Potent Inhibitors of Acyl-CoA:Cholesterol Acyltransferase. Structure–Activity Relationships of Novel *N*-(4-Oxochroman-8-yl)amides

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Novel *N*-(4-oxochroman-8-yl)amide derivatives **1** were synthesized and tested for their ability to inhibit rabbit small intestinal ACAT (acyl-CoA:cholesterol acyltransferase) in vitro and to lower serum total cholesterol in cholesterol-fed rats in vivo. Among the synthesized compounds, *N*-(7-alkoxy-4-oxochroman-8-yl)amide derivatives showed potent ACAT inhibitory activity both in vitro and in vivo. The structure–activity relationships of these *N*-(4-oxochroman-8-yl)amides and related compounds are discussed on the basis of these two assays. The carbonyl group at position 4 of the 4-chromanone was essential for potent ACAT inhibitory activity. *N*-(Chromon-8-yl) derivatives were less potent than *N*-(4-oxochroman-8-yl) derivatives. An alkoxy group at position 7 of the 4-chromanone moiety was important for potent ACAT inhibitory activity. In the *N*-(7-alkoxy-4-oxochroman-8-yl)amide derivatives, another necessary factor to elicit the potent ACAT inhibitory activity was lipophilicity of the molecules. The highly lipophilic acid amides *N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**35**) and 4-[[6-(4-chlorophenoxy)hexyl]oxy]-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide (**63**) showed potent activity. Introduction of a highly lipophilic alkoxy group at position 7 of the 4-chromanone moiety instead of methoxy group also resulted in potent activity. In this case, highest inhibitory activity was obtained by *N*-[7-(decyloxy)-4-oxochroman-8-yl]-2,2-dimethylpropanamide (**65**). The most potent compound, *N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**35**, TEI-6522), showed significant ACAT inhibitory activity (rabbit small intestine IC_{50} = 13 nM, rabbit liver IC_{50} = 16 nM), foam cell formation inhibitory activity (rat peritoneal macrophage IC_{50} = 160 nM), and extremely potent serum cholesterol-lowering activity in cholesterol-fed rats (61% at a dose of 0.1 mg/kg/day po).[1]

Introduction

Acyl-CoA:cholesterol acyltransferase (ACAT)[2] is the intracellular enzyme responsible for catalyzing the esterification of free cholesterol in various tissues. This enzyme plays a key role in intestinal dietary cholesterol absorption, the secretion of very low density lipoproteins (VLDL) from the liver, and the accumulation of cholesteryl esters by macrophages in the artery.[3] It has been demonstrated that inhibition of ACAT in the intestine prevents the absorption of cholesterol and reduces the total plasma cholesterol level in several cholesterol-fed animals.[4,5] In addition, it has been reported that inhibition of ACAT in the liver can reduce the release of lipoprotein into the circulation and effectively reduce the total plasma cholesterol level.[6,7] Furthermore, the inhibition of ACAT in the arterial wall may effectively prevent the formation of foam cells which are thought to play an important role in atherosclerosis.[8] Therefore, a systemically available ACAT inhibitor is an attractive target for new treatments of hyperlipidemia and atherosclerosis.

In recent years a number of ACAT inhibitors have been reported.[9] Most of them consist of an aromatic ring moiety and a lipophilic long-chain moiety and fall into two major classes: amide derivatives and urea derivatives. At the time we initiated this research, ACAT inhibitors of these two classes, CL-277082 (**2**)[10] and CI-976 (**3**),[11] had been reported (Figure 1). Our interest in this area was to find more potent ACAT inhibitors,

Figure 1. General structures for *N*-(4-oxochroman-8-yl)amide derivatives **1** and *N*-(bicyclic-aryl)amides **4**. ACAT inhibitors: CL-277082 (**2**) and CI-976 (**3**).

particularly in vivo, than those known such as CI-976. It was believed that a bioavailable ACAT inhibitor with more potent ACAT inhibitory activity in vitro might have more potent hypocholesterolemic and antiatherosclerotic effects in vivo. In the structure of the fatty acid anilide **3**, the long-chain aliphatic acyl moiety seems to mimic structurally the acyl moiety of long-chain fatty acyl-CoA, one of the substrates of ACAT. Therefore, it was our view that functionalities in the long-chain aliphatic acyl moiety did not play a key role in potent ACAT inhibition. It was also reported that a substitution pattern on the benzene ring of the fatty acid

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Scheme 1. Preparation of Target Molecules by Method B[a]

Y = $C(CH_3)_2(CH_2)_9CH_3$

[a] Reagents: (a) HNO_3, Ac_2O, 15 °C; (b) H_2 (1 atm), 5% Pd/C, EtOH, room temperature; (c) CH_3I, K_2CO_3, acetone, reflux, 14 h.

anilide is important for ACAT inhibitory activity.[11b] For these reasons, our research interest focused on the discovery of a novel aryl moiety for potent inhibition. We expected that modification of the aryl moiety could increase activity by adding a favorable interaction with ACAT. Following this concept, we initiated a search for novel aryl moieties which were able to introduce new functionalities. We designed and synthesized novel amide derivatives having a bicyclic *N*-aryl moiety represented by **4** and tested for their ability to inhibit ACAT.

These derivatives which include novel *N*-(dihydro-1-benzopyran-8-yl)amide derivatives were tested for their ability to inhibit intestinal ACAT in vitro and to lower serum total cholesterol in cholesterol-fed rats in vivo. Among the synthesized compounds, *N*-(4-oxochroman-8-yl)amide derivatives represented by the general structure **1** showed potent ACAT inhibitory activity both in vitro and in vivo. In this paper, we describe the synthesis and structure–activity relationships of these novel ACAT inhibitors.

Chemistry

A coupling of the corresponding aromatic amine with the appropriate acid chloride in the presence of triethylamine (method A) was used to synthesize the majority of compounds (general structures **1** and **4**) described in this paper. Preparation of compounds **40** and **41**, which have an amino group at position 6 of the 4-chromanone, was achieved by method B as outlined in Scheme 1. Nitration of *N*-(7-methoxy-4-oxochroman-8-yl)amide **35** afforded *N*-(7-methoxy-6-nitro-4-oxochroman-8-yl)amide **39**, which was reduced by catalytic hydrogenation to the corresponding *N*-(6-amino-7-methoxy-4-oxochroman-8-yl)amide. Methylation of the amino group with CH_3I/K_2CO_3/acetone gave 6-methylamino derivative **40** and 6-dimethylamino derivative **41**. The benzamide analog **62** was prepared as shown in Scheme 2 (method C). 8-Amino-7-methoxy-4-chromanone (**9b**) was acylated with 4-hydroxybenzoic acid using DCC as a coupling agent. Alkylation of the resulting 4-hydroxybenzamide with alkyl bromide/K_2CO_3 gave **62**.

Preparations of arylamine intermediates which were used in methods A and C are outlined in Schemes 3–6. 7-Substituted 8-aminochromones **8a–c,e**, 7-substituted 8-amino-4-chromanones **9b,d–f**, and 7-substituted 8-aminochroman **10b** were synthesized as shown in Scheme 3. 7-Substituted chromones **6a–f** were prepared from

Scheme 2. Preparation of Target Molecule **62** by Method C[a]

R = $(CH_2)_6OCH_2CH(CH_3)_2$

[a] Reagents: (a) 4-hydroxybenzoic acid, DCC, DMAP, CH_2Cl_2, room temperature; (b) RBr, K_2CO_3, CH_3CN, reflux.

Scheme 3. Preparation of 8-Aminochromones, 8-Amino-4-chromanones, and 8-Aminochroman[a]

5a: R = CH_3, X = H
5b: R = OCH_3, X = H
5c: R = OCH_3, X = CH_2CH_3
5d: R = $O(CH_2)_2CH_3$, X = H
5e: R = $O(CH_2)_9CH_3$, X = H
5f: R = Cl, X = H

[a] Reagents: (a) XCO_2Et, Na powder, ether, room temperature; (b) HCl/CH_3COOH, 100 °C; (c) HNO_3, H_2SO_4, 10 °C; (d) Fe powder, AcOH/H_2O, 100 °C; (e) H_2, 5% Pd/C, Et_3N/dioxane, room temperature; (f) H_2, 5% Pd/C, HCl/EtOH, room temperature.

the corresponding 4-substituted 2-hydroxyacetophenones **5a–f** by (a) condensation with the corresponding ester using sodium powder[12] followed by (b) treatment with acid. (c) Nitration[13] of 7-substituted chromones **6a–f** with HNO_3/H_2SO_4 afforded selectively 7-substituted 8-nitrochromones **7a–f**. Selective introduction of the nitro group at position 8 could be achieved only by nitration of the chromones **6a–f**. Nitration of 4-substituted 2-hydroxyacetophenones or 7-substituted 4-chromanones gave a mixture of nitrated isomers. (d) Reduction of the nitro group of 7-substituted 8-nitrochromones **7a–c,e** with iron[14] afforded 7-substituted 8-aminochromones **8a–c,e**. (e) Selective reduction of the nitro group and the double bond of **7b,d–f** to the corresponding 7-substituted 8-amino-4-chromanones **9b,d–f** was achieved by catalytic hydrogenation in the presence of Pd/C. It was necessary to carry out the hydrogenation under a basic condition in order to avoid reduction of the carbonyl group at position 4 to a hydroxy group. (f) Hydrogenation of the carbonyl group of **9b** in the presence of Pd/C under an acidic condition[15] afforded 7-substituted 8-aminochroman **10b**.

8-Amino-7-methyl-4-chromanone (**12**) was prepared as shown in Scheme 4. Reaction of 3-methyl-2-nitrophenol with 3-bromopropionic acid gave phenoxypropionic acid **11**. Cyclization of **11** using phosphorus pentoxide[16] followed by reduction of the nitro group afforded 8-amino-7-methyl-4-chromanone (**12**). 8-Amino-5,7-dimethyl-4-chromanone (**14**) was prepared as shown in Scheme 5. Reaction of 4-chloro-3,5-xylenol with 3-chloropropionyl chloride gave the corresponding phenyl ester. Fries rearrangement of the ester followed by

Scheme 4. Preparation of 8-Amino-7-methyl-4-chromanone[a]

[a] Reagents: (a) $BrCH_2CH_2COOH$, K_2CO_3, acetone, reflux, 14 h; (b) 1. P_2O_5, benzene, reflux, 4 h, 2. Fe powder, $AcOH/H_2O$, 100 °C, 1 h.

