5.916(\pm2.137)$$
$$n = 16, r = 0.920, r^2_{cv} = 0.64, s = 0.37,$$
$$F_{3,12} = 21.92(5.95)$$
Outlier 5 (12)

MMP-13

$$\log(1/IC_{50}) = 8.220(\pm0.467) - 0.320(\pm0.192)\log P - 0.891(\pm0.422)I_{1,CC} - 0.531(\pm0.403)I_{1,N}$$
$$n = 17, r = 0.910, r^2_{cv} = 0.70, s = 0.29,$$
$$F_{3,13} = 20.78(5.74)$$
Outlier 20 (13)

TACE

$$\log(1/IC_{50}) = 0.491(\pm0.258)I_{1,CC} + 0.429(\pm0.280)I_{4,Br} - 0.891(\pm0.309)I_{1,N} - 0.284(\pm0.122)\log P + 7.457(\pm0.342)$$
$$n = 18, r = 0.905, r^2_{cv} = 0.64, s = 0.19,$$
$$F_{4,13} = 14.79(5.20)$$
Outliers 6, 15 (14)

MMP-1

$$\log(1/IC_{50}) = 7.276(\pm0.549) - -0.596(\pm0.234)\log P$$
$$n = 9, r = 0.916, r^2_{cv} = 0.67, s = 0.22,$$
$$F_{1,7} = 36.46(12.25)$$
Outlier 5, 12, 13, 19 (15)

However, in the case of TACE inhibition (Eq. 14), $I_{1,CC}$ is found to have a positive effect but $I_{1,N}$ a negative effect. Acetylene-derived substituents are long linear chains and thus might be creating steric-problems while interacting, presumably, with the active sites of MMP-9 and MMP-13, but in TACE the active site may be capable of accommodating them well. Nitrogen-containing substituents, that are unfavorable to TACE also, might be eliciting their negative effect through some unwanted electronic interactions with the enzyme. For the TACE inhibition, bromine at R^4, as usual, is shown to be better than any other R^4-substituent (Eq. 14). The MMP-1 inhibition is not found to be affected by any other parameter except $\log P$, which is showing a negative effect (Eq. 15).

3.1. Conclusion

From this QSAR study we find that in anthranilic acid-based MMP inhibitors the hydrophobic character of the molecules is not beneficial to the activity and in almost all the cases it has the adverse effect. Thus it appears that MMPs provide little opportunity to the molecules to have hydrophobic interactions, instead there can be strong electronic interactions between them, in which the sulfonamide group present in the molecules might play a major role in addition to the hydroxamic acid moiety chelating with the zinc atom of the MMPs. QSAR study points out that the interaction of sulfonamide group with the enzyme can be greatly helped by the presence of the substituents of high electronic characterstics at the sulfonamide nitrogen or at the aromatic rings, affecting the electronic properties of nitrogen or sulfur or of both of sulfonamide group. The large substituents at the aromatic rings however might sometimes produce some steric problems, but those having some electronic character and being of reasonable size might have some electronic interactions with the receptors.

Acknowledgments

One of the authors, S. Kumaran, is thankful to CSIR, New Delhi, for providing him an SRF.

