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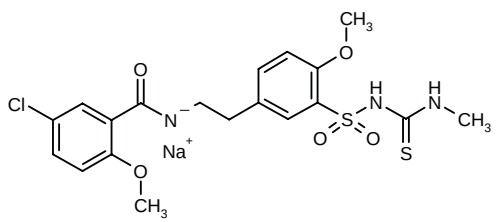
Clamikalant Sodium

Prop INNM

Antiarrhythmic
K_{ATP} Channel Blocker

HMR-1098
HMR-1883 (as free acid)

5-Chloro-2-methoxy-*N*-[2-[4-methoxy-3-(3-methylthioureidosulfonyl)phenyl]ethyl]benzamide sodium salt



$C_{19}H_{21}ClN_3NaO_5S_2$ Mol wt: 493.9659

CAS: 261717-22-0
CAS: 158751-64-5 (as free acid)

EN: 255449

Synthesis

Condensation of 2-(4-methoxyphenyl)ethylamine (I) with either 5-chloro-2-methoxybenzoic acid (II) by means of CDI and TEA (1) or 5-chloro-2-methoxybenzoyl chloride (III) by means of pyridine and DMAP (1, 2) gives the corresponding benzamide (IV), which by treatment with chlorosulfonic acid yields the sulfonyl chloride (V). Reaction of compound (V) with aqueous ammonia in acetone affords the expected sulfonamide (VI), which is finally treated with methyl isothiocyanate (VII) by means of either *t*-BuOK (1) or NaH (2) in DMF. Scheme 1.

Introduction

Sudden cardiac death, a leading cause of mortality in Western countries, is considered to be due in most cases to reentry arrhythmias resulting from myocardial ischemia. Opening of ATP-sensitive potassium (K_{ATP}) channels has been found to play a critical role in this process. This channel is activated only during myocardial ischemia, but not under normal physiological conditions. Opening of the channel results in a shortening of the action potential duration (APD) and a derangement of electrophysiological parameters. Thus, pharmacological blockade of the K_{ATP} channel was hypothesized to have no effect in the absence of ischemia, but to abrogate these ischemia-related detrimental effects and thereby prevent the development of arrhythmias (1, 3).

