# Mono- and Bis(aminomethyl)phenylacetic Acid Esters as Short-Acting Antiarrhythmic Agents. 2@

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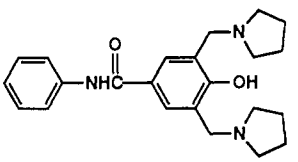
The synthesis, antiarrhythmic activity, and blood hydrolysis properties of a series of mono- and bis(aminomethyl)phenylacetic acid esters related to a previously reported class Ic antiarrhythmic agent (ACC-9358) are described. Of the various oxa-, aza-, thia-, and carbacyclic esters initially prepared in the bis(pyrrolidinomethyl)-4-hydroxyphenylacetic acid series, the 1,4-benzodioxanyl-2-methyl (**3q**) and the thienyl-2-methyl (**3l**) esters were evaluated *in vivo* for antiarrhythmic efficacy. In addition, a number of monoappended phenylacetic esters of **3q** with or without the 4-hydroxy group were also prepared for evaluation of antiarrhythmic, lipophilic, and metabolic properties. Of these compounds, **3q** possessed the most desirable pharmacological and pharmacokinetic profile.

We had previously reported[1] on a series of ester derivatives[2] of an orally active class Ic antiarrhythmic agent (ACC-9358)[3] which underwent clinical evaluation.[4] This work was aimed at identifying a metabolically-labile, short-acting (SA) analog of this antiarrhythmic that would be effective in suppressing life-threatening arrhythmias when administered intravenously and possess fewer side effects than currently available parenterally administered antiarrhythmic agents such as lidocaine.[5] This type of compound should possess the pharmacokinetic properties that would allow the rapid build-up of the blood levels necessary for efficacy upon intravenous administration. However, upon termination of the infusion of this agent, it would be rapidly removed from the blood due to its metabolic inactivation via enzymatic hydrolysis by serum esterases, a property of the therapeutically useful ultrashort acting β-bocker, esmolol.[6,7]




ACC-9358

Many of the previously described compounds did indeed possess the rapid metabolic inactivation due to blood hydrolysis that was desired of an agent with a predictable pharmacokinetic profile. In addition, central nervous system (CNS) liability, generally associated with lipophilic agents that can more readily penetrate the blood brain barrier,[8] such as lidocaine and flecainide,[9] appeared to be diminished.[1] However, the proper balance of potency, duration, and lipophilic character was not adequately met when selected members of this series were more thoroughly evaluated *in vivo*.[1,10] In particular, compounds from this study that possessed good efficacy *in vitro* and in the ouabain intoxicated dog model along with desired blood hydrolysis properties failed to show sufficient activity in the Harris dog model. Since we considered good potency in this test to be a necessary property of our desired drug, we continued our investigation of the effect of the nature of the alcohol portion of the ester series on pharmacological and pharmacokinetic parameters. While we had previously evaluated esters derived from straight-chain or branched alkanols, we have now extended this work to aromatic and heterocyclic alcohols.

## Chemistry

Previous studies of potential SA antiarrhythmic esters had identified a single methylene spacer between the aromatic nucleus and carboxyl group as optimal for producing compounds with the desired biological half-life (~10 min).[1,11] This linkage was generally maintained for all new compounds. Our initial focus was on agents derived from alcohols containing a cyclic or heterocyclic ring system and possessing pyrrolidinylmethyl substituents at both 3- and 5-positions of the 4-hydroxyphenylacetic acid portion of the molecule. These compounds as well as certain monoaminomethyl analogs were prepared from 4-hydroxyphenylacetic esters **1**[1,12] by mono- or bis-aminomethylation depending on reaction conditions and the amount of Mannich reagent (Scheme I).

Mono-appendage analogs devoid of the hydroxyl group on the phenylacetic acid moiety were prepared in the 1,4-benzodioxan-2-methanol ester series via the route shown in Scheme II. Bromination of ester **4** in $CCl_4$ with NBS in the presence of light at room temperature afforded a preponderance of monobromo ester **5** accompanied by the α-bromo ester isomer (10–15%) as indicated by resonances at 4.35 ppm ($CH_2Br$) and 5.35 ppm (CHBr), respectively. Alkylation of pyrrolidine with this mixture afforded the desired 3- or 4-substituted phenyl amino esters **6**.