Scheme 5. Preparation of 8-Amino-5,7-dimethyl-4-chromanone[a]

[a] Reagents: (a) 1. $ClCO(CH_2)_2Cl$, 95 °C, 2. $AlCl_3$, 130 °C; (b) 1. HNO_3, H_2SO_4, room temperature, 2. H_2, 5% Pd/C, Et_3N/AcOEt.

Scheme 6. Preparation of 7-Alkoxy-8-amino-4-chromanones[a]

17g: R = $(CH_2)_6Ph$
17h: R = $(CH_2)_4O(Ph\text{-}p\text{-}OCH_3)$

[a] Reagents: (a) $BBr_3/CHCl_3$, −78 °C → room temperature; (b) HNO_3, H_2SO_4, room temperature; (c) 1. RBr, K_2CO_3, LiI, DMF, 90 °C, 2. H_2, 5% Pd/C, Et_3N/dioxane.

cyclization using $AlCl_3$ at 130 °C afforded 6-chloro-5,7-dimethyl-4-chromanone (**13**). Nitration of the chromanone followed by both reduction of the nitro group and hydrogenolysis of the C-Cl bond by catalytic hydrogenation under a basic condition gave 8-amino-5,7-dimethyl-4-chromanone (**14**). 8-Amino-7-[(6-phenylhexyl)oxy]-4-chromanone (**17g**) and 8-amino-7-[4-[(4-methoxyphenyl)oxy]butoxy]-4-chromanone (**17h**) were prepared as shown in Scheme 6. Cleavage of the methoxy group of 7-methoxychromone (**6b**) using BBr_3 gave 7-hydroxychromone (**15**). Nitration of chromone **15** afforded 7-hydroxy-8-nitrochromone (**16**), which was alkylated by the corresponding alkyl bromides followed by catalytic hydrogenation under the same basic condition as step e in Scheme 3 to afford chromanone compounds **17g,h**.

The acid chlorides used in the general method A were prepared as follows. α,α-Dimethyl carboxylic acids were prepared by alkylation of the dianion of the isobutyric acid by treatment with 2 equiv of LDA. Alternatively, alkylation of the anion of methyl isobutyrate by treatment with 1 equiv of LDA followed by hydrolysis gave the carboxylic acids. The acid chlorides were prepared from the corresponding carboxylic acids by treatment with thionyl chloride. Some of the α,α-dimethylalkanoyl chlorides substituted by an alkoxy or aryloxy group were prepared from the corresponding methyl 2-(bromoalkyl)-isobutyrate which was prepared by alkylation of the anion of methyl isobutyrate using the corresponding dibromoalkane. 4-Alkoxybenzoyl chlorides were prepared from methyl 4-hydroxybenzoate.

Results and Discussion

The structures and the biological activities of the synthesized compounds are shown in Tables 1−7. The ACAT inhibitory activities were determined using [1-^{14}C]-oleoyl-CoA as enzyme substrate and small intestinal microsomes from cholesterol-fed rabbits as enzyme source. The IC_{50}, which is the concentration that inhibited 50% of the enzyme activity, was determined for all compounds. Serum total cholesterol-lowering activity was assessed in the cholesterol-fed animal model in which male Wistar rats were administered an oral dose of tested compound once a day and then allowed to consume overnight a diet supplemented with cholesterol (2%), cholic acid (1%), casein (20%), sucrose (45%), coconut oil (12%), KC flock (4%), vitamin mixture (1%), mineral mixture (7%), and dried fish powder (8%). After 3 days of oral administration and cholesterol feeding, the animals were fasted for 16 h, and blood samples were collected. Serum total cholesterol was measured, and the percent change vs the difference between the control and normal levels was determined.

The compounds listed in Table 1 were synthesized to study the effects of substituents on the 4-chromanone ring of the *N*-(4-oxochroman-8-yl)amides. In this study, we used the acyl moieties A−D listed in the table. Roth *et al.* reported[11b] that in the series of *N*-(2,4,6-trimethoxyphenyl)amides, the anilides of α,α-disubstituted saturated fatty acids possessing the group A or B were found to have ACAT inhibitory activities both in vitro and in vivo. During the course of our investigation, we found that α,α-dimethylalkanoyl amides substituted by a phenoxy group, such as C and D in Table 1, also have similar in vitro and in vivo activities as analogs of A or B. For these reasons, using these acyl structures A−D, novel *N*-(bicyclic-aryl)amides were synthesized.

In the series of *N*-(4-oxochroman-8-yl)amide derivatives (Table 1), among the substitution groups R_1 at the 7-position of the chromanone, the 7-alkoxy derivatives **35** and **37** showed the most potent activity in vitro. The activity was decreased in the order alkoxy (**35**, **37**) > chloro (**38**) > methyl (**32**). To study further the structure−activity relationships of these *N*-(4-oxochroman-8-yl)amides, we synthesized *N*-(chromon-8-yl)amides and the related bicyclic arylamides shown in Table 2. In comparison to the chromanone analogs **33** and **35**, the corresponding chromone analogs **42** and **43** showed reduced activity. From the results of these chromone compounds, we found that sp^3 carbons at positions 2 and 3 (chromanone ring) were better than sp^2 carbons at the same positions (chromone ring). The reason for this effect is unknown but might be related to conformational change between the chromanone ring and the chromone ring. Replacement of the C=O group at position 4 of **35** by the CH_2 group (**45**) resulted in a dramatic loss of activity.

Thus, it became obvious that the *N*-(7-alkoxy-4-oxochroman-8-yl)amide is one of the optimal structures for potent ACAT inhibitory activity. The results of the above series revealed the following features. (1) The carbonyl group at position 4 of the chromanone was essential for potent activity. (2) Substituents at the 7-position of the chromanone had significant effects on

Table 1. Chemical Properties and Biological Data for N-(4-Oxochroman-8-yl)amides

Y = (A) $C(CH_3)_2(CH_2)_9CH_3$; (B) 1-cyclopentyl-$(CH_2)_9CH_3$; (C) $C(CH_3)_2(CH_2)_6O$-4-chlorophenyl; (D) $C(CH_3)_2(CH_2)_5O$-4-chlorophenyl

compd	R_1	R_2	R_3	Y	yield, %[a] (method)	mp, °C	formula[b]	ACAT inhibition IC_{50}, μM[c]	percent change TC,[d] % (mg/kg)[e]
31	CH_3	H	H	B	88 (A)	61–62	$C_{26}H_{39}NO_3$	0.17	NT[f]
32	CH_3	H	H	A	89 (A)	80–81	$C_{24}H_{37}NO_3$	0.21	−48 (10)
33	CH_3	H	H	D	78 (A)	94	$C_{25}H_{30}NO_4Cl$	0.47	−53 (10)
34	CH_3	H	CH_3	D	96 (A)	95–96	$C_{26}H_{32}NO_4Cl$	0.40	NT[f]
35	OCH_3	H	H	A	77 (A)	130–131	$C_{24}H_{37}NO_4$	0.013	−61 (0.1)
36	OCH_3	H	H	C	73 (A)	89–90	$C_{26}H_{32}NO_5Cl$	0.064	−53 (0.3)
37	$O(CH_2)_2CH_3$	H	H	A	70 (A)	131–133	$C_{26}H_{41}NO_4$	0.014	NT[f]
38	Cl	H	H	A	91 (A)	oil	$C_{23}H_{34}NO_3Cl$	0.15	NT[f]
39	OCH_3	NO_2	H	A	32 (B-a)	85–86	C_{24}[g]$H_{36}N_2O_6$	0.034	NT[f]
40	OCH_3	$NHCH_3$	H	A	45 (B-c)	oil	$C_{25}H_{40}N_2O_4$	0.049	NT[f]
41	OCH_3	$N(CH_3)_2$	H	A	33 (B-c)	oil	$C_{26}H_{42}N_2O_4$	>0.2	NT[f]

[a] Yield (%) of final step. [b] Satisfactory elemental analyses were obtained for C, H, and N unless otherwise indicated. [c] IC_{50} (μM) for the enzyme obtained from rabbit intestine microsomes. [d] Serum total cholesterol-lowering activity in the cholesterol-fed rat expressed as the ratio of the observed reduction to the difference between the control and normal levels × 100. [e] Dose: compounds were administered orally to rats at the indicated dose once a day for 3 days. [f] Not tested. [g] Calcd, 64.26; found, 63.74.

Table 2. Chemical Properties and Biological Data for N-(4-Chromon-8-yl)amides and Related Compounds

X–NH–C(=O)–Y

compd	X	Y[d]	yield, %[a] (method)	mp, °C	formula[b]	ACAT inhibition IC_{50}, μM[c]
42	7-H_3C-4-chromon-8-yl	D	76 (A)	94–96	$C_{25}H_{28}NO_4Cl$	>0.5
43	7-H_3CO-4-chromon-8-yl	A	70 (A)	amorphous solid	$C_{24}H_{35}NO_4$	0.077
44	7-H_3CO-2-CH_2CH_3-4-chromon-8-yl	A	76 (A)	oil	$C_{26}H_{39}NO_4$	0.78
45	7-H_3CO-chroman-8-yl	A	95 (A)	oil	$C_{24}H_{39}NO_3$	0.18
46	7-H_3C-4-oxo-tetrahydroquinolin-8-yl	B	46 (A)	81–82	$C_{26}H_{40}N_2O_2$	0.43
47	6-H_3CO-4-oxochroman-5-yl	C	86 (A)	76–77	$C_{26}H_{32}NO_5Cl$	0.18

[a–c] See corresponding footnotes of Table 1. [d] See corresponding structures in Table 1.

ACAT inhibitory activity. Optimal activity was obtained in the case of an alkoxy group. The methoxy group at this position was preferable for potent in vivo activity. (3) Substituents at positions 5 and 6 of the chromanone were acceptable, except for a dimethylamino group at position 6. (4) The -O- group at position 1 of the chromanone could be replaced by an -NH- group, but the -O- group was preferable. (5) As the aryl moiety, chromanone rings were preferable to chromone rings. In addition, we examined some N-(7-methyl-4-oxochroman-8-yl)urea derivatives; however, all of those resulted in rather reduced activity (data not shown). For these reasons, N-(7-methoxy-4-oxochroman-8-yl)amides were selected for further investigation.

