Investigation of (Oxodioxolenyl)methyl Carbamates as Nonchiral Bioreversible Prodrug Moieties for Chiral Amines

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The preparation of (oxodioxolenyl)methyl carbamates and their evaluation as novel nonchiral prodrug moieties for chiral primary and secondary amino functional drugs are described. 4-(Carbamoylmethyl)-2-oxo-1,3-dioxolene derivatives of 3,4-dimethoxyphenethylamine with 5-methyl, 5-phenyl, and 5-anisyl substitution (**5a**, **5b**, and **5c**) on the dioxolenone ring were prepared as model amine prodrugs by a one step process involving displacement of *p*-nitrophenol from appropriately substituted (oxodioxolenyl)methyl *p*-nitrophenyl carbonates. Plasma enzyme-catalyzed dioxolenone ring opening of these carbamates led to a cascade reaction resulting in the rapid and quantitative regeneration of the parent amine drug. Aryl substitution did not significantly alter the hydrolysis rates of these dioxolenone carbamates in buffers at pH 1 and 7.4 or in rat plasma, although the hydrolysis rates of 5-phenyl- (**1b**) and 5-anisyl-4-methyl-1,3-dioxol-4-en-2-one (**1c**) in pH 7.4 phosphate buffer were 2−3-fold faster than that of the 5-methyl-substituted analog (**1a**). Application of this prodrug strategy to the chiral fibrinogen receptor antagonist L-734,217 resulted in a prodrug that gave quantitative reconversion in rat and dog plasma *in vitro* and oral bioavailability of 23 ± 6% in dogs for the parent drug.

Among the many prodrug approaches[1,2] available for primary and secondary amine drugs, (acyloxy)alkyl carbamylation[1,3,4] is probably one of the most versatile.[5] The attributes that make these modified carbamates attractive are their ease of preparation, chemical stability, fast breakdown triggered by enzyme-catalyzed ester hydrolysis, and non-ionizability at physiological pH that make them more lipid soluble. The ease of variation of the acyl portion of the prodrug group allows great latitude in introducing changes in lipophilicity or aqueous solubility[6] as desired. Since the (acyloxy)alkyl carbamates are double esters of acetals, which are often derived from formaldehyde or acetaldehyde, these aldehydes are formed as side products[7] on hydrolysis. As the toxicity of formaldehyde generated during breakdown of (acyloxy)methyl esters in the body is a topic of controversy, the use of acetaldehyde-derived (acyloxy)-ethyl carbamate prodrugs is often preferred. However, (acyloxy)ethyl carbamylation of chiral amines results in the formation of a pair of diastereoisomeric prodrugs, because of the additional chiral center in the pro moiety. The susceptibility of such diastereomeric pairs to enzyme-catalyzed hydrolysis could be different, because of the chiral nature of the enzymes. We have observed[8] that such diastereomeric pairs formed from some chiral amino drugs can undergo hydrolytic breakdown at widely different rates in plasma. Consequently, we have been interested in a prodrug strategy for amines that would confer neutrality at physiological pH and bioreversibility in plasma, without introducing additional chiral centers.

The (5-methyl-2-oxo-1,3-dioxol-4-enyl)methyl group has been used to derivatize carboxylic acid functions in biologically active β-lactams[9,10] and amino acids.[11] This group has also been used as an amine pro moiety for the piperazino group of norfloxacin.[12] A tertiary amine derivative of norfloxacin was generated by bromide displacement from (bromomethyl)dioxolenone by the secondary piperazino nitrogen. However, the amine preferentially attacked the vinylene carbonate carbon, resulting in ring-opened products[12] when the substrates were dioxolenones carrying a secondary bromide.

Although alkaline hydrolysis of the vinylene carbonate ring in such esters and amines would generate diacetyl and carbon dioxide, the *in vivo* hydrolysis mechanism has been reported[13] to be different from that *in vitro*. No diketones were detected in a study of the metabolites of (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esters of ampicillin.[13] Instead, hydrolysis by serum or tissue esterases has been reported[7,14,15] to produce nontoxic acetoin and 2,3-butanediol. Diacetyl, acetoin, and 2,3-butanediol have shown no mutagenicity in bacteria, and diacetyl had no micronucleus-inducing capacity in mouse bone marrow erythrocytes.[16] Besides producing nontoxic breakdown products, this pro group has the advantage that the trigger site is devoid of a chiral center.

A novel approach to applying the (oxodioxolenyl)-methyl prodrug strategy to amines would be to form the corresponding carbamate derivatives, which would have the advantages of (acyloxy)alkyl carbamylation mentioned above without introducing a chiral center in the pro moiety. These (oxodioxolenyl)methyl carbamates are expected to break down *in vitro* as shown in Scheme 1 with the generation of two molecules of carbon dioxide and one molecule of an α-diketone with the regeneration of the parent amine. Since the breakdown of the dioxolenone ring by amino group attack on the reactive

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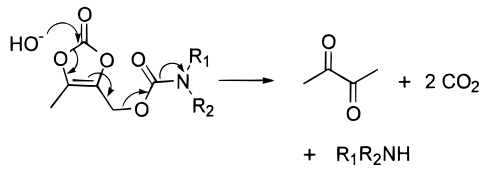
Scheme 1

