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Cyanoguanidine-based lactam derivatives as a novel class of orally bioavailable factor Xa inhibitors

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ABSTRACT

The *N,N′*-disubstituted cyanoguanidine is an excellent bioisostere of the thiourea and ketene aminal functional groups. We report the design and synthesis of a novel class of cyanoguanidine-based lactam derivatives as potent and orally active FXa inhibitors. The SAR studies led to the discovery of compound **4** (BMS-269223, K_i = 6.5 nM, EC_{2xPT} = 32 μM) as a selective, orally bioavailable FXa inhibitor with an excellent in vitro liability profile, favorable pharmacokinetics and pharmacodynamics in animal models. The X-ray crystal structure of **4** bound in FXa is presented and key ligand–protein interactions are discussed.

The trypsin-like serine protease factor Xa (FXa) has been one of the major targets for antithrombotic agent development for some time.[1] Within the blood coagulation cascade, factor Xa functions at the point where the intrinsic and extrinsic coagulation pathways converge,[2] and FXa is the key enzyme responsible for thrombin activation. Thrombin plays a major role in thrombosis and hemostasis by mediating a feed-back loop that amplifies its production, inducing platelet aggregation and converting fibrinogen to fibrin which ultimately leads to clot formation. Selective FXa inhibitors are believed to have a wider therapeutic window than direct thrombin inhibitors, since FXa inhibition could significantly reduce thrombin generation and prevent thrombus formation, while the basal levels of thrombin would still facilitate hemostasis and reduce unwanted bleeding risk.[2c] Recent preclinical and clinical data indicate that selective inhibition of factor Xa is a highly effective approach to the prevention and treatment of arterial and venous thromboembolism.[3]

Factor Xa contains a deep S1 cavity and a box-like S4 enclosure near the enzyme's active site. Potent FXa inhibitors generally require an S1 and an S4 binding element which are connected through an L-shaped scaffold. We have previously disclosed a series of caprolactam-based FXa inhibitors containing a thiourea **1**[4] or a ketene aminal **2**[5] as linkers of the P1 and P4 pharmacophores. While these compounds are selective and orally active FXa inhibitors, their in vivo efficacy was limited by their moderate in vitro potencies and short plasma half lives. In this Letter, we describe the cyanoguanidine as an alternative bioisostere to the thiourea and ketene aminal motifs that can adopt the desired L-shaped conformation, and the detailed SAR studies of both P1 and P4 groups. The X-ray structure of compound **4** (BMS-269223) bound to FXa and the detailed analysis of its interactions with FXa, as well as the PK/PD data and in vivo pharmacology of compound **4**, will also be discussed.

The *N,N′*-disubstituted cyanoguanidine is known to be an excellent bioisostere of *N,N′*-disubstituted thiourea from previous SAR studies of histamine H_2-receptor antagonists.[6] For example, the cynaoguanidine moiety in Cimetidine is a bioisostere of the thiourea functional group in Metiamide[6a] (Scheme 1). Similar to its thiourea and 1-nitroketene aminal analogs[4,5], the 1-methyl-3-phenyl-2-cyanoguanidine (compound **3**) is predicted to prefer the *anti–syn1* conformation by gas phase ab initio calculations.[7]

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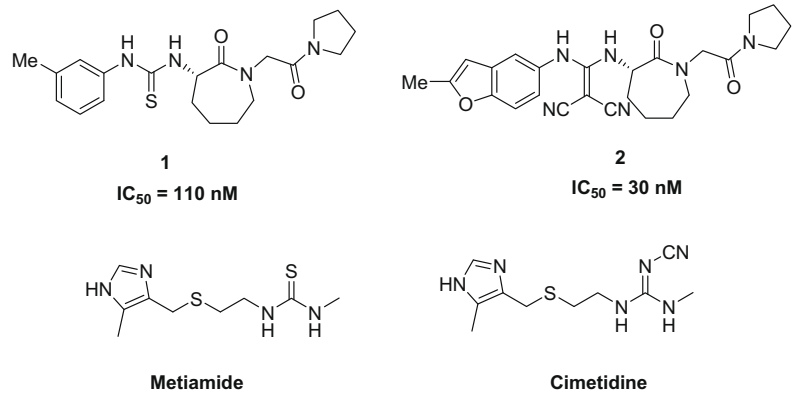
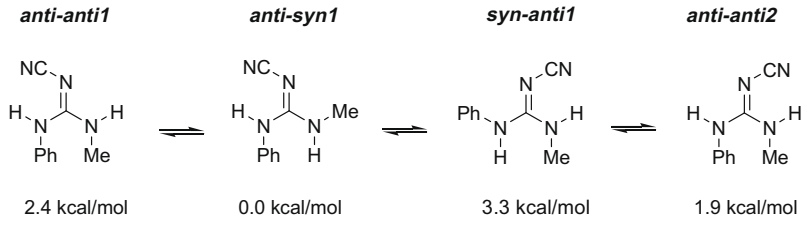


Scheme 1. The thiourea **1**, ketene aminal **2**, Metiamide and Cimetidine.



