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Vernakalant Hydrochloride

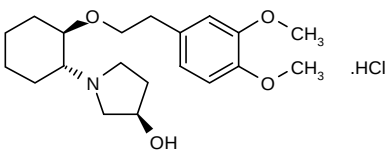
Antiarrhythmic Drug
Dual Sodium/Potassium Channel Blocker

Prop INNM; USAN

RSD-1235

1-[(1*R*,2*R*)-2-[2-(3,4-Dimethoxyphenyl)ethoxy]cyclohexyl]pyrrolidin-3(*R*)-ol hydrochloride

InChI=1/C20H31NO4.ClH/c1-23-19-8-7-15(13-20(19)24-2)10-12-25-18-6-4-3-5-17(18)21-11-9-16(22)14-21;/h7-8,13,16-18,22H,3-6,9-12,14H2,1-2H3;1H/t16-,17-,18-;/m1./s1



$C_{20}H_{32}ClNO_4$
Mol wt: 385.9251

CAS: 748810-28-8

CAS: 794466-70-9 (free base)

EN: 299039

Abstract

Atrial fibrillation is a debilitating disorder associated with a high risk of stroke. It is characterized by rapid, disorganized impulses in the atrium and ineffective atrial contractions, which show up as irregular P waves on the ECG trace. Rhythm control agents restore the heart to sinus rhythm by inhibiting ion channels in the myocardium and stabilizing the atrial impulses. However, current therapies are not atrial-specific and can promote life-threatening arrhythmias in the ventricles. Vernakalant hydrochloride (RSD-1235) is a mixed ion channel blocker with selectivity for atrial ion channels that does not promote ventricular arrhythmia. An i.v. formulation is in development for acute conversion of patients with atrial fibrillation or atrial flutter, and an oral formulation is being developed for the maintenance of sinus rhythm in patients at risk of developing atrial fibrillation.

Synthesis

Vernakalant can be obtained following several related synthetic strategies:

Condensation of (1*S*,2*R*)-2-[2-(3,4-dimethoxyphenyl)-ethoxy]cyclohexyl tosylate (I) with 3(*R*)-benzyloxypyrrolidine (II) provides vernakalant benzyl ether (III), which is then debenzylated by catalytic hydrogenolysis over Pd/C (1). In a more direct approach, tosylate (I) is condensed with 3(*R*)-hydroxypyrrolidine (IV) to provide vernakalant (1, 2). An alternative strategy consists of the cyclization of (1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexylamine (V) with (*R*)-2-acetoxysuccinic anhydride (VI) by means of acetyl chloride or with ethyl 4-chloro-3(*R*)-hydroxybutyrate (VII) to give, respectively, the cyclic imide (VIIIa) or the pyrrolidinone (VIIIb), which is subsequently reduced and deprotected by means of Red-Al to yield the title hydroxypyrrolidine derivative (2). The *O*-benzyl precursor of vernakalant (III) can alternatively be obtained by condensation of 2(*R*)-[3(*R*)-benzyloxy-1-pyrrolidinyl]cyclohexan-1(*R*)-ol (IX) with 3,4-dimethoxyphenethyl trichloroacetimidate (X) (prepared from dimethoxyphenethyl alcohol [XI] and trichloroacetonitrile) in the presence of trifluoromethanesulfonic acid (2, 3). A related strategy for preparing the succinimide precursor of vernakalant (VIIIa) consists of the condensation of 2(*R*)-acetoxy-*N*-[2(*R*)-hydroxy-1(*R*)-cyclohexyl]succinimide (XII) with imidate (X) in the presence of boron trifluoride etherate (4). Scheme 1.

The tosylate precursor (I) can be prepared by a number of different methods. Microbial dihydroxylation of chlorobenzene (XIII) gives (1*S*,2*S*)-3-chlorocyclohexa-3,5-diene-1,2-diol (XIV), which is further hydrogenated to (XV) in the presence of Rh/Al_2O_3. Regioselective tosylation of (XV), followed by hydrogenation of the resulting monotosylate (XVI) over Pd/C, leads to (1*S*,2*R*)-2-hydroxycyclohexyl tosylate (XVII). Subsequent coupling of (XVII) with imidate (X) provides the target intermediate (I) (1). In a different method, ketalization of (*S,S*)-1,2-cyclohexanediol (XVIII) with 2,2-dimethoxypropane provides the acetonide (XIX), which is oxidized to 2(*S*)-hydroxycyclohexanone (XX) by treatment with bis(trifluoromethyl)-dioxirane (BTDO). Subsequent tosylation of (XX) furnish-

