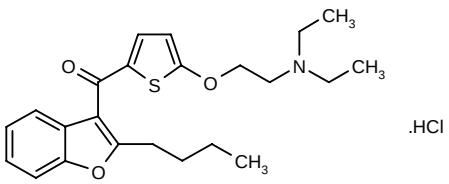
Drugs of the Future 1999, 24(9): 961-965

CCC: 0377-8282/99

E047/1

Antiarrhythmic

1-(2-Butyl-1-benzofuran-3-yl)-1-[5-[2-(diethylamino)ethoxy]-2-thienyl]methanone hydrochloride



$C_{23}H_{29}NO_3S.HCl$ Mol wt: 436.0130

CAS: 128995-51-7
CAS: 128995-52-8 (as free base)

EN: 209716

Synthesis

E047/1 was synthesized as outlined in Scheme 1.

2-Butylbenzofuran (I) was acylated with 5-methoxythiophen-2-carbonyl chloride (II) in chloroform at 0 °C to give the methanone compound (III). Ether cleavage of (III) was accomplished with borontribromide in chloroform to give the hydroxy compound (IV). Compound (IV) was treated with sodium methanolate and subsequently reacted with diethylaminoethylchloride in diethylcarbonate (DEC) to give the alkylated product. This was treated with hydrochloric acid to yield crystaline E047/1. The final product was purified by two recrystallizations from an acetone/water mixture.

Description

Yellowish powder, slightly soluble in water.

Introduction

The results of the Cardiac Arrhythmia Suppression Trial (CAST) showed that class I antiarrhythmic drugs may not be desirable in certain clinical situations and showed a higher mortality than placebo (1). Thus, interest and research in class III antiarrhythmic drugs has increased (2), but pure class III agents have shown a higher incidence of proarrhythmia as indicated by clinical studies (3). Despite these negative results with antiarrhythmic drugs, amiodarone, a drug which possesses characteristics of class I and class III antiarrhythmics as well as β-blocking and calcium channel blocking effects, has shown a decrease in arrhythmic death and a low risk in proarrhythmic activity. Amiodarone prolongs action potential duration and repolarization time, both of which reduce membrane excitability and may account for the drug's antifibrillatory properties (4). Amiodarone has become a reliable therapeutic agent in patients with severe underlying cardiomyopathy or coronary artery disease complicated by supraventricular or ventricular rhythm disturbances (5, 6). Although the therapeutic efficacy of amiodarone has been established, its general use is limited by its unfavorable pharmacokinetics. The need for careful consideration of the risks and benefits of treatment before implementation of amiodarone is supported by the possible occurrence of a wide array of potentially serious adverse effects, such as abnormal liver function tests, thyroid dysfunction and pulmonary fibrosis (7).

E047/1, a newly developed amiodarone derivative without iodine, also has a variety of actions on ion channels with predominant class III properties. E047/1 is thought to have the same high therapeutic potential and efficacy as amiodarone but with fewer side effects.

Pharmacokinetics and Metabolism

Excretion and plasma kinetics of total radioactivity following oral and intravenous administration of [^{14}C]-E047/1 to rats and dogs were investigated. Following oral administration, 100% of the dose was recovered within 7 days. The main route of elimination of total radioactivity was via feces and accounted for 78-87% of the dose in both species. A similar pattern of elimination of radioactivity was observed following intravenous administration. Similar elimination profiles of total radioactivity following both routes of administration indicate good absorption of the oral dose. High levels of radioactivity in feces suggest biliary elimination to be of importance in the excretion of the drug.

The nature of the metabolites was investigated following single intravenous administration of [^{14}C]-E047/1

