Substituted Chromenes as Potent, Orally Active 5-Lipoxygenase Inhibitors

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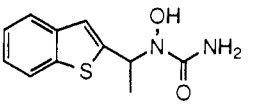
A series of chromene derivatives was synthesized and evaluated for their *in vitro* and *ex vivo* 5-lipoxygenase (5-LO) inhibitory activity. These compounds were prepared by condensation of appropriate salicyl aldehydes with α,β-unsaturated carbonyl compounds, followed by transformation to the corresponding hydroxamic acids or *N*-hydroxyureas. Placement of phenoxy or *p*-fluorophenoxy substituents at the 6 position of the chromene ring led to a dramatic increase in the *in vitro* potency as demonstrated by the guinea pig PMN 5-LO assay. Chromene hydroxamic acids, in general, behaved poorly in the *ex vivo* dog model. On the other hand, replacement of the hydroxamic acid function with *N*-hydroxyurea yielded potent and long-lasting 5-LO inhibitors in the dog model. In most cases, the oral efficacy of the chromene *N*-hydroxyureas correlated very well with their *in vitro* activity. Compounds **43** (CGS 23885) and **55** (CGS 24891) are among the most potent inhibitors prepared, showing IC_{50} values of 48 and 51 nM, respectively. The values for the duration of action (DA) for compounds **43** and **55** are 21 and 20 h, respectively, following intravenous (iv) administration of 1.0 mg/kg. In the oral (po) experiments, **43** and **55** have DA's of 14 and 15 h, respectively, at a 1.0 mg/kg dose. In both iv and po experiments, **43** and **55** showed sustained maximal inhibition (>95%) at earlier time points. The oral ED_{50} values of **43** and **55** in the *ex vivo* dog model are 0.23 and 0.23 mg/kg, respectively, at 6.0 h, and 2.37 and 1.63 mg/kg, respectively, at 24 h. Compound **43**, which inhibits sheep seminal vesicle cyclooxygenase (CO) with an IC_{50} value of 36 μM, was shown to be a selective 5-lipoxygenase inhibitor in the *ex vivo* study. These compounds compare favorably with zileuton (A-64077) in all the parameters examined.

Introduction

Conversion of arachidonic acid (AA) by the 5-lipoxygenase (5-LO) enzyme results in the formation of 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE), which is subsequently metabolized to a series of highly potent leukotrienes (LT's). These oxygenated eicosanoids are implicated in inflammatory and allergic reactions.[1] LTB_4, a non-peptidic LT, is a potent chemotactic agent to a number of proinflammatory leukocytes *in vitro* and promotes aggregation, chemokinesis, and superoxide release by these cells.[2-4] *In vivo*, LTB_4 causes leukocyte accumulation in a number of animal models, including rabbit,[5] rat,[6] guinea pig,[6] pig,[7] and hamster.[8] This phenomenon was also demonstrated in human.[9,10] Increased vascular permeability upon administration of LTB_4 is also noted.[11] Peptidic LT's, which include LTC_4, LTD_4 and LTE_4, are known as "slow reacting substances of anaphylaxis" (SRS-A). These peptido-LT's are known to induce contraction of human airway smooth muscle preparation[12] and mucus formation in human airways.[13] Administration of LTD_4 by aerosol to human results in a prolonged bronchoconstriction.[14-17]

It is becoming increasingly evident that leukotrienes are extremely important mediators in human disease states. For example, elevated levels of LT's are detected in sputum from asthmatics,[18] bronchoalveolar lavage fluid and nasal washes from allergic rhinitis patients following antigen challenge,[19-21] scales from patients with psoriasis,[22-24] synovial fluid from rheumatoid arthritis[25,26] and gout[27] patients, and inflamed colonic mucosa[28,29] and rectal dialysis fluid[30] from patients suffering from inflammatory bowel disease. Since conventional antiinflammatory therapies, such as NSAID treatment, are far from being satisfactory in many of these diseases, new and improved methods to fight these conditions are actively being sought.

It has long been hypothesized that 5-LO inhibitors could provide novel treatment for inflammatory diseases. Recent clinical data on zileuton (A-64077)[31] demonstrated promising therapeutic benefits of this 5-lipoxygenase inhibitor in several inflammatory diseases including asthma,[32-34] allergic rhinitis,[35] inflammatory bowel disease,[36,37] and rheumatoid arthritis.[38]



Zileuton (A-64077)

Numerous attempts have been made in the last decade to identify and develop 5-LO inhibitors as therapeutic agents.[39] In particular, since Corey's disclosure that hydroxamic acid derivatives of arachidonic acid and its analogs exhibit potent 5-LO inhibitory activities in the RBL 5-LO assay,[40] the hydroxamate-based 5-LO inhibitors have been intensely investigated.[41] As a continuation of our previous work,[42,43] we would like to disclose our research effort directed toward the discovery of potent, orally active 5-lipoxygenase inhibitors based on the chromene template.

Chemistry

Chromene hydroxamic acids (**7-9**) were synthesized according to the following procedure (Scheme I). The intermediate chromene-3-carboxylates (**4-6**) were prepared by the reaction of appropriately substituted salicyl

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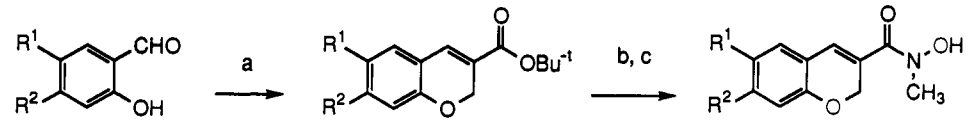
Scheme I[a]



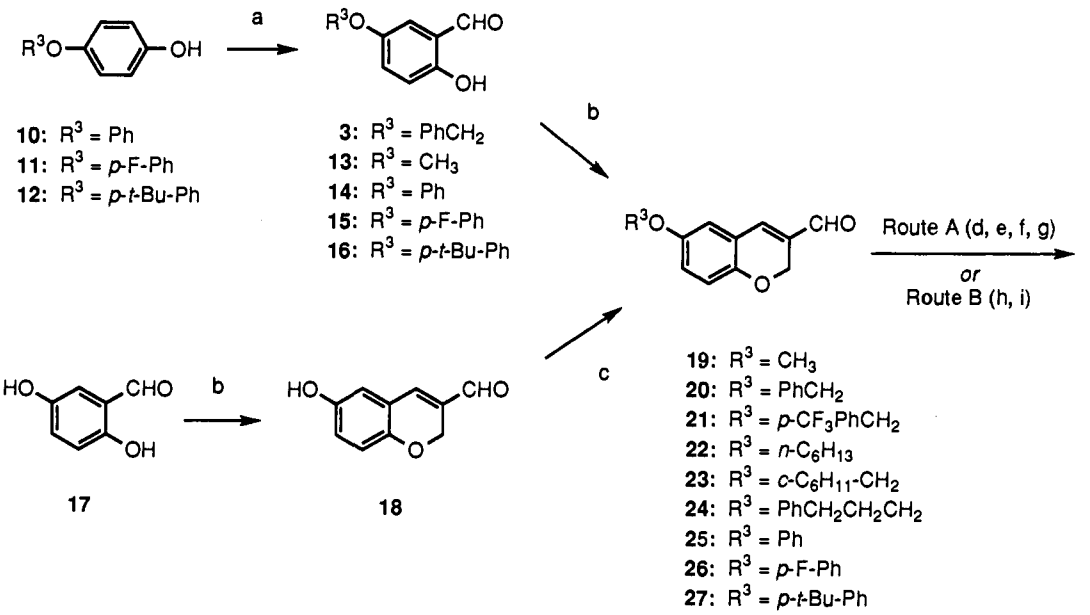
1: $R^1 = H, R^2 = H$
2: $R^1 = H, R^2 = CH_3O$
3: $R^1 = BnO, R^2 = H$

4: $R^1 = H, R^2 = H$
5: $R^1 = H, R^2 = CH_3O$
6: $R^1 = BnO, R^2 = H$

7: $R^1 = H, R^2 = H$
8: $R^1 = H, R^2 = CH_3O$
9: $R^1 = BnO, R^2 = H$

[a] Reagents and conditions: (a) *tert*-butyl acrylate, K_2CO_3; (b) TFA; (c) $(COCl)_2$, DMF, and then $HN(OH)CH_3$.

Scheme II[a]



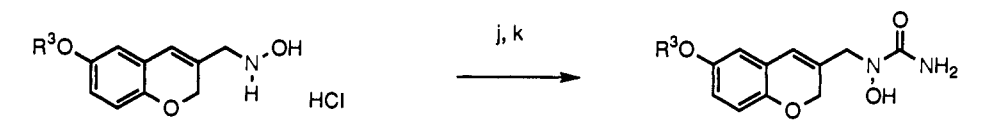
10: $R^3 = Ph$
11: $R^3 = p$-F-Ph
12: $R^3 = p$-*t*-Bu-Ph

3: $R^3 = PhCH_2$
13: $R^3 = CH_3$
14: $R^3 = Ph$
15: $R^3 = p$-F-Ph
16: $R^3 = p$-*t*-Bu-Ph

17

18

19: $R^3 = CH_3$
20: $R^3 = PhCH_2$
21: $R^3 = p$-CF_3PhCH_2
22: $R^3 = n$-C_6H_{13}
23: $R^3 = c$-C_6H_{11}-CH_2
24: $R^3 = PhCH_2CH_2CH_2$
25: $R^3 = Ph$
26: $R^3 = p$-F-Ph
27: $R^3 = p$-*t*-Bu-Ph



28: $R^3 = CH_3$
29: $R^3 = PhCH_2$
30: $R^3 = p$-CF_3PhCH_2
31: $R^3 = n$-C_6H_{13}
32: $R^3 = c$-C_6H_{11}-CH_2
33: $R^3 = PhCH_2CH_2CH_2$
34: $R^3 = Ph$
35: $R^3 = p$-F-Ph
36: $R^3 = p$-*t*-Bu-Ph

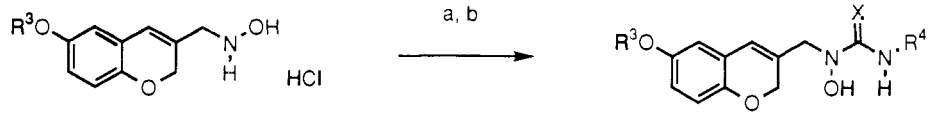
37: $R^3 = CH_3$
38: $R^3 = PhCH_2$
39: $R^3 = p$-CF_3PhCH_2
40: $R^3 = n$-C_6H_{13}
41: $R^3 = c$-C_6H_{11}-CH_2
42: $R^3 = PhCH_2CH_2CH_2$
43: $R^3 = Ph$
44: $R^3 = p$-F-Ph
45: $R^3 = p$-*t*-Bu-Ph

[a] Reagents and conditions: (a) NaOH, $CHCl_3$, 70 °C; (b) CH_2=CHCHO, K_2CO_3, dioxane, reflux; (c) R^3X, K_2CO_3; (d) $NaBH_4$, EtOH; (e) Br_2·PPh3; (f) $H_2NOC(CH_3)_2OCH_3$, EtN, DMF; (g) HCl, MeOH; (h) H_2NOH, pyridine; (i) BH_3·py, CF_3COOH, and then HCl; (j) NaOH; (k) TMS-N=C=O, dioxane, reflux.

aldehydes (**1** - **3**) with α,β-unsaturated esters.[44] Use of *tert*-butyl acrylate is essential to prevent partial hydrolysis of the ester under the reaction conditions. Hydrolysis and condensation *via* the acid chlorides gave the corresponding hydroxamic acids (**7–9**).

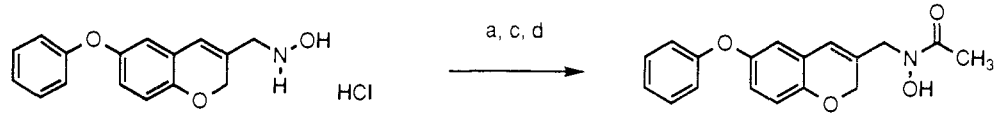
Similarly, as shown in Scheme II, condensation of the 5-alkoxy-substituted salicyl aldehydes (**3, 13–16**) with acrolein gave the corresponding 6-alkoxychromene-3-carboxaldehydes (**19–27**).[44] The starting salicyl aldehydes (**3, 14–16**) were prepared in ~ 30% yields by the conventional Reimer–Tiemann method.[45] Compounds **20–24** were prepared from 6-hydroxy derivative (**18**) by alkylation (K_2CO_3, DMF). The alkylation method is preferable when applicable, due to much better overall yields. The aldehydes (**19–27**) were converted to the hydroxylamine derivatives (**28–36**) through two methods. The aldehydes were reduced ($NaBH_4$) and treated with dibromotriphenylphosphorane. The allylic bromides thus formed were then condensed with *O*-((2-methoxy-2-propyl)oxy)hydroxylamine[46] and deprotected (route A, allylic bromide method). All the hydroxylamines in Scheme II (**28–36**) were prepared through this route. Alternatively, the aldehydes were converted to their oximes and treated with borane–pyridine complex (route B, oxime

Scheme III[a]



34: R^3 = Ph
35: R^3 = *p*-F-Ph

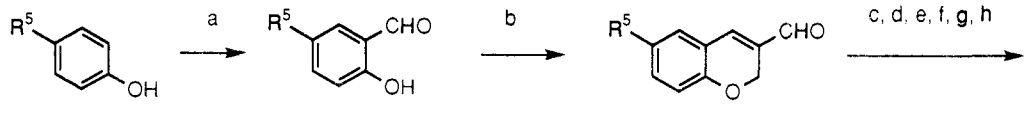
46: X = S, R^3 = Ph, R^4 = H
47: X = O, R^3 = Ph, R^4 = CH_3
48: X = O, R^3 = Ph, R^4 = CH_2CH_3
49: X = O, R^3 = Ph, R^4 = $CH_2CH_2CH_3$
50: X = O, R^3 = Ph, R^4 = $CH(CH_3)_2$
51: X = O, R^3 = Ph, R^4 = $CH_2CH_2CH_2CH_3$
52: X = O, R^3 = Ph, R^4 = $C(CH_3)_3$
53: X = O, R^3 = Ph, R^4 = Ph
54: X = O, R^3 = Ph, R^4 = $PhCH_2$
55: X = O, R^3 = *p*-F-Ph, R^4 = CH_3
56: X = O, R^3 = Ph, R^4 = $CH_2CH{=}CH_2$
57: X = O, R^3 = Ph, R^4 = $CH_2COOCH_2CH_3$



34 58

[a] Reagents and conditions: (a) NaOH; (b) $R^4N{=}C{=}X$; (c) AcCl, Et_3N, (d) LiOH, *i*-PrOH/H_2O.

