Class III Antiarrhythmic Activity in Vivo by Selective Blockade of the Slowly Activating Cardiac Delayed Rectifier Potassium Current I_{Ks} by (*R*)-2-(2,4-Trifluoromethyl)-*N*-[2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl]acetamide

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The high incidence of sudden cardiac death (SCD) is of continuing medical concern.[1,2] The primary mechanism of SCD is the degeneration of normal cardiac rhythm into ventricular tachycardia followed by ventricular fibrillation.[3] The underlying cause of these rhythm disturbances in most cases is coronary artery disease that has resulted in prior ischemic damage to the heart. The classification system of Vaughn Williams,[4] defines several major classes of antiarrhythmic action. Class I antiarrhythmic agents block sodium channels, thereby inhibiting impulse conduction and contractility in the myocardium. Class II agents are β blockers, and class III agents act by delaying repolarization of cardiac myocytes. The consequence of delayed repolarization is a lengthening of the action potential duration (APD) of the cell and a concomitant increase in the effective refractory period (ERP). The cardiac arrhythmia suppression trial (CAST)[5] demonstrated that conventional antiarrhythmic treatment with certain class I agents actually increased mortality compared with placebo. Since CAST, there has been increasing interest in compounds that exert their antiarrhythmic effects by means other than sodium channel blockade.[6]

The outward delayed rectifier potassium current, I_K, that contributes to repolarization, consists of two kinetically distinct and identifiable currents, a rapidly activating, I_{kr}, and a slowly activating component, I_{Ks}.[7] Selective blockade of either I_{Kr} or I_{Ks} would lead to a prolongation of the refractory period and be, by definition, a class III effect. Clinically, changes in the APD and ERP of ventricular cells are reflected in the length of the QT interval of the electrocardiogram, thus providing a convenient, clinical measurement of drug action. The development of an effective antiarrhythmic agent for the prevention of SCD has been a long-standing goal for these laboratories.[8]

Most selective class III antiarrhythmic agents, notably D-sotalol,[9] dofetilide,[10] and MK-499[8] from these laboratories, selectively block I_{kr}.[11] Recent work on I_{Kr} blocking agents has shown the tendency of members of this class to exhibit proarrhythmic effects in vivo. The incidence of the polymorphic ventricular tachycardia torsade de pointes has been significant (2−5%) in clinical trials with I_{Kr} blocking class III agents.[12] The proarrhythmia seen with this class is related to their reverse rate dependent effects on cardiac refractoriness[13] whereby they prolong APD more at slow rates than at rapid rates. Exaggeration of this effect may occur at very slow rates leading to exaggerated QT intervals and early afterdepolarizations[14] which are thought to be one mechanism of torsade de pointes.[15] Conversely, at faster heart rates the class III effect of these compounds (lengthening of ERP, QT interval prolongation) is diminished leading to lowered efficacy.

Because I_{Ks} deactivates slowly, it tends to become relatively more important for repolarization at faster rates. A selective I_{Ks} blocker would therefore not demonstrate reverse use dependence.[11,17] Such a class III agent would then be inherently safer than a blocker of I_{Kr}. Currently there are no selective I_{Ks} blocking class III antiarrhythmic agents in use. Several marketed compounds, including amiodarone,[18] as well as at least one compound in development, Azimilide,[19] exhibit blockade of I_{Ks} as part of their spectrum of pharmacological activity. Amiodarone is a nonspecific agent that interacts with a variety of ion channels and receptors but has shown utility as an effective antiarrhythmic agent. Azimilide predominantly blocks I_{Kr} and also effects L-type Ca channels. Described herein is a summary of the discovery of L-768,673 (**1**), an orally active, potent, and selective I_{Ks} blocking agent that exerts significant class III activity in vivo and does not cause early afterdepolarizations in vitro.