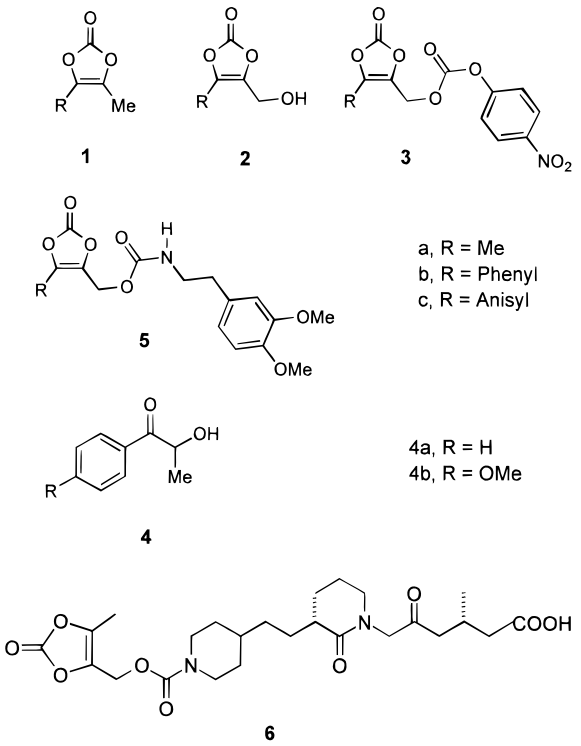


vinylene carbonate functionality would be precluded in the carbamate, this approach would be potentially useful for primary amines as well. In this work,[17] we report the synthesis of methyl-, phenyl-, and anisyl-substituted (oxodioxolenyl)methyl carbamate prodrugs and a study of their kinetic properties in buffers and in plasma. These compounds were synthesized to evaluate the effect of aromatic substitution on the rate of dioxolenone ring opening, which is presumed to be the rate-determining step in the regeneration of the amine drug. The results of the application of this prodrug strategy to improve the bioavailability of a chiral zwitterionic fibrinogen receptor antagonist are also reported.

Chemistry

4-(Hydroxymethyl)-5-methyldioxol-4-en-2-one (**2a)** was prepared from 4,5-dimethyl-1,3-dioxolenone[9] (**1a**) by bromination with *N*-bromosuccinimide followed by displacement of bromide by formate[18] and acid-catalyzed hydrolysis, according to published procedures.[19] Methylphenylvinylene carbonate[20,21] (**1b**) was prepared by two different methods. In the first approach, 1-hydroxy-1-phenylpropan-2-one, obtained by hydration of the acetylene adduct of benzaldehyde, was carbonylated with phosgene and *N*,*N*-dimethylaniline. The product distribution in the chloroformylation reaction of this benzylic alcohol was temperature dependant. Above 0−5 °C, 1-phenyl-1-chloropropan-2-one was the predominant product presumably because of a S_Ni reaction of the intermediate benzylic chloroformate. However, the chloroformate was stable when the reaction was carried out below 5 °C. Isolation of the chloroformate followed by pyrolysis at 170 °C resulted in its cyclization to the vinylene carbonate **1b** in moderate yields. In the similar chloroformylation reaction of 1-hydroxy-1-anisylpropan-2-one with phosgene and *N*,*N*-dimethylaniline, the intermediate benzylic chloroformate rearranged quickly, even at temperatures as low as −25 °C, giving exclusively the benzylic chloride, presumably because of the increased stabilization of the *p*-anisyl cation. At temperatures below −25 °C the chloroformylation reaction was too slow.

In an alternate method for the preparation of **1b**, α-hydroxypropiophenone[22] (**4a**) was prepared by bromide displacement in α-bromopropiophenone by formate using triethylammonium formate,[18] followed by acid-catalyzed ester hydrolysis. The α-hydroxy ketone **4a** was chloroformylated with phosgene in the presence of 2 equiv of *N*,*N*-dimethylaniline. The initially formed α-keto chloroformate cyclized *in situ*, in refluxing 1,1-dichloroethane to the required vinylene carbonate **1b**. Anisylmethylvinylene carbonate (**1c**) was also prepared by this method, starting from 2-hydroxy-1-*p*-anisylpropan-1-one[22] (**4b)**. In this case, the anisyl-substituted α-keto chloroformate cyclized readily at room temperature. Allylic bromination with *N*-bromosuccinimide was used to functionalize the methyl groups in both anisylmethyl- and phenylmethylvinylene carbonates **1b** and **1c**. Displacement of bromide by formate,[18] followed by mild acid-catalyzed hydrolysis of the formate esters, resulted in the formation of the allylic alcohols **2b** and **2c**. The 5-substituted (hydroxymethyl)dioxolenones **2a**, **2b**, and **2c** were converted to the corresponding *p*-nitrophenyl carbonates **3a**, **3b**, and **3c** by reaction with *p*-nitrophenyl chloroformate. These carbonates could be readily purified by chromatography or crystallization and were stable on storage in a desiccator for several weeks at room temperature.



The methyl-, phenyl-, and anisyl-substituted (oxodioxolenyl)methyl carbamates of primary and secondary amines were prepared by displacement of *p*-nitrophenol from the corresponding (oxodioxolenyl)methyl *p*-nitrophenyl carbonates **3a**, **3b**, and **3c** by the amines. Reaction of an equimolar mixture of 3,4-dimethoxyphenethylamine, which was chosen as a model amino compound for the present work, and the *p*-nitrophenyl carbonates in dimethylformamide at room temperature resulted in the formation of the corresponding carbamates **5a**, **5b**, and **5c** in quantitative yields. Products arising from the attack of the amine on the vinylene carbonate carbonyl group were not detected in this reaction. However, attempts to prepare the carbamate **5a** by the reaction of 3,4-dimethoxyphenethylamine with 4-(chloroformylmethyl)-5-methyldioxol-4-en-2-one, derived from the corresponding hydroxymethyl derivative and bis(trichloromethyl) carbonate, resulted in poor yields. The major product of the reaction was bis[4-(5-methyl-2-oxo-1,3-dioxolenyl)] carbonate.

Results and Discussion

Since the rate-determining step in the breakdown of the (oxodioxolenyl)methyl carbamates is the vinylene carbonate ring opening,[7] the stability of methyl-, phenyl-, and anisylmethylvinylene carbonates (**1a**, **1b**, and **1c**) in pH 7.4 phosphate buffer at 37 °C was investi-

Table 1. First-Order Rate Data for the Hydrolysis of 5-Substituted 4-[[(3′,4′-Dimethoxyphenethyl)amino]-carbonyl]methyl]-1,3-dioxol-4-en-2-one at 37 °C

hydrolysis medium	half-life (min)		
	5a	**5b**	**5c**
0.05 M phosphate buffer pH 7.4	258	134	207
0.1 M hydrochloric acid pH 1.0	>3000[a]	3550	3180
rat plasma	11	2	2
dog plasma		11	14

[a] No detectable hydrolysis after 48 h.

gated. The decrease in the absorbance of the observed UV maxima at 210, 256, and 261 nm was used for the measurement of the rates of breakdown of **1a**, **1b**, and **1c**, respectively. The change in absorbance observed was consistent with pseudo-first-order kinetics for 4−5 half-lives. The half-life of dimethylvinylene carbonate (**1a**) was 210 min, whereas the half-lives of phenyl- (**1b**) and anisyl- (**1c**) methylvinylene carbonates were 49 and 60 min, respectively. The results indicate that aryl substitution on the dioxolenone ring has a destabilizing influence. The increased lability of the aryl-substituted vinylene carbonates could be due to increased electron deficiency of the carbonyl group in these styrene type systems as a result of conjugation of the double bond with the aromatic ring.