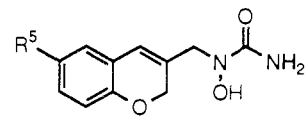
Scheme IV[a]



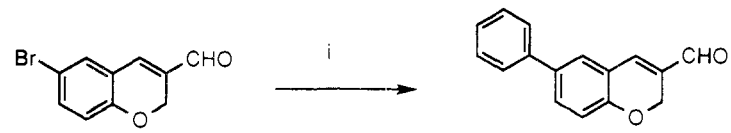
59: R^5 = *n*-C_7H_{15}

60: R^5 = *n*-C_7H_{15}
61: R^5 = Br

62: R^5 = *n*-C_7H_{15}
63: R^5 = Br
64: R^5 = Ph



65: R^5 = *n*-C_7H_{15}
66: R^5 = Br
67: R^5 = Ph



63 64

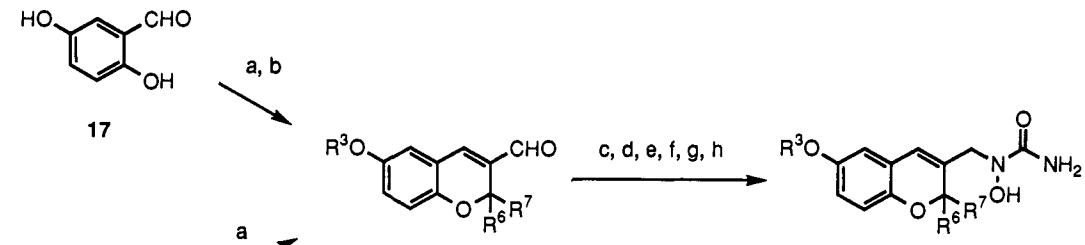
[a] Reagents and conditions: (a) NaOH, $CHCl_3$, 70 °C; (b) $CH_2{=}CHCHO$, K_2CO_3, dioxane, reflux; (c) $NaBH_4$, EtOH; (d) Br_2-PPh_3; (e) $H_2NOC(CH_3)_2OCH_3$, Et_3N, DMF; (f) HCl, MeOH; (g) NaOH; (h) TMS-N=C=O, dioxane, reflux; (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, NaOAc.

method). *The presence of a strong acid (e.g. CF_3COOH) in the reduction step is essential*[47] since no reduction took place under standard conditions (aqueous HCl). This oxime route was employed to prepare **34** and **35** in Scheme II. Base treatment of the hydroxylamine derivatives (**28–36**) followed by reaction with isocyanates or an isothiocyanate results in the formation of the desired *N*-hydroxyureas (**37–57**) (Schemes II and III). An acetohydroxamate (**58**) was prepared by *N,O*-bis-acetylation, followed by selective mono-*O*-hydrolysis.[41d]

As described in Scheme IV, 6-alkyl- and -halo-substituted derivatives (**65–67**) were prepared through a similar route. The highly chemoselective nature of the palladium-catalyzed cross-coupling reaction with phenylboronic acid[48] allows the conversion of **63** to **64** without affecting the α,β-unsaturated aldehyde functionality.

As shown in Scheme V, mono- and bis-2-substituted 6-phenoxychromene-3-carboxaldehydes (**69–72**) were synthesized by condensation of 5-phenoxysalicyl aldehyde (**14**) with appropriate α,β-unsaturated aldehydes. Com-

Scheme V[a]

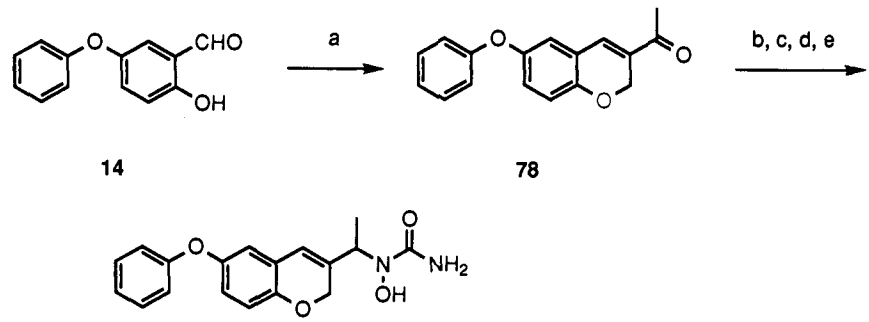


68: $R^3 = PhCH_2$, $R^6 = CH_3$, $R^7 = H$
69: $R^3 = Ph$, $R^6 = CH_3$, $R^7 = H$
70: $R^3 = Ph$, $R^6 = CH_2CH_2CH_3$, $R^7 = H$
71: $R^3 = Ph$, $R^6 = Ph$, $R^7 = H$
72: $R^3 = Ph$, $R^6 = CH_3$, $R^7 = CH_3$

73: $R^3 = PhCH_2$, $R^6 = CH_3$, $R^7 = H$
74: $R^3 = Ph$, $R^6 = CH_3$, $R^7 = H$
75: $R^3 = Ph$, $R^6 = CH_2CH_2CH_3$, $R^7 = H$
76: $R^3 = Ph$, $R^6 = Ph$, $R^7 = H$
77: $R^3 = Ph$, $R^6 = CH_3$, $R^7 = CH_3$

[a] Reagents and conditions: (a) $C(R^6)(R^7)$=CHCHO, K_2CO_3, dioxane, reflux; (b) BnBr, K_2CO_3, DMF; (c) $NaBH_4$, EtOH; (d) Br_2-PPh_3; (e) $H_2NOC(CH_3)_2OCH_3$, Et_3N, DMF; (f) HCl, MeOH; (g) NaOH; (h) TMS-N=C=O, dioxane, reflux.

Scheme VI[a]



[a] Reagents and conditions: (a) CH_2=$CHCOCH_3$, K_2CO_3, dioxane, reflux; (b) H_2NOH, pyridine; (c) BH_3-py, CF_3COOH, and then HCl; (d) NaOH; (e) TMS-N=C=O, dioxane, reflux.

pound **68** was generated by the reaction of **17** with crotonaldehyde, followed by alkylation with benzyl bromide. These 2-substituted derivatives (**68–72**) were no longer suitable for the oxime-reduction route (see Scheme II), presumably due to increased steric hindrance. The starting oximes were recovered unreacted under a variety of conditions using borane-pyridine as the reducing agent. Thus, the aldehydes (**68–72**) were converted into their hydroxyurea derivatives (**73–77**) *via* the allylic bromides (Scheme V).

Methyl ketone (**78**) was converted into the α-methyl-substituted *N*-hydroxyurea (**79**) through the oxime route, albeit in a low yield (Scheme VI, see also the Experimental Section). This is due to sluggish reduction of the oxime with borane–pyridine complex. Steric influence in this reduction step is reminiscent of that of 2-substituted analogs (Scheme V).

Finally, the potential of dihydrochromene derivatives was explored (Scheme VII). Catalytic hydrogenation of **43** was successfully employed to obtain **80**. Unexpected *dihydro*chromene derivative (**83**) was obtained when 7-methoxychromene-3-carboxaldehyde (**82**) was treated with borane–pyridine complex under the standard conditions. The product of 1,2-reduction was not detected in the reaction mixture. It is likely that **83** was formed by initial 1,4-reduction of the α,β-unsaturated oxime, followed by *in situ* 1,2-reduction of the saturated oxime thus formed. The reason for the unusual reactivity of **82** is not clear at this moment. The resultant hydroxylamine (**83**) was converted into the *N*-hydroxyurea (**84**) in a straightforward manner.

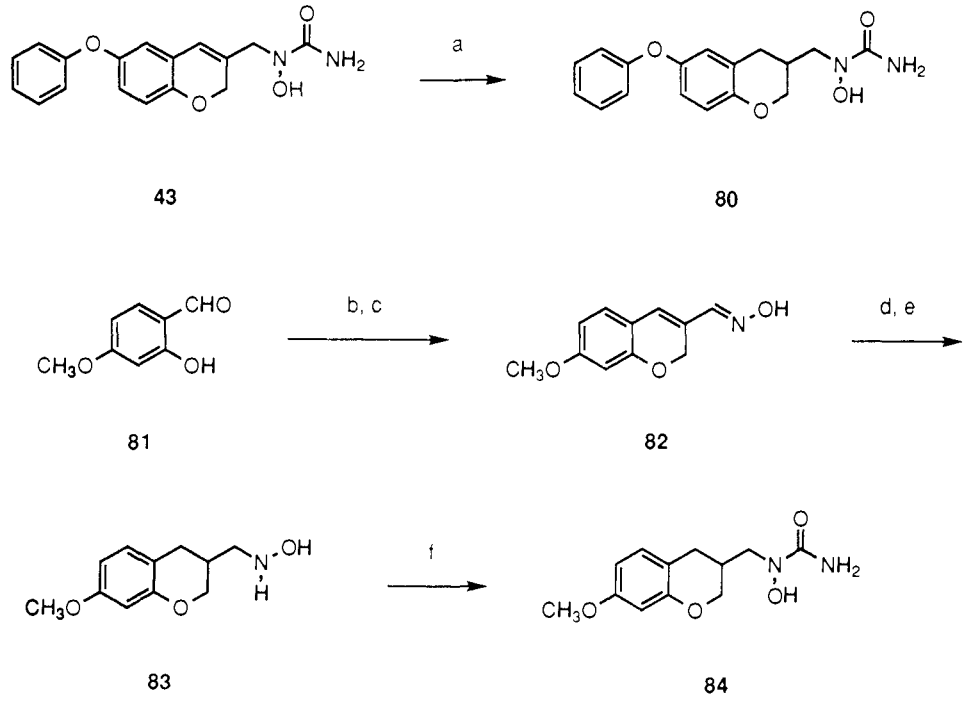
Biological Results and Discussion

***In Vitro* Guinea Pig PMN 5-LO Assay.** *In vitro* 5-LO inhibitory activity was determined by measuring production of 5-hydroxyeicosatetraenoic acid (5-HETE) and LTB_4 in guinea pig polymorphonuclear leukocytes (PMN's).[43] The assay is based on A23187-stimulated conversion of [^{14}C]AA in leukocytes to form the desired products, which are measured by a radiometric thin-layer chromatographic assay. The IC_{50} values for both products were calculated as the concentration of the test compound at which the synthesis of 5-HETE and LTB_4 were reduced to 50% of their respective control values. The results are summarized in Table I.

For hydroxamic acids (**7–9**), increase in potency is evident as the lipophilicity of the molecule increases. Thus, 6-benzyloxy analog (**9**) represents the most potent compound among those prepared, inhibiting 5-HETE and LTB_4 production with IC_{50} values of 100 and 61 nM, respectively. The *in vitro* data are in good agreement with a QSAR study[41p] on over 100 hydroxamic acid-based 5-LOI's which suggested the importance of overall lipophilicity of the molecule.

A series of *N'*-unsubstituted *N*-hydroxyureas (**37–45**) was subsequently synthesized and evaluated. The importance of the presence of a lipophilic side chain is again apparent for this class of inhibitors. For example, 6-benzyloxy derivative (**38**) is about 8–10 times more potent than the corresponding 6-methoxy derivative (**37**). Replacement of the benzyloxy group with an aryloxy moiety resulted in a further increase in potency. Compounds **43** and **44** inhibited guinea pig PMN 5-lipoxygenase with

Scheme VII[a]



[a] Reagents and conditions: (a) H_2, Pd/C; (b) CH_2=CHCHO, K_2CO_3, dioxane, reflux; (c) H_2NOH, pyridine; (d) BH_3·py, CF_3COOH, and then HCl; (e) NaOH; (f) TMS-N=C=O, dioxane, reflux.

IC_{50}'s of 43 and 45 nM for 5-HETE production, respectively, and 48 and 49 nM for LTB_4, respectively. A *tert*-butyl group on the aryloxy substituent is detrimental (**45**). Groups other than alkoxy groups at the 6-position are also tolerated (**65–67**), although these compounds are less potent. The aforementioned QSAR study also suggested the presence of a 12-Å boundary of hydrophobic binding region from the hydroxamic acid moiety.[41p] In the present study, placement of a lipophilic groups beyond the 12-Å radius appears to have a negative effect on inhibitory potency. The X-ray crystallographic data of the compound **43** indicated that the distance between the nitrogen atom of the N–OH moiety and the hydrogen atom of the para position of the phenoxy group of **43** to be 12.238 Å. Any groups larger than phenoxy or *p*-fluorophenoxy appear to transcend beyond the proposed 12-Å boundary. Similar improvement in potency by changing the benzyloxy substituent to the phenoxy has been previously reported in the acetohydroxamate series.[41f]

Attention was then focused on the *N*-hydroxyurea pharmacophore region (**46–58**). Small alkyl substituents seem to be well accommodated around the *N'*-position (**47–51**). Thus, a slight (1.7-fold) increase in potency was observed with *N'*-ethyl derivative (**48**) when compared with **43**. Further increase in size at this position, however, leads to gradual loss in *in vitro* activity (**52–54**). While the thiourea (**46**) is about 4-fold less potent than **43**, the acetohydroxamate (**58**, IC_{50} = 68 nM for 5-HETE and 74 nM for LTB_4) is essentially equipotent with the *N*-hydroxyurea (**43**) in the *in vitro* assay.

Placement of alkyl and aryl groups at the 2-position of the chromene ring leads to moderate erosion in inhibitory activity (**73–77**). This effect is more pronounced with larger groups (e.g. **76–78**). Steric effect is also evident with compound **79**, which has an α-methyl substituent to the *N*-hydroxyurea pharmacophore. This led to an approximately 4-fold loss in activity as compared to its desmethyl analog (**43**). Negative steric impact at the immediate vicinity of the hydroxamic acid pharmacophore was also reported.[41p] The double bond of the chromene ring does not seem to be essential for the inhibitory activity of this class of compound. Compound **80**, obtained by catalytic hydrogenation of **43**, shows practically the same level of *in vitro* inhibition as **43**.