## Pharmacology

Antiarrhythmic activity was determined *in vitro* in the acetylstrophanthidin-induced arrhythmia in guinea pig right atrium (GPRA) and *in vivo* in the 24-h Harris[13] or

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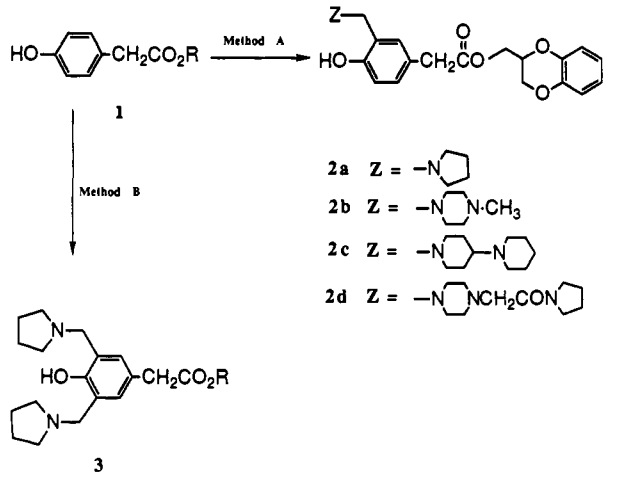
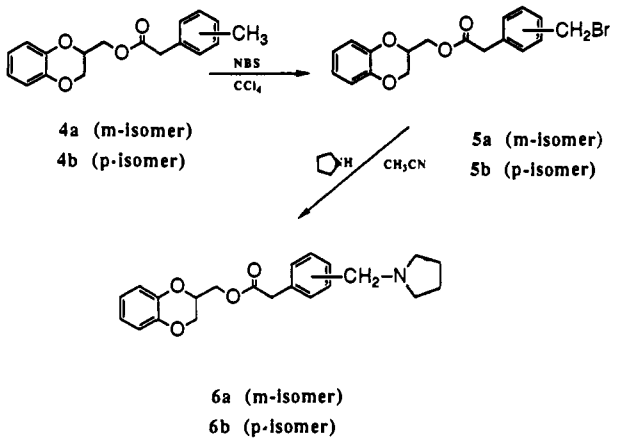
**Scheme I**




**Scheme II**




ouabain-intoxicated dog models as previously described.[3] Standardized *in vitro* incubation conditions to determine half-life in human blood have been previously reported.[1,14]

## Results and Discussion

Our initial focus was to assess the *in vitro* antiarrhythmic activity of the cyclic and heterocyclic alcohol esters in the 3,5-bis appendage series shown in Table I. Of these various oxa-, aza-, thia-, and carbacylic esters, compounds **3a,d,e,j–l,q** showed consistent ability to convert acetylstrophanthidin-induced arrhythmias in guinea pig right atria to normal sinus rhythm with an $ED_{50}$ of less than 10 μg/mL, our arbitrary cutoff point for further evaluation. These agents were then tested for their metabolic lability in whole human blood. Four of these esters (**3d,e,j,k**) showed half-lives which were longer than the 8-10-min range that appeared to be most desirable based on earlier work in the β-blocker area.[6,7] One ester **3l** had a half-life shorter than the desired range, but it, along with **3q**, was selected for further pharmacological evaluation.[15]

Each of these compounds demonstrated greater potency than lidocaine in the 24-h Harris dog model and equal potency to lidocaine in the ouabain-intoxicated dog model (Table II). Moreover, their distribution coefficients (DC), a measure of lipophilic character and a property associated with the potential ability of a compound to penetrate the blood–brain barrier,[8] were considerably lower than lidocaine, suggesting minimal CNS liability. Further structural modifications were then carried out on one of these compounds to determine the effect of these changes on DC, antiarrhythmic activity, and human blood elimination half-life. In this study, various monoaminomethylene appendage analogs of the benzodioxolane methanol ester **3q** were prepared and evaluated for their pharmacological and pharmacokinetic properties.

The initial compound in this series, **2a**, showed considerable improvement in antiarrhythmic potency over the bis-appendage analog **3q** in the GPRA *in vitro* assay. However, the distribution coefficient of this molecule was found to be considerably higher than that reported for lidocaine and the bis-appendage members of this series. Moreover, when this compound was evaluated for antiarrhythmic efficacy in the conscious 24-h Harris dog model, behavioral mannerisms (head wobble, vocalization, excessive limb movement) consistently seen with compounds that have been reported to show CNS activity in humans[16] were observed.