The hydrolysis half-lives of the (oxodioxolenyl)methyl carbamates **5a**, **5b**, and **5c** at the physiologically relevant conditions of pH 1 and pH 7.4 at 37 °C are shown in Table 1. The hydrolysis kinetics at pH 7.4 were by measured by following the disappearance of the prodrug or the appearance of 3,4-dimethoxyphenethylamine in 0.05 M phosphate buffer at 37 °C for 4−5 half-lives. In the case of **5a**, where both the disappearance of the prodrug and the formation of 3,4-dimethoxyphenethylamine were measured, the half-life obtained for the disappearance was 252 min and that found for the formation of the hydrolysis product was 263 min. There was greater than 90% recovery of 3,4-dimethoxyphenethylamine from the prodrug. The aryl-substituted carbamates **5b** and **5c** hydrolyzed 2−3-fold slower compared to the corresponding vinylene carbonate precursors **1b** and **1c**. The difference in the half-lives between the carbamate and the vinylene carbonate precursor was not significant in the case of the methyl-substituted analog **5a**. The half-life of the carbamate **5a** was similar to the 220 ± 138 min half-life reported[11] for the (5-methyl-2-oxo-1,3-dioxol-4-en-4-yl)methyl ester of methyldopa in pH 7.4 phosphate buffer at 37 °C. The similarity in the hydrolysis half-lives in the ester and carbamate is consistent with the vinylene carbonate ring opening being the rate-determining initial step. Substitution of a *tert*-butyl group in the 5-position of the (oxodioxolenyl)methyl group in the methyldopa ester[11] resulted in an increase in the hydrolysis half-life to 696 ± 246 min from the 220 ± 138 min half-life found for the methyl-substituted analog. However, the effect of 5-phenyl and 5-anisyl substitution in the carbamates on the hydrolysis rates at pH 7.4 was insignificant in the present study.

The (5-methyl-2-oxo-1,3-dioxol-4-en-4-yl)methyl carbamate derivative **6** of the of the non-peptide fibrinogen receptor antagonist[23,24] [[3(*R*)-[2-(piperidin-4-yl)ethyl]-2-oxopiperidinyl]acetyl]-3(*R*)-methyl-*β*-alanine[25] (L-734,217) was prepared with a view to reversibly change its charge state at pH 7.4 in order to improve its bioavailability. This modification resulted in an increase in its apparent partition coefficient between 1-octanol and 0.01 M hydrochloric acid or pH 7.4 (0.02 M) phosphate buffer. The observed log *P* value for L-734,217 at both pH 1 and pH 7.4 was −3, whereas that for the prodrug was 1.3 at pH 2 and −1.3 at pH 7.4. The increase in the partition coefficient was accompanied by a decrease in the solubility of the prodrug to approximately 15 and 5 mg/mL, respectively, in pH 7.4 buffer and water at 25 °C. The zwitterionic L-734,217 had an aqueous solubility of >100 mg/mL. The intrinsic activity (IC_{50}) of **6** in human gel-filtered platelet aggregation assay[25,26] was 23 μM, whereas that for L-734,217 was 23 nM. The hydrolysis half-lives of the prodrug in different hydrolytic media are presented in Table 2. There was greater than 90% regeneration of L-734, 217 from the prodrug in rat and dog plasma. The hydrolysis reactions followed pseudo-first-order kinetics for 4−5 half-lives. This is in contrast to rat plasma hydrolysis of pivaloxyethyl carbamate[8] of L-734,217, which because of the additional chiral center in the pro moiety was an inseparable mixture of a pair of diastereomers and showed 50% hydrolysis in rat plasma within the first 2 min, but very slow hydrolysis afterward.

Table 2. Hydrolysis Half-Lives of (5-Methyl-2-oxo-1,3-dioxol-4-en-4-yl)-methyl Carbamate Derivative **6** at 37 °C

hydrolysis medium	half-life (min)
pH 7.4 phosphate buffer (0.02 M)	660
pH 10 carbonate buffer (0.02 M)	9
pH 1 hydrochloric acid (0.1 M)	>3000[a]
Hank's balanced salt solution	110
rat plasma at 25 °C	25
dog plasma	26

[a] No detectable hydrolysis after 48 h.

Bioavailability Evaluation

A bioavailability screening of the prodrug **6** was carried out on the basis of pharmacodynamic response[25,26] from the ratio of oral activity to intravenous activity (po/iv). The compound was given at doses of 0.1 mg/kg iv bolus in normal saline and 1 mg/kg orally in sterile water to conscious mongrel dogs, and blood samples were withdrawn at selected time intervals for measurement of inhibition of platelet aggregation response to ADP and collagen *ex vivo*. The effects of the administration of **6** expressed as percent inhibition of aggregation using the extent of ADP-induced aggregation and the rate of collagen-induced aggregation, at selected time points, are depicted in Figure 1. The results of the iv experiment show that the prodrug is converted to L-734,217 *in vivo*. The activity of the prodrug following iv administration at 0.1 mg/kg was comparable to that observed with L-734,217 at 0.03 mg/kg. At these doses, platelet aggregation was 100% inhibited immediately after iv dosing, and the platelet function returned to within 20% of baseline in 3−4 h. The minimum iv dose of **6** required to produce a response equivalent to that produced by 0.03 mg/kg iv of L-734,217 was not determined. The oral administration resulted in an inhibition of platelet aggregation response to ADP that was equal to or greater than 90% from 60 to 300 min and remained at 65% at 480 min after dosing. The inhibition of aggregation in response to

