Bioorganic & Medicinal Chemistry Letters 27 (2017) 2650–2654

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Neutral macrocyclic factor VIIa inhibitors

Nicholas R. Wurtz *, Brandon L. Parkhurst, Indawati DeLucca, Peter W. Glunz, Wen Jiang, Xiaojun Zhang, Daniel L. Cheney, Jeffrey M. Bozarth, Alan R. Rendina, Anzhi Wei, Tim Harper, Joseph M. Luettgen, Yiming Wu, Pancras C. Wong, Dietmar A. Seiffert, Ruth R. Wexler, E. Scott Priestley

Bristol-Myers Squibb Research and Development, Princeton, NJ 08534, United States

ARTICLE INFO

Article history:
Received 14 December 2016
Revised 28 March 2017
Accepted 1 April 2017
Available online 19 April 2017

Keywords:
TF-FVIIa
Macrocycles
Anticoagulant
Neutral P1

ABSTRACT

Factor VIIa (FVIIa) inhibitors have shown strong antithrombotic efficacy in preclinical thrombosis models with limited bleeding liabilities. Discovery of potent, orally active FVIIa inhibitors has been largely unsuccessful due to the requirement of a basic P1 group to interact with Asp189 in the S1 binding pocket, limiting their membrane permeability. We have combined recently reported neutral P1 binding substituents with a highly optimized macrocyclic chemotype to produce FVIIa inhibitors with low nanomolar potency and enhanced permeability.

Vitamin K antagonists and heparins have been part of the standard of care for thromboembolic disorders for many years, but these antithrombotic therapies possess significant limitations. Vitamin K antagonists, such as warfarin, have significant drug and food interactions, which create a challenge for maintenance of the desired therapeutic effect without excessive bleeding.[1] Heparins are parenterally administered, which prevents their widespread use in long-term therapy. Several decades of research have produced anticoagulants targeting thrombin or FXa that demonstrate improved efficacy with decreased bleeding in clinical studies.[2,3] Even though these new therapies are replacing the older antithrombotics, research to find safe, effective anticoagulants to complement existing therapies continues.

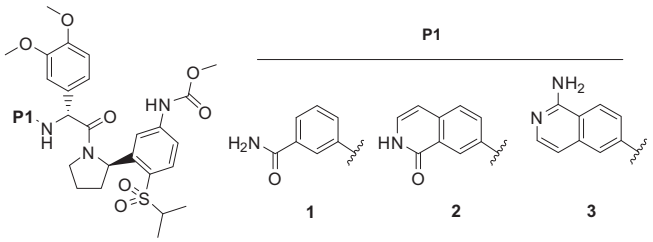
The extrinsic pathway in the clotting cascade is initiated by the tissue factor-Factor VIIa complex (TF-FVIIa) that activates Factors IX and X.[4] This protein complex has attracted significant interest because small molecule FVIIa inhibitors have strong efficacy in preclinical models of thrombosis with minimal effect on provoked bleeding at antithrombotic doses.[5] Inhibition of the TF-FVIIa complex may also have therapeutic potential in other areas such as cancer or inflammation due both to its antithrombotic effect as well as impact on other signaling pathways.[6–8] Despite years of study, the discovery of a potent, orally bioavailable FVIIa inhibitor clinical candidate remains elusive.[9]

Recently we have reported the discovery of potent phenylpyrrolidine FVIIa inhibitors with a series of neutral P1[10] substituents (Fig. 1).[11] Compound **1** with a *m*-aminobenzamide P1 group is moderately potent with good selectivity and served as a starting point for optimization. A FVIIa fragment screening effort lead to the identification of a series of bicyclic amide P1 binding groups, such as the isoquinolinone, which were incorporated into the phenylpyrrolidine scaffold to afford compounds such as **2**, which resulted in a significant increase in potency and permeability.[11] These neutral P1 groups have potential advantages over the more commonly reported basic P1 groups such as amidines which typically lack permeability since they exist as charged species at physiological pH. Additionally, neutral P1 substituents often have improved selectivity because they lack the dominant salt bridge formed between cationic P1 groups, such as amidines, and Asp189, which is located at the base of the S1 pocket of many serine proteases. Weakly basic P1 groups, such as the aminoisoquinoline shown in compound **3**, are a significant advance,[12–15] but the discovery of orally active FXa inhibitors demonstrates the potential advantages of utilizing neutral groups that bind in the S1 pocket.[2] While the installation of neutral P1 groups in the phenylpyrrolidine chemotype demonstrated improved permeability and selectivity over the weakly basic aminoisoquinoline, the molecules still do not reach sufficient potency and clotting activity for the desired antithrombotic effect.