The analogs listed in Tables 3–5 were synthesized to examine the effect of the acyl moiety (-CO-Y group in general structure **1**). The 7-methoxy(or 7-methyl)-4-oxochroman-8-yl group was selected as the common

Table 3. Chemical Properties and Biological Data for *N*-(4-Oxochroman-8-yl)amides

compd	R_1	R	yield, %[a] (method)	mp, °C	formula[b]	ACAT inhibition IC_{50}, μM[c]	percent change TC,[d] % (mg/kg)[e]
48	OCH_3	$(CH_2)_7CH_3$	97 (A)	136–137	$C_{22}H_{33}NO_4$	0.031	−71 (1)
35	OCH_3	$(CH_2)_9CH_3$	77 (A)	130–131	$C_{24}H_{37}NO_4$	0.013	−61 (0.1)
49	OCH_3	$(CH_2)_{11}CH_3$	66 (A)	121–122	$C_{26}H_{41}NO_4$	0.0075	NT[f]
50	OCH_3	$(CH_2)_6O(CH_2)_2CH_3$	69 (A)	120–122	$C_{23}H_{35}NO_5$	0.030	NT[f]
51	CH_3	$(CH_2)_6OCH_2CH(CH_3)_2$	70 (A)	amorphous solid	$C_{24}H_{37}NO_4$	0.09	NT[f]
52	OCH_3	$(CH_2)_6OCH_2CH(CH_3)_2$	75 (A)	119–122	$C_{24}H_{37}NO_5$	0.026	−61 (1)

[a–f] See corresponding footnotes of Table 1.

Table 4. Chemical Properties and Biological Data for *N*-(4-Oxochroman-8-yl)amides

compd	R_1	*n*	Z	R	yield, %[a] (method)	mp, °C	formula[b]	ACAT inhibition IC_{50}, μM[c]	percent change TC,[d] % (mg/kg)[e]
53	CH_3	1	bond	H	87 (A)	136	$C_{21}H_{23}NO_3$	>1.0	NT[f]
54	OCH_3	6	bond	H	86 (A)	101–102	$C_{26}H_{33}NO_4$	0.044	NT[f]
55	OCH_3	3	bond	$(CH_2)_2CH_3$	94 (A)	122–124	$C_{26}H_{33}NO_4$	0.027	−54 (1)
56	OCH_3	3	bond	$O(CH_2)_5CH_3$	75 (A)	105–110	$C_{29}H_{39}NO_5$	0.016	−65 (3)
57	OCH_3	3	bond	$CH_2CH(CH_3)_2$	90 (A)	129–130	$C_{27}H_{35}NO_4$	0.017	NT[f]
58	CH_3	4	O	Cl	87 (A)	oil	$C_{24}H_{28}NO_4Cl$	0.51	NT[f]
33	CH_3	5	O	Cl	78 (A)	94	$C_{25}H_{30}NO_4Cl$	0.47	−53 (10)
36	OCH_3	6	O	Cl	73 (A)	89–90	$C_{26}H_{32}NO_5Cl$	0.064	−53 (0.3)

[a–f] See corresponding footnotes of Table 1.

aryl moiety. The results of α,α-dimethylalkanoic acid amides are shown in Table 3. As the R group shown in Table 3, alkyl or alkoxyalkyl groups in the C_8–C_{12} range functioned well for ACAT inhibitory activity. The activity was increased depending on the length of the alkyl chain, in the order of carbon numbers 8 (**48**) < 10 (**35**) < 12 (**49**). A branched alkyl group was introduced at the end of the alkyl chain to increase metabolic stability. Introduction of a methyl group into the straight alkyl chain analog **50** (isobutyloxy analog **52**) retained activity in vitro and resulted in potent in vivo activity. *N*-(7-Methyl-4-oxochroman-8-yl)amide **51** of this branched alkyl series showed similar in vitro activity to the corresponding 2,2-dimethyldodecanamide **32**.

The compounds listed in Table 4 were synthesized to examine the effect of introduction of a benzene ring into the acyl moiety. Introduction of a lipophilic phenylalkyl group (Z = bond) into the acyl moiety (**55**–**57**) retained in vitro activity compared with the corresponding 2,2-dimethyldodecanamide **35**. In the series of *N*-(7-methoxy-4-oxochroman-8-yl)amides, potent activities were obtained when the acyl moiety had a lipophilic group in the C_6–C_9 range (as a total number) in addition to the benzene ring. **55** and **56** showed reduced in vivo activity to the corresponding 2,2-dimethyldodecanamide **35**. Introduction of a lipophilic phenoxyalkyl group (Z = O) into the acyl moiety (**33**, **36**, **58**) reduced in vitro potency compared with the corresponding 2,2-dimethyldodecanamides. However, **33** and **36** showed similar potent in vivo cholesterol-lowering activity to the corresponding 2,2-dimethyldodecanamides **32** and **35**, respectively. Among them, 8-(4-chlorophenoxy)-2,2-dimethyloctanamide derivative **36** was found to be one of the most active compounds in vivo.

The effects of substituents on the benzene ring of *N*-(4-oxochroman-8-yl)benzamides were examined; the results are shown in Table 5. The *N*-(4-oxochroman-8-yl)benzamide derivatives were found to have potent ACAT inhibitory activity in vitro, when they had a highly lipophilic substituent, such as decyloxy (**61**), [6-(isobutyloxy)hexyl]oxy (**62**), and [6-(4-chlorophenoxy)-hexyl]oxy (**63**), at the para position. However, **61** was relatively less effective in vivo in spite of potent activity in vitro. Interestingly, 4-[[6-(4-chlorophenoxy)hexyl]-oxy]-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide (**63**) showed potent activity in vivo.

From these results it is clear that molecular lipophilicity of the *N*-(4-oxochroman-8-yl)amide derivatives is a very important factor for potent ACAT inhibitory activity. In general, introduction of a highly lipophilic group, such as a long alkyl, phenylalkyl, phenoxyalkyl, or alkoxyphenyl, into the acyl moiety resulted in high activity in vitro. One possible interpretation of this effect is that these lipophilic acyl moieties might enhance the interaction between the inhibitors and their binding site in ACAT, although the structure of the inhibitor's binding site is unknown. In vivo activity was

Table 5. Chemical Properties and Biological Data for *N*-(4-Oxochroman-8-yl)benzamides

compd	R_1	R_2	R_3	yield, %[a] (method)	mp, °C	formula[b]	ACAT inhibition IC_{50}, μM[c]	percent change TC,[d] % (mg/kg)[e]
59	CH_3	H	H	68 (A)	148	$C_{17}H_{15}NO_3$	>1.0	NT[f]
60	CH_3	H	OCH_3	59 (A)	189–190	$C_{18}H_{17}NO_4$	>1.0	NT[f]
61	OCH_3	H	$O(CH_2)_9CH_3$	80 (A)	160–161	$C_{27}H_{35}NO_5$	0.012	−14 (3)
62	OCH_3	H	$O(CH_2)_6OCH_2CH(CH_3)_2$	77 (C)	148–150	$C_{27}H_{35}NO_6$	0.040	NT[f]
63	OCH_3	H	$O(CH_2)_6OC_6H_4(4\text{-}Cl)$	76 (A)	160–162	$C_{29}H_{30}NO_6Cl$	0.026	−79 (3)
64	OCH_3	CH_3	$O(CH_2)_9CH_3$	49 (A)	106–108	$C_{29}H_{39}NO_5$	>0.2	NT[f]

[a–f] See corresponding footnotes of Table 1.

Table 6. Chemical Properties and Biological Data for *N*-(7-Alkoxy-4-oxochroman-8-yl)-2,2-dimethylpropanamides and Related Compounds

X–NH–C(=O)–$C(CH_3)_3$

compd	X	yield, %[a] (method)	mp, °C	formula[b]	ACAT inhibition IC_{50}, μM[c]	percent change TC[d] % (mg/kg)[e]
65	$H_3C(CH_2)_9O$– (8-methyl-4-oxochroman-7-yl)	64 (A)	151–152	$C_{24}H_{37}NO_4$	0.014	-79 (1)
66	$H_3C(CH_2)_9O$– (8-methyl-4-oxochromen-7-yl)	52 (A)	109	$C_{24}H_{35}NO_4$	0.13	NT[f]
67	H_3CO–C_6H_4–$O(CH_2)_4O$– (8-methyl-4-oxochroman-7-yl)	61 (A)	119–121	$C_{25}H_{31}NO_6$	0.043	NT[f]
68	C_6H_5–$(CH_2)_6O$– (8-methyl-4-oxochroman-7-yl)	96 (A)	140–141	$C_{26}H_{33}NO_4$	0.024	NT[f]

[a–f] See corresponding footnotes of Table 1.

dramatically changed by modification of the acyl moiety. Among the series of the *N*-(7-methoxy-4-oxochroman-8-yl)amide derivatives, *N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**35**), 8-(4-chlorophenoxy)-*N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyloctanamide (**36**), *N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyl-8-[(2-methylpropyl)oxy]octanamide (**52**), and 4-[[6-(4-chlorophenoxy)hexyl]oxy]-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide (**63**) showed potent activity both in vitro and in vivo.

Recognizing the importance of the molecular lipophilicity, we turned our attention to the effect of a lipophilic group at a position different from the acyl moiety. Introduction of the lipophilic alkoxy group to the 7-position on the chromanone ring of *N*-(7-alkoxy-4-oxochroman-8-yl)amides was examined; the results are shown in Tables 6 and 7. A large lipophilic alkoxy group at position 7 of the *N*-(4-oxochroman-8-yl)amide functioned well for potent ACAT inhibitory activity. Interestingly, high lipophilicity of the acyl moiety was not necessary when the molecule had enough lipophilicity on the alkoxy group at position 7 of the *N*-(4-oxochroman-8-yl) moiety. For example, when the position of the decyl group was switched from the acyl moiety (**35**) to the alkoxy group at the 7-position of the chromanone ring (**65**), the high in vitro potency was retained. Thus, these *N*-(7-alkoxy-4-oxochroman-8-yl)amide analogs **35** and **65**, which have the same highly lipophilic group at different positions of a common skeleton, were found to show similar potent activity both in vitro and in vivo. A similar relationship was observed between the corresponding chromone analogs **43** and **66**. These results suggest that the large lipophilic alkoxy groups can favorably interact with a lipophilic binding site in ACAT.