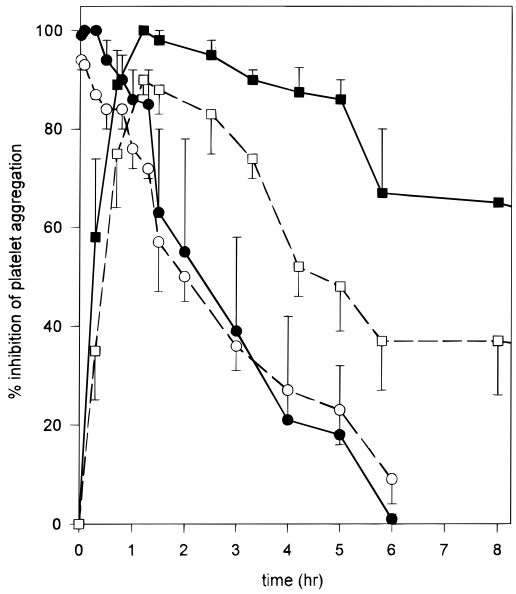


Figure 1. Effect of **6** on *ex vivo* platelet aggregation, expressed as percent inhibition over time in response to 10 μM ADP + 1 μM epinephrine (extent of inhibition): (●) 0.1 mg/kg iv bolus; (■) 1 mg/kg oral in dogs, or in response to 10 μg/mL collagen + 1 μM epinephrine (rate of inhibition); (○) 0.1 mg/kg iv bolus; (□) 1 mg/kg oral in dogs ($n = 3$). Data are plotted as mean ± SEM.

collagen was 90−50% for the duration of 60−300 min post oral administration. The oral bioavailability estimated from the ratio of the area under the curve for oral activity to that of the dose corrected intravenous activity based on inhibition of platelet aggregation *ex vivo* was 23 ± 6% ($n = 3$). This oral bioavailability was not substantially greater than that seen with L-734,-217 in similar studies in dogs. The parent drug is not well absorbed in other animal species such as rats and monkeys.

Conclusions. Conversion of primary and secondary amine drugs to (oxodioxolenyl)methyl carbamates, which do not carry a chiral center in the pro-moiety, is a versatile alternative to (acyloxy)alkyl carbamylation for prodrug modification, especially for chiral amines. The (oxodioxolenyl)methyl carbamates are cleaved rapidly and quantitatively in rat and dog plasma *in vitro* to regenerate the parent amines. The utility of this strategy is exemplified by its application to the chiral fibrinogen receptor antagonist L-734,217. The prodrug **6** gave quantitative reconversion in rat and dog plasma *in vitro* unlike the corresponding pivaloxyethyl carbamate with an additional chiral center in the pro moiety that regenerated only 50% of the parent drug rapidly. Results of the oral bioavailability studies in dogs, which showed 23 ± 6% bioavailability, confirm the usefulness of this approach to drug delivery. A few of the probable reasons for this prodrug not achieving a greater increase in bioavailability are the following: (a) Optimum partition coefficient and solubility properties were not realized in the prodrug. (b) Partial hydrolysis of the prodrug could have occurred in the intestinal lumen prior to absorption. (c) The increase in molecular weight on prodrug modification may have slowed the rate of absorption.

Although aromatic substitution in the vinylene carbonates **1b** and **1c** resulted in 3−4-fold decreases in hydrolysis half-lives, such changes were not apparent on aryl substitution in the model carbamate prodrugs **5b** and **5c**. In contrast, there was a large increase in hydrolytic half-life when the substitution in the 5-position of the (oxodioxolenyl)methyl esters[11] was changed from methyl to *tert*-butyl. The favorable hydrolysis rates of the phenyl- and anisyl-substituted (oxodioxolenyl)methyl carbamates in buffers and plasma suggest their usefulness as alternative pro group candidates.

Experimental Section

Chemistry. ^{1}H and ^{13}C NMR spectra were run on a Bruker AC200 instrument using tetramethylsilane as internal reference for protons and $CDCl_3$ as internal reference for carbons. IR spectra were taken on a Mattson Galaxy 5000 FTIR spectrometer. Ultraviolet spectral measurements were performed on a Shimadzu UV-2101PC spectrophotometer, equipped with a temperature-controlled sample compartment, using quartz cells of one centimeter path length. The pH measurements were made at room temperature on a Fisher Accumet Model 815MP pH meter using gel-filled Ag/AgCl combination electrodes. Melting points were determined on an Electrothermal 9200 capillary melting point apparatus and are reported uncorrected. High-performance liquid chromatographic measurements (HPLC) were performed on a system consisting of a SSI 300 pump equipped with a SSI 210 guardian and pulse damper, an ABI Analytical Spectraflow 757 variable-wavelength UV detector, and a Perkin-Elmer ISS 200 autoinjector or a Rheodyne 7121 manual valve with a 20 μL sample loop. Microanalysis were performed by Oneida Research Services, Whitesboro, NY.

1-(*p*-Methoxyphenyl)-2-hydroxypropan-1-one (4b).[22] To an ice-cold solution of formic acid (9.2 g, 0.2 mol) in acetonitrile (30 mL) was added a solution of triethylamine (20.2 g, 0.2 mol) in acetonitrile (20 mL) with stirring. α-Bromo-*p*-anisophenone (39 g, 0.16 mol) (prepared by bromination of *p*-anisophenone in acetic acid) dissolved in acetonitrile (50 mL) was added to the above solution of triethylammonium formate, and the reaction mixture was stirred at room temperature for 16 h. The triethylammonium bromide formed was filtered off, and the solid was washed with ice-cold acetonitrile. The residue obtained on evaporation of the filtrate was taken up in ethyl acetate and was washed with water, aqueous sodium bicarbonate, and brine. The organic layer, after drying over sodium sulfate, was evaporated to furnish 1-*p*-anisyl-2-(formyloxy)-propan-1-one as a light yellow oil (32.9 g, 99%): ^{1}H NMR ($CDCl_3$) δ 1.57 (d, $J = 7$ Hz, 3 H, Me), 3.88 (s, 3 H, OMe), 6.09 (q, $J = 7$ Hz, 2 H, MeC*H*), 2.96 (d, $J = 5$ Hz, 2 H, Ar*H*), 7.94 (d, $J = 5$ Hz, 2 H, Ar*H*), 8.13 (s, 1 H, formyl *H*).