***Ex Vivo* Dog Model.** The compounds were subsequently evaluated following a single intravenous (iv) or oral (po) dose in an *ex vivo* dog model.[43] This model was used to determine *in vivo* 5-LO inhibition using *ex vivo* stimulation of whole blood with the calcium ionophore, A23187. The method allows for the calculation of the time that the test compounds are biologically active in the circulation, which is a function of plasma clearance or inactivation. The product, LTB_4, was quantitated by radioimmunoassay. Inhibition of A23187-stimulated LTB_4 formation was calculated as the change in LTB_4 at each time point following compound administration (iv or po) compared to the value of LTB_4 before dosing. The duration of action (DA) following iv or po administration was defined as the period of time from maximum inhibition of A23187-stimulated LTB_4 formation to the point where the 50% level of maximum inhibition is reached. The DA was determined graphically from a plot of percent inhibition of A23187-stimulated LTB_4 formation vs time. A number of compounds are effective in inhibiting A23187-stimulated LTB_4 formation in dog blood following iv or po administration. The results are shown in Table II.

Chromene hydroxamic acids (**7–9**) are generally short acting and exhibit poor *ex vivo* efficacy. Compound **9**, which is the most potent among this class of compounds, showed good (90% at 15 min) inhibition following intravenous administration of 1.0 mg/kg. However, only 51% inhibition of A23187-stimulated LTB_4 formation was observed after 30 min following oral administration of 3.0 mg/kg. The inhibition rapidly disappeared, and no effect was seen after 6 h. No oral activity was observed with **7** and **8**. This is probably due to rapid hydrolytic degradation of the hydroxamic acid functionality *in vivo*, as demonstrated previously.[41d]

Table I. *In Vitro* Guinea Pig PMN 5-LO Assay

compd	molecular formula	mp, °C	anal.[a]	n[b]	IC_{50}, μM[c] 5-HETE	IC_{50}, μM[c] LTB_4
7	$C_{11}H_{11}NO_3$	70–73	C, H, N	1	0.83	0.18
8	$C_{12}H_{13}NO_4$	115–117	C, H, N	1	0.40	0.41
9	$C_{18}H_{17}NO_4$	143–146	C, H, N	2	0.10 (0.056, 0.15)	0.061 (0.060, 0.061)
37	$C_{12}H_{14}N_2O_4$	165–167	C, H, N	3	3.6 ± 0.42	3.9 ± 0.51
38	$C_{18}H_{18}N_2O_4$	159–161	C, H, N	2	0.44 (0.30, 0.56)	0.38 (0.21, 0.54)
39	$C_{19}H_{17}F_3N_2O_4$	160–162	C, H, N	2	0.43 (0.38, 0.48)	0.49 (0.39, 0.58)
40	$C_{17}H_{24}N_2O_4$	147–148	C, H, N	2	0.28 (0.25, 0.30)	0.34 (0.32, 0.36)
41	$C_{18}H_{24}N_2O_4$	129–135	C, H, N	3	1.36 ± 0.69	1.39 ± 0.50
42	$C_{20}H_{22}N_2O_4$	145–147	C, H, N	2	0.13 (0.088, 0.18)	0.16 (0.13, 0.18)
43	$C_{17}H_{18}N_2O_4$	165–167	C, H, N	7	0.043 ± 0.003	0.048 ± 0.007
44	$C_{17}H_{15}FN_2O_4$	179–180	C, H, N	2	0.042 (0.035, 0.048)	0.049 (0.043, 0.055)
45	$C_{21}H_{24}N_2O_4$	137–140	C, H, N	2	2.4 (2.0, 2.8)	1.9 (1.7, 2.2)
46	$C_{17}H_{18}N_2O_3S$	138–144	C, H, N, S	2	0.18 (0.15, 0.20)	0.20 (0.19, 0.22)
47	$C_{18}H_{18}N_2O_4$	157–159	C, H, N	2	0.041 (0.026, 0.056)	0.036 (0.034, 0.038)
48	$C_{19}H_{20}N_2O_4$	155–157	C, H, N	2	0.027 (0.024, 0.029)	0.024 (0.022, 0.026)
49	$C_{20}H_{22}N_2O_4$	134–137	C, H, N	2	0.034 (0.034, 0.034)	0.039 (0.039, 0.039)
50	$C_{20}H_{22}N_2O_4$	129–130	C, H, N	2	0.049 (0.040, 0.057)	0.063 (0.035, 0.091)
51	$C_{21}H_{24}N_2O_4$	135–136	C, H, N	2	0.065 (0.034, 0.095)	0.069 (0.032, 0.11)
52	$C_{21}H_{24}N_2O_4$	148–150	C, H, N	1	4.4	6.2
53	$C_{23}H_{20}N_2O_4$	168–171	C, H, N	2	0.24 (0.16, 0.31)	0.25 (0.14, 0.35)
54	$C_{24}H_{22}N_2O_4$	135–140	C, H, N	2	0.44 (0.27, 0.62)	0.44 (0.26, 0.61)
55	$C_{18}H_{17}FN_2O_4$	171–172	C, H, N	3	0.045 ± 0.004	0.051 ± 0.005
56	$C_{20}H_{20}N_2O_4$	127–132	C, H, N	2	0.037 (0.024, 0.049)	0.044 (0.029, 0.059)
57	$C_{21}H_{26}N_2O_6$	136–138	C, H, N	3	0.068 ± 0.000	0.074 ± 0.000
58	$C_{18}H_{17}NO_4$	153–157	C, H, N	2	0.086 (0.051, 0.12)	0.12 (0.075, 0.16)
65	$C_{18}H_{26}N_2O_3$	147–150	C, H, N	2	0.31 (0.25, 0.37)	0.37 (0.34, 0.40)
66	$C_{11}H_{11}BrN_2O_3$	150–155	C, H, N	4	1.4 ± 0.69	1.4 ± 0.50
67	$C_{17}H_{18}N_2O_3$	148–153	C, H, N	2	0.24 (0.13, 0.35)	0.23 (0.18, 0.28)
73	$C_{19}H_{20}N_2O_4$	132–136	C, H, N	2	0.22 (0.18, 0.26)	0.26 (0.25, 0.27)
74	$C_{18}H_{18}N_2O_4$	122–124	C, H, N	2	0.12 (0.11, 0.12)	0.087 (0.056, 0.12)
75	$C_{20}H_{22}N_2O_4$	oil	C, H, N	2	0.88 (0.68, 1.1)	0.87 (0.65, 1.1)
76	$C_{23}H_{20}N_2O_4$	158–161	C, H, N	2	0.31 (0.11, 0.50)	0.32 (0.13, 0.51)
77	$C_{19}H_{20}N_2O_4$	124–127	C, H, N	3	0.31 ± 0.13	0.44 ± 0.20
79	$C_{18}H_{18}N_2O_4$	169–171	C, H, N	2	0.20 (0.20, 0.20)	0.26 (0.23, 0.29)
80	$C_{17}H_{18}N_2O_4$	177–178	C, H, N	2	0.053 (0.052, 0.053)	0.079 (0.060, 0.097)
84	$C_{12}H_{18}N_2O_4$	169–172	C, H, N	1	>3.0	>3.0
zileuton				4	1.8 ± 0.17	2.2 ± 0.36

[a] Elemental analyses were within ±0.4% of the calculated values. The ^1H NMR, ^{13}C NMR, IR, and MS data for all the compounds are fully consistent with the assigned structures. [b] n = number of experiments. [c] *In vitro* 5-LO inhibitory activity was determined based on conversion of [^{14}C]AA to 5-LO products in guinea pig PMN's. The IC_{50} values are defined to be the concentrations of test compounds at which the amount of a product formed is reduced to 50% of the control value. The values reported here are calculated for 5-HETE and LTB_4 production and represent the means of at least two independent experiments (data shown in the parentheses), except for the compounds **7**, **8**, **52**, and **84**. The SEM values are provided when $n > 3$. Nordihydroguaiaretic acid (NDGA), which showed the IC_{50} values of 1.97 ± 0.18 μM for 5-HETE and 2.50 ± 0.45 μM for LTB_4, respectively, was used as the standard.

In 1988, two groups reported improved oral activities of hydroxamic acid-based 5-LO inhibitors by "reversing" the pharmacophore.[41e-g] Further improvement in the *in vivo* profile was observed by the conversion into the *N*-hydroxyurea functionality.[31,41i-k,r] As expected, dramatic improvement in both intravenous and oral activities was achieved by the same structural manipulation in our chromene series. For example, the benzyloxy-substituted chromene *N*-hydroxyurea (**38**) clearly demonstrates a striking contrast with its counterpart **9**. Thus, **38**, given 1.0 mg/kg iv, shows an improved DA (19 h), with maximal inhibition (>95%) through a 3.0-h period. In oral ex-

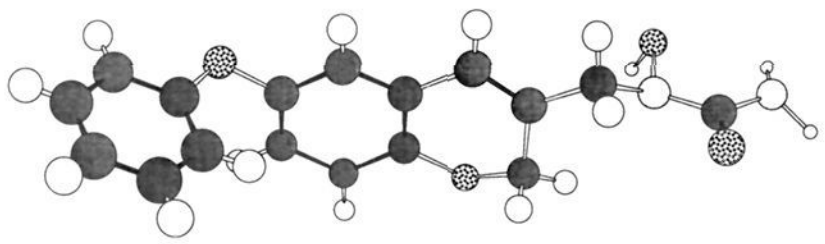


Figure 1. Chem3D Representation of **43** Determined by X-Ray Crystallography.

periments, the inhibition of A23187-stimulated LTB_4 synthesis returns to the 50% level only after 13 h following a 3.0 mg/kg dose of **38**. The effect is dose dependent. These data are especially noteworthy since **9** is about 4 times more active than **38** *in vitro* (see Table I).

For the *N'*-unsubstituted *N*-hydroxyureas, *ex vivo* efficacy seems to correlate fairly well with *in vitro* activity. Both **43** and **44**, which are significantly more potent *in vitro* than **9**, show excellent intravenous and oral DA's after a dose of 1.0 mg/kg, with sustained maximal (>95%) inhibition at earlier time points. It is noteworthy that the time course of the inhibition upon iv and po administration is almost superimposable at 1.0 mg/kg. This suggests excellent oral bioavailability of **43** and **44** in the dog.

Compounds with 6-substituents other than phenoxy or *p*-fluorophenoxy are uniformly less efficacious *ex vivo* when compared at a 1.0 mg/kg oral dose. As mentioned before, the data correlate very well with the *in vitro* results (Table I).

The size of *N'*-substituent has a definite role in oral efficacy. In the *ex vivo* model following a po dose of 1.0 mg/kg, the *N'*-methyl derivative (**47**) is essentially equipotent with **43**. However, as the steric bulk increases at the *N'*-position, oral DA's become significantly shorter, despite the fact that these *N'*-substituted compounds are equal or superior inhibitors *in vitro* as compared to the unsubstituted counterpart **43**.

The acetohydroxamic acid (**58**), which is practically equivalent to **43** in the *in vitro* assay, failed to exhibit any inhibition following the oral administration of 1.0 mg/kg.

Among the 2-substituted series (**73–76**), only the methyl derivatives, **73**, **74**, and **77**, are orally active at 1.0 mg/kg po, demonstrating good correlation with the *in vitro* activity. Superiority of phenoxy substituent over benzyloxy at the 6-position is again evident in this class of compounds (cf. **73** vs **74**).

Compounds 43 and 55. Based on these results, **43** and **55** were selected for closer examination. Both compounds showed consistent and potent *in vitro* 5-LO inhibitory activity in both dog and human whole blood, as measured by A23187-stimulated LTB_4 production. In contrast, weak inhibition against sheep seminal vesicle cyclooxygenase (CO) was observed with **43** (IC_{50} = 36 μM), while **55** did not exhibit any appreciable inhibition at the concentrations tested (>100 μM). Over 800-fold difference in *in vitro* inhibitory activity between 5-LO and CO suggests the possibility of selective inhibition of 5-LO *in vivo*. This aspect will be discussed later. Modest inhibition against human platelets 12-LO by **43** (IC_{50} = 0.64 μM) and **55** (IC_{50} = 0.41 μM) may have an additional positive impact in certain inflammatory disease conditions. No inhibitory activity was observed for thromboxane synthetase (TxS) by either compound (IC_{50} > 20 μM) (Table III). A dose-dependent effect on 5-LO inhibition in the *ex vivo* dog model was shown with compounds **43** and **55** (Table II). The oral ED_{50} values for both compounds were determined graphically at 1, 3, 6, 9, and 24 h after compound administration from a plot of percent inhibition of A23187-

