Synthesis and Biological Evaluation of Antiplatelet 2-Aminochromones

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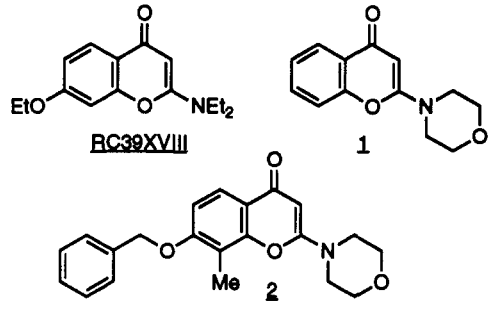
The synthesis and biological evaluation of a series of antiplatelet 2-morpholinylchromones has been described. Modification of the C-7 phenylmethoxy group of 8-methyl-7-(phenylmethoxy)-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (**2**) has led to the discovery of a series of 7-[(aminoethyl)oxy]-8-methyl derivatives which are potent inhibitors of ADP-induced platelet aggregation. Several members of this class proved active in preventing platelet-dependent thrombus formation in the dog, including 8-methyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (**39**) which was devoid of hemodynamic effects at the effective antithrombotic dose.

The processes of activation and subsequent aggregation of blood platelets play a significant role in thrombolytic disorders. The searches for pharmacological inhibitors[1,2] of these events have focused on several approaches including receptor antagonists and enzyme inhibitors of mediators of platelet aggregation such as thromboxane A_2,[3] serotonin,[4] and platelet activating factor.[5] Agents which elevate cyclic AMP, such as prostacyclin, inhibit platelet function regardless of the agonist responsible for the activation.[6] A strategy based on the inhibition of binding of plasma fibrinogen with the platelet GPIIb/IIIa complex[7] also achieves wide-spectrum platelet inhibitory activity, but without the hemodynamic problems[8] associated with cyclic AMP promoters.

The 2-aminochromones have recently been described as a new class of antiplatelet agents.[9,10] A series of compounds typified by RC39XVIII have defined an SAR for this class requiring a 2-diethylamino group in the 2-position as well as an electron-donating group such as hydroxy or ethoxy at C-7 of the chromone.[10a,b] Our efforts in this area have focused on the 2-morpholinyl derivative **1**, which was identified as having inhibitory activity against ADP-induced platelet aggregation after being isolated as a byproduct of the reaction between 3-bromochromone and morpholine.[9,11] A preliminary SAR study focusing on simple substitution of the aromatic portion of the chromone nucleus of **1** led to the 7-(phenylmethoxy)-8-methyl analog **2**, which was found to be 3-fold more potent than **1** with an IC_{50} *in vitro* of 46 μM.[9] Our efforts to improve upon the potency of this compound encompassed a strategy based on the modification of the C-7 ethereal substituent. The potential requirement of a methyl group at C-8 of the 2-aminochromone for antiplatelet activity was also evaluated. Herein, we report on the results of this study which has led to the identification of a series of 7-(cyclic aminoethyloxy)-8-methyl-2-morpholinylchromones as potent inhibitors of ADP-induced platelet aggregation. Moreover, several of these derivatives (**34**, **37**, and **39**) have been evaluated in a canine model of platelet dependent thrombus formation[12] and have shown significant efficacy.



Chemistry

Modification of the phenylmethoxyl substituent of **2** required an efficient preparation of phenol **7** (Scheme I). This was accomplished utilizing a novel synthesis of 2-aminochromones via the condensation of BF_2 complexes of 2′-hydroxyacetophenones with phosgeniminium salts.[13] Acetylation of **3** followed by treatment with BF_3·OEt_2 afforded the BF_2 complex **4** in 76% overall yield. Reaction of **4** with 4-(dichloromethylene)morpholinium chloride (**5**) (65 °C, 24 h) produced **6**. Liberation of the BF_2 complex (H_2O, CH_3CN) promoted cyclization to afford chromone **7** upon basic hydrolysis of the acetate protecting group (67% from **4**). The compounds **9** in Table I were prepared according to two paths. In those cases where the required alkyl halide was readily available,[14] alkylation of **7** was performed with either K_2CO_3 (60 °C to reflux, CH_3CN) or NaH (DMF, 60 °C) as the base. In some instances, **7** was alkylated under phase-transfer conditions with ethylene dibromide to produce bromide **8** which was reacted with a variety of secondary amines to produce additional examples of **9**.

