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Nonbenzamidine Compounds as Selective Factor Xa Inhibitors

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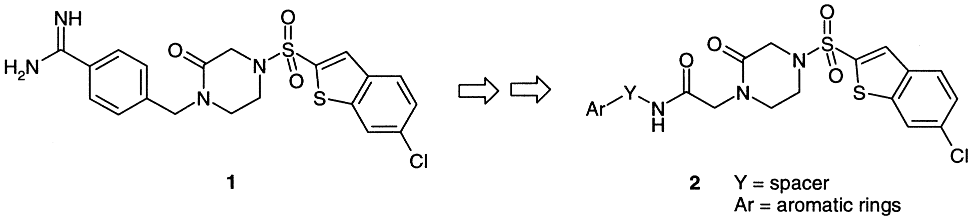
Abstract—Nonbenzamidine compounds (imidazole, pyridine, pyrimidine, and thiazole derivatives) as selective serine protease factor Xa inhibitors are discussed. © 2000 Elsevier Science Ltd. All rights reserved.

Factor Xa is a serine protease converting prothrombin to thrombin in the well-established cascade of blood coagulation. Abnormal blood clotting is responsible for a number of cardiovascular diseases. In addition, it is therapeutically beneficial to control the blood coagulation properties for patients undergoing surgery. The selective inhibition of factor Xa has been advanced as a desirable target for therapeutic intervention and the topic has been extensively reviewed for the management of thrombotic disorders.[1–6]

Most of the known factor Xa inhibitors[5] are benzamidine derivatives that contain a very polar basic group that is likely responsible for poor absorption and PK/PD properties for this class of molecules. Compound **1** was identified as a potent factor Xa inhibitor with a K_i of 1.3 nM.[7] In an ongoing effort to discover novel factor Xa inhibitors, our primary objective was to explore the opportunities to replace the benzamidine group of compound **1**.[8]

Our initial strategy was to insert a glycine unit between the amidine group and the piperazin-2-one[7] template. Factor Xa substrates and known thrombin inhibitors contain a glycine group in a similar region.[9] It was anticipated that the insertion of a glycine linker would be well tolerated. Secondly, the insertion of a glycine linker would bring more freedom to explore a larger variety of basic replacements for the benzamidine pharmacophore (**1**). Less basic functional groups such as imidazole, pyridine and pyrimidine were proposed to be able to interact with factor Xa. It might be very difficult to maintain good interactions with the enzyme for these types of groups incorporated in relatively rigid systems like compound **1**. Thirdly, the amide bond derived from the glycine might offer hydrogen bonding possibilities with the enzyme backbone. Fourthly, it is also conceivable that cyclization of the amide bond with the Ar ring properly substituted would bring structural diversity to the target molecules **2**, which otherwise would be difficult to access. Finally, ease of synthesis is essential for rapid development of SAR. It was obvious that a large variety of glycine amides could be synthesized quickly.

The synthesis of nonbenzamidine factor Xa inhibitors **2** is exemplified in Scheme 1. Alkylation of the commercially available piperazin-2-one (**3**) with *t*-butyl bromoacetate was uneventful in the presence of sodium hydride in DMF. Catalytic hydrogenation with palladium on carbon



1

2 Y = spacer
Ar = aromatic rings

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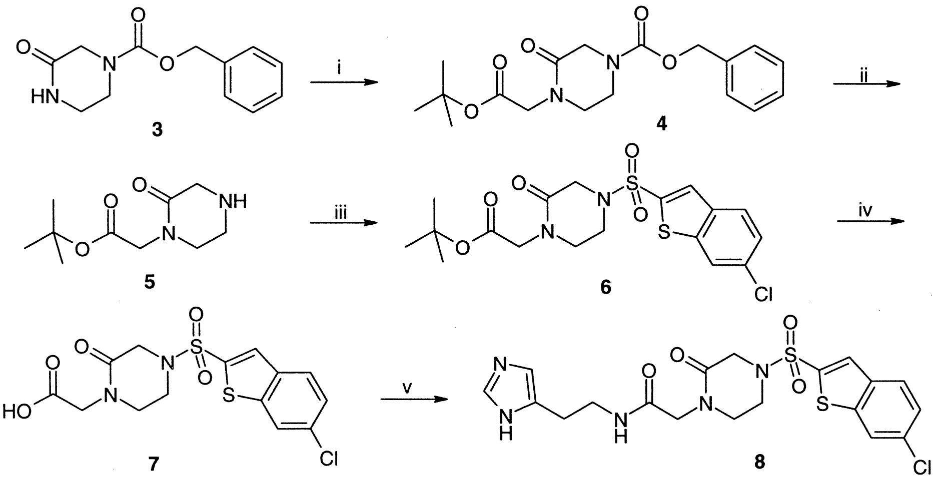
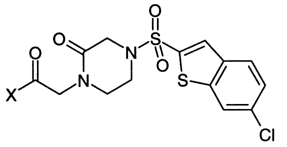


