Soft Drugs. 12. Design, Synthesis, and Evaluation of Soft Bufuralol Analogues

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In the search for more potent but still short-acting β-blockers (BB), the methyl, ethyl, isopropyl, *tert*-butyl, cyclohexyl, 2-(1-adamantyl)ethyl, and methylthiomethyl esters of the acidic inactive metabolite of bufuralol were synthesized based on the "inactive metabolite" approach. The cleavage of the ester bond by blood and tissue esterases rapidly deactivates these compounds, resulting in an ultrashort duration of action. The β-antagonist potencies and time courses of actions of the new "soft" BBs were characterized by recording ECG and intra-arterial blood pressure (BP) in rats. In the isoproterenol-induced tachycardia model, while bufuralol at an iv dose of 1 mg/kg (3.8 μmol/kg) diminished heart rate (HR) for at least 2 h, the effects of the soft drugs lasted for only 10−30 min at equimolar dose. The inactive metabolite did not decrease HR significantly. The first four members of this series of compounds showed the highest β-blocking potencies, ranging between 25% and 50% of that of bufuralol. Next, the effects of these most active compounds on resting HR and BP were evaluated in comparison to esmolol. Infused for 10 min at a rate of 20 μmol/kg/min, esmolol decreased HR and mean arterial pressure (MAP) by 40% and 60%, respectively. The soft drugs at doses ranging only between 2 and 4 μmol/kg/min resulted in a 20−40% decrease in HR and a 30−50% reduction in MAP. However, the time courses of both the bradycardic and hypotensive effects of the soft drugs were superimposable to that of esmolol, diminishing within 60 min after the discontinuation of the infusions.

Introduction

β-Blockers are widely used in the treatment of various cardiovascular diseases,[1−7] including angina pectoris, hypertension, and cardiac arrhythmias. Their efficacy and safety have also been well-established in reducing the risk of mortality and nonfatal reinfarction in survivors of acute myocardial infarction.[1] However, the use of β-blockers in seriously ill patients is limited, because of potentially adverse effects (i.e. bradycardia, hypotension, aggravation of heart failure, and bronchospasm). The ultrashort-acting β-antagonist esmolol is often used to control acute supraventricular arrhythmias, myocardial ischemia (acute myocardial infarction and unstable angina), and perioperative and postoperative hypertension in critically ill patients.[8] In the structure of esmolol (Figure 1), an ethylene-extended methyl ester group is included, which makes the molecule susceptible to rapid hydrolysis by esterases.[7,9,10] If unwanted side effects occur during esmolol treatment, one can expect the rapid disappearance of adverse reactions after the discontinuation of the infusion, as the terminal half-life of esmolol is short, only 9.2 min.[8]

The use of β-blockers is often also complicated by their oxidative metabolic transformation to products with significant β-receptor-blocking activities but different biological half-lives.[11] For example, bufuralol[12,13] (Figure 1) is a potent, nonselective β-blocker[14−16] that has proven to be very effective in lowering blood pressure and heart rate. It undergoes a complex series of metabolic transformations in humans to alcohol and ketone metabolites that also possess significant β-receptor-blocking activities while having longer half-lives.[17−22] The oxidative transformation of bufuralol by the hepatic cytochrome P450 isozymes is under genetic control and falls under the debrisoquine/spartein phenotype.[23−26] A genetically determined defect of the hydroxylation occurs in up to 10% of the Caucasian population (poor metabolizers).[26] This situation can further complicate the pharmacokinetic profile by increasing drug bioavailability and prolonging the elimination half-life so as to produce more intense and sustained β-blockade[27−29] that, in turn, can lead to severe hypotension and bradycardia.[30]

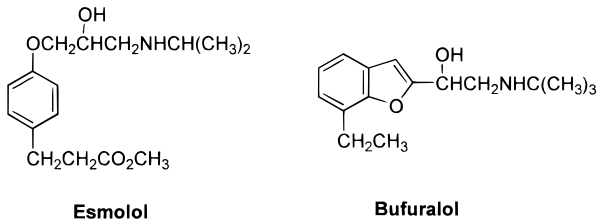

Figure 1. Chemical structures of esmolol and bufuralol.

As the soft drug concept is particularly suitable for addressing the above-mentioned therapeutic problems,[31,32] we previously reported a series of soft β-blockers which revealed an ultrashort duration of action and predictable metabolism by applying the "inactive metabolite" approach.[33−36] Continuing this search for more potent and short-acting β-blockers, we selected the

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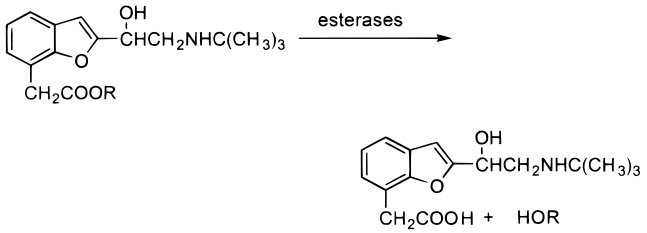
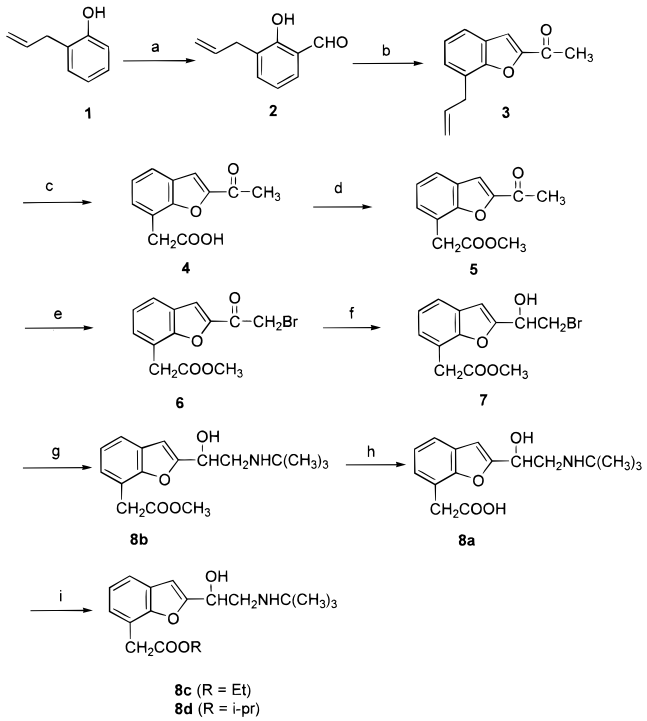
Scheme 1. Structural Features of the Soft Drugs and Their Metabolic Pathways



Scheme 2[a]



[a] Reagents: (a) tributylamine, $SnCl_4$, $(CH_2O)_n$, benzene, 100 °C, 12 h; (b) KOH, $ClCH_2COCH_3$, EtOH, reflux, 1 h; (c) $KMnO_4/NaIO_4$, *t*-BuOH, 70 °C, 24 h; (d) MeOH, H_2SO_4, reflux, 4 h; (e) Br_2, $CHCl_3$, rt, 30 min; (f) B_2H_6, THF, 0 °C, 30 min; (g) (i) 10 N NaOH, THF, rt, 1 h, (ii) *tert*-butylamine, 2-propanol, rt, 36 h; (h) (i) 2 N KOH, THF, rt, 2 h, (ii) HCl−ether, obtained as HCl salt form; (i) H_2SO_4, ROH, rt, 4 h.

inactive metabolite of bufuralol to design a new series of short-acting β-blockers in the present study. Seven different sized alkyl moieties were selected to serve as the ester functionalities to reactivate the inactive metabolite of bufuralol. This design strategy considered the observations that not only the rate of hydrolytic deactivation can be controlled by the ester structure but also esterases ubiquitously present in blood and tissues should quickly hydrolyze the labile ester functionality to produce the corresponding inactive acetic acid derivative as shown in Scheme 1. Here, we report the syntheses, stabilities, and biological evaluations of seven soft bufuralol analogues (**8**).