The preparation of compounds lacking a methyl at C-8 of the chromone were prepared from 2′,4′-dihyroxyacetophenone using identical chemistry (Table II). In addition, several compounds were synthesized to examine the effects of introducing a methyl group to the C-3 position of the chromone. Application of the phosgeniminium salt chemistry to the use of 2′-hydroxypropiophenones allowed for the conversion of **10** to chromone phenol **12** in 40% yield (Scheme II). Alkylation of **12** as for **7** produced the compounds **13** (Table II).

An examination of the effects of modification of the C-8 methyl substituent was undertaken for one of the more

† Medicinal Chemistry Research.
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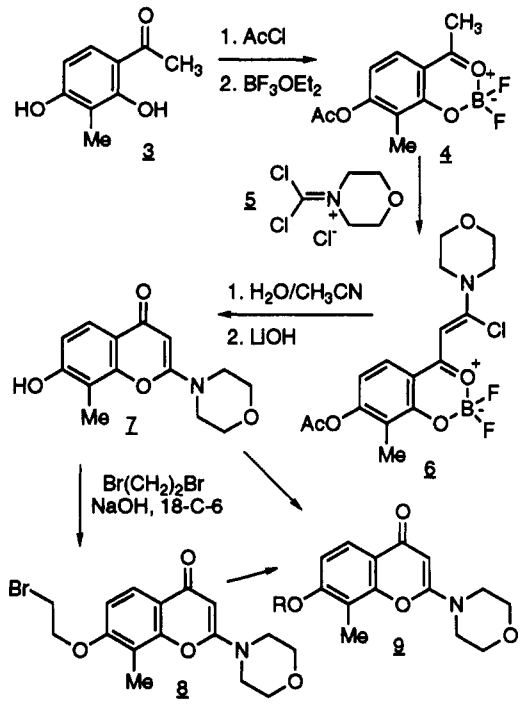
Scheme I

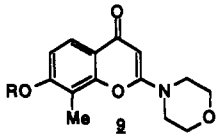


potent derivatives, **39** (Scheme III). Acetylation and BF_2 complex formation of **14a**[15], followed by condensation with iminium salt **5** afforded the 8-iodochromone **15a**. Palladium(II)-catalyzed coupling[16] of **15a** with either tetraethyl- or tetravinyltin followed by basic hydrolysis of the acetate protecting group produced the required phenols **16** (Y = ethyl, vinyl). An analogous iminium salt reaction with the BF_2 complex derived from **14b**[17] gave the 8-allylchromone **15b** which upon hydrogenation afforded the 8-propyl derivative **15c**. Acetate removal from **15b** and **15c** gave phenols **16** (Y = allyl, propyl). Alkylation of **16** with ethylene dibromide followed by treatment with 4-methylpiperazine gave the desired compounds **17** (Table III).

Results and Discussion

The 2-aminochromones prepared accordingly were tested for their ability to inhibit ADP-induced human platelet aggregation (Tables I–III). The initial modifications to the C-7 phenylmethoxy group of **2** were designed to examine the use of alternate aryl substituents (Table I). Interestingly, although introduction of a 1-naphthylmethoxy group produced a marked improvement in activity for **22**, such was not the case for the corresponding regioisomer **23**. We were especially intrigued by the increase in antiplatelet activity that was produced by introducing a nitrogen atom (in the form of a pyridine in **24** and **25**) to the phenylmethoxy group of **2**. This observation led to a strategy to explore a series of compounds in which a heteroatom (N, O, S) was positioned two carbons removed from the oxygen atom at C-7. The utilization of a methyl ester (**26**), methyl ketone (**28**), or methyl ether (**31**) at this position resulted in relatively potent inhibitors (IC_{50}'s 7–12 μM); however, the corre-