Macrocyclic inhibitors of FVIIa[16–18] (e.g., compound **4**, Fig. 2) provide an alternative to the phenylpyrrolidines as a way to restrict the bioactive conformation of phenylglycine-based

* Corresponding author.
E-mail address: nicholas.wurtz@bms.com (N.R. Wurtz).

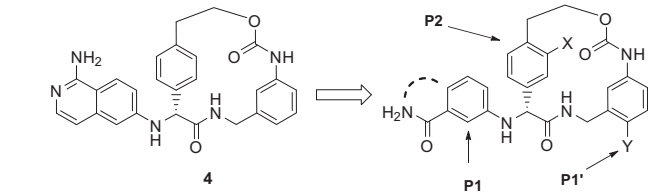
http://dx.doi.org/10.1016/j.bmcl.2017.04.008
0960-894X/



	1	2	3
FVIIa K_i, nM[a]	190	13	1.8
FVII def PT, μM[a]	8.6	7.3	3.5
PAMPA, nm/s, pH 7.4	24	87	2
tissue kallikrein K_i, nM	>10000	>10000	110

[a] FVIIa enzyme assays and the FVIIa-deficient prothrombin time assay were performed according to established protocols.[4]

Fig. 1. Comparison of phenylpyrrolidine FVIIa inhibitors with different P1 groups.



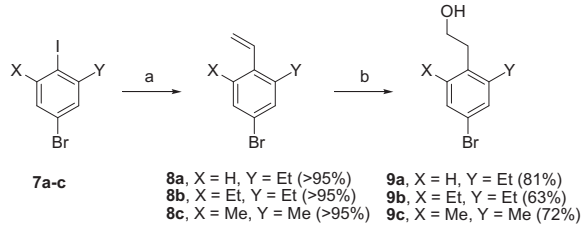
FVIIa K_i, nM[a]	140
FVII def PT, μM[a]	45.5
PAMPA, nm/s, pH 7.4	0
tissue kal K_i, nM	14

[a] FVIIa enzyme assays and the FVIIa-deficient prothrombin assay were performed according to established protocols.[4]

Fig. 2. Introduction of the *m*-aminobenzamide P1 into the macrocyclic FVIIa chemotype.

inhibitors. The rigid macrocyclic scaffold efficiently displays P1 groups as well as provides access to key hydrophobic S2 and S1′ binding pockets necessary for high affinity binding. Initially reported with the weakly basic aminoisoquinoline, the macrocycles are very potent compounds with little permeability and poor selectivity vs. tissue kallikrein. Incorporation of the neutral P1 groups into the macrocycle chemotype was undertaken to determine if the resulting FVIIa inhibitors would be permeable with improved potency and selectivity.