Table II. Inhibition of *ex Vivo* LTB_4 Production in Dog Blood

compd	dose, mg/kg (route)	n[a]	maximum inhibitors, %[b] (times, h)[c]	duration of action (DA), h[d,e] iv	duration of action (DA), h[d,e] po
7	3.0 (po)	1	inactive		ND
8	1.0 (iv)	1	97 (0.08)	0.45	
	3.0 (po)	1	inactive		ND
9	1.0 (iv)	1	90 (0.25)	0.45	
	3.0 (po)	1	51 (0.5)		<1.0
37	1.0 (iv)	1	>95 (0.08–0.5)	1.2	
	3.0 (po)	1	>95 (0.25–1.0)		3.1
	10.0 (po)	1	>95 (0.25–3.0)		>6.0
38	1.0 (iv)	1	>95 (0.08–3.0)	19	
	0.3 (po)	1	60 (0.5)		5.0
	1.0 (po)	1	59 (0.5–1.0)		5.0
	3.0 (po)	1	>95 (0.25–1.0)		13
	10.0 (po)	1	>95 (1.0–6.0)		≫6.0
39	1.0 (iv)	1	82 (0.08)	3.0	
	10.0 (po)	1	>95 (1.0–6.0)		>6.0
40	3.0 (po)	1	60 (1.0)		2.2
41	1.0 (po)	1	inactive		ND
42	1.0 (po)	1	>90 (1.0)		4.0
	3.0 (po)	1	>95 (0.5–3.0)		>6.0
43	1.0 (iv)	3	>95 (0.08–6.0)	21 ± 5.6	
	0.1 (po)	3	70 (1)		3.3 ± 1.1
	0.3 (po)	3	93 (3)		8.7 ± 1.4
	1.0 (po)	6	>95 (1–3)		14 ± 2.0
	3.0 (po)	3	>95 (1–9)		35 ± 7.2
44	1.0 (iv)	3	>95 (0.08–9.0)	24 ± 4.9	
	0.3 (po)	3	85 (1.0)		7.7 ± 0.58
	1.0 (po)	3	>95 (0.5–3.0)		13 ± 3.1
	3.0 (po)	3	>95 (0.5–9.0)		31 ± 2.8
45	1.0 (po)	1	inactive		ND
46	1.0 (po)	1	inactive		ND
47	1.0 (iv)	1	>95 (0.08–3.0)	8.4	
	1.0 (po)	1	>95 (1.0–3.0)		11
48	1.0 (iv)	1	>95 (0.08–1.0)	5.1	
	1.0 (po)	1	60 (1.0)		3.8
49	1.0 (iv)	1	>95 (0.08–1.0)	8.1	
	1.0 (po)	1	inactive		ND
50	1.0 (po)	1	inactive		ND
51	1.0 (po)	1	inactive		ND
52	1.0 (po)	1	inactive		ND
53	1.0 (po)	1	inactive		ND
54	1.0 (po)	1	inactive		ND
55	1.0 (iv)	3	>95 (0.08–9.0)	20 ± 1.7	
	0.1 (po)	4	65 (1.0)		3.9 ± 0.71
	0.3 (po)	3	91 (1.0)		9.8 ± 4.2
	1.0 (po)	3	>95 (1.0–6.0)		15 ± 4.0
	3.0 (po)	3	>95 (>24)		42 ± 9.7
56	1.0 (po)	1	80 (1.0)		4.2
57	1.0 (po)	1	inactive		ND
58	1.0 (po)	1	inactive		ND
65	1.0 (po)	1	inactive		ND
66	10.0 (po)	1	>95 (0.25–3.0)		3.8
67	1.0 (po)	1	60 (1.0)		1.0
73	1.0 (po)	1	91 (1.0)		2.8
74	1.0 (iv)	1	>95 (0.08–3.0)	5.0	
	1.0 (po)	1	>95 (0.5–6.0)		9.0
75	1.0 (po)	1	inactive		ND
76	1.0 (po)	1	inactive		ND
77	1.0 (po)	1	65 (0.25–1.0)		2.6
79	1.0 (po)	1	inactive		ND
80	1.0 (iv)	1	>95 (0.08–3.0)	7.4	
	1.0 (po)	1	>95 (3.0)		4.8
84	ND				
zileuton	1.0 (iv)	3	>95 (0.08–3.0)	8.5 ± 0.59	
	1.0 (po)	3	>95 (0.25–1.0)		9.8 ± 1.2

[a] n = number of experiments. [b] *Ex vivo* inhibition was determined by the measurement of A23187-stimulated LTB_4 production in dog blood at certain time intervals following either iv or po dose. See text for details. [c] The number in the parentheses refers to the time point(s) where maximum inhibition was achieved. [d] Duration of action (DA) was defined as the period of time from where maximum inhibition of LTB_4 formation is achieved to the point where 50% level of maximum inhibition is reached. In the case of >95% inhibition of the 5-LO activity in dog blood, the earliest time point whereupon total inhibition was achieved was considered to be the time of maximum inhibition. The SEM values are provided where $n \geq 3$. [e] ND = not determined.

Table III. *In Vitro* Data for **43** and **55**

assay	IC$_{50}$, μM[a]		
	43	**55**	zileuton
cyclooxygenase (CO)[b]	36 ± 4.3	>100	>100
12-lipoxygenase (12-LO)[c]	0.64 ± 0.05	0.41 ± 0.02	55 ± 11
thromboxane synthetase (TxS)[d]	>20	>20	>20
5-LO (dog whole blood)	0.11 ± 0.02	0.11 ± 0.02	0.84 ± 0.12
5-LO (human whole blood)	0.89 ± 0.16	0.41 ± 0.10	5.12 ± 0.75

[a] The IC$_{50}$ values are defined to be the concentrations of test compounds at which the amount of product formed is reduced to 50% of the control value and represent the means of at least three separate experiments. [b] Sheep seminal vesicle CO. The assay was carried out using indomethacin (IC$_{50}$ = 16 ± 1.2 μM) as the standard. [c] Human platelet 12-LO. Eicosatetraynoic acid (ETYA, IC$_{50}$ = 0.050 ± 0.010 μM) was used as the standard. [d] Human platelet TxS. UK 37,238-01 (IC$_{50}$ = 0.028 ± 0.002 μM) was used as the standard.

stimulated LTB$_4$ formation vs compound concentration (log mg/kg). The ED$_{50}$ values for compound **43** are <0.1, <0.1, 0.23, 0.43, and 2.37 mg/kg at 1, 3, 6, 9, and 24 h, respectively; while those for compound **55** are <0.1, <0.1, 0.23, 0.38, and 1.63 mg/kg at 1, 3, 6, 9, and 24 h, respectively. In comparison, the ED$_{50}$'s for zileuton over the same time points are <0.3, <0.3, 0.46, 1.03, and 3.63 mg/kg, respectively. In this dog model both compounds are at least 1.5–2.0 times more potent than zileuton at all time points. In separate experiments, when tested at 3.0 mg/kg po, **43** had no effect on *ex vivo* production of PGE$_2$, a cyclooxygenase product, in the dog model. As shown in Table II, LTB$_4$ production was completely inhibited through the 9.0-h period at this dose. The data therefore demonstrate excellent selective *in vivo* 5-LO inhibition over CO in the dog.

Conclusion

Inhibitors of 5-lipoxygenase based on the chromene template were synthesized and evaluated both *in vitro* and *ex vivo*. Proper selection of the 6-substituent seems to be critical for potent *in vitro* inhibitory activity. Phenoxy and *p*-fluorophenoxy groups were found to be optimal. *In vivo* superiority of the *N*-hydroxyurea pharmacophore over either the hydroxamic acid or the acetohydroxamate group was demonstrated in the *ex vivo* dog model. This is probably due to the relatively stable nature of the *N*-hydroxyurea functionality toward hydrolytic degradation *in vivo*. Compounds **43** (CGS 23885) and **55** (CGS 24891) were selected for further evaluation. These compounds inhibit guinea pig PMN 5-LO with IC$_{50}$ values of 48 and 51 nM, respectively, as determined by LTB$_4$ production. Little or no inhibition by **43** and **55** was observed in the sheep seminal vesicle CO and human platelet TxS assays. **43** and **55** are modestly active against human platelet 12-LO at the IC$_{50}$ values of 0.64 and 0.41 μM, respectively. Both compounds showed long DA's after either iv or po administration at a 1.0 mg/kg dose in the *ex vivo* dog model. The inhibition is clearly dose dependent. In the oral studies, the ED$_{50}$ values for *ex vivo* 5-LO inhibition in the dog for **43** and **55** are 0.23 and 0.23 mg/kg at 6 h, respectively, and 2.37 and 1.63 mg/kg at 24 h, respectively. Moreover, comparison between the iv and po experiments at 1.0 mg/kg suggests excellent oral bioavailability by **43** and **55** in the dog. Further studies on **43** and **55** including the *in vivo* pharmacological evaluation are subject to future publications.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-250 or a Bruker AC-300 spectrometer. A Bruker AC-300 spectrometer was used for ^{13}C NMR spectra. IR and MS spectra were measured on a Nicolet 5SXB FTIR spectrometer and a Hewlett-Packard GC/MS 5985B spectrometer, respectively. Microanalyses were carried out at Robertson Laboratory, Inc., Madison, NJ.

DMF, dioxane, methylene chloride, and acetonitrile were all of anhydrous grade obtained from Aldrich Chemicals. THF was distilled from benzophenone ketyl just prior to use. All the other chemicals are from commercial suppliers and used as received, unless otherwise mentioned. *p*-(Fluorophenoxy)phenol was prepared according to the literature procedure.[49] As a general rule, all the reactions were carried out under an inert atmosphere.

General Procedure for the Synthesis of *N*-Methylhydroxamic Acids (7–9). *tert*-Butyl 6-(Benzyloxy)chromene-3-carboxylate (6). 5-(Benzyloxy)-2-hydroxybenzaldehyde **3**[45] (2.01 g, 8.80 mmol) was dissolved in 30 mL of DMF and treated successively with potassium carbonate (1.22 g, 8.80 mmol) and *tert*-butyl acrylate (1.22 g, 13.2 mmol). The mixture was heated at 100 °C for 1 h. The temperature was gradually raised to 135 °C over a period of 2 h and held at 135 °C for 1 h. The resultant dark mixture was cooled and evaporated to remove most of DMF. The residue was partitioned between ether and water, and the aqueous phase was discarded. The organic layer was dried (MgSO$_4$), evaporated, and purified by silica gel chromatography (6% ethyl acetate/hexane) to give the title compound **6** (1.85 g, 62%) as a yellow crystalline solid: mp 64–67 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.53 (s, 9 H), 4.89 (s, 2 H), 5.01 (s, 2 H), 6.7–6.9 (m, 3 H), 7.2–7.5 (m, 6 H) ppm.

***N*-Hydroxy-*N*-methyl-6-(benzyloxy)chromene-3-carboxamide (9).** The *tert*-butyl ester **6** (1.1 g, 3.25 mmol) was dissolved in 10 mL of trifluoroacetic acid, and the mixture was stirred at room temperature overnight. This was poured into 50 mL of water, and the precipitate was collected by filtration. The solid was washed with water several times and dried *in vacuo*. Crystallization from ethyl acetate/hexane gave a yellow solid (402 mg, 46%): mp 189 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.83 (s, 2 H), 5.04 (s, 2 H), 6.7–7.1 (m, 3 H), 7.3–7.6 (m, 6 H) ppm.

The resulting carboxylic acid (362 mg, 1.33 mmol) and DMF (97 mg, 1.33 mmol) were dissolved in 5 mL of methylene chloride. To this was added oxalyl chloride (0.38 g, 2.99 mmol), and the mixture was stirred until no further gas evolution was observed (2 h). This acid chloride solution was slowly added to a mixture of *N*-methylhydroxylamine hydrochloride (0.44 g, 5.32 mmol) and triethylamine (0.81 g, 7.98 mmol) in THF/water (4.1 mL/0.99 mL). The resultant mixture was stirred at room temperature for 1 h and poured onto 100 mL of 2 N aqueous HCl. The mixture was extracted twice with methylene chloride, and the combined organic phase was dried (MgSO$_4$). Evaporation followed by trituration of the residual solid with ethyl acetate/hexane gave the title compound **9** (252 mg, 61%) as a pale yellow solid: mp 143–146 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.16 (s, 3 H), 4.75 (s, 2 H), 5.03 (s, 2 H), 6.7–7.6 (m, 9 H), 10.06 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 165.62, 153.04, 148.11, 137.15, 129.25, 128.40, 127.79, 127.68, 122.51, 117.18, 116.20, 113.97, 69.74, 65.25, 37.09 ppm; IR (KBr) 1640 cm^{-1}; MS (CI/CH$_4$) 312 (M + 1). Anal. (C$_{18}$H$_{17}$NO$_4$) C, H, N.

***N*-Hydroxy-*N*-methylchromene-3-carboxamide (7).** This compound was prepared from salicyl aldehyde **1** according to the procedure described for **9**: mp 70–73 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.17 (s, 3 H), 4.84 (s, 2 H), 6.84 (d, J = 8.0 Hz, 1 H), 6.94 (t, J = 7.5 Hz, 1 H), 7.23 (m, 3 H), 10.04 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 165.58, 154.12, 130.74, 129.19, 128.32, 126.98, 121.86, 121.78, 115.57, 65.24, 37.10 ppm; IR (KBr) 1636 cm^{-1}; MS (CI/CH$_4$) 206 (M + 1). Anal. (C$_{11}$H$_{11}$NO$_3$) C, H, N.

***N*-Hydroxy-*N*-methyl-7-methoxychromene-3-carboxamide (8).** This compound was prepared from 4-methoxy-2-hydroxybenzaldehyde **2** according to the procedure described for **9**: mp 115–117 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.15 (s, 3 H), 3.74 (s, 3 H), 4.81 (s, 2 H), 6.44 (d, J = 2.5 Hz, 1 H), 6.54 (dd, J = 2.5 and 8.4 Hz, 1 H), 7.17 (d, J = 8.4 Hz, 1 H), 7.20 (s, 1 H), 9.98 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 165.88, 161.65, 155.67, 129.72, 129.40, 123.40, 114.04, 107.94, 101.29, 65.40, 55.37, 37.19 ppm; IR (KBr) 1631 cm^{-1}. Anal. (C$_{12}$H$_{13}$NO$_4$) C, H, N.

5-Phenoxy-2-hydroxybenzaldehyde (14): Typical Procedure for Reimer–Tiemann Formylation. 4-Phenoxyphenol (**10**, 20.2 g, 107 mmol) and sodium hydroxide (3.8 g, 845 mmol) were dissolved in a water–ethanol (130 mL/26 mL) mixture and heated at 70 °C. To this was added chloroform (24.6 g, 215 mmol) dropwise over a 45-min period, and the heating was continued for 3 h. The mixture was cooled to room temperature and then evaporated. The aqueous phase was acidified with 12 N HCl to pH 1–3 and extracted twice with ether. The extracts were dried ($MgSO_4$) and evaporated. Silica gel chromatography (10% ethyl acetate/hexane) of the residual oil gave the title compound (**14**, 6.2 g, 27%) as a yellow solid: mp 54–55 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 6.9–7.4 (m, 8 H), 9.84 (s, 1 H), 10.82 (s, 1H) ppm.

