Drugs of the Future 2001, 26(12): 1139-1148

CCC: 0377-8282/2001

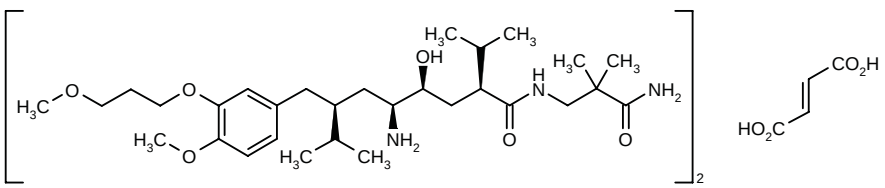
Aliskiren Fumarate

Prop INNM

Antihypertensive
Renin Inhibitor
Treatment of Heart Failure
Treatment of Renal Failure

CGP-60536B
SPP-100B

(2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide hemifumarate



$2C_{30}H_{53}N_3O_6.C_4H_4O_4$ Mol wt: 1219.5990

CAS: 173334-58-2
CAS: 173334-57-1 (as free base)
CAS: 173399-03-6 (as monohydrochloride)

EN: 267580

Synthesis

Aliskiren can be obtained by several different ways:

a) Alkylation of 3-hydroxy-4-methoxybenzyl alcohol (I) with 1-bromo-3-methoxypropane (II) gives ether (III). Subsequent conversion of benzyl alcohol (III) into bromide (IV) is carried out using bromotrimetylsilane. The chiral isovaleryloxazolidinone (V) is alkylated with bromide (IV) by means of LiHMDS to afford (VI), which is hydrolyzed to the (*S*)-2-aryl-2-isopropylpropionic acid (VII) by means of lithium peroxide. The reduction of acid (VII) to the corresponding alcohol with $NaBH_4/I_2$ reagent, followed by treatment with PPh_3 and NBS, provides bromide (VIII). Alkylation of the chiral dimethoxydihydropyrazin (IX) with bromide (VIII) produces (X). Further hydrolysis of the pyrazine ring of (X) with HCl, followed by Boc protection of the resulting (*S*,*S*)-amino ester, yields compound (XI). Reduction of the ester group of (XI) with DIBAL gives aldehyde (XII). This compound is condensed with the Grignard reagent (XIII) to afford the diastereomeric mixture of amino alcohols (XIV). Treatment of mixture (XIV) with 2,2-dimethoxypropane (XV) and TsOH produces a mixture of oxazolidines, from which the required (*S*,*S*,*S*)-isomer (XVI) is isolated by flash chromatography. Hydrogenolitic deprotection of the benzyl ether of (XVI) gives alcohol (XVII). This alcohol is oxidized to aldehyde with NMMO and tetrapropylammonium perruthenate (TPAP), and further oxidized to carboxylic acid (XVIII) with $KMnO_4$ and tetrabutylammonium bromide (TBAB). Coupling of (XVIII) with aminoamide (XIX) by means of diethyl cyanophosphonate and TEA gives (XX). Finally, acid hydrolysis of the oxazolidine ring and Boc protecting groups of (XX) furnishes the corresponding amino alcohol, which is finally converted to the hemifumarate salt (1, 2). Scheme 1.

b) The intermediate γ-butyrolactone (XXVIII) has been obtained as follows: Allylation of the imidazolidinone intermediate (V) with allyl bromide (XXI) and LiHMDS in THF gives the chiral intermediate (XXII), which by dihy-

