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Bioorganic & Medicinal Chemistry Letters 16 (2006) 1596–1600
Bioorganic & Medicinal Chemistry Letters

Factor VIIa inhibitors: Gaining selectivity within the trypsin family

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Received 20 October 2005; revised 7 December 2005; accepted 7 December 2005
Available online 18 January 2006

Abstract—Within the trypsin family of coagulation proteases, obtaining highly selective inhibitors of factor VIIa has been challenging. We report a series of factor VIIa (fVIIa) inhibitors based on the 5-amidino-2-(2-hydroxy-biphenyl-3-yl)-benzimidazole (**1**) scaffold with potency for fVIIa and high selectivity against factors IIa, Xa, and trypsin. With this scaffold class, we propose that a unique hydrogen bond interaction between a hydroxyl on the distal ring of the biaryl system and the backbone carbonyl of fVIIa lysine-192 provides a basis for enhanced selectivity and potency for fVIIa.

The development of novel antithrombotic agents for the treatment of coagulation disorders is an active area of research in the pharmaceutical industry. The enzymes (Factors IIa, Xa, VIIa, IXa, and XIa) that comprise the extrinsic and intrinsic pathways of coagulation, leading to the formation of a blood clot, are trypsin-family serine proteases.[1] Preclinical models of thrombosis in several species have suggested that a selective inhibitor of the coagulation proteases earlier in the cascade (Factors VIIa and IXa) may have a greater therapeutic/safety index than inhibition of proteases later in the cascade (Factors Xa and IIa).[2–4] Based on this pharmacology guidance, we chose to develop potent and selective inhibitors of factor VIIa-tissue factor complex (fVIIa) as an effective strategy for treatment of coagulation disorders.

We have previously described the development of active site small-molecule inhibitors which interact with both fVIIa and factor Xa (fXa).[5] Within the trypsin family of coagulation proteases, developing highly selective inhibitors of Factor VIIa has proved difficult.[6] Herein, we report on the further development of our 5-amidino-2-(2-hydroxy-biphenyl-3-yl)-benzimidazole **1** scaffold to achieve increased potency for factor VIIa and high selectivity against trypsin and the late coagulation pathway proteases; fIIa, fXa (see Fig. 1).

Our efforts toward developing a selective fVIIa inhibitor began with the broad spectrum trypsin-family protease inhibitor, **1**. The potency of **1** is mediated by a unique network of hydrogen bonds to the catalytic Ser-195, common to all proteases in this family. This protease-inhibitor binding paradigm is observed at high resolution in a large set of crystal structures (>400 structures).[7–10] Compound **1** was chosen for further optimization to obtain a highly selective fVIIa compound due to its initial potency for fVIIa (K_i = 0.074 μM), high solubility, and excellent parenteral pharmacokinetic profile.[11]

	K_i(μM)
fVIIa	0.074
fIIa	210
fXa	2.4
Trypsin	6.7

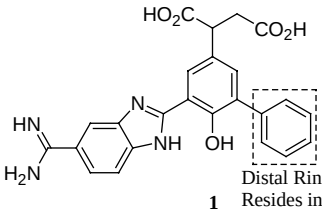

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Figure 1. The potency for **1** versus fVIIa, fXa, fIIa, and trypsin.

Keywords: Factor VIIa; Trypsin; Factor Xa; Thrombin; fIIa; Selectivity; Suzuki; Amidine; Lysine-192; Crystallography; Inhibitor.
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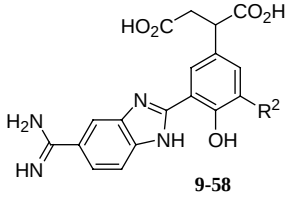
doi:10.1016/j.bmcl.2005.12.040

Compound **1**, while possessing good selectivity for IIa, had suboptimal selectivity for fXa and trypsin. Our initial goal was to gain 1000-fold selectivity for fVIIa versus fIIa, fXa, and trypsin (Table 1). From crystallography and modeling analysis, further improvements in selectivity against fXa and trypsin were envi-