Two large lipophilic spaces therefore seemed to have been discovered in the binding site of these ACAT inhibitors, one which interacted with the acyl moiety and the other which interacted with the 7-alkoxy group of the aryl moiety. The result of structural overlaps of the active compounds (**35** and **65**) leads to two possible interpretations of the relationship between these lipo-

Table 7. Chemical Properties and Biological Data for *N*-[7-(Decyloxy)-4-oxochroman-8-yl)]amides

compd	Y	yield, %[a] (method)	mp, °C	formula[b]	ACAT inhibition IC_{50}, μM[c]
69	$-CH_3$	74 (A)	152–153	$C_{21}H_{31}NO_4$	0.30
70	$-C(CH_3)_2(CH_2)_9CH_3$	93 (A)	amorphous solid	$C_{33}H_{55}NO_4$	0.85
71	$-C(CH_3)_2(CH_2)_6O-C_6H_4-Cl$	95 (A)	amorphous solid	$C_{35}H_{50}NO_5Cl$	0.14
72	$-C_6H_4-O(CH_2)_9CH_3$	86 (A)	106–107	$C_{36}H_{53}NO_5$	>0.1
73	$-C_6H_4-O(CH_2)_6O-C_6H_4-Cl$	47 (A)	84–85	C_{38}[d] $H_{48}NO_6Cl$	0.54

[a–c] See corresponding footnotes of Table 1. [d] Calcd, 70.19; found, 69.73.

Table 8. Biological Activities of Selected Compounds

compd	ACAT inhibition: rabbit intestine IC_{50}, nM[a]	ACAT inhibition: rabbit liver IC_{50}, nM[b]	hypocholesterolemic activity (rat) percent change TC,[c] % (mg/kg)[d]	foam cell formation inhibition (rat) IC_{50}, nM[e]
35	13	16	−66 (0.3)	160
65	14	22	−45 (0.3)	130
63	26	59	−56 (0.3)	220
36	64	NT[f]	−53 (0.3)	NT[f]
CI-976	140	149	−50 (3.0)	3800

[a] IC_{50} (nM) for the enzyme obtained from rabbit intestine microsomes. [b] IC_{50} (nM) for the enzyme obtained from rabbit liver microsomes. [c] Serum total cholesterol-lowering activity in the cholesterol-fed rat expressed as the ratio of the observed reduction to the difference between the control and normal levels × 100. [d] Dose: compounds were administered orally to rats at the indicated dose once a day for 3 days. [e] IC_{50} (nM) for acetyl-LDL-induced cholesteryl ester accumulation in rat peritoneal macrophages. [f] Not tested.

philic allowed spaces. (1) There are two independent lipophilic spaces around the acyl moiety and around the 7-alkoxy group of the aryl moiety. (2) There is only one common lipophilic space. From this point of view, the analogs listed in Table 7 were synthesized to examine lipophilic sites in the pharmacophore of the *N*-(7-alkoxy-4-oxochroman-8-yl)amide inhibitors. In this series, the *N*-[7-(decyloxy)-4-oxochroman-8-yl]amide structure was selected as the common arylamide moiety. Replacement of the *tert*-butyl group at the acyl moiety of **65** by a methyl group (**69**) resulted in a dramatic loss of activity. Interestingly, all the compounds having two large lipophilic groups (**70**−**73**) were less active than the corresponding 7-methoxy analogs. For example, when the methoxy group of the *N*-(7-methoxy-4-oxochroman-8-yl)amides **35** and **63** was replaced by the decyloxy group, as in **70** and **73**, the activity was reduced by *ca.* 20−60-fold. Among the compounds in Tables 6 and 7, *N*-[7-(decyloxy)-4-oxochroman-8-yl]-2,2-dimethylpropanamide (**65**) showed potent activity in vivo and was found to be the optimal structure for *N*-[7-(decyloxy)-4-oxochroman-8-yl]amide derivatives. Thus, it was found that among these *N*-(7-alkoxy-4-oxochroman-8-yl)amides, compounds which have two large lipophilic groups showed dramatically decreased activity. The highly lipophilic substituent either at the 7-position of the chromanone or at the acyl moiety was necessary and sufficient for potent ACAT inhibitory activity. One possible interpretation of this observation is that there is only one large allowed area for the lipophilic group in the binding site of these inhibitors, and the volume of this area is not enough for two large lipophilic groups to interact. Furthermore, these lipophilic groups might increase the affinity for membrane. ACAT is reported to be a membrane protein located in the endoplasmic reticulum;[2a] therefore, the molecular lipophilicity might be important for achieving potent activity.

Selected compounds **35**, **65**, **63**, and CI-976 were further evaluated for their ability to inhibit rabbit liver ACAT and acetyl-LDL-induced cholesteryl ester accumulation in rat peritoneal macrophages (foam cell formation). The results of these in vitro assays and the in vivo effect on total plasma cholesterol concentrations in cholesterol-fed rats are summarized in Table 8. In vitro, our compounds displayed high inhibitory potency (rabbit intestine IC_{50} = 13−64 nM, rabbit liver IC_{50} = 16−59 nM) and foam cell formation inhibitory activity (rat peritoneal macrophage IC_{50} = 160−220 nM). Under the same conditions, the IC_{50} value of CI-976 was 140 nM (rabbit intestine), 149 nM (rabbit liver), and 3800 nM (rat peritoneal macrophage), respectively. Furthermore, these compounds were *ca.* 10-fold more potent with respect to hypocholesterolemic activity in vivo than CI-976, that is, in cholesterol-fed rats, our

compounds lowered serum cholesterol 45–66% at a dose of 0.3 mg/kg/day. Under the same conditions, CI-976 lowered serum cholesterol 25% at a dose of 1.0 mg/kg/day and 50% at a dose of 3.0 mg/kg/day. On the basis of these findings, we conclude that the *N*-(7-alkoxy-4-oxochroman-8-yl)amide is one of the optimal structures for the potent ACAT inhibitory activity, particularly in vivo. Inhibitors such as **35** may serve as useful therapeutic agents for the treatment of hyperlipidemia and atherosclerosis. Compounds **35**, **65**, and **63** were selected for further pharmacological and toxicological studies.

Conclusion

This study has identified a novel series of *N*-(7-alkoxy-4-oxochroman-8-yl)amides with potent ACAT inhibitory activities. Examination of structure–activity relationships in this series has revealed the following features. (1) The carbonyl group at position 4 of the 4-chromanone was essential for potent activity. (2) A substituent at position 7 of the 4-chromanone moiety was important. Optimal in vitro activity was obtained in the case of an alkoxy group. This 7-alkoxy group was also important for potent in vivo activity. (3) sp^3 carbons at positions 2 and 3 (chromanone ring) were better than sp^2 carbons at the same positions (chromone ring). (4) The necessary factor to elicit the potent ACAT inhibitory activity was high lipophilicity of the molecules. Introduction of a lipophilic group either at the 7-position of the chromanone ring or at the acyl moiety resulted in potent activity.

Thus, two series of highly potent ACAT inhibitors were found. (1) In the series of *N*-(7-methoxy-4-oxochroman-8-yl)amides, the highly lipophilic carboxylic acid amides *N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**35**), 8-(4-chlorophenoxy)-*N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyloctanamide (**36**), and 4-[[6-(4-chlorophenoxy)hexyl]oxy]-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide (**63**) showed potent ACAT inhibitory activity both in vitro and in vivo. (2) In the series of *N*-[7-(decyloxy)-4-oxochroman-8-yl]amides, *N*-[7-(decyloxy)-4-oxochroman-8-yl]-2,2-dimethylpropanamide (**65**) was the optimal compound for potent ACAT inhibitory activity both in vitro and in vivo. The most potent compound among them, *N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**35**, TEI-6522), showed significant in vitro inhibition of rabbit intestinal ACAT (IC_{50} = 13 nM, 11-fold more potent than CI-976), rabbit hepatic ACAT (IC_{50} = 16 nM, 9-fold more potent than CI-976), and foam cell formation (rat peritoneal macrophage IC_{50} = 160 nM, 24-fold more potent than CI-976). This ACAT inhibitor showed the most potent total serum cholesterol-lowering activity in cholesterol-fed rats (61% at a dose of 0.1 mg/kg/day po, *ca.* 10-fold more potent than CI-976).

Experimental Section

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-5300 spectrometer. NMR spectra were acquired in the indicated solvent on a JEOL-EX270, JEOL-GX400 FTNMR, or Hitachi R-90H spectrometer with Me_4Si as an internal standard. The abbreviations are as follows: s = singlet, t = triplet, q = quartet, m = multiplet, br = broad. Mass (MS) spectra were taken on a Hitachi M-80B instrument. Elemental analyses were performed by Toray Research Center Inc. or the Analytical Reseach Department, Teijin Ltd. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Thin layer chromatography (TLC) was performed on E. Merck Kieselgel 60 F-254 plates. Column chromatography was performed with E. Merck silica gel 60 (40–63 μm, 230–400 mesh) under low pressure. Unless otherwise noted, materials were obtained from a commercial source and used without further purification. CI-976 was synthesized in our laboratory following the published procedure[11b] and characterized by NMR and elemental analysis (C, H, N).

Assay of in Vitro ACAT Inhibitory Activity of Rabbit Intestinal Microsomes. Preparation of a Japanese white rabbit intestinal mucosa microsome and assay of the ACAT activity were based on a method established by Salome and Field[17] with some modifications. The Japanese white rabbit intestinal mucosa was homogenized using a 40 mM phosphate buffer (pH 7.4; buffer A) containing 30 mM EDTA, 50 mM KCl, and 0.1 M sucrose and centrifuged at 10000*g* for 30 min at 4 °C to provide a supernatant. The supernatant was further centrifuged at 105000*g* for 1 h at 4 °C to provide a precipitate. The precipitate was resuspended in buffer A to provide a microsome fraction; 1% (v/v) of a dimethyl sulfoxide solution of each test compound was added to buffer A containing 43 μM serum albumin and 0.5 mg/mL microsome fraction, and the mixture was heated at 37 °C for 5 min. Then, 43 μM oleoyl-CoA containing [1-^{14}C]oleoyl-CoA (3.7 kBq) was added, and the mixture was heated at 37 °C for 10 min. The reaction was terminated by the addition of chloroform–methanol (2:1, v/v) containing 10 mg/mL cholesteryl oleate. Then, 0.111 kBq of [^{3}H]cholesteryl oleate and 1 N hydrochloric acid were added, and the mixture was stirred. The cholesteryl oleate extracted into the chloroform layer was isolated by thin-layer chromatography on plastic sheets (TLC plastic sheets, silica gel 60; Merck Co.), and the radioactivity was measured as the ACAT activity. For all test compounds, the IC_{50}, which is the concentration that inhibited 50% of the enzyme activity, was determined.

