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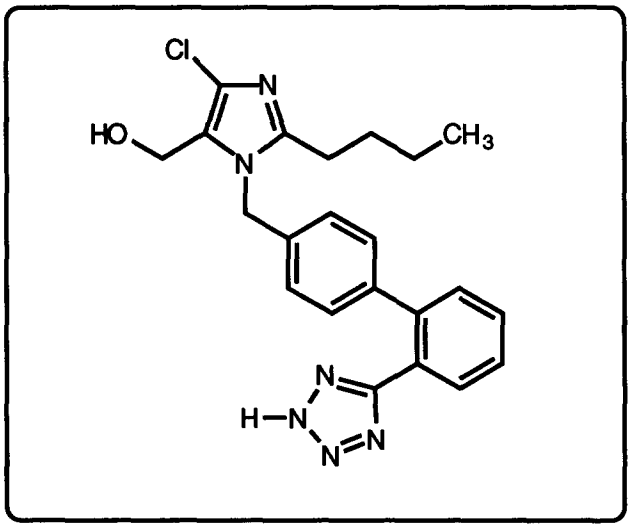
NEW DRUGS—REPORTS OF NEW DRUGS RECENTLY APPROVED BY THE FDA

Losartan



Structure
$C_{22}H_{23}ClN_6O$

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole

Supply: Monopotassium salt, $C_{22}H_{22}ClKN_6O$, mp 263–264.5 °C.

DUP 753, MK-0954
COZAAR®*: monopotassium salt.
HYZAAR®* : combination with hydrochlorothiazide.

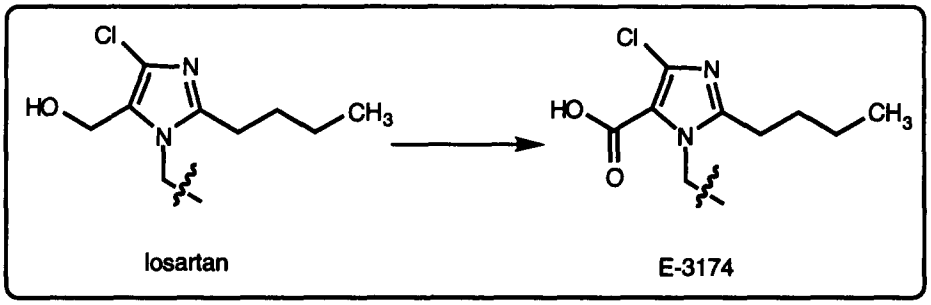
Mechanism of action: Angiotensin II receptor (type AT_1) antagonist.

Therapeutic category: Antihypertensive.

Synthesis: Losartan can be prepared by connecting the imidazole 'head' to the biphenyltetrazole 'tail'.

Summary: Losartan[1] is a nonpeptide angiotensin II receptor antagonist and differs from angiotensin-converting enzyme (ACE) inhibitors by producing direct antagonism of the AT_1 angiotensin II receptor.[2] This specificity is speculated to potentially produce an efficacious drug with fewer adverse effects particularly cough and angioedema.[3] Oral losartan 10 to 80 mg produces dose-dependent inhibition of the pressor response to exogenously administered angiotensin I and II in healthy subjects: these effects correlated with plasma levels of the active metabolite of losartan, E-3174. The oral bioavailability of losartan is approximately 33%, and peak serum levels occur 1 h after oral doses; the drug is metabolized to an active 5-carboxylic acid metabolite (E-3174) which accounts for the long duration of antihypertensive effects (up to 24 h). The metabolite appears to interact competitively at the AT_1 receptor and has very slow dissociation kinetics.[4–6]

*Registered trademark of E. I. du Pont de Nemours and Company, Willmington, Delaware, U.S.A.



The elimination half-life of 6 to 9 hours has been reported for E-3174.[5] Losartan lacks the angiotensin II agonist properties[7] of earlier peptide antagonists (e.g., saralasin); this specificity is claimed to confer potentially greater efficacy and an improved tolerability profile compared to ACE inhibitors.[8] In hospitalized patients with mild-to-moderate hypertension, oral losartan 50 mg once daily has been superior to placebo in reducing blood pressure over a period of 5 days. Antihypertensive efficacy has been comparable to enalapril in limited studies; the drug is also being evaluated in congestive heart failure.[9,10]

Manufacturer: Merck & Co., Inc., West Point, PA 19486, U.S.A. by DuPont Pharma, Wilmington, DE 19880, U.S.A.

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