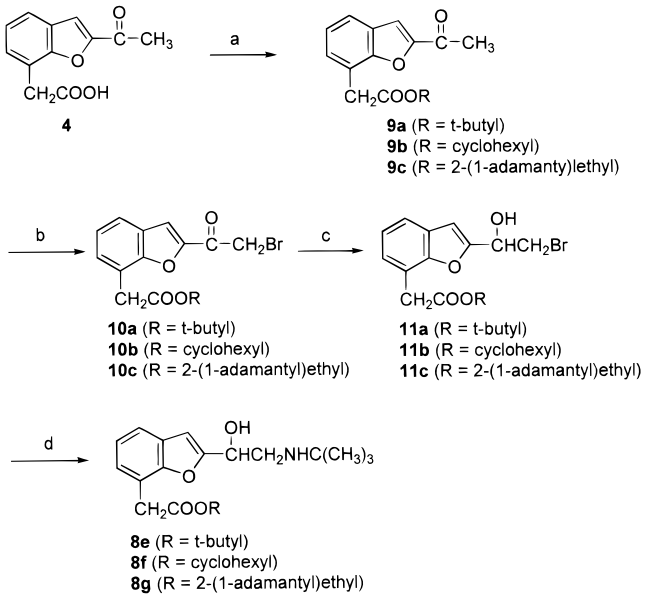
Results and Discussion

Chemistry. The key intermediate **8a** for the synthesis of soft analogues was prepared according to the methods depicted in Scheme 2. Formylation of 2-allylphenol (**1**) with paraformaldehyde[37] in the presence of tributylamine and Sn(IV) chloride gave aldehyde **2**, which was converted into the 7-allyl-2-acetylbenzofuran (**3**) by treating of chloroacetone in ethanol.[12,38] The oxidative cleavage of **3** with potassium permanganate/sodium periodate[39] afforded the substituted acetic acid **4** in moderate yield.

After esterification of **4** with methanol, the resulting methyl ester **5** was reacted with bromine in chloroform[40] to give **6**, which was then reduced with diborane in tetrahydrofuran[40] to alcohol **7**. Epoxidation of **7** followed by opening of the resulting epoxide with *tert*-butylamine in 2-propanol produced **8b**.[41] Finally, basic hydrolysis of the methyl ester followed by neutralization provided the acid **8a**.

From **8a** we tried to prepare all of the designed analogues by esterification with the corresponding alcohols. However, we failed to prepare the bulkier esters (**8e**−**8i**) under various esterification conditions,[42−45] and only the ethyl (**8c**) and isopropyl (**8d**) analogues were obtained in moderate yields. Thus, the bulkier esters **8e**−**8i** were prepared from **4** (Scheme 3). Since the benzofuranylacetic acid has low reactivity toward the acid-catalyzed esterification with the bulky alcohols, the acid **4** was first converted into the acid chloride with thionyl chloride and then treated with the corresponding alcohols to give the desired alkyl esters **9**. Subsequently, the methods used for **8b** were applied for the syntheses of **8e**−**8g**. The methylthiomethyl ester (**8h**) was prepared from the reaction of the potassium salt, generated by base hydrolysis of **8b** with equimolar KOH in ethanol and water,[46,47] with methylthiomethyl chloride in benzene[45] (Scheme 4).

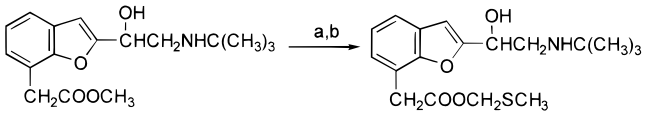
Scheme 3[a]



[a] Reagents: (a) (i) $SOCl_2$, CH_2Cl_2, reflux, 2 h, (ii) ROH; (b) Br_2, $CHCl_3$, rt, 30 min; (c) B_2H_6, THF, 0 °C, 30 min; (d) (i) 10 N NaOH, THF, rt, 1 h, (ii) *tert*-butylamine, 2-propanol, rt, 36 h.

Stabilities of the Soft Analogues in Aqueous Buffer Solutions. The hydrolysis rates of the soft drugs at physiological pH = 7.4 and under basic conditions pH = 12 were investigated in order to assess their chemical stabilities. At physiological pH, the soft analogues **8b**−**8h** did not undergo significant hydrolysis within 24 h. Alternatively, at pH = 12 the esters **8b**−**8h** were readily hydrolyzed to the acidic metabolite **8a**.

Scheme 4[a]



8b **8h**

[a] Reagents: (a) KOH, EtOH/H_2O (1:1), rt, 2 h; (b) NaI, 18-crown-6, $ClCH_2SCH_3$, benzene, 70 °C, reflux.

Table 1. Chemical Hydrolysis of β-Blocker Esters[a]

compd	k (min^{-1})	$t_{1/2}$ (min)	C_0 (M)
8b (methyl)	0.096	7.2	1.2×10^{-5}
8c (ethyl)	0.084	8.2	1.3×10^{-5}
8d (isopropyl)	0.015	45.7	1.3×10^{-5}
8e (*tert*-butyl)	0.091	75.7	1.4×10^{-5}
8f (cyclohexyl)	0.045	15.2	1.3×10^{-5}
8g (2-(1-adamantyl)ethyl)	0.0016	150.0	1.1×10^{-5}
8h (methylthiomethyl)	0.027	25	1.1×10^{-5}

[a] Apparent pseudo-first-order hydrolytic rate constants (k), half-lives ($t_{1/2}$), and initial concentrations (C_0) in 0.01 N sodium hydroxide at pH = 12.0 and 37.0 ± 0.1 °C.

Table 2. Enzymatic Hydrolysis of β-Blocker Esters[a]

compd	k (min^{-1})	$t_{1/2}$ (min)	C_0 (M)
8b (methyl)		*b*	1.2×10^{-5}
8c (ethyl)		*b*	1.3×10^{-5}
8d (isopropyl)	0.0417	16.6	1.3×10^{-5}
8e (*tert*-butyl)	0.007	99.0	1.4×10^{-5}
8f (cyclohexyl)	0.111	6.2	1.3×10^{-5}
8g (2-(1-adamantyl)ethyl)		*b*	1.1×10^{-5}
8h (methylthiomethyl)		*b*	1.1×10^{-5}

[a] Apparent pseudo-first-order hydrolytic rate constants (k), half-lives ($t_{1/2}$), and initial concentrations (C_0) in rat blood at 37.0 ± 0.1 °C. [b] A half-life is less than 0.15 min, which indicates that more than 95% of the compound was metabolized in 0.15 min.

The hydrolytic half-lives generally increased with increasing steric hindrance of the alkyl group within each ester (Table 1). Thus, the 2-(1-adamantyl)ethyl and *tert*-butyl analogues showed longer half-lives with 150 and 75.7 min, respectively, while the methyl ester hydrolyzed with an ultrashort half-life of 7.3 min.