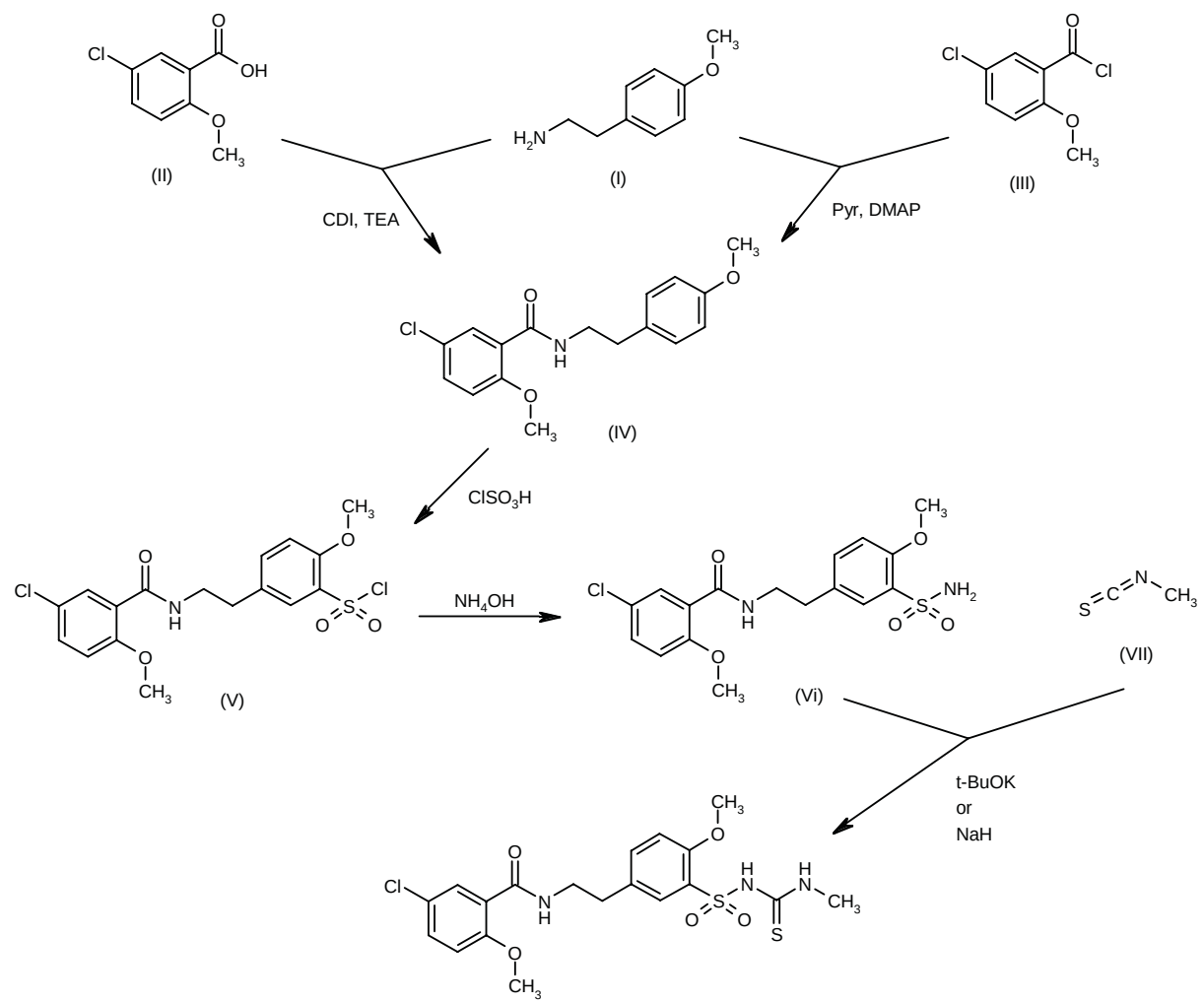
ATP-sensitive potassium channels consist of a pore-forming subunit known as Kir6.2 and a regulatory protein known as the sulfonylurea receptor, SUR. Three isoforms of SUR have been identified: SUR1 expressed in pancreatic β-cells, SUR2A expressed in heart and skeletal muscle, and SUR2B expressed in vascular smooth muscle cells. The sulfonylurea glibenclamide was shown a number of years ago to improve the electrophysiological changes and ventricular fibrillation associated with ischemia, but was not further developed for this indication due to its lack of tissue selectivity and the risk of undesired metabolic and hemodynamic effects. In addition to the cardiac K_{ATP} channel, glibenclamide also blocks pancreatic K_{ATP} channels resulting in insulin secretion, and the vascular smooth muscle K_{ATP} channel (1, 3). This led Aventis researchers to search for new sulfonylureas with selectivity for cardiac K_{ATP} channels. HMR-1883, an *m*-anisamidoethylbenzenesulfonylthiourea, was discovered to block cardiac K_{ATP} channels more effectively than pancreatic and vascular channels. The sodium salt of this compound, HMR-1098 (clamikalant sodium), is currently in phase II clinical trials (1, 4).

Pharmacological Actions

The pharmacology of HMR-1883/HMR-1098 has been extensively studied *in vitro* and *in vivo*. In guinea pig papillary muscle, neither HMR-1883 nor glibenclamide at a concentration of 20 μM had an effect on the APD, but both compounds antagonized the APD shortening induced by the KATP channel opener rilmakalim, with IC_{50} values of 1.8 μM for HMR-1883 and 0.33 μM for glibenclamide at pH 7.4; under more acidic conditions characteristic of ischemia, the respective IC_{50} values were 0.6 μM and 0.14 μM. Moreover, hypoxia-induced shortening of the APD was significantly attenuated by the

N.E. Mealy, L. Martín, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Clamikalant Sodium



sulfonylureas, about 50% at a concentration of 20 μM. Experiments were also performed using isolated guinea pig ventricular myocytes. Rilmakalim-induced shortening of the APD was again antagonized by HMR-1883 and glicenclamide, with respective IC_{50} values of 0.4 μM and 10 nM at pH 6.5 (3 μM and 52 nM, respectively, at pH 7.4), as were rilmakalim-induced whole-cell currrents (IC_{50} = 0.8 μM and 20 nM, respectively, at pH 7.4). In isolated perfused guinea pig hearts exposed to hypoxia to increase coronary flow, glibenclamide was able to completely inhibit the increase in flow at a concentration of 1 μM, whereas HMR-1883 at this concentration had no effect and at 10 μM it inhibited the increase in coronary flow by only 18%. Experiments in rat pancreatic β-cells confirmed the selectivity of HMR-1883. Whereas glibenclamide depolarized the cell potential half-maximally at 9 nM, a concentration of HMR-1883 of 20 μM was required for a similar effect (3, 5-7).