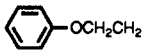
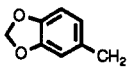
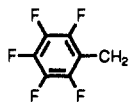
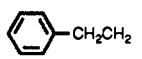
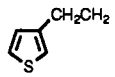
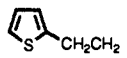
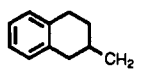
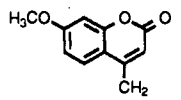
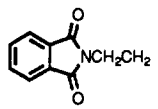
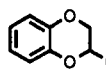
We initially associated the considerable difference in the DC between the mono- and the bis-appendage members of this series with the absence of a fully protonated pyrrolidine group when only one appendage is present. The pyrrolidino group contained in **2a** is hydrogen bonded to the phenolic proton,[17] thus diminishing its basicity.[18] We assumed that the presence of a protonated amine at physiological pH was the dominant factor affecting the overall lipophilicity of the molecule. To overcome this undersirable increase in lipophilic character, we focused our subsequent synthesis on analogs with (a) a second basic center on the single appendage (**2b,c**); (b) no phenol hydroxyl group available for hydrogen bonding (**6a,b**); (c) a hydrophilic amide (**2d**) (Table III).

All of these agents except **2d** showed good *in vitro* antiarrhythmic activity (<10 μg/mL). Of those possessing the desired antiarrhythmic potency *in vitro*, only **2c** possessed a DC lower than lidocaine (~19). The difference in the DC between **2b** and **2c** was associated with transannular electrostatic effects that would be more apparent in the hydrogen-bonded piperazine–methyl appendage of **2b** than in the hydrogen-bonded piperidinopiperiderino–methyl appendage of **2c**. This would tend to make protonation of the methylated nitrogen of **2b** more difficult than the 4-piperidine nitrogen of **2c** and result in **2b**, even though it contains five methylene units less than **2c**, still being a more lipophilic molecule than **2c**, as was observed.

The large DC of both **6a** and **6b** were surprising in view of the absence of the intramolecular hydrogen bonding site to lower the basicity of the amino functionality of these molecules. These data suggested that the phenolic OH group, while diminishing basicity and hydrophilicity of molecules like **2a** via hydrogen bonding, is significantly contributing to the overall hydrophilicity to offset this effect. The low DC value for **2d** is also indicative of the significant contribution that the amide makes to the overall lipophilicity of the molecule, presumably through its hydrogen-bonding capability.

Results from the *in vitro* human blood metabolism studies of these single appendage molecules are also shown in Table III. In general, these compounds are hydrolyzed much more rapidly than the members of the bis-appendage series. These rather short blood half-lives would prevent the build-up of efficacious blood levels of these compounds, thus precluding them from further consideration as potential therapeutics.

**Table I.** Physical Properties, Antiarrhythmic Activity, and Hydrolysis Rates of Various Esters of 3,5-Bis(pyrrolidinomethyl)-4-hydroxyphenylacetic Acid

