Synthesis and Evaluation of Carbamate Prodrugs of a Phenolic Compound

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A series of carbamates of the phenolic compound 1 were prepared and evaluated *in vivo* as its prodrug. Each carbamate was orally administered to rats, and plasma concentrations of the parent compound 1 were measured with the passage of time. We judged which carbamate was suitable for the prodrug of 1 from both the *AUC* value of 1 and absence of the carbamate in plasma. The *AUC* value of 1 after oral administration of 2b was approximately 40-fold higher than that for an administration of 1, and the bioconversion from 2b to 1 was excellent. As a whole, di-substituted carbamates resulted in higher plasma concentrations of 1 than did mono-substituted ones. However di-substituted carbamates were almost always detected in plasma. As a result, we found that the ethycarbamoyl derivative 2b demonstrates the best prodrug property in this series.

Key words prodrug; carbamate; capillarisin

We have synthesized the phenolic compound, **1**, both from the natural product, capillarisin[1] and from 3,4,5-trimethoxyphenol,[2] in order to develop an aldose reductase (AR) inhibitor. Compound **1** showed good *in vitro* activity with an IC_{50} of 3×10^{-8} mol/l against rat lens AR, and was therefore considered as a lead structure for an AR inhibitor.[3] However the pharmacokinetic (PK) properties of **1** were not satisfactory, since the area under the concentration–time curve (*AUC*) value after administration to rats (84.3 mg/kg, *p.o.*) was only 1.55 μg·min/ml.

Many prodrugs have been developed to improve the oral bioavailability of such phenolic compounds. An ideal prodrug has both good absorption and bioconversion characteristics. Carbamate esters are one of the most popular types of prodrugs, with examples reported for duocarmycin,[4] camptothecin,[5] entacapone[6] and 3-PPP.[7]

We also studied carbamate derivatives of **1** in search of an ideal prodrug (Fig. 1). In this paper, we describe the synthesis of carbamate derivatives of **1** and the evaluation of their PK properties *in vivo*.

Chemistry

To prepare carbamate derivatives of **1**, we used isocyanates or carbamoyl chlorides. All isocyanates (**3a**—**h**) and some carbamoyl chlorides (**3i**—**l**) were commercially available reagents, and the other carbamoyl chlorides (**3m**—**z**) were prepared by the method A, B or C, as depicted in Chart 1 and Table 1. Method A was a one-step reaction of an amine with triphosgene. Method B was a two-step reaction, protection of the hydroxyl group on the amine, followed by reaction with triphosgene. Method C was a four-step reaction, sequential alkylation of the amine, protection, reduction, and chloroformylation. Synthetic methods for carbamate derivatives of **1** are shown in Chart 2 and Table 2. The reaction of phenolic compound **1** with isocyanate (**3a**—**h**) in the presence of a catalytic amount of triethylamine afforded mono-substituted carbamates (**2a**—**h**, Method D). Di-substituted carbamates (**2i**—**s**) were obtained by reaction of **1** with carbamoly chloride (**3i**—**s**) in pyridine (Method E). The other di-substituted carbamates (**2t**—**z**) were prepared by a two-step reaction, condensation, followed by deprotection (Method F and G).

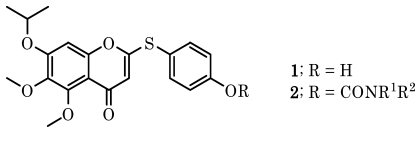

Fig. 1. Parent Compound **1** and its Prodrugs **2**

Results and Discussion

Prodrugs possessing both high absorbability and bioconversion increase the plasma concentration of the parent compound after oral administration. To search for such a prodrug, we screened carbamate esters of **1** *in vivo* using rats. Though we could not evaluate the absorbability and the bioconversion of prodrugs separately by this *in vivo* method, our aim was the selection of compounds based on the *AUC* value of the parent compound **1** and absence of the prodrug in plasma.

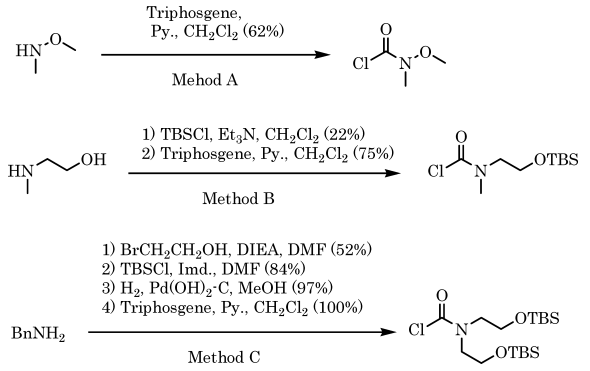

Chart 1. Typical Synthetic Methods for Carbamoyl Chlorides (Method A, B and C)

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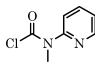
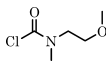
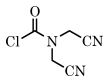
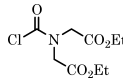
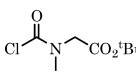
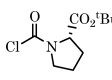
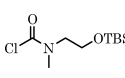
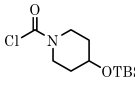
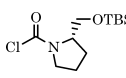
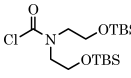
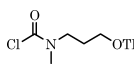
Table 1. Structures and Synthetic Methods for Isocyanates and Carbamoyl Chlorides **3a**—**z**

Method	Structure (compound No.)
Commercial	MeNCO (**3a**), EtNCO (**3b**), ^{n}PrNCO (**3c**), ^{i}PrNCO (**3d**), $ClCH_2CH_2NCO$ (**3e**), PhNCO (**3f**), $EtO_2CCH_2CH_2NCO$ (**3g**), $MeO_2CCH(CH_2CH_2SMe)NCO$ (**3h**),  (**3i**),  (**3j**),  (**3k**),  (**3l**)
A	 (**3m**),  (**3n**),  (**3o**),  (**3p**),  (**3q**),  (**3r**),  (**3s**),  (**3t**),  (**3u**)
B	 (**3v**),  (**3w**),  (**3x**)
C	 (**3y**),  (**3z**)

