

A New Prodrug Strategy for Amino Compounds

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Extremely water-soluble drugs due to a presence of many hydrophilic functional groups like hydroxyl and amino groups are generally not orally bioavailable. In the case of amino drugs, converting them to amide prodrugs, by analogy to ester prodrugs, is mostly unsuccessful since the hydrolysis of amide bond is normally much slower than that of ester bond, leading to an inefficient production of drugs from prodrugs. RS-7897, a new organic nitrate, consists of aminoethylnitrate (AEN) and L-2-oxothiazolidine-4-carboxylic acid (OTCA) with two components being bound by the amide bond. AEN was more active in vasodilation than RS-7897, and therefore, RS-7897 was the prodrug of the amino compound, AEN. In rats and dogs, RS-7897 was well absorbed orally, and the hydrolysis of the amide bond occurred rapidly in the liver. Quite interesting, the activity was detected in the hepatic supernatant fraction rather than in the microsomal fraction, and purification of the enzyme demonstrated that the activity is due to pyroglutamylaminopeptidase I (PAP-1). OTCA was thought to serve as the substrate of PAP-1 as a consequence of structural similarity to pyroglutamyl group. Compounds with the sulfur atom in OTCA being substituted with other hetero atoms also served as the PAP-1 substrates. These analogs of pyroglutamic acid were thought to be utilized as a promoiety of the amide prodrugs for increased oral absorption and rapid liberation of the drugs from the prodrugs.