Scheme 2. Relative energies of conformers of 1-methyl-3-phenyl-2-cyanoguanidine **3**.

Scheme 2 shows the four lowest energy conformers for **3**. The other possible conformers are disfavored due to the internal steric interactions between the nitrogen substituents and the cyano group. The *anti–syn1* conformation affords the best combination of relief from steric crowding between the cyano, the phenyl and methyl groups.

Replacement of the 1,1-dicyanoketene aminal functionality in **2** with a cyanoguanidine gave compound **4** with an IC_{50} of 12 nM against FXa and EC_{2xPT} of 30 μM (Table 1).[8] This compound is about threefold more potent than **2** (IC_{50} = 30 nM), indicating that both compounds likely adopt similar conformations when bound to FXa, and that the cyanoguanidine may even be a better linker than the ketene aminal in **2**. Similar SARs are observed for both series when the P1 group is a mono- or disubstituted phenyl group (data not shown).[5] In addition, analogs with a P1 group derived from alkylamines were uniformly poor FXa inhibitors, similar to results found in the thiourea series (data not shown).[4] Thus, we focused our efforts in SAR optimization on compound **4**.

Early efforts were concentrated on the possible isosteres of the 2-methylbenzofuran-7-yl pharmacophore to improve the potency. All efforts to replace the 2-methylbenzofuran with other bicyclic aryls resulted in significant losses in activity (Table 1). For example, the 2-napthyl analog (**5**, IC_{50} = 780 nM) is about 60-fold less potent than **4**; replacement of the oxygen atom in 2-methyl benzofuran with either a sulfur (**6**, IC_{50} = 2882 nM) or NH (**10**, IC_{50} > 34,000 nM) led to analogs with much poorer activity compared to **4**. The isomeric 2-methylbenzofuran-6-yl analog **7** is completely inactive; while changing the 3-CH in the furan ring to a nitrogen atom led to compound **8** (IC_{50} = 2677 nM) with a 223-fold loss of activity. Other isosteric heteroaryl replacements (compounds **11–14**) are much less potent than **4**.

We next studied the SAR of substitutions on the 2-methyl benzofuran pharmacophore. Most changes to the substitution pattern on the furan ring resulted in significant losses in activity (Table 2). For example, the analog without the 2-methyl substituent (**15**, IC_{50} = 84 nM) is sevenfold less potent than **4**, while increasing the size of the 2-substituent from methyl to ethyl, resulted in a loss in activity of >1000-fold (**16**, IC_{50} = 15,538 nM). Changing the 2-methyl- to a 2-cyano-benzofuran led to a 20-fold less active compound **17** (IC_{50} = 2600 nM), while relocating the methyl group to the 3 position resulted in a 245-fold loss in activity (**18**, IC_{50} = 2939 nM). The 2,3-dimethyl substituted analog **19** is about 30-fold less active than **4**.

The SAR for the substituents of the phenyl ring of the 2-methyl benzofuran was also explored. While the 7-fluoro-2-methyl benzofuran analog (**20**, IC_{50} = 11 nM) has similar anti-FXa activity as compound **4**, both the 4- and 6-fluoro analogs (**21** and **22**) are less active. Increasing the size of the 7-substituent beyond a fluorine atom also produced less active compounds, with the 7-Cl (**23**) and 7-methyl (**24**) analogs showing about twofold loss of activity compared to **4**. Incorporation of bulkier 7-trifluoromethyl (**25**) and 7-methoxy (**26**) substituents led to significant losses of activity.

We also studied the SAR of the central caprolactam ring by varying its ring size and the chirality of its amino group. The results are summarized in Table 3. Compound **4**, the *S*-enantiomer with a seven-membered lactam ring, is the most potent analog among these compounds. It is about 77-fold more potent than its *R*-enantiomer **30** (IC_{50} = 940 nM) and the corresponding (*S*)-six-membered valerolactam analog **29** (IC_{50} = 928 nM). Both enantiomers of the five-membered lactam are very weak inhibitors of FXa. The racemic form of the eight-membered lactam analog **31** is also less potent than **4** with an IC_{50} of 195 nM.

With the optimized P1 pharmacophore and central lactam ring in hand, we next turned our attention to the SAR studies of the P4 binding groups. Similar to the thiourea series,[4] the replacement of the pyrrolidine with non-cyclic amines, or modest changes to the ring size (azetidine and piperidine) led to significant losses in potency (data not shown). Substitutions at the C-2 and C-3 positions on the pyrrolidine ring were well tolerated but none of these ana-