Bioorganic & Medicinal Chemistry Letters 19 (2009) 6882–6889

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Aroylguanidine-based factor Xa inhibitors: The discovery of BMS-344577

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ARTICLE INFO

Article history:
Received 10 July 2009
Revised 17 October 2009
Accepted 20 October 2009
Available online 23 October 2009

Keywords:
Factor Xa inhibitor
Aroylguanidine
CYP3A4 inhibition
Orally active

ABSTRACT

We report the design and synthesis of a novel class of *N*,*N*′-disubstituted aroylguanidine-based lactam derivatives as potent and orally active FXa inhibitors. The structure–activity relationships (SAR) investigation led to the discovery of the nicotinoyl guanidine **22** as a potent FXa inhibitor (FXa IC_{50} = 4 nM, $EC_{2\times PT}$ = 7 μM). However, the potent CYP3A4 inhibition activity (IC_{50} = 0.3 μM) of **22** precluded its further development. Detailed analysis of the X-ray crystal structure of compound **22** bound to FXa indicated that the substituent at the 6-position of the nicotinoyl group of **22** would be solvent-exposed, suggesting that efforts to attenuate the unwanted CYP activity could focus at this position without affecting FXa potency significantly. Further SAR studies on the 6-substituted nicotinoyl guanidines resulted in the discovery of 6-(dimethylcarbamoyl) nicotinoyl guanidine **36** (BMS-344577, IC_{50} = 9 nM, $EC_{2\times PT}$ = 2.5 μM), which was found to be a selective, orally efficacious FXa inhibitor with an excellent in vitro liability profile, favorable pharmacokinetics and pharmacodynamics in animal models.

Thrombo-embolic disorders are the largest cause of human mortality and morbidity.[1] Current therapeutic drugs such as warfarin and heparin suffer from problems including a narrow therapeutic dose window, slow onset and offset of action, or patient variability and the need for periodic monitoring.[2] Improvement in the treatment and prevention of thrombotic diseases remains an important medical need. Selective inhibitors of the serine proteases in the coagulation cascade have been the targets for anti-thrombotic drug development for some time.[3] Within the coagulation cascade, activated blood coagulation factor X (FXa) is the key physiological activator of prothrombin and is the obligate enzyme in converting prothrombin to thrombin to begin the blood clot formation process. Extensive preclinical and clinical proof-of-principle data show that inhibition of FXa is effective in both venous and arterial thrombosis.[3,4]

Several selective and orally active FXa inhibitors, such as rivaroxaban,[5] razaxaban and apixaban,[6] LY517717,[7] YM150,[8] DU-176b,[9] have progressed into advanced clinical trials for the prevention and treatment of thromboembolic diseases.

We have previously reported several series of caprolactam based FXa inhibitors containing a thiourea **1**,[10] a ketene aminal **2**,[11] and a cyanoguanidine **3**[12] as linkers of P1 and P4 pharmacophores (Scheme 1). While this group of compounds includes selective and orally active FXa inhibitors, in general their in vivo efficacy has been limited by their moderate in vitro potency and high plasma protein binding.[13] In this Letter, we first describe the new SAR findings for a range of substituents at the central guanidine nitrogen in the *N*,*N*′-disubstituted guanidine series. We then disclose a detailed SAR investigation of aroylguanidines, which led to compound **22** with potent anticoagulation activity (IC_{50} = 4 nM, $EC_{2\times PT}$ = 7 μM).[14] We next present the X-ray structure of **22** bound to FXa and further SAR investigation around this molecule to significantly reduce its CYP3A4 inhibition activity. Finally, we disclose the pharmacokinetic parameters and in vivo characterizations of compound **36** (BMS-344577), an optimized compound in this series which progressed to advanced preclinical development.

The cyanoguanidine compound **3** was chosen as the new starting lead since it has the optimized P1 and P4 pharmacophores attached to the central guanidine-caprolactam core.[12] We first surveyed the SAR of the central guanidine nitrogen substituent and selected analogs are shown in Table 1. In general, the cyano group can be replaced with a variety of electron withdrawing groups (**4**–**12**) without significant loss of inhibitory potency against human FXa (IC_{50}). However, the concentrations to double the prothrombin time ($EC_{2\times PT}$) are on the order of 10^3-fold higher

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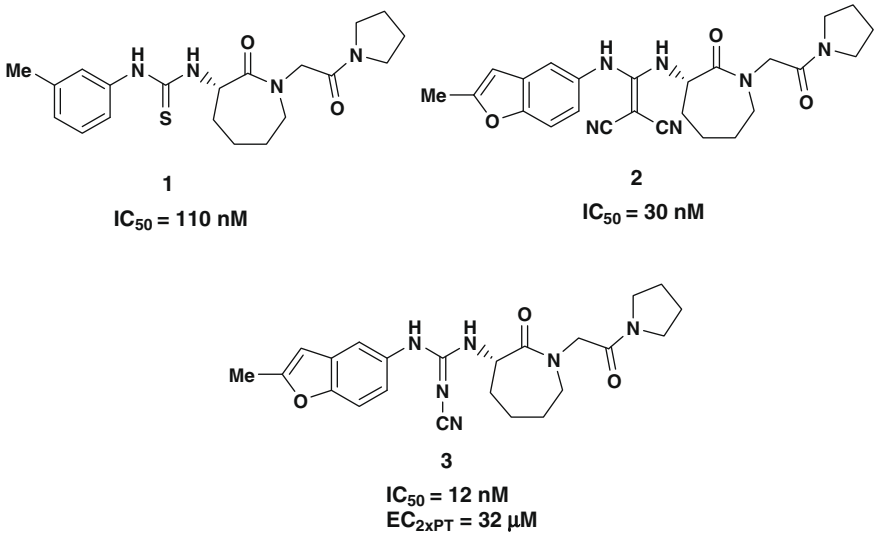
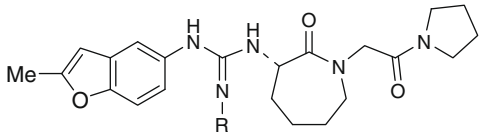
doi:10.1016/j.bmcl.2009.10.084



