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(54) Title: SERINE PEPTIDASE MODULATORS

(57) Abstract

The present invention relates to new compounds having modulatory (inhibitory and stimulatory) activity on serine peptidases and proteases in general and dipeptidyl peptidase IV, prolyl oligopeptidase (PO), dipeptidyl peptidase II (DPP II), fibroblast activation protein α (FAPα), lysosomal Pro–X carboxypeptidase and elastase in particular. These new compounds can be used for the treatment of a variety of disease states in which these peptidases are involved.

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SERINE PEPTIDASE MODULATORS

Field of the invention

The present invention relates to novel modulators (inhibitors and stimulators) of serine peptidases and proteases in general and dipeptidyl peptidase IV, prolyl oligopeptidase (PO), dipeptidyl peptidase II (DPP II), fibroblast activation protein α (FAPα), lysosomal Pro-X carboxypeptidase and elastase in particular. The invention further relates to the preparation and use of these compounds for selective modulation (inhibition or stimulation) of serine peptidases and proteases and to pharmaceutical preparations comprising them. The terms "peptidase" and "protease" are used interchangeably.

Background of the invention

Serine peptidases/proteases, like granzymes, mast cell tryptase, elastases, trypsin-like enzymes, prolyl oligopeptidase, dipeptidyl peptidase II and dipeptidyl peptidase IV are involved in various processes that take place in the body, such as blood coagulation, inflammation, immune response, and control of peptide hormone metabolism in general. Although serine peptidases are a physiological necessity they may also constitute a potential health hazard in case serine peptidase activity in the body is not controlled.

Serine peptidases have been described to be involved in various medical indications. Blood coagulation serine proteases are for example responsible for vascular clotting as well as cerebral and coronary infarction. Chymotrypsin-like enzymes and plasmin are involved in tumour invasion, tissue remodeling and clot dissociation. Pancreatitis, emphysema, rheumatoid arthritis, inflammation and adult respiratory distress syndrome may in some instances be caused by the uncontrolled proteolysis by other serine proteases such as elastase.

Serine peptidases form a large group with many members that are divided into clans and families. One member of the clan SC is dipeptidyl peptidase IV (DPP IV, EC 3.4.14.5), which is a highly specific exopeptidase with a serine type mechanism of protease activity, cleaving off dipeptides from the amino-terminus of peptides with proline or alanine at the penultimate position. In addition the slow release of dipeptides of the type X-Gly or X-Ser is reported for some naturally occurring peptides. DPP IV is constitutively expressed on epithelial and endothelial cells of a variety of different tissues, and is also found in body fluids. In the hematopoietic system, DPP IV was identified as the leukocyte antigen CD26.

Prolyl oligopeptidase (PO, EC 3.4.21.26) was discovered in the human uterus as an oxytocin-degrading enzyme. The enzyme shows a high specificity for proline residues and hydrolyses the peptide bond at its carboxyl side, provided the proline is not at the peptide amino-terminus. This endopeptidase has like DPPIV, a serine type mechanism and it is characterised by its activity on oligopeptides. PO cleaves specifically the Pro-Xaa bond in biological active peptides (substance P, ocytoxin, vasopressin, gonadoliberin, bradykinin, neurotensin) and it is likely to participate in the *in vivo* regulation of their actions. A role for PO in memory and other neural processes has been proposed (Yoshimoto T. and Ito K. in Handbook of proteolytic enzymes, eds. Barrett et al., Academic Press, 1998, p. 272-374).

Fibroblast activation protein α (FAPα) was discovered as a cell surface antigen of cultured normal fibroblasts. Its expression *in vivo* revealed to be very restricted on normal cells. In contrast, activated tumor stromal fibroblasts found in certain carcinomas express high levels of FAPα. The biological role of FAPα expression remains to be elucidated but speculations on functions in tissue remodeling and repair have been made (Rettig, FAPα in Barrett *supra*, p. 385-389).

Dipeptidyl peptidase II (DPPII, EC 3.4.14.2) releases N-terminal dipeptides from oligopeptides, provided their N-termini are unsubstituted. The preferred P1 residues are Ala and Pro. An increase in serum DPPII has been observed in cancer patients and extremely high levels of DPPII are present in human carcinoma cells. DPPII can be inhibited by the classical (unspecific) inhibitors of serine type peptidases (J.K.McDonald in Barrett, supra, p. 408-411).

Elastases are defined by their ability to release soluble peptides from insoluble elastin fibers by a proteolytic process called elastinolysis. Elastase belongs to the chymotrypsin family of leucocyte serine-type proteases. Human leucocyte elastase (EC 3.4.21.37) preferentially cleaves peptides with a Val in P1 but also peptide bonds with Ala, Ser and Cys in P1 are hydrolyzed and it is believed to possess an extended substrate-binding site. The possible involvement of leucocyte elastase in inflammatory diseases, triggered the search for development of specific inhibitors. Moreover, a pathological role in lung emphysema, cystic fibrosis and adult respiratory distress syndrome has been suggested (J. Bieth in Barrett, supra, p. 54-60; D.Farley et al. in Pharmaceutical Enzymes, ed. A. Lauwers and S. Scharpé, Marcel Dekker, Inc., 1997, p. 306-326).

Lysosomal Pro-X carboxypeptidase (prolylcarboxypeptidase, angiotensinase C, EC 3.4.16.2) cleaves C-terminal amino acids from peptides with the general structure X-Pro-Y, where X is either a blocking group, another protected amino acid, or a peptide, and Y is an aromatic or aliphatic amino acid with a free carboxylic group. The enzyme is recovered from the lysosomal fraction of different tissues. Although the enzyme has an acidic pH optimum for small synthetic substrates (pH 5.0), it retains 50% of its maximal activity at physiological pH towards larger peptide substrates. (Des-Arg9)-bradykinin and angiotensin II are possible natural substrates for lysosomal Pro-X

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