Metabolism of the Soft Analogues in Biological Media. The stability and the metabolic pathway of the soft drugs in biological media were examined in rat blood. The metabolism of the soft drugs in rat blood follows a pseudo-first-order kinetics, and all soft drugs were converted to the corresponding acid metabolite **8a** without formation of other metabolites. As expected, compounds **8b**, **8c**, and **8h** which have less sterically hindered alkyl groups show shorter half-lives then the bulkier **8d**−**8f** esters (Table 2). These results can be explained with the facile attack by hydrolytic enzymes on the less hindered ester linkage. However, similar differences between chemical and enzymatic cleavage rate for an 2-(1-adamantyl)ethyl ester **8g** were observed for the soft β-blockers derived from metotrolol.[35]

Biological Evaluation. 1. Effects on Isoproterenol-Induced Tachycardia. There were no statistically significant differences in the baseline heart rate and blood pressure parameters between the different groups of rats receiving the different compounds. The average heart rate increased by 23.68% (from 355.26 ± 23.49/min to 439.4 ± 20.59/min) after the sc injection of 50 μg/kg isoproterenol. Relative to this isoproterenol-induced tachycardia, the iv bolus injection of bufuralol at a dose of 1 mg/kg (3.8 μmol/kg) resulted in a 35−40% decrease in heart rate (Figure 2.). The maximal bradycardic action of the drug developed after 30 min and remained stable for the total course of the experiment (up to 120 min) after the bolus injection. The bolus injection of the soft bufuralol analogues **8b**−**8h** at equimolar doses (3.8 μmol/kg) resulted in a significant but temporary decrease (10−20%) in heart rate. The most active compounds in this model were **8d**, **8e**, **8b**, and **8c**, while **8f**−**8h** (the compounds with the bulkier ester groups) showed weaker bardycardic actions against the isoproterenol-induced tachycardia. Bufuralol and the soft analogues were all administered as an iv bolus injection, so the kinetics of their effects included first a distribution and second an elimination phase. While the primary aim of this study was not a pharmacokinetic evaluation, one can assume that the disappearance of the effects of the soft analogues was primarily the result of the enzymatic inactivation by esterases present in blood and tissues. In accordance with the soft nature of these compounds, their bradycardic action lasted for only 10−30 min. After 30 min, as shown by cluster analysis, the effects of the soft drugs did not differ significantly any more from those of either the vehicle or the inactive metabolite **8a** (Figure 2), which even at a dose of 10 μmol/kg did not decrease heart rate significantly. On the contrary, while the distribution of bufuralol had to be very similar after the bolus injection, its effect lasted for up to 120 min, mainly because of the differences in its metabolic and elimination properties.

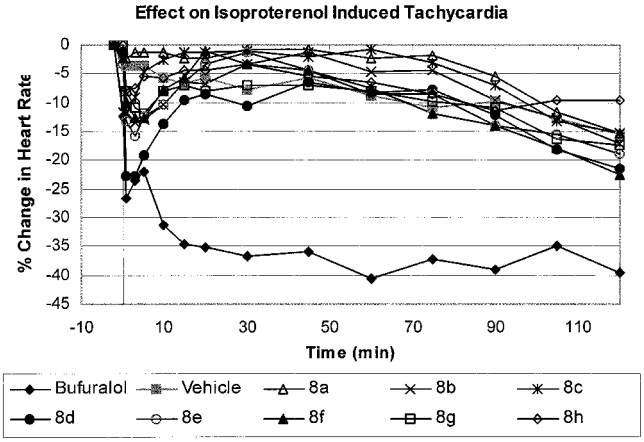


Figure 2. Effects of vehicle, bufuralol, and the soft analogues of bufuralol on isoproterenol-induced tachycardia in the rat. Bufuralol (1 mg/kg = 3.8 μmol/kg) and the soft analogues of bufuralol (3.8 μmol/kg) were all dissolved in 10% DMSO in 30% HPBCD. The symbols represent the mean values of at least three animals; error bars are omitted for better visibility. The cluster analysis of heart rate data established three different clusters. Between 0 and 5 min the cluster for vehicle and **8a** was significantly different from the clusters of bufuralol and **8b**−**8h**, while the cluster for bufuralol was different significantly from those of vehicle and **8a**−**8h** from 10 to 120 min ($p < 0.05$).

2. Effects on Resting Heart Rate and Blood Pressure. Esmolol is an ultrashort-acting β-blocker that is available as an iv injection formulation. In the clinical setting esmolol is usually applied at a 500 μg/kg/min loading dose for 1 min, followed by a titration phase with stepwise increments of dose between 50 and 300 μg/kg/min to reach the necessary decrease in heart rate and/or blood pressure. Following this, esmolol is

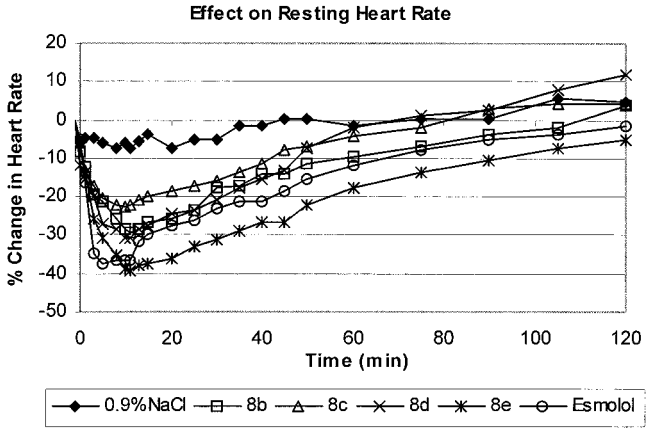


Figure 3. Effects of 0.9% NaCl, compounds **8b**−**8e**, and esmolol-HCl infusions on resting heart rate. Drugs were dissolved in 0.9% NaCl and were infused for 10 min. Infusion rates were 2 μmol/kg/min for **8b**, **8d**, and **8e**, 4 μmol/kg/min for **8c**, and 20 μmol/kg/min for esmolol-HCl. The symbols represent the mean values of at least three animals; error bars are omitted for better visibility. Cluster analysis demonstrated that there was a significant difference between the active drugs and vehicle for up to 60 min ($p < 0.05$), while there was no difference between esmolol-HCl and compounds **8b**−**8e**.

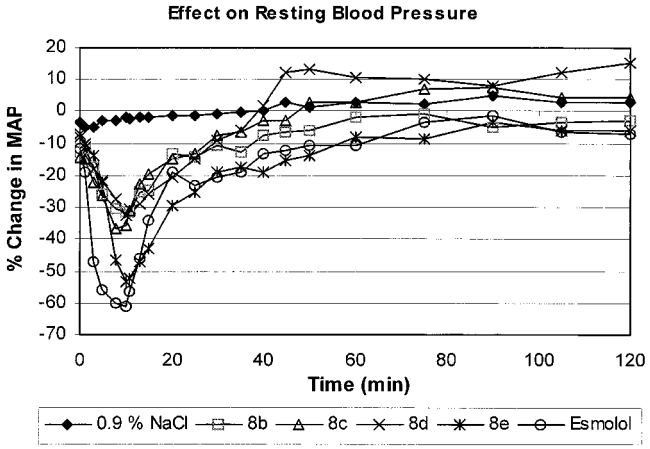


Figure 4. Effects of 0.9% NaCl, compounds **8b**−**8e**, and esmolol-HCl infusions on resting blood pressure (mean arterial pressure = MAP). Drugs were dissolved in 0.9% NaCl and were infused for 10 min. Infusion rates were 2 μmol/kg/min for **8b**, **8d**, and **8e**, 4 μmol/kg/min for **8c**, and 20 μmol/kg/min for esmolol-HCl. The symbols represent the mean values of at least three animals; error bars are omitted for better visibility. Cluster analysis demonstrated that there was a significant difference between the active drugs and vehicle for up to 40 min ($p < 0.05$), while there was no difference between esmolol-HCl and compounds **8b**−**8e**.