| compd | R | mp, °C | formula | GPRA[a] (n)[b] | *in vitro* (n = 3) human blood half-life, min |
|---|---|---|---|---|---|
| **3a** |  | 115 | $C_{25}H_{31}N_3O_5 \cdot 2HCl \cdot 2H_2O$ | 5.2 ± 1.7[c] (4/4) | 6.2 ± 1.7[c] |
| **3b** |  | 106–108 | $C_{26}H_{34}N_2O_4 \cdot 2(C_4H_4O_4)$ | 16.2 ± 5.5 (4/4) | 2.5 ± 0.8 |
| **3c** |  | 85 | $C_{26}H_{32}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$ | 10.7 ± 5.2 (3/4) | 9.2 ± 1.2 |
| **3d** |  | 85–87 | $C_{25}H_{27}F_5N_2O_3 \cdot 2HCl \cdot 0.5H_2O$ | 7.5 ± 1.4 (4/4) | 11.0 ± 1.7 |
| **3e** |  | 77–80 | $C_{26}H_{34}N_2O_3 \cdot 2HCl \cdot 1.25H_2O$ | 2.8 ± 0.8 (4/4) | 16.8[e] |
| **3f** |  | 70–75 | $C_{23}H_{30}N_2O_4 \cdot 2HCl \cdot 2H_2O$ | 27.5 ± 5.4 (6/6) | 10.1 ± 2.2 |
| **3g** |  | 70–75 | $C_{23}H_{30}N_2O_4 \cdot 2HCl \cdot 1.5H_2O$ | 29.4 ± 12.7 (5/5) | 2.5 ± 0.35 |
| **3h** |  | 114–116 | $C_{23}H_{34}N_2O_4 \cdot 2(C_4H_4O_4)$[d] | 40.0 (1/4) | 3.5[e] |
| **3i** |  | 116–118 | $C_{24}H_{36}N_2O_4 \cdot 2(C_4H_4O_4)$ | 20.0 (1/3) | 3.3 ± 1.7 |
| **3j** |  | 60 | $C_{24}H_{32}N_2O_3S \cdot 2HCl \cdot 2H_2O$ | 6.2 ± 1.2 (4.4) | 34.8 ± 10.6 |
| **3k** |  | 65 | $C_{24}H_{32}N_2O_3S \cdot 2HCl \cdot 2H_2O$ | 3.0 ± 1.1 (4/4) | 35.9 ± 10.2 |
| **3l** |  | 80–83 | $C_{23}H_{30}N_2O_3S \cdot 2HCl \cdot H_2O$ | 5.5 ± 4.0 (4/4) | 3.5[e] |
| **3m** |  | 94–96 | $C_{29}H_{36}N_2O_3 \cdot 2(C_4H_4O_4)$ | 6.0 ± 4.0 (2/4) | 2.3 ± 0.2 |
| **3n** |  | 101–103 | $C_{29}H_{34}N_2O_6 \cdot 2(C_4H_4O_4)$ | 11.7 ± 4.4 (3/3) | ND[f] |
| **3p** |  | 90–95 | $C_{23}H_{33}N_3O_5 \cdot 2HCl \cdot 1.5H_2O$ | 23.3 ± 8.8 (3/5) | 3.8 ± 0.45 |
| **3q** |  | 125–127 | $C_{27}H_{34}N_2O_5 \cdot 2(C_4H_4O_4)$ | 7.3 ± 3.6 (5/5) | 7.1 ± 0.57 |

[a] Effective dose of compound to convert acetylstrophanthidin-induced arrhythmia in guinea pig right atria to normal sinus rhythm (NSR) in μg/mL. [b] Number of tissues converted to NSR/number of tissues tested. [c] Standard error of the mean. [d] All $C_4H_4O_4$ salts are maleates. [e] One determination. [f] Not determined.

**Table II.** *In Vivo* Antiarrhythmic Activity of **3l** and **3q**

| | ouabain dog[a] $ED_{50}$, mg/kg (no. animals) | Harris dog, eff dose,[b] mg/kg (no. animals) | DC[c] |
|---|---|---|---|
| **3q** | 4.8 ± 0.6 (n = 5) | 14.0 ± 2.8 (n = 5)[d] | 2.62 |
| **3l** | 3.8 ± 0.7 (n = 4) | 10.5 ± 4.3 (n = 5)[d] | 0.73 |
| lidocaine | 8.8 ± 3.0 (n = 6) | 37.5 ± 1.0 (n = 6) | 19.2 |

[a] Cumulative administered dose required for the production of 50% normal sinus beats. Compounds were infused at 500 μg/kg/min. [b] Cumulative administered dose required for the production of 80% normal sinut beats. Compound **3l** was infused at 225 μg/kg/min and compound **3q** at 150 μg/kg/min; lidocaine was infused at 300 μg/kg/min. [c] Distribution coefficient; average of two determinations. [d] Significantly lower effective dose than that of lidocaine ($p < 0.05$, Student's *t*-test).

## Summary

We have prepared a series bis-appended 4-hydroxyphenylacetic acid esters. Evaluation of the antiarrhythmic, hydrolytic, and lipophilic properties of these molecules had disclosed two compounds, **3l** and **3q**, with the most favorable efficacy and pharmacokinetic profiles. One of these esters, **3q**, was further modified with regard to number and position of the pendant and presence of the hydroxy group. Monopendant compounds were rapidly cleaved by human blood esterases, making them unsuitable as potential SA antiarrhythmics. In contrast to members of the previously reported series, selected agents of this bis-pendant series possessed Harris dog activity. Of the compounds in this study, **3q** was chosen for consideration as a potential development candidate based on its pharmacological, lipophilic, and pharmacokinetic properties.