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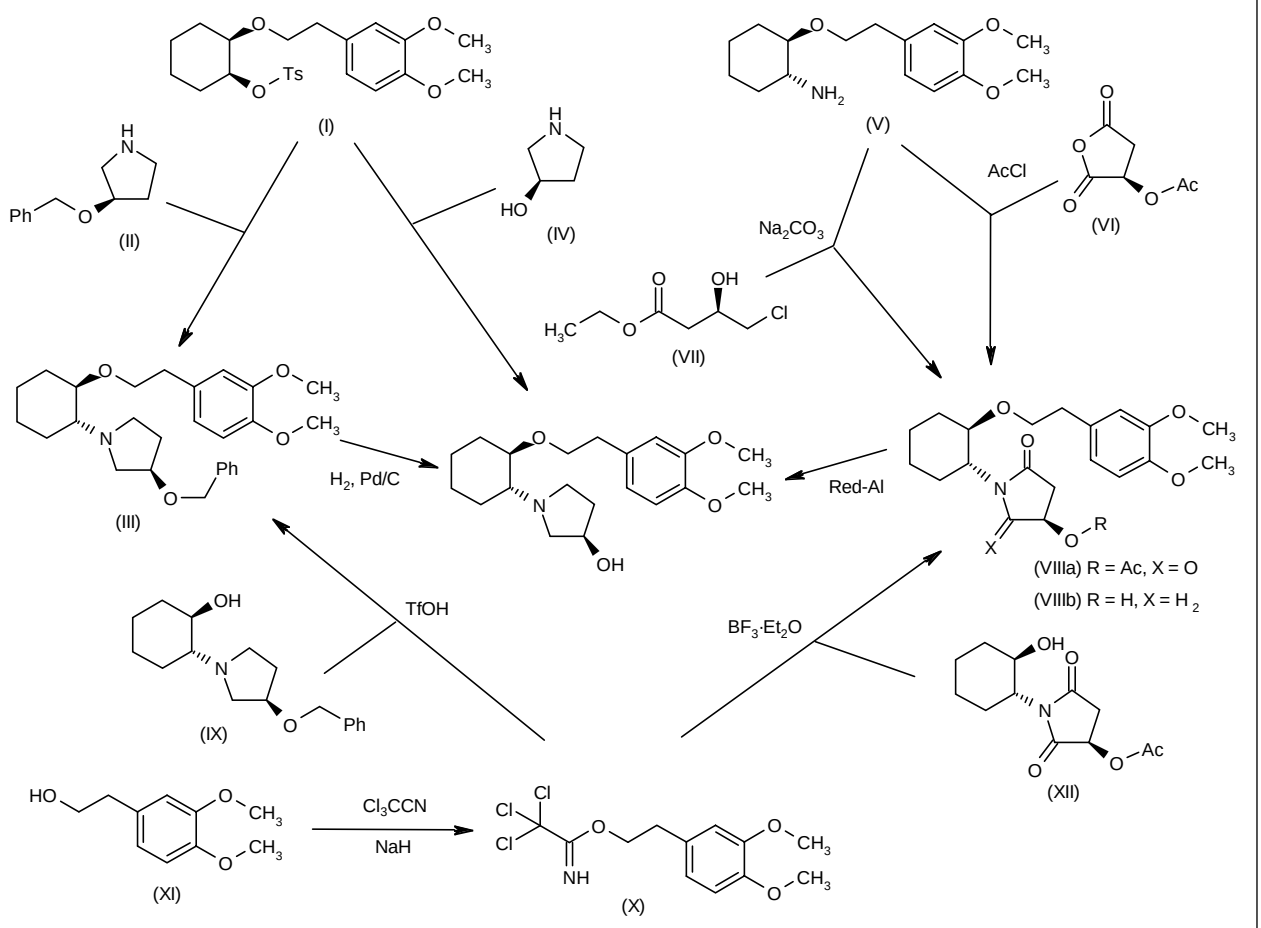
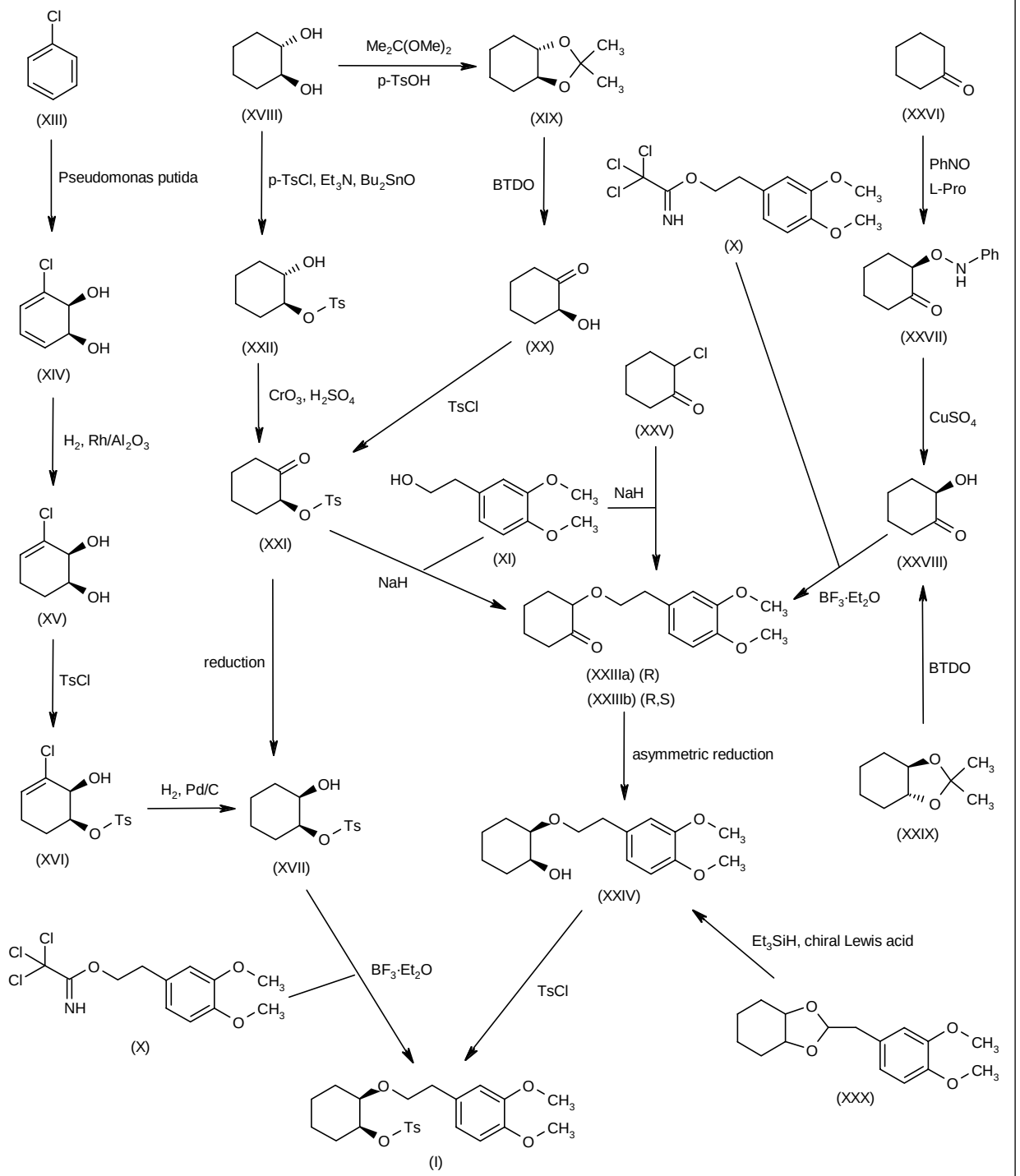
Scheme 1: Synthesis of Vernakalant