6-Methoxychromene-3-carboxaldehyde (19): Typical Procedure for Condensation with α,β-Unsaturated Aldehydes and Ketones. 5-Methoxy-2-hydroxybenzaldehyde **13** (25 g, 0.16 mol) and potassium carbonate (22.7 g, 0.16 mol) were taken in 300 mL of 1,4-dioxane and treated with acrolein (13.8 g, 0.25 mol). The mixture was heated at 100 °C for 1 h and allowed to cool. The mixture was diluted with water and extracted three times with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated. The residual oil was dissolved in a minimal amount of ethyl acetate (~40 mL) and passed through 40 g of silica gel. The gel was successively washed with several portions of a hexane/ether mixture (3:1) until no further fluorescent material eluted. The organic phase was evaporated, and the residue was crystallized from ethyl acetate/hexane to give the aldehyde **19** (22.6 g, 72%) as a yellow solid. The mother liquor was concentrated to afford a second crop (5.6 g, 18%): mp 49–50 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 3.79 (s, 3 H), 4.98 (d, J = 1.1 Hz, 2 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.82 (d, J = 8.9 Hz, 1 H), 6.88 (dd, J = 2.8 and 8.9 Hz, 1 H), 7.23 (s, 1 H), 9.59 (s, 1 H) ppm.

6-(Benzyloxy)chromene-3-carboxaldehyde (3): Typical Procedure for Alkylation of 6-Hydroxychromene-3-carboxaldehyde (18). Potassium carbonate (39.2 g, 0.28 mol) and 6-hydroxychromene-3-carboxaldehyde (**18**, 25.0 g, 0.14 mol), prepared from 5-hydroxysalicyl aldehyde (**17**) according to the procedure described for **19**, were taken in 500 mL of DMF and treated with benzyl bromide (26.7 g, 0.14 mol). The mixture was stirred overnight at room temperature. Water was added, and three extractions with methylene chloride were carried out. The extract was dried ($MgSO_4$) and evaporated. The residue was crystallized from hot ethyl acetate to give 6-(benzyloxy)chromene-3-carboxaldehyde (**3**) as a yellow solid (32.15 g, 90%): mp 112–114 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 4.98 (s, 2 H), 5.04 (s, 2 H), 6.82 (m, 2 H), 6.95 (dd, J = 2.9 and 8.9 Hz, 1 H), 7.20 (s, 1 H), 7.3–7.5 (m, 5 H), 9.58 (s, 1 H).

3-[(*N*-Hydroxyamino)methyl]-6-methoxychromene Hydrochloride (28): Representative Method for the Preparation of 3-[(Hydroxyamino)methyl]chromenes (Route A, Allylic Bromide Method). The carboxaldehyde **19** (8.5 g, 44.7 mmol) was suspended in 100 mL of absolute ethanol and treated with sodium borohydride (0.68 g, 44.7 mmol). After 15 min, the resultant mixture was evaporated, partitioned between ether and water, and quenched by addition of 2 N aqueous HCl. Ether was removed, and the aqueous phase was extracted twice with ether. The combined organic phases were dried ($MgSO_4$) and evaporated. Purification of the residual oil by silica gel chromatography (15% ethyl acetate/hexane) gave the desired alcohol as a yellow oil (6.7 g, 78%) which partially solidified while stored in a refrigerator: ^1H NMR (250 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 4.22 (s, 2 H), 4.73 (s, 2 H), 6.36 (br s, 1 H), 6.56 (d, J = 2.9 Hz, 1 H), 6.66 (dd, J = 2.9 and 8.7 Hz, 1 H), 6.74 (d, J = 8.7 Hz, 1 H) ppm.

The above alcohol (4.35 g, 22.6 mmol) was dissolved in 70 mL of dry acetonitrile and treated with dibromotriphenylphosphorane (9.56 g, 22.6 mmol). After 15 min, the mixture was evaporated *in vacuo*. The residue was triturated with 100 mL of an ether/hexane mixture (1:1). The solid was removed by filtration (medium frit) and washed with several 50-mL portions of the ether/hexane mixture. The organic extracts were combined and evaporated to give the bromide as a gray solid mass (5.67 g, 98%), free of any phosphine-originated impurity. This material was used in the next step without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 4.09 (s, 2 H), 4.77 (s, 2 H), 6.50 (br s, 1 H), 6.57 (d, J = 2.7 Hz, 1 H), 6.70 (dd, J = 2.7 and 8.8 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H) ppm.

The bromide (2.32 g, 9.09 mmol) in 10 mL of DMF was added to a stirred solution of *O*-[(2-methoxy-2-propyl)oxy]hydroxylamine[46] (2.87 g, 27.28 mmol) and triethylamine (1.01 g, 10.0 mmol) in 30 mL of DMF. The reaction was allowed to proceed overnight. The reaction mixture was diluted with water and extracted three times with ether. The combined ether phases were dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (15% ethyl acetate/hexane to give the acetal-protected hydroxylamine (1.68 g, 66%) as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 1.36 (s, 6 H), 3.25 (s, 3 H), 3.60 (s, 2 H), 3.75 (s, 3 H), 4.77 (s, 2 H), 6.34 (br s, 1 H), 6.55 (d, J = 2.9 Hz, 1 H), 6.65 (dd, J = 2.9 and 8.7 Hz, 1 H), 6.72 (d, J = 8.7 Hz, 1 H) ppm.

The protected hydroxylamine (1.68 g, 6.01 mmol) was dissolved in 15 mL of methanol and treated with 2.5 mL of 12 N HCl. The mixture was stirred for 1 h and evaporated *in vacuo*. The residual solid was triturated with an ether/hexane mixture (1:1) and collected by filtration. Drying of the crystalline solid under high vacuum afforded the hydrochloride salt **28** (1.17 g, 80%): mp 147–153 °C; ^1H NMR (250 MHz, DMSO-d_6) δ 3.39 (s 3 H), 3.68 (s, 2 H), 4.73 (s, 2 H), 6.65 (s, 1 H), 6.72 (s, 3 H), 10.95 (br s, 1 H), 11.67 (br s, 2 H) ppm.

3-[(*N*-Hydroxyamino)methyl]-6-phenoxychromene Hydrochloride (34) (Route B, Oxime Method). 6-Phenoxychromene-3-carboxaldehyde (**25**, 5.00 g, 19.8 mmol) was dissolved in 175 mL of pyridine/EtOH (1:1) and treated with hydroxylamine hydrochloride (2.07 g, 29.7 mmol). The mixture was stirred for 1 h at room temperature and partitioned between ether and water. The aqueous layer was extracted with ether (2×), and the combined ether extract was washed with 2 N HCl (2×), dried ($MgSO_4$), and evaporated to give the desired oxime as a pale yellow solid (5.08 g, 96%): mp 172–178 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 5.02 (s 2 H), 6.04 (s, 1 H), 6.7–7.2 (m, 8 H), 7.2–7.5 (m, 3 H), 7.82 (s, 1 H) ppm.

The oxime (4.58 g, 17.1 mmol) was dissolved in 25 mL of methylene chloride and 25 mL of trifluoroacetic acid. The solution was cooled in an ice-bath and treated slowly with borane–pyridine complex (6.37 g, 68.5 mmol). The ice bath was removed, and the reaction was allowed to proceed for 2 h at room temperature. This was again cooled to 0 °C and treated with 12 N HCl (26 mL). The resultant suspension was stirred at room temperature overnight. Methylene chloride was removed *in vacuo*, and the mixture was brought to pH 8 with ammonium hydroxide. Water was added, and the mixture was extracted with ether (3×). To the combined organic layer was added 12 N HCl until acidic, and the precipitate formed was collected by filtration. This was sequentially rinsed with ethanol and ether and dried *in vacuo* at 50 °C. Recrystallization from ethanol gave the desired hydrochloride salt **34** as a white solid (2.06 g, 40%): mp 171–173 °C; ^1H NMR (250 MHz, DMSO-d_6) δ 3.86 (s, 2 H), 4.82 (s, 2 H), 6.66 (s, 1 H), 6.84 (m, 3 H), 6.91 (d, J = 7.5 Hz, 2 H), 7.07 (t, J = 7.5 Hz, 1 H), 7.34 (t, J = 7.5 Hz, 2 H), 10.95 (br s, 1 H), 11.73 (br s, 2 H) ppm.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-methoxychromene (37): General Procedure for the Synthesis of the Hydroxyureas (37–45). The hydrochloride salt **28** (480 mg, 1.97 mmol) was suspended in ether and treated with 2 N aqueous sodium hydroxide. The ether layer was removed, and the aqueous phase was extracted three times with ether. The combined organic phases were dried over magnesium sulfate and evaporated to give the free hydroxylamine derivative (407 mg, 100%) as a pale yellow solid. This amine and trimethylsilyl isocyanate (322 mg, 2.79 mmol) were dissolved in 15 mL of 1,4-dioxane, and the mixture was heated at reflux for 30 min. The mixture was cooled to 5 °C and treated with aqueous saturated ammonium chloride solution. Two extractions with ethyl acetate were carried out, and the combined organic layer was dried ($MgSO_4$). Evaporation followed by crystallization from ethyl acetate/hexane gave the urea derivative **37** (217 mg, 44%): mp 165–167 °C; ^1H NMR (250 MHz, DMSO-d_6) δ 3.67 (s, 3 H), 4.04 (s, 2 H), 4.61 (s, 2 H), 6.34 (s, 1 H), 6.65 (br s, 2 H), 6.66 (m, 3 H), 9.39 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.57, 153.76, 146.56, 132.66, 123.01, 120.74, 115.55, 113.58, 111.45, 66.38, 55.38, 52.12 ppm; IR (KBr) 1650 cm^{-1}; MS (CI/CH_4) 251 (M + 1). Anal. ($C_{12}H_{14}N_2O_4$) C, H, N.

6-(Benzyloxy)-3-[[*N*-(aminocarbonyl)-*N*-hydroxyamino]methyl]chromene (38). This compound was prepared according

to the general procedure described for **37** from **20** *via* route A: mp 159–161 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.07 (s, 2 H), 4.67 (s, 2 H), 5.03 (s, 2 H), 6.33 (s, 1 H), 6.41 (br s, 2 H), 6.1–6.3 (m, 3 H), 7.2–7.5 (m, 5 H), 9.39 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.57, 152.79, 146.76, 137.33, 132.68, 128.38, 127.71, 127.58, 123.01, 120.69, 115.57, 114.70, 112.57, 69.66, 66.40, 52.12 ppm; IR (KBr) 1650 cm^{-1}; MS (CI/CH_4) 327 (M + 1). Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-[[4-(trifluoromethyl)benzyl]oxy]chromene (39). This compound was prepared according to the general procedure described for **37** from **21** *via* route A: mp 160–162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.04 (s, 2 H), 4.62 (s, 2 H), 5.14 (s, 2 H), 6.34 (s, 1 H), 6.41 (br s, 2 H), 6.6–6.8 (m, 3 H), 7.64 (d, J = 8.1 Hz, 2 H), 7.74 (d, J = 8.1 Hz, 2 H), 9.38 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.57, 152.47, 146.93, 142.28, 132.79, 127.89, 125.26, 125.21, 124.52 (q, J_{C-F} = 271 Hz), 123.08, 120.61, 115.63, 114.68, 112.59, 68.74, 66.41, 52.11 ppm; IR (CH_2Cl_2) 1693 cm^{-1}; MS (CI/CH_4) 395 (M + 1). Anal. ($C_{18}H_{17}F_3N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-(*n*-hexyloxy)chromene (40). This compound was prepared according to the general procedure described for **37** from **22** *via* route A: mp 147–148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (t, J = 6.7 Hz, 3 H), 1.2–1.5 (m, 6 H), 1.65 (quintet, J = 6.5 Hz, 2 H), 3.86 (t, J = 6.5 Hz, 2 H), 4.04 (s, 2 H), 4.61 (s, 2 H), 6.34 (s, 1 H), 6.41 (br s, 2 H), 6.64 (m, 3 H), 9.37 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.57, 153.13, 146.47, 132.54, 122.98, 120.80, 115.51, 114.26, 112.11, 67.83, 66.35, 52.13, 30.99, 28.72, 25.18, 22.05, 13.89 ppm; IR (KBr) 1647 cm^{-1}; MS (CI/CH_4) 321 (M + 1). Anal. ($C_{17}H_{24}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-(cyclohexylmethoxy)chromene (41). This compound was prepared according to the general procedure described for **37** from **23** *via* route A: mp 129–135 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.9–1.4 (m, 5 H), 1.6–1.9 (m, 6 H), 3.68 (d, J = 6.3 Hz, 2 H), 4.04 (s, 2 H), 4.61 (s, 2 H), 6.33 (s, 1 H), 6.41 (br s, 2 H), 6.63 (m, 3 H), 9.38 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.54, 153.26, 146.42, 132.49, 122.94, 120.78, 115.48, 114.27, 112.07, 73.18, 66.31, 52.10, 37.07, 29.24, 26.02, 25.22 ppm; IR (KBr) 1642 cm^{-1}; MS (CI/CH_4) 333 (M + 1). Anal. ($C_{18}H_{24}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-[(3-phenylpropyl)oxy]chromene (42). This compound was prepared according to the general procedure described for **37** from **24** *via* route A: mp 145–147 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.02 (m, 2 H), 2.71 (t, J = 7.2 Hz, 2 H), 3.87 (t, J = 6.3 Hz, 2 H), 4.04 (s, 2 H), 4.62 (s, 2 H), 6.34 (s, 1 H), 6.41 (br s, 2 H), 6.65 (m, 3 H), 7.1–7.4 (m, 5 H), 9.37 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.59, 153.06, 146.58, 141.43, 132.58, 128.33, 125.81, 123.01, 120.79, 115.56, 114.35, 112.20, 67.10, 66.37, 52.14, 31.47, 30.45 ppm; IR (KBr) 1651 cm^{-1}; MS (CI/CH_4) 355 (M + 1). Anal. ($C_{20}H_{22}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-phenoxychromene (43). This compound was prepared according to the general procedure described for **37** from **25**. Both route A and route B were used: mp 165–167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.04 (s, 2 H), 4.69 (s, 2 H), 6.37 (s, 1 H), 6.45 (br s, 2 H), 6.78 (s, 3 H), 6.92 (d, J = 8.6 Hz, 2 H), 7.07 (t, J = 7.5 Hz, 1 H), 7.35 (dd, J = 7.5 and 8.6 Hz, 2 H), 9.38 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.56, 157.85, 149.82, 148.93, 132.87, 129.84, 123.49, 122.54, 120.20, 119.49, 117.26, 116.10, 66.49, 52.05 ppm; IR (KBr) 1645 cm^{-1}; MS (CI/CH_4) 313 (M + 1). Anal. ($C_{17}H_{18}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-(4'-fluorophenoxy)chromene (44). This compound was prepared according to the general procedure described for **37** from **26** *via* route A: mp 179–180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.05 (s, 2 H), 4.70 (s, 2 H), 6.36 (s, 1 H), 6.46 (br s, 2 H), 6.77(s, 3 H), 6.97 (m, 2 H), 7.17 (tt, J = 3.2 and 8.8 Hz, 2 H), 9.41 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.60, 157.70 ($^1J_{C-F}$ = 248.5 Hz), 153.89 ($^4J_{C-F}$ = 2.0 Hz), 150.40, 148.90, 132.99, 123.56, 120.22, 119.22 ($^3J_{C-F}$ = 8.1 Hz), 119.07, 116.20 ($^2J_{C-F}$ = 26.5 Hz), 116.20, 116.17, 66.54, 52.09 ppm; IR (KBr) 3484, 1649 cm^{-1}; MS (CI/CH_4) 331 (M + 1). Anal. ($C_{17}H_{15}FN_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-(4'-*tert*-butylphenoxy)chromene (45). This compound was prepared according to the general procedure described for **37** from **27** *via* route A: mp 137–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (s, 9 H), 4.04 (s, 2 H), 4.69 (s, 2 H), 6.36 (s, 1 H), 6.42 (br s, 2 H), 6.75 (s, 3 H), 6.84 (d, J = 8.8 Hz, 2 H), 7.35 (d, J = 8.8 Hz, 2 H), 9.38 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.56, 155.44, 150.20, 148.74, 144.88, 132.82, 126.47, 123.42, 120.23, 119.24, 117.04, 116.91, 116.03, 66.48, 52.05, 33.90, 31.23 ppm; IR (KBr) 3460, 1651 cm^{-1}; MS (CI/CH_4) 369 (M + 1). Anal. ($C_{21}H_{24}N_2O_4$) C, H, N.