## Experimental Section

**Chemistry.** Melting points were determined on the Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were determined on a Varian T-60A or EM-360 or an

**Table III.** Physical Properties, Antiarrhythmic Activity, and Hydrolysis Rates of Mono(aminomethyl)phenyl- and -hydroxyphenylacetic Acid Esters

| compd | mp, °C | formula | GPRA[a] (n)[b] | DC[c] | *in vitro* (n = 3) human blood half-life, min |
|---|---|---|---|---|---|
| **2a** | 154–156 | $C_{22}H_{25}NO_5 \cdot HCl$ | 1.2 ± 0.25 (4/4) | 36.3 | <1[d] |
| **2b** | 188–190 | $C_{23}H_{28}N_2O_5 \cdot C_4H_4O_4$[f] | 2.5 ± 0.87 (4/4) | 24.0 | ND[e] |
| **2c** | 233–234 | $C_{26}H_{36}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$ | 8.3 ± 1.7 (3/3) | 9.6 | <1 |
| **2d** | 120 | $C_{28}H_{35}N_3O_6 \cdot 2HCl \cdot 0.33H_2O$ | 22.5 ± 2.5 (4/4) | 7.1 | <1 |
| **6a** | 151–153 | $C_{22}H_{25}NO_4 \cdot C_2H_2O_4$[g] | 6.9 ± 0.9 (8/8) | 39.5 | <1 |
| **6b** | 131–133 | $C_{22}H_{25}NO_4 \cdot C_2H_2O_4$ | 10.0 ± 0.0 (4/4) | 22.1 | <1 |

[a] Effective dose of compound to convert acetylstraphanthidin-induced arrhythmia in guinea pig right atria to normal sinut rhythm (NSR) in μg/mL. [b] Number of tissues converted to NSR/number of tissues tested. [c] Distribution coefficient; average of two determinations. [d] Half-life not was determined because more than 90% of the drug was metabolized in 1 min under standardized incubation conditions. [e] Not determined. [f] Maleic acid salt. [g] Oxalic acid salt.

IBM NR-80 spectrometer in $CDCl_3$, $Me_2SO$-$d_6$, or $CD_3OD$ with tetramethylsilane as internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

**1,4-Benzodioxan-2-ylmethyl 4-Hydroxyphenylacetate (1q).** The synthesis of this precursor is representative of the esters used to prepare the compounds in Table I.

To a stirred solution of 3.32 g (0.02 mol) of 2-(hydroxymethyl)-1,4-benzodioxan and 3.0 g (0.03 mol) of triethylamine in 100 mL of ether was added, dropwise, a solution of 3.75 g (0.022 mol) of 4-acetoxyphenylacetyl chloride[12] in 50 mL of ether. The reaction mixture was stirred at room temperature for 20 h and then filtered. The filtrate was washed once with 1 N HCl solution and three times with 5% aqueous sodium carbonate solution. The ether solution was then dried ($MgSO_4$) and filtered. The filtrate was evaporated to give 1,4-benzodioxan-2-ylmethyl 4-acetoxyphenylacetate as a yellow oil that was used in the subsequent hydrolysis reaction without purification.

A 4.6-g (0.0134-mol) portion of the crude oil was taken up into 150 mL of acetonitrile and 1.3 g (0.018 mol) of pyrrolidine was added, and the solution was heated at reflux for 3 h. After removal of the volatiles at reduced pressure, the remaining oil was taken up into ether, washed once with 1 N HCl solution and twice with brine, and dried ($MgSO_4$). Solvent removal gave an oil that was dissolved in a minimum amount of ether followed by a volume of hexanes that did not cause the oil to separate. The solid that formed upon standing was collected and recrystallized from ether/hexanes to afford 2.5 g (62%) of 1,4-benzodioxan-2-ylmethyl 4-hydroxyphenylacetate (**1q**): mp 82–84 °C; NMR ($CDCl_3$) 3.60 ppm ($CH_2CO$). Anal. ($C_{17}H_{16}O_5$) C, H.