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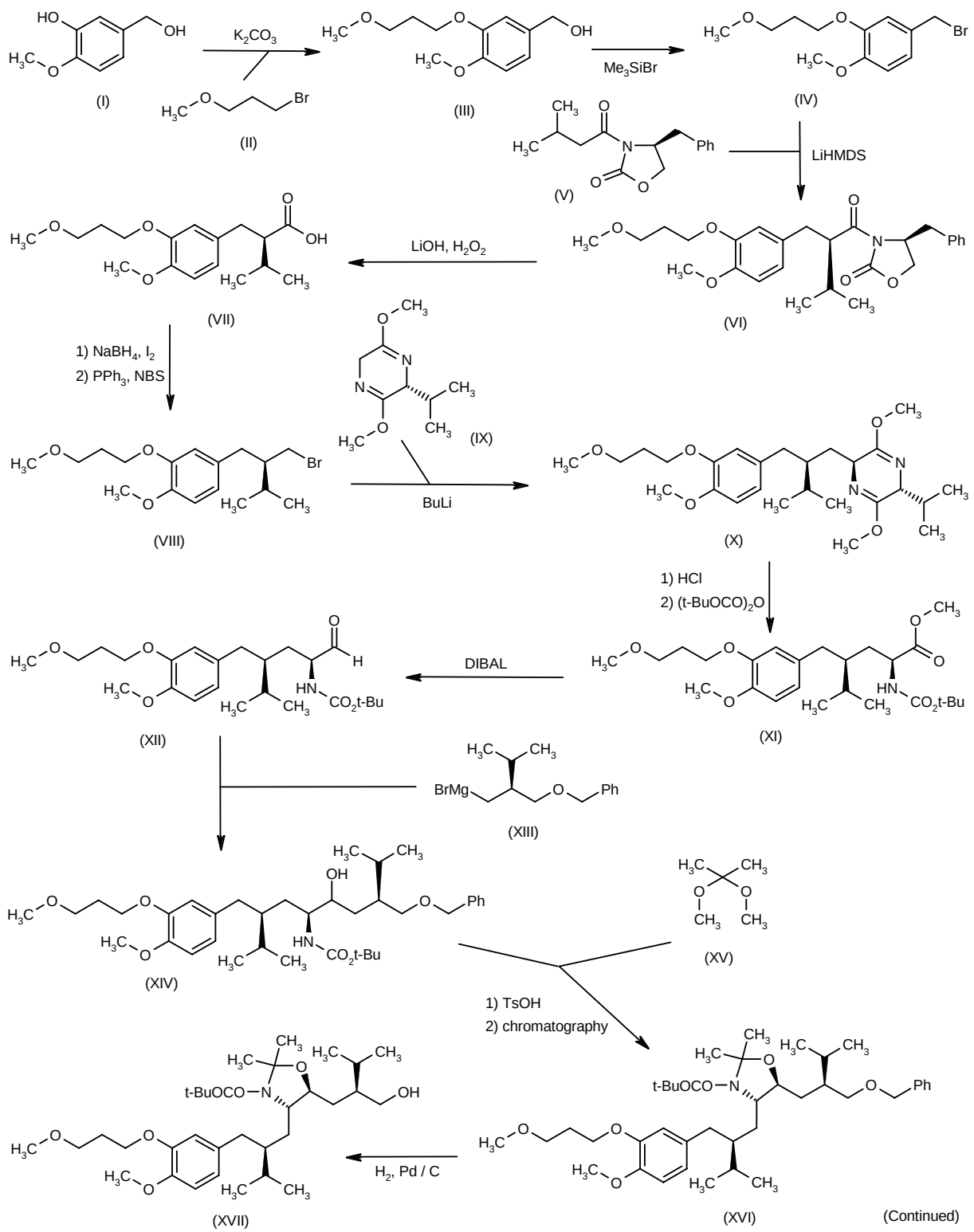
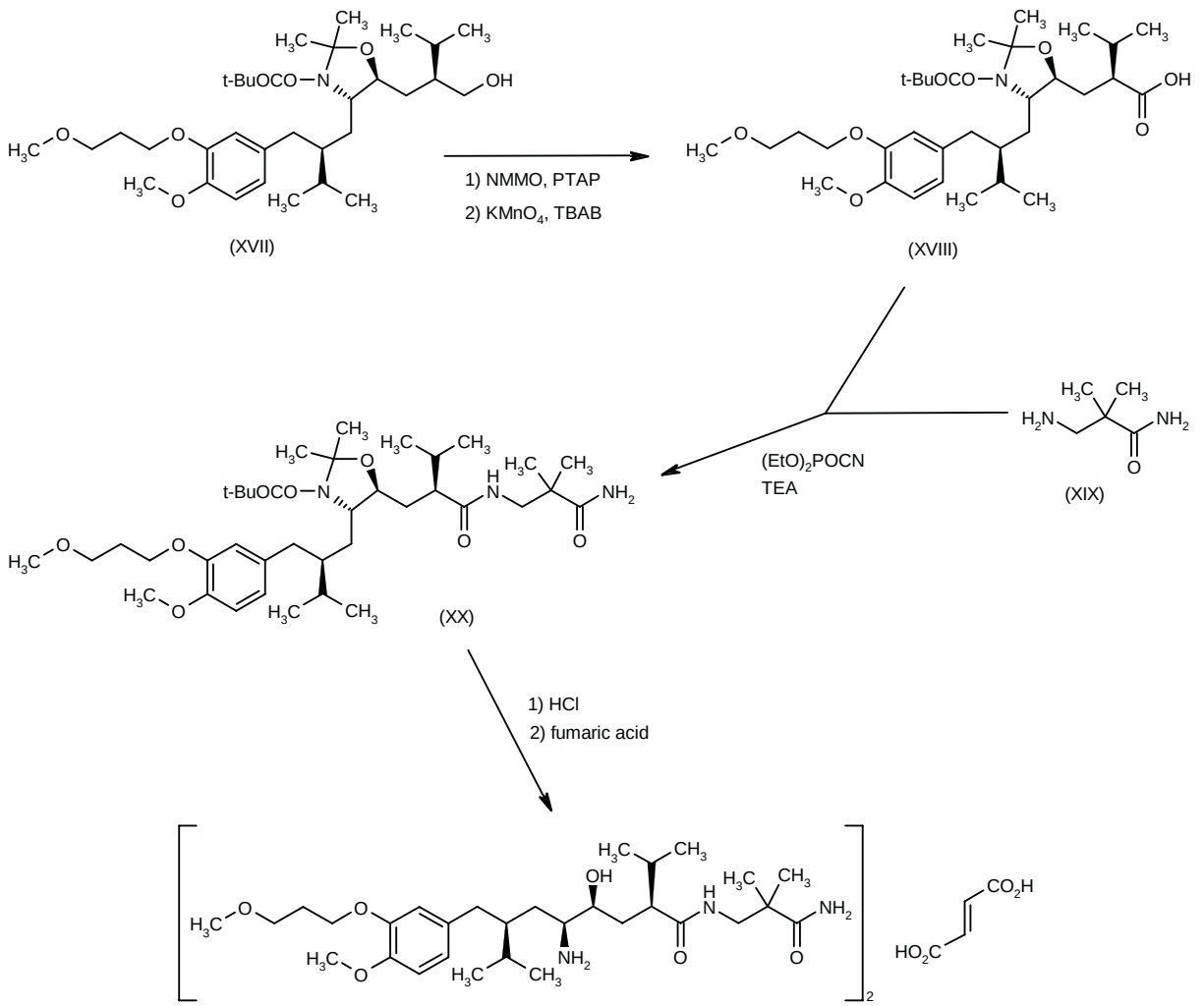
Scheme 1: Synthesis of Aliskiren Fumarate



Scheme 1: Synthesis of Aliskiren Fumarate (Cont.)