3-[[*N*-(Aminothiocarbonyl)-*N*-hydroxyamino]methyl]-6-phenoxychromene (46). 3-[(*N*-Hydroxyamino)methyl]-6-phenoxychromene (**34**) (0.41 g, 1.51 mmol) was dissolved in 20 mL of 1,4-dioxane and treated with 0.28 g (2.15 mmol) of trimethylsilyl isothiocyanate. The mixture was heated at reflux for 30 min and allowed to cool. The mixture was diluted with water and extracted with ethyl acetate (3×). The organic layers were combined, dried ($MgSO_4$), and evaporated. Crystallization of the residual solid gave 0.28 g of the title thiourea derivative **46** as a tan solid (57%): mp 138–144 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.74 (s, 4 H), 6.38 (s, 1 H), 6.79 (m, 3 H), 6.92 (d, J = 8.4 Hz, 2 H), 7.08 (t, J = 7.6 Hz, 1 H), 7.33 (dd, J = 7.6 and 8.4 Hz, 2 H), 7.60 (br s, 1 H), 7.86 (br s, 1 H), 10.02 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 179.95, 157.88, 149.94, 149.04, 131.68, 129.89, 123.42, 122.62, 120.69, 119.70, 117.46, 117.34, 116.24, 66.19, 54.15 ppm; IR (KBr) 3428, 1593 cm^{-1}; MS (CI/CH_4) 329 (M + 1). Anal. ($C_{17}H_{18}N_2O_3S$) C, H, N, S.

3-[[*N*-Hydroxy-*N*-[(*N'*-methylamino)carbonyl]amino]methyl]-6-phenoxychromene (47): Typical Procedure for the Condensation with Alkyl Isocyanates. The hydroxylamine hydrochloride salt **34** was treated with aqueous 1 N NaOH and extracted with ether (2×). The combined ether layer was dried ($MgSO_4$) and evaporated to give free hydroxylamine. This was dissolved in 50 mL of 1,4-dioxane and treated with 1.5 equiv of methyl isocyanate. The mixture was heated at reflux for 30 min and cooled. Aqueous saturated ammonium chloride was added, and the mixture was extracted with ether (2×). The organic layer was dried ($MgSO_4$) and evaporated. Crystallization of the residue from THF/hexane gave 0.95 g of the product **47** as a colorless solid (64%): mp 157–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (d, J = 4.6 Hz, 3 H), 4.04 (s, 2 H), 4.70 (s, 2 H), 6.37 (s, 1 H), 6.78 (s, 3 H), 6.92 (d, J = 8.4 Hz, 2 H), 7.00 (q, J = 4.6 Hz, 1 H), 7.06 (t, J = 7.4 Hz, 1 H), 7.35 (dd, J = 7.4 and 8.4 Hz, 2 H), 9.33 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.35, 157.91, 149.85, 148.99, 132.89, 129.88, 123.55, 122.58, 120.39, 119.57, 117.38, 117.29, 116.14, 66.58, 53.00, 26.55 ppm; IR (KBr) 1644 cm^{-1}; MS (CI/CH_4) 327 (M + 1). Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

3-[[*N*-[(*N'*-Ethylamino)carbonyl]-*N*-hydroxyamino]methyl]-6-phenoxychromene (48). This compound was prepared from **34** by the reaction with ethyl isocyanate: mp 155–157 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.01 (t, J = 7.2 Hz, 3 H), 3.07 (dq, J = 4.8 and 7.2 Hz, 2 H), 4.03 (s, 2 H), 4.69 (s, 2 H), 6.36 (s, 1 H), 6.77 (s, 3 H), 6.91 (d, J = 8.6 Hz, 2 H), 7.04 (t, J = 4.8 Hz, 1 H), 7.05 (t, J = 7.3 Hz, 1 H), 7.33 (dd, J = 7.3 and 8.6 Hz, 2 H), 9.30 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 160.71, 157.89, 149.85, 148.98, 132.91, 129.89, 123.54, 122.58, 120.38, 119.55, 117.35, 117.29, 116.14, 66.57, 52.93, 34.26, 15.48 ppm; IR (KBr) 3429, 1633 cm^{-1}. MS (CI/CH_4) 341 (M + 1). Anal. ($C_{18}H_{20}N_2O_4$) C, H, N.

3-[[*N*-[(*N'*-Propylamino)carbonyl]-*N*-hydroxyamino]methyl]-6-phenoxychromene (49). This compound was prepared from **34** by the reaction with *n*-propyl isocyanate: mp 134–137 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (t, J = 7.4 Hz, 3 H), 1.41 (sextet, J = 7.4 Hz, 2 H), 3.00 (dt, J = 6.0 and 7.4 Hz, 2 H), 4.03 (s, 2 H), 4.69 (s, 2 H), 6.36 (s, 1 H), 6.77 (s, 3 H), 6.73 (d, J = 8.4 Hz, 2 H), 7.03 (t, J = 6.0 Hz, 1 H), 7.06 (t, J = 7.4 Hz, 1 H), 7.33 (dd, J = 7.4 and 8.4 Hz, 2 H), 9.33 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 160.84, 157.89, 149.87, 138.97, 132.90, 129.88, 123.54, 122.60, 120.37, 119.54, 117.31, 116.14, 66.58, 52.93, 41.24, 22.94, 11.22 ppm; IR (KBr) 3409, 1639 cm^{-1}; MS (CI/CH_4) 355 (M + 1). Anal. ($C_{20}H_{22}N_2O_4$) C, H, N.

3-[[*N*-[(*N'*-Isopropylamino)carbonyl]-*N*-hydroxyamino]methyl]-6-phenoxychromene (50). This compound was prepared from **34** by the reaction with isopropyl isocyanate: mp 129–130 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (d, J = 6.6 Hz, 6 H), 3.76 (d septet, J = 5.3 and 6.6 Hz, 1 H), 4.04 (s, 2 H), 4.70 (s, 2 H), 6.37 (s, 1 H), 6.72 (d, J = 5.3 Hz, 1 H), 6.78 (s, 3 H), 6.93 (d, J = 8.3 Hz, 2 H), 7.06 (t, J = 7.3 Hz, 1 H), 7.34 (dd, J = 7.3 and 8.3 Hz, 2 H), 9.34 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz,

DMSO-d_6) δ 160.02, 157.86, 149.81, 148.95, 132.87, 129.86, 123.52, 122.57, 120.34, 119.54, 117.32, 116.14, 66.52, 52.89, 41.34, 22.68 ppm; IR (KBr) 3426, 1620 cm^{-1}; MS (CI/CH_4) 355 (M + 1). Anal. ($C_{20}H_{22}N_2O_4$) C, H, N.

3-[[*N*-[(*N'*-Butylamino)carbonyl]-*N*-hydroxyamino]methyl]-6-phenoxychromene (51). This compound was prepared from **34** by the reaction with *n*-butyl isocyanate: mp 135–136 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, *J* = 7.2 Hz, 3 H), 1.24 (sextet, *J* = 7.2 Hz, 2 H), 1.37 (quintet, *J* = 7.2 Hz, 2 H), 3.03 (dt, *J* = 6.3 and 7.2 Hz, 2 H), 4.03 (s, 2 H), 4.69 (s, 2 H), 6.36 (s, 1 H), 6.76 (s, 3 H), 6.92 (d, *J* = 8.3 Hz, 2 H), 7.02 (t, *J* = 6.3 Hz, 1 H), 7.06 (t, *J* = 7.4 Hz, 1 H), 7.33 (dd, *J* = 7.4 and 8.3 Hz, 2 H), 9.32 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 160.82, 157.89, 149.88, 148.97, 132.89, 129.87, 123.54, 122.60, 120.36, 119.53, 117.32, 116.14, 66.60, 52.94, 39.11, 31.88, 19.44, 13.70 ppm; IR (KBr) 3405, 1637 cm^{-1}; MS (CI/CH_4) 369 (M + 1). Anal. ($C_{21}H_{24}N_2O_4$) C, H, N.

3-[[*N*-[(*N'*-*tert*-Butylamino)carbonyl]-*N*-hydroxyamino]methyl]-6-phenoxychromene (52). This compound was prepared from **34** by the reaction with *tert*-butyl isocyanate: mp 148–150 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (s, 9 H), 4.02 (s, 2 H), 4.69 (s, 2 H), 6.21 (s, 1 H), 6.36 (s, 1 H), 6.77 (s, 3 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 7.06 (t, *J* = 7.4 Hz, 1 H), 7.33 (dd, *J* = 7.4 and 8.4 Hz, 2 H), 9.41 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 159.79, 157.89, 149.86, 148.97, 132.84, 129.88, 123.52, 122.59, 120.46, 119.56, 117.35, 117.29, 116.15, 66.54, 52.58, 49.67, 28.85 ppm; IR (KBr) 3389, 1643 cm^{-1}; MS (CI/CH_4) 369 (M + 1). Anal. ($C_{21}H_{24}N_2O_4$) C, H, N.

3-[[*N*-Hydroxy-*N*-[(*N'*-phenylamino)carbonyl]amino]methyl]-6-phenoxychromene (53). This compound was prepared from **34** by the reaction with phenyl isocyanate: mp 168–171 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.19 (s, 2 H), 4.76 (s, 2 H), 6.42 (s, 1 H), 6.71 (m, 3 H), 6.92 (d, *J* = 7.8 Hz, 2 H), 6.97 (t, *J* = 8.3 Hz, 1 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 7.26 (t, *J* = 7.9 Hz, 2 H), 7.34 (dd, *J* = 7.3 and 8.3 Hz, 2 H), 7.61 (d, *J* = 7.9 Hz, 2 H), 9.05 (s, 1 H), 9.81 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 157.89, 157.66, 149.92, 149.01, 139.28, 132.33, 129.88, 128.41, 123.47, 122.61, 122.41, 120.66, 119.67, 119.50, 117.44, 117.33, 116.19, 66.54, 52.16 ppm; IR (KBr) 1638 cm^{-1}; MS (CI/CH_4) 389 (M + 1). Anal. ($C_{23}H_{20}N_2O_4$) C, H, N.

3-[[*N*-Hydroxy-*N*-[(*N'*-benzylamino)carbonyl]amino]methyl]-6-phenoxychromene (54). This compound was prepared from **34** by the reaction with benzyl isocyanate: mp 135–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.08 (s, 2 H), 4.24 (d, *J* = 6.3 Hz, 2 H), 4.70 (s, 2 H), 6.36 (s, 1 H), 6.65-7.40 (m, 13 H), 7.62 (t, *J* = 6.3 Hz, 1 H), 9.44 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 160.81, 157.50, 149.91, 148.98, 140.50, 132.72, 129.89, 128.07, 127.09, 126.52, 123.52, 122.62, 120.38, 119.58, 117.35, 117.30, 116.15, 66.62, 52.85, 42.95, ppm; IR (KBr) 1628 cm^{-1}; MS (CI/CH_4) 403 (M + 1). Anal. ($C_{24}H_{22}N_2O_4$) C, H, N.

3-[[*N*-[(*N'*-Methylamino)carbonyl]-*N*-hydroxyamino]methyl]-6-(4'-fluorophenoxy)chromene (55). This compound was prepared from **35** by the reaction with methyl isocyanate: mp 171–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (d, *J* = 3.5 Hz, 3 H), 4.03 (s, 2 H), 4.69 (s, 2 H), 6.36 (s, 1 H), 6.76 (s, 3 H), 6.98 (m, 3 H), 7.17 (t, *J* = 8.8 Hz, 2 H), 9.31 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.43, 157.70 ($^1J_{C-F}$ = 238.4 Hz), 153.90 ($^4J_{C-F}$ = 2.0 Hz), 150.40, 148.92, 132.95, 123.56, 120.37, 119.21 ($^3J_{C-F}$ = 8.5 Hz), 119.09, 116.70 ($^2J_{C-F}$ = 23.4 Hz), 116.19, 116.15, 66.59, 52.98, 26.54 ppm; IR (KBr) 3455, 1636 cm^{-1}; MS (CI/CH_4) 345 (M + 1). Anal. ($C_{18}H_{17}FN_2O_4$) C, H, N.