The above formate ester was dissolved in methanol (150 mL), and concentrated hydrochloric acid (0.5 mL) was added. After the reaction mixture was stirred at room temperature for 4 h, the methanol was evaporated off. The residue was taken up in ethyl acetate and washed free of acid. Evaporation of solvent gave a yellow liquid (26.76 g, 94%), which was vacuum distilled to obtain the pure α-hydroxy ketone (21.4 g, 74%): bp 100 °C/0.2 mm; ^{1}H NMR ($CDCl_3$) δ 1.44 (d, $J = 7$ Hz, 3 H, Me), 1.85 (s, br, 1 H, O*H*), 3.89 (s, 1 H, OMe), 5.11 (m, 1 H, MeC*H*), 6.97 (d, 2 H, Ar*H*), 7.92 (d, 2 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 22.57, 55.5, 68.81, 114.02, 125.98, 130.97, 164.11, 200.62; IR (film) 3461, 1674 (C═O),1600, 1261 cm^{-1}. Anal. ($C_{10}H_{12}O_3$) C, H.

1-Phenyl-2-(formyloxy)propanone: ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3 H, Me), 6.12 (q, 1 H, MeC*H*), 7.45−7.65 (m, 3 H, Ar*H*), 7.92−7.97 (m, 2 H, Ar*H*), 8.13 (s, 1 H, formyl H); ^{13}C NMR ($CDCl_3$) δ 17.16, 70.98, 128.45, 128.83, 133.74, 134.11, 159.99 (formate C═O), 195.8 (C═O); IR (film) 1726, 1698 cm^{-1}.

1-Phenyl-2-hydroxy-1-propanone (4a):[22] bp 72 °C/0.4 mm; ^{1}H NMR ($CDCl_3$) δ 1.45 (d, $J = 7$ Hz, 3 H, Me), 3.86 (d, $J = 6.3$ Hz, 1 H, O*H*), 5.173 (m, 1 H, MeC*H*), 7.45−7.62 (m, 3 H, Ar*H*), 7.90−7.95 (m, 2 H, Ar*H*); IR (film) 3462, 1683 cm^{-1}. Anal. ($C_9H_{10}O_2$) C, H.

4-(*p*-Methoxyphenyl)-5-methyl-1,3-dioxol-4-en-2-one (1c). To a cold solution (−5 °C) of α-hydroxyanisphenone (20.6 g, 114 mmol) in ethylene dichloride (100 mL) was added

triphosgene (13.3 g, 44.8 mmol). *N*,*N*-Dimethylaniline (32 g, 264 mmol) dissolved in ethylenedichloride (50 mL) was added dropwise in the course of 1 h to the reaction mixture, which was maintained at −5 to 5 °C. The reaction mixture was allowed to warm to room temperature and left to stir overnight. It was washed with water, 1 N hydrochloric acid, water, and brine. The organic layer was dried over sodium sulfate and evaporated to furnish a light green solid, which was crystallized from hexane to obtain the pure dioxolenone (18.56 g, 78.7%) as colorless crystals: mp 96−97 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H, Me), 3.83 (s, 3 H, OMe), 6.96 (d, J = 4.6 Hz, Ar*H*), 7.38 (d, J = 4.6 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 10.45, 55.3, 114.41, 117.96, 126.69, 133.61, 137.35, 152.29 (vinylene C=O), 160.06; IR (KBr) 1805 (C=O), 1517, 1260 cm^{-1}; EIMS *m*/*e* 206 (M^+), 134, 119. Anal. ($C_{11}H_{10}O_4$) C, H.

4-Phenyl-5-methyl-1,3-dioxol-4-en-2-one (1b):[20,21] mp 84−85 °C (CCl_4); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3 H, Me), 7.39−7.47 (m, 5 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 10.7, 125.04, 125.53, 128.93, 128.97, 135.04, 137.37, 152.14 (vinylene C=O); IR (KBr) 1814 (C=O), 1245, 1199 cm^{-1}; EIMS *m*/*e* 176, 104, 78.

4-(Bromomethyl)-5-(*p*-methoxyphenyl)-1,3-dioxol-4-en-2-one. *N*-Bromosuccinimide (9.5 g, 53.3 mmol) and benzoyl peroxide (500 mg) were added to a solution of **1c** (10 g, 48.5 mmol) in freshly distilled carbon tetrachloride (250 mL). The reaction mixture was refluxed under an argon atmosphere for 16 h. It was cooled in an ice bath and filtered. The filtrate was washed with water and brine and dried over sodium sulfate. The residue obtained on evaporation (14.4 g) was crystallized from carbon tetrachloride to furnish the pure bromomethyl derivative (8.34 g, 60%) as a light yellow solid. This compound had a tendency to decompose on standing at room temperature: ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3 H, Me), 4.43 (s, 2 H, CH_2), 7.03 (d, J = 9 Hz, Ar*H*), 7.47 (d, J = 9 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 19.94 (CH_2Br), 55.44, 114.8, 116.49, 127.62, 128.42, 132.74, 139.93, 150.89 (C=O), 161.20; IR (KBr) 1821 (C=O), 1691, 1607, 1252 cm^{-1}; EIMS *m*/*e* 286, 285 (M^+), 205 (M^+ − Br).

4-(Bromomethyl)-5-phenyl-1,3-dioxol-4-en-2-one:[13] mp 96−97 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 4.44 (s, 2 H, CH_2Br), 7.47−7.55 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.45 (CH_2Br), 124.18, 125.91, 129.32, 130.42, 134.11, 139.69, 150.72 (C=O); IR (KBr) 1823 (C=O); EIMS *m*/*e* 254, 256 (M^+), 175, 103, 104, 77.

4-(Hydroxymethyl)-5-phenyl-1,3-dioxol-4-en-2-one (2b). To an ice-cold solution of the above 4-(bromomethyl)-5-phenyl-1,3-dioxol-4-en-2-one (6.49 g, 25.4 mmol) and formic acid (2.07 g, 44 mol) in acetonitrile (20 mL) was added dropwise triethylamine (4.13 g, 41 mmol) in the course of 10 min. After 20 min at ice bath temperature, the reaction mixture was stirred at room temperature for 90 min. It was diluted with water to about 150 mL and extracted with ethyl acetate. The organic extract was washed successively with water, aqueous sodium bicarbonate, water, and brine and dried over sodium sulfate. Evaporation of the solvent gave an oily residue (5.29 g, 94.6%); ^{1}H NMR ($CDCl_3$) δ 5.20 (s, 2 H, CH_2), 7.47−7.59 (m, 5 H, Ar*H*), 8.17 (s, 1 H, formyl *H*).