administered as a continuous infusion of a dose, which maintains the desired heart rate and blood pressure control. Because of time limitations in the present experiments, only a shorter single-dose infusion was used, resulting in significant heart rate and blood pressure reductions. However, this period was not long enough to reach "steady state". It was expected, however, that the effects of the soft bufuralol analogues infused for 10 min with a pump would be similar to that of esmolol applied in the same way. The most active compounds **8b**−**8e**, converted into their corresponding HCl salt forms, were investigated on the resting heart rate and blood pressure in comparison to esmolol-HCl and the vehicle (0.9% NaCl solution), respectively. First, the doses to reach similar heart rate and blood pressure reductions by the end of the 10-min infusion periods were determined. It was found that compounds **8b**−**8e** at a dose of 2 μmol/kg/min and compound **8c** at 4 μmol/kg/min were approximately equipotent with esmolol at a dose of 20 μmol/kg/min. All the soft bufuralol analogues and esmolol decreased heart rate (by 20−40% on average) during the course of the infusion (i.e. 10 min). After the discontinuation of the drug administration, heart rates gradually returned to baseline values, mostly within 60 min, and were not significantly different any more from the values of normal saline (Figure 3). Blood pressure changes were similar, but the effect of esmolol at a dose of 20 μmol/kg/min was more pronounced, resulting in a 60% decrease in mean arterial pressure (MAP). Although **8b**−**8d** only decreased MAP by 30−40% on average, and **8e** resulted in more than 50% decrease in MAP, these MAP reductions were obtained at smaller doses (i.e. 2−4 μmol/kg/min). Again, after the cessation of the infusions, blood pressure values returned to baseline values (Figure 4). The kinetics of the heart rate and blood pressure changes were superimposable on the changes evoked by esmolol, as the cluster analysis demonstrated that only the effects of the vehicle (0.9% NaCl) were significantly different from the active compounds. The soft bufuralol analogues resulted in a comparable heart rate decrease at doses of 1/5 to 1/10 that of esmolol. With respect to their MAP-reducing capabilities they still showed somewhat higher intrinsic activity than esmolol, although their MAP reduction effect did not reach the extent of esmolol. The bufuralol analogues apparently possess β-blocking efficacy at lower doses than esmolol, but only 30−40% decreases in MAP were observed for all, except one (**8e,** over 50%), of the new analogues compared to the 60% decrease obtained with esmolol at a dose of 20 μmol/kg/min.

Experimental Section

Materials and Methods. Deutrated and nondeutrated solvents were obtained from Aldrich Chemical Co. The solvents used for HPLC were spectral grade. Melting points were measured on Fisher Johns melting point appratus and were uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Varian EM 390 spectrophotometer (^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz). Chemical shifts are reported in parts per million units (ppm) on the δ scale downfield from tetramethylsilane which was used as an internal standard. The solvents used are given in parentheses for each spectrum reported. Multiplicities of protons are designated as singlet (s), double (d), triplet (t), quartet (q) or multiplet (m). Infrared (IR) spectra were recorded on a Perkin-Elmer 240 spectrophotometer. Solid samples were run as either a KBr pellet or a Nujol mull; liquid samples were analyzed neat as a thin film between NaCl plates. Mass spectra and elemental analyses were performed by the Department of Environmental Engineering, Ajou University, Suwon, Korea.

Analytical Method. The HPLC system used consisted of a Waters 600 pump, a Rheodyne 7125 injector with a 20-μL loop, a Spectroflow variable-wavelength UV/VIS detector and HP 3396 integrator. The soft analogues and the acid metabolite were analyzed by using Waters normal-phase μ Bondpack amine column (30-cm × 3.9-mm i.d.) which provided complete separation of acidic metabolite peak from the ester peak. The mobile phase included two solvent systems: the isocratic system of methanol for the chemical hydrolysis and the gradient system of methanol−water (9:1) for the enzymatic hydrolysis. The detector wavelength was set at 254 nm. The

flow rate of the mobile phase was 1 mL/min. The retention times of the ester compounds were between 2.3 and 2.7 min, while the retention time of the common acidic metabolite was 6.1 min. The calibration curve was linear ($r = 0.993-0.998$) for the compounds injected over the range of 10−120 μM.

3-Allylsalicylaldehyde (2). To a solution of 2-allylphenol (100 g, 740 mmol) in benzene (2 L) were added tin(IV) chloride (16.6 g, 60.0 mmol) and tributylamine (17.4 g, 240 mmol). The mixture was stirred for 20 min at room temperature, and then paraformaldehyde (36.0 g, 1.20 mol) was added. The resulting mixture was heated at 100 °C for 8 h. After cooling, the reaction mixture was poured into cold water (300 mL) and acidified to pH 2 with 2 N hydrochloric acid. The aqueous layer was extracted with ether (3 × 50 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give the residue, which was purified by column chromatography on silica gel (hexane:EtOAc, 4:1) to afford 61.0 g (50%) of **2** as a yellow oil: mp 45 °C; IR (neat) 3098, 2844, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.41 (d, 2H, CH_2CH=CH$_2$, $J = 6.4$ Hz), 4.04−5.15 (m, 2H, CH=CH_2), 5.90−6.15 (m, 1H, CH=CH$_2$), 6.92−7.00 (m, 1H, ArH), 7.39−7.44 (m, 2H, ArH), 9.85 (s, 1H, CHO), 11.32 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) 33.0, 116.2, 119.5, 131.8, 135.7, 137.1, 196.6. Anal. ($C_{10}H_{10}O_2$) C, H.

2-Acetyl-7-allylbenzofuran (3). To a solution of **2** (60.0 g, 369 mmol) in absolute ethanol (100 mL) was added pellet KOH (3.0 g). The resulting mixture was warmed until the suspension turned into a clear solution. To this was added chloroacetone (5.00 g, 63.0 mmol) dropwise and the resulting dark solution was refluxed for 15 min. After the reaction mixture was poured into 200 mL of ice−water, the ethanol was removed under reduced pressure. The aqueous layer was extracted with ether (3 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to give a reddish residue, which was purified by column chromatography on silica gel (hexane:EtOAc, 20:1) to afford 44.1 g (60%) of **3** as a white solid: mp 43 °C; IR (KBr) 3000, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.60 (s, 3H, COCH_3), 3.71 (d, 2H, $J = 6.6$ Hz, CH_2CH=CH$_2$), 5.1−5.23 (m, 2H, CH=CH_2), 6.01−6.15 (m, 1H, CH=CH$_2$), 7.28−7.31 (m, 2H, ArH), 7.52 (s, 1H, furan-H) 7.54−7.59 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) 26.1, 33.3, 112.7, 116.3, 152.3, 188.1. Anal. ($C_{13}H_{12}O_2$) C, H.