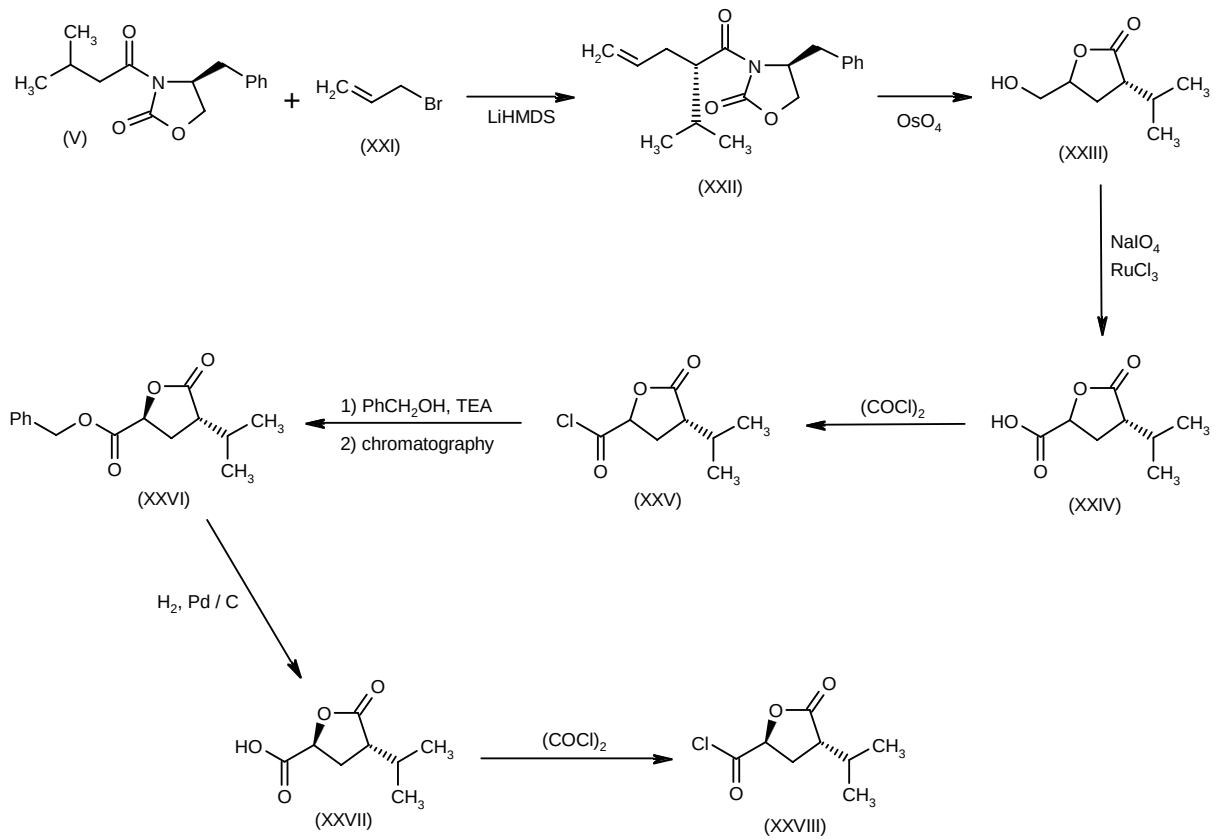


droxylation and cleavage of the chiral auxiliary with OsO_4 and NMMO in *tert*-butanol/acetone/water yields the lactone alcohol (XXIII). Oxidation of (XXIII) with $NaIO_4$ and $RuCl_3$ in CCl_4/acetonitrile/water affords the carboxylic acid (XXIV), which by treatment with $(COCl)_2$ in toluene provides the acyl chloride (XXV). Esterification of (XXV) with benzyl alcohol gives the corresponding benzyl ester as a diastereomeric mixture, from which the desired isomer (XXVI) is separated by flash chromatography. Hydrogenolysis of the benzyl ester (XXVI) with H_2 over Pd/C in ethyl acetate yields the carboxylic acid (XXVII), which is treated with oxalyl chloride in toluene to afford the desired γ-butyrolactone intermediate (XXVIII) (3). Scheme 2.

The reduction of the chiral propionic acid (VII) with $NaBH_4$ in THF gives the primary alcohol (XXIX), which by reaction with $SOCl_2$ and pyridine in $CHCl_3$ yields the chloride (XXX). Condensation of (XXX) with the butyrolactone intermediate (XXVII) by means of Mg and dibromoethane affords the ketonic adduct (XXXI). Reduction of the exocyclic carbonyl group of (XXXI) with $NaBH_4$ in THF/methanol provides a 3:1 diastereomeric mixture of the desired chiral alcohol (XXXII) and its OH-epimer (XXXIII) that are separated by flash chromatography. Reaction of (XXXII) with MsCl and TEA, followed by treatment with NaN_3, affords the azido derivative (XXXIV), which is condensed with 4-amino-3,3-dimethylbutyramide (XIX) by means of 2-hydroxypyridine and TEA to provide the adduct (XXXV). Finally, the azido group of (XXXV) is reduced with H_2 over Pd/ in methanol to yield the target amino alcohol (3). Scheme 3.