3-[[*N*-[(*N'*-Allylamino)carbonyl]-*N*-hydroxyamino]methyl]-6-phenoxychromene (56). This compound was prepared from **34** by the reaction with allyl isocyanate: mp 127–132 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.67 (dd, *J* = 5.7 and 7.3 Hz, 2 H), 4.05 (s, 2 H), 4.70 (s, 2 H), 5.01 (dd, *J* = 1.8 and 8.8 Hz, 1 H), 5.09 (dd, *J* = 1.8 and 17.2 Hz, 1 H), 5.80 (ddd, *J* = 7.3, 8.8 and 17.2 Hz, 1 H), 6.37 (s, 1 H), 6.78 (s, 3 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 7.06 (t, *J* = 7.3 Hz, 1 H), 7.18 (t, *J* = 5.7 Hz, 1 H), 7.34 (dd, *J* = 7.3 and 8.4 Hz, 2 H), 9.41 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 160.57, 157.86, 149.83, 148.95, 136.27, 132.76, 129.86, 123.50, 122.57, 120.42, 119.56, 117.35, 117.28, 116.14, 114.48, 66.53, 52.83, 41.79 ppm; IR (KBr) 3412, 1638 cm^{-1}; MS (CI/CH_4) 353 (M + 1). Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

3-[[*N*-[[*N'*-[(Ethoxycarbonyl)methyl]amino]carbonyl-*N*-hydroxyamino]methyl]-6-phenoxychromene (57). This compound was prepared from **34** by the reaction with (ethoxycarbonyl)methyl isocyanate: mp 136–138 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.72 (t, *J* = 7.1 Hz, 3 H), 3.77 (d, *J* = 6.0 Hz, 2 H), 4.06 (s, 2 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 4.69 (s, 2 H), 6.38 (s, 1 H), 6.77 (s, 3 H), 6.92 (d, *J* = 7.7 Hz, 2 H), 7.06 (t, *J* = 7.4 Hz, 1 H), 7.34 (t, *J* = 7.4 Hz, 2 H), 7.36 (t, *J* = 6.0 Hz, 1 H), 9.56 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 170.45, 160.70, 157.86, 149.86, 148.96, 132.44, 129.87, 123.49, 122.59, 120.43, 119.56, 117.31, 116.14, 66.43, 60.24, 52.55, 41.63, 14.08 ppm; IR (KBr) 3455 cm^{-1}. Anal. ($C_{21}H_{22}N_2O_6$) C, H, N.

3-[(*N*-Hydroxy-*N*-acetylamino)methyl]-6-phenoxychromene (58). The hydroxylamine hydrochloride salt (**34**) was treated with a base to give the free hydroxylamine as described in the preparation of **47**. The hydroxylamine (0.67 g, 2.48 mmol) and pyridine (0.49 g, 6.19 mmol) were dissolved in 30 mL of THF and cooled to 0 °C. Acetyl chloride (0.49 g, 6.19 mmol) was slowly added, and the mixture was stirred for 45 min at 0 °C. The mixture was then diluted with ethyl acetate, washed with aqueous 2 N HCl, dried ($MgSO_4$), and evaporated to give the crude bisacetate. This was dissolved in 40 mL of a 2-isopropanol/water mixture (1:1) and treated with 0.94 g (25 mmol) of LiOH monohydrate for 20 min at room temperature. The mixture was diluted with ether, and the organic phase was removed. The aqueous layer was brought to pH ~ 3 with 2 N HCl and extracted with ether (3×). The combined acidic extracts were dried ($MgSO_4$) and evaporated. Crystallization of the residue from ethyl acetate/hexane gave 0.35 g (50%) of the title monoacetate **58** as a tan solid: mp 153–157 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.03 (s, 3 H), 4.20 (s, 2 H), 4.68 (s, 2 H), 6.36 (s, 1 H), 6.80 (m, 3 H), 6.92 (d, *J* = 8.3 Hz, 2 H), 7.06 (t, *J* = 7.4 Hz, 1 H), 7.34 (dd, *J* = 7.4 and 8.3 Hz, 2 H), 9.90 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 170.98, 160.23, 157.87, 149.92, 148.91, 131.46, 129.89, 123.34, 122.62, 120.40, 119.73, 117.45, 117.33, 116.20, 66.23, 49.39 ppm; IR (KBr) 1629 cm^{-1}; MS (CI/CH_4) 312 (M + 1). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-*n*-heptylchromene (65). This compound was prepared using the procedure described for **37** from **60** *via* the allylic bromide method (route A): mp 147–150 °C. ; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, *J* = 6.5 Hz, 3 H), 1.24 (m, 8 H), 1.49 (m, 2 H), 2.46 (t, *J* = 7.5 Hz, 2 H), 4.03 (s, 2 H), 4.64 (s, 2 H), 6.33 (s, 1 H), 6.41 (s, 2 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 6.82 (d, *J* = 1.9 Hz, 1 H), 6.87 (dd, *J* = 1.9 and 8.1 Hz, 1 H), 9.36 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.61, 150.78, 135.04, 131.59, 128.28, 126.02, 121.99, 120.80, 114.74, 66.40, 52.16, 34.30, 31.25, 31.13, 28.53, 22.08, 13.94 ppm; IR (KBr) 3452, 1648 cm^{-1}; MS (CI/CH_4) 319 (M + 1). Anal. ($C_{18}H_{26}N_2O_3$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-bromochromene (66). This compound was prepared using the procedure described for **37** from **61** *via* route A: mp 150–155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.03 (s, 2 H), 4.74 (s, 2 H), 6.40 (s, 1 H), 6.45 (s, 2 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 7.23 (m, 2 H), 9.41 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.61, 151.99, 133.29, 130.95, 128.43, 124.48, 119.45, 117.23, 112.45, 66.64, 52.08 ppm; IR (KBr) 3482, 1652 cm^{-1}; MS (CI/CH_4) 299, 231 (M + 1). Anal. ($C_{11}H_{11}BrN_2O_3$) C, H, N.

6-Phenylchromene-3-carboxaldehyde (64). The bromo aldehyde **62** (5.00 g, 20.9 mmol), phenylboronic acid (2.81 g, 23.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (725 mg, 0.63 mmol) were dissolved in 50 mL of toluene and treated with 25 mL of aqueous 2 N sodium carbonate under nitrogen. The mixture was heated at reflux for 6 h. The reaction mixture was cooled and extracted with ether (3×). The combined ethereal extracts were dried ($MgSO_4$) and evaporated. Flash chromatography (silica gel, 5% ethyl acetate/hexane) gave the coupling product **64** (1.98 g, 40%) as a yellow solid: mp 109–111 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.06 (s, 2 H), 6.94 (d, *J* = 6.0 Hz, 1 H), 7.2–7.6 (m, 8 H), 9.60 (s, 1 H) ppm.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-phenylchromene (67). This compound was prepared from 6-phenylchromene-3-carboxaldehyde (**64**) according to the procedure described for **37** through the allylic bromide method: mp 148–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.06 (s, 2 H), 4.75 (s, 2 H), 6.46 (s, 2 H), 6.48 (s, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 7.3–7.5 (m, 5 H), 7.60 (d, *J* = 8.5 Hz, 2 H), 9.42 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.61, 152.50, 139.75, 133.47, 132.06, 128.83, 126.86, 126.80, 126.13, 124.52, 122.55, 120.65, 115.49, 66.68,

52.18 ppm; IR (KBr) 1643 cm^{-1}; MS (CI/CH_4) 297 (M + 1). Anal. ($C_{17}H_{18}N_2O_3$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-(benzyloxy)-2-methylchromene (73). This compound was prepared from **68** according to the procedure described for **37** through the allylic bromide method: mp 132–136 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.25 (d, J = 6.5 Hz, 3 H), 3.88 (d, J = 16.1 Hz, 1 H), 4.24 (d, J = 16.1 Hz, 1 H), 4.83 (q, J = 6.5 Hz, 1 H), 5.00 (s, 2 H), 6.29 (s, 1 H), 6.39 (br s, 2 H), 6.65 - 6.75 (m, 3 H), 7.25–7.5 (m, 5 H), 9.39 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.32, 152.63, 145.34, 137.36, 136.39, 128.39, 127.72, 127.62, 122.48, 119.79, 116.15, 114.84, 112.25, 71.73, 51.66, 18.50 ppm; IR (KBr) 1636 cm^{-1}; MS (CI/CH_4) 341 (M + 1). Anal. ($C_{19}H_{20}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-2-methyl-6-phenoxychromene (74). This compound was prepared from the corresponding phenoxy aldehyde **69** according to the procedure described for **37** through the allylic bromide method: mp 122–124 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.30 (d, J = 6.4 Hz, 3 H), 3.88 (d, J = 16.1 Hz, 1 H), 4.25 (d, J = 16.1 Hz, 1 H), 4.92 (q, J = 6.4 Hz, 1 H), 6.32 (s, 1 H), 6.41 (br s, 2 H), 6.79 (s, 3 H), 6.92 (d, J = 8.4 Hz, 2 H), 7.08 (t, J = 7.3 Hz, 1 H), 7.85 (dd, J = 7.3 and 8.4 Hz, 2 H), 9.41 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.35, 157.88, 149.72, 147.63, 136.60, 129.88, 123.00, 122.59, 119.60, 119.40, 117.38, 117.05, 116.69, 72.05, 51.66, 18.71 ppm; IR (KBr) 1639 cm^{-1}; MS (CI/CH_4) 327 (M + 1). Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-phenoxy-2-propylchromene (75). The compound was prepared from 6-phenyl-2-propylchromene-3-carboxaldehyde (**70**) according to the procedure described for **37** through the allylic bromide method: oil; ^1H NMR (300 MHz, DMSO-d_6) δ 0.88 (t, J = 6.6 Hz, 3 H), 1.3–1.7 (m, 4 H), 3.87 (d, J= 16.3 Hz, 1 H), 4.76 (d, J = 16.3 Hz, 1 H), 4.76 (d, J = 9.0 Hz, 1 H), 6.32 (s, 1 H), 6.39 (br s, 2 H), 6.77 (m, 3 H), 6.93 (d, J = 8.2 Hz, 2 H), 7.06 (t, J = 7.4 Hz, 1 H), 7.34 (dd, J = 7.4 and 8.2 Hz, 2 H), 9.40 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.33, 157.84, 149.69, 147.56, 136.08, 129.88, 123.27, 122.61, 119.55, 119.52, 117.41, 116.99, 116.68, 75.28, 51.68, 33.90, 18.12, 13.60 ppm; IR (KBr) 3486, 1651 cm^{-1}; MS (CI/CH_4) 355 (M + 1). Anal. ($C_{20}H_{22}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-2-phenyl-6-phenoxychromene (76). This compound was prepared from the corresponding phenoxy aldehyde **71** according to the procedure described for **37** through the allylic bromide method: mp 158–161 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 3.72 (d, J = 16.5 Hz, 1 H), 4.07 (d, J = 16.5 Hz, 1 H), 5.86 (s, 1 H), 6.42 (br s, 2 H), 6.58 (s, 1 H), 6.70 (m, 2 H), 6.83 (d, J = 2.7 Hz, 1 H), 6.94 (d, J = 8.0 Hz, 2 H), 7.07 (t, J = 7.3 Hz, 1 H), 7.85 (m, 7 H), 9.48 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.46, 157.67, 149.91, 147.57, 138.63, 133.67, 129.91, 128.64, 127.40, 122.74, 122.71, 120.06, 119.65, 117.57, 117.51, 116.54, 77.10, 51.72 ppm; IR (KBr) 3487, 1647, 1619 cm^{-1}; MS (CI/CH_4) 389 (M + 1). Anal. ($C_{23}H_{20}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-2,2-dimethyl-6-phenoxychromene (77). This compound was prepared from **72** according to the general procedure described for **37** through the allylic bromide method: mp 124–127 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.39 (s, 6 H), 4.09 (s, 2 H), 6.27 (s, 1 H), 6.41 (br s, 2 H), 6.76 (m, 3 H), 6.42 (d, J = 8.4 Hz, 2 H), 7.06 (t, J = 7.4 Hz, 1 H), 7.34 (dd, J = 7.4 and 8.4 Hz, 2 H), 9.34 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.20, 157.82, 149.60, 147.94, 138.20, 129.84, 123.19, 122.57, 119.46, 119.14, 117.39, 116.72, 77.84, 50.95, 25.40 ppm; IR (KBr) 3478, 1666 cm^{-1}; MS (CI/CH_4) 341 (M + 1). Anal. ($C_{19}H_{20}N_2O_4$) C, H, N.

3-[1'-[*N*-(Aminocarbonyl)-*N*-hydroxyamino]ethyl]-6-phenoxychromene (79). The oxime (1.06 g, 3.77 mmol) derived from ketone **78**, according to the procedure described for **19**, was dissolved in 7.0 mL of trifluoroacetic acid and 7.0 mL of methylene chloride and cooled to 0 °C. To this was added borane–pyridine complex (7.0 g, 75.4 mmol) in 10 mL of methylene chloride at 0 °C. After the addition, the mixture was heated at 40 °C for 3 h. The mixture was allowed to cool and treated with 12 N HCl (15 mL). This was heated to 40 °C for 1 h. This mixture was cooled to 0 °C and brought to pH 10 by addition of ammonium hydroxide. Three extractions with ether were carried out. The combined ether layer was dried ($MgSO_4$) and evaporated to give the hydroxylamine (620 mg), contaminated with the starting oxime. This material was used without further purification.