Results and Discussion. The observation that compound **2**, in development as a CCK-B antagonist,[20] markedly increased the electrocardiographic QT interval in dogs at high (100 mpk) oral doses led to its evaluation in a single cell voltage clamp protocol. These studies revealed that **2** was a potent blocker of I_{Ks} in isolated guinea pig ventricular myocytes. The concentrations required for 50% block of the I_{Ks} and I_{Kr} currents (IC_{50}) were 214 nM and 5000 nM, respectively (Table 1). The *S* enantiomer **2b** was significantly less potent (IC_{50} = 10 μM) for blockade of the I_{Ks} current. This key finding of a moderately selective I_{Ks} blocker became the impetus for a medicinal chemistry program.

Replacement of the urea group with amides at the C-3 amine resulted in compounds that exhibited comparable potencies for blockade of I_{Ks} and minimized CCK-B receptor affinity (compounds **3**−**10**, Table 1). The addition of halogens to the aryl ring greatly improved activity of the benzoyl, phenylacetyl, and phenylpropionyl series (compare compounds **4, 6**, and **9** to **3, 5**, and **8**). The introduction of polar substituents on the amide side chain resulted in severe losses of potency for I_{Ks} blockade (compounds **11**−**13**). It was clear that nonpolar, lipophilic substitution enhanced I_{Ks} blockade and other lipophilic groups such as the cyclohexylpropionamide side chain provided potent inhibition of I_{Ks} (compound **14**). Removal of the N-1 methyl and replacement

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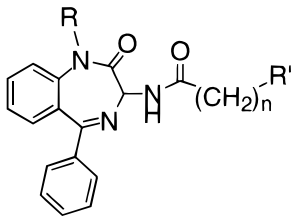
Table 1. Effect of Substitution on I_{Ks} Potency



compd[a]	abs conf	R	*n*	R′	I_{Ks} IC_{50} (nM)[b]	I_{Kr} IC_{50} (nM)[c] or % inhn at concn (nM)	CCK-B IC_{50} (nM)[e]	mp °C
2[20]	*R*	Me	0	*m*-NHPhCH$_3$	214	5000	2 ± 0.3	
2b[20]	*S*	Me	0	*m*-NHPhCH$_3$	10000	10000	151 ± 12	
3	*R*	Me	0	phenyl	600[d]	23% at 1000	>1000	224−225
4	*R*	Me	0	3,5-dichlorophenyl	45[d]	17% at 1000		179−180
5	*R*	Me	1	phenyl	300[d]	31% at 1000	>1000	241−242
6	*R*	Me	1	2,4-dichlorophenyl	35			209−210
7	*R*	Me	1	2,4-bis(trifluoromethyl)phenyl	140			100−103
8	*R*	Me	2	phenyl	200[d]	32% at 1000	>1000	179
9	*R*	Me	2	2,4-dichlorophenyl	14[d]	31% at 100	>1000	92−95
10	*R*	Me	0	CH=CH−2,4-dichlorophenyl	6[d]	1500	>1000	137−139
11	*R*	Me	0	CH(NH$_2$)CH$_2$Ph	2800[d]	8800	>1000	84−86
12	*R*	Me	2	4-aminophenyl	4400[d]		>1000	175−178
13	*R*	Me	2	4-acetamidophenyl	>10000		>1000	138−142
14	*R*	Me	2	cyclohexyl	10[d]	1000	>1000	144−145
15	*RS*	H	2	cyclohexyl	1000			192−193
16	*RS*	Me$_2$NCH$_2$CH$_2$	2	2,4-dichlorophenyl	520[d]	100	>1000	199−201
17	*R*	*i*-Pr	2	cyclohexyl	20[d]		>1000	154−155
18	*R*	*i*-Pr	0	3,5-dichlorophenyl	6			140−141
19	*S*	*i*-Pr	0	3,5-dichlorophenyl	110	6% at 1000		140−141
20	*R*	*i*-Pr	1	3,5-dichlorophenyl	10[d]		>1000	90−96
21	*R*	F$_3$CCH$_2$	0	3,5-dichlorophenyl	11[d]	25% at 100		140−143
22	*R*	F$_3$CCH$_2$	1	3,5-dichlorophenyl	30	4000		93−100
23	*R*	F$_3$CCH$_2$	1	2,4-dichlorophenyl	9	2400		143−145
24	*S*	F$_3$CCH$_2$	1	2,4-bis(trifluoromethyl)phenyl	60[d]	35% at 1000	>1000	
1	*R*	F$_3$CCH$_2$	1	2,4-bis(trifluoromethyl)phenyl	6[d]	6000	>1000	132−134