An extensive study on the stereoselective reduction of the ketonic adduct (XXXI) has been performed. No better diastereoselectivity than 3:1 has been obtained for the synthesis of the chiral alcohol (XXXII). However, excellent diastereoselectivity (97:3) has been obtained for the syn-

Scheme 2: Synthesis of Intermediate (XXVIII)



thesis of its OH-epimer, alcohol (XXXIII), with K-selectride in THF, which could potentially provide access to the target amino alcohol via a double inversion protocol.

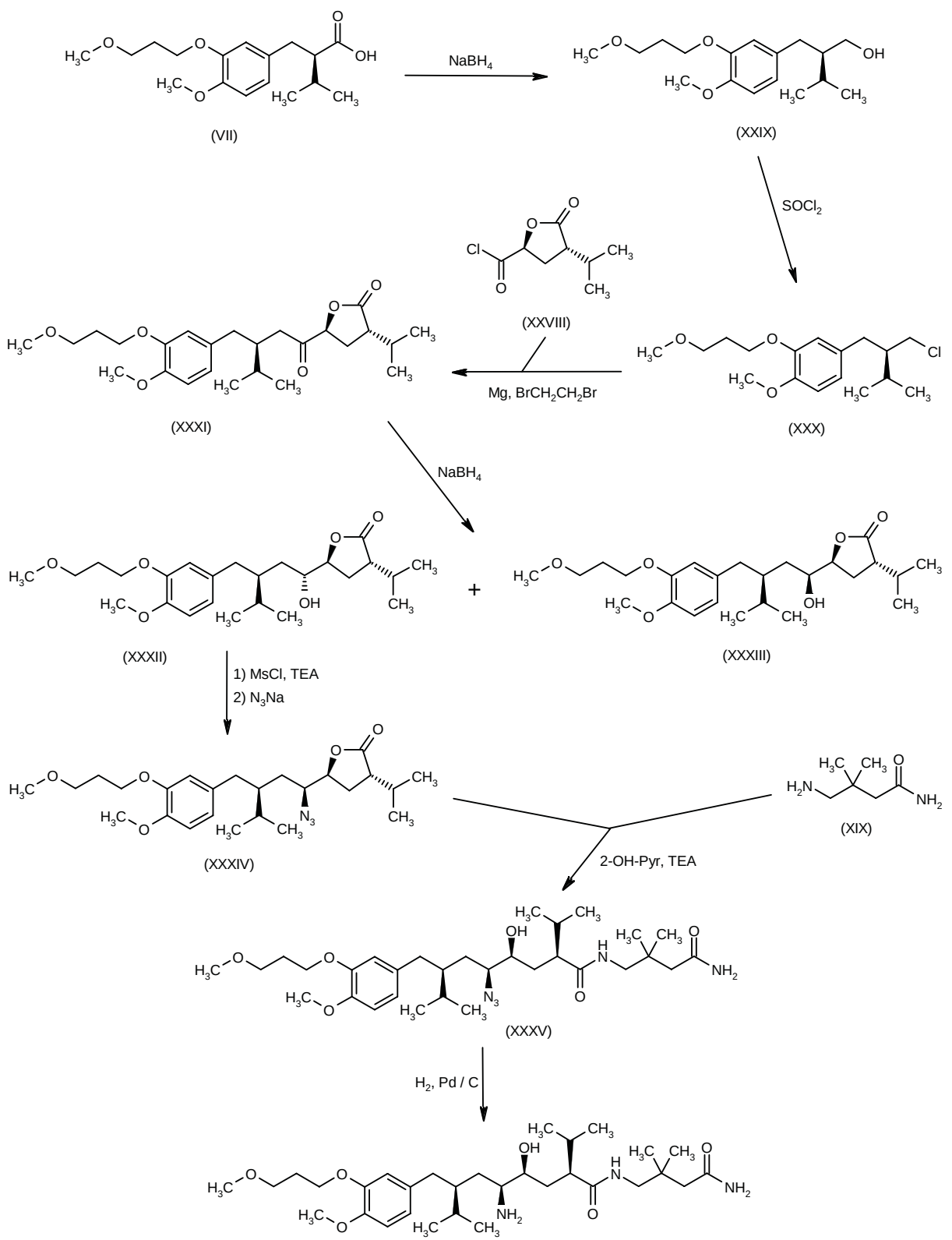
c) Alternatively, the chiral phenylpropyl chloride (XXX) can also be prepared as follows: Reduction of the cinnamic acid (XXXVI) with H_2 over Pd/C in ethyl acetate gives the phenylpropionic acid (XXXVII), which is treated with oxalyl chloride to yield the acyl chloride (XXXVIII). Condensation of (XXXVIII) with (+)-pseudoephedrine (XXXIX) by means of NaOH in toluene/water affords the chiral amide (XL), which is enantioselectively alkylated with 2-iodopropane (XLI) by means of LDA in THF to provide the adduct (XLII). Reduction of the amide group of (XLII) with BH_3/NH_3 in THF gives the already reported primary alcohol (XXIX), which is finally treated with $POCl_3$ in hot toluene to afford the phenylpropyl chloride intermediate (XXX) (4). Scheme 4.