[2-(Acetyl)benzofuran-7-yl]acetic Acid (4). To a solution of 7-allyl-2-acetylbenzofuran (40.0 g, 200 mmol) in *t*-BuOH (100 mL) was added dropwise the mixture of $KMnO_4$ (32.0 mg, 0.20 mmol), $NaIO_4$ (225 g, 1.05 mol), and K_2CO_3 (29.0 g, 209 mmol) in *t*-BuOH−H_2O (7:3, 4 L). After the reaction mixture was stirred at 70 °C for 20 h, the solvent mixture was evaporated. The residue was purified by column chromatography on silica gel (methylene chloride:methanol, 4:1) to afford 26.2 g (60%) of **4** as a white solid: mp 143 °C; IR (KBr) 3377, 2933, 1699, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.54 (s, 3H, COCH_3), 3.86 (s, 2H, CH_2COO), 7.25−7.35 (m, 2H, ArH), 7.61−7.65 (m, 1H, ArH), 7.63 (s, 1H, furan-H); ^{13}C NMR ($CDCl_3$) 24.8, 33.1, 112.2, 118.1, 120.5, 122.3, 125.2, 127.6, 150.6, 152.5, 170.1, 186.1. Anal. ($C_{12}H_{10}O_4$) C, H.

Methyl [2-(Acetyl)benzofuran-7-yl]acetate (5). To a solution of **4** (18.0 g, 82.5 mmol) in MeOH (100 mL) was added concentrated H_2SO_4 (4 mL) at 0 °C. After the reaction mixture was heated at 70 °C for 1 h, it was diluted with 50 mL of H_2O. The methanol was evaporated, and the aqueous layer was extracted with chloroform (3 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (hexane:EtOAc, 1:1) to afford 17.4 g (91%) of **5** as a white solid: mp 84 °C; IR (KBr) 3139, 2958, 1735, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.58 (s, 3H, COCH_3), 3.71 (s, 2H, OCH_3), 3.90 (s, 2H, CH_2COO) 7.33 (dd, 1H, ArH, $J = 7.7$ Hz, 7.6 Hz), 7.37 (d, 1H, ArH, $J = 7.7$ Hz), 7.49 (s, 1H, furan-H), 7.61 (d, 1H, ArH, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$) 26.4, 34.6, 52.1, 112.9, 118.9, 122.3,124.0, 127.0, 129.0, 152.7, 154.1, 170.9, 188.5. Anal. ($C_{13}H_{12}O_4$) C, H.

Methyl [2-(Bromoacetyl)benzofuran-7-yl]acetate (6). To a solution of **5** (10.0 g, 43.0 mmol) in chloroform (250 mL) was added Br_2 (2.40 mL, 47.5 mmol) dropwise. The reaction mixture was refluxed for 30 min at room temperature. When the reddish solution had turned yellow, 50 mL of $NaHCO_3$ was added. The resulting mixture was stirred for 30 min and then H_2O (20 mL) was added. The reaction mixture was extracted with chloroform (2 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (hexane:EtOAc, 4:1) to afford 8.7 g (65%) of **6** as a white solid: mp 93 °C; IR (KBr) 3124, 2953, 1729, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.75 (s, 3H, OCH_3), 4.0 (s, 2H,CH_2COO), 4.4 (s, 2H, COCH_2Br), 7.32−7.43 (m, 2H, ArH), 7.65−7.67 (m, 1H, ArH), 7.66 (s, 1H, furan-H); ^{13}C NMR ($CDCl_3$) 30.6, 34.6, 52.1, 114.7, 119.0, 122.5, 124.4, 126.8, 129.6, 150.1, 154.4, 170,7, 182.0. Anal. ($C_{13}H_{11}O_4$ Br) C, H.

Methyl [2-(1-Hydroxy-2-bromoethyl)benzofuran-7-yl]-acetate (7). To a solution of diborane (50 mL, 1 M solution in THF) was added compound **6** (8.10 g, 26.0 mmol) in THF (40 mL) dropwise at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The reaction was quenched with 10 mL of methanol, acidified with 1 N HCl, and then extracted with ether (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel (hexane: EtOAc, 1:4) to afford 6.5 g (80%) of **7** as a white solid: mp 80 °C; IR (KBr) 3499, 3124, 2960, 1736, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.67−3.84 (m, 2H, CH_2Br), 3.69 (s, 3H, OCH_3), 3.91 (s, 2H, CH_2COO), 5.01−5.06 (m, 1H, CH(OH)), 6.70 (s, 1H, furan-H), 7.16−7.19 (m, 2H, ArH), 7.43−7.48 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) 34.8, 35.5, 52.0, 67.8, 104.2, 117.3, 120.6, 122.9, 125.2, 127.6, 153.1, 155.8, 171.4. Anal. ($C_{13}H_{13}O_4Br$) C, H.

Methyl [2-[1-Hydroxy-2-(*tert*-butylamino)ethyl]benzofuran-7-yl]acetate (8b). To a solution of **7** (6.40 g, 20.4 mmol) in THF (150 mL) was added 10 N NaOH (1.0 mL). After the reaction mixture was stirred for 2 h, the solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride (50 mL) and the resulting solution was dried over anhydrous magnesium sulfate, filtered and evaporated to give the crude epoxide which was used in the next reaction without further purification. The crude epoxide was dissolved in 2-propanol (5 mL) and added to *tert*-butylamine (3.02 mL, 28.2 mmol). The reaction mixture was stirred for 36 h and evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH, 120:10:1) to afford 4.3 g (69%) of **8b** as a white solid: mp 82 °C; IR (KBr) 2968−3400, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.25 (s, 9H, C(CH_3)$_3$), 3.09−3.24 (m, 2H, CH_2 NH), 3.70 (s, 3H, OCH_3), 3.91 (s, 2H, CH_2COO), 4.41 (br, 1H, NH) 5.15−5.18 (m, 1H, CHOH), 6.72 (s, 1H, furan-H), 7.14−7.20 (m, 2H, ArH), 7.42−7.45 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) 28.7, 34.8, 46.2, 50.6, 51.9, 66.1, 103.1, 117.4, 119.9, 122.8, 124.7, 128.0, 153.2, 158.8, 171.3. Anal. ($C_{17}H_{23}NO_4$) C, H, N.

[2-[1-Hydroxy-2-(*tert*-butylamino)ethyl]benzofuran-7-yl]acetic Acid Hydrochloride (8a). To a solution of **8b** (3.76 g, 12.3 mmol) in THF (10 mL) was added 2 N KOH (10 mL). After the reaction mixture was stirred for 2 h, it was neutralized with 1 N HCl solution. After most of solvent was evaporated, the resulting solid residue was dissolved again in THF (100 mL) and then filtered. The filtrate was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was dissolved in methylene chloride followed by addition with ethereal HCl to afford 3.3 g (82%) of **8a** as a hydrogen chloride salt: IR (KBr) 2968−3400, 1720 cm^{-1}; ^{1}H NMR (D_2O) 1.45 (s, 9H, C(CH_3)$_3$), 3.42−3.61 (m, 2H, CH_2NH), 3.85 (s, 2H,CH_2COO), 5.12−5.23 (s, 1H, CHOH), 6.90 (s, 1H, furan-H), 7.11−7.32 (m, 2H, ArH), 7.52−7.60 (m, 1H, ArH); ^{13}C NMR (D_2O) 27.6, 47.2, 47.8, 60.8, 66.5, 107.7, 122.9, 123.9, 126.3, 128.8, 130.3, 140.0, 156.4, 157.3, 182.7. Anal. ($C_{16}H_{22}O_4$-NCl) C, H, N.