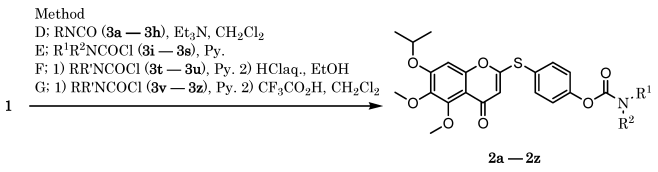


Chart 2. Synthetic Methods for Carbamates **2a**—**z** (Method D, E, F and G)

Carbamate derivatives (**2a**—**z**) were suspended in 1% Tween 80 solution and were orally administered to rats at a dose of 100 mg/kg respectively. At 15, 30, 60 and 120 min after administration, blood samples were collected, and the plasma concentration of **1** was measured by HPLC. Chemical features of each carbamate (**2a**—**z**), the *AUC* values of **1**, and existence of unchanged carbamates after the administration are summarized in Table 2.

No carbamates were detected in the plasma after administration of mono-substituted carbamates. It is thought that these carbamates were metabolized to the parent compound by a first pass effect, since their structures tended to hydrolyze easily. Therefore it seems that the *AUC* values of **1** after administration of these were a reflection of their absorbability. Methylcarbamoyl derivative **2a** and ethylcarbamoyl derivative **2b** increased the *AUC* values of **1**, 10-fold and 40-fold respectively, in comparison with the case of oral administration of **1**. From the viewpoints of hydrophobicity and size of the molecule, it is considered that the absorbability of **2a** and **2b** were good. The other mono-substituted carbamates, **2c**—**h**, were not suitable as the prodrugs of **1**. Probably, they were not absorbed due to rapid hydrolysis in a digestive organ before absorption as carbamates.

In general, di-substituted carbamates resulted in higher plasma concentrations of **1** than did mono-substituted ones, with the exception of some compounds. We think this is due to the fact that di-substituted carbamates are more resistant to hydrolysis than mono-substituted ones. However, bioconversion from di-substituted carbamates to the parent compound **1** was at the same time inhibited because of their high stability.

The smallest di-substituted carbamate **2i** improved the *AUC* value of **1** approximately 100-fold. However, **2i** was detectable in the plasma, indicating its bioconversion was inadequate. Although **2k**, **2l**, **2m**, **2n**, **2s**, **2t** and **2u** didn't improve the *AUC* values of **1** compared to **2i**, they were not detected in the plasma. It is thought that they either were not absorbed or they were metabolized to a compound other than **1**. Compounds **2j**, **2q** and **2r** did not improve the *AUC* values of **1**, and were detected in the plasma. Although they were absorbed, they were considered unsuitable due to their poor bioconversion.

It is well known that di-substituted carbamates are converted to alcohols by carboxylesterases (CEs),[8,9] P450[10,11] and/or intramolecular cyclization reaction[12—14] (Chart 3). We thought that although dimethylcarbamoyl derivative **2i** was metabolized by CEs or P450 in the liver, it wasn't converted to parent compound **1** perfectly. To increase bioconversion, we designed di-substituted carbamates susceptible to chemical conversion (intramolecular cyclization reaction) in addition to enzymolysis. Namely, compounds bearing a nucleophile on their pro-moiety, **2o**, **2p**, **2v**, **2w**, **2x**, **2y** and **2z**, were prepared. They showed high *AUC* for **1**, as expected. Hydroxyl derivatives (**2v**, **2x**) showed higher *AUC* values of **1** than the corresponding methoxyl derivatives (**2o**, **2p**). This result suggests participation of the intramolecular cyclization reaction in the bioconversion. It is considered that the difference between **2v** and **2z**, which differed in alkyl chain length, was due to differences in the ease of cyclization of their 5-member and 6-member rings, respectively. It seems that the hydrophobicity of both **2w** and **2y** was too low, as their absorbability was low when compared with **2v**. However, carbamates, **2o**, **2p**, **2v**, **2w**, **2x**, **2y**, and **2z**, all of which possessed nucleophiles and showed high *AUC* values of **1**, were also detectable in plasma, just as for **2i**. Therefore they are not ideal structures as prodrugs of **1**.

Table 2. Chemical and PK Properties of Carbamates **2a**—**z** and a Parent Compound **1**

Compd.	NR^1R^2	CLogP[a)]	mp	*AUC* of **1**[b)]	Carbamate[c)]
2a	NHMe	3.04	174—175	18.46±4.95	−
2b	NHEt	3.57	159—160	67.38±6.82	−
2c	NH^nPr	4.10	156—157	2.69±1.84	−
2d	NH^iPr	3.88	155—157	4.94±1.61	−
2e	$NHCH_2CH_2Cl$	3.64	158—159	2.78±1.47	−
2f	NHPh	5.10	168—169	ND[d)]	−
2g	$NHCH_2CH_2CO_2Et$	3.82	132—134	1.20±1.38	−
2h	$NHCH(CH_2CH_2SMe)CO_2Me$	3.39	108—109	1.83±2.08	−
2i	NMe_2	3.26	122—123	156.55±56.53	+
2j	NMe(Ph)	5.17	118—119	2.75±1.71	+
2k		3.18	160—161	17.52±3.94	−
2l		3.62	127—128	9.65±3.18	−
2m	NMe(2-Py)	3.67	153—154	ND[d)]	−
2n	NMe(OMe)	3.90	129—131	2.75±1.70	−
2o	$NMe(CH_2CH_2OMe)$	3.51	103—105	111.34±66.14	+
2p		4.02	113—114	65.42±8.43	+
2q	$NMe(CH_2CN)$	2.69	134—135	7.54±0.73	+
2r	$N(CH_2CN)_2$	2.12	183—184	ND[d)]	+
2s	$N(CH_2CO_2Et)_2$	4.44	120—121	ND[d)]	−
2t	$NMe(CH_2CO_2H)$	3.01	161—163	ND[d)]	−
2u		3.51	168—170	ND[d)]	−
2v	$NMe(CH_2CH_2OH)$	2.75	124—125	164.35±51.38	+
2w		2.37	157—159	42.27±15.04	+
2x		3.26	114—117	94.65±15.48	+
2y	$N(CH_2CH_2OH)_2$	2.23	129—130	33.76±12.29	+
2z	$NMe(CH_2CH_2CH_2OH)$	3.06	126—127	84.67±36.14	+
1	Parent compound	3.30	213—215	1.55±1.00[e)]	