d) The chiral azido intermediate (XXXIV) can also be obtained as follows: Reaction of (+)-pseudoephedrine isovaleramide (XLIII) with allyl bromide (XXI) by means of LDA in THF gives the pentenoyl amide (XLIV), which is treated with NBS in DME/water to yield the spiro compound (XLV). Hydrolysis of the bromomethyl group of (XLV) with tetrabutylammonium acetate and K_2CO_3 affords the carbinol (XLVI), which is oxidized to aldehyde (XLVII) with SO_3/pyridine and TEA in DMSO/dichloromethane. Condensation of (XLVII) with the propyl chloride intermediate (XXX) by means of Mg, dibromoethane and $CeCl_3$ in refluxing THF provides the already reported chiral hydroxylactone (XXXII), which is treated first with 4-bromobenzenesulfonyl chloride and then with NaN_3 to give the desired azido derivative (XXXIV) (4). Scheme 5.

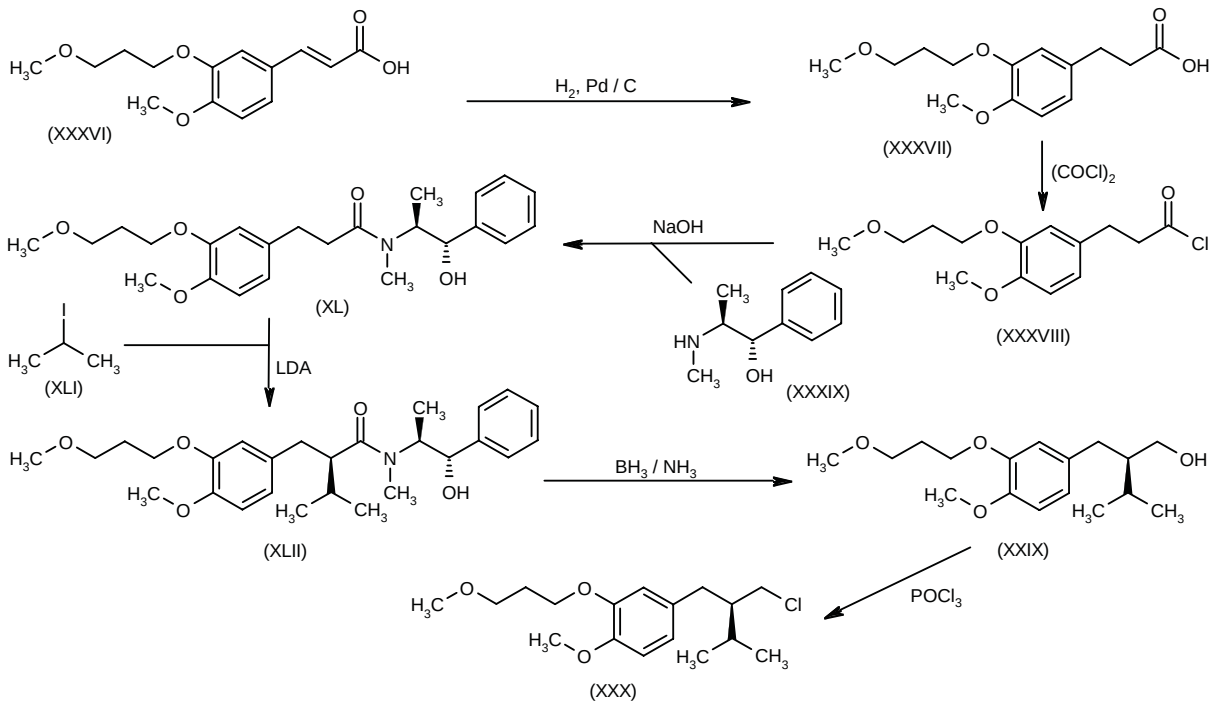
e) Alternatively, the chiral azido intermediate (XXXIV) can also be synthesized as follows: Alkylation of oxazolidinone (V) with 1-chloro-3-iodopropene (XLVIII) by means of LiHMDS in THF gives compound (XLIX), which is condensed with the magnesium derivative of the phenylpropyl chloride (XXX) to yield, after working up, amide (L). Bromination of (L) with NBS and phosphoric acid affords the bromolactone (LI), which by treatment with NaN_3 in tripropylene glycol/water provides the azido derivative (XXXIV) (5). Scheme 6.

f) Alternatively, the spiro aldehyde (XLVII) is treated with *N*-benzylhydroxylamine in dichloromethane to give nitrone (LII), which is submitted to a Grignard reaction with the magnesium derivative of intermediate (XXX) in THF to afford the adduct (LIII) as a mixture of epimers at