Ethyl [2-[1-Hydroxy-2-(*tert*-butylamino)ethyl]benzofuran-7-yl]acetate (8c). To a solution of **8a** (1.00 g, 3.00 mmol) in EtOH (10 mL) was added concentrated H_2SO_4 (0.2 mL). After the reaction mixture was stirred for 1 h at 60 °C,

the solvent was evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH, 120:10:1) to afford 0.41 g (42%) of **8c** as a yellow solid: mp 82 °C; IR (KBr) 2968−3460, 1739 cm^{-1} ; ^1H NMR ($CDCl_3$) 1.25 (s, 9H, C(CH_3)$_3$), 1.35 (s, 3H, OCH_2CH_3), 3.12 (m, 2H, CH_2-NH), 3.92 (s, 2H, CH_2COO), 4.27 (q, 2H, OCH_2CH$_3$), 5.01−5.08 (m, 1H, C*H*OH), 6.80 (s, 1H, furan-*H*), 7.15−7.21 (m, 2H, Ar*H*), 7.52−7.60 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) 14.7, 28.7, 34.9, 46.2, 50.4, 60.7, 66.1, 102.9, 117.5, 119.8, 122.7, 124.6, 128.0, 128.1, 153.2, 158.9, 170.8. Anal. ($C_{18}H_{25}NO_4$) C, H, N.

Isopropyl [2-[1-Hydroxy-2-(*tert*-butylamino)ethyl]benzofuran-7-yl]acetate (8d). To a solution of **8a** (1.00 g, 3.0 mmol) in *i*-PrOH (5 mL) was added concentrated H_2SO_4 (0. 1 mL). After the reaction mixture was stirred for 1 h at 60 °C, the solvent was evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH, 120:10:1) to afford 0.42 g (41%) of **8d** as a white solid: mp 83 °C; IR (KBr) 2970−3460, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) 1.12 (s, 9H, C(CH_3)$_3$), 1.23 (d, 6H, J = 6. 3 Hz, CH(CH_3)$_2$), 2.80−3.12 (m, 2H, CH_2NH), 3.87 (s, 2H, CH_2COO), 4.78−4.82 (m, 1H, C*H*OH), 5.01−5.08 (m, 1H, C*H*(CH$_3$)$_2$), 6.67 (s, 1H, furan-*H*), 7.15−7.1 7 (m, 2H, Ar*H*), 7.42−7.44 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 21.6, 28.8, 35.4, 46.1, 50.4, 66.2, 68.2, 103.1, 117.8, 119.8, 122.8, 124.7, 128.0, 153.3, 158.7, 170.4. Anal. ($C_{19}H_{27}$-NO_4) C, H, N.

***tert*-Butyl [2-(Acetyl)benzofuran-7-yl]acetate (9a).** To a solution of **4** (2.00 g, 9.10 mmol) in CH_2Cl_2 (20 mL) was added $SOCl_2$ (2.18 g, 18.3 mmol). After the reaction mixture was stirred for 1 h at 60 °C, the solution was concentrated to dryness. The residue was dissolved in *t*-BuOH (1.01 g, 13.6 mmol) and the resulting solution was stirred for 2 h at room temperature. After the reaction mixture was diluted with 50 mL of H_2O, it was extracted with chloroform (2 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel with hexanes−EtOAc (1:1) to afford 1.6 g (63%) of **9a** as a white solid: mp 85 °C; IR (KBr) 3120, 2976, 1722, 1674 cm^{-1}; ^1H NMR ($CDCl_3$) 1.46 (s, 9H, C(CH_3)$_3$), 2.61 (s, 3H, COCH_3), 3.90 (s, 2H, CH_2COO), 7.31−7.37 (m, 2H, Ar*H*), 7.50 (s, 1H, furan-*H*), 7.59−7.61 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 26.4, 28.3, 36.1, 81.2, 113.0, 119.7, 122.0,123.8, 126.9, 128.9, 152.6, 154.3, 169.8, 188.6. Anal. ($C_{16}H_{18}O_4$) C, H.

Cyclohexyl [2-(Acetyl)benzofuran-7-yl]acetate (9b). This compound was prepared in the same fashion as **9a**. From compound **4** (2.00 g, 9.1 mmol), 1.6 g (58%) of **9b** was obtained as a white solid: mp 81 °C; IR (KBr) 2923, 1728, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) 1.40−1.85 (s, 10H, (CH_2)$_5$), 2.61(s, 3H, COCH_3), 3.90 (s, 2H, CH_2COO), 4.80−4.84 (m, 1H, OCH), 7.31−7.37 (m, 2H, Ar*H*), 7.50 (s, 1H, furan-*H*), 7.59−7.64 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 23.5, 25.2, 26.6, 31.4, 35.4, 76.3, 113.0, 119.4, 122.1, 124.0, 126.9, 128.9, 152.6, 154.2, 170.0, 188.6. Anal. ($C_{18}H_{20}O_4$) C, H.

2-(1-Adamanthyl)ethyl [2-(Acetyl)benzofuran-7-yl]acetate (9c). This compound was prepared in the same fashion as **9a**. From **4** (2.00 g, 9.17 mmol), 1.5 g (43%) of **9c** was obtained as a yellow oil: IR (neat) 2058, 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) 1.34−1.87 (m, 17H, −adamantylethyl), 2.59 (s, 3H, COCH_3), 3.96 (s, 2H, CH_2COO), 4.16 (t, 2H, COOCH_2), 7.31−7.37 (m, 2H, Ar*H*), 7.50 (s, 1H, furan-*H*), 7.59−7.64 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 26.1, 28.2, 30.8, 34.5, 37.2, 42.0, 62.1, 113.1, 119.5, 122.0, 124.0, 127.2, 129.8, 152.2, 154.0, 171.6, 188.1. Anal. ($C_{24}H_{28}O_4$) C, H.

***tert*-Butyl 2-[2-(Bromoacetyl)benzofuran-7-yl]acetate (10a).** This compound was prepared in the same fashion as **6**. From **9a** (1.60 g, 5.83 mmol), 1.21 g (58%) of **10a** was obtained as a white solid: mp 83 °C; IR (KBr) 3039, 2979, 1718, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) 1.46 (s, 9H, C(CH_3)$_3$), 4.41(s, 2H, CH_2-Br), 3.90 (s, 2H, CH_2COO), 7.31−7.61 (m, 3H, Ar*H*), 7.70 (s, 1H, furan-*H*); ^{13}C NMR ($CDCl_3$) 28.0, 30.1, 36.1, 81.2, 114.9, 119.8, 122.2, 124.3, 126.2, 130.1, 128.9, 150.6, 154.3, 169.8, 182.6. Anal. ($C_{16}H_{17}O_4Br$) C, H.

Cyclohexyl [2-(Bromoacetyl)benzofuran-7-yl]acetate (10b). This compound was prepared in the same fashion as **6**. From **9b** (1.60 g, 5.49 mmol), 1.31 g (62%) of **10b** was obtained as a white solid: mp 81 °C; IR (KBr) 2923, 1701, 1690 cm^{-1}; ^1H NMR($CDCl_3$) 1.40−1.85 (s, 10H, (CH_2)$_5$), 3.90 (s, 2H, CH_2 COO), 4.40 (s, 2H, CH_2Br), 4.80−4.84 (m, 1H, OC*H*), 7.31−7.37 (m, 2H, Ar*H*), 7.50 (s, 1H, furan-*H*), 7.59−7.64 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 23.5, 24.5, 30.4, 31.4, 34.3, 72.3, 114.0, 119.4, 122.1, 124.0, 126.9, 129.1, 150.2, 154.1, 170.0, 182.1. Anal. ($C_{18}H_{19}O_4Br$) C, H.