a) Chem Draw Ultra 8.0. *b*) $AUC_{0—120\,min}$ of **1** (μg·min/ml), at a dose of 100 mg/kg, mean±S.D. (n=3). *c*) −; Carbamate was not detected in plasma. +; Carbamate was detected in plasma. *d*) Not detected. *e*) At a dose of 84.3 mg/kg.

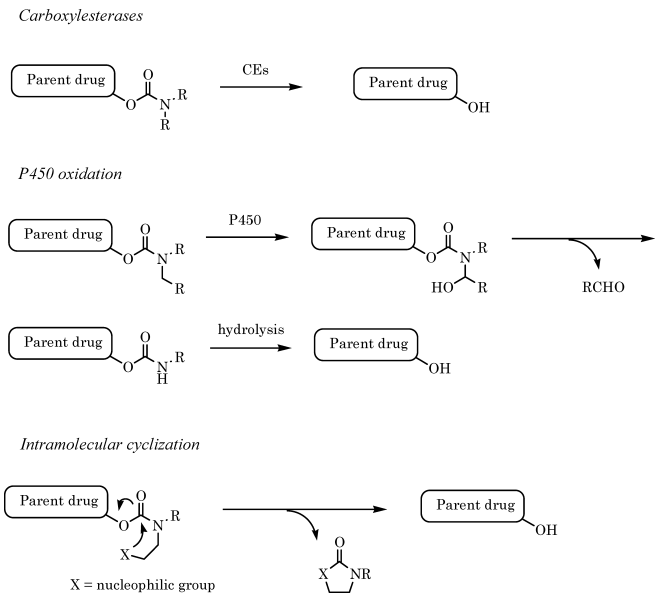


Chart 3. Bioconversion Mechanism from a Carbamate to a Phenol

Conclusion

The purpose of this investigation is to attempt to increase the plasma concentration of the phenolic compound **1** by a prodrug strategy. Several carbamates of **1** were synthesized and their PK properties evaluated *in vivo*. Among them, an ethylcarbamoyl derivative **2b** showed the most favorable PK property as a prodrug. The *AUC* value of **1** after oral administration of **2b** was approximately 40-fold higher than that for an administration of **1**. In addition the bioconversion from **2b** to **1** was good. Carbamate esters like these will be good prodrugs for phenolic compounds.

Experimental

Melting points were measured by the use of a Yanaco micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL FX-200 (200 MHz) using tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 270-30. MS were recorded on a JEOL DX-300. Elemental analyses were performed on a Heraus CHN-O-Rapid, and analytical results obtained for these elements are within ±0.4% of the theoretical values.

Typical Procedure for the Preparation of Carbamoyl Chlorides 3m—u (Method A). Methoxylmethylcarbamoyl Chloride (3n) To a solution of triphosgene (1.92 g, 6.46 mmol) in dichloromethane (30 ml) was added pyridine (2.6 ml, 32 mmol) and the mixture was stirred at 0 °C for 20 min. A suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (628 mg,

6.5 mmol) in dichloromethane (30 ml) was added dropwise to the above mixture and the mixture was stirred at room temperature for 1 h. After adding H_2O (30 ml), the mixture was extracted with dichloromethane (30 ml×2), dried over Na_2SO_4 and concentrated to give the title compound (0.49 g, 62%) as oil. ^{1}H-NMR ($CDCl_3$) δ: 3.08 (0.6H, s), 3.33 (2.4H, s), 3.68 (0.6H, s), 3.78 (2.4H, s).

Typical Procedure for the Preparation of the Carbamoyl Chlorides 3v—x (Method B). [2-(*tert*-Butyldimethylsiloxy)ethyl]methylcarbamoyl Chloride (3v) 1) A mixture of *N*-methylethanolamine (3.28 g, 43.67 mmol), *tert*-butyldimethylsilyl chloride (13.16 g, 87.34 mmol) and triethylamine (12.08 ml, 87.34 mmol) in dichloromethane (60 ml) was stirred at room temperature for 24 h. After adding H_2O (60 ml), the mixture was extracted with dichloromethane (60 ml×2), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (dichloromethane/MeOH=4/1) to give 2-(*tert*-butyldimethylsiloxy)-*N*-methylethylamine (1.79 g, 22%).

2) To a solution of triphosgene (2.58 g, 8.70 mmol) in dichloromethane (15 ml) was added pyridine (4.22 ml, 52.2 mmol) and the mixture was stirred at 0 °C for 20 min. A solution of the above compound (1.65 g, 8.71 mmol) in dichloromethane (15 ml) was added dropwise to the above mixture and the mixture was stirred at room temperature for 2 h. After adding H_2O (30 ml), the mixture was extracted with dichloromethane (30 ml×2), dried over Na_2SO_4 and concentrated to give the title compound (1.65 g, 75%) as oil. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 3.11 (1.5H, s), 3.21 (1.5H, s), 3.50 (1H, t, J=5.4 Hz), 3.58 (1H, t, J=5.4 Hz), 3.80 (1H, t, J=5.4 Hz), 3.81 (1H, t, J=5.4 Hz).