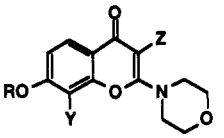
Table I. Structures, Formulas and Inhibitory Activity against ADP-Induced Human Platelet Aggregation of 2-Morpholinylchromones



compd	R	mp (°C)	formula	analyses	IC_{50} (μM)[d]
2	CH_2Ph	181.5–182.5	$C_{21}H_{21}NO_4$	C, H, N	40 ± 24
18	CH_3	224.5–225.5	$C_{15}H_{17}NO_4$	C, H, N	41 ± 15
19	CH_2(4-OMe)phenyl	171–172	$C_{22}H_{23}NO_5$	C, H, N	47 ± 10
20	CH_2(2-OMe)phenyl	202–203	$C_{22}H_{23}NO_5$	C;[a] H, N	44 ± 13
21	$CH_2CH{=}CH_2$	191–192	$C_{17}H_{19}NO_4$	C, H, N	58 ± 15
22	CH_2(1-naphthyl)	205.5–207	$C_{25}H_{23}NO_4$	C, H, N	13 ± 6
23	CH_2(2-naphthyl)	158.5–159.5	$C_{25}H_{23}NO_4$	C, H, N	65 ● 14
24	CH_2(2-pyridyl)	174–175.5	$C_{20}H_{20}N_2O_4$	C, H, N	19 ± 5
25	CH_2(3-pyridyl)	182.5–184	$C_{20}H_{20}N_2O_4$	C, H, N	4 ± 2
26	CH_2CO_2Me	181–182	$C_{17}H_{19}NO_6$	C, H, N	9 ± 3
27	CH_2COPh	226.5–227.5	$C_{22}H_{21}NO_5$	C, H, N	43 ● 17
28	CH_2COMe	206.5	$C_{17}H_{19}NO_5$	C, H, N	12 ± 4
29	$(CH_2)_2NEt_2$	162–162.5	$C_{20}H_{28}N_2O_4$	C, H, N	2.6 ± 0.4
30	$(CH_2)_2NEtPh$	146–147	$C_{24}H_{28}N_2O_4$	C, H, N	43 ● 8
31	$(CH_2)_2OMe$	172–173	$C_{17}H_{21}NO_5$	C, H, N	7 ± 2
32	$(CH_2)_2SMe$	182.5–184	$C_{17}H_{21}NSO_4$	C, H, N, S	14 ● 5
33	$(CH_2)_2NEt((CH_2)_2OH)$	144–145	$C_{20}H_{28}N_3O_5$	C, H, N	14 ± 5
34	$(CH_2)_2$(1-piperidinyl)	154–156	$C_{21}H_{28}N_2O_4$	C, H, N	5 ± 2
35	$(CH_2)_2$(1-pyrrolidinyl)	136–138	$C_{20}H_{26}N_2O_4$	C, H, N	4 ± 2
36	$(CH_2)_2$(4-morpholinyl)	170.5–172.5	$C_{20}H_{26}N_2O_5$	C, H, N	4 ± 1.6
37	$(CH_2)_2$(4-thiomorpholinyl)	207.5	$C_{20}H_{26}N_2SO_4$	C, H, N	4.3 ± 1.9
38	$(CH_2)_2$(1-homopiperidinyl)	153–154	$C_{22}H_{30}N_2O_4$	C, H;[b] N	3 ± 1.3
39	$(CH_2)_2$(4-Me-1-piperazinyl)	159–159.5	$C_{21}H_{29}N_3O_4$	C, H, N	0.85 ± 0.3
40	$(CH_2)_2$(1-piperazinyl)	112–114	$C_{20}H_{27}N_3O_4$	H; C, N[c]	4 ● 0.33
41	$(CH_2)_2$(4-CH_2Ph-1-piperazinyl)	138–139	$C_{27}H_{33}N_3O_4$	C, H, N	11 ● 3.5
42	$(CH_2)_2$(4-$(CH_2)_2$OH-1-piperazinyl)	192.5–193.5	$C_{22}H_{31}N_3O_5$	C, H, N	12 ± 8.6
43	$(CH_2)_2$(4-Ph-1-piperazinyl)	242.5–243.5	$C_{26}H_{31}N_3O_4$	C, H, N	>75
44	CH_2(1-cyclohexyl-1*H*-tetrazol-5-yl)	218–220	$C_{22}H_{27}N_5O_4$	C, H, N	12 ± 5
45	CH_2(1-t-butyl-1*H*-tetrazol-5-yl)	261–263	$C_{20}H_{25}N_5O_4$	C, H, N	2 ● 0.5
46	CH_2(1-methyl-1*H*-tetrazol-5-yl)	230–232	$C_{21}H_{19}N_5O_4$	C, H, N	2.8 ± 1.9
47	CH_2(1-phenyl-1*H*-tetrazol-5-yl)	238–241	$C_{22}H_{21}N_5O_4$	C, H, N	8 ± 5