es 2(*S*)-tosyloxycyclohexanone (XXI). Alternatively, the chiral tosyl ketone (XXI) can be obtained by monotosylation of diol (XVIII) in the presence of Bu_2SnO to afford the hydroxy tosylate (XXII), which is subjected to Jones oxidation, giving ketone (XXI). The diastereoselective reduction of ketone (XXI) then provides an alternative route to 2(*R*)-hydroxy tosylate (XVII). Alternatively, the chiral tosyl ketone (XXI) is condensed with the sodium alkoxide of 3,4-dimethoxyphenethyl alcohol (XI) to yield the 2(*R*)-ether (XXIIIa). Stereoselective reduction of ketone (XXIIIa) utilizing bulky reducing agents such as L-Selectride, LS-Selectride or alpine boranes gives the (*S*)-cyclohexanol (XXIV), which can be further converted to tosylate (I) under the usual conditions. Similarly, the phenethyl alcohol (XI) can be reacted with 2-chlorocyclohexanone (XXV) by means of NaH to yield the racemic ketone ether (XXIIIb), which is enantioselectively reduced to the (1*S*,2*R*)-phenethoxycyclohexanol (XXIV) under Noyori's asymmetric hydrogenation conditions. A further route to the phenethoxy ketone (XXIIIa) consists of the enantioselective α-oxyamination of cyclohexanone (XXVI) with nitrosobenzene in the presence of L-proline to produce the chiral hydroxylamine derivative (XXVII), which is subsequently cleaved to 2(*R*)-hydroxycyclohexanone (XXVIII) by treatment with $CuSO_4$, and then coupled with imidate (X) in the presence of boron trifluoride etherate. Optionally, 2(*R*)-hydroxycyclohexanone (XXVIII) can be obtained by oxidation of the (1*R*,2*R*)-cyclohexanediol acetonide (XXIX) with BTDO. Another method for obtaining the (1*S*,2*R*)-phenethoxy cyclohexanol (XXIV) is based on the asymmetric reduction of (3,4-dimethoxyphenyl)-acetaldehyde cyclohexanediol acetal (XXX) by means of triethylsilane in the presence of chiral Lewis acids (2). Scheme 2.

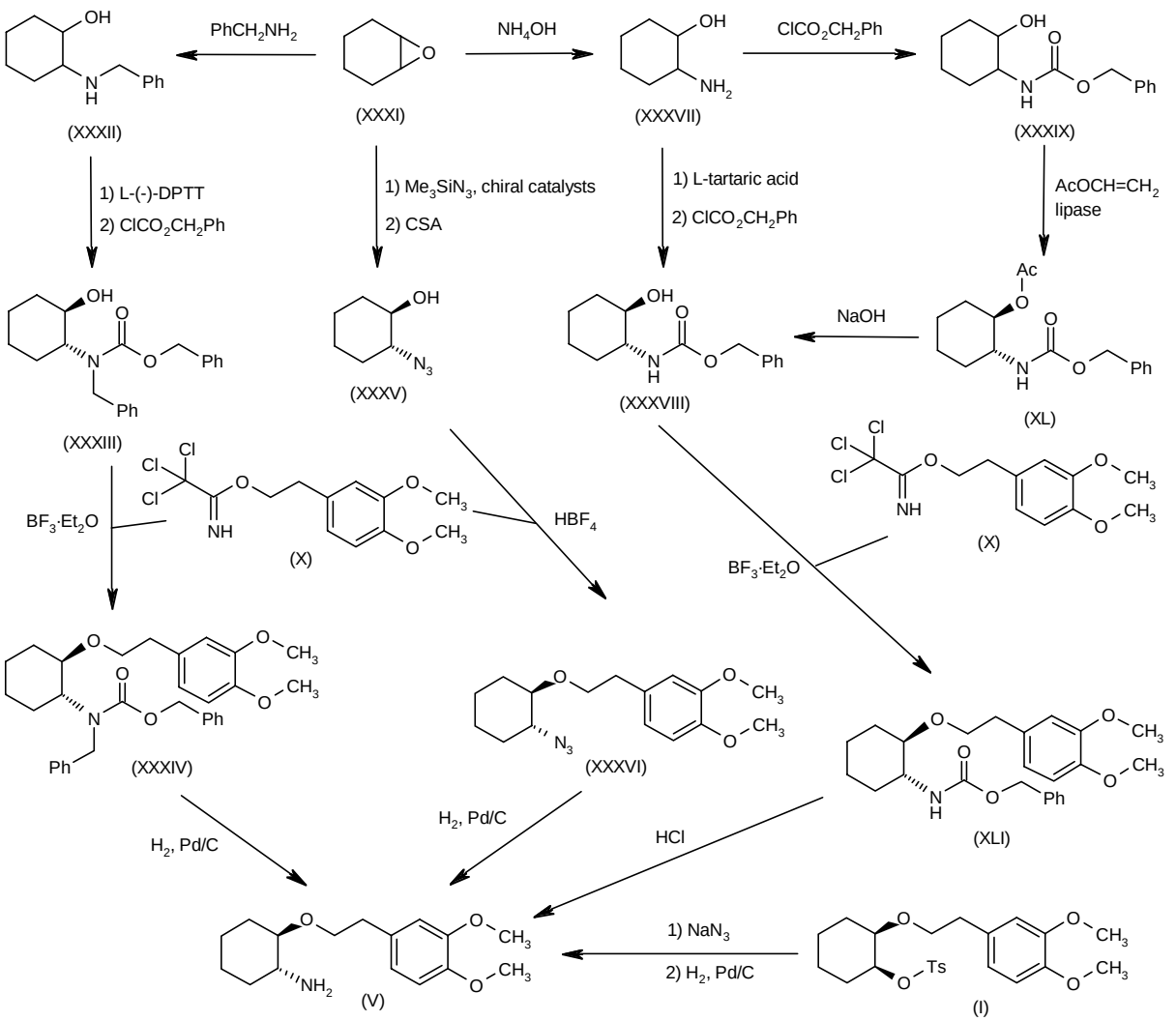
The precursor (1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)-ethoxy]cyclohexylamine (V) can be prepared as follows. Ring opening of cyclohexene oxide (XXXI) with benzylamine affords racemic *trans*-2-benzylaminocyclohexanol (XXXII) which, after resolution with L-(–)-di-*p*-toluoyltartaric acid, is treated with benzyl chloroformate to produce the chiral carbamate (XXXIII). Subsequent condensation of the cyclohexanol derivative (XXXIII) with imidate (X) yields the dimethoxyphenethyl ether (XXXIV), from which the *N*-benzyl and carbobenzoxy protecting groups are