The above formyl ester (5.29 g, 24 mmol) was dissolved in methanol (50 mL) and diluted with water (15 mL). Concentrated hydrochloric acid (0.5 mL) was added to the reaction mixture and stirred at room temperature for 2 h. Most of the methanol was evaporated off, and the residue taken up in ethyl acetate was washed with water, aqueous sodium bicarbonate, water, and brine. The organic layer on drying over sodium sulfate and evaporation furnished a solid (4.59 g, 99%) which was crystallized from chloroform−hexane to give the pure **2b** (4.26 g, 92%): mp 97−98 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (t, J = 4.7 Hz, 1 H, O*H*), 4.66 (d, J = 4.7 Hz, 2 H, CH_2), 7.45−7.58 (m, 5 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 54.12 (CH_2), 124.45, 125.93, 129.08, 131.1, 137.08, 140.04, 151.97 (vinylene C=O); EIMS *m*/*e* 192 (M^+), 118, 105, 91, 77. Anal. ($C_{10}H_8O_4$) C, H.

4-(Hydroxymethyl)-5-(*p*-methoxyphenyl)-1,3-dioxol-4-en-2-one (2c): mp 100−101 °C (from chloroform−hexane); ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H, OMe), 4.64 (s, 2 H, CH_2), 6.98 (d, J = 9 Hz, 2 H, Ar*H*), 7.48 (d, J = 9 Hz, 2 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 54.26 (CH_2), 55.41, 114.61, 116.92, 127.65, 135.73, 140.21, 151.95 (vinylene C=O), 160.99; IR (KBr) 3474, 1811, 1699, 1609, 1518, 1272 cm^{-1}; EIMS *m*/*e* 222 (M^+), 148, 135, 121. Anal. ($C_{11}H_{10}O_5$) C, H.

(5-Methyl-2-oxo-1,3-dioxol-4-en-4-yl)methyl *p*-Nitrophenyl Carbonate (3a). 4-(Hydroxymethyl)-5-methyl-1,3-dioxolenone[18] (5.59 g, 43 mmol) and pyridine (3.74 g, 47 mmol) were dissolved in chloroform (50 mL) and cooled in an ice bath. 4-Nitrophenyl chloroformate (9.46 g, 47 mmol) dissolved in chloroform (50 mL) was added dropwise to the above solution. After the reaction mixture was stirred for 16 h at room temperature, it was cooled in ice and was washed successively with ice-cold 1% aqueous sodium hydroxide, 1 N hydrochloric acid, water, and brine. The organic layer was dried over sodium sulfate and evaporated to obtain a solid (11.2 g), which was crystallized from chloroform−hexane to furnish the pure 4-nitrophenyl carbonate **3a** (9.11 g, 81%): mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3 H, Me), 5.05 (s, 2 H, CH_2), 7.41 (d, 2 H, Ar*H*), 8.3 (d, 2 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 9.43, 58.07 (CH_2), 121.69, 125.35, 132.15, 141.42, 145.57, 151.66 (vinylene C=O), 152.19, 155.05 (C=O); IR (KBr) 1811 (C=O), 1779 (C=O), 1525, 1247, 1207 cm^{-1}. Anal. ($C_{12}H_9NO_8$) C, H, N.

(5-Phenyl-2-oxo-1,3-dioxol-4-en-4-yl)methyl *p*-nitrophenyl carbonate (3b): mp 157−158 °C (from benzene−hexane); ^{1}H NMR ($CDCl_3$) δ 5.31 (s, 2 H, CH_2), 7.4−7.58 (m, 7 H, Ar*H*), 8.30 (d, J = 9 Hz, 2 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 59.43 (CH_2), 121.68, 123.83, 125.41, 126.26, 129.35, 130.91, 142.75, 145.74, 150.89 (vinylene C=O), 152.15, 155.15 (C=O); IR (KBr) 1815 (C=O), 1781 (C=O), 1519, 1242, 1216 cm^{-1}; EIMS *m*/*e* 357 (M^+), 175. Anal. ($C_{17}H_{11}NO_8$) C, H, N.

(5-(*p*-Methoxyphenyl)-2-oxo-1,3-dioxol-4-en-4-yl)-methyl *p*-nitrophenyl carbonate (3c): mp 129−130 °C (from chloroform−hexane); ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3 H, OMe), 5.29 (s, 2 H, CH_2), 7.01 (d, J = 8.8 Hz, 2 H, anisyl *H*), 7.42 (d, J = 9.1 Hz, 2 H, Ar*H*), 7.54 (d, J = 8.8 Hz, anisyl *H*), 8.31 (d, J = 9.1 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 55.45, 59.6 (CH_2), 114.83, 116.05, 121.68, 125.37, 127.93, 130.14, 142.92, 145.69, 151.05 (vinylene C=O), 152.16, 155.17 (C=O), 161.57; IR (KBr) 1826 (C=O), 1771 (C=O), 1616, 1521, 1252, 1213 cm^{-1}; EIMS *m*/*e* 387 (M^+), 343, 300, 258. Anal ($C_{18}H_{13}NO_9$) C, H, N.