[a] C: calcd, 69.28; found, 68.54. [b] C: calcd, 68.37; found, 67.74; H: calcd, 7.82; found, 7.37. [c] C: calcd, 64.32; found, 62.52; N: calcd, 11.25; found, 10.68. [d] All values are mean ● SD (n = 3).

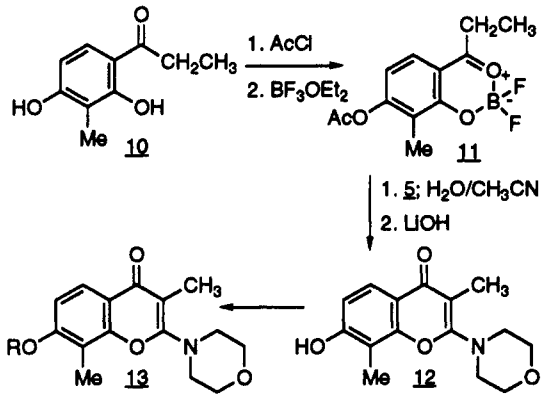
Table II. Structures, Formulas and Inhibitory Activity against ADP-Induced Platelet Aggregation of 2-Morpholinylchromones



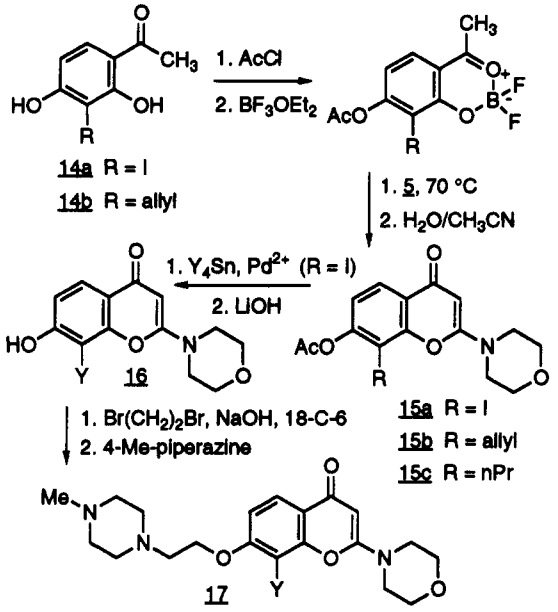
compd	R	Y	Z	mp (°C)	formula	analyses	IC_{50} (μM)[a]
48	CH_2Ph	Me	Me	136–137.5	$C_{22}H_{23}NO_4$	C, H, N	>75
49	CH_2(1-naphthyl)	Me	Me	204–206	$C_{26}H_{25}NO_4$	C, H, N	>75
50	CH_2CO_2Me	Me	Me	174–175	$C_{18}H_{21}NO_6$	C, H, N	59 ± 16
51	CH_2(2-pyridyl)	H	H	274–276	$C_{19}H_{18}N_2O_4$	C, H, N	53 ± 10
52	CH_2(1-naphthyl)	H	H	195–195.5	$C_{24}H_{21}NO_4$	C, H, N	41 ± 7

[a] All values are mean ± SD (n = 3).

Scheme II



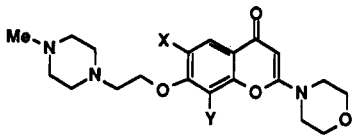
Scheme III



sponding phenyl ketone (**27**) was only modestly effective. The 5-tetrazole (**44–47**) and methyl sulfide (**32**) groups proved to be effective bioisosteres for the carboxylate and ether substituents, respectively.