Using single human cardiomyocytes, as above, HMR-1883 was demonstrated to be more potent under acidic conditions in blocking K_{ATP} channels. At physiological pH (7.3), HMR-1883 produced half-maximal block of rilmakalim-induced currents at 0.6 μM, whereas an IC_{50} of 0.3 μM was obtained at more acidic pH (6.5) (8).

Isolated rat hearts were subjected to 15 min of ischemia followed by 30 min of reperfusion. The duration of postischemic ventricular fibrillation was inhibited by HMR-1883 (1 and 10 μM) in a concentration-dependent manner. During the reperfusion period, HMR-1883 improved the recovery of dP/dt_{max} and significantly reduced the levels of lactate dehydrogenase and creatine kinase (3, 9).

The cardiac electrophysiological effects of glibenclamide and HMR-1883 during regional ischemia-reperfusion have been examined in isolated rabbit hearts. Pretreatment with HMR-1883 (3 μmol/l) or glibenclamide

(3 μmol/l) prior to left coronary artery branch occlusion (45 min) followed by reperfusion (45 min) was associated with inhibition of the shortening of the epicardial activation-recovery interval in the ischemic area seen during ischemia, as well as inhibition of the increased dispersion of the activation-recovery interval seen during late ischemia and reperfusion. The sulfonylureas had no effect in nonischemic areas. Ventricular fibrillation was seen in half of the vehicle-treated hearts, whereas both HMR-1883 and glibenclamide completely prevented the occurrence of ventricular fibrillation. Moreover, the elevation in S-T segment seen in early ischemia was prevented by both sulfonylureas. However, unlike glibenclamide, HMR-1883 did not appear to suppress the recovery of coronary flow reduced during ischemia (10-12). Another study in ischemic rabbit hearts with electrically induced ventricular fibrillation exposed to 10 μM HMR-1098, the sodium salt of HMR-1883, demonstrated its ability to prevent ischemia-induced APD shortening, which correlated with reductions in the dispersion of ventricular repolarization and the window of vulnerability for induction of ventricular fibirllation (13).

In isolated perfused working rat hearts continuously paced during low-flow ischemia, HMR-1098 (3 μmol/l) displayed cardiodepressant effects which were not seen in a model of ischemia/reperfusion in anesthetized rats treated at a dose of 10 mg/kg i.v. In the *in vivo* model, HMR-1098 had no significant effect on mean arterial blood pressure, heart rate, aortic blood flow or myocardial infarct size compared to untreated animals (14). In another study, HMR-1883 at doses of 3 and 10 mg/kg i.v. reduced mortality from 61% in vehicle-treated rats subjected to 5 min of ischemia followed by 10 min of reperfusion, to 30% and 13%, respectively, and it also shortened the duration of ventricular fibrillation. Glibenclamide showed similar effects. However, only HMR-1883 significantly reduced the incidence and duration of ventricular fibrillation in animals subjected to a longer period of ischemia (30-min occlusion). Oral pretreatment with HMR-1883 2 and 4 mg/kg also reduced mortality from 65% in vehicle-treated controls to 40% and 20%, respectively, and dose-dependently reduced the duration of ventricular fibrillation. Whereas HMR-1883 had no effect on blood glucose or insulin, antifibrillatory doses of glibenclamide were associated with increases in plasma insulin and decreases in blood glucose levels (3, 15).

As glibenclamide has been reported to abolish the beneficial cardioprotective effects of ischemic preconditioning, a study was performed in anesthetized rabbits subjected to 30-min occlusion of the left descending coronary artery followed by 2-h reperfusion, preceded by two periods of 5-min occlusion followed by 10-min reperfusion.Glibenclamide (0.3 mg/kg) or HMR-1883 (3 mg/kg) was administered prior to the first preconditioning or 5 min prior to long-term ischemia. In contrast to glibenclamide which signfiicantly increased myocardial infarct size (as a percentage of area at risk) in the absence of ischemic preconditioning and abolished the beneficial effect of ischemic preconditioning, HMR-1883 had no effect on myocardial infarct size in the presence or absence of ischemic preconditioning. However, both HMR-1883 and glibenclamide prevented the ischemia-induced shortening of the monophasic action potential (MAP) duration (3, 16-19).