Typical Procedure for the Preparation of the Carbamoyl Chlorides 3y—z (Method C). Bis[2-(*tert*-butyldimethylsiloxy)ethyl]carbamoyl Chloride (3y) 1) A mixture of benzylamine (4 ml, 37.6 mmol), 2-bromoethanol (8 ml, 112.8 mmol) and *N*,*N*-diisopropylethylamine (19.6 ml, 112.8 mmol) in DMF (50 ml) was stirred at room temperature for 4 d. After adding H_2O (100 ml), the mixture was extracted with dichloromethane (100 ml×2), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (dichloromethane/MeOH=20/1) to give 2,2′-(benzylimino)diethanol (3.80 g, 52%). ^{1}H-NMR ($CDCl_3$) δ: 2.73 (4H, t, J=5.3 Hz), 3.63 (4H, t, J=5.3 Hz), 3.71 (2H, s), 7.20—7.40 (5H, m).

2) A mixture of the above compound (6.09 g, 31.19 mmol), *tert*-butyldimethylsilyl chloride (14.10 g, 93.57 mmol) and imidazole (12.74 g, 187.14 mmol) in DMF (120 ml) was stirred at room temperature for 20 h. After adding H_2O (200 ml), the mixture was extracted with EtOAc (200 ml×2), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc=50/1) to give *N*-benzyl-2,2′-bis(*tert*-butyldimethylsiloxy)diethylamine (11.04 g, 84%). ^{1}H-NMR ($CDCl_3$) δ: 0.02 (12H, s), 0.87 (18H, s), 2.67 (4H, t, J=6.6 Hz), 3.66 (4H, t, J=6.6 Hz), 3.71 (2H, s), 7.20—7.40 (5H, m).

3) To a solution of the above compound (11.04 g, 26.05 mmol) in MeOH (330 ml) was added 20% $Pd(OH)_2$/C (1.1 g) and the mixture was hydrogenated at atmospheric pressure for 3 h. The reaction mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc=10/7) to give 2,2′-bis(*tert*-butyldimethylsiloxy)diethylamine (8.45 g, 97%). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (12H, s), 0.90 (18H, s), 2.76 (4H, t, J=5.2 Hz), 3.75 (4H, t, J=5.2 Hz).

4) To a solution of triphosgene (1.78 g, 5.99 mmol) in dichloromethane (20 ml) was added pyridine (2.91 ml, 35.96 mmol) and the mixture was stirred at 0 °C for 10 min. A solution of the above compound (2.00 g, 5.99 mmol) in dichloromethane (20 ml) was added dropwise to the above mixture and the mixture was stirred at room temperature for 2 h. After adding H_2O (40 ml), the mixture was extracted with dichloromethane (40 ml×2), dried over Na_2SO_4 and concentrated to give the title compound (2.43 g, 100%) as oil. ^{1}H-NMR ($CDCl_3$) δ: 0.058 (6H, s), 0.068 (6H, s), 0.89 (9H, s), 0.90 (9H, s), 3.58 (2H, t, J=5.0 Hz), 3.68 (2H, t, J=5.0 Hz), 3.77—3.85 (4H, m).

Typical Procedure for the Preparation of the Carbamates 2a—h (Method D). 7-Isopropoxy-5,6-dimethoxy-2-{{4-[(methylcarbamoyl)oxy]phenyl}thio}-4*H*-chromen-4-one (2a) To a solution of **1** (504.2 mg, 1.30 mmol) in dichloromethane (5 ml) was added methyl isocyanate (0.115 ml, 1.95 mmol) and triethylamine (0.036 ml, 0.259 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and purified by flash chromatography on silica gel (hexane/EtOAc=1/1) to give the title compound (534.8 mg, 92%). Recrystallization from EtOAc–chloroform afforded colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 2.92 (3H, d, J=4.9 Hz), 3.85 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.09 (1H, br d), 5.82 (1H, s), 6.59 (1H, s), 7.23 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1732, 1628. FAB-MS m/z: 446 (MH^+). *Anal.* Calcd for $C_{22}H_{23}NO_7S$: C, 59.32; H, 5.20; N, 3.14. Found: C, 59.18; H, 5.34; N, 3.10.

2-{{4-[(Ethylcarbamoyl)oxy]phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2b) Yield from **1**: 89%. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.3 Hz), 1.42 (6H, d, J=6.1 Hz), 3.33 (2H, m), 3.85 (3H, s), 3.91 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.11 (1H, br t), 5.83 (1H, s), 6.59 (1H, s), 7.23 (2H, d, J=8.8 Hz), 7.57 (2H, d, J=8.8 Hz). IR (KBr) cm^{-1}: 1752, 1632, 1612, 1586. FAB-MS m/z: 460 (MH^+). *Anal.* Calcd for $C_{23}H_{25}NO_7S$: C, 60.12; H, 5.48; N, 3.05. Found: C, 60.09; H, 5.56; N, 3.11.

7-Isopropoxy-5,6-dimethoxy-2-{{4-[(propylcarbamoyl)oxy]-phenyl}thio}-4*H*-chromen-4-one (2c) Yield from **1**: 75%. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.4 Hz), 1.43 (6H, d, J=6.1 Hz), 1.62 (2H, m), 3.25 (2H, m), 3.85 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.16 (1H, br t), 5.83 (1H, s), 6.59 (1H, s), 7.23 (2H, d, J=8.7 Hz), 7.57 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1746, 1612, 1589. FAB-MS m/z: 474 (MH^+). *Anal.* Calcd for $C_{24}H_{27}NO_7S$: C, 60.87; H, 5.75; N, 2.96. Found: C, 60.87; H, 5.86; N, 2.99.