The crude hydroxylamine (620 mg, ~2.19 mmol) was treated with trimethylsilyl isocyanate (360 mg, 3.11 mmol) in 20 mL of 1,4-dioxane. The solution was heated at reflux for 30 min. The solution was cooled and partitioned between EtOAc and water. The organic layer was dried ($MgSO_4$) and evaporated. The residue was crystallized from acetonitrile to give the desired *N*-hydroxyurea **79** (60 mg, 9%): mp 169–171 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.22 (d, J = 6.7 Hz, 3 H), 4.63 (d, J = 14.7 Hz, 1 H), 4.74 (d, J = 14.7 Hz, 1 H), 4.75 (q, J = 6.7 Hz, 1 H), 6.35 (s, 1 H), 6.41 (s, 2 H), 6.77 (m, 2 H), 6.79 (s, 1 H), 6.92 (d, J = 8.7 Hz, 2 H), 7.06 (t, J = 7.4 Hz, 1 H), 7.34 (dd, J = 7.4 and 8.7 Hz, 2 H), 9.00 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.61, 157.87, 149.86, 148.97, 136.42, 129.85, 123.73, 122.56, 119.49, 119.12, 117.48, 117.32, 116.05, 66.66, 53.83, 13.53 ppm; IR (KBr) 3462, 1658 cm^{-1}; MS (CI/CH_4) 327 (M + 1). Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-6-phenoxy-3,4-dihydrochromene (80). The chromene **43** (100 mg, 0.32 mmol) and 5% palladium on charcoal (106 mg) were suspended in 40 mL of ethanol and stirred in a Parr bottle under H_2 pressure (45 psi) for 2 h. The mixture was filtered through Celite and evaporated. Pure material **80** was obtained as a colorless solid by crystallization from THF/hexane (70 mg, 70%): mp 177–178 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.31 (m, 1 H), 2.50 (m, 1 H), 2.76 (dd, J = 5.1 and 16.6 Hz, 1 H), 3.2–3.5 (m, 2 H), 3.81 (dd, J = 8.7 and 10.5 Hz, 1 H), 4.20 (br d, J = 8.7 Hz, 1 H), 6.34 (s, 2 H), 6.76 (s, 3 H), 6.90 (d, J = 7.8 Hz, 2 H), 7.04 (t, J = 7.2 Hz, 1 H), 7.32 (dd, J = 7.2 and 7.8 Hz, 2 H), 9.39 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.73, 158.02, 150.59, 148.92, 129.83, 122.87, 122.46, 120.67, 118.58, 117.29, 117.18, 68.14, 50.94, 30.34, 28.29 ppm; IR (KBr) 3477, 1644 cm^{-1}; MS (CI/CH_4) 315 (M + 1). Anal. ($C_{17}H_{18}N_2O_4$) C, H, N.

3-[[*N*-(Aminocarbonyl)-*N*-hydroxyamino]methyl]-7-methoxy-3,4-dihydrochromene (84). The oxime **82** (2.14 g, 11.3 mmol) was dissolved in 30 mL of a CF_3COOH/CH_2Cl_2 mixture (1:1) and cooled in an ice bath. To this was added borane–pyridine complex (4.18 g, 45.0 mmol) slowly. After completion of the addition, the cooling bath was removed and the mixture was stirred for 3 h at room temperature. This was again cooled to 0 °C and treated with 15 mL of 12 N HCl. This was allowed to reach room temperature and was stirred overnight. Methylene chloride was removed *in vacuo*, and the mixture was brought to pH ~ 8 with ammonium hydroxide. Water was then added, and the mixture was extracted with ether (3×). The organic layer was dried ($MgSO_4$) and evaporated. The last traces of pyridine were removed under high vacuum to give 2.11 g of the crude 3-[(*N*-hydroxylamino)methyl]*dihydrochromene*, **83**. This sample, contaminated with a significant quantity of the oxime **82**, was used without further purification.

The crude hydroxylamine **83** (1.99 g, ~10.3 mmol) was dissolved in 75 mL of 1,4-dioxane and treated with trimethylsilyl isocyanate (1.69 g, 14.7 mmol). The mixture was heated at reflux for 30 min and cooled. Aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate (2×). The organic layer was dried ($MgSO_4$) and evaporated. Repeated crystallization from acetonitrile gave 112 mg of the desired *N*-hydroxyurea **84** as a tan solid (4% from **82**): mp 169–172 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.26 (m, 1 H), 2.40 (dd, J = 8.9 and 15.7 Hz, 1 H), 2.69 (dd, J = 4.6 and 15.7 Hz, 1 H), 3.30 (m, 2 H), 3.66 (s, 3 H), 3.78 (dd, J = 8.7 and 10.7 Hz, 1 H), 4.17 (dd, J = 1.4 and 10.4 Hz, 1 H), 6.30 (d, J = 2.4 Hz, 1 H), 6.33 (br s, 2 H), 6.40 (dd, J = 2.4 and 8.3 Hz, 1 H), 6.92 (d, J = 8.3 Hz, 1 H), 9.38 (s, 1 H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 161.70, 158.45, 154.86, 130.30, 113.30, 106.83, 101.06, 68.09, 54.96, 50.96, 30.60, 27.52 ppm; IR (KBr) 3487, 1643 cm^{-1}; MS (CI/CH_4) 253 (M + 1). Anal. ($C_{12}H_{16}N_2O_4$) C, H, N.

***In Vitro* Guinea Pig PMN 5-LO Assay.** Peritoneal leukocytes were collected from male Hartley strain guinea pigs (250–300 g, Elmhill Laboratories, Chelmsford, MA) approximately 18 h after injection of 5 mL of a neutral 7% caseinate solution. The cells were washed once with Gey's solution containing heparin (25 units/mL) and then once with Gey's solution without heparin. A small aliquot was removed for staining and microscopic examination. Typically, the leukocyte population consisted of more than 80% PMNs. The cells were resuspended in 100 mM

Tris-HCl buffer (pH 7.8) with 5.5 mM glucose and 2.0 mM $CaCl_2$ and adjusted to a concentration of 5×10^7 cells/mL.

A radiometric thin-layer chromatographic assay similar to those described by Walker and Dawson[50] and Jakschik and Lee[51] was used to measure the formation of 5-HETE and DiHETE products from [^{14}C]arachidonic acid. The assay was started by the addition of 250 μL of cells to 250 μL of test compound in the above buffer with 2.0 μM indomethacin. The mixture was incubated at 37 °C for 5 min. A 25-μL solution of A23187 (40 μM, Calbiochem Corp., La Jolla, CA) and 1-[^{14}C]AA (80 μM, New England Nuclear, Boston, MA) was added to the incubation mixture, and after 5 min at 37 °C, the reaction was terminated by addition of 100 μL of 1.0 N HCl. The radioactive products were evaporated to dryness, and the residue was dissolved in acetone, spotted on thin-layer plates, and chromatographed in the organic phase of ethyl acetate/isooctane/acetic acid/H_2O (110:50:20:100). The radioactive zones were located with a Berthold TLC scanner. Those corresponding to 5-HETE and LTB_4 were scraped off, transferred to liquid scintillation vials, and counted. The IC_{50} values were calculated as the concentration of test compound at which the synthesis of 5-HETE and LTB_4 was reduced to 50% of their respective control values.

***In Vitro* Sheep Seminal Vesicle CO Assay.** Lyophilized sheep seminal vesicle microsomes, isolated as previously described,[52] were utilized as the source of cyclooxygenase (CO). The conversion of [^{14}C]AA to PGE_2 was measured by a modification of the procedure described by Takeguchi et al.[52] Test drugs, dissolved in 0.1 M Tris-HCl (pH 8.4) buffer or, if necessary, in a 1% volume of ethanol, were present in the incubation mixture over a wide range of concentration. PG's were extracted into ethyl acetate, the extracts were evaporated to dryness, and the residue was dissolved in acetone, spotted on thin-layer plates, and chromatographed in toluene/acetone/acetic acid (100:100:3). The plates were scanned, and the radioactive zones corresponding to PGE_2 were scraped off, transferred to liquid scintillation vials, and counted. The IC_{50} values were calculated as the concentration of test compound which reduced the formation of PGE_2 to 50% of the control.

***In Vitro* Human Platelet 12-LO Assay.** A radiometric thin-layer chromatographic assay similar to that described by Nugteren[53] was used to measure the formation of 12-HETE from the cytoplasmic fraction of lysed human platelets. Test compounds, dissolved 0.1 M Tris-HCl buffer (pH 8.0) containing 1 mM of glutathione and 10 μM indomethacin, were present over a wide range of concentrations. The assay was started by preincubation of the properly diluted enzyme preparation (50% conversion of [^{14}C]AA to 12-HETE) with inhibitor at 37 °C for 5 min. 1-[^{14}C]-AA was added to the incubation mixture, and after 15 min at 37 °C, the reaction was terminated by addition of 100 μL of 1.0 N HCl. The radioactive products and excess substrate were extracted into ethyl acetate, the extracts were evaporated to dryness, and the residue was dissolved in acetone, spotted on thin-layer plates, and chromatographed in petroleum ether/ethyl ether/acetic acid (50:50:1). The radioactive zones were located with a Berthold TLC-scanner. Those corresponding to 12-HETE were scraped off, transferred to liquid scintillation vials, and counted. The IC_{50} values were calculated as the concentration of test compound which inhibited the conversion of AA to 12-HETE by 50% of the control value.

***In Vitro* Human Platelet Thromboxane Synthetase (TxS) Assay.** A radiometric thin-layer chromatographic assay similar to that described by Sun[54] was used to measure the formation of TxB_2, PGE_2, and PGF_2 from endoperoxide (PGH_2) generated from AA in situ.[55] 1-[^{14}C]AA was incubated with an enzyme mixture consisting of solubilized and partially purified CO from sheep seminal vesicles[56] and a crude microsomal preparation of TxS from lysed human platelets.[54,57] The relative amounts of the two enzyme preparations were adjusted to ensure the preferential synthesis of TxB_2, in such a manner that the ratio of the amount of TxB_2 synthesized to the combined amounts of PGE_2 and PGF_2 was in linear proportion to the concentration of TxS. Test compounds, dissolved in 0.1 M Tris-HCl (pH 7.5) or, when necessary, in a 1% volume of ethanol, were present in the incubation medium over a wide range of concentrations. At the end of the incubation period (30 min), PGE_2 was reduced to $PGF_{2\alpha}$ by addition of $NaBH_4$. The radioactive products and excess substrate were extracted into ethyl acetate, the extracts were evaporated to dryness, and the residues were dissolved in acetone, spotted on thin-layer plates, and chromatographed in toluene/acetone/glacial acetic acid (100:100:3). The radioactive zones were located with a Berthold TLC-scanner; those corresponding to TxB_2 and $PGF_{2\alpha}$ were scraped off, transferred to liquid scintillation vials, and counted. The ratio of counts for $TxB_2/PGF_{2\alpha}$ was calculated for each concentration of test compound. The IC_{50} values were calculated as the concentration of test compound at which the ratio of $TxB_2/PGF_{2\alpha}$ was reduced to 50% of the control value.

***In Vitro* Inhibition of LTB_4 Formation in Dog Whole Blood.** Experiments were performed with beagle dogs of either sex, weighing 8–15 kg. The dogs were fasted 16–18 h before experimentation but allowed free access to water. Blood was collected by venipuncture of the external jugular veins into a syringe containing 75 μL of a mixture of 40 mM *d,l*-serine and 25 units of heparin/mL of blood. One-milliliter samples of blood were preincubated at 37 °C for 5 min with the desired concentration of test compound delivered in 10 μL of DMSO. The reaction was started by the addition of A23187 and *N*-formyl-Met-Leu-Phe (fMLP), 100 and 10 μM final concentrations, respectively. After 15 min at 37 °C the reaction was terminated by placing the samples on ice. Plasma was removed following centrifugation at 350*g* for 15 min. LTB_4 was quantitated by redioimmunoassay using kits supplied by Advanced Magnetics Inc. (Cambridge, MA) according to the manufacturer's procedures either immediately or within 1 day of storage at −80 °C. Normal plasma was used to determine nonspecific binding. The IC_{50} values were calculated as the concentration of test compound at which the synthesis of LTB_4 was reduced to 50% of their respective control values.

***In Vitro* Inhibition of LTB_4 Formation in Human Whole Blood.** Experiments were performed using a modification of the methods of Sweeney et al.[58] with normal human volunteers of either sex who were medication free for at least 2 weeks. Blood was collected into a syringe containing 75 μL of a mixture of 40 mM *d,l*-serine and 25 units of heparin/mL of blood. One-milliliter samples of blood were preincubated at 37 °C for 5 min with the desired concentration of a test compound delivered in 10 μL of DMSO. The reaction was started by the addition of A23187 and *N*-formyl-Met-Leu-Phe (fMLP) at the final concentrations of 100 and 10 μM, respectively. After 15 min at 37 °C, the reaction was terminated by placing the samples on ice. Plasma was removed following centrifugation at 350*g* for 15 min. LTB_4 was quantitated by radioimmunoassay using kits supplied by Amersham Corp. (Arlington Heights, IL) according to the manufacturer's procedures either immediately or within 1 day of storage at −80 °C. Normal plasma was used to determine nonspecific binding. The IC_{50} values were calculated as the concentration of test compound at which the synthesis of LTB_4 was reduced to 50% of their respective control values.

***Ex Vivo* Inhibition of LTB_4 Formation in the Dog following Intravenous Administration.** The methods for blood collection, stimulation, and determination of LTB_4 used were the same as those described in *in vitro* dog study (*vide supra*). Blood (3 mL) was collected at −1, 0, 0.08, 0.25, 0.5, 1, 3, 6, 9, and 24 h relative to iv dosing and divided into three 1-mL aliquots; 1 mL was used as an unstimulated control and 2 mL were stimulated as above. The compounds were injected in the forearm as a bolus dose dissolved in 0.1 mL of DMA/PEG 400 (25:75)/kg body weight. Inhibition of LTB_4 formation was calculated as the mean change in LTB_4 at each time point compared to the mean of the values obtained at −1 and 0 h. The duration of action was determined graphically from a plot of percent inhibition vs time.

***Ex Vivo* Inhibition of LTB_4 Formation following Oral Administration.** The methods used were the same as those described in *ex vivo* dog iv study (*vide supra*) except that compound was administered po by intubation as a suspension in fortified cornstarch (3% cornstarch suspension in water with 0.33% Tween 80 and 5% PEG 400) at a volume of 5 mL/kg body weight. Blood samples were taken at -1, 0, 0.25, 0.5, 1, 3, 6, 9, and 24 h relative to administration of the compound or vehicle. The ED_{50} value was determined graphically from a plot of % inhibition vs log mg/kg po.

The X-ray Structure Determination of 43. The X-ray structure determination was performed using a Nicolet R3m/V

diffractometer with the SCHELLXTL PLUS software on a MicroVax II computer. The crystal was monoclinic, space group $P2/m$ with cell constants a = 16.901(3), b = 5.2193(8), and c = 19.214(3) Å.

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Supplementary Material Available: Methods of data collection and crystal data for **43** and tables listing atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients, and torsion angles (8 pages). Ordering information is given on any current masthead page.

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