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Peptidyl prolyl isomerase Pin1-inhibitory activity of D-glutamic and D-aspartic acid derivatives bearing a cyclic aliphatic amine moiety

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ABSTRACT

Pin1 is a peptidyl prolyl isomerase that specifically catalyzes *cis–trans* isomerization of phosphorylated Thr/Ser-Pro peptide bonds in substrate proteins and peptides. Pin1 is involved in many important cellular processes, including cancer progression, so it is a potential target of cancer therapy. We designed and synthesized a novel series of Pin1 inhibitors based on a glutamic acid or aspartic acid scaffold bearing an aromatic moiety to provide a hydrophobic surface and a cyclic aliphatic amine moiety with affinity for the proline-binding site of Pin1. Glutamic acid derivatives bearing cycloalkylamino and phenylthiazole groups showed potent Pin1-inhibitory activity comparable with that of known inhibitor VER-1. The results indicate that steric interaction of the cyclic alkyl amine moiety with binding site residues plays a key role in enhancing Pin1-inhibitory activity.

Pin1 (protein interacting with never in mitosis A-1) is a member of the peptidyl prolyl isomerase (PPIase) family, and specifically catalyzes *cis–trans* isomerization of phosphorylated Thr-Pro or phosphoryl Ser-Pro peptide bonds in its substrate proteins and peptides. There are three subfamilies of PPIase: cyclophilins (Cyps), FK506-binding proteins (FKBPs), and purvulins. Pin1 is a member of the purvulin family and is the only enzyme that catalyzes isomerization of phosphorylated substrates in humans.[1,2] Pin1 is reported to be involved in regulation of kinase signaling processes by mediating change in the ratio of *cis*-/*trans*-conformers of phosphorylated proteins.[3] For example, signal transduction pathways involving cyclin-dependent kinases and MAP kinases, as well as cell cycle controllers, are known to be regulated by Pin1 activity.[4] Substrates of Pin1 includes cancer-related signaling proteins such as cyclin D1, NF-kappaB, and p53.[5–8] Furthermore, Pin1 is overexpressed in various types of cancer cells, including prostate cancer, rectal cancer, hepatic cancer, and esophageal cancer.[2] It was also reported that the prognosis of prostate cancer is related to the expression level of Pin1 in the cancer cells.[9] Based on these reports, Pin1 may be a new therapeutic target for these cancers. Pin1 is also involved in the pathogenesis of Alzheimer's disease by isomerizing phosphorylated tau proteins, resulting in a reduction of tau-dependent fibril formation. Thus, Pin1 catalyzes a unique reaction, and it is also considered to contribute to the temporal regulation of protein phosphorylation, acting like a 'molecular timer'.[10] The catalytic domain of Pin1 enzyme, containing the cation-recognition site, consists of Lys63, Arg68, and Arg69, which serve to stabilize the phosphoryl moiety of the substrate peptide via electrostatic effect[11] (Fig. 1).

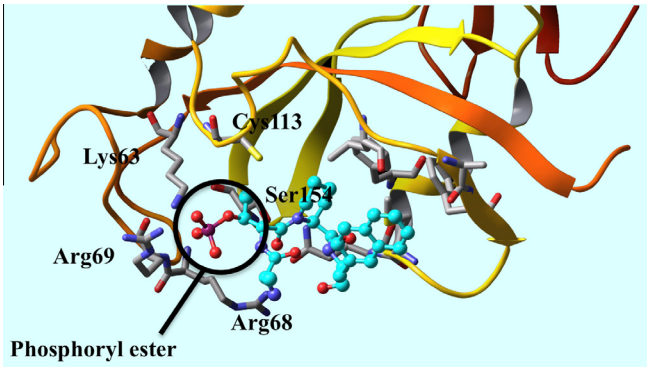

Figure 1. Structure of Pin1 catalytic domain with D-peptide (PDB 2ITK).

Several Pin1 inhibitors (**1**–**7**) have been reported to date, as illustrated in Figure 2.[11–19] Very recently, it was reported that all-trans retinoic acid (ATRA) (**8**) is also an inhibitor of Pin1.[19] Among these inhibitors, compound **4** has a very high affinity for the Pin1 catalytic