7-Isopropoxy-2-{{4-[(isopropylcarbamoyl)oxy]phenyl}thio}-5,6-dimethoxy-4*H*-chromen-4-one (2d) Yield from **1**: 86%. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, d, J=6.2 Hz), 1.43 (6H, d, J=6.1 Hz), 3.85 (3H, s), 3.92 (3H, s), 4.61 (1H, septet, J=6.1 Hz), 4.92 (1H, m), 5.82 (1H, s), 6.60 (1H, s), 7.24 (2H, d, J=8.8 Hz), 7.56 (2H, d, J=8.8 Hz). IR (KBr) cm^{-1}: 1742, 1630, 1610, 1582. FAB-MS m/z: 474 (MH^+). *Anal.* Calcd for $C_{24}H_{27}NO_7S$: C, 60.87; H, 5.75; N, 2.96. Found: C, 60.61; H, 5.86; N, 2.92.

2-{{4-{[(2-Chloroethyl)carbamoyl]oxy}phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2e) Yield from **1**: 91%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=5.9 Hz), 3.60—3.70 (4H, m), 3.85 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=5.9 Hz), 5.62 (1H, br t), 5.83 (1H, s), 6.60 (1H, s), 7.25 (2H, d, J=8.8 Hz), 7.59 (2H, d, J=8.8 Hz). IR (KBr) cm^{-1}: 1754, 1628, 1612, 1580. FAB-MS m/z: 494 (MH^+). *Anal.* Calcd for $C_{23}H_{24}ClNO_7S$: C, 55.93; H, 4.90; N, 2.84. Found: C, 56.08; H, 4.98; N, 2.97.

2-{[4-(Carbaniloxy)phenyl]thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2f) Yield from **1**: 55%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 3.85 (3H, s), 3.92 (3H, s), 4.61 (1H, septet, J=6.1 Hz), 5.85 (1H, s), 6.60 (1H, s), 7.00 (1H, br s), 7.15 (1H, m), 7.31 (2H, d, J=8.8 Hz), 7.35—7.50 (4H, m), 7.62 (2H, d, J=8.8 Hz). IR (KBr) cm^{-1}: 1736, 1712, 1628, 1610. FAB-MS m/z: 508 (MH^+). *Anal.* Calcd for $C_{27}H_{25}NO_7S$: C, 63.89; H, 4.96; N, 2.76. Found: C, 63.36; H, 4.94; N, 2.69.

Ethyl {{{4-[(7-Isopropoxy-5,6-dimethoxy-4-oxo-4*H*-chromen-2-yl)thio]phenoxy}carbonyl}amino}propionate (2g) Yield from **1**: 75%. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.2 Hz), 1.43 (6H, d, J=6.0 Hz), 2.63 (2H, t, J=6.0 Hz), 3.56 (2H, q, J=6.0 Hz), 3.85 (3H, s), 3.92 (3H, s), 4.20 (2H, q, J=7.2 Hz), 4.62 (1H, septet, J=6.0 Hz), 5.68 (1H, t, J=6.0 Hz), 5.84 (1H, s), 6.59 (1H, s), 7.24 (2H, d, J=8.7 Hz), 7.57 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1738, 1632. FAB-MS m/z: 532 (MH^+).

Methyl *N*-{{4-[(7-Isopropoxy-5,6-dimethoxy-4-oxo-4*H*-chromen-2-yl)thio]phenoxy}carbonyl}-L-methionate (2h) Yield from **1**: 66%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 2.14 (3H, s), 2.00—2.40 (2H, m), 2.61 (2H, t, J=7.3 Hz), 3.82 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 4.52—4.71 (2H, m), 5.80 (1H, m), 5.85 (1H, s), 6.58 (1H, s), 7.25 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1744, 1632. FAB-MS m/z: 578 (MH^+). *Anal.* Calcd for $C_{27}H_{31}NO_9S_2$: C, 56.14; H, 5.41; N, 2.42. Found: C, 56.06; H, 5.54; N, 2.57.

Typical Procedure for the Preparation of the Carbamates 2i—s (Method E). 2-{{[4-(Dimethylcarbamoyl)oxy]phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2i) To a solution of **1** (6.06 g, 15.6 mmol) in pyridine (60 ml) was added *N*,*N*-dimethylcarbamoyl chloride (2.87 ml, 31.2 mmol) and the mixture was stirred at 50 °C for 7 h. After adding 3 N-HCl (300 ml), the mixture was extracted with EtOAc (200 ml×2), dried over Na_2SO_4 and concentrated. The residue was purified by recrystallization from EtOAc–hexane to give the title compound (5.78 g, 81%). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 3.03 (3H, s), 3.12 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 4.61 (1H, septet, J=6.1 Hz), 5.82 (1H, s), 6.60 (1H, s), 7.23 (2H, d, J=8.8 Hz), 7.58 (2H, d, J=8.8 Hz). IR (KBr) cm^{-1}: 1728, 1638, 1612, 1588. EI-MS m/z: 459 (M^+). *Anal.* Calcd for $C_{23}H_{25}NO_7S$: C, 60.12; H, 5.48; N, 3.05. Found: C, 59.88; H, 5.57; N, 3.06.