[a] All compounds gave satisfactory spectral and analytical data (C, H, and N; ±0.4% of theoretical values). [b] Molar concentration of compound required to inhibit 50% of the I_{Ks} current in isolated guinea pig myocytes during a 1 s voltage clamp step from −50 to +50 mV ($n \geq 3$ for all concentrations tested) (see ref 19 for protocol). IC_{50} value determined graphically from concentration response relationships. [c] Molar concentration of compound required to inhibit 50% of the I_{Kr} current in isolated guinea pig myocytes during a 0.5 s voltage clamp step from −50 to −10 mV (see ref 19 for protocol). [d] $n \geq 4$. [e] Concentration for half-maximal inhibition of binding of [^{125}I]CCK-8 to receptors in guinea pig cerebral cortex.[20]

with hydrogen was detrimental to I_{Ks} blocking activity (compound **15**). Incorporation of polar groups at this position also had a detrimental effect on potency and selectivity (compound **16**). Replacement of the N-1 methyl group with lipophilic groups, such as isopropyl or trifluoroethyl, gave compounds that were similar in terms of in vitro potency for I_{ks} (compounds **17**−**24**). As in the lead compound **2**, optimal I_{Ks} activity requires the absolute stereochemistry at C-3 to be *R* (compound **18** vs **19** and **1** vs **24**)

Promising compounds were evaluated for oral activity in dogs equipped with Holter monitors. At an oral dose of 10 mpk compound **9** ellicited a QT interval prolongation of approximately 10% that dissipated over several hours, indicating a clear, albeit short-lived, class III effect. In vitro metabolic studies of **9** with liver microsomes, as well as literature precedent for related benzodiazepines,[21] suggested that N-1 dealkylation was a major metabolic pathway. The N-1 trifluoroethyl series was therefore chosen in an attempt to minimize this particular pathway. In addition, several metabolites in which the amide side chain had been hydroxylated were isolated indicating that the aromatic ring, and side chains were also major sites of metabolic degradation. In view of these results compounds with shorter side chains and electron withdrawing groups such as trifluoromethyl (to minimize oxidation) on the aromatic ring were studied. Of the compounds reported here, **1** displayed enhanced oral activity in Holter-monitored dogs (Figure 1). At doses of between 0.1 and 1 mpk there was a 5−15% increase in QT interval that lasted for the duration of the monitoring period (15 h) (Figure 1).

On the basis of its oral activity profile, **1** was chosen for detailed pharmacological study. The full hemodynamic profile of **1** in chloralose anesthetized dogs after iv administration showed dose dependent increases in QT intervals consistent with I_{Ks} blockade. There were no significant changes in ventricular excitation threshold, heart rate, or mean arterial pressure. There was also no effect on A−V nodal or ventricular conduction. After dosing as a methocell suspension, **1** had an oral bioavailability of 27% in dogs and 40% in rats.