The most potent antiplatelet agents in this series were those incorporating an aminoethyloxyl substituent in the C-7 position of the 2-aminochromone. With the exception of *N*-ethylaniline (**30**), the use of acyclic and cyclic secondary amines produced equally potent derivatives. Ring size for the cyclic amines (**34–40**) was not a significant factor. However, the piperazine group was particularly effective in this regard with **39** and **40** affording IC_{50}'s against ADP-induced platelet aggregation of 0.85 and 4 μM, respectively. Interestingly, the antiplatelet activity

Table III. Structures, Formulas, and Inhibitory Activity against ADP-Induced Human Platelet Aggregation of 2-Morpholinylchromones



compd	Y	X	mp (°C)	formula	analyses	IC_{50} (μM)[c]
53	H	H	148–149	$C_{20}H_{27}N_3O_4$	C, H, N	35 ± 13
54	Et	H	124–124.5	$C_{22}H_{31}N_3O_4$	C, H, N	4 ± 3
55	vinyl	H	151–152	$C_{22}H_{29}N_3O_4$	C, H, N	3 ± 2.1
56	allyl	H	165–165.5	$C_{23}H_{31}N_3O_4$	C, H, N	8.9 ± 6.2
57	*n*-propyl	H	158–159	$C_{23}H_{33}N_3O_4$	C;[a] H, N	69 ± 11
58[b]	Me	Me	135–136.5	$C_{22}H_{31}N_3O_4$	C, H, N	1.4 ± 1

[a] C: calcd, 66.48; found, 65.96. [b] Reference 18. [c] All values are mean ± SD (n = 3).

was reduced (**41, 42**) or essentially lost (**43**) for compounds with bulkier groups at the 4-position of the piperazine ring.

The placement of a methyl group at C-3 of the 2-aminochromone was examined as a potential means of improving the potency of these agents. The three compounds prepared in this regard (**48–50**, Table II) showed a significant reduction in activity relative to their desmethyl counterparts. The replacement of the methyl group at C-8 with a hydrogen in a relatively potent antiplatelet compound also led to a large reduction in potency (**51–53**). The effect of the C-8 methyl group on antiplatelet activity was further examined by systematically increasing the size of this substituent using the potent derivative **39** as a template (Table III). The C-8 position of **39** readily tolerated an ethyl or vinyl group, but a significant decrease or loss of activity resulted with the substitution of an allyl or propyl group, respectively. Finally, introduction of a methyl group to the C-6 position of **39** afforded no loss in inhibitory activity (**58**).[18]

In order to assess the *in vivo* potency and pharmacology of this series of 2-aminochromones, **34**, **37**, and **39** were selected for study in a canine model of coronary, platelet-dependent thrombus formation.[12] In this model, cyclical declines in blood flow (CFRs) occur spontaneously and periodically after placement of an obstructive cylinder on the coronary artery. Consistent interruption of platelet thrombus formation occurs only with platelet-specific inhibitory drugs such as prostacyclin,[8] thromboxane synthesis inhibitors,[19] and fibrinogen receptor antagonists.[20,21] Heparin and vasodilatory agents such as sodium nitroprusside are ineffective or inconsistent in this model. Aspirin[19] and thromboxane receptor antagonists[22] are only effective in about 50% of animals tested. In addition to coronary blood flow, the effects of these agents on blood pressure, heart rate, and bleeding times were also exam-

Table IV. *In Vivo* Inhibitory Effects of Compounds **34**, **37**, and **39** on Cyclical Flow Reductions Induced by Intracoronary Platelet Aggregation in Stenosed Canine Coronary Arteries[a]

	in vivo antiaggregatory parameters		
intravenous dose (μg/kg + μg/kg/min)	CFR rating (0–3)[b]	time to onset (min)[c]	time to offset (min)[d]
	Compound **34**		
300 + 30 (n = 2–4)	1.3 ± 0.8	2	67
1000 + 100 (n = 4)	2.5 ± 0.3	7 ± 5	23 ± 12
	Compound **37**		
100 + 10 (n = 3)	2.0 ± 0	17.0 ± 1.6	5.3 ± 1.0
300 + 30 (n = 3)	2.3 ± 0.3	9.0 ± 4.6	12.0 ± 1.2
	Compound **39**		
30 + 3 (n = 4)	0 ± 0	ND	ND
100 + 10 (n = 10)	1.9 ± 0.3	5 ± 2	25 ± 6
300 + 30 (n = 4)	3.0 ± 0	1 ± 0	60 ± 13
1000 + 100 (n = 4)	3.0 ± 0	1 ± 0	73 ± 21

