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Invited review

Aspartic protease inhibitors containing tertiary alcohol transition-state mimics

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ABSTRACT

Aspartic proteases (APs) are a class of enzymes engaged in the proteolytic digestion of peptide substrates. APs play important roles in physiological and infectious pathways, making them plausible drug targets. For instance in the treatment of HIV infections, access to an efficient combination of protease and reverse transcriptase inhibitors have changed a terminal illness to a chronic but manageable disease. However, the benefits have been limited due to the emergence of drug resistant viral strains, poor pharmacokinetic properties of peptidomimetic inhibitors and adverse effects associated with the treatment. In the 1980s, D. Rich and co-workers proposed a novel strategy for the development of AP inhibitors by replacing the secondary hydroxyl group with a tertiary alcohol as part of the transition state (TS) mimicking moiety. This strategy has been extensively explored over the last decade with a common belief that masking of the polar group, e.g. by intramolecular hydrogen bonding, has the potential to enhance transcellular transport. This is the first review presenting the advances of AP inhibitors comprising a tertiary hydroxyl group. The inhibitors have been classified into different *tert*-hydroxy TS mimics and their design strategies, synthesis, biological activities, structure–activity-relationships and X-ray structures are discussed.
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1. Introduction

1.1. Aspartic proteases: mechanism of action, relevance in the field of drug discovery and development of transition state mimicking inhibitors

Proteases are a family of enzymes that catalyze the hydrolysis of peptide bonds in proteins and polypeptides, a reaction that is vital to both physiological and pathological processes. The human genome encodes over 500 proteases (MEROPS database), making this group one of the largest enzyme families. Proteases are commonly classified into six classes: serine, threonine, cysteine, glutamic, metallo and aspartic proteases (APs) [1–3]. APs are the smallest class in the human genome with only 15 members, but they have long been a rich source of potential drug molecules in the field of drug discovery [4]. The APs have been classified into two clans: clan AA and clan AD, based on their tertiary structures. Clan AA consists of two families: family A1, which contains the classical aspartic proteases (renin, pepsin A, pepsin C, cathepsin D, cathepsin E, BACE-1, BACE-2 and napsin A) and family A2, which contains proteases such as HIV-1 protease that can be integrated into the human genome by retroviruses. Clan AD comprises of presenilins and signal peptide peptidase, which are the intra-membrane cleaving proteases [1–3].

APs use an aspartic acid (Asp) dyad to hydrolyze peptide bonds. Most APs bind to 6–10 amino acid residues in the substrate, which can then be used to design substrate-based inhibitors. APs also have one or more flaps in their structure that close down to cover the substrate/inhibitor, resulting in further interactions within the complex. For example, in the case of the dimeric AP HIV-1 protease, it is thought that a water molecule in the active site is activated by a deprotonated aspartic acid (Asp25 or Asp125), which facilitates a nucleophilic addition to the amide carbonyl carbon in the substrate to form a tetrahedral intermediate compound [the transition state (TS) [5]; Fig. 1]. The other aspartic acid can donate a proton to the

Abbreviations: AIDS, acquired immune deficiency syndrome; AD, Alzheimer's disease; Aβ, amyloid beta; AP, aspartic protease; Asp, aspartic acid; Cl_{int}, intrinsic clearance; CC_{50}, 50% of the cytotoxic concentration; EC_{50}, half the maximum effective concentration; HIV, human immunodeficiency virus; IC_{50}, concentration required to inhibit enzyme activity by 50%; K_i, inhibition constant; Me^3AHPPA, 4-amino-3-hydroxy-3-methyl-5-phenylpentanoic acid; Me^3Sta, 4-amino-3-hydroxy-3,6-dimethylheptanoic acid; P_{app}, permeability; PDB, protein data bank; PI, protease inhibitor; SAR, structure–activity-relationship; TBS, *tert*-butyldimethylsilyl; TS, transition state; WHO, World Health Organization.

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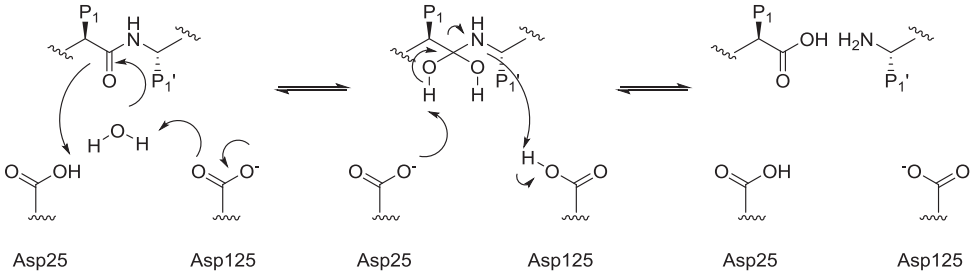

Fig. 1. The mechanism of peptide bond cleavage by an AP, as exemplified by HIV-1 protease. Since HIV-1 protease is a dimeric C-2 symmetric AP, the active aspartic acids are denoted Asp25 and Asp125.

nitrogen in the amide bond and the TS thus separates into two products: an acid fragment (the N-terminal product) and an amine fragment (the C-terminal product) [6,7]. A detailed description of the proteases molecular structures is beyond the scope of this review and have been reviewed elsewhere [2,3,8].