Scheme 2: Synthesis of Intermediate (I)



removed by hydrogenolysis over Pd/C to furnish the target intermediate (V). Similarly, ring opening of epoxide (XXXI) with trimethylsilyl azide utilizing either Jacobsen's (salen)Cr(III) catalyst or Nugent's Zr C_3-symmetrical complex, followed by acidic desilylation, furnishes (*R,R*)-2-azidocyclohexanol (XXXV). After coupling of (XXXV) with imidate (X), catalytic hydrogenation of the resulting azido ether (XXXVI) provides amine (V). In an alternative method, aminolysis of cyclohexene oxide (XXXI) produces racemic *trans*-2-aminocyclohexanol (XXXVII),

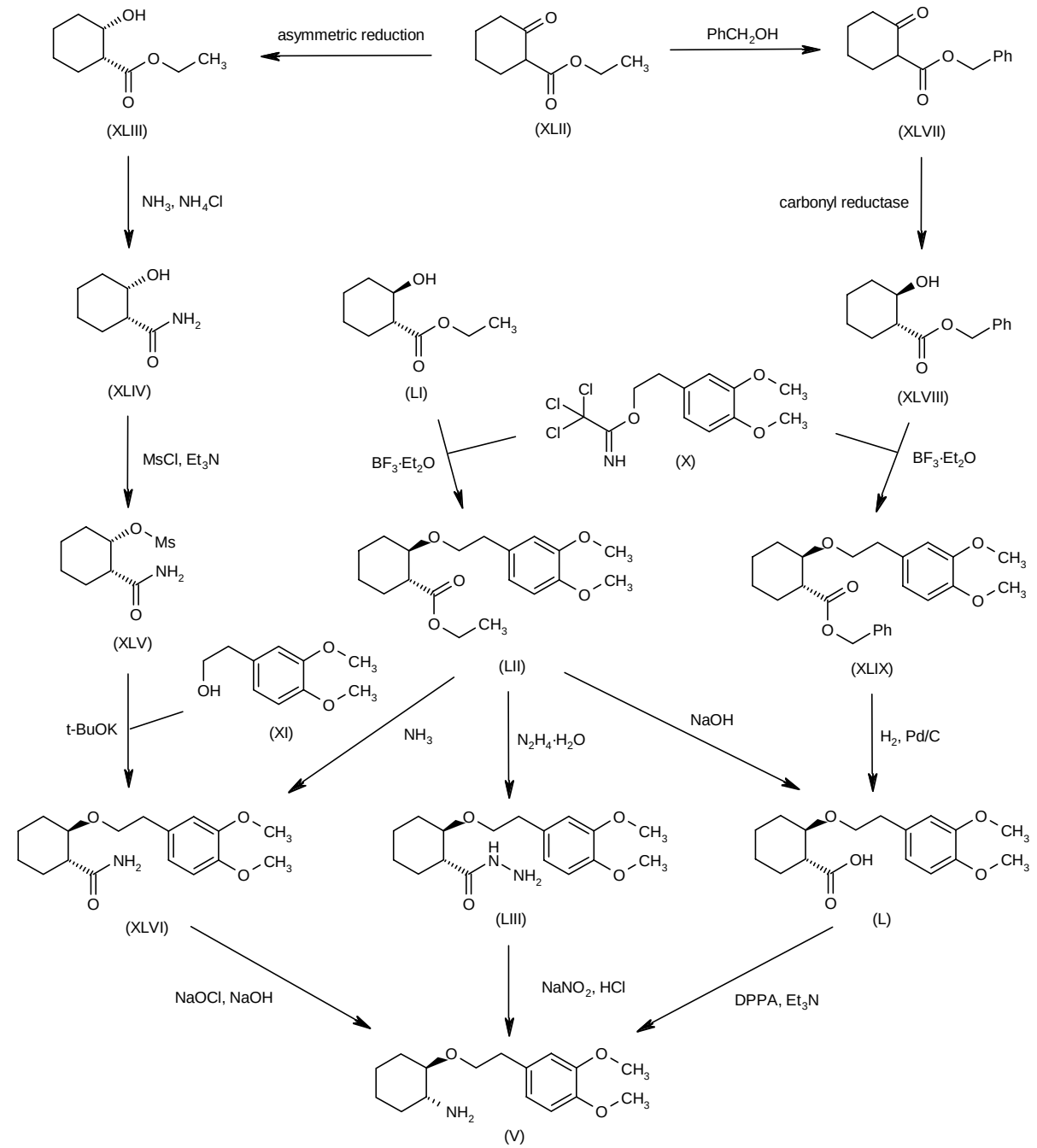
Scheme 3: Synthesis of Intermediate (V)



which, after resolution with L-tartaric acid, is reacted with benzyl chloroformate to give (*R,R*)-2-(benzyloxycarbonylamino)cyclohexanol (XXXVIII). Optionally, the chiral carbamate (XXXVIII) can be obtained by reaction of racemic aminocyclohexanol (XXXVII) with benzyl chloroformate, followed by enantioselective acetylation of the obtained compound (XXXIX) with vinyl acetate in the presence of lipase, to furnish the (*R,R*)-acetate (XL), which is then hydrolyzed to (XXXVIII) under alkaline conditions. Coupling of (*R,R*)-2-(benzyloxycarbonylamino)cyclohexanol (XXXVIII) with imidate (X) produces the carbobenzoxy-protected amino ether (XLI), which is then hydrolyzed to (V) in refluxing 6N HCl. A different route to the intermediate amine (V) consists of displacement of tosylate (I) with NaN_3, followed by catalytic hydrogenation of the resulting alkyl azide (2). Scheme 3.

