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Protease inhibitors and their peptidomimetic derivatives as potential drugs

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Abstract

Precise spatial and temporal regulation of proteolytic activity is essential to human physiology. Modulation of protease activity with synthetic peptidomimetic inhibitors has proven to be clinically useful for treating human immunodeficiency virus (HIV) and hypertension and shows potential for medicinal application in cancer, obesity, cardiovascular, inflammatory, neurodegenerative diseases, and various infectious and parasitic diseases. Exploration of natural inhibitors and synthesis of peptidomimetic molecules has provided many promising compounds performing successfully in animal studies. Several protease inhibitors are undergoing further evaluation in human clinical trials. New research strategies are now focusing on the need for improved comprehension of protease-regulated cascades, along with precise selection of targets and improved inhibitor specificity. It remains to be seen which second generation agents will evolve into approved drugs or complementary therapies.

Keywords: Protease; Protease inhibitors; Therapeutic application; Clinical trials; Approved drugs

Abbreviations: α1-PI, alpha1-protease inhibitor; 3D-QSAR, three-dimensional quantitative structure–activity relationship; ACE, angiotensin-converting enzyme; AIDS, acquired immune deficiency syndrome; BBI, Bowman-Birk inhibitor; BBIC, Bowman-Birk inhibitor concentrate; CCK, cholecystokinin; CMV, human cytomegalovirus; DNA, deoxyribonucleic acid; DP IV, dipeptidyl peptidase IV; ECM, extracellular matrix; FDA, Food and Drug Administration; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRV, human rhinovirus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; IL, interleukin; MMP, matrix metalloproteases; NF-κB, nuclear factor kappa B; PPI, potato protease inhibitor; RNA, ribonucleic acid; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome associated coronavirus; SLPI, secretory leukocyte protease inhibitor; TACE, TNF-α converting enzyme; TIMP, tissue inhibitors of matrix metalloproteases; TNF-α, tumor necrosis factor-alpha; uPA, urokinase plasminogen-activating enzyme.

Contents

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1. Introduction

Many biological functions rely on proteases, including food digestion, lysosomal degradation, and signaling cascades. Since the hydrolysis of the peptide bond catalyzed by proteases is essentially irreversible, an extensive regulatory network of protease inhibitors has evolved to ensure targeted spatial and temporal control of their activity.

Naturally occurring protease inhibitors control proteolysis within an organism, as well as inactivate proteases of competing or predatory species. Inhibitors can be generally classified into 2 large groups based on their structural dichotomy: low molecular weight peptidomimetic inhibitors and protein protease inhibitors composed of one or more peptide chains. Protease inhibitors can be further classified into 5 groups (serine, threonine, cysteine, aspartyl and metalloprotease inhibitors) according to the mechanism employed at the active site of proteases they inhibit. Some protease inhibitors interfere with more than one type of protease. For example, the serine family of protease inhibitors (serpins) is generally thought of as active against serine proteases, yet contains several important inhibitors of cysteine proteases as well.

Proteolytic inhibition by protease inhibitors can occur via 2 mechanisms: irreversible trapping reactions and reversible tight-binding reactions (Rawlings et al., 2004). Inhibitors which bind through a trapping mechanism change conformation after cleaving an internal peptide bond and "trap" the enzyme molecule covalently; neither the inhibitor nor protease can participate in further reactions. In tight-binding reactions, the inhibitor binds directly to the active site of the protease; these reactions are reversible and the inhibitor can dissociate from the enzyme in either the virgin state, or after modification by the protease.

As therapeutic agents, protease inhibitors have been investigated in the past decade chiefly for the treatment of human immunodeficiency virus (HIV) and hypertension. They are commonly used in combination therapy with reverse transcriptase inhibitors to reduce the viral load in HIV positive individuals; however, they show formidable efficacy even when used in monotherapy (Arribas et al., 2005). The unique bonds cleaved by the HIV protease, Phe-Pro, Phe-Leu, and Phe-Thr, enabled the design of inhibitors that are highly selective for the viral protease (Patick & Potts, 1998). The introduction of protease inhibitors between 1995 and 1996 has been correlated with a significant increase in survival time in acquired immune deficiency syndrome (AIDS) patients, dwarfing the effect of previously used antiretroviral agents (Schwarcz et al., 2000). Currently, there are 8 approved protease inhibitors for HIV treatment, including tipranavir, indinavir, saquinavir, and lopinavir. New generations of inhibitors are designed to maximize efficacy and overcome viral resistance to previously used drugs (Table 1). One of several promising second-generation HIV protease inhibitors is TMC-114 (Fig. 1), currently in phase III clinical trials.

Angiotensin-converting enzyme (ACE) inhibitors provide another well-established example of protease inhibitors as therapeutic agents. ACE catalyzes the hydrolysis of angiotensin I to angiotensin II, a potent vasoconstrictor, and inactivates bradykinin, a vasodilator (Ottaviani et al., 2005). ACE inhibitors thus reduce blood pressure by decreasing peripheral vascular resistance. It has also been found that ACE inhibitors reduce proteinuria and stabilize renal function, making them useful in treating diabetic nephropathy.

The use of ACE inhibitors began in 1977 with the approval of captopril. Other ACE inhibitors have since joined the market (Table 1). ACE inhibitors have similar blood pressure lowering efficacy as other antihypertensives, but exhibit improved tolerability, fewer side effects and desirable metabolic profiles (Ibrahim, 2006). A novel combined ACE/neutral endopeptidase inhibitor, omapatrilat (Fig. 1), is currently in clinical trials. Aliskiren (SPP100), a renin inhibitor developed by Novartis (Wood et al., 2003), may represent the first of a new family of antihypertensive drugs that inhibit the renin–angiotensin system at an earlier step than ACE inhibitors (Nussberger et al., 2002). This new mechanism is unlikely to produce the cough or angioedema side effects linked with ACE inhibitor use.

The success of HIV protease and ACE inhibitors has led to interest in the development of protease inhibitors to treat other conditions. Protease inhibitors show potential as antiviral agents which can be engineered to inhibit specific essential viral proteases while leaving the body's own cells unharmed. This review will focus on the potential use of protease inhibitors in a wide variety of disease states.

2. Infectious agents and diseases

2.1. Hepatitis C virus

The hepatitis C virus (HCV) is a member of the Flaviviridae family. Hepatitis, caused by HCV, is a liver disease spread by contact with infected blood. Persons harboring HCV may show no symptoms, or may suffer from symptoms such as jaundice, fatigue, nausea, and abdominal pain. Possible long term effects of hepatitis C include chronic liver disease, cirrhosis, hepatocellular carcinoma, and need for liver transplant HCV has become the paramount target of antiviral protease inhibitor research,