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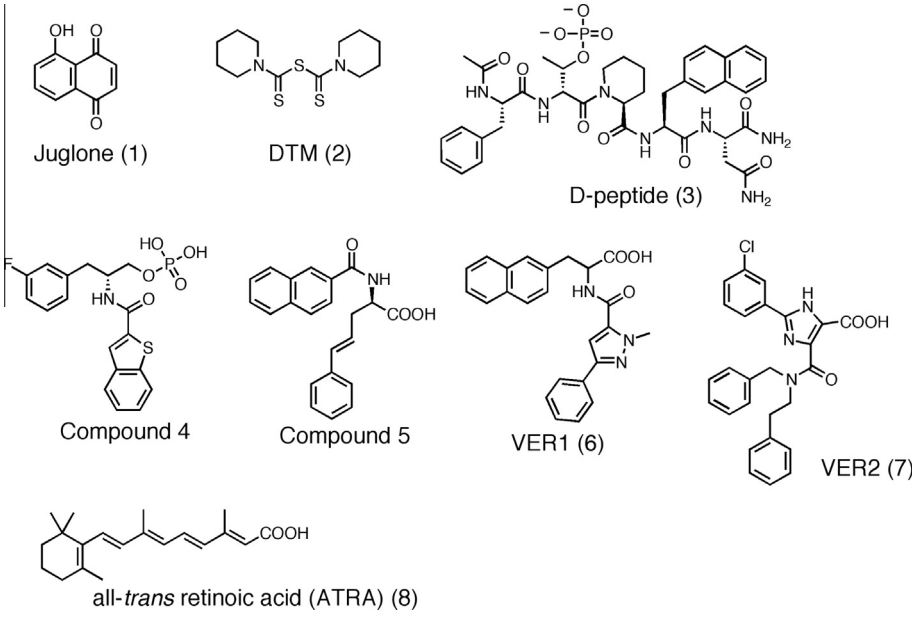

Figure 2. Previously reported Pin1 inhibitors.

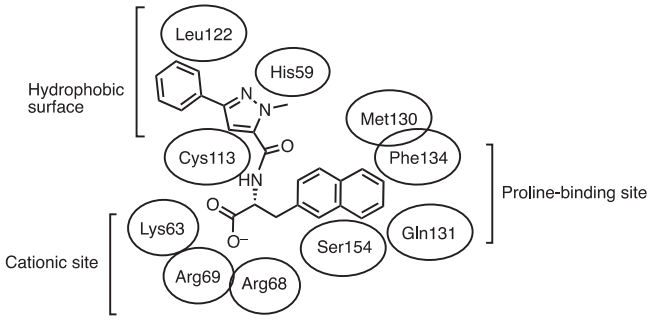

Figure 3. Schematic illustration of the interaction of Pin1 catalytic site and VER1.

site, but is not applicable to cell-based systems due to its high hydrophilicity arising from the presence of the phosphonate group. On the other hand, inhibitors bearing a carboxyl group, instead of a phosphonate group, such as VER1 (**6**) and VER2 (**7**) are applicable to cells, and show cell growth-inhibitory activity.

Structural analysis of VER1–Pin1 complexes has shown that VER1 binds to Pin1 mainly through three interactions: ionic interaction of the carboxylate group of VER1 with the cationic pocket in the Pin1 catalytic site, hydrophobic interaction of the aromatic group of VER 1 with the proline-binding pocket of Pin1, and interaction of another aryl group of VER1 with the hydrophobic surface of the Pin1 catalytic site (Figs. 3 and S1).

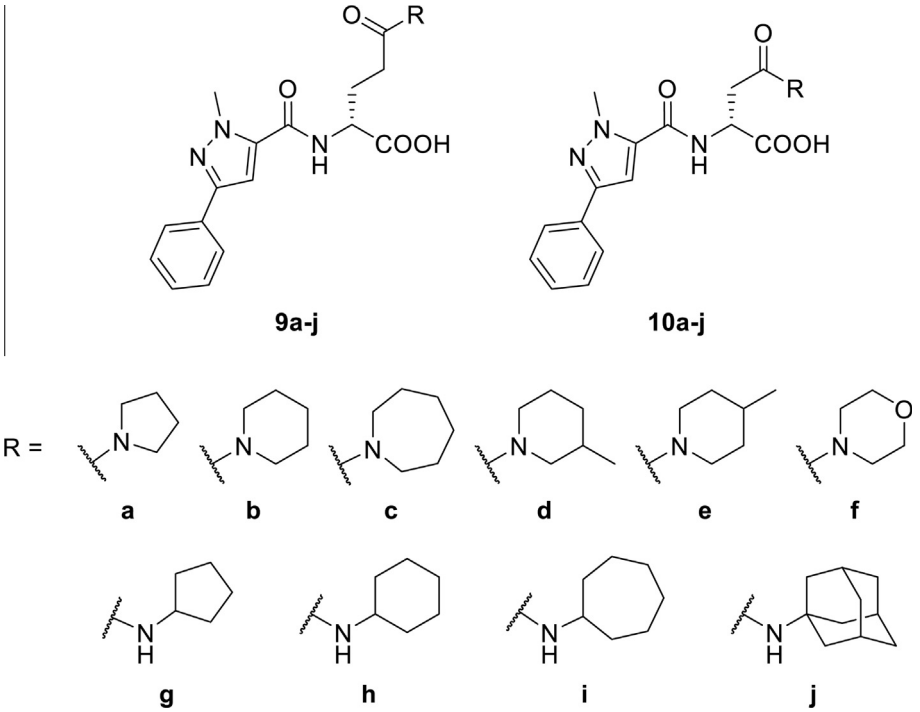

Figure 4. Molecular design for Glu/Asp-scaffold Pin1 inhibitor candidates.