Several alternative routes to the intermediate amine (V) are shown in Scheme 4. The asymmetric reduction of ethyl 2-oxocyclohexanecarboxylate (XLII) gives the (1*R*,2*S*)-hydroxy ester (XLIII), which is converted to amide (XLIV) by treatment with aqueous ammonia and ammonium chloride. After activation of the hydroxyl group of (XLIV) as the corresponding mesylate (XLV), displacement with the potassium alkoxide of 3,4-dimethoxyphenethyl alcohol (XI) affords the *trans*-amide ether (XLVI). The target amine (V) is then obtained by Hofmann rearrangement of carboxamide (XLVI) employing NaOCl and NaOH. A different resolution method involves transesterification of ethyl 2-oxocyclohexanecarboxylate (XLII) with benzyl alcohol, followed by enzymatic reduction of the resulting benzyl keto ester (XLVII) with carbonyl reductase to provide the (1*R*,2*R*)-hydroxy ester (XLVIII). Coupling of (XLVIII) with imidate (X) furnishes the benzyl phenethoxycyclohexanecarboxylate (XLIX), which is subjected to benzyl group hydrogenolysis to provide acid (L). This compound can also be obtained by condensation of

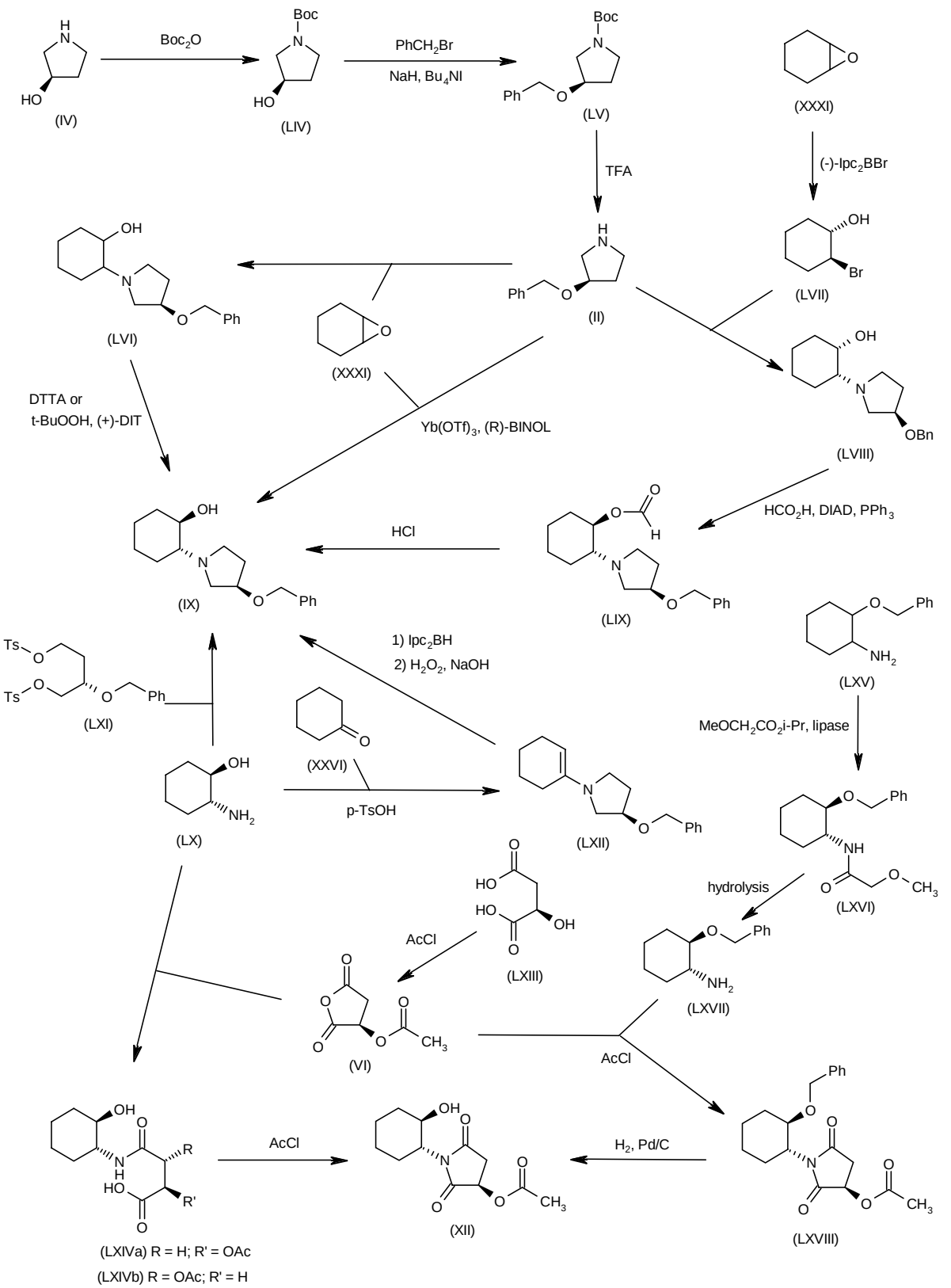
Scheme 4: Synthesis of Intermediate (V)



ethyl 2(*R*)-hydroxy-1(*R*)-cyclohexanecarboxylate (LI) with 3,4-dimethoxyphenethyl trichloroacetimidate (X), followed by alkaline hydrolysis of the obtained ethyl 2-phenethoxycyclohexanecarboxylate (LII). Optionally, the ethyl ester (LII) can be converted to amide (XLVI) by reaction with methanolic ammonia, or to hydrazide (LIII) by treatment with hydrazine hydrate in EtOH. Conversion of acid (L) to the target amine (V) can then be accomplished by Curtius rearrangement employing diphenylphosphoryl azide. Analogously, diazotization of hydrazide (LIII), followed by Curtius rearrangement of the intermediate acyl azide and alkaline hydrolysis results in the target amine (V) (2). Scheme 4.