Assay of in Vitro ACAT Inhibitory Activity of Rabbit Liver. Assay of the liver ACAT activity was based on a method established by Suckling[18] with some modifications. The liver microsomes were prepared using a 0.154 M phosphate buffer (pH 7.4; buffer B) containing 40 mM NaF from Japanese white rabbits; 1% (v/v) of a dimethyl sulfoxide solution of each test compound was added to buffer B containing 36 μM bovine serum albumin, 2 mM dithiothreitol, 0.5 mg/mL microsome fraction, and sonicated liposome preparation (phosphatidylcholine:phophatidylseline:cholesterol = 3:1:8, 8 mg/mL cholesterol), and the mixture was heated at 37 °C for 3 min. Then, 43 μM oleoyl-CoA containing [1-^{14}C]oleoyl-CoA (3.7 kBq) was added, and the mixture was heated at 37 °C for 10 min. Produced cholesteryl oleate was measured by the same method as that used in the intestinal microsome ACAT assay. For all test compounds, the IC_{50}, which is the concentration that inhibited 50% of the enzyme activity, was determined.

Assay of Percent Change of Serum Total Cholesterol Level. Male Wistar rats (8–9 weeks old, 200 g body weight, n = 6/group) were preliminarily fed a normal diet (CE-2 manufactured by CLEA Japan Inc.) for 7 days. Thereafter, high-cholesterol animals were fed a diet supplemented with cholesterol and fat (2% cholesterol, 1% cholic acid, 20% casein, 45% sucrose, 12% coconut oil, 4% KC flock, 1% vitamin mixture, 7% mineral mixture, and 8% dried fish powder; product of CLEA Japan Inc.) for 3 days; normal animals were continuously fed a normal diet for 3 days. During the cholesterol-loading period, the test compound suspended in 0.5% methyl cellulose solution was orally administered at a dose of 0.1–10 mg/kg once a day for 3 days. The vehicle alone was administered to the high-cholesterol control and normal animals. After the last administration, the test animals were fasted for 16 h and blood samples were collected from the abdominal aorta under ether anesthesia. The serum cholesterol level was measured by enzymatic method. The results were compared with those of the control and are shown in the tables as percent change in serum total cholesterol. Percent change of serum total cholesterol (%) = $[(A - B)/(B - C)] \times$

100, wherein A represents the total cholesterol level of serum in the group of rats to which the test compound was administered and B and C represent the total cholesterol level of serum in the control and normal group of rats, respectively.

Assay of Inhibitory Activity of Macrophage Foam Cell Formation. Peritoneal macrophages were collected from nonstimulated male Wistar rats (250−300 g) and suspended in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine serum, streptomycin (0.1 mg/mL), and penicillin (100 units/mL) (10% FBS-DMEM). Macrophages (3×10^6) in 1 mL of 10% FBS-DMEM were seeded to each plastic dish (35 mm diameter) and incubated for 2 h at 37 °C in 5% CO_2. The monolayers thus formed were washed three times with 1.0 mL of Dulbecco's modified Eagle medium supplemented with 3% bovine serum albumin, streptomycin, and penicillin (3% BSA-DMEM). Each well was incubated with 1 mL of 3% BSA-DMEM containing 25 μg/mL acetylated human LDL, 10 μmol/mL [^{14}C]oleate−BSA conjugate (16.7 kBq), and each test compound for 16 h at 37 °C in 5% CO_2. Control well was incubated without test compound, and blank well was incubated without acetylated human LDL and test compound. Then, each well was washed four times with 1.5 mL of phosphate-buffered saline. Cellular lipids were extracted with 1 mL of *n*-hexane−2-propanol (3:2, v/v) containing 20 μg/mL [^{3}H]cholesteryl oleate (167 Bq). The cholesteryl oleate extracted was isolated by thin layer chromatography, and the radioactivity was measured as the cellular cholesteryl ester accumulation. For all test compounds, the IC_{50}, which is the concentration that inhibited 50% of the cellular cholesteryl ester accumulation, was determined.

Preparation of 7-Substituted Chromones 6a−f. General Procedure. Sodium (12.7 g, 0.55 mol) in dry xylene (100 mL) was heated until the sodium was melted, and the mixture was stirred vigorously. After the sodium turned into powder, the mixture was cooled to room temperature, the xylene was removed by decantation, and the powdered sodium was washed twice with dry ether (50 mL). To a well-stirred suspension of the powdered sodium in dry ether (100 mL) was slowly added a solution of 2-hydroxy-4-methoxyacetophenone (**5b**; 30.7 g, 0.185 mmol) and ethyl formate (41.0 g, 0.55 mmol) in dry ether (100 mL) under Ar at 0 °C. Stirring was continued at 0 °C for 1 h and then at room temperature for 14 h. The reaction mixture was poured into ice−water (400 mL) containing 12.5% acetic acid and extracted with ethyl acetate (600 mL). The organic layer was evaporated, and the residue was mixed with glacial acetic acid (150 mL) and concentrated HCl (10 mL) and then heated at 100 °C for 0.5 h. Acetic acid was removed under reduced pressure, and 300 mL of water was added. The mixture was basified by adding $NaHCO_3$ (pH 8) and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford 7-methoxychromone (**6b**): 31.10 g, 95% yield, colorless solid; mp 107−108 °C (recrystallization from AcOEt/hexane); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.91 (s, 3 H), 6.28 (d, 1 H, *J* = 5.9 Hz), 6.84 (d, 1 H, *J* = 2.3 Hz), 6.98 (dd, 1 H, *J* = 8.9, 2.3 Hz), 7.78 (d, 1 H, *J* = 5.9 Hz), 8.12 (d, 1 H, *J* = 8.9 Hz).

Chromones **6a,c−f** were similarly prepared using this method.

Preparation of 7-Substituted 8-Nitrochromones 7a−f. General Procedure. Nitric acid (61%, 14.2 g, 1.05 equiv) in concentrated sulfuric acid (20 mL) was slowly added to a solution of 7-methoxychromone (**6b**; 26.4 g, 0.150 mmol) in concentrated sulfuric acid (100 mL) with stirring at 0−15 °C (ice−water bath). The reaction mixture was stirred for 1 h in an ice−water bath and then poured into ice. The precipitated product was filtered, washed with water, and dried. Recrystallization from AcOEt (800 mL) afforded 7-methoxy-8-nitrochromone (**7b**): 27.42 g, 83% yield, pale yellow needles; mp 229−232 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 4.06 (s, 3 H), 6.35 (d, 1 H, *J* = 6.1 Hz), 7.13 (d, 1 H, *J* = 9.2 Hz), 7.79 (d, 1 H, *J* = 6.1 Hz), 8.29 (d, 1 H, *J* = 9.2 Hz).

Nitrochromones **7a,c−f** were similarly prepared using this method.

8-Amino-7-methoxychromone (8b). Fe powder (4.60 g, 82.4 mmol) was added to a well-stirred mixture of **7b** (4.47 g, 20.2 mmol) and acetic acid (25 mL) in H_2O (200 mL) at 100 °C. The reaction was allowed to proceed at 100 °C for 15 h. The Fe powder was removed by filtration, and the mixture was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, and the solvent was removed at reduced pressure to afford 8-amino-7-methoxychromone (**8b**): 1.69 g, 44% yield, yellow solid; mp 95−98 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.98 (s, 3 H), 4.08 (br, 2 H), 6.25 (d, 1 H, *J* = 5.9 Hz), 6.95 (d, 1 H, *J* = 8.9 Hz), 7.61 (d, 1 H, *J* = 8.9 Hz), 7.83 (d, 1 H, *J* = 5.9 Hz).

Aminochromones **8a,c,e** were similarly prepared using this method.

8-Amino-7-methoxy-4-chromanone (9b). A solution of 7-methoxy-8-nitrochromone (**7b**; 40.0 g, 0.181 mmol) in 1,4-dioxane (700 mL) and triethylamine (80 mL) was hydrogenated at 1 atm for 21 h in the presence of 5% palladium on charcoal (12 g in 40 mL of H_2O) at room temperature. The catalyst was removed by filtration through Celite and washed with EtOH (300 mL). The combined filtrate was evaporated. To the concentrated mixture was added CH_2Cl_2 (300 mL), and the organic layer was washed successively with H_2O and brine and dried over $MgSO_4$. After removal of the solvent, the crude product was recrystallized (from CH_2Cl_2/*tert*-butyl methyl ether) to give 8-amino-7-methoxy-4-chromanone (**9b**): 28.98 g, 83% yield, colorless prisms; mp 83−84 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.78 (t, 2 H, *J* = 6.3 Hz), 3.8 (br, 1 H), 3.92 (s, 3 H), 4.56 (t, 2 H, *J* = 6.3 Hz), 6.59 (d, 1 H, *J* = 8.7 Hz), 7.39 (d, 1 H, *J* = 8.7 Hz). Anal. ($C_{10}H_{11}NO_3$) C, H, N.

Aminochromanones **9d,f** were similarly prepared using this method.

8-Amino-7-(decyloxy)-4-chromanone (9e). A solution of 7-(decyloxy)-8-nitrochromone (**7e**; 69.54 g, 200 mmol) in 1,4-dioxane (800 mL) and triethylamine (100 mL) was hydrogenated at 1 atm for 20 h in the presence of 5% palladium on charcoal (20 g) at 40 °C. The catalyst was removed by filtration through Celite and washed with EtOH (400 mL). The combined filtrate was evaporated. The crude product was recrystallized (from MeOH) to give 8-amino-7-(decyloxy)-4-chromanone (**9e**): 50.86 g, 80% yield, pale yellow prisms; mp 64 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 3 H, *J* = 6.6 Hz), 1.2−1.6 (m, 14 H), 1.82 (dt, 2 H, *J* = 14.2, 6.5 Hz), 2.77 (t, 2 H, *J* = 6.3 Hz), 3.81 (br, 1 H), 4.06 (t, 2 H, *J* = 6.6 Hz), 4.56 (t, 2 H, *J* = 6.3 Hz), 6.57 (d, 1 H, *J* = 8.7 Hz), 7.36 (d, 1 H, *J* = 8.7 Hz).

7-Hydroxychromone (15). BBr_3 (403 μL, 4.26 mmol) was added to a solution of 7-methoxychromone (**6b**; 500 mg, 2.84 mmol) in CH_2Cl_2 (10 mL) with stirring under Ar at −78 °C. Stirring was continued at −78 °C for 1 h and then at room temperature for 20 h. The reaction mixture was poured into ice−water, neutralized by $NaHCO_3$ to pH 5, and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford 7-hydroxychromone (**15**): 403 mg, 88% yield, yellow solid; mp 217−218 °C dec; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.03 (br, 1 H), 6.28 (d, 1 H, *J* = 6.0 Hz), 6.86 (d, 1 H, *J* = 2.0 Hz), 6.92 (dd, 1 H, *J* = 8.9, 2.0 Hz), 7.78 (d, 1 H, *J* = 6.0 Hz), 8.12 (d, 1 H, *J* = 8.9 Hz).