[a] All values are mean ± SEM. [b] See experimental section for a description of the CFR (cyclic flow reduction) rating system. [c] Time interval between the start of drug treatment and the first change in the CFR pattern of blood flow in the stenosed coronary artery. [d] Time interval between the end of drug treatment and the restoration of the CFR pattern to control levels.

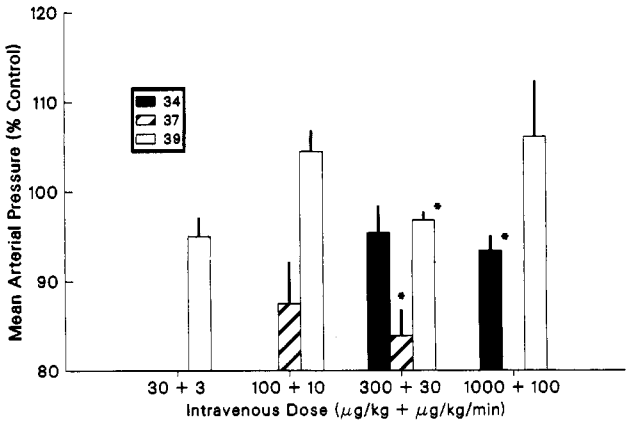


Figure 1. Effects of the 2-aminochromones **34**, **37**, and **39** on blood pressure in the open-chest, anesthetized dog. * $p < 0.05$ vs control values via a paired T-test.

ined. In all cases, the agents were administered iv in saline solution as their water-soluble mesylate or bismesylate salts.

Platelet thrombus formation was interrupted when the 7-(piperidinylethyl)oxy derivative, **34** was given as an initial bolus of 1 mg/kg followed by a constant infusion of 100 μg/kg/min (Table IV). A lower dose (300 μg/kg plus 30 μg/kg/min) was relatively ineffective. At the higher dose of 1 mg/kg plus 100 μg/kg/min, **34** was associated with a transient decrease in blood pressure and severe tachycardia (Figures 1 and 2). *Ex vivo* platelet function was studied concomitant to inhibition of CFRs and was suppressed 25 min into the infusion with recovery occurring at 1 h posttermination of the infusion. Bleeding times and platelet count were relatively unaffected by **34**.

Evaluation of the corresponding thiomorpholinyl derivative **37** in this model found the 300 μg/kg plus 30 μg/kg/min dose as well as a 100 μg/kg plus 10μg/kg/min dose to be modestly effective in eliminating the platelet-dependant CFR's. However, this agent resulted in a significant lowering of blood pressure and increase in heart rate at the effective antithrombotic dose (Figures 1 and 2). In addition, the functional half-life of **37** was reduced relative to the other compounds tested in this model as

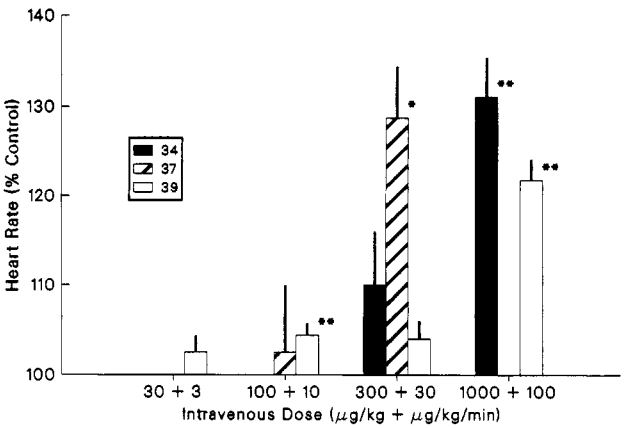


Figure 2. Effects of the 2-aminochromones **34**, **37**, and **39** on heart rate in the open-chest, anesthetized dog. * $p < 0.05$, ** $p < 0.01$ vs control values via a paired T-test.

determined by the time for reestablishment of CFR's following termination of the infusion (Table IV).