References and notes

1. Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem* **2000**, *43*, 305–341.
2. Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359–1472.
3. Leff, R. L. *Ann. N. Y. Acad. Sci.* **1999**, *878*, 201–207.
4. Shlopov, B. V.; Lie, W.-R.; Mainardi, C. L.; Cole, A. A.; Chubinskaya, S.; Hasty, K. A. *Arthritis Rheum.* **1997**, *40*, 2065–2074.
5. Ahrens, D.; Koch, A. E.; Pope, R. M.; Steinpicarella, M.; Niedbala, M. J. *Arthritis Rheum.* **1996**, *39*, 1576–1587.
6. Blaser, J.; Triebel, S.; Maajosthusmann, U.; Rimisch, J.; Krahlmateblowski, U.; Freudenberg, W.; Fricke, R.; Tschesche, H. *Clin. Chim. Acta* **1996**, *244*, 17–33.
7. Cawston, T. E. *Pharmacol. Ther.* **1996**, *70*, 163–182.
8. Bramhall, S. R. *Int. J. Pancreatol* **1997**, *21*, 1–12.
9. Lafleur, M.; Underwood, J. L.; Rappolee, D. A.; Werb, Z. *J. Exp. Med.* **1996**, *184*, 2311–2326.
10. Wojtowicz-Praga, S. M.; Dickson, R. B.; Hawkins, M. *Invest. New Drugs* **1997**, *15*, 61–75.
11. Cuzner, M. L.; Opdenakker, G. *J. Neuroimmunol.* **1999**, *94*, 1–14.
12. Yong, V. W.; Krekoski, C. A.; Forsyth, P. A.; Bell, R.; Edwards, D. R. *J. Neuroimmunol.* **1996**, *69*, 141–149.
13. Matyszak, M. K.; Perry, V. H. *J. Neuroimmunol.* **1996**, *69*, 141–149.
14. Coker, M. L.; Thomas, C. V.; Clair, M. J.; Hendrick, J. W.; Krombach, S. R.; Galis, Z. S.; Spinale, F. G. *Am. J. Physiol.* **1998**, *274*, H1516–H1523.
15. Spinale, F. G.; Coker, M. L.; Krombach, S. R.; Mukherjee, R.; Hallak, H.; Houck, W. V.; Clair, M. J.; Kribbs, S. B.; Johnson, L. L.; Peterson, J. T.; Zile, M. R. *Circ. Res.* **1999**, *85*, 364–376.
16. Tyagi, S. C. *Cardiovasc. Pathol.* **1998**, *7*, 153–159.
17. Bode, W.; Fernandez-Catalan, C.; Tschesche, H.; Grams, F.; Nagase, H.; Skos, K. *Cell Mol. Life Sci.* **1999**, *55*, 639–652.
18. Beckett, R. P.; Whittaker, M. *Exp. Opin. Ther. Patents* **1998**, *8*, 259–282.
19. Whittaker, M.; Brown, P. *Curr. Opin. Drug Discov. Dev.* **1998**, *1*, 157–164.
20. Summers, J. B.; Davidsen, S. K.. In Bristol, J. A., Ed.; Annual Reports in Medicinal Chemistry; Academic Press: Michigan, 1998; Vol. 33, pp 131–140.
21. Rhomberg, W. *Curr. Opin. Oncol. Endocr. Metab. Invest. Drugs* **1999**, *1*, 507–524.
22. (a) For recent comprehensive reviews, see: Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, J. H. *Chem. Rev.* **1999**, *99*, 2735–2776; (b) Beckett, R. P.; Whittaker, M. *Exp. Opin. Ther. Patents* **1998**, *8*, 259–282; (c) Zask, A.; Levin, J. L.; Killar, L. M.; Skotnicki, J. S. *Curr. Pharm. Des.* **1996**, *2*, 624–661.
23. Kumar, D.; Gupta, S. P. *Bioorg. Med. Chem.* **2003**, *11*, 421–426.
24. Gupta, S. P.; Kumar, D.; Kumaran, S. *Bioorg. Med. Chem.* **2003**, *11*, 1975–1981.
25. Gupta, S. P.; Kumaran, S. *Bioorg. Med. Chem.* **2003**, *11*, 3065–3071.
26. Gupta, S. P.; Maheswaran, V.; Pande, V.; Kumar, D. *J. Enzyme Inhib. Med. Chem.* **2003**, *18*, 7–13.
27. Levin, J. I.; Du, M. T.; DiJoseph, J. F.; Killar, L. M.; Sung, A.; Walter, T.; Sharr, M. A.; Roth, C. E.; Moy, F. J.; Powers, R.; Jin, G.; Cowling, R.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 235–238.
28. Levin, J. I.; Chen, J.; Du, M.; Hogan, M.; Kincaid, S.; Nelson, F. C.; Venkatesan, A. M.; Wehr, T.; Zask, A.; DiJoseph, J.; Killar, L. M.; Skala, S.; Sung, A.; Sharr, M.; Roth, C.; Jin, G.; Cowling, R.; Mohler, K. M.; Black, R. A.; March, C. J.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2189–2192.
29. Levin, J. I.; Chen, J. M.; Du, M. T.; Nelson, F. C.; Wher, T.; DiJoseph, J. F.; Killar, L. M.; Skala, S.; Sung, A.; Sharr, M. A.; Roth, C. E.; Jin, G.; Cowling, R.; Di, L.; Sherman, M.; Xu, Z. B.; March, C. J.; Mohler, K. M.; Black, R. A.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2975–2978.
30. Levin, J. I.; Chen, J. M.; Du, M. T.; Nelson, F. C.; Killar, L. M.; Skala, S.; Sung, A.; Jin, G.; Cowling, R.; Barone, D.; March, C. J.; Mohler, K. M.; Black, R. A.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1199–1202.
31. Nelson, F. C.; Zask, A. *Exp. Opin. Invest. Drugs* **1999**, *8*, 383–392.
32. Lowe, C. *Exp. Opin. Ther. Patents* **1998**, *8*, 1309–1322.
33. Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **1999**, *42*, 2295–2314.
34. Yoshihara, Y.; Nakamura, H.; Obata, K.; Yamada, H.; Hayakawa, T.; Fujikawa, K.; Okada, Y. *Ann. Rheum. Dis.* **2000**, *59*, 455–-61.