7-Hydroxy-8-nitrochromone (16). In a 25 mL round-bottomed flask was placed a solution of 7-hydroxychromone (0.406 g, 2.50 mmol) in concentrated H_2SO_4 (2.2 mL). The flask was cooled in an ice bath, and the nitrating mixture (concentrated H_2SO_4, 0.53 mL, and concentrated HNO_3, 0.18 mL, 2.8 mmol) was added dropwise over a period of 3 min. The mixture was stirred with ice cooling for 5 h. Crushed ice was added, and the mixture was warmed to room temperature. The separated solid was collected by filtration, washed with water, and dried under vacuum at 100 °C to give 7-hydroxy-8-nitrochromone (**16**): 0.487 g, 94% yield, pale yellow solid; mp 272 °C; ^{1}H NMR (CD_3OD, 270 MHz) δ 6.27−6.40 (m, 1 H), 7.05−7.18 (m, 1 H), 8.00−8.18 (m, 2 H).

8-Amino-7-[(6-phenylhexyl)oxy]-4-chromanone (17g). K_2CO_3 (0.169 g, 1.22 mmol) and LiI (0.019 g, 0.14 mmol) were added to a solution of 7-hydroxy-8-nitrochromone (**16**; 0.226 g, 1.09 mmol) and (6-bromohexyl)benzene (0.261 g, 1.08 mmol) in dimethylformamide (5 mL). The mixture was heated at 90 °C for 24 h with stirring. The reaction mixture was poured

into water and extracted with AcOEt. The combined organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a solid which was purified by column chromatography (hexane–AcOEt, 1:1) to give 8-nitro-7-[(6-phenylhexyl)oxy]chromone as a white solid: 0.268 g, 68% yield; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.30–1.59 (m, 4 H), 1.65 (tt, 2 H, J = 7.6, 7.3 Hz), 1.83 (tt, 2 H, J = 6.6, 6.3 Hz), 2.62 (t, 2 H, J = 7.6 Hz), 4.20 (t, 2 H, J = 6.3 Hz), 6.34 (d, 1 H, J = 5.9 Hz), 7.09 (d, 1 H, J = 9.2 Hz), 7.12–7.33 (m, 5 H), 7.78 (d, 1 H, J = 5.9 Hz), 8.26 (d, 1 H, J = 9.2 Hz).

In a 25 mL round-bottomed flask were placed 8-nitro-7-[(6-phenylhexyl)oxy)]chromone (0.266 g, 0.72 mmol), 5% palladium on charcoal (104 mg), triethylamine (0.50 mL), and dioxane (4 mL). The mixture was stirred under hydrogen at room temperature for 24 h. Filtration through Celite, evaporation of the solvent, and column chromatography (SiO_2, 40 g, hexane–ethyl acetate, 4:1) gave 8-amino-7-[(6-phenylhexyl)-oxy]-4-chromanone (**17g**): 0.164 g, 67% yield, white solid; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.30–1.59 (m, 4 H), 1.66 (tt, 2 H, J = 7.6, 7.3 Hz), 1.83 (tt, 2 H, J = 6.9, 6.6 Hz), 2.62 (t, 2 H, J = 7.6 Hz), 2.77 (t, 2 H, J = 6.3 Hz), 3.80 (brs, 2 H), 4.06 (t, 2 H, J = 6.6 Hz), 4.56 (t, 2 H, J = 6.3 Hz), 6.55 (d, 1 H, J = 8.9 Hz), 7.15–7.30 (m, 5 H), 7.36 (d, 1 H, J = 8.9 Hz).

Aminochromanone **17h** was similarly prepared using this method.

***N*-(7-Methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (35, TEI-6522). Method A.** 2,2-Dimethyldodecanoyl chloride (49.6 g, 201 mmol) was slowly added to a solution of 8-amino-7-methoxy-4-chromanone (**9b**; 38.7 g, 200 mmol) and triethylamine (28 mL, 200 mmol) in dichloromethane (350 mL) with stirring at 10 °C (ice bath). The reaction mixture was stirred for 20 h at room temperature and then cooled with an ice bath; 2 N HCl (350 mL) was added to the reaction mixture, and the mixture was extracted with AcOEt (2 × 500 mL). The combined extracts were washed with 2 N HCl (350 mL) and brine (350 mL) and dried over $MgSO_4$. After removal of the solvent, the crude product was recrystallized (from 600 mL of acetonitrile) to give *N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**35**, TEI-6522): 62.2 g, 77% yield, white solid; mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 3 H, J = 6.3 Hz), 1.15–1.47 (m, 22 H), 1.58 (t, 2 H, J = 7.9 Hz), 2.78 (t, 2 H, J = 6.3 Hz), 3.88 (s, 3 H), 4.53 (t, 2 H, J = 6.3 Hz), 6.64 (d, 1 H, J = 8.9 Hz), 6.76 (br, 1 H), 7.85 (d, 1 H, J = 8.9 Hz); IR (KBr) 1610, 1678 cm^{-1}. Anal. ($C_{24}H_{37}NO_4$) C, H, N.

4-[[6-[(4-Chlorophenyl)oxy]hexyl]oxy]-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide (63). Method A. 4-[[6-(4-Chlorophenoxy)hexyl]oxy]benzoyl chloride (96.8 g, 0.263 mmol) was slowly added to a solution of 8-amino-7-methoxy-4-chromanone (**9b**; 48.5 g, 0.251 mol) and triethylamine (38.1 g, 1.5 equiv) in dichloromethane (700 mL) with stirring at room temperature. The reaction mixture was stirred for 14 h at room temperature, and then dichloromethane (2 L) was added to the reaction mixture to dissolve the precipitated product. The solution was washed successively with 1 N HCl (2 × 250 mL), 1 N NaOH (2 × 250 mL), H_2O (250 mL), and brine and dried over $MgSO_4$. After removal of the solvent, the crude product was recrystallized (from 2-butanone, 1.8 L) to give 4-[[6-[(4-chlorophenyl)oxy)hexyl]oxy]-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide (**63**): 99.30 g, 76% yield, white solid; mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.5–1.65 (m, 4 H), 1.75–1.95 (m, 4 H), 2.79 (t, 2 H, J = 6.3 Hz), 3.90 (s, 3 H), 3.95 (t, 2 H, J = 6.3 Hz), 4.04 (t, 2 H, J = 6.3 Hz), 4.55 (t, 2 H, J = 6.3 Hz), 6.69 (d, 1 H, J = 8.9 Hz), 6.82 (d, 2 H, J = 9.2 Hz), 6.95 (d, 2 H, J = 8.9 Hz), 7.22 (d, 1 H, J = 9.2 Hz), 7.22 (br, 1 H), 7.87 (d, 1 H, J = 8.9 Hz), 7.89 (d, 1 H, J = 8.9 Hz). Anal. ($C_{29}H_{30}NO_6Cl$) C, H, N.

***N*-[7-(Decyloxy)-4-oxochroman-8-yl]-2,2-dimethylpropanamide (65). Method A.** Pivaloyl chloride (30.15 g, 0.25 mol) was slowly added to a solution of 8-amino-7-(decyloxy)-4-chromanone (**9e**; 78.86 g, 0.25 mol) and triethylamine (25.3 g, 0.25 mol) in dichloromethane (600 mL) with stirring at room temperature. The reaction mixture was stirred for 10 min at room temperature and then poured into 2 N HCl (500 mL, ice cold), and the mixture was extracted with AcOEt (2 × 750 mL). The combined extracts were washed with 2 N HCl (400 mL) and brine (300 mL) and dried over $MgSO_4$. After removal of the solvent, the crude product was recrystallized (from AcOEt, 2 L) to give *N*-[7-(decyloxy)-4-oxochroman-8-yl)-2,2-dimethylpropanamide (**65**): 64.56 g, 64% yield, white solid; mp 151–152 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 3 H, J = 6.6 Hz), 1.15–1.55 (m, 14 H), 1.34 (s, 9 H), 1.7–1.83 (m, 2 H), 2.77 (t, 2 H, J = 6.4 Hz), 4.03 (t, 2 H, J = 6.3 Hz), 4.54 (t, 2 H, J = 6.4 Hz), 6.61 (d, 1 H, J = 8.9 Hz), 6.77 (br, 1 H), 7.82 (d, 1 H, J = 8.9 Hz). Anal. ($C_{24}H_{37}NO_4$) C, H, N.

***N*-(7-Methoxy-6-nitro-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (39). Method B.** Nitric acid (61%, 310 mg, 3.0 mmol) was slowly added to a solution of *N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**35**; 1.21 g, 3.0 mmol) in acetic anhydride (10 mL) with stirring at 0–15 °C (ice–water bath). The reaction mixture was stirred for 3 h in an ice–water bath and then poured into ice. The mixture was basified by adding 2 N NaOH (pH >10) and extracted with AcOEt. The combined organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a solid which was purified by column chromatography (hexane–AcOEt, 7:3) to give *N*-(7-methoxy-6-nitro-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**39**): 353 mg, 26% yield, pale yellow solid; mp 85–86 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 3 H, J = 6.5 Hz), 1.2–1.4 (m, 22 H), 1.60 (br, 2 H), 2.83 (t, 2 H, J = 6.4 Hz), 3.91 (s, 3 H), 4.59 (t, 2 H, J = 6.4 Hz), 6.70 (s, 1 H), 6.81 (s, 1 H). Anal. ($C_{24}H_{36}N_2O_6$) H, N; C: calcd, 64.26; found, 63.74.