The 4-methylpiperazinyl derivative **39** was evaluated over a wide dose range in the dog. Bolus administration of **39** at 1 mg/kg followed by 100 μg/kg/min was highly effective, with inhibition of CFRs occurring in all animals tested. This dose was associated with a slight and transient hypotension and tachycardia which appeared to be only related to the initial bolus dose. *Ex vivo* platelet function at this dose was highly attenuated with inhibition lasting greater than 3 h following termination of the infusion. A lower dose of **39** (300 μg/kg plus 30 μg/kg/min) was also determined to be effective in all animals (Table IV). This lower dose was not associated with any hemodynamic changes, and *ex vivo* platelet function was inhibited initially by approximately 60%, returning toward control at 1 h. Lower doses of **39** were found to be partially effective or not effective at all. Bleeding times were elevated slightly by **39** at the effective antithrombotic doses, and platelet counts were unaffected. Additional experiments were conducted in separate open chest anesthetized dogs to evaluate hemodynamic effects of **39** at doses significantly higher than its minimum effective dose (300 μg/kg plus 30 μg/kg/min). At a 10-fold multiple higher dose (3 mg/kg followed by 300 μg/kg/min), **39** significantly decreased blood pressure and produced a large reflex increase in heart rate.

The hemodynamic side effects of these antiplatelet 2-aminochromones appear to be a direct result of their mechanism of action. Studies with this class of compounds have shown them to inhibit platelet cAMP-dependent phosphodiesterase leading to elevated levels of cAMP.[10cd,23] Specifically, **22** was found to be a potent inhibitor of the low K_m cAMP-dependent phosphodiesterase with an IC_{50} of 400 nM in platelet cytosol.[23] This platelet enzyme is similar to that found in vascular smooth muscle.[24] Although **39** elicited a 10-fold separation between its antiplatelet activity and hypotensive and tachycardiac effects *in vivo*, the hemodynamic effects associated with this class of compounds remains the major limitation to their development as potential antithrombotics.

Conclusion

The synthesis and biological evaluation of a series of antiplatelet 2-morpholinylchromones has been described. Modification of the C-7 phenylmethoxy group of **2** has led to the discovery of a series of 7-[(aminoethyl)oxy]-8-methyl

derivatives which are potent inhibitors of ADP-induced platelet aggregation. Several members of this class proved active in preventing platelet-dependent thrombus formation in the dog, including **39** which was devoid of hemodynamic effects at the effective antithrombotic dose. The search for 2-aminochromones with greater selectivity for the platelet vs the vasculature has become the challenge for future work in this area.

Experimental Section

IR spectra were taken as a Nujol mull (unless otherwise indicated). ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise indicated) at 300 MHz. Melting points are corrected. Thin-layer chromatography was performed on Merck precoated glass TLC plates with silica gel 60-F254 and stained with a solution of 75 g of ammonium molybdate, 2.5 g of cerric sulfate, and 500 mL of 10% H_2SO_4 (v/v). Column chromatography was performed with Merck silica gel 60 (230–400 mesh).

4'-(Acetyloxy)-2'-hydroxy-3'-methylacetophenone. A suspension of 2',4'-dihydroxy-3'-methylacetophenone (**3**, 97.8 g, 0.588 mol, 90%) in 1 L of CH_2Cl_2 was treated with 82 mL (0.588 mol) of Et_3N and cooled to 0 °C. Acetyl chloride (41.8 mL, 0.588 mol) was added dropwise over a 30-min period, and the reaction mixture was stirred at 0 °C for 2 h and at room temperature overnight. The mixture was filtered, and the organics were washed once with saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated. Recrystallization from absolute EtOH afforded 89.9 g (82%) of the acetate: mp 71–73 °C; ^1H NMR δ 2.08 (s, 3), 2.34 (s, 3), 2.60 (s, 3), 6.62 (d, 1), 7.61 (d, 1), 12.81 (s, 1); ^{13}C NMR δ 8.5, 20.7, 26.5, 112.8, 117.0, 119.6, 128.5, 154.6, 162.3, 168.3, 203.8; IR 2925, 1748, 1633, 1456, 1369, 1329, 1228, 1088, 771 cm^{-1}. Anal. ($C_{11}H_{12}O_4$) C, H.