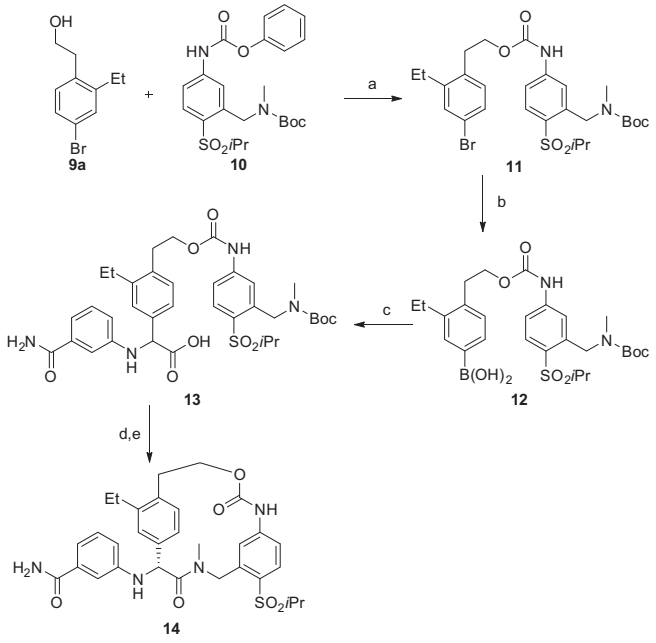
The macrocycle chemotype can be assembled from three key fragments containing the P1, P2 and P1′ binding units. We set out to make a variety of substituents on the internal phenyl ethyl alcohol to access the hydrophobic P2 binding pocket. *p*-Bromophenylethanols, the key intermediates for this route, proved difficult to synthesize when symmetrically disubstituted. Using 1,3-substituted 5-bromo-2-iodobenzenes **7a–c** as starting materials, the aryliodide could be selectively exchanged in preference to the arylbromide to form the corresponding organolithium or Grignard species, but efforts to find a suitable electrophile that did not require a multistep homologation were unsuccessful. Palladium coupling with a zinc enolate occurred selectively at the less hindered bromide, providing an undesired product. After trying several vinylation protocols, we discovered that coupling trimethyl(vinyl)silane in the presence of KF, *n*-Bu_4NCl and Pd $(dba)_2$[19] was a robust, high yielding solution that worked for both electron rich and electron poor substituents (Scheme 1). After the Pd-mediated vinylation, the resulting stilbenes could be converted



Scheme 1. Synthesis of substituted *p*-bromophenethylalcohols. (a) trimethyl(vinyl) silane (4 eq), KF (3 eq), *n*-Bu_4NCl (2 eq), $Pd(dba)_2$ (0.1 eq), toluene (0.5 M), molecular sieves, 170 °C, 45 min; (b) 9-BBN (10 eq), THF, 120 °C; NaOH, H_2O_2.

to the desired phenethyl alcohol by hydroborylation with 9-BBN. This sequence was routinely carried out on multigram scale.

The synthesis of macrocycle **14** is shown as an example of assembly of the key fragments (Scheme 2). *p*-Bromophenethanol **9a** was coupled with the phenyl carbamate **10** in the presence of sodium hydride in good yield. As previously reported,[16] bromide **11** was converted into boronic acid **12** via Suzuki-Miyaura conditions and the hydrolysis of the resulting boronic ester during purification by preparative HPLC. A mixture of the P1 group, in this case *m*-aminobenzamide, glyoxylic acid and the boronic acid was heated in the microwave to yield the desired phenylglycine via a Petasis reaction.[12,20] Deprotection of the Boc-group followed by PyBOP or BOP mediated cyclization using slow addition of the starting material to the coupling reagents over several hours provided the desired macrocycle. A mixture of atropisomers (2:1 inactive:active) was observed after cyclization. Atropisomers could be separated by preparative HPLC and the enantiomers could be separated by chiral HPLC either pre- or post- cyclization. When the atropisomers did not readily interconvert (e.g., compound **14**), the inactive isomer could be recycled by heating in DMSO at 100 °C for 2 days to again reach the thermal dynamic equilibrium (2:1 mixture) and repurified. Multiple inhibitor-FVIIa co-crystal



Scheme 2. Example of synthetic route for macrocycles. (a) NaH (2.5 eq), THF, rt, 92%; (b) Bis(neopentyl glycolato)diboron, $PdCl_2(dppf)$, KOAc, 80 °C, 4 h; prep HPLC (0.1% TFA, MeOH/water), 59%; (c) 3-aminobenzamide, glyoxylic acid, acetonitrile/DMF, μwave, 100 °C, 600 s, 86%; (d) HCl; (e) PyBOP, DMAP, DIEA, 26% over 2 steps.