4-[[(3′,4′-Dimethoxyphenethyl)carbamoyl]methyl]-5-phenyl-1,3-dioxol-4-en-2-one (5b). A solution of 3,4-dimethoxyphenethylamine (0.905 g, 5 mmol) and (5-phenyl-2-oxo-1,3-dioxol-4-en-4-yl)methyl *p*-nitrophenyl carbonate (**3b**) (1.79 g, 5 mmol) in dimethylformamide (10 mL) was stirred at room temperature for 16 h. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate. The organic extract was washed successively with water, 1 N hydrochloric acid, ice-cold 2% aqueous sodium carbonate, water, and brine. The extract was dried over sodium sulfate and evaporated to obtain a light yellow foam (2.01 g), which was purified by preparative TLC using a Chromatotron on silica gel plates. Elution with ethyl acetate−hexane (35:65) gave the pure carbamate **5a** (1.47 g, 74%) as an oil which solidified on standing. An analytical sample was prepared by crystallization from chloroform−hexane: mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 2.78 (t, J = 7 Hz, 2 H, $ArCH_2$), 3.45−3.55 (m, 2 H, $NHCH_2$), 3.89 (s, 6 H, OMe), 4.86 (m, 1 H, NH), 5.14 (s, 2 H, CH_2), 6.73−6.86 (m, 3 H, Ar*H*), 7.48−7.53 (m, 3 H, Ar*H*), 7.61−7.66 (m, 2 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 35.49, 42.42, 55.5, 55.86, 55.91, 111.52, 111.98, 120.69, 124.28, 126.03, 129.13, 130.28, 130.83, 133.45, 141.13, 147.87, 149.15, 151.34 (vinylene C=O), 155.26 (C=O); IR (KBr) 3370 (NH), 1826 (C=O), 1718 (C=O), 1516, 1235 cm^{-1}; FABMS *m*/*e* 399 (M^+), 208, 175; HRMS calcd for $C_{21}H_{21}NO_7$ 399.1318, found 399.1317. Anal. ($C_{21}H_{21}NO_7$) C, H, N.

4-[[(3′,4′-Dimethoxyphenethyl)carbamoyl]methyl]-5-methyl-1,3-dioxol-4-en-2-one (5a): ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3 H, Me), 2.76 (t, J = 7 Hz, 2 H, $ArCH_2$), 3.42 (m, 2 H, $NHCH_2$), 3.86 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 4.8 (s, 2 H, CH_2), 4.97 (t, br, 1 H, NH), 6.7−6.83 (m, 3 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 9.18, 35.38, 42.25, 53.94 (vinylic CH_2), 55.71, 55.76, 111.19, 111.72, 120.56, 130.75, 133.91, 139.71, 147.6, 148.88, 152.15 (vinylene C=O), 155.26 (C=O); IR (film) 3368 (NH), 1818 (C=O), 1722 (C=O), 1519, 1267 cm^{-1}; EIMS *m*/*e* 337 (M^+), 207, 164, 151, 130. Anal. ($C_{16}H_{19}NO_7$) C, H, N.

4-[[(3′,4′-Dimethoxyphenethyl)carbamoyl]methyl]-5-(*p*-methoxyphenyl)-1,3-dioxol-4-en-2-one (5c): mp 109−

110 °C (chloroform−hexane); ^{1}H NMR ($CDCl_3$) δ 2.78 (t, J = 7 Hz, 2 H, $ArCH_2$), 3.46 (m, 2 H, $NHCH_2$), 3.85 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 4.9 (t, br, 1 H, NH), 5.07 (s, 2 H, CH_2), 6.70−6.79 (m, 3 H, Ar*H*), 6.98 (d, J = 9 Hz, 2 H, Ar*H*), 7.54 (d, J = 9 Hz, 2 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 35.51, 42.42, 55.38, 55.61 (vinylic CH_2), 55.86, 55.91, 111.53, 111.99, 114.64, 116.61, 127.71, 130.86, 132.12, 133, 141.31, 147.88, 149.16, 151.53 (vinylene C=O), 155.36, 161.32; IR (KBr) 3314 (NH), 1815 (C=O), 1703 (C=O), 1551, 1517, 1255 cm^{-1}; EIMS *m/e* 429 (M^+); HRMS calcd for $C_{22}H_{23}NO_8$ 429.1424, found 429.1429. Anal. ($C_{22}H_{23}NO_8$) C, H, N.

[[3(*R*)-[2-[1-[(5′-Methyl-2′-oxo-1′,3′-dioxol-4′-en-4′-yl)-methyl]carbamoyl]piperidin-4-yl]ethyl]-2-oxopiperidinyl]-acetyl]-3(*R*)-methyl-β-alanine (6). A mixture of [[3(*R*)-(2-piperidin-4-ylethyl)-2-oxopiperidinyl]acetyl]-3(*R*)-methyl-β-alanine (L-734,217, 706 mg, 2 mmol) and **5a** (290 mg, 2 mmol) in dimethylformamide (10 mL) was stirred at room temperature for 16 h. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated to obtain a residue (1.3 g), which was purified by chromatography over Sephadex LH20 (50 g). Elution with chloroform gave the pure (oxodioxolenyl)methyl carbamate **6** as a resinous substance (954 mg): ^{1}H NMR ($CDCl_3$) δ 0.9−2.1 (m, 13 H), 1.27 (d, 3 H), 2.18 (s, 3 H), 2.35 (m, 1 H), 2.52 (d, 2 H), 2.75 (m, 2 H), 3.42 (m, 2 H), 3.97 (q, 2 H), 4.08 (m, 2 H), 4.32 (m, 1 H), 4.83 (s, 2 H), 6.35 (br, 1 H), 7.01 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 9.33, 19.87, 21.38, 25.95, 28.73, 31.68, 31.93, 33.44, 35.79, 39.71, 41.31, 41.99, 44.27, 49.83, 51.79, 54.55, 134.12, 139.69, 152.35, 154.31, 168.14, 174.07; HRFABMS *m/e* calcd for $C_{24}H_{34}N_3O_9$ (M − 1) 508.2313, found 508.2295.

Kinetic Measurements. (a) Buffer Hydrolysis of Vinylene Carbonates 1a, 1b, and 1c. The buffer-catalyzed hydrolysis of the vinylene carbonates was studied in pH 7.4 (0.05 M) phosphate buffer containing 10% methanol as a cosolvent. The reaction was followed by UV spectroscopy by recording absorbance changes at a wavelength that showed maximal change on hydrolysis at 37 °C. This corresponded to decrease in absorbance at 202, 256, and 261 nm for **1a**, **1b**, and **1c,** respectively. The reaction was initiated by adding 200 μL of a methanolic solution of the vinylene carbonate to 1.8 mL of the buffer contained in quartz cuvette thermostated at 37 °C. The initial concentrations of **1a**, **1b**, and **1c** were 9×10^{-5}, 3×10^{-5}, and 4×10^{-5} M, respectively. Absorbance readings were taken at 5 min intervals. The observed pseudo-first-order rate constants were obtained by fitting absorbance changes through 4−5 half-lives to the standard first-order rate equation.