7-Isopropoxy-5,6-dimethoxy-2-{{4-[(methylphenylcarbamoyl)-oxy]phenyl}thio-4*H*-chromen-4-one (2j) Yield from **1**: 87%. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, d, J=6.1 Hz), 3.44 (3H, s), 3.84 (3H, s), 3.91 (3H, s), 4.61 (1H, septet, J=6.1 Hz), 5.82 (1H, s), 6.57 (1H, s), 7.19—7.47 (7H, m), 7.56 (2H, d, J=8.6 Hz). IR (KBr) cm^{-1}: 1730, 1638, 1610. EI-MS m/z: 521 (M^+). *Anal.* Calcd for $C_{28}H_{27}NO_7S$: C, 64.48; H, 5.22; N, 2.69. Found: C, 64.35; H, 5.31; N, 2.73.

7-Isopropoxy-5,6-dimethoxy-2-{{4-[(morphorinocarbonyl)-oxy]phenyl}thio}-4*H*-chromen-4-one (2k) Yield from **1**: 80%. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, d, J=6.4 Hz), 3.59 (2H, br s), 3.70 (2H, br s), 3.77 (4H, m), 3.85 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.4 Hz), 5.81 (1H, s), 6.60 (1H, s), 7.23 (2H, d, J=8.8 Hz), 7.59 (2H, d, J=8.8 Hz). IR (KBr) cm^{-1}: 1724, 1632, 1612. EI-MS m/z: 501 (M^+). *Anal.* Calcd for $C_{25}H_{27}NO_8S$: C, 59.87; H, 5.43; N, 2.79. Found: C, 59.57; H, 5.54; N, 2.80.

7-Isopropoxy-5,6-dimethoxy-2-{{4-[(4-methyl-1-piperazinyl)carbonyl]oxy}phenyl}thio}-4*H*-chromen-4-one (2l) Yield from **1**: 90%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.0 Hz), 2.36 (3H, s), 2.48 (4H, t, J=5.1 Hz), 3.65 (4H, m), 3.85 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.82 (1H, s), 6.60 (1H, s), 7.22 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1726, 1634, 1610. EI-MS m/z: 514 (M^+). *Anal.* Calcd for $C_{26}H_{30}NO_7S$: C, 60.69; H, 5.88; N, 5.44. Found: C, 60.55; H, 6.06; N, 5.51.

7-Isopropoxy-5,6-dimethoxy-2-{{4-{[methyl(2-pyridyl)carbamoyl]oxy}phenyl}thio}-4*H*-chromen-4-one (2m) Yield from **1**: 93%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 3.63 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.84 (1H, s), 6.59 (1H, s), 7.13 (1H, dd, J=4.2, 8.4 Hz), 7.28 (2H, d, J=8.7 Hz), 7.61 (2H, d, J=8.7 Hz), 7.73 (2H, m), 8.47 (1H, m). IR (KBr) cm^{-1}: 1732, 1628, 1612, 1588. EI-MS m/z: 522 (M^+). *Anal.* Calcd for $C_{27}H_{26}N_2O_7S$: C, 62.06; H, 5.01; N, 5.36. Found: C, 61.92; H, 5.13; N, 5.39.

7-Isopropoxy-5,6-dimethoxy-2-{{4-[(methoxymethycarbamoyl)-oxy]phenyl}thio}-4*H*-chromen-4-one (2n) Yield from **1**: 90%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.0 Hz), 3.31 (3H, s), 3.82 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.0 Hz), 5.85 (1H, s), 6.55 (1H, s), 7.28 (2H, d, J=8.6 Hz), 7.60 (2H, d, J=8.6 Hz). IR (KBr) cm^{-1}: 1720, 1638. EI-MS m/z: 475 (M^+).

7-Isopropoxy-5,6-dimethoxy-2-{{4-{[(2-methoxyethyl)methylcarbamoyl]oxy}phenyl}thio}-4*H*-chromen-4-one (2o) Yield from **1**: 97%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.0 Hz), 3.08 (1.5H, s), 3.18 (1.5H, s), 3.40 (3H, s), 3.50—3.75 (4H, m), 3.85 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.83 (1H, s), 6.59 (1H, s), 7.26—7.39 (2H, m), 7.57 (2H, d, J=8.6 Hz). IR (KBr) cm^{-1}: 1728, 1632. EI-MS m/z: 503 (M^+).

7-Isopropoxy-5,6-dimethoxy-2-{{4-{[(*S*)-2-(methoxymethyl)-1-pyrrolidinyl]carbonyl}oxy}phenyl}thio}-4*H*-chromen-4-one (2p) Yield from **1**: 83%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 1.85—2.15 (4H, m), 3.38 (3H, s), 3.45—3.70 (4H, m), 3.85 (3H, s), 3.92 (3H, s), 4.20—4.25 (1H, m), 4.62 (1H, septet, J=6.1 Hz), 5.82 (1H, s), 6.59 (1H, s), 7.25 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1726, 1630, 1612. EI-MS m/z: 529 (M^+). *Anal.* Calcd for $C_{27}H_{31}NO_8S$: C, 61.23; H, 5.90; N, 2.64. Found: C, 61.27; H, 5.96; N, 2.74.

{{{4-[(7-Isopropoxy-5,6-dimethoxy-4-oxo-4*H*-chromen-2-yl)thio]phenoxy}carbonyl}methylamino}acetonitrile (2q) Yield from **1**: 100%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 3.16 (1.2H, s), 3.26 (1.8H, s), 3.85 (3H, s), 3.92 (3H, s), 4.36 (1.2H, s), 4.39 (0.8H, s), 4.62 (1H, septet, J=6.1 Hz), 5.85 (1H, s), 6.58 (1H, s), 7.24 (2H, d, J=8.7 Hz), 7.61 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1736, 1638, 1608, 1582. EI-MS m/z: 484 (M^+). *Anal.* Calcd for $C_{24}H_{24}N_2O_7S$: C, 59.49; H, 4.99; N, 5.78. Found: C, 59.54; H, 5.01; N, 5.85.