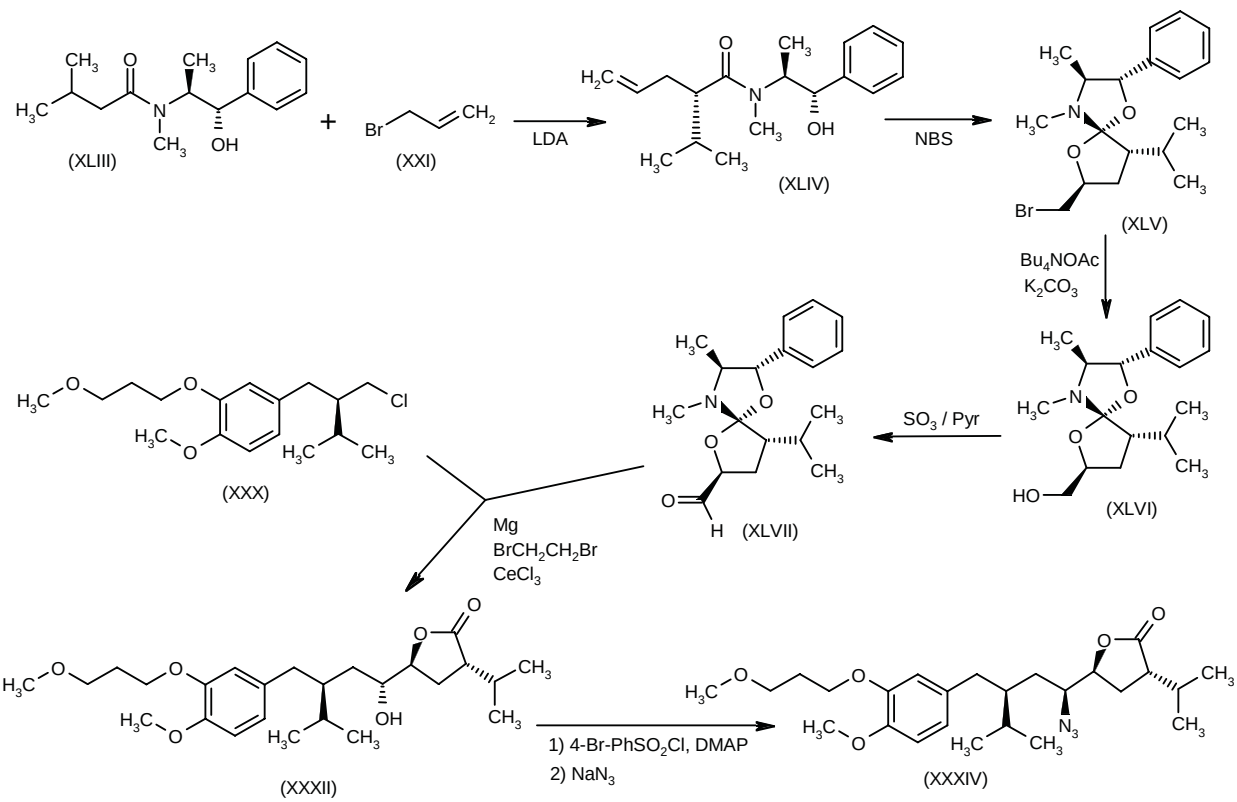
Scheme 3: Synthesis of Aliskiren



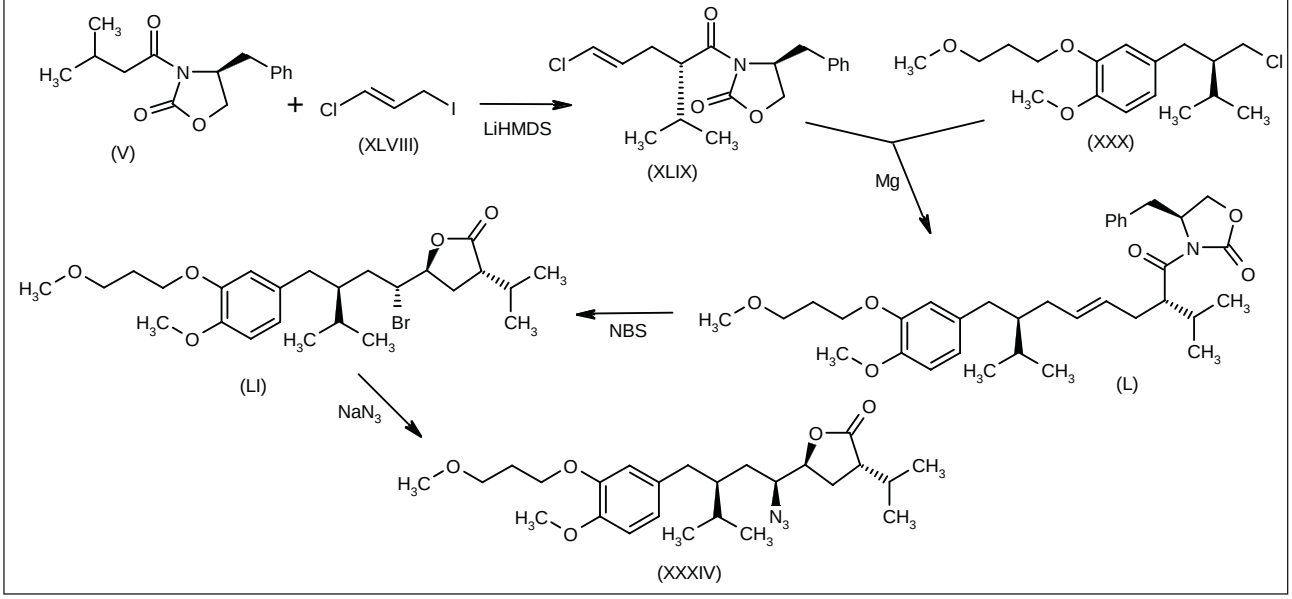
Scheme 4: Synthesis of Intermediate (XXX)