The effects of HMR-1883 have also been examined in anesthetized pigs under conditions of myocardial ischemia. In animals subjected to occlusion of a branch of the left circumflex coronary artery, resulting in reductions in MAP duration and in upstroke velocity, treatment with HMR-1883 (3 mg/kg i.v.) significantly attenuated the MAP shortening by 59% compared to untreated controls, and it also attenuated the decrease in upstroke velocity by about 53%. The compound, on the other hand, had no significant effect on blood pressure, left ventricular end-diastolic pressure or left ventricular contractility before, during or after ischemia (3, 20).

Other experiments in pigs investigated the effects of HMR-1883 on sudden cardiac arrhythmic death and electrocardiographic changes following myocardial occlusion. Survival was increased in animals pretreated with HMR-1883 (3 mg/kg i.v.) from 33% in control animals to 91%. The K_{ATP} blocker did not affect hemodynamics or ECG under baseline conditions and had no effect on hemodynamics during occlusion, but it significantly attenuated the ischemia-induced depression of the S-T segment and prolongation of the Q-J time (3, 21, 22).

The hypothesis that HMR-1098 could prevent atrial effective refractory period (ERP) shortening during atrial fibrillation was examined in dogs given a bolus of 3 mg/kg followed by a continuous infusion of 17 μg/kg/min throughout the study. The animals had pharmacological autonomic blockade with atropine and propranolol and rapid right atrial pacing. Progressive shortening of the high right atrial ERP and the MAP duration at 90% repolarization (MAP_{90}) was seen in the control animals. Although HMR-1098 had no significant effect on atrial electrical remodeling during the first 3 h, it restored high right atrial ERP to baseline levels at later time points, consistent with the presence of ischemia (23).

Another study in conscious dogs with healed myocardial infarction demonstrated the ability of HMR-1883 to prevent ventricular fibrillation induced by acute myocardial ischemia during exercise. At a dose of 3 mg/kg i.v. prior to coronary artery occlusion during submaximal exercise, ventricular fibrillation was prevented in 11 of 13 animals, similar to glibenclamide at a dose of 1 mg/kg i.v., which protected 6 of 7 dogs. The decrease in refractory period was prevented by both HMR-1883 and glibenclamide. HMR-1883 also attenuated the depression in the S-T segment, as well as T-wave oscillations in the protected animals. However, in contrast to glibenclamide, HMR-1883 had no significant effect on coronary blood flow, left ventricular dP/dt_{max} or plasma insulin or blood glucose in fasted dogs (3, 24-27).

The results from a study in anesthetized dogs indicated that HMR-1883 does not behave as a classic antiarrhythmic agent. The K_{ATP} channel blocker had no effect on the incidence of ventricular extrasystoles or

tachycardia induced by digoxin, whereas it significantly increased the dose of digoxin required to induce ventricular fibrillation and delayed ventricular fibrillation and death in these animals. HMR-1883 had no effect per se on hemodynamics or ECG and it did not alter the positive inotropic effect of digoxin (3, 28).

Toxicology

Toxicological studies have been conducted in mice, rats and dogs. The LD_{50} in mice and rats was > 2000 mg/kg p.o. and > 200 mg/kg i.v. In subchronic toxicity studies in rats and dogs, reproductive studies in rats and rabbits, and chronic toxicity studies in rats and dogs, the major abnormal finding was a mild decrease in erythrocytes, mainly in female rats, and a transient decrease in blood glucose was also reported. No deleterious effects on reproduction and no mutagenic or clastogenic effects have been seen (3).

Pharmacokinetics and Metabolism

Studies on the pharmacokinetics, distribution, elimination and metabolism of HMR-1883 have been performed in several animal species after both i.v. and oral administraton of labeled and unlabeled drug. In rats given an i.v. dose of 3 mg/kg, significant plasma levels (16.6 μg/ml) were measured at 5 min after administration, with mean plasma half-lives of 5 min and 1.4 h and no detecable drug after 24 h. Orally administered drug (10 mg/kg) produced peak plasma levels of 9.7 μg/ml at 2 h, with levels at 24 h of 0.8 μg/ml. The absolute oral bioavailability was estimated to be 85.6% (3).