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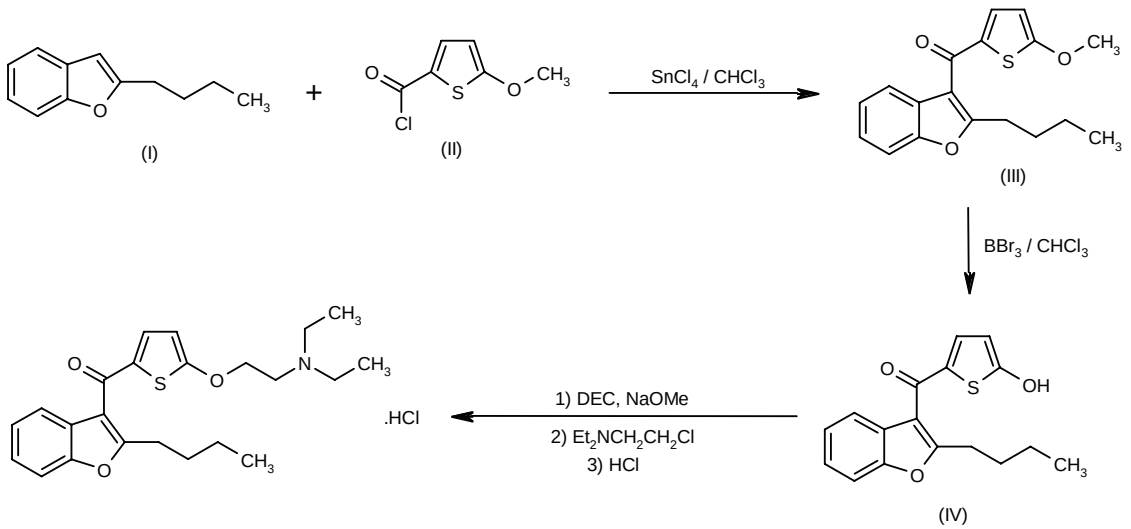
Scheme 1: Synthesis of E047/1



in both dog and rat plasma, sampled at 10 min postdose. A high proportion of the recovered radioactivity (~29% in dog and ~32% in rat) was eluted with a retention time similar to parent material. The proportions of this component decreased with time to ~12% after 4 h in the dog and approx. 13% after 1 h in the rat. At later times this component was no longer detected. The remaining radioactivity was generally polar in nature.

Pharmacological Actions

The available experimental data show that the newly developed benzofuran derivative E047/1 possessed favorable pharmacokinetic and antiarrhythmic efficacy. In isolated Langendorff perfused guinea pig hearts (8, 9), E047/1 dose-dependently increased conduction intervals and effective refractory periods. On the other hand, application of E047/1 did not significantly decrease heart rate (10). Furthermore, E047/1 possessed a marked antifibrillatoric efficacy in an *in vitro* ventricular fibrillation model using isolated Langendorff perfused guinea pig hearts. E047/1 (5 μM) time-dependently reduced ventricular fibrillation (VF) and ventricular tachycardia (VT) during reperfusion of the hearts. After 90 min, at the end of the observation period, VF and VT occurrence were reduced by about 87% (11).

The effect of E047/1 on the different ion channel currents was investigated in guinea pig myocytes using the patch-clamp technique. Inward rectifier potassium current (Ik_{ir}) was more markedly decreased by E047/1 in a time- and concentration-dependent manner as compared to amiodarone. E047/1 at a concentration of 10 μM blocked both the fast (Ik_r) and the slow (Ik_s) component of the delayed rectifier (Fig.1A), whereas Ik_r and Ik_s were only partially inhibited by amiodarone (10 μM). Calculation of the envelope of tail test showed that E047/1 (10 μM) completely blocked the tail current (Ik_s) and was comparable to E4031 (10 μM) a pure class III reference substance (Fig.1B). Reduction of the sodium current was less pronounced than with amiodarone. The current voltage relationship showed that calcium currents were significantly inhibited by E047/1 and was similar to amiodarone (Fig.2).

In vivo studies using instrumented dogs revealed a similar profile in reduction and depression of arrhythmias. In an ischemia/reperfusion model, during reperfusion after coronary artery occlusion for 1-2 h, the hearts of anesthetized dogs produced an accelerated ventricular rhythm interrupted by a high number of premature ventricular complexes. Intravenous bolus application of E047/1 (6.4 mg/kg b.w.) caused a significant reduction of the observed reperfusion arrhythmias over a period of 45 min in 7 out of 8 experiments (Fig. 3). Also the accelerated ventricular rate was reduced by 11% immediately after infusion. In addition, no effects were observed on hemodynamic parameters.

The antiarrhythmic effects of E047/1 were compared with those of lidocaine, bretylium, amiodarone and flecainide on spontaneous postinfarct arrhythmias in conscious dogs according to the model of Harris (12, 13). Dogs underwent a left thoracotomy under sterile surgical conditions and the left anterior descending coronary artery was exposed and ligated in two stages, resulting in acute myocardial infarction and severe ventricular tachyarrhythmias. Twenty-two hours after myocardial infarction, dogs were randomly assigned to receive one of the antiarrhythmic compounds.