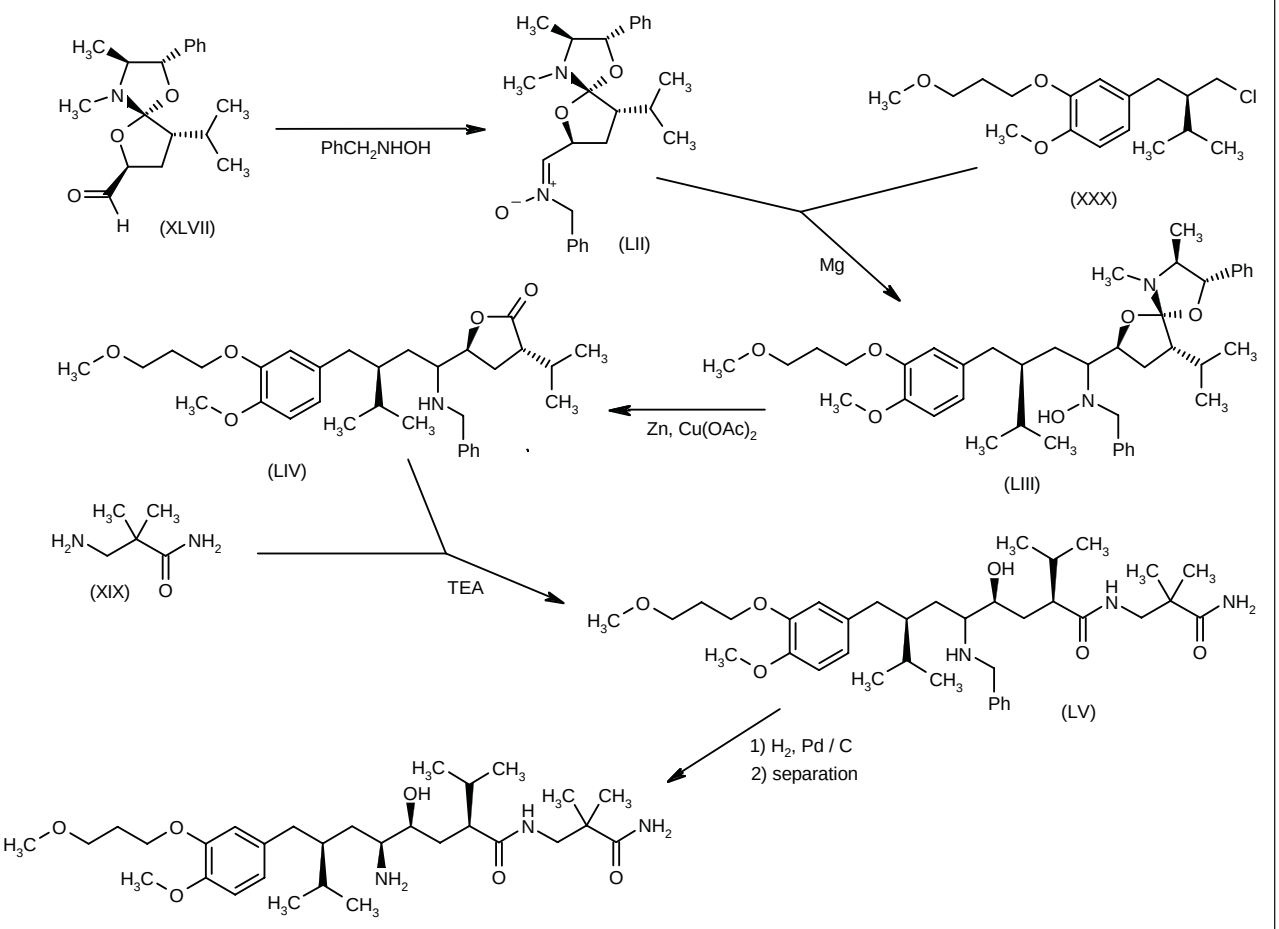
Scheme 5: Synthesis of Intermediate (XXXIV)



Scheme 6: Synthesis of Intermediate (XXXIV)



Scheme 7: Synthesis of Aliskiren



the amino group. Simultaneous *N*-dehydroxylation and cleavage of the spiro function of (LIII) by means of Zn, $Cu(OAc)_2$ in AcOH/water gives lactone (LIV), which is condensed with 3-amino-2,2-dimethylpropionamide (XIX) by means of TEA and 2-hydroxypyridine giving the adduct (LV). Finally, the benzylamino group of (LV) is removed with H_2 over Pd/C in methanol to yield a mixture of two epimers at the amino group, from which aliskiren is separated. (6). Scheme 7.

Introduction

The renin-angiotensin system (RAS) (Fig. 1) is known to participate in the regulation of blood pressure, in addition to renal function and electrolyte balance (7, 8), and intervention in this cascade has been the subject of much investigation as a treatment for hypertension and congestive heart failure. Inhibitors of angiotensin-converting enzyme (ACE) have demonstrated utility in the treatment of these cardiovascular disorders (9-13), but they are also associated with adverse events, including cough and angioneurotic edema (14), possibly due to their interaction with other related peptides. Angiotensin II receptor antagonists have also been developed for pharmacological intervention in the RAS. However, inhibition of the first, rate-limiting enzyme in the cascade, angiotensinogen, resulting in inhibition of the release of angiotensin I, is considered to represent an even more specific means of interfering with the RAS. Renin is the only known substrate for angiotensinogen and thus appears to be an essential and extremely specific enzyme, and thereby represents an ideal target for the development of antihypertensive drugs. A number of peptide inhibitors of human renin have been developed but were unsuitable for drug development. Researchers at Novartis used structure-based design to develop novel nonpeptide renin inhibitors. Their efforts culminated in the discovery of CGP-60536, which was selected as a clinical candidate being evaluated as the hemifumarate salt (2).

