Design, synthesis and biological activity of novel peptidyl benzyl ketone FVIIa inhibitors

Herein is described the synthesis of a novel class of peptidyl FVIIa inhibitors having a C-terminal benzyl ketone group. This class is designed to be potentially suitable as stabilization agents of liquid formulations of rFVIIa, which is a serine protease used for the treatment of hemophilia A and B inhibitor patients. A library of compounds was synthesized with different tripeptide sequences, N-terminals and D-amino acids in the P3 position. Cbz-D-Phe–Phe–Arg–bk (33) was found to be the best candidate with a potency of Ki = 8 IM and no substantial inhibition of related blood coagulation factors (thrombin and FXa). Computational studies revealed that 33 has a very stable binding conformation due to intramolecular hydrogen bonds, which cannot be formed with L-Phe in the P3 position. Nonpolar amino acids were found to be superior, probably due to a minimization of the cost of desolvation upon binding to FVIIa.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Novo Nordisk AS
Contributors: Storgaard, M., Henriksen, S. T., Zaragoza, F., Peschke, B., Tanner, D. A.
Pages: 3918-3922
Publication date: 2011
Peer-reviewed: Yes

Publication information
Journal: Bioorganic & Medicinal Chemistry Letters
Volume: 21
ISSN (Print): 0960-894X
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 2.53 SJR 0.81 SNIP 0.853
Web of Science (2017): Impact factor 2.442
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.52 SJR 0.849 SNIP 0.85
Web of Science (2016): Impact factor 2.454
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 2.55 SJR 0.923 SNIP 0.877
Web of Science (2015): Impact factor 2.486
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 2.43 SJR 0.942 SNIP 0.885
Web of Science (2014): Impact factor 2.42
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 2.47 SJR 0.931 SNIP 0.902
Web of Science (2013): Impact factor 2.331
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 2.49 SJR 1.091 SNIP 0.934
Web of Science (2012): Impact factor 2.338
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 2.7 SJR 1.122 SNIP 0.964
Web of Science (2011): Impact factor 2.554
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.08 SNIP 0.989
Web of Science (2010): Impact factor 2.661
Keywords: Serine protease inhibitor, C-Terminal modified peptide, Activated factor VII, Stabilization agent, Peptidyl benzyl ketone

DOIs: 10.1016/j.bmcl.2011.05.025