European Journal of Medicinal Chemistry 44 (2009) 2787–2795

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design of novel aminopyrrolidine factor Xa inhibitors from a screening hit

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ARTICLE INFO

Article history:
Received 7 November 2008
Received in revised form
28 November 2008
Accepted 17 December 2008
Available online 3 January 2009

Keywords:
Anticoagulant
Oral bioavailability
Factor Xa inhibitor
Biased screen
Computer-aided design
X-ray analysis
Clotting assay

ABSTRACT

Starting from a hit identified by focused screening, 3-aminopyrrolidine factor Xa inhibitors were designed. The binding mode as determined by X-ray structural analysis as well as the pharmacokinetic behaviour of selected compounds is discussed.

1. Introduction

Prevention of coagulation is required in a wide range of patients presenting with conditions such as venous thromboembolism, atrial fibrillation and acute coronary syndromes. Anticoagulants currently in clinical use include the parenterally administered unfractionated heparin and low molecular weight heparins (LMWHs) as well as the orally administered coumarins. Heparin and the LMWHs are indirect inhibitors of thrombin and factor Xa. The coumarins act by inhibiting γ-carboxylation in the biosynthesis of coagulation factors prothrombin, VII, IX and X. This mechanism leads to a slow on-set of action. Additionally, the coumarins suffer from substantial food and drug interaction and high protein binding [1], rendering it very difficult to maintain a balanced plasma exposure. Careful and regular monitoring of the patient is therefore required [2].

During the last decades substantial efforts have been devoted to the search for an orally bioavailable replacement of the coumarins. Out of countless research programs, the first compound to have reached the market was Ximelagatran [3] from AstraZeneca, which is a double prodrug of the direct thrombin inhibitor Melagatran. Ximelagatran was launched in France in 2004 under the trade name Exanta, but has been withdrawn from the market due to concerns about long-term liver damage and possible risk of heart attacks [4]. In the meantime Pradaxa® [5], (developed by Boehringer Ingelheim), like Ximelagatran a double prodrug of a direct thrombin inhibitor, has been approved by the European Medicines Agency in spring 2008 and has since been launched in Germany and the UK [6]. Johnson & Johnson/Bayer have submitted an application for US new drug approval (NDA) of its oral F.Xa inhibitor Xarelto® [7], and just recently the drug was approved in Canada [8]. Bristol-Myers Squibb's oral F.Xa inhibitor Apixaban [9] is currently in phase III clinical studies [10]. Oral anticoagulants which have been studied in phase III clinical trials have been discussed in recent review articles [11]. Several oral factor Xa inhibitors are being investigated in phase II clinical trials. The results of these studies have been reviewed extensively [12].

The serine protease factor Xa has a unique role in the coagulation cascade. It is located at the convergence point of the intrinsic and extrinsic pathways and therefore represents an interesting target for the development of a novel anticoagulant. During the past few years enormous efforts have been devoted to the search

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doi:10.1016/j.ejmech.2008.12.025

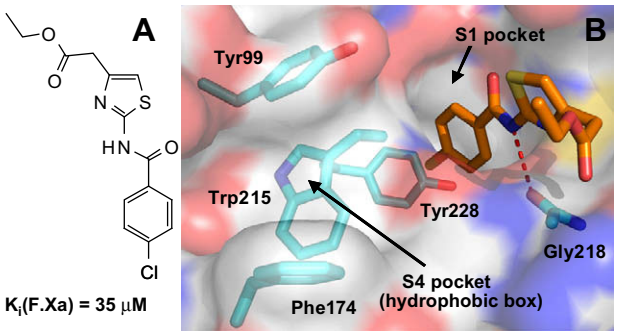


Fig. 1. (A) Hit from biased screen. (B) Model of screening hit bound to the active site of F.Xa.

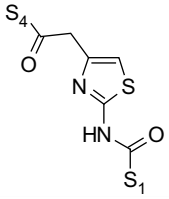
for an orally active and selective factor Xa inhibitor resulting in a great number of disclosed structures [13].

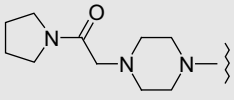
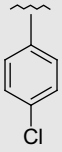
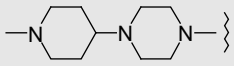
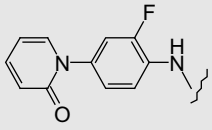
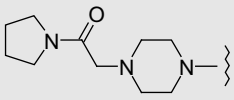
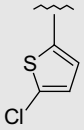
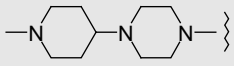
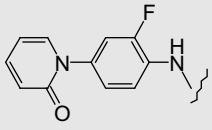
Here we report the identification of novel 3-aminopyrrolidine factor Xa inhibitors starting from a hit originated from a biased screen. Recently a similar series of aminopyrrolidine factor Xa inhibitors has been published by a research group from Bristol-Myers Squibb [14].

2. Results and discussion

Like other proteases of the coagulation cascade, factor Xa possesses an S_1 specificity pocket recognizing basic motifs by means of the Asp189 side chain at its bottom. Inhibitors with typical basic S_1 binding elements such as amidines suffer often from poor bioavailability. At the outset of this project, ample precedence in the literature indicated that chlorinated phenyl or heteroaromatic rings would be good neutral motifs for binding to the S_1 pocket [15]. A focused screen of the Roche compound collection was performed under the following procedure: (i) selecting all chlorinated planar cycles without substituents in either *ortho* position, (ii) docking these into the coordinates of a published protein crystal structure (PDB code 1nfy) with the constraint of holding the C–Cl bond in a position allowing a chlorine–aromatic interaction with Tyr228 and (iii) removing typical GPCR ligands and highly flexible compounds from the solution set. This resulted in about 8000 compounds, for which single point

Table 1
Binding affinity, functional activity and selectivity of aminothiazoles **1**–**6**.



Compound	S1	S4	K_i (μM)		Thrombin F.VIIa	2 × PT (μM)	2 × aPTT (μM)	log *D*	Solubility (μg/mL)
			F.Xa	Thrombin					
1			0.442	2.8	6.3	17.8	32.0	2.2	>580
2			0.162	8.6	53	8.9	20.9	0.6	>620
3			0.112	>35	>310	45.6	70.1	>3.0	<1.0
4			0.099	5.9	60	12.2	33.8	2.1	>640
5			0.032	15.3	480	4.4	10.4	1.0	>620
6			0.018	>35	>1950	43.8	73.3	>3.0	<1.0