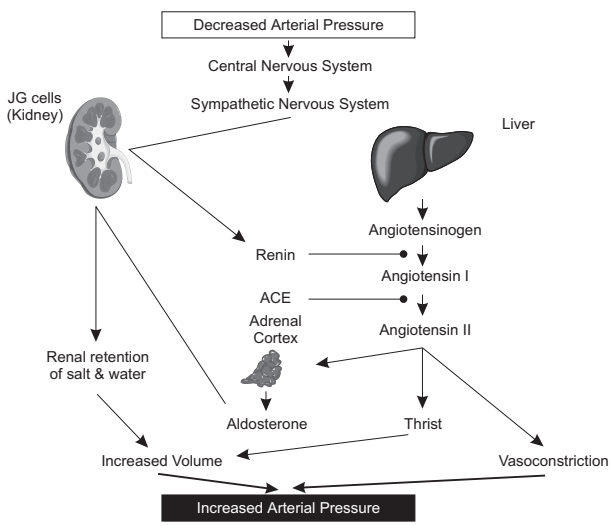


Fig. 1. Renin angiotensin system.

Pharmacological Actions

Aliskiren was shown to be a highly potent inhibitor of purified and plasma human renin (IC_{50} = 0.0006 μM for both enzymes) with extremely high specificity over porcine pepsin (IC_{50} > 100 μM). Oral administration to conscious sodium-depleted marmosets led to a marked, dose-dependent (1-10 mg/kg) and long-lasting (up to 24 h) reduction in mean arterial pressure and complete inhibition of plasma renin activity (2, 15).

The renin inhibitory activity of aliskiren and selected compounds in preclinical development are shown in Table I.

Table I: Renin inhibitory activity of aliskiren and selected compounds in preclinical development (data from Prous Science Integrity®).

Compound	Inhibition: Human plasma (IC_{50}, nM)	Inhibition: Human enzyme[a] (IC_{50}, nM)	Ref.
Aliskiren fumarate	0.6	0.6	2
BILA-2157-BS	1.4-2.5	NR	22
CGP-54061	3.0	0.4	23
CGP-55128A	0.6	NR	24
CGP-56346A	0.5	NR	24
CGP-56962A	0.7	0.4	23
CGP-62198A	0.3	0.6	25
JTP-2724	NR	0.7	26
JTP-3072	45.0	NR	27
JTP-4129	46.0	NR	27

[a]Recombinant human enzyme; NR: Data not reported.

Pharmacokinetics

Due to the high potency of the compound, the need for sensitive assays for evaluating its pharmacokinetics was identified. A direct microradioimmunoassay was proven to be specific, sensitive and suitable for drug toxicokinetic studies in animals and for human clinical studies (16).

Another analytical method was also developed for determination of aliskiren in animal and human plasma and urine. This fully automated high-performance liquid chromatography method with fluorescence detection was found to have a limit of quantitation of 4.5 ng/ml for plasma and 9.0 ng/ml for urine. The method was applied to rat, rabbit, marmoset and human plasma samples following oral administration of the fumarate. In rabbits administered doses of 10, 50 or 100 mg/kg aliskiren fumarate as a solution by gavage, rapid absorption was demonstrated, with peak plasma levels reached at 0.25 h, followed by rapid elimination from plasma (17).

Clinical Studies

The safety, tolerability, pharmacokinetics and pharmacodynamics of aliskiren fumarate were assessed in a randomized, placebo-controlled, parallel-group, crossover trial in 18 healthy male volunteers administered escalating doses as an oral solution once daily for 8 days. The subjects were given aliskiren at doses of 40, 80, 160 or 640 mg, placebo or enalapril 20 mg. Peak plasma concentrations were reached after 0.5-6 h following administration, with a half-life of 20-45 h. Aliskiren effectively inhibited all components of the RAS cascade, with dose-dependent decreases in plasma renin activity, angiotensin I and angiotensin II levels. Its effects were long lasting (up to 24 h) and the dose of 160 mg appeared to provide near-maximal effects at least equivalent to those of enalapril. No significant effects on blood pressure were observed, as expected in this population. Aliskiren was well tolerated at all doses, headache being the only drug-related adverse event reported (18, 19).

A multicenter, double-blind, randomized, parallel-group trial has also examined the efficacy and safety of aliskiren fumarate in 226 patients with mild to moderate hypertension. In this dose-ranging trial, treatment consisted of single daily oral doses of drug ranging from 37.5-300 mg, or the angiotensin II receptor blocker losartan 100 mg, for 4 weeks. All patients tolerated the treatments well at all doses, with no significant differences in the safety profiles of the two drugs. A clear dose-response relationship was observed for the reduction in blood pressure. Statistically significant lowering of daytime systolic blood pressure, the primary endpoint of the study, was measured at doses of 75, 150 and 300 mg aliskiren (20).

Aliskiren is currently being evaluated as the hemifumarate salt in phase II clinical trials by licensee Speedel as a potential treatment for hypertension, heart failure and chronic renal failure (20, 21).

Manufacturers

Novartis Pharma AG (CH); licensed to Speedel Pharma AG (CH).

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