**Method A. 1,4-Benzodioxan-2-ylmethyl 3-(1-Pyrrolidinylmethyl)-4-hydroxyphenylacetate (2a).** The following procedure is representative of the synthesis of the mono-appended 4-hydroxyphenylacetic esters. To 20 g (0.067 mol) of **1q** in 400 mL of acetonitrile was added a solution of 6.7 mL (0.089 mol) of 37% formaldehyde solution in 5.8 mL (0.070 mol) of pyrrolidine previously mixed at ca. 0 °C for 5 min before addition. The reaction mixture was stirred for 20 h at ambient temperature. After solvent removal *in vacuo*, the residue was taken up into ether. Following filtration, the filtrate was washed four times with $H_2O$ and dried ($MgSO_4$). Solvent removal gave an oil which was chromatographed using a silica gel column with $CHCl_3$/EtOH/$NH_4OH$ (95:4:1) as the eluent to afford 15 g (70%) of desired ester **2a**. Conversion to the hydrochloride salt was followed by crystallization from 2-propanol–ether to give crystalline material, mp 154–156 °C.

**Method B.** The bis(1-pyrrolidinylmethyl)-4-hydroxyphenylacetate derivatives **3** were prepared according to previously described methods[1] and converted to the salts shown in Table I.

**1,4-Bendioxan-2-ylmethyl 3-(Bromomethyl)phenylacetate (5a).** To 8.3 g (0.0245 mol) of 1,4-benzodioxan-2-ylmethyl 3-methylphenylacetate **4a** in 100 mL of $CCl_4$ was added 4.9 g (0.0275 mol) of *N*-bromosuccinimide, and the reaction mixture was exposed to an incandescent light source for 1.5 h. The insoluble material was removed by filtration, and the solvent was evaporated from the filtrate *in vacuo*. The NMR spectrum of the resulting oil (10.8 g) indicated a preponderance of desired product **5a** by the presence of a resonance at 4.35 ppm ($CH_2Br$). This material was used without further purification.

**1,4-Benzodioxan-2-ylmethyl 3-(1-Pyrrolidinylmethyl)-phenylacetate (6a).** To 10.8 g (ca. 0.025 mol) of crude **5a** in 200 mL of acetonitrile was added 5 mL (4.26 g, 0.06 mol) of pyrrolidine, and the solution was stirred at ambient temperature overnight. Solvent removal *in vacuo* gave an oil that was taken up into 60 mL of 25% HCl solution. The acidic solution was extracted once with ether and then basified with 25% aqueous NaOH solution before extracting with three portions of ether. The combined extracts were washed with water and then brine and dried over $MgSO_4$. Solvent removal *in vacuo* gave an oil that was purified via chromatographic purification over silica gel using ethyl acetate as the eluent. The purified free base was treated with oxalic acid in ethanol to provide 5.46 g (52%) of **6a** as its oxalate salt, mp 151–153 °C.

**Distribution Coefficient Determination.** A 0.1 M phosphate buffer solution, prepared by dissolving 4.3 g of sodium hydrogen phosphate and 18.3 g of disodium hydrogen phosphate in 1.6 L of distilled $H_2O$ and adjusting the pH to 7.4 with 0.1 N NaOH solution or 0.1 N HCl solution, was shaken vigorously with 1.6 L of 1-octanol for 16 h. The layers were separated and stored in dark glass bottles. About 5 mg of compound was dissolved into 10 mL of phosphate buffer solution. The solution was then diluted with additional buffer until the absorbance of the resultant solution read between 0.4 and 0.9 at 280 nm. A 5-mL portion of initial undiluted compound solution was then vigorously shaken with 5 mL of 1-octanol, previously saturated with the phosphate buffer. The solution was then centrifuged for 5 min, and the octanol layer was removed. The remaining aqueous solution was diluted as necessary to obtain an absorbance reading between 0.4 and 0.9. The distribution coefficient was calculated by dividing the absorbance of the initial reading × the dilution factor minus the absorbance of the final reading × the dilution factor by the Absorbance of the final reading × the dilution factor, i.e.,

$$DC = \frac{\text{Abs(i)} \times \text{dilution factor} - \text{abs(f)} \times \text{dilution factor}}{\text{abs(f)} \times \text{dilution factor}}$$

## References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(11) This half-life was chosen to provide compounds with the desireable properties described. Clinical experience with the SA β-blocker esmolol had established the fact that a compound with about a 20-min *in vitro* elimination half-life in human blood permits rapid buildup of efficacious blood levels of drug.[14] However, termination of the drug's activity has not always been as prompt as desired. Thus, we chose a shorter (ca. 10 min) elimination half-life in this series to improve upon this property. The *in vitro* half-life of esmolol had also been established in the same human blood hydrolysis assay used for this series of antiarrhythmics.

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