***N*-[6-(Methylamino)-7-methoxy-4-oxochroman-8-yl]-2,2-dimethyldodecanamide (40) and *N*-[6-(Dimethylamino)-7-methoxy-4-oxochroman-8-yl]-2,2-dimethyldodecanamide (41). Method B.** A solution of *N*-(7-methoxy-6-nitro-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**39**; 248 mg, 0.55 mmol) in EtOH (5 mL) was hydrogenated at 1 atm for 4 h in the presence of 5% palladium on charcoal (100 mg) at room temperature. The catalyst was removed by filtration through Celite and washed with EtOH (50 mL). The combined filtrate was evaporated to afford crude *N*-(6-amino-7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide, which was dissolved in acetone (10 mL). To this solution were added K_2CO_3 (800 mg, 5.8 mmol) and iodomethane (3.0 mL, 48 mmol). The mixture was refluxed for 24 h with stirring. The solid was removed by filtration and washed with AcOEt (50 mL). The combined filtrate was evaporated to afford an oil which was purified by column chromatography (hexane–AcOEt, 1:1) to give *N*-[6-(methylamino)-7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (**40**): 107 mg, 45% yield, yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 3 H, J = 6.9 Hz), 1.2–1.45 (m, 16 H), 1.5–1.65 (m, 2 H), 2.70 (t, 2 H, J = 6.6 Hz), 2.90 (d, 3 H, J = 4.9 Hz), 3.83 (s, 3 H), 4.38 (t, 2 H, J = 6.6 Hz), 5.64 (s, 1 H), 6.48 (s, 1 H), 9.11 (m, 1 H); HRMS for $C_{25}H_{40}N_2O_4$: m/z calcd 433.3066, found 433.3100. Anal. ($C_{25}H_{40}N_2O_4$) C, H, N.

***N*-[6-(Dimethylamino)-7-methoxy-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (41):** 82 mg, 33% yield, yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 3 H, J = 6.9 Hz), 1.2–1.45 (m, 16 H), 1.5–1.7 (m, 2 H), 2.66 (t, 2 H, J = 6.3 Hz), 2.94 (s, 6 H), 3.83 (s, 3 H), 4.40 (t, 2 H, J = 6.3 Hz), 5.94 (s, 1 H), 6.56 (s, 1 H); HRMS for $C_{26}H_{42}N_2O_4$ m/z calcd 447.3223, found 447.3112. Anal. ($C_{26}H_{42}N_2O_4$) C, H, N.

***N*-(7-Methoxy-4-oxochroman-8-yl)-4-[[6-[(2-methylpropyl)oxy]hexyl]oxy]benzamide (62). Method C.** 4-Hydroxybenzoic acid (215 mg, 1.55 mmol) was added to a solution of 8-amino-7-methoxy-4-chromanone (**9b**; 300 mg, 1.55 mmol), 4-(dimethylamino)pyridine (30 mg, 0.25 mmol), and dicyclohexylcarbodiimide (320 mg, 1.55 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 3 h, and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane–AcOEt, 1:3) to give 4-hydroxy-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide: 183 mg, 38% yield, white amorphous solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.71 (t, 2 H, J = 6.4 Hz), 3.83 (s, 3 H), 4.48 (t, 2 H, J = 6.4 Hz), 6.83 (d, 2 H, J = 8.5 Hz), 6.87 (d, 1 H, J = 8.9 Hz), 7.75 (d, 1 H, J = 8.9 Hz), 7.85 (d, 2 H, J = 8.5 Hz), 9.21 (s, 1 H), 10.05 (br, 1 H).

K_2CO_3 (40 mg, 1.5 equiv) and 6-[(2-methylpropyl)oxy]hexyl bromide (46 mg, 0.19 mmol) were added to a solution of 4-hydroxy-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide (60 mg, 0.19 mmol) in CH_3CN (2 mL). The mixture was refluxed for 5 h with stirring. The solid was removed by filtration and washed with AcOEt (50 mL). The combined filtrate was evaporated to afford a solid which was purified by column chromatography (hexane–AcOEt, 1:1) to give *N*-(7-methoxy-4-oxochroman-8-yl)-4-[[6-[(2-methylpropyl)oxy]hexyl]oxy]-benzamide (**62**): 69.6 mg, 77% yield, white solid; mp 148–150 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (d, 6 H, *J* = 6.8 Hz), 1.4–1.7 (m, 6 H), 1.8–1.9 (m, 3 H), 2.79 (t, 2 H, *J* = 6.4 Hz), 3.17 (d, 2 H, *J* = 6.6 Hz), 3.42 (t, 2 H, *J* = 6.4 Hz), 3.90 (s, 3 H), 4.03 (t, 2 H, *J* = 6.4 Hz), 4.55 (t, 2 H, *J* = 6.4 Hz), 6.69 (d, 1 H, *J* = 8.7 Hz), 6.96 (d, 2 H, *J* = 8.7 Hz), 7.20 (br, 1 H), 7.88 (d, 3 H, *J* = 8.7 Hz). Anal. ($C_{27}H_{35}NO_6$) C, H, N.

***N*-(7-Methyl-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (32).** This product was prepared in a similar manner to that described in method A using 8-amino-7-methyl-4-chromanone (**12**; 100 mg, 0.564 mmol) and 2,2-dimethyldodecanoyl chloride (143 mg, 1.1 equiv) to give a solid which was purified by column chromatography (hexane–AcOEt) to give **32**: 196 mg, 89% yield, white solid; mp 80–81 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.8–1.8 (m, 27 H), 2.24 (s, 3 H), 2.76 (t, 2 H, *J* = 6.0 Hz), 4.53 (t, 2 H, *J* = 6.0 Hz), 6.88 (d, 1 H, *J* = 8.0 Hz), 7.00 (br, 1 H), 7.69 (d, 1 H, *J* = 8.0 Hz). Anal. ($C_{24}H_{37}NO_3$) C, H, N.

7-[(4-Chlorophenyl)oxy]-2,2-dimethyl-*N*-(5,7-dimethyl-4-oxochroman-8-yl)heptanamide (34). This product was prepared in a similar manner to that described in method A using 8-amino-5,7-dimethyl-4-chromanone (**14**; 57.3 mg 0.30 mmol) and 7-(4-chlorophenoxy)-2,2-dimethylheptanoyl chloride (99.5 mg, 0.33 mmol) to give a solid which was purified by column chromatography (hexane–AcOEt) to give **34**: 132 mg, 96% yield, white solid; mp 95–96 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.03–1.97 (m, 8 H), 1.32 (s, 6 H), 2.19 (s, 3 H), 2.58 (s, 3 H), 2.73 (t, 2 H, *J* = 6.6 Hz), 3.92 (t, 2 H, *J* = 5.9 Hz), 4.46 (t, 2 H, *J* = 6.6 Hz), 6.68 (s, 1 H), 6.79 (d, 2 H, *J* = 9.0 Hz), 6.95 (br, 1 H), 7.20 (d, 2 H, *J* = 9.0 Hz). Anal. ($C_{26}H_{32}NO_4Cl$) C, H, N.

8-[(4-Chlorophenyl)oxy]-*N*-(7-methoxy-4-oxochroman-8-yl)-2,2-dimethyloctanamide (36). This product was prepared in a similar manner to that described in method A using 8-amino-7-methoxy-4-chromanone (**9b**; 193 mg, 0.72 mmol) and 8-(4-chlorophenoxy)-2,2-dimethyloctanoyl chloride (228 mg, 0.72 mmol) to give a solid which was purified by column chromatography (hexane–AcOEt) to give **36**: 242 mg, 73% yield, white solid; mp 89–90 °C (recrystallized from hexane/AcOEt); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.27–1.95 (m, 10 H), 1.30 (s, 6 H), 2.75 (t, 2 H, *J* = 6.4 Hz), 3.87 (s, 3 H), 3.91 (t, 2 H, *J* = 5.9 Hz), 4.51 (t, 2 H, *J* = 6.4 Hz), 6.63 (d, 1 H, *J* = 9.0 Hz), 6.73 (s, 1 H), 6.79 (d, 2 H, *J* = 9.2 Hz), 7.21 (d, 2 H, *J* = 9.2 Hz), 7.84 (d, 1 H, *J* = 9.0 Hz). Anal. ($C_{26}H_{32}NO_5Cl$) C, H, N.

2,2-Dimethyl-*N*-[7-(propyloxy)-4-oxochroman-8-yl]-dodecanamide (37). This product was prepared in a similar manner to that described in method A using 8-amino-7-(propyloxy)-4-chromanone (**9d**; 524 mg, 2.37 mmol) and 2,2-dimethyldodecanoyl chloride (584 mg, 2.37 mmol) to give a solid which was purified by column chromatography (hexane–AcOEt) to give **37**: 714 mg, 70% yield, white solid; mp 131–133 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.88 (t, 3 H, *J* = 5.7 Hz), 1.02 (t, 3 H, *J* = 7.0 Hz), 1.14–1.57 (m, 18 H), 1.30 (s, 6 H), 1.77 (tq, 2 H, *J* = 7.0, 6.4 Hz), 2.77 (t, 2 H, *J* = 6.4 Hz), 4.00 (t, 2 H, *J* = 6.4 Hz), 4.52 (t, 2 H, *J* = 6.4 Hz), 6.61 (d, 1 H, *J* = 8.8 Hz), 6.76 (s, 1 H), 7.82 (d, 1 H, *J* = 8.8 Hz). Anal. ($C_{26}H_{41}NO_4$) C, H, N.

***N*-(7-Chloro-4-oxochroman-8-yl)-2,2-dimethyldodecanamide (38).** This product was prepared in a similar manner to that described in method A using 8-amino-7-chloro-4-chromanone (**9f**; 39.1 mg, 0.20 mmol) and 2,2-dimethyldodecanoyl chloride (52 mg, 0.21 mmol) to give a oil which was purified by column chromatography (hexane–AcOEt) to give **38**: 74.1 mg, 91% yield, colorless oil; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.88 (t, 3 H, *J* = 6.1 Hz), 1.00–1.76 (m, 18 H), 1.32 (s, 3 H), 2.81 (t, 2 H, *J* = 6.4 Hz), 4.56 (t, 2 H, *J* = 6.4 Hz), 6.94 (br, 1 H), 7.09 (d, 1 H, *J* = 8.6 Hz), 7.76 (d, 1 H, *J* = 6.4 Hz). Anal. ($C_{23}H_{34}NO_3Cl$) C, H, N.

***N*-(7-Methoxychromon-8-yl)-2,2-dimethyldodecanamide (43).** This product was prepared in a similar manner to that described in method A using 8-amino-7-methoxychromone (**8b**; 190 mg, 0.99 mmol) and 2,2-dimethyldodecanoyl chloride (254 mg, 1.0 mmol) to give an amorphous solid which was purified by column chromatography (hexane–AcOEt, 6:1) to give **43**: 279 mg, 70% yield, amorphous solid; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.87 (t, 3 H, *J* = 6 Hz), 1.0–1.8 (m, 24 H), 3.94 (s, 3 H), 6.25 (d, 1 H, *J* = 6.0 Hz), 6.97 (br, 1 H), 6.99 (d, 1 H, *J* = 9.2 Hz), 7.75 (d, 1 H, *J* = 6.0 Hz), 8.11 (d, 1 H, *J* = 9.2 Hz). Anal. ($C_{24}H_{35}NO_4$) C, H, N.