(b) Hydrolysis of 5a, 5b, and 5c at pH 1. The hydrolysis of **5a**, **5b**, and **5c** were followed by UV spectroscopy as described above using 0.1 N hydrochloric acid as the hydrolysis medium at 37 °C. The decrease in absorbance at 203, 256, and 267 nm were followed for the breakdown of **5a**, **5b**, and **5c,** respectively.

(c) Hydrolysis of 5a, 5b, and 5c at pH 7.4. The buffer hydrolysis of the (oxodioxolenyl)methyl carbamates were carried out in pH 7.4 (0.05 M) phosphate buffer, using 10% acetonitrile as a cosolvent. HPLC was used to measure the concentration of the starting material remaining or the hydrolysis product formed. The chromatography was carried out on a 10 cm, 4.6 mm i.d. Brownlee spheri-5 C-18 cartridge fitted with a similar 3 cm guard column at ambient temperature. The mobile phase for **5a** was 30% acetonitrile in water containing 0.5 mL/L of phosphoric acid and 0.5 mL/L of triethylamine at a flow rate of 2 mL/min. The UV detector was set at 280 nm. The retention time for **5a** was 5.7 min and that for 3,4-dimethoxyphenethylamine was 1.2 min. Dimethoxydopamine was the only product observed in the reaction. The half-life measured for the degradation of **5a** was 252 min and that measured simultaneously for the formation of dimethoxydopamine was 263 min.

The mobile phase used for the phenyl-substituted carbamate **5b** was 35% acetonitrile in water containing 0.5 mL/L of phosphoric acid and 0.5 mL/L of triethylamine at a flow rate of 2 mL/min. The column effluent was monitored at 256 nm. The retention time for **5b** was 7.2 min. Under similar conditions the anisyl-substituted analog **5c** with detection at 267 nm had a retention time of 9.7 min.

Hydrolysis of 6 in Plasma. The progress of hydrolysis of the (oxodioxolenyl)methyl carbamate **6** was followed by measuring the concentration of L-734,217 formed by esterase-catalyzed hydrolysis at 37 °C in rat or dog plasma. The reaction was initiated by adding a solution of **6** in pH 7.4 phosphate buffer to the plasma pre-equilibrated at 37 °C in a thermostated water bath. The initial concentration of **6** was 2×10^{-4} M. Samples (200 μL) were pipetted out at intervals, added to 400 μL of saturated ammonium sulfate solution, vortex mixed for 30 s to precipitate the plasma proteins, and centrifuged at 10000*g* for 10 min. The supernatants were injected into an HPLC for analysis on a 20 cm Brownlee spheri-5 (4.6 mm i.d.) C-18 cartridge fitted with a similar 3 cm guard column at ambient temperature. The mobile phase was aqueous 0.01 M K_2HPO_4, pH adjusted to 6.5 with phosphoric acid, containing 3% by volume of acetonitrile at a flow rate of 1.2 mL/min. The absorbance of L-734,217 at 210 nm was used to estimate its concentration. The retention time was 10.6 min. The observed rate constant was obtained by fitting the concentration changes through 4−5 half-lives to the standard first-order rate equation.

Rat and Dog Plasma Hydrolysis of 5a, 5b, and 5c. These experiments were conducted as above but using acetonitrile to precipitate plasma proteins instead of aqueous ammonium sulfate. The chromatographic conditions used were the same as that used for the hydrolysis study in pH 7.4 phosphate buffer (see above).

Octanol/Water Partition Coefficient of 6. To a pre-equilibrated mixture of 1-octanol (2 mL) and 0.01 N hydrochloric acid (8 mL) or 1-octanol (5 mL) and 0.02 M pH 7.4 phosphate buffer (5 mL) in a capped centrifuge tube was added 606 μg and 1.009 mg, respectively, of **6**, and the mixture was shaken at room temperature for 5 min. The mixture was then centrifuged at 8000 rpm for 5 min. The octanol and aqueous layers were separated, and the concentration of **6** in each layer was determined by HPLC on a Brownlee spheri-5 RP-18 (22 cm × 4.6 mm) column fitted with a similar guard column. The mobile phase was 35% acetonitrile in 0.01 M potassium phosphate buffer adjusted to pH 3 with phosphoric acid at a flow rate of 1.3 mL/min, and the detection was at 210 nm. The retention time was 6.6 min.

Bioavailability. Purpose-bred mongrel dogs of either sex (7.7−11.8 kg) were randomly assigned to an iv/po crossover study with the prodrug **6**, n = 3 per group. Blood samples were taken for measurement of *ex vivo* platelet aggregation prior to administration of compound and at selected time points following dosing. The prodrug was given iv at 0.1 mg/kg in normal saline and po at 1 mg/kg in sterile water.

Platelet-rich plasma (PRP) was prepared by centrifugation of whole blood at 150*g* for 5 min, and the platelet concentration was adjusted to 2×10^8 platelets/mL with time-matched platelet-poor plasma (PPP). PRP (300 μL, 2×10^8 platelets/mL) was incubated at 37 °C for 3 min prior to the addition of the agonist. Platelet aggregation was measured by the percentage change in light transmittance (PPP represents 100%) under stirring conditions (1100 rpm) at 37 °C in a Biodata Platelet Aggregation Profiler, Model PAP-4, and was initiated by the addition of 10 μM ADP + 1 μM epinephrine (extent of aggregation) or 10 μg/mL collagen + 1 μM epinephrine (rate of aggregation). Epinephrine is used to enhance the aggregation response of canine platelets to other agonists. The aggregometer was standardized with platelet-poor plasma representing 100% light transmittance. The extent of aggregation is determined as the peak percent of aggregation achieved based on a maximum of 100% (standardized with PPP), and the maximum slope represents the maximum sustained rate of aggregatory response. The effect of administration of the compound on the extent and the rate of aggregation is expressed as the percent inhibition of aggregation using the baseline, pretreatment aggregation response as 100%. The results are expressed graphically in Figure 1. The oral bioavailability was estimated from the ratio of oral activity to the dose corrected intravenous activity.

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