2-(1-Adamantyl)ethyl [2-(Bromoacetyl)benzofuran-7-yl]acetate (10c). This compound was prepared in the same fashion as **6**. From **9c** (1.51 g, 3.9 mmol), 1.20 g (66%) of **10c** was obtained as a yellow oil: mp 83 °C; IR (neat) 2958, 1737, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) 1.34−1.87 (m, 17H, −adamantylethyl), 3.96 (s, 2H, CH_2COO), 4.16 (t, 2H, COOCH_2), 4.45 (s, 2H, CH_2Br), 7.31−7.37 (m, 2H, Ar*H*), 7.60 (s, 1H, furan-*H*), 7.59−7.64 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 28.3, 30.2, 31.5, 35.0, 36.7, 42.2, 61.6, 114.8, 119.1, 122.4, 124.3, 126.7, 129.7, 150.0, 154.3, 170.3, 182.0. Anal. ($C_{24}H_{27}O_4Br$) C, H.

***tert*-Butyl [2-(1-Hydroxy-2-bromoethyl)benzofuran-7-yl]acetate (11a).** This compound was prepared in the same fashion as **7**. From **10a** (1.60 g, 5.8 mmol), 1.10 g (91%) of **11a** was obtained as a white solid: mp 75 °C; IR (KBr) 3402, 2918, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) 1.46 (s, 9H, C(CH_3)$_3$), 2.91 (br, 1H, OH), 3.80−3.88 (m, 2H, CH_2Br), 3.90 (s, 2H, CH_2COO) 5.08−5.10 (m, 1H, C*H*OH), 6.71 (s, 1H, furan-*H*) 7.20−7.25 (m, 2H, Ar*H*), 7.44−7.48 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 28.0, 36.4, 68.1, 81.08, 104.4, 118.5, 120.1, 123.1, 125.5, 127.7, 150.6, 155.4, 170.2. Anal. ($C_{16}H_{19}O_4Br$) C, H.

Cyclohexyl [2-(1-Hydroxy-2-bromoethyl)benzofuran-7-yl]acetate (11b). This compound was prepared in the same fashion as **7**. From **10b** (1.30 g, 3.5 mmol), 1.12 g (84%) of **11b** was obtained as a white solid: mp 81 °C; IR (KBr) 3419, 2923, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) 1.40−1.85 (s, 10H, (CH_2)$_5$), 3.90 (s, 2H, CH_2COO), 3.70−3.80 (s, 2H, CH_2Br), 4.80−4.84 (m, 1H, OC*H*), 5.11−5.19 (m, 1H, C*H*OH), 6.71 (s, 1H, furan-*H*), 7.31−7.37 (m, 2H, Ar*H*), 7.59−7.63 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 23.5, 25.3, 31.4, 35.6, 36.4, 68.1, 73.2, 104.4, 118.2, 120.2, 123.1, 125.4, 127.7, 153.0, 155.5, 170.3. Anal. ($C_{18}H_{21}O_4$ Br) C, H.

2-(1-Adamantyl)ethyl [2-(1-Hydroxy-2-bromoethyl)-benzofuran-7-yl]acetate (11c). This compound was prepared in the same fashion as **7**. From **10c** (1.20 g, 2.6 mmol), 1.02 g (85%) of **11c** was obtained as a yellow oil: IR (neat) 3404, 2972, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) 1.26−1.89 (m, 17H, −adamantylethyl), 3.41(br, 1H, OH), 3.41−3.44 (m, 2H, CH_2Br), 3.89 (s, 2H, CH_2COO), 4.16 (t, 2H, COOCH_2), 5.10−5.19 (m, 1H, C*H*OH), 6.73 (s, 1H, furan-*H*), 7.31−7.37 (m, 2H, Ar*H*), 7.44−7.46 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 28.4, 31.6, 35.3, 36.1, 36.8, 42.1, 61.6, 68.0, 104.3, 117.7, 120.2, 123.0, 125.4, 127.7, 153.3, 155.6, 171.1. Anal. ($C_{24}H_{29}O_4Br$) C, H.

***tert*-Butyl [2-[1-Hydroxy-2-(*tert*-butylamino)ethyl]benzofuran-7-yl]acetate (8e).** This compound was prepared in the same fashion as **8b**. From **11a** (1.00 g, 2.8 mmol), 1.10 g (33%) of **8e** was obtained as a yellow oil: IR (neat) 3200−3460, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) 1.12 (s, 9H, C(CH_3)$_3$), 1.44 (s, 9H, OC(CH_3)$_3$), 2.35 (br, 1H, N*H*) 3.00−3.04 (m, 2H, CH_2NH), 3.82 (s, 2H, CH_2COO), 4.80−4.84 (m, 1H, C*H*OH), 6.68 (s, 1H, furan-*H*), 7.15−7.18 (m, 2H, Ar*H*), 7.42−7.45 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 27.9, 28.8, 36.4, 46.1, 50.6, 66.2, 68.2, 103.1, 118.2, 119.7, 122.7, 124.7, 127.9, 153.3, 158.7, 170.2. Anal. ($C_{20}H_{29}NO_4$) C, H, N.

Cyclohexyl [2-[1-Hydroxy-2-(*tert*-butylamino)ethyl]-benzofuran-7-yl]acetate (8f). This compound was prepared in the same fashion **8b**. From **11b** (1.10 g, 2.80 mmol), 0.35 g (32%) of **8f** was obtained as a white solid: mp 83 °C; IR (KBr) 3200−3460, 1743 cm^{-1}; ^1H NMR ($CDCl_3$) 1.18 (s, 9H, C(CH_3)$_3$), 1.19−1.79 (m, 10H, (CH_2)$_5$), 2.98−3.04 (m, 2H, CH_2NH), 3.62 (br, 1H, N*H*), 3.89 (s, 2H, CH_2COO), 4.79−4.84 (m, 1H, OC*H*), 4.85−4.91 (m, 1H, C*H*OH), 6.66 (s, 1H, furan-*H*), 7.14−7.17 (m, 2H, Ar*H*), 7.40−7.45 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 23.3, 25.1, 28.5, 31.3, 35.3, 46.2, 50.4, 66.2, 72.9, 102.9, 117.8, 119.7, 122.6, 124.6, 127.9, 153.2, 158.8, 170.2. Anal. ($C_{22}H_{31}NO_4$) C, H, N.

2-(1-Adamantyl)ethyl [2-[1-Hydroxy-2-(*tert*-butylamino)ethyl]benzofuran-7-yl]acetate (8g). This compound was

prepared in the same fashion as **8b**. From **11c** (1.02 g, 2.20 mmol), 0.33 g (85%) of **8g** was obtained as a slick oil: IR (neat) 3200−3460, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) 1.18 (s, 9H, $C(CH_3)_3$), 1.19−1.79 (m, 17H, −adamantylethyl) 2.98−3.04 (m, 2H, CH_2-NH), 3.62 (br, 1H, N*H*), 3.89 (s, 2H, CH_2COO), 4.15 (t, 2H, OCH_2), 4.80−4.92 (m, 1H, C*H*OH), 6.66 (s, 1H, furan-*H*), 7.14−7.17 (m, 2H, Ar*H*), 7.40−7.45 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 28.4, 28.8, 31.5, 35.2, 36.8, 42.1, 46.2, 50.5, 61.3, 66.1, 103.0, 117.5, 119.8, 122.7, 124.7, 128.0, 153.3, 158.8, 170.9. Anal. ($C_{28}H_{39}NO_4$) C, H, N.