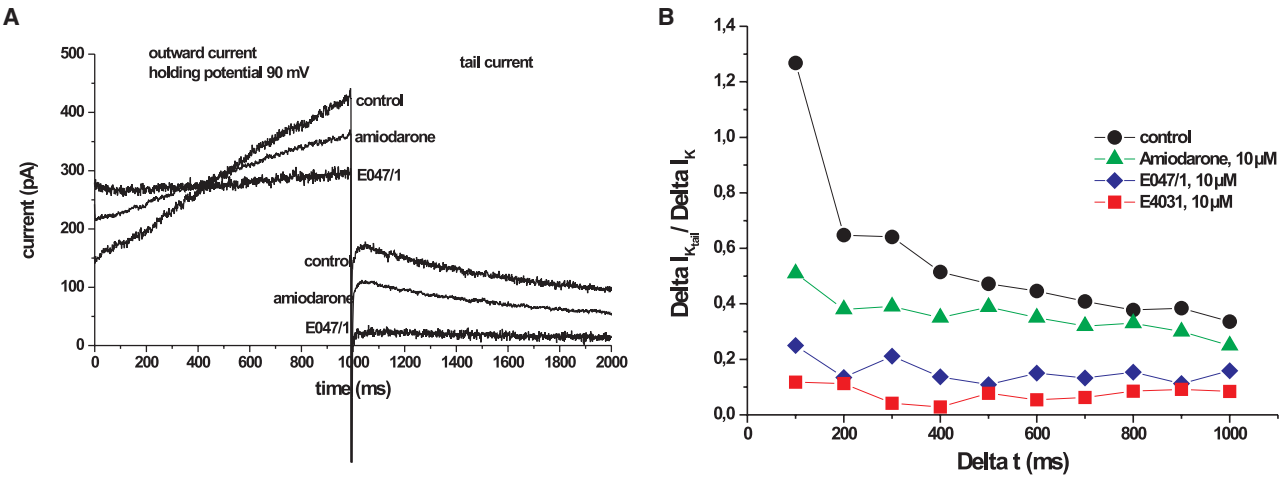


Fig. 1. A) Effects of E047/1 (10 µM) and amiodarone (10 µM) on the fast outward and slow tail component of the delayed rectifier potassium current. B) Calculation of the envelope of tail test. Evaluation of the ion channel blocking activity on the tail current of the delayed rectifier potassium channel by E047/1 (10 µM), E4031 (10 µM), a selective potassium channel blocker, and amiodarone (10 µM). Each value represents the mean of 5 experiments.

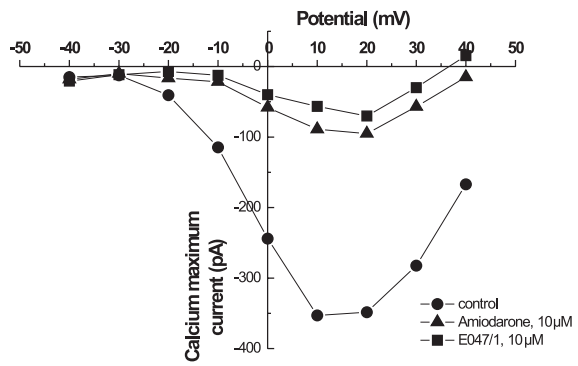


Fig. 2. Comparison of the calcium current-voltage relationship of E047/1 (10 µM) and amiodarone (10 µM). Data represent the mean of 5 experiments.

All investigated drugs, except bretylium, decreased the total number of ventricular beats. E047/1 reduced ectopies by 44% immediately after the administration of the bolus. The antiarrhythmic effect, a further reduction of the ectopic beats up to 62%, continued throughout the drug infusion. Amiodarone reduced ventricular ectopies by 30% immediately after the bolus, and the number of ectopies was reduced to a similar degree throughout the entire observation period. Flecainide exhibited a decreasing effect of total ventricular ectopies, which reached its maximum only at the 60 min measurement, reducing ectopies by 38%. Lidocaine showed only a tendency (p = 0.06) towards a minor decrease. With flecainide and lidocaine, the number of ectopies per minute returned to baseline 1 h after discontinuation of the infusion (Fig. 4).