The pyrrolidine building blocks are in turn synthesized as shown in Scheme 5. 3(*R*)-Hydroxypyrrolidine (IV) is protected as the *N*-Boc derivative (LIV), followed by

Scheme 5: Synthesis of Intermediates (II), (IX) and (XII)



O-alkylation with benzyl bromide and acidic deprotection of the resulting benzyl ether (LV) to furnish 3(*R*)-benzyloxypyrrolidine (II). Condensation of pyrrolidine (II) with cyclohexene oxide (XXXI) gives the *trans*-pyrrolidinocyclohexanol (LVI) as a diastereomeric mixture, which is separated either by crystallization with di-*p*-toluoyl-L-tartaric acid (DTTA) or by diastereoselective *N*-oxidation of the undesired diastereoisomer to furnish the target isomer (IX). Alternatively, intermediate (IX) can be obtained by ring opening of epoxide (XXXI) with pyrrolidine (II) in the presence of chiral catalysts. In a different strategy, enantioselective ring opening of cyclohexene oxide (XXXI) with *B*-bromodiisopinocamphenylborane provides the optically enriched *trans*-bromohydrin (LVII), which is then condensed with benzyloxypyrrolidine (II) to yield the (1*S*,2*R*)-pyrrolidinocyclohexanol (LVIII). Inversion of the configuration of alcohol (LVIII) to produce (IX) is then accomplished by Mitsunobu coupling with formic acid, followed by acidic hydrolysis of the resulting (1*R*,2*R*)-formate ester (LIX). Further synthetic strategies leading to the pyrrolidinocyclohexanol (IX) involve cyclization of (*R,R*)-2-aminocyclohexanol (LX) with 2(*R*)-benzyloxy-1,4-butanediol ditosylate (LXI), and condensation of (LX) with cyclohexanone (XXVI), followed by asymmetric hydroboration and oxidative work-up of the resulting enamine (LXII) (2). Alternatively, (*R,R*)-2-aminocyclohexanol (LX) can be converted to the intermediate acetoxysuccinimide (XII) by condensation with 2(*R*)-acetoxysuccinic anhydride (VI) (prepared from L-malic acid [LXIII] and acetyl chloride) to produce a regioisomeric mixture of succinamic acids (LXIVa) and (LXIVb), which undergoes cyclization to imide (XII) upon heating with acetyl chloride (4). Similarly, racemic *trans*-2-benzyloxycyclohexylamine (LXV) is resolved by enantioselective *N*-acylation with isopropyl methoxyacetate in the presence of lipase, followed by hydrolysis of the resulting (*R,R*)-methoxyacetamide (LXVI) to provide (LXVII) (5). Acylation of (*R,R*)-2-benzyloxycyclohexylamine (LXVII) with *O*-acetylmalic anhydride (VI), followed by cyclization with acetyl chloride, yields the *N*-(2-benzyloxycyclohexyl)succinimide (LXVIII), which is then debenzylated to (XII) by catalytic hydrogenation over Pd/C (4). Scheme 5.

Background

Atrial fibrillation is a common cardiac disorder associated with significant morbidity and mortality. The condition affects an estimated 2.2 million people in the United States and the lifetime risk for developing atrial fibrillation is estimated to be 1 in 4 for men and women over the age of 40. Atrial fibrillation is a major risk factor for stroke, and the predominant risk factor after 80 years of age (6-11).

Atrial fibrillation is characterized by rapid, disorganized electrical impulses that result in ineffective atrial contractions. On the ECG trace, atrial fibrillation shows up as irregular P waves. The major goal in the treatment of atrial fibrillation is to restore and maintain normal rhythm. A number of agents are currently available, including quinidine, procainamide, disopyramide, flecainide, amiodarone, propafenone, sotalol and dofetilide, which mostly act by blocking sodium and potassium (I_{Kr}) channels. However, they are not always effective, are not selective for the atria and are associated with serious adverse events, most notably proarrhythmic effects and also torsade de pointes, mainly due to additional ventricular effects (12).

Vernakalant hydrochloride (RSD-1235) is a mixed sodium and potassium channel blocker with specificity for atrial ion channels. The agent is effective at converting atrial fibrillation to sinus rhythm in animal models and is not associated with proarrhythmia or torsade de pointes. An i.v. formulation of vernakalant is under development for the acute conversion of atrial fibrillation to sinus rhythm, and an oral formulation is being developed to maintain sinus rhythm in patients who are at risk of reverting back to atrial fibrillation. The i.v. formulation was recently submitted for regulatory review in the U.S. for the acute conversion of atrial fibrillation to sinus rhythm, and the oral formulation is presently being tested in phase II clinical trials (12-14).

Preclinical Pharmacology

In isolated rat myocytes, 30 μM vernakalant reduced the overshoot and extended the duration of the action potential. Using whole-cell patch-clamp recordings, the IC_{50} for the cloned human atrium-specific Kv1.5 channel was 13 μM compared to 38, 30 and 21 μM for rat Kv4.3, rat Kv4.2 and human ERG channels; using guinea pig ventricular myocytes, no blockade of the inwardly rectifying K^+ current I_{K1} (IC_{50} > 1 mM) or of L-type calcium channels (IC_{50} > 200 μM) was seen. Against the fast-acting sodium channel $Na_V1.5$ (I_{Na} current), the IC_{50} varied with the stimulation frequency (40 μM at 0.25 Hz and 9 μM at 20 Hz) and the extent of depolarization (107 μM at –120 mV and 31 μM at –60 mV). Thus, it appears that the atrial-selective antiarrhythmic effect of vernakalant is due to potassium channel blockade and frequency- and rate-dependent sodium channel blockade (14, 15).

Site-directed mutagenesis of the potassium Kv1.5 channel, followed by expression and functional analysis in HEK293 cells, identified amino acid residues critical for the binding of vernakalant and suggested a unique binding site (16).

A detailed analysis of the role played by vernakalant in inhibiting the fast sodium current I_{Na} showed that the late I_{Na} current in particular was inhibited to a greater extent than the early or sustained currents. Increased late I_{Na} activity during the repolarization phase of the action potential contributes to early afterdepolarization, which in turn triggers torsade de pointes. Although vernakalant displays little effect on ventricular repolarization in rabbit Purkinje fibers, suggesting little proarrhythmic potential, it was able to attenuate the prolongation of action potentials induced by dofetilide, as well as early afterdepolarizations. Furthermore, it prevented or inhibited class III antiarrhythmic agent-induced torsade de pointes in a rab-

bit model, which was suggested to be due, at least in part, to its blockade of the late I_{Na} current (17-21).