Methylthiomethyl [2-[1-Hydroxy-2-(*tert*-butylamino)-ethyl]benzofuran-7-yl]acetate (8h). The potassium salt of **8a** was prepared as follows: The solution of **8b** (1.20 g, 3.93 mmol) and KOH (0.22 g, 3.93 mmol) in ethanol−water (1:1, 100 mL) was refluxed for 10 h. After the ethanol was removed under reduced pressure, the aqueous layer was washed with methylene chloride (30 mL) and then concentrated to give the product in quantitative yield, which was used for next reaction without further purification. Potassium [2-[1-hydroxy-2-(*tert*-butylamino)ethyl]benzofuran-7-yl]acetate (1.00 g, 3.0 mmol), sodium iodide (0.12 g, 0.8 mmol) and 18-crown-6 (0.27 g, 1.0 mmol) were dried over phosphorus pentoxide under reduced pressure and then suspended in dried benzene (100 mL). Chloromethylmethyl sulfide (0.75 g, 7.7 mmol) was then added to the suspension, and the reaction mixture was refluxed for 15 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and washed with saturated aqueous sodium carbonate solution (3 × 80 mL) followed by brine (2 × 80 mL). The organic layer was dried and evaporated to give a crude oil product, which was purified by column chromatography on silica gel (CH_2Cl_2:MeOH:NH_4OH, 120:10:1) to afford 0.45 g (46%) of **8h** as a yellow oil: IR (KBr) 3200−3460, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) 1.26 (s, 9H, $C(CH_3)_3$), 2.17 (s, 3H, SCH_3) 3.12−3.18 (m, 2H, CH_2NH), 3.96 (s, 1H, CH_2-COO), 4.20 (br, 1H, NH) 5.11−5.13 (m, 1H, C*H*OH) 6.73 (s, 1H, furan-*H*), 7.17−7.20 (m, 2H, Ar*H*), 7.44−7.48 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$) 15.2, 28.1, 35.2, 46.2, 53.0, 65.3, 68.6, 103.8, 117.2, 120.3, 123.0, 125.0, 128.0, 153.3, 157.6, 170.5. Anal. ($C_{18}H_{25}NO_4S$) C, H, N, S.

Stability in Aqueous Buffer Solutions. Isotonic phosphate buffer solutions (0.5 mM) of pH = 7.4 and 12 at 37 °C were used. Solutions of the bufuralol analogues were added to the buffered solutions to result an initial concentration of 120 μM. Samples (0.1 mL) were withdrawn at selected time intervals, diluted with cold methanol (0.9 mL), vortexed and placed in a freezer. The final sample concentration was 12 μM. Samples (**8a**−**8h**) were kept at 0 °C until analyzed by HPLC. The pseudo-first-order rate constant for hydrolysis of **8a**−**8h** was determined by linear regression from the plot of natural logarithm of the HPLC peak area versus time.

Metabolism and Stability in Biological Media. The stability of soft analogues was determined in freshly collected Sprague−Dawley male rat blood. The heparinized blood was used within 30 min. Compound solutions in methanol (0.1 mL) were mixed with blood (0.9 mL) at 37 °C. Samples (0.1 mL) were withdrawn at selected time intervals, mixed with cold methanol (0.9 mL), vortexed, and placed in a freezer. When all samples had been collected, they were centrifuged at 24 000 rpm for 3 min. The final sample concentration was 12 μM. The supernatant was analyzed for the compounds and their metabolite **8a** by HPLC as described earlier.

Animal Studies. Male Sprague−Dawley rats (Harlan Sprague Dawley Inc., Indianapolis, IN) (weight: 400−460 g) were anesthetized with Na-pentobarbital (50 mg/kg ∼ 0.1 mL/100 g) ip. Both jugular veins and the left carotid artery were isolated, and the latter was tied up cranially with a surgical silk (Ethicon 4-0, Ethicon Inc., Australia). A plastic catheter (Intracath 19GA, Becton Dickinson, Sandy, UT) containing 10% Na-heparin (Elkins-Sinn Inc., Cherry Hill, NJ) in normal saline (100 U/mL Na-heparin) was introduced into the artery and fixed with surgical silk. The catheter was connected to a pressure transducer (Ohmeda P23-XL, Ohmeda Medical Devices Division Inc., Madison, WI) filled with the same heparinized 0.9% NaCl solution to register beat-to-beat arterial pressure. Needle electrodes were inserted sc and together with the pressure transducer were joined to a Gould TA 2000 recorder (Gould Inc., Cleveland, OH). Leads II, aVF and intra-arterial blood pressure were monitored simultaneously throughout the experiments and recorded at certain intervals at 50 mm/s paper speed. Baseline heart rate and blood pressure parameters were recorded for 25 or 30 min, at every 5 min, before any drugs were given. Drug administrations were carried out as either bolus injections into the jugular veins or as infusions for 10 min through a plastic catheter (Terumo 24 GA *3/4″, Terumo Medical Corp., Elkton, MD) inserted into the jugular vein on either side. During the first series of experiments 50 μg/kg isoproterenol (Sigma, St. Louis, MO) was injected sc at −5 min. Heart rate and blood pressure were recorded at −5, −4 and −2 min. At 0 min the soft bufuralol analogues as free base forms dissolved in 10% DMSO (Fisher Scientific, Fair Lawn, NJ) in 30% hydroxypropyl-β-cyclodextrin (HPBCD) (Pharmos Inc., Alachua, FL) or bufuralol (α-(*tert*-butylamino)methyl-7-ethyl-2-benzofuranmethanol; Roche Products Ltd., Welwyn Garden City, U.K.) dissolved in the same vehicle or vehicle (i.e. 10% DMSO in 30% HPBCD) was injected into the jugular vein as bolus injections. Heart rate and blood pressure were registered at 1, 3, 5, 10, 15, 20, 25, 30, 40, 45, 50, 60, 70, 80, 90, 105 and 120 min. The percent changes in heart rate were calculated as follows: % change in HR = $(HR_t - HR_{-2})/HR_{-2} \times 100$, relative to the maximal isoproterenol-induced heart rate increase registered at −2 min, where t = 0, 1, 3, ... 120 min. During the second series of experiments the methyl (**8b**), ethyl (**8c**), isopropyl (**8d**), and *tert*-butyl (**8e**) analogues of bufuralol were converted to their corresponding HCl salt forms and were dissolved in 0.9% NaCl. Baseline heart rate and blood pressure values were registered again at every 5 min for 30 min. At 0 min the four bufuralol analogues, or esmolol-HCl diluted with 0.9% NaCl (Brevibloc, 2.5 g/10 mL, Ohmeda Pharmaceutical Products Division Inc., Liberty Corner, NJ), were infused into the jugular vein for 10 min with a syringe pump (Sage Instruments, model 341B, Orion Res. Inc., Boston, MA). The doses were 2 μmol/kg/min for **8b**, **8d**, and **8e**, 4 μmol/kg/min for **8c**, and 20 μmol/kg/min for esmolol. The percent changes in heart rate and blood pressure values (mean arterial pressure: MAP) were calculated relative to the average baseline values recorded between −30 and 0 min, i.e.: % change in HR = $(HR_t - HR_{av})/HR_{av} \times 100$, or % change in MAP = $(MAP_t - MAP_{av})/MAP_{av} \times 100$, where t = 1, 3, ... 120 min. Each compound and vehicle were administered to at least three different animals, and the average and the standard deviation of all heart rate and blood pressure data were calculated. All data were subjected to cluster analysis and to multivariate analysis of variance for repeated measures (GLM Repeated Measures of ANOVA) with the SPSS for Windows 7.5 program. Statistically significant difference between the effects of the different compounds was accepted at $p < 0.05$. In Figures 2−4, the average values are represented without error bars.

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