The potential efficacy of E047/1 on the termination and reinduction of atrial fibrillation (AF) have been investigated in an anesthetized canine model. The method for inducing AF via vagal stimulation and pacing of the hearts of anesthetized dogs has been described previously (14). E047/1 (1, 2 or 3 mg/kg bolus infusion) induced a dose-dependent increase in the termination of AF. Irrespective of dose, the mean time to termination of AF after drug administration was 4.4 + 1.7 min. With respect to prevention of reinduction once termination had occurred, both the 3 mg/kg and 6 mg/kg doses had a significant effect (Fig. 5). These effects were associated with drug-induced slowing of atrial conduction and prolongation of the atrial effective refractory period.

Clinical Studies

Results of phase I clinical studies have confirmed that E047/1 is well tolerated in healthy volunteers. The study

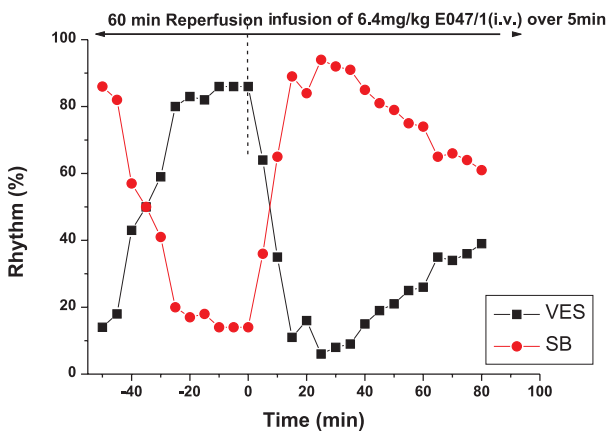


Fig. 3. Intravenous infusion of E047/1 (6.4 mg/kg b.w.) over 5 min after 60 min of reperfusion significantly reduced ventricular arrhythmia in an *in vivo* dog model. Data were obtained from 8 different dogs. VES= ventricular extrasystoles, SB = sinus beats.

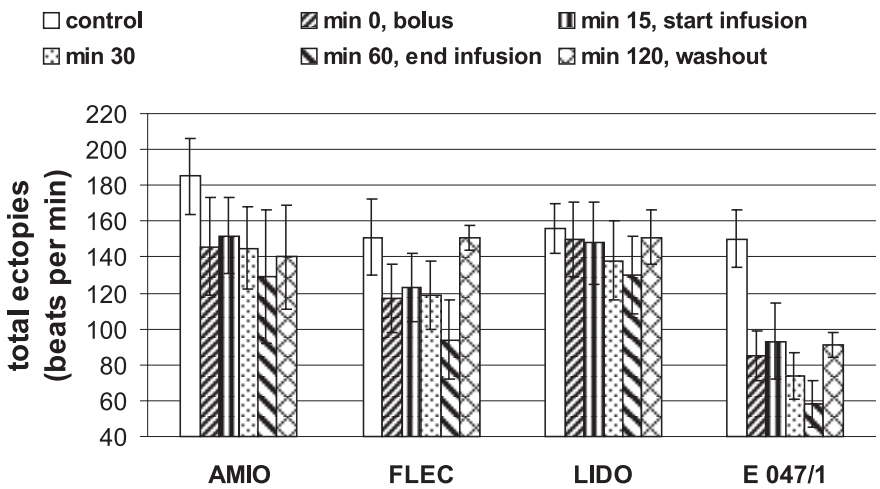


Fig. 4. Antiarrhythmic effect of E047/1, lidocaine, amiodarone and flecainide on spontaneous postinfarct arrhythmias in conscious dogs. Drugs were applied as a bolus infusion over 5 min followed by a continuous infusion for 60 min. Following concentrations were used: E047/1: 6 mg/kg bolus + 6 mg/kg inf.; lidocaine: 1 mg/kg bolus + 0.08 mg/kg inf.; amiodarone 10 mg/kg bolus + 0.03 mg/kg inf.; flecainide: 1 mg/kg bolus + 0.05 mg/kg inf. 8 dogs were investigated in each substance group.