In dogs, the distribution half-life was 10-14 min after a dose of 3 mg/kg i.v., and the elimination half-life was 0.6-0.7 h. Levels at 24 h after administration were below the detection limits. Total clearance was 4.1-4.5 ml/min/kg and the AUC was 11.1-12.3 μg·h/ml. Peak plasma levels of 7.1-22.9 μg/ml were attained at 0.25-0.5 h after an oral dose of 10 mg/kg. Plasma levels were undetectable at 8-24 h. The AUC was 17.3-26.2 μg·h/ml and the absolute oral bioavailability was 40-70% (3).

Studies in rats administered [^{14}C]-HMR-1883 at a dose of 3 mg/kg i.v. showed the highest concentrations of radioactivity in the liver and kidneys, followed by plasma. Following oral administration at a dose of 10 mg/kg, the highest levels of radioactivity were detected in the liver, mesenteric lymph nodes and kidneys, followed by plasma. In both cases, most of the radioactivity was eliminated in 96 h (3).

Excretion studies in rats and dogs administered doses of 3 mg/kg i.v. or 10 mg/kg p.o. indicated that the drug is mainly eliminated via the feces (70-87%), with the rest in the urine (10-17%). High plasma protein binding, particularly to albumin, was seen in rats, rabbits, dogs and man. *In vivo* in rats administered 3 mg/kg HMR-1883 i.v. or 10 mg/kg p.o., almost all of the radioactivity in plasma was due to the unchanged drug. Several metabolites were detected, two of which were identified (Fig. 1), and accounted for < 2% of the total radioactivity. One of these metabolites was also detected in the bile of a dog administered 100 mg/kg i.v. HMR-1883 (3).

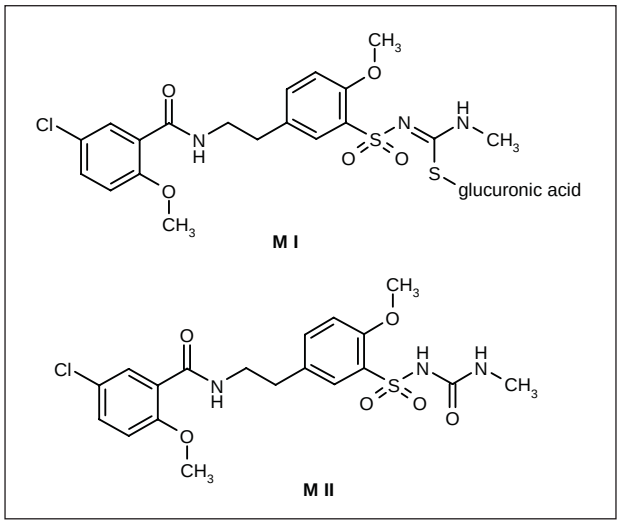


Fig. 1

Clinical Studies

Phase I studies in healthy volunteers have examined single i.v. (37.5-400 mg) and oral doses (50-900 mg), as well as multiple oral does (3 x 300 to 2 x 600 mg for up to 5 days) given as the free acid or the sodium salt. Peak plasma levels of 8-70 μg/ml were achieved after i.v. doses and up to 30 μg/ml following oral administration. Elimination was triphasic with a rapid distribution phase and two elimination phases with respective half-lives of 0.6-0.9 h and 5-9 h. The bioavailability of orally administered drug was affected by the pharmaceutical formulation and food. Peak plasma levels of up to 15 μg/ml were reached after a dose of 600 mg with the best formulation, and plasma levels of at least 0.5-1.0 μg/ml, extrapolated from preclinical models as the minimum effective concentration for protection against ischemia-induced ventricular fibrillation, were maintained for 8-12 h after repeated oral doses. No effects on Q-T interval or other ECG parameters have been reported. Insulin release is seen with higher i.v. doses, but only moderate insulin secretion has been observed with oral doses. One case of manageable hypoglycemia was reported after the highest i.v. dose (3).

HMR-1098 has been evaluated for its safety in patients undergoing coronary angioplasty in comparison to placebo. No proarrhythmic effects or other side effects were observed, moderate effects were seen on insulin levels and no clinically relevant changes in blood glucose were observed (3)

Manufacturer

Aventis Pharma AG (DE).

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