{{{4-[(7-Isopropoxy-5,6-dimethoxy-4-oxo-4*H*-chromen-2-yl)thio]phenoxy}carbonyl}imino}diacetonitrile (2r) Yield from **1**: 88%. ^{1}H-NMR (acetone-d_6) δ: 1.40 (6H, d, J=6.0 Hz), 3.79 (3H, s), 3.82 (3H, s), 4.60—4.90 (5H, m), 5.75 (1H, s), 6.84 (1H, s), 7.47 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1742, 1636, 1610. EI-MS m/z: 509 (M^+). *Anal.* Calcd for $C_{25}H_{23}N_3O_7S$: C, 58.93; H, 4.55; N, 8.25. Found: C, 58.79; H, 4.61; N, 8.32.

Diethyl {{{4-[(7-Isopropoxy-5,6-dimethoxy-4-oxo-4*H*-chromen-2-yl)thio]phenoxy}carbonyl}imino}diacetate (2s) Yield from **1**: 100%. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.1 Hz), 1.32 (3H, t, J=7.1 Hz), 1.42 (6H, d, J=6.1 Hz), 3.84 (3H, s), 3.92 (3H, s), 4.20—4.32 (8H, m), 4.62 (1H, septet, J=6.1 Hz), 5.84 (1H, s), 6.58 (1H, s), 7.22 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1754, 1728, 1632, 1610. *Anal.* Calcd for $C_{29}H_{33}NO_{11}S$: C, 57.70; H, 5.51; N, 2.32. Found: C, 57.60; H, 5.60; N, 2.36.

Typical Procedure for the Preparation of the Carbamates 2t—u (Method F). {{{4-[(7-Isopropoxy-5,6-dimethoxy-4-oxo-4*H*-chromen-2-yl)thio]phenoxy}carbonyl}methylamino}acetic Acid (2t) 1) A mixture of **1** (518.2 mg, 1.34 mmol) and **3t** (1.00 g) in pyridine (6 ml) was stirred at room temperature for 20 h. After adding 3 N-HCl (20 ml), the mixture was extracted with EtOAc (30 ml×2), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc=10/7) to give *tert*-butyl {{{4-[(7-isopropoxy-5,6-dimethoxy-4-oxo-4*H*-chromen-2-yl)thio]phenoxy}carbonyl}methylamino}acetate (776.7 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, d, J=6.0 Hz), 1.50 (4.5H, s), 1.51 (4.5H, s), 3.07 (1.5H, s), 3.17 (1.5H, s), 3.84 (3H, s), 3.92 (3H, s), 4.00 (1H, s), 4.03 (1H, s), 4.62 (1H, septet, J=6.0 Hz), 5.83 (0.5H, s), 5.85 (0.5H, s), 6.58 (1H, s), 7.19 (1H, d, J=8.7 Hz), 7.24 (1H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz). EI-MS m/z: 559 (M^+).

2) To a solution of the above compound (740 mg, 1.32 mmol) in dichloromethane (7 ml) was added trifluoroacetic acid (1 ml), and the mixture was stirred at room temperature for 24 h. After adding H_2O (20 ml), the mixture was extracted with chloroform (20 ml×2), dried over Na_2SO_4 and concentrated. The residue was purified by recrystallization from EtOAc–hexane to give the title compound (551.3 g, 83%). ^{1}H-NMR (acetone-d_6) δ: 1.40 (6H, d, J=6.0 Hz), 3.06 (1.5H, s), 3.21 (1.5H, s), 3.79 (3H, s), 3.81 (3H, s), 4.15 (1H, s), 4.27 (1H, s), 4.81 (1H, septet, J=6.0 Hz), 5.68 (0.5H, s), 5.70 (0.5H, s), 6.84 (1H, s), 7.30 (1H, d, J=8.7 Hz), 7.36 (1H, d, J=8.7 Hz), 7.71 (1H, d, J=8.7 Hz), 7.72 (1H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1728, 1608. FAB-MS m/z: 504 (MH^+). *Anal.* Calcd for $C_{24}H_{25}NO_9S$: C, 57.25; H, 5.00; N, 2.78. Found: C, 57.08; H, 5.18; N, 2.78.

***N*-{{4-[(7-Isopropoxy-5,6-dimethoxy-4-oxo-4*H*-chromen-2-yl)thio]phenoxy}carbonyl}-L-proline (2u)** Yield from **1**: 53%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 2.01—2.59 (4H, m), 3.53—3.81 (2H, m), 3.84 (3H, s), 3.91 (1.5H, s), 3.92 (1.5H, s), 4.47—4.68 (2H, m), 5.77 (0.5H, s), 5.86 (0.5H, s), 6.59 (0.5H, s), 6.60 (0.5H, s), 7.23 (1H, d, J=8.7 Hz), 7.27 (1H, d, J=8.7 Hz), 7.54 (1H, d, J=8.7 Hz), 7.58 (1H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1722, 1606. EI-MS m/z: 529 (M^+).

Typical Procedure for the Preparation of the Carbamates 2v—z (Method G). 2-{{4-{[(2-Hydroxyethyl)methylcarbamoyl]oxy}phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2v) 1) A mixture of **1** (500 mg, 1.29 mmol) and **3v** (974 mg, 3.87 mmol) in pyridine (5 ml) was stirred at room temperature for 24 h. After adding 3 N-HCl (30 ml), the mixture was extracted with EtOAc (30 ml×2), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc=2/1) to give 2-{{4-{[2-(*tert*-butyldimethylsiloxy)ethyl]methylcarbamoyl}oxy}phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (793.8 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.090 (3H, s), 0.092 (3H, s), 0.92 (9H, s), 1.43 (6H, d, J=6.1 Hz), 3.09 (1.5H, s), 3.19 (1.5H, s), 3.47 (1H, t, J=5.5 Hz), 3.56 (1H, t, J=5.5 Hz), 3.80—3.88 (2H, m), 3.84 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.82 (0.5H, s), 5.83 (0.5H, s), 6.59 (1H, s), 7.21 (1H, d, J=8.7 Hz), 7.22 (1H, d, J=8.7 Hz), 7.58 (d, 2H, J=8.7 Hz). EI-MS m/z: 603 (M^+).

