Darunavir

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1. DESCRIPTION

Human immunodeficiency virus 1 (HIV-1) aspartyl protease performs a critically important step in the viral life cycle. Immature viral Gag and Gag–Pol polyproteins are processed by cleavage to form structural and enzyme components, before assembly into nascent, infectious virions. Darunavir is a synthetic nonpeptidyl small molecule analog of amprenavir that inhibits the dimerization and catalytic activity of the protease enzyme (Hayashi *et al.,* 2014; Koh *et al.,* 2007), thereby preventing viral maturation. The chemical structure is similar to that of amprenavir; however, the terminal tetrahydrofuran (THF) group is fused to a second THF group, to form a bis-THF moiety.

The chemical name of darunavir is [(1R,5S,6R)-2,8-dioxabicyclo[3.3.0]oct-6-yl] *N*-[(2S,3R)-4-[(4-aminophenyl) sulfonyl-(2-methylpropyl)amino]-3-hydroxy-1-phenyl-butan-2-yl] carbamate, and its molecular structure is depicted in Figure 245.1. It has a molecular weight of 547.66 Da. A darunavir concentration of 1 μM is approximately equivalent to 0.5 μg/l.

The development of darunavir (TMC-114, UIC 94017) involved an extensive screening process, where structural analogs of amprenavir were evaluated for their activity against a panel of recombinant HIV clinical isolates, including those with known protease inhibitor resistance (de Bethune and Hertogs, 2006; Yoshimura *et al.*, 2002). Further modification of the prototype compound TMC-126 lead to TMC-114, a molecule with superior pharmacokinetic properties and lesser potential for the *in vitro* selection of mutants with reduced susceptibility (Surleraux *et al.,* 2005).

The chemical structure of darunavir is similar to that of amprenavir; however, the presence of additional hydrogen bonds between darunavir and the protease enzyme result in a strength of binding two orders of magnitude higher: the equilibrium dissociation constant (K_d) for darunavir is 4.5×10^{-12} M and that of amprenavir is 3.9×10^{-10} M (King *et al.,* 2004).

Darunavir ethanolate, a second-generation protease inhibitor, is marketed under the trade name Prezista by Janssen-Cilag. It received regulatory approval by the US FDA in June 2006. Regulatory approval was granted in Europe in late 2006 and TGA registration in Australia in March 2007.

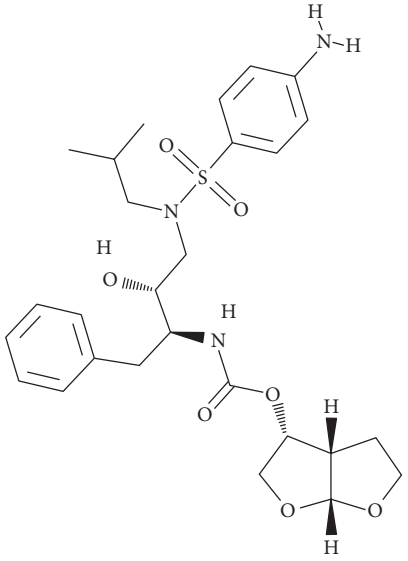

Figure 245.1. Chemical structure of darunavir.

In January 2015, Prezcobix, a single pill combination of darunavir and cobicistat, a CYP3A inhibitor, was approved for use by the FDA. Registered as Rezolsta in Europe, it was granted approval in November 2014. In Australia, this fixed-dose combination was registered under the trade name Prezcobix in September 2015.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Darunavir is active in cell culture against a broad range of HIV-1 group M clades (A, B, C, D, E, F, G) and group O isolates, with reported 50% effective concentration (EC_{50}) values ranging across studies from < 0.1 to 5 nM and EC_{90} values