When vernakalant was infused before and during coronary artery occlusion in rats, it prevented ischemia-induced atrial fibrillation in a dose-dependent manner (IC_{50} = 1.5 μg/kg/min). On the ECG trace, the P-R, QRS and R-P intervals were all prolonged. An extended R-P interval suggests that its protective action may be due, in part, to the blockade of early potassium channels (14).

Vernakalant terminated experimentally induced atrial fibrillation in anesthetized dogs in a dose-dependent manner at loading doses of 1-8 mg/kg i.v. At 4 and 8 mg/kg, vernakalant terminated atrial fibrillation in 7 of 7 and 4 of 4 dogs, respectively, without altering the R-R, P-R or Q-T intervals, and the QRS interval increased by 10-20% at 4 mg/kg, depending on the basic cycle length. The intra-atrial conduction time for both the left (10-43%) and the right atria (3-72%) increased in a dose- and rate-dependent manner. The atrial fibrillation cycle length also increased in a dose-dependent manner, *e.g.*, by 22% at 1 mg/kg, 45% at 2 mg/kg and 69% at 4 mg/kg vernakalant. In anesthetized macaques, 2.5, 5 and 10 mg/kg vernakalant i.v. increased the atrial ERP by 18%, 33% and 43%, respectively, without significantly affecting the ventricular refractory period (22).

Atrial remodeling was achieved in 6 anesthetized AV node-ablated dogs by atrial/ventricular pacing at 400/80 beats/min for 1 week. Following induction, atrial fibrillation was sustained in 1 dog, which was reversed by 4 mg/kg vernakalant infused over 10 min. In the remaining dogs, the mean duration of atrial fibrillation was 107 s, which was reduced to 62, 15 and 5 s, respectively, following 10-min infusion of 1, 2 and 4 mg/kg vernakalant. The left atrial ERP was increased by approximately 80-90% at the highest dose, depending on the basic cycle length, while the ERP of the right ventricle increased by only 11% at this dose. The QRS interval increased 15% at the highest dose in a rate-dependent fashion and the Q-T interval remained unchanged. The highest dose of vernakalant reduced the systolic blood pressure from 107 to 59 mmHg (23).

Atrial remodeling was also induced in 6 goats by repetitive induction of atrial fibrillation over a 48-h period. Subsequent administration of vernakalant (0.2 mg/kg/h i.v.) reversed remodeling and prolonged the left and right atrial refractory periods, resulting in decreased atrial fibrillation duration (from 120 to 70 s). In another goat model of persistent atrial fibrillation, vernakalant (0.2 mg/kg/h) prolonged the atrial fibrillation cycle length (107 to 156 ms), resulting in conversion to sinus rhythm in all 6 goats after 62 min of infusion (24).

Pharmacokinetics and Metabolism

The bioavailability of oral vernakalant was determined in a prospective, randomized, placebo-controlled, double-blind trial. Twenty-four healthy volunteers received either oral vernakalant (5 mg/kg; n=6) or placebo (n=2) after an overnight fast, oral vernakalant (5 mg/kg; n=6) or placebo (n=2) after a meal, or oral vernakalant (7.5 mg/kg; n=6) or placebo (n=2) in the fasting state. There were no significant changes in laboratory tests, vital signs or ECG intervals. The C_{max} was 1.3-1.9 μg/ml, t_{max} was approximately 30-60 min and oral bioavailability (calculated using previous i.v. data) was about 60-70%, with no significant differences among the treatment groups (25).

A phase I study of oral vernakalant in healthy volunteers demonstrated that the agent was safe and well tolerated and provided dose-proportional plasma concentrations. The maximum dose given was 900 mg twice daily for 7 days. Steady-state plasma levels were achieved within 3-4 days, and at the maximum dose, the blood levels approached those seen following i.v. dosing. Laboratory, vital signs and ECG measurements (including Q-T interval) were unchanged, and there were no serious adverse events (26).

Clinical Studies

In a single-blind, placebo-controlled, dose-escalating study, 29 healthy subjects were randomized to receive single doses of vernakalant (0.1-5 mg/kg) or placebo infused i.v. over 10 min. There were no serious adverse events, headache and mild taste disturbance being the most commonly reported effects. Vital signs, laboratory results and blood pressure were all unchanged on either treatment. Heart rate and ECG intervals increased with the active treatment; for example, in the group receiving the highest dose of vernakalant, the heart rate increased from 61 to 70 beats/min from baseline to end of infusion, and the P-R, QRS and Q-T intervals increased from 169, 88 and 384 ms to 184, 100 and 419 ms, respectively. All effects resolved spontaneously within 30 min postinfusion. Plasma C_{max} increased linearly with dose, ranging from 0.08 to 4 μg/ml over the dose range, and the elimination half-life was 2 h (27, 28).

Nineteen patients with atrial fibrillation were administered i.v. vernakalant at either 2 mg/kg over 10 min followed by 0.5 mg/kg/h for 35 min (n=10), or 4 mg/kg over 10 min followed by 1 mg/kg/h for 35 min (n=9). At baseline in the lower dose group, 5 of 10 patients had 9 episodes of transient atrial tachycardia with a mean duration of 26 s. After vernakalant treatment, 3 patients had 1 episode each of atrial tachycardia lasting 4.4 s. Dose-dependent prolongation of atrial refractoriness was seen and the agent slightly prolonged AV node, but not ventricular, conduction and refractoriness; no serious adverse events were reported (29-31).

In a multicenter, double-blind, parallel-group phase II study, 56 patients with recent-onset atrial fibrillation (continuous duration of 3-72 h at the time of randomization) were randomized to vernakalant 0.5 mg/kg followed by 1 mg/kg, vernakalant 2 mg/kg followed by 3 mg/kg or placebo, all by i.v. infusion over 10 min. The second dose was administered 30 min after the first and was only given if atrial fibrillation was present. Atrial fibrillation terminated within 30 min of the last infusion in 61% of patients in the higher dose group *versus* 5% of patients on placebo.