2) A solution of the above compound (716.1 mg, 1.19 mmol) in a 1% solution of 36% HCl in EtOH (10 ml) was stirred at room temperature for 1 h. After adding H_2O (30 ml), the mixture was extracted with EtOAc (30 ml×2), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc=1/5) to give the title compound (467.5 mg, 80%). Recrystallization from EtOAc–hexane afforded colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 3.10 (1.5H, s), 3.20 (1.5H, s), 3.50—3.65 (2H, m), 3.85 (3H, s), 3.80—3.90 (2H, m), 3.92 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.83 (1H, s), 6.59 (1H, s), 7.24 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1726, 1612. EI-MS m/z: 489 (M^+). *Anal.* Calcd for $C_{24}H_{27}NO_8S$: C, 58.88; H, 5.56; N, 2.86. Found: C, 58.77; H, 5.56; N, 2.89.

2-{{4-{[(4-Hydroxypiperidino)carbonyl]oxy}phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2w) Yield from **1**: 57%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.0 Hz), 1.53—1.76 (2H, m), 1.94—2.05 (2H, m), 3.34—3.55 (2H, m), 3.85 (3H, s), 3.92 (3H, s), 3.93—4.02 (3H, m), 4.62 (1H, septet, J=6.0 Hz), 5.82 (1H, s), 6.59 (1H, s), 7.22 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1730, 1610. EI-MS m/z: 515 (M^+).

2-{{4-{{[(*S*)-2-(Hydroxymethyl)-1-pyrolidinyl]carbonyl}oxy}-phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2x) Yield from **1**: 89%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.0 Hz), 2.17—1.86 (4H, m), 3.57—3.75 (4H, m), 3.85 (3H, s), 3.92 (3H, s), 3.99—4.30 (1H, m), 4.62 (1H, septet, J=6.0 Hz), 5.83 (1H, s), 6.59 (1H, s), 7.26 (2H, d, J=8.6 Hz), 7.59 (2H, d, J=8.6 Hz). IR (KBr) cm^{-1}: 1724, 1622. EI-MS m/z: 515 (M^+).

2-{{4-{[Bis(2-hydroxyethyl)carbamoyl]oxy}phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2y) Yield from **1**: 67%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.1 Hz), 3.58—3.70 (4H, m), 3.84 (3H, m), 3.91 (3H, s), 3.90—3.96 (4H, m), 4.62 (1H, septet, J=6.1 Hz), 5.80 (1H, s), 6.60 (1H, s), 7.24 (2H, d, J=8.7 Hz), 7.59 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1720, 1702, 1630, 1612. FAB-MS m/z: 520 (MH^+). *Anal.* Calcd for $C_{25}H_{29}NO_9S$: C, 57.79; H, 5.63; N, 2.70. Found: C, 57.63; H, 5.70; N, 2.69.

2-{{4-{[(3-Hydroxypropyl)methylcarbamoyl]oxy}phenyl}thio}-7-isopropoxy-5,6-dimethoxy-4*H*-chromen-4-one (2z) Yield from **1**: 79%. ^{1}H-

NMR ($CDCl_3$) δ: 1.42 (6H, d, J=6.1 Hz), 1.80—2.00 (2H, m), 3.04 (1H, s), 3.12 (2H, s), 3.50—3.85 (4H, m), 3.84 (3H, s), 3.92 (3H, s), 4.62 (1H, septet, J=6.1 Hz), 5.83 (1H, s), 6.59 (1H, s), 7.22 (2H, d, J=8.7 Hz), 7.59 (2H, d, J=8.7 Hz). IR (KBr) cm^{-1}: 1724, 1710, 1636, 1614, 1588. FAB-MS m/z: 504 (MH^+). *Anal.* Calcd for $C_{25}H_{29}NO_8S$: C, 59.63; H, 5.80; N, 2.78. Found: C, 59.62; H, 5.93; N, 2.80.

Pharmacokinetic (PK) Evaluation in Rats Test compounds suspended in 1% Tween 80 solution at a concentration of 100 mg/10 ml were administered orally to male Sprague-Dawley rats (Charles River Japan Inc.) aged 8 weeks old at a dose of 100 mg/kg (n=3). At 15, 30, 60 and 120 min after administration, blood samples were collected from the caudal vein using a heparinized syringe. The plasma samples were prepared by centrifugation (3000 rpm for 10 min at 4 °C) and then stored at −20 °C until analysis. The plasma samples (0.05 ml) were mixed with MeOH (0.15 ml) and an internal standard solution (0.05 ml) for 20 min, and centrifuged at 3000 rpm for 20 min at 4 °C. The samples were concentrated, diluted with 1% phosphoric acid in MeOH (0.1 ml) and filtered. The samples (0.04 ml) were injected onto a HPLC system equipped with a TSK gel ODS-80TM column (4.6×150 mm), and eluted with 55% acetonitrile in water at a flow rate 1.0 ml/min and monitored by UV detection at 303 nm. The plasma concentration of the parent compound **1** and the prodrug were measured by HPLC using an internal standard. PK parameters for the compounds were estimated using a non-compartmental method. *AUC* was determined by the trapezoidal rule.

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