Further voltage clamp studies showed that **1** had no effect on the inward rectifier K^+ current (I_{K1}) in isolated guinea pig myocytes. In human atrial myocytes the transient outward current (I_{to}) and ultrarapid activating delayed rectifier, I_{kur}, were unaffected by **1**. Human Kv1.5 expressed in Xenopus oocytes was also unaffected by the compound. At high concentrations (>300 nM) **1** blocked L-type calcium currents with an IC_{50} of 3 μM. At doses sufficient to block all of the I_{Ks} current, **1** caused only a 30% increase in APD indicating a self-limiting effect to I_{Ks} blockade with this compound. Also there was no indication of early afterdepolarizations at any of the concentrations tested. In contrast, at doses

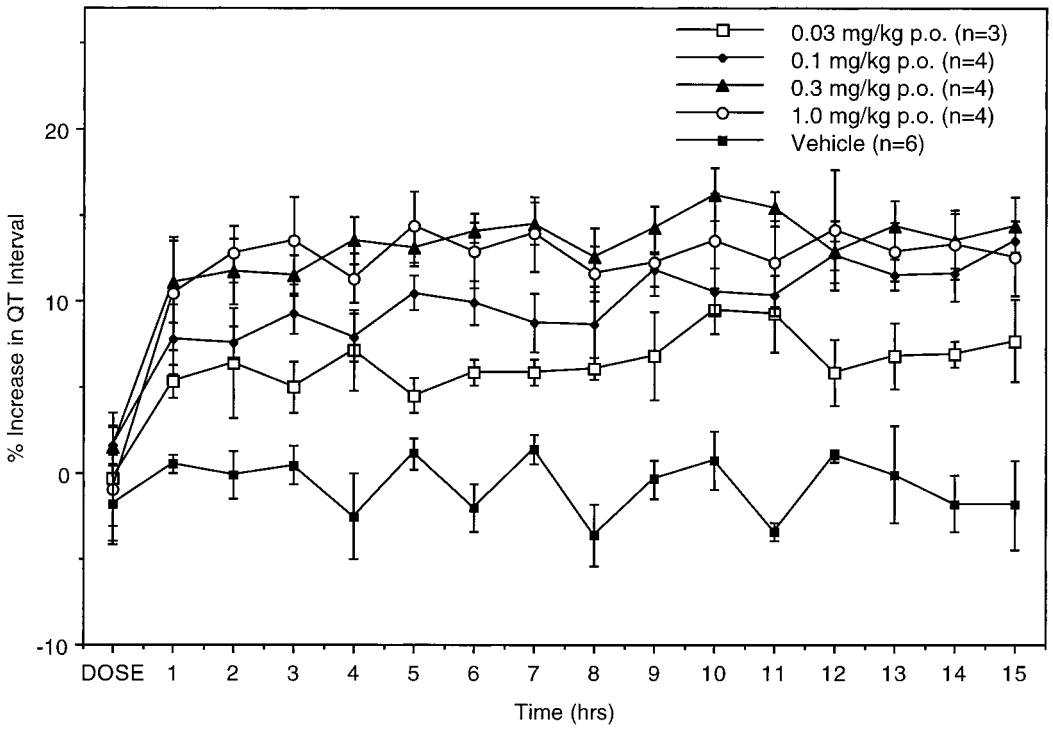
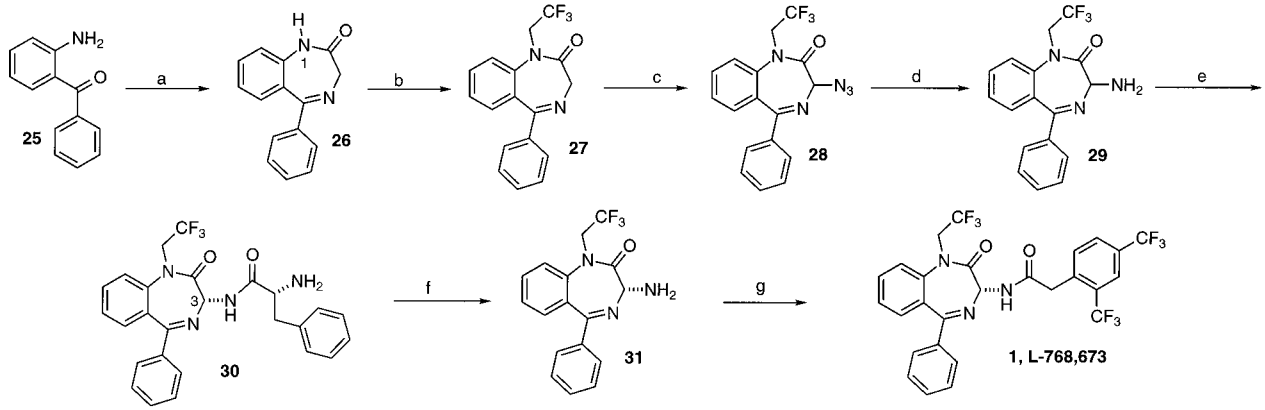