Secondary endpoints were the number of patients in sinus rhythm at 30 min and at 1 h, and the time to conversion to sinus rhythm. All three endpoints were also improved on active treatment compared to placebo. Serious adverse events were experienced by 4 placebo patients and 1 on the low dose of vernakalant (ventricular tachycardia). Cardiac events, mostly ventricular tachycardia and ventricular premature beats, were the most frequent adverse events in all groups. Mild paresthesia was reported in 2 patients on the higher dose of vernakalant, which was probably attributable to the active treatment. There was no significant difference in the Q-T, Q-T_c and QRS intervals between the active and placebo treatment groups. Changes in blood pressure were not substantially different between the groups. The mean plasma C_{max} was 5.8 μg/ml in those receiving both infusions at the higher dose and 2.6 μg/ml after a single 2 mg/kg infusion. The terminal elimination half-life was 3.1 h after a single infusion (32-34).

In the ACT I (Atrial arrhythmia Conversion Trial I), a double-blind, placebo-controlled, multicenter phase III study, 336 patients with atrial fibrillation (220 with an atrial fibrillation duration of 3 h to 7 days and 116 with a duration of 8-45 days) were randomized 2:1 to vernakalant (3 mg/kg followed by 2 mg/kg) or placebo administered by a 10-min infusion. The second dose was administered 15 min after the first if atrial fibrillation persisted. The primary endpoint, sinus rhythm occurring within 90 min of treatment and lasting > 1 min in the 3-h to 7-day atrial fibrillation patient group, was met by 52% of patients on active treatment (median conversion time = 11 min) *versus* 4% on placebo. Of these patients, only 1 had relapsed by 24 h. Of the patients in the 8-45-day prior atrial fibrillation group, 8% had conversion to sinus rhythm on active treatment compared to 0% on placebo. Over the 30 days following drug administration, 13% of patients in the vernakalant groups and 18% in the placebo group experienced serious adverse events. The most common serious adverse event was recurrence of atrial fibrillation, seen in 6% of those on active treatment and 12% of those on placebo. A transient alteration in taste was the most common nonserious, drug-related effect. No drug-related torsade de pointes was reported (35, 36).

The ACT III (Atrial arrhythmia Conversion Trial III), another randomized, placebo-controlled, multicenter phase III trial, evaluated vernakalant for the treatment of patients with atrial fibrillation or atrial flutter. Patients (n=276; 23 of whom had atrial flutter) were randomized 1:1 to receive vernakalant (3 mg/kg followed 15 min later by a second infusion of 2 mg/kg if warranted) or placebo by 10-min infusion. The primary endpoint was the number of patients with a prior 3-h to 7-day duration of atrial fibrillation achieving sinus rhythm of > 1 min duration and within 90 min of drug administration. A total of 52% of patients in the active treatment group met the primary endpoint *versus* 4% on placebo. Among those meeting the primary endpoint, the time to sinus rhythm conversion was 8 min. Of the 12 patients with atrial flutter randomized to active treatment, 1 achieved sinus rhythm *versus* none of those randomized to placebo. Of the patients with a prior atrial fibrillation duration of 8-45 days, there was no significant difference between placebo and active treatment. Over the 30 days subsequent to treatment, 10% of those on active treatment and 13% of those on placebo experienced a serious adverse event; there was 1 death in the active treatment group due to critical aortic stenosis. Transient alterations in taste and sneezing were the most common adverse events. Vernakalant was not associated with torsade de pointes (37-39).

In a combined analysis of the ACT I and ACT III trials, of patients with short-duration atrial fibrillation, 51.1% of those receiving vernakalant achieved sinus rhythm for at least 1 min within 90 min of treatment compared to 3.8% of those receiving placebo. In the overall population, including those with prior atrial fibrillation of up to 45 days, conversion to sinus rhythm was achieved by 36.9% and 3% of patients on active therapy and placebo, respectively. Conversion was rapid (median of 1-11 min). Of those who converted to sinus rhythm in the overall population, 92.3% were still in sinus rhythm at 7 days post-treatment. In some cases, the use of background medication appeared to influence the rate of conversion to sinus rhythm, with a trend for more effective conversion among those on sotalol, no effect among those on β-blockers or calcium channel blockers, and reduced efficacy among those taking digoxin. However, definite conclusions regarding the influence of background medicine could not be drawn due to insufficient numbers of participants in the studies. Serious adverse events occurred in 12.1% of vernakalant- and 15.7% of placebo-treated patients. The most common adverse events in the vernakalant group were transient alterations in taste (28.3%), sneezing (17.1%) and dizziness (11.3%), but no drug-related torsade de pointes was seen. The use of background medicine did not affect the incidence of adverse events (40-43).

An ongoing placebo-controlled, randomized phase III study is evaluating i.v. vernakalant in patients experiencing atrial fibrillation or atrial flutter following valvular and/or coronary artery bypass graft surgery (44). Another nonrandomized, open-label, uncontrolled phase III trial in patients with symptomatic atrial fibrillation is evaluating the safety and efficacy of i.v. vernakalant (45).

Oral vernakalant (RSD-1235-SR) is under development for patients at risk of recurrent atrial fibrillation/atrial flutter following conversion to sinus rhythm. In a double-blind, multicenter phase IIa study, patients with atrial fibrillation were randomized to oral vernakalant (300 or 600 mg) or placebo twice daily for 28 days. After 3 days, those still in atrial fibrillation were electrically cardioverted. A total of 171 patients were successfully cardioverted and continued to receive treatment for the full study period. Of those in the 300-mg group, 61% were still in sinus rhythm at the end of the study as opposed to 43% of those receiving placebo. The difference between the 600-mg group and placebo did not reach significance. Twelve patients were discontinued during the study for reasons unrelated to atrial fibrillation. Serious adverse events

occurred in 8% of patients on placebo, 10% of those on 300 mg and 11% of those on 600 mg, and there were no drug-related episodes of torsade de pointes (46, 47).

In February 2007, the U.S. Food and Drug Administration (FDA) accepted for review an NDA for the intravenous formulation of vernakalant hydrochloride for the acute conversion of atrial fibrillation to sinus rhythm (13).

Sources

Cardiome Pharma Corp. (CA); co-developed with Astellas Pharma US, Inc. (US).

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