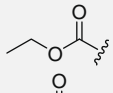
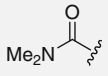
Scheme 1. The thiourea **1**, ketene aminal **2** and cyanoguanidine **3**.

than the corresponding IC_{50}s for these compounds, and all of them are less potent than compound **3** in $EC_{2\times PT}$. For example, although the nitroguanidine **4**, sulfonylguanidines **5** and **7**, and sulfamoylguanidine **6** have similar IC_{50}s against FXa as **3**, their $EC_{2\times PT}$s (all >50 μM) are weaker compared to **3** (32 μM). Compounds with a carbonyl group attached to the central guanidine nitrogen, including acetylguanidine **8**, ethoxylcarbonylguanidine **9**, carbamoylguanidine **10** and **11** are all less potent than **3** both in IC_{50} and $EC_{2\times PT}$; only the benzoylguanidine **12**[15] shows twofold improvement in IC_{50} (6 nM) compared to **3**.

Table 1
General survey of central guanidine nitrogen substituents



3-12

Compd	R	IC_{50}[a] (nM)	$EC_{2\times PT}$[b] (μM)
3	NC–	12	32
4	O_2N–	25	>50
5	MeO_2S–	10	60
6	H_2NO_2S–	12	>50
7	PhO_2S–	24	>50
8		17	70
9		32	34
10		28	60
11		15	55
12		6	48

[a] IC_{50} values are measured against Human FXa utilizing the cleavage of a synthetic substrate S-2222.
[b] Concentration of inhibitor required to double the prothrombin based clotting time in human plasma. Data are the average of two independent determinations.

We thus focused on replacing the benzoyl group in **12** with a variety of substituted benzoyl groups and with different heteroaroyls to further improve the anti-FXa activity. Selected analogs are listed in Table 2 to illustrate the SAR. Substituents on the benzoyl group strongly impact the anti-FXa activities both in IC_{50} and $EC_{2\times PT}$. Substituents at the *ortho*-position of the benzoyl group have a detrimental effect and lead to significant losses in anti-FXa activity (data not shown). For *meta*-substituted analogs, we found that while compounds with less polar substituents (**13** and **14**) have similar anti-FXa activities as **12**, the more polar analogs (**15** and **16**) exhibit improved $EC_{2\times PT}$ values but are less potent in IC_{50} compared to **12**. The *para*-substituted benzoylguanidines (compounds **17**–**20**) are the most potent analogs in the substituted benzoylguanidine series with more polar analogs having significantly improved $EC_{2\times PT}$ values compared to **12**. For example, the 4′-methoxycarbonyl benzoylguanidine (**17**, *c*log *P* = 4.6) has an IC_{50} = 6 nM and $EC_{2\times PT}$ = 18 μM; the more polar amide analogs **19** and **20** (*c*log *P* = 3.12 and 3.07) both have IC_{50} = 4 nM and $EC_{2\times PT}$ = 4 and 5 μM, respectively.

Changing the benzoyl group in **12** to a heteroaroyl also resulted in improvement in $EC_{2\times PT}$ (compounds **21**–**27**), although compounds with a nitrogen atom adjacent to the aroyl carbonyl group usually are less potent (compounds **21**, **24** and **28**) in the enzymatic assay (IC_{50}). For example, the picolinoyl guanidine **21** (IC_{50} = 55 nM, $EC_{2\times PT}$ = 16 μM) is about ninefold less potent in IC_{50} than its benzoyl analog **17** (IC_{50} = 6 nM, $EC_{2\times PT}$ = 18 μM), but both exhibit similar $EC_{2\times PT}$ values. The nicotinoyl guanidine **22** (IC_{50} = 4 nM, $EC_{2\times PT}$ = 7 μM) and isonicotinoyl guanidine **23** (IC_{50} = 3 nM, $EC_{2\times PT}$ = 16 μM) are more potent than **12**, with compound **22** having a better $EC_{2\times PT}$. Most of the five-membered heteroaroyl guanidines (**25**, **26** **27**) have similar IC_{50} values as **12**, along with slightly improved $EC_{2\times PT}$ values. The more polar 2-methyl-2*H*-5-tetrazoloyl guanidine **28** is about ninefold less potent in IC_{50} (56 nM) but still has slightly improved $EC_{2\times PT}$ (28 μM) compared to **12**.

To understand the binding mode of aroylguanidines in FXa, an X-ray crystal structure of compound **22** bound to FXa was determined at 1.9 Å resolution (PDB entry 3K9X). The structure is shown in Figure 1.[16] The overall binding motif is similar to that observed for compound **3**.[12] The nicotinoyl guanidine adopts an anti-syn conformation[12] with the nicotinoyl group anti to the 2-methyl