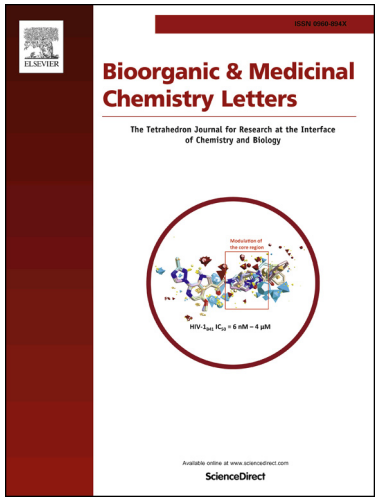

Trypsin inhibitors for the treatment of pancreatitis

Trixi Brandl, Oliver Simic, Philip R. Skaanderup, Kenji Namoto, Frederic Berst, Claus Ehrhardt, Nikolaus Schiering, Irene Mueller, Julian Woelcke

PII: S0960-894X(16)30742-9
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.07.029
Reference: BMCL 24073

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 1 June 2016
Revised Date: 12 July 2016
Accepted Date: 13 July 2016

Please cite this article as: Brandl, T., Simic, O., Skaanderup, P.R., Namoto, K., Berst, F., Ehrhardt, C., Schiering, N., Mueller, I., Woelcke, J., Trypsin inhibitors for the treatment of pancreatitis, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.07.029

ELSEVIER

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Trypsin inhibitors for the treatment of pancreatitis

Trixi Brandl[a,*], Oliver Simic[a], Philip R. Skaanderup[a], Kenji Namoto[a], Frederic Berst[a], Claus Ehrhardt[a], Nikolaus Schiering[a], Irene Mueller[a] and Julian Woelcke[b]

[a]*Novartis Pharma AG, Novartis Institutes for BioMedical Research, Novartis Campus, CH-4002 Basel, Switzerland*
[b]*Novartis Pharma AG, Cardio Metabolic Development Franchise, Novartis Campus, CH-4002 Basel, Switzerland*

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Trypsin inhibitor
Pancreatitis
hERG inhibition
X-ray crystal structure

ABSTRACT

Proline-based trypsin inhibitors occupying the S1-S2-S1' region were identified by an HTS screening campaign. It was discovered that truncation of the P1' moiety and appropriate extension into the S4 region led to highly potent trypsin inhibitors with excellent selectivity against related serine proteases and a favorable hERG profile.

Acute and chronic pancreatitis are serious conditions characterized by inflammation, fibrosis as well as endocrine and exocrine dysfunction of the pancreas. The unmet medical need is reflected in a high incidence rate,[1] and a mortality of up to 40% in the US.[1-3] Pancreatitis is the result of genetic and environmental factors leading to inappropriate activation of trypsin as well as other proteases and lipases causing direct pancreatic injury which in turn triggers an inflammatory response. The genetic contribution to risk for hereditary pancreatitis is due to autosomal dominant gain-of-function mutations in the cationic trypsinogen gene PRSS1[4-6] and to loss-of-function mutations in the gene of the endogenous trypsin inhibitor Kazal type 1 (SPINK1).[7] Premature activation of trypsinogen within the acinar cells of the pancreas is considered to be an early event in the onset of pancreatitis.[8,9] This enhanced intracellular proteolytic activity results in cell injury and triggers an inflammatory response. Recent investigation of pathophysiologic markers indicates trypsinogen and other pancreatic proteases have a close correlation to disease severity.[3] Trypsin activation is believed to be a pivotal step in the onset of the disease.

Consequently, trypsin inhibitors have gained some interest as early as the 1960s when aprotinin, a Kunitz type serine protease inhibitor was widely used for patients with acute pancreatitis. However, effectiveness of aprotinin could never be confirmed, most likely due to insufficient plasma and peritoneal levels of the drug after intravenous administration.[10] Subsequently, non-peptidic irreversible trypsin inhibitors like gabexate (intravenous) and camostat (oral) were launched in Japan. These compounds display activity against several other serine proteases and show very short *in vivo* half-lives, limiting their broader use.[11,12]

Therefore, potent and selective trypsin inhibitors with favorable intravenous pharmacokinetic properties would be attractive for the development of novel drugs for the treatment of pancreatitis.

By screening our in-house compound library,[13,14] a series of benzyl amine-substituted proline derivatives emerged as an interesting hit class. Compound **1** displayed good trypsin activity in the sub micro-molar range (Figure **1**) combined with a remarkable selectivity against a panel of related S1-serine proteases (Table **4**). In addition, physico-chemical properties were in an acceptable range with a solubility of >1 mM at pH 6.8 and a measured logP of 3.0.