Scheme 1. Synthesis of imidazole analogues as factor Xa inhibitors. (i) NaH, DMF, *t*-butyl bromoacetate, 70%; (ii) Pd/C, H_2, MeOH, 80%; (iii) $ArSO_2Cl$, TEA, DCM, 92%; (iv) TFA, DCM, 99%; (v) DCC, histamine, 86%.

Table 1. Factor Xa inhibitory activity



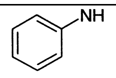
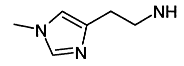
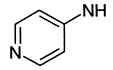
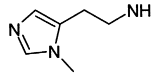
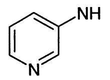
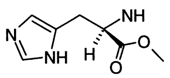
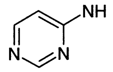
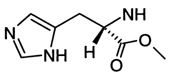
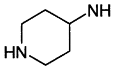
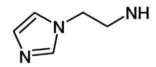
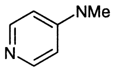
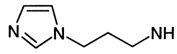
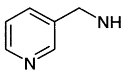
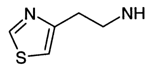
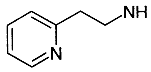
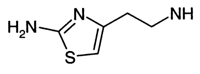
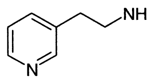
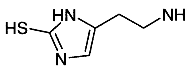
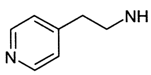
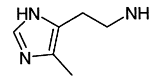
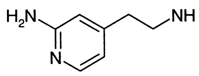
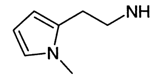
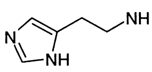
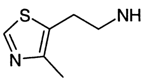
Compound	X	K_i (nM)	Compound	X	K_i (nM)
9		>1200	**20**		430
10		170	**21**		12
11		>1200	**22**		>1200
12		97	**23**		>1200
13		>1200	**24**		>1200
14		>1200	**25**		>1200
15		>1200	**26**		160
16		140	**27**		620
17		250	**28**		620
18		59	**29**		340
19		140	**30**		>1200
8		21	**31**		270

Table 2. Selectivity profiles of factor Xa inhibitors

Compound	K_i (nM)					
	FXa	Thrombin	Trypsin	APC	Plasmin	*t*-PA
8	21	>4000	>2900	>18 000	>7300	>8700
21	12	>4000	>2900	>18 000	>7300	>8700

of ester **4** afforded amine **5** which was then treated with the corresponding sulfonyl chloride.[8] The *t*-butyl ester **6** was hydrolyzed with trifluroacetic acid/dichloromethane. Acid **7** was then converted to a variety of amides[10] via standard coupling procedures starting with the acid chloride or mixed anhydride.

Factor Xa and other serine protease assays were performed as previously described.[11] The results of the glycine amide series as factor Xa inhibitors are included in Table 1. Phenyl analogue **9** was inactive against factor Xa, clearly indicating that the binding affinity of this class inhibitors is not solely derived from the combination of piperazin-2-one template and chlorobenzothienylsulfonamide. However, inclusion of nitrogen atoms into the phenyl ring enhances potency against factor Xa depending on the position of nitrogen atom(s) as in compounds (**10**, **11**, **12** vs **9**). Saturation of the pyridine ring as well as methylation of the amide bond greatly decrease the inhibitory activity (**13**, **14** vs **10**). Insertion of spacers (CH_2 or CH_2CH_2) afforded compounds **15**, **16**, **17** and **18**. Once again, the potency of these compounds depends on the position of the nitrogen atom and also the length of linker between the glycine group and pyridine ring. Compound **18** is the most potent inhibitor among the pyridine analogues with a K_i of 59 nM. Further substitution of the pyridine ring with an amino group, producing compound **19**, actually decreases the potency by ~2-fold.