Table 1. SAR data for selected compounds **1**, **9**–**58**



9-58

Compound	R^2	Selectivity ratios versus fVIIa			
		fVIIa K_i (μM)	IIa	Xa	Trypsin
1	Phenyl	0.074	2,838	32	91
9	**2-Hydroxy-5-fluorophenyl**	**0.004**	**>55,500**	**1800**	**4400**
10	**2-Hydroxy-5-chlorophenyl**	**0.0054**	**27,800**	**722**	**2500**
11	**2-Hydroxy-5-nitrophenyl**	**0.006**	**25,000**	**1450**	**8500**
12	**2-Hydroxy-5-aminophenyl**	**0.010**	**15,800**	**505**	**1789**
13	**2-Hydroxy-5-cyanophenyl**	**0.012**	**12,000**	**848**	**2960**
14	**2-Hydroxyphenyl**	**0.013**	**20,800**	**458**	**1077**
15	2-Hydroxy-3-bromo-5-chlorophenyl	0.009	17,000	216	398
16	2-Hydroxy-3,5-dichlorophenyl	0.014	10,700	171	421
17	2-Hydroxy-4,6-dichlorophenyl	0.025	6000	112	192
18	3-(Hydroxymethyl)phenyl	0.021	5744	86	216
19	3-Nitrophenyl	0.022	9545	42	268
20	2-Nitrophenyl	0.022	5455	109	25
21	3,5-Dichlorophenyl	0.027	33,300	43	98
22	3,5-Dimethylphenyl	0.029	29,700	62	1077
23	3-Acetylphenyl	0.033	5512	73	197
24	3-Aminophenyl	0.036	3333	128	250
25	3-Methylphenyl	0.038	3947	61	108
26	*N*-(3-Methylphenyl)acetamide	0.054	2778	28	102
27	2-Thiomethylphenyll	0.064	1719	63	103
28	3-Chlorophenyl	0.066	2273	24	59
29	3,5-Difluorophenyl	0.068	9706	24	115
30	3-Isopropylphenyl	0.076	11,800	17	40
31	3-Cyanophenyl	0.077	1458	21	71
32	3-Hydroxyphenyl	0.088	1705	41	99
33	5-Chlorothiophene	0.11	5636	17	10
34	3-Acetamidylphenyl	0.11	1182	51	118
35	3-(Difluoromethoxy)phenyl	0.12	5917	16	51
36	2-Methoxyphenyl	0.12	3750	30	55
37	3-Chloro-4-fluorophenyl	0.13	6923	15	34
38	2-Methoxyphenyl	0.13	1154	54	123
39	5-(Hydroxymethyl)thiophene	0.13	1100	25	33
40	2-Fluorophenyl	0.135	1000	17	43
41	2,3,5-Trichlorophenyl	0.21	714	35	39
42	2,5-Dichlorophenyl	0.25	600	20	35
43	2,3-Dichlorophenyl	0.27	556	31	44
44	3,4-Phenyldioxolone	0.28	536	13	20
45	2-Methoxy-5-cyanophenyl	0.28	540	24	54
46	2-Methoxy-5-fluorophenyl	0.33	455	39	52
47	2-Aminophenyl	0.42	357	18	41
48	4-Methylphenyl	0.42	310	11	8
49	4-Chlorophenyl	0.44	341	7	2
50	2-Methylphenyl	0.50	200	12	16
51	3-Pyridyl	0.55	209	14	31
52	2-(Hydroxymethyl)phenyl	0.73	205	13	16
53	3-(Aminomethyl)phenyl	0.78	192	9	18
54	4-Hydroxyphenyl	0.88	170	14	10
55	4-Methoxyphenyl	2.25	67	3	1
56	2-Acetylphenyl	4.0	38	16	28
57	H	6.4	>24	3	1
58	4-*tert*-Butylphenyl	16	9	4	1

Data shown are factor VIIa K_i and *fold*-selective ratios (anti-target K_i/fVIIa K_i) for coagulation factors IIa, Xa, and trypsin.[16,17]