***N*-(7-Methoxychroman-8-yl)-2,2-dimethyldodecanamide (45).** This product was prepared in a similar manner to that described in method A using 8-amino-7-methoxychroman (**10b**; 100 mg, 0.56 mmol) and 2,2-dimethyldodecanoyl chloride (153 mg, 1.0 equiv) to give an oil which was purified by column chromatography (hexane–AcOEt) to give **45**: 206 mg, 95% yield, colorless oil; mp <25 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3 H, *J* = 6.8 Hz), 1.2–1.5 (m, 22 H), 1.5–1.65 (m, 2 H), 1.96 (dt, 2 H, *J* = 10.6, 6.4 Hz), 2.74 (t, 2 H, *J* = 6.4 Hz), 3.78 (s, 3 H), 4.16 (t, 2 H, *J* = 6.4 Hz), 6.44 (d, 1 H, *J* = 8.7 Hz), 6.73 (br, 1 H), 6.86 (d, 1 H, *J* = 8.7 Hz). Anal. ($C_{24}H_{39}NO_3$) C, H, N.

8-[(4-Chlorophenyl)oxy]-*N*-(6-methoxy-4-chromanon-5-yl)-2,2-dimethyloctanamide (47). This product was prepared in a similar manner to that described in method A using 5-amino-6-methoxy-4-chromanone (120 mg, 0.62 mmol) and 8-(4-chlorophenoxy)-2,2-dimethyloctanoyl chloride (197 mg, 1.0 equiv) to give a solid which was purified by column chromatography (hexane–AcOEt, 5:1) to give **47**: 257 mg, 86% yield, pale yellow solid; mp 76–77 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.32 (s, 6 H), 1.2–1.9 (m, 10 H), 2.76 (t, 2 H, *J* = 6.4 Hz), 3.81 (s, 3 H), 3.90 (t, 2 H, *J* = 6.4 Hz), 4.43 (d, 2 H, *J* = 6.4 Hz), 6.76 (d, 1 H, *J* = 9.2 Hz), 6.78 (d, 2 H, *J* = 9.3 Hz), 7.15 (d, 1 H, *J* = 9.2 Hz), 7.20 (d, 2 H, *J* = 9.3 Hz). Anal. ($C_{26}H_{32}NO_5Cl$) C, H, N.

1-Decyl-*N*-(7-methyl-1,2,3,4-tetrahydro-4-oxoquinolin-8-yl)-1-cyclopentanecarboxamide (46). This product was prepared in a similar manner to that described in method A using 8-amino-7-methyl-1,2,3,4-tetrahydroquinolin-4-one (104 mg, 0.59 mmol) and 1-decyl-1-cyclopentanecarbonyl chloride (165 mg, 0.61 mmol) to give a solid which was purified by column chromatography (hexane–AcOEt, 3:1) to give **46**: 112 mg, 46% yield, white solid; mp 81–82 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 3 H, *J* = 6.6 Hz), 1.2–1.8 (m, 24 H), 2.15–2.25 (m, 2 H), 2.21 (s, 1 H), 2.67 (t, 2 H, *J* = 6.6 Hz), 3.56 (t, 2 H, *J* = 6.6 Hz), 4.70 (br, 1 H), 6.64 (d, 1 H, *J* = 7.9 Hz), 6.73 (br, 1 H), 7.75 (d, 1 H, *J* = 7.9 Hz). Anal. ($C_{26}H_{40}N_2O_2$) C, H, N.

***N*-(7-Methoxy-4-oxochroman-8-yl)-2,2-dimethyl-8-[(2-methylpropyl)oxy]octanamide (52).** This product was prepared in a similar manner to that described in method A using 8-amino-7-methoxy-4-chromanone (**9b**; 198 mg, 1.0 mmol) and 2,2-dimethyl-8-[(2-methylpropyl)oxy]octanoyl chloride (272 mg, 1.0 mmol) to give a solid which was purified by column chromatography (hexane–AcOEt, 3:1) to give **52**: 321 mg, 75% yield, white solid; mp 119–122 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.88 (d, 6 H, *J* = 6.6 Hz), 1.30 (s, 6 H), 1.1–2.2 (m, 11 H), 2.76 (t, 2 H, *J* = 6.4 Hz), 3.15 (d, 2 H, *J* = 6.6 Hz), 3.38 (t, 2 H, *J* = 6.1 Hz), 3.87 (s, 3 H), 4.52 (t, 2 H, *J* = 6.6 Hz), 6.63 (d, 1 H, *J* = 9.0 Hz), 6.74 (br, 1 H), 7.84 (d, 1 H, *J* = 9.0 Hz). Anal. ($C_{24}H_{37}NO_5$) C, H, N.

***N*-(7-Methoxy-4-oxochroman-8-yl)-2,2-dimethyl-5-(4-propylphenyl)pentanamide (55).** This product was prepared in a similar manner to that described in method A using 8-amino-7-methoxy-4-chromanone (**9b**; 58 mg, 0.30 mmol) and 2,2-dimethyl-5-(4-propylphenyl)pentanoyl chloride (267 mg, 0.30 mmol) to give a solid which was purified by column chromatography (hexane–AcOEt, 6:4) to give **55**: 119 mg, 94% yield, white solid; mp 122–124 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, 3 H, *J* = 7.2 Hz), 1.30 (s, 6 H), 1.5–1.8 (m, 6 H), 2.54 (t, 2 H, *J* = 7.6 Hz), 2.60 (t, 2 H, *J* = 7.6 Hz), 2.75 (t, 2 H, *J* = 6.5 Hz), 3.82 (s, 3 H), 4.46 (t, 2 H, *J* = 6.5 Hz), 6.63 (d, 1 H, *J* = 8.9 Hz), 6.71 (br, 1 H), 7.07 (d, 2 H, *J* = 8.3 Hz), 7.10 (d, 2 H, *J* = 8.3 Hz), 7.84 (d, 1 H, *J* = 8.9 Hz). Anal. ($C_{26}H_{33}NO_4$) C, H, N.

4-(Decyloxy)-*N*-(7-methoxy-4-oxochroman-8-yl)benzamide (61). This product was prepared in a similar manner to that described in method A using 8-amino-7-methoxy-4-chromanone (**9b**; 100 mg, 0.52 mmol) and 4-(decyloxy)benzoyl chloride (154 mg, 1.0 equiv) to give a solid which was purified by column chromatography (hexane−AcOEt, 1:1) to give **61**: 215 mg, 80% yield, white solid; mp 160−161 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.89 (t, 3 H, J = 6.9 Hz), 1.2−1.6 (m, 14 H), 1.81 (dt, 2 H, J = 7.9, 6.6 Hz), 2.79 (t, 2 H, J = 6.4 Hz), 3.90 (s, 3 H), 4.02 (t, 2 H, J = 6.6 Hz), 4.55 (t, 2 H, J = 6.4 Hz), 6.69 (d, 1 H, J = 8.9 Hz), 6.96 (d, 2 H, J = 8.6 Hz), 7.21 (br, 1 H), 7.88 (d, 1 H, J = 8.9 Hz), 7.89 (d, 2 H, J = 8.6 Hz). Anal. ($C_{27}H_{35}NO_5$) C, H, N.

***N*-[7-(Decyloxy)chromon-8-yl]-2,2-dimethylpropanamide (66).** This product was prepared in a similar manner to that described in method A using 8-amino-7-(decyloxy)-chromone (**8e**; 301 mg, 0.948 mmol) and pivaloyl chloride (120 mg, 0.99 mmol) to give a solid which was purified by column chromatography (hexane−AcOEt, 1:1) to give **66**: 200 mg, 52% yield, white solid; mp 109 °C (recrystallized from AcOEt/hexane); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.89 (t, 3 H, J = 6.6 Hz), 1.15−1.56 (m, 14 H), 1.38 (s, 9 H), 1.82 (tt, 2 H, J = 6.3, 6.3 Hz), 4.10 (t, 2 H, J = 6.3 Hz), 6.26 (d, 1 H, J = 6.3 Hz), 6.99 (br, 1 H), 7.01 (d, 1 H, J = 8.9 Hz), 7.79 (d, 1 H, J = 6.3 Hz), 8.10 (d, 1 H, J = 8.9 Hz). Anal. ($C_{24}H_{35}NO_4$) C, H, N.

***N*-[7-[(6-Phenylhexyl)oxy]-4-oxochroman-8-yl]-2,2-dimethylpropanamide (68).** This product was prepared in a similar manner to that described in method A using 8-amino-7-[(6-phenylhexyl)oxy]-4-chromanone (**17g**; 163 mg, 0.48 mmol) and pivaloyl chloride (62 mg, 0.51 mmol) to give a solid which was purified by column chromatography (hexane−AcOEt, 1:1) to give **68**: 195 mg, 96% yield, white solid; mp 140−141 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.22−1.57 (m, 4 H), 1.33 (s, 9 H), 1.64 (tt, 2 H, J = 7.6, 7.3 Hz), 1.77 (tt, 2 H, J = 6.6, 6.3 Hz), 2.61 (t, 2 H, J = 7.6 Hz), 2.77 (t, 2 H, J = 6.3 Hz), 4.02 (t, 2 H, J = 6.3 Hz), 4.53 (t, 2 H, J = 6.3 Hz), 6.60 (d, 1 H, J = 8.9 Hz), 7.15−7.30 (m, 5 H), 7.82 (d, 1 H, J = 8.9 Hz). Anal. ($C_{26}H_{33}NO_4$) C, H, N.

***N*-[7-(Decyloxy)-4-oxochroman-8-yl]acetamide (69).** This product was prepared in a similar manner to that described in method A using 8-amino-7-(decyloxy)-4-chromanone (**9e**; 404 mg, 1.26 mmol) and acetyl chloride (102 mg, 1.30 mmol) to give a solid which was purified by column chromatography (hexane−AcOEt) to give **69**: 338 mg, 74% yield, white solid; mp 152−153 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (t, 3 H, J = 6.6 Hz), 1.11−1.50 (m, 14 H), 1.79 (tt, 4 H, J = 6.6, 6.6 Hz), 2.17 (br, 3 H), 2.78 (t, 2 H, J = 6.6 Hz), 4.05 (t, 2 H, J = 6.6 Hz), 4.55 (t, 2 H, J = 6.6 Hz), 6.64 (d, 1 H, J = 8.9 Hz), 7.85 (d, 1 H, J = 8.9 Hz). Anal. ($C_{21}H_{31}NO_4$) C, H, N.

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