Further improvement of potency is realized through replacement of the pyridine ring with an imidazole group. Compound **8** was found to be a potent factor Xa inhibitor with a K_i of 21 nM and an excellent selectivity against other serine proteases as shown in Table 2. It was also demonstrated to be a competitive inhibitor of factor Xa (data not shown). Interestingly, the N^3-methylated compound **21** is marginally more active than its parent, but 40-fold more potent than the corresponding N^1-methylated analogue **20**. The discovery of potent imidazole analogues is very interesting because this pharmacophore has never been reported as being a factor Xa inhibitor although very recently an imidazole group has independently been used as a S1 binding element in the search of thrombin inhibitors by several investigators.[12,13] Substitution of histamine with either D- or L-histadine affords compounds **22** and **23**, both of which are essentially inactive against factor Xa. The >50-fold loss of inhibitory activity observed with the isomeric imidazole analogue **24** seems to suggest that the orientation of imidazole group is critical for interactions with factor Xa, which is also true for compounds **28** and **29**. Expansion of the linker by an additional methylene group does not affect potency (**24** vs **25**). Significant decrease of activity was observed when the imidazole group of **8** was replaced by thiazoles or pyrrole (**26**, **27**, **30** and **31** vs **8** and **21**). Although the binding mode of this class of inhibitors with factor Xa has not been determined, such results might be explained by differences in basicity and hydrogen bond donor/acceptor possibilities.

In summary, we have discovered a novel series of glycine amide analogues as factor Xa inhibitors. It is clearly demonstrated that the imidazole derivatives **8** and **21** are potent inhibitors of factor Xa. This class of compounds is very selective against factor Xa over other serine proteases tested. These types of analogues can be readily synthesized and might prove useful in the further exploration of SAR around other serine protease targets. Optimization of these prototype compounds may lead to the discovery of novel anti-coagulation drugs.

References and Notes

1. Kaiser, B.; Hauptmann, J. *Cardiovasc. Drug Rev.* **1994**, *12*, 225.
2. Scarborough, R. M. *J. Enz. Inhib.* **1998**, *14*, 15.
3. Sturzebecher, J.; Hauptman, J. *Thromb. Res.* **1998**, *93*, 203.
4. Zhu, B.-Y.; Scarborough, R. M. *Curr. Opin. Cardiov. Pulmon. Ren. Investig. Drugs* **1999**, *1*, 63.
5. Ewing, W. R.; Pauls, H. W.; Spada, A. P. *Drugs Future* **1999**, *24*, 771.
6. Al-Obeidi, F.; Ostrem, J. A. *Exp. Opin. Ther. Pat.* **1999**, *9*, 931.
7. Ewing, W. R.; Becker, M. R.; Li, A.; Davis, R. S.; Jiang, J. Z.; Zulli, A.; Choi-Sledeski, Y. M.; Pauls, H. W.; Myers, M. R.; Spada, A. P.; Maignan, S.; Guilloteau, J-P.; Mikol, V.; Brown, K. D.; Colussi, D.; Chu, V.; Leadley, R. J.; Cheney, D.; Mason, J. *Abstracts of Papers*, 219th National Meeting of the American Chemical Society, San Francisco, CA, 26-30 March 2000; American Chemical Society: Washington, DC, 2000; MEDI161.
8. Ewing, W. R.; Becker, M. R.; Choi-Sledeski, Y. M.; Pauls, H. W.; He, W.; Condon, S. M.; Davis, R. S.; Hanney, B. A.; Spada, A. P.; Burns, C. J.; Jiang, J. Z.; Li, A.; Myers, M. R.; Lau, W. F.; Poli, G. B. WO 9937304A1, 1999.
9. Fevig, J. M.; Wexler, R. R. *Annu. Rep. Med. Chem.* **1999**, *34*, 81.
10. All final compounds were purified by HPLC and fully characterized.
11. Chu, V.; Brown, K.; Colussi, D.; Choi, Y. M.; Green, D.; Pauls, H.; Spada, A.; Perrone, M.; Leadley, R.; Dunwiddie, C. T. *Thromb. Res.* **2000**, in press.
12. Isaacs, R. C. A.; Newton, C. L.; Solinsky, M. G.; Naylor-Olsen, A. M. *Abstracts of Papers*, 217th National Meeting of the American Chemical Society, Anaheim, CA, 21-25 March 1999; American Chemical Society: Washington, DC, 1999; MEDI005.
13. Wiley, M. R.; Weir, L. C.; Briggs, S. L.; Chirgadze, N. Y.; Clawson, D.; Gifford-Moore, D. S.; Schacht, A. L.; Smith, G. F.; Vasudevan, V.; Zornes, L. L.; Klimkowski, V. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2767.