Figure 1. Duration of Class III effect of **1** in conscious dogs after single dose administration. Compound **1** was administered orally as a suspension in 1% methylcellulose at several doses. Class III activity was determined by examination of the electrocardiographic QT interval as recorded on Holter monitors. Values are mean ± SEM.

Scheme 1. Synthesis of **2**[a]



[a] Reagents: (a) bromoacetyl bromide, CH_2Cl_2 then NH_4OH, EtOH (86%); (b) ICH_2CF_3, Cs_2CO_3, DMF (60%); (c) KOt-Bu, trisyl azide, THF; (d) PPh_3, THF, H_2O (83% from **26**); (e) Boc-D-Phe-OH, EDC, HOBT, DMF then HCl(g), EtOAc then separate diastereomers (46%); (f) PhNCS, CH_2Cl_2 then TFA (71%); (g) 2,4-bis(trifluoromethyl)phenylacetic acid, EDC, HOBT then crystallize (78%).

sufficient to cause a 30% APD prolongation, I_{Kr} blockers cause early afterdepolarizations.[14]

Chemistry. The preparation of **1** is shown in Scheme 1. Aminobenzophenone (**25**) was acylated with bromoacetyl bromide and then treated with ammonia in ethanol to effect cyclization to the benzodiazepine nucleus **26** in a modification of the published method.[22] Alkylation of the amide nitrogen is accomplished with trifluoroethyl iodide and cesium carbonate in DMF to generate **27**. The N-1 methyl compounds and the N-1 isopropyl compounds were prepared in a similar fashion. The introduction of an amine at C-3 was carried out in two steps using 2,4,6-trimethylbenzenesulfonyl azide as the source of nitrogen. Treatment of **27** with potassium *tert*-butoxide and then trisyl azide[23] at −78 °C gave azide **28** after workup. Reduction to the amine **29** was conveniently done with triphenylphosphine. The resolution of enantiomers was carried out at this point by derivatizing with phenylalanine and removing the BOC protecting group to give **30** after chromatographic separation of the diastereomers.[24] The absolute stereochemistry was confirmed by single-crystal X-ray analysis of **30**. Removal of the phenylalanine via an Edman degradation gave 3-R amine **31**. Acylation of **31** with 2,4-bis(trifluoromethyl)phenylacetic acid gave **1**.

In conclusion, the compounds based on the benzodiazepine nucleus described herein are potent and selective I_{Ks} blocking class III antiarrhythmic agents both in vitro and in vivo. An appreciation for the in vitro metabolism of compounds in this class has led to the discovery of compound **1** which exhibits excellent oral activity in dogs providing significant increases in electrocardiographic QT interval for >15 h after a single dose and displays good oral bioavailability. The combination of in vitro selectivity and long lasting activity after oral dosing suggest that **1** be considered a candi-

date for evaluation in humans. More extensive pharmacological evaluation of **1** and its congeners is ongoing and will be the subject of forthcoming publications.

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Supporting Information Available: Hemodynamic data for iv dosing of **1** in Chloralose-anesthetized dogs, full experimental procedures for the preparation of **1**, elemental analyses, and NMR data for all new compounds reported herein (18 pages). Ordering information is given on any current masthead page.

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