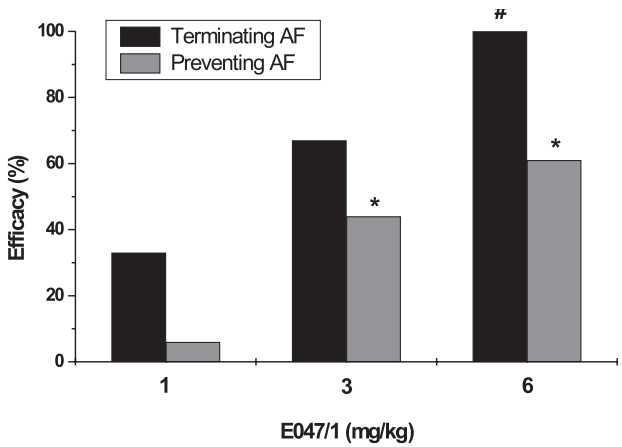


Fig. 5. Efficacy of E047/1 in terminating and preventing reinduction of atrial fibrillation (AF) for 30 min after drug administration. Comparison for termination is with control (were AF = 6/6) and comparison for reinduction is with dose 1 (1 mg/kg over 2 min). $^{*}p < 0.05$ *vs.* dose 1; $^{\#}p < 0.05$ *vs.* control: n = 6.

involved 32 subjects administered 8 intravenous bolus infusions over 15 min up to 240 mg. Following infusion of E047/1, pharmacokinetic studies showed that peak plasma concentration increased in a linear manner with dose level. The peak plasma concentration was achieved at 15 min, at the time of the end of infusion. The elimination half-life of E047/1 in plasma was approximately 6 h.

After coronary bypass grafting and in patients after mitral or aortic valve surgery, frequent PVCs, couplets, triplets and ventricular tachycardia (VT) may compromise hemodynamics, alter myocardial oxygen balance and predispose to ventricular fibrillation (VF). The therapeutic approach remains controversial and the ideal antiarrhythmic drug is not yet available.

In a postoperative, phase II dose-finding study, E047/1 was investigated in 40 patients after cardiac surgery, including patients after coronary bypass grafting and patients after mitral or aortic valve surgery. The objective of the study was to investigate the efficacy, safety and tolerability of E047/1. The drug was administered as a bolus infusion (1, 2 or 3 mg/kg b.w.) over 10 min followed by a continuous infusion (1 mg/kg/h) for 2 h.

Immediately after bolus infusion, ventricular ectopies were reduced by up to 55% by all doses of E047/1,

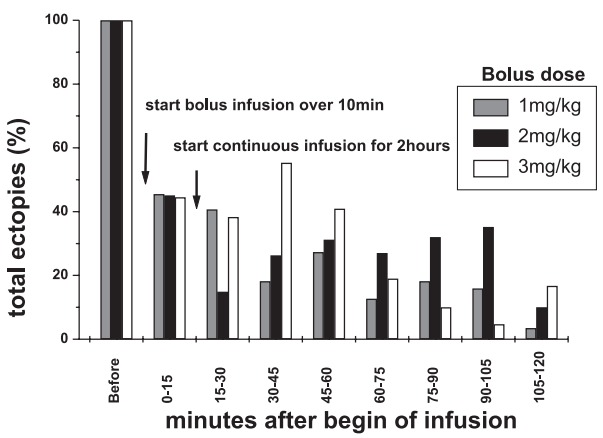


Fig. 6. E047/1 decreased ventricular arrhythmia in patients after cardiac surgery. A bolus infusion of E047/1 (1, 2 or 3 mg/kg b.w. over 10 min) was followed by a continuous infusion of 1 mg/kg/h E047/1 for 2 h.

indicating a broad therapeutical dose range. The incidence of ventricular arrhythmic events was further reduced until the end of continuous drug infusion period (Fig. 6). Therefore, E047/1 did not influence conduction times and hemodynamic parameters. E047/1 was effective in all patients without adverse effects. At a bolus dose of 3 mg/kg a short interim reduction of blood pressure was observed which returned to baseline a few minutes after the end of bolus infusion. The rate of drug response was highest with the 2 mg/kg bolus dose and, therefore, this dose regimen seems to be the most effective.

Manufacturer

Ebewe Arzneimittel GmbH (AT), available for licensing.

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