Following standard nomenclature, the amino acids on the C-terminal side of the scissile bond are denoted P_1'-P_2'-P_3'…-P_n', while those on the N-terminal side are denoted P_1-P_2-P_3…-P_n. The corresponding pockets in the enzyme are denoted S_1'-S_2'-S_3'…-S_n' and S_1-S_2-S_3…-S_n on the C-terminal and N-terminal sides of the scissile bond, respectively (Fig. 2) [9]. The crystal structures of most of the A1 human APs have been solved [10–15]; some of them are presented in later sections of this review as X-ray crystallography depictions of enzyme–inhibitor complexes.

There are a number of factors that should be considered when developing protease inhibitors (PIs) as oral therapeutic drugs. The ideal PI should be very potent and highly selective for the specific protease, with appropriate pharmacokinetic and pharmacodynamic characteristics. Because peptides are usually associated with low bioavailability and short half-lives, the candidates should be minimally peptidic in nature. Further, to be potential pharmaceutical compounds, they should have low toxicity, a high therapeutic index, high membrane permeation characteristics, good oral bioavailability and a clearance rate that will allow administration of only one or two doses a day. Strategies for discovering PIs include natural product screening, mimicking the natural peptide substrate and replacing the scissile amide bond with a non-cleavable isostere and computer-assisted substrate-based design using information on the structure of the substrate or inhibitor–enzyme complex obtained by nuclear magnetic resonance (NMR) spectroscopy and/or X-ray crystallography.

The investigations into the use of APs as drug targets were pioneered with the development of renin and HIV-1 PIs [3,16,17]. Substrate-based inhibitors, which mimicked the TS in the peptide cleavage process but contained a non-cleavable isostere in place of the scissile amide bond, were developed in these early strategies [3,16]. Pepstatin A (Iva-Val-Val-Sta-Ala-Sta), first isolated by Umezawa et al. [18], is a naturally occurring inhibitor of APs that has been used as a model compound in this respect. Pepstatin A contains the amino acid statine [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid; Sta] as a putative TS mimic and is active against most APs with inhibition constant (K_i) values in the range of 0.1–1 nM. Synthetic manipulations of the pepstatin structure have led to the discovery of novel, potent renin and other AP inhibitors.

The AP renin plays an important physiological role in the regulation of blood pressure. It controls the first (rate-limiting) enzymatic step in the renin-angiotensin system (RAS) by catalyzing the cleavage of the Leu10–Val11 peptide bond in angiotensinogen, to release the decapeptide angiotensin I. Renin is an essential and specific enzyme and angiotensinogen is its only known physiological substrate [19,20]. Despite the fact that the first renin

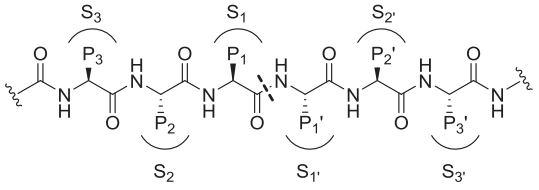

Fig. 2. The nomenclature commonly used to describe amino acid moieties and the corresponding enzyme pockets of APs. The scissile bond is denoted by a dashed line.

inhibitor, Aliskiren, was only approved in 2007 [21], the results of research efforts in this area over the past 30 years have proven invaluable when targeting other APs such as HIV-1 protease. Although no tertiary alcohol renin inhibitors have been reported to date, we decided to briefly include them in this review because the first APs to be targeted for drug development, pioneered by Daniel Rich in the early 1980s, were the renin inhibitors [22,23]. Fig. 3 shows examples of various potent secondary alcohol-based renin inhibitors. The concept of replacing the scissile peptide bond by non-cleavable isosteres in the TS intermediate was introduced by Szelke et al. [24] as a result of the early research into renin inhibitors. This strategy has since become so successful that it has become the primary method of designing AP inhibitors [3,25,26].

Most of the AP inhibitors available on the market today (excluding tipranavir) possess peptidomimetic characteristics with a non-hydrolyzable bond replacing the scissile bond. The most commonly used TS mimic, as seen in the HIV-1 PIs, is the hydroxyethylene moiety [17]. However, many other TS mimics have been successfully tested as AP inhibitors and these are exemplified in Fig. 4. These *sec*-hydroxy TS mimics have been reviewed extensively in the literature, for example by Leung et al. [25] and Cooper [26].

Our group has been engaged in the development of novel HIV-1 PIs since the mid 1990s [27–46]. Inspired by the work of Lam et al. [47], we initially targeted symmetric and asymmetric cyclic HIV-1 PIs [48–51]. Following the approval of linear HIV-1 PIs by the FDA in 1995, the focus moved to linear inhibitors. Structural fragments that seemed potentially interesting were obtained from molecules such as indinavir, launched in 1996 and atazanavir, launched in 2003 (Fig. 5). Interestingly, atazanavir was the first PI to be recommended for once-daily administration, thus reducing the tablet burden for the patient. The prediction of binding affinities/energies and selectivity obtained from computational molecular dynamics simulations [52,53] and free-energy perturbation simulations [54], most of which were conducted by Johan Åqvist's team in the early 2000s, was an important contribution to the development of AP inhibitors.

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