Development of a Novel Angiotensin II AT1 Receptor Antagonist, Olmesartan Medoxomil

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Angiotensin receptor blockers (ARBs) inhibit the biological actions of angiotensin, which is implicated in the genesis and maintenance of hypertension and other cardio-vascular diseases. The first orally active ARB, losartan, was reported in 1989, and attracted a lot of attention in the R&D community worldwide. We at Sankyo began a search aiming at a more favorable ARB in 1990. Among the imidazole compounds synthesized, a compound that had a hydroxymethyl group at the 4-position and a carboxylic acid at the 5-position was found to have a potent and long-lasting biological action. The activity optimization of this lead compound resulted in olmesartan (OL). Although the oral administration of OL produced a potent and long-lasting inhibitory action, the bioavailability of the compound turned out to be as low as 4% in rats, which might be improved by derivatization to a prodrug. Several esters were synthesized and olmesartan medoxomil (OLM) was chosen as the candidate compound for further development. The most significant feature of OL is that it has the 1-hydroxy-1-methylethyl group at the 4-position of the imidazole ring. This hydroxyl group contributes to the unique pharmacological properties of OL in two ways. First, it underlies the insurmountable inhibitory activity and inverse agonist activity of OL. Secondly, it accounts for the metabolic stability of OL: most ARBs are metabolized by CYPs while OL is not. Clinical trials have demonstrated that OLM is more potent than any other ARBs tested. OLM was first launched in the US in 2002 and is now marketed in 51 countries throughout the world.