7-Hydroxy-8-methyl-2-morpholinyl-4*H*-1-benzopyran-4-one (7). A suspension of 4'-(acetyloxy)-2'-hydroxy-3'-methylacetophenone (199.6 g, 0.96 mol) in 1.8 L of Et_2O was treated with BF_3-OEt_2 (176.5 mL, 1.43 mol) and stirred overnight at room temperature. The solid was filtered and washed well with Et_2O to afford 229.1 g (93%) of the BF_2 complex **4**. The BF_2 complex **4** was combined with 4-(dichloromethylene)morpholinium chloride (**5**, 200 g, 0.98 mol) in 2.4 L of dichloroethane and heated at 65 °C overnight. The precipitate was filtered and washed with Et_2O (175 g). The filtrate afforded an additional 47 g of solid upon chilling at −33 °C overnight. A suspension of each lot in CH_3CN (12 mL/g) was treated with H_2O (1.2 mL/g) and stirred overnight at room temperature. After the larger lot was chilled at −33 °C (48 h), the precipitated solid was collected and the filtrate was combined with the smaller lot and evaporated. A suspension of the solid in 2 L of 1:1 MeOH/H_2O was treated with 55 g (1.31 mol) of LiOH–H_2O and stirred 30 min at room temperature. The pH of the reaction mixture was adjusted to 5.9 with 10% HCl, and the precipitated solid was washed successively with MeOH and Et_2O to afford 96 g (45%) of the phenol **7**. The smaller lot and filtrate was similarly hydrolyzed with LiOH to provide 37 g (17%) of **7**: mp >300 °C; ^1H NMR (DMSO-d_6) δ 7.60 (d, J = 8.5 Hz, 1), 6.85 (d, J = 8.5 Hz, 1), 5.36 (s, 1), 3.72 (m, 4), 3.46 (m, 4), 2.19 (s, 3); ^{13}C NMR (DMSO-d_6) δ 177.5, 164.1, 160.8, 154.8, 124.4, 116.7, 114.2, 112.3, 87.2, 67.1, 46.2, 10.0; IR 3482, 1624, 1573, 1464, 1327, 1256 cm^{-1}; MS calcd for $C_{14}H_{15}NO_4$ 261.1001, found 261.1099.

8-Methyl-2-(4-morpholinyl)-7-(naphthyl-1-methyloxy)-4*H*-1-benzopyran-4-one (22). A suspension of **7** (261 mg, 1.0 mmol) in 5 mL of CH_3CN was treated successively with K_2CO_3 (829 mg, 6.0 mmol) and 1-(bromomethyl)naphthalene (300 mg, 1.36 mmol), and the mixture was heated at 75 °C for 2.5 h. The cooled reaction mixture was evaporated, and solid residue was washed with 25 mL of CH_2Cl_2 and filtered. The filtrate was concentrated in vacuo and washed with Et_2O. The crude material was twice recrystallized from EtOAc to afford 200 mg (50%) of **22**: mp 205.5–207 °C; ^1H NMR δ 2.25 (s, 3), 3.49 (m, 4), 3.84 (m, 4), 5.45 (s, 1), 5.60 (s, 2), 7.13 (d, 1), 7.46–7.62 (m, 4), 7.87–8.05 (m, 4); ^{13}C NMR δ 8.5, 44.6, 65.8, 69.2, 86.5, 109.0, 113.4, 116.9, 123.4, 123.7, 125.2, 125.9, 126.4, 128.7, 129.1, 131.3, 131.7, 133.6, 152.8, 159.6, 162.7, 177.5; IR 1620, 1571, 1420, 1250 cm^{-1}; Anal. ($C_{25}H_{23}NO_4$) C, H, N.

8-Methyl-2-(4-morpholinyl)-7-(2-pyridinylmethoxy)-4*H*-1-benzopyran-4-one (24). A suspension of **7** (20 g, 76.5 mmol) in 200 mL of DMF was treated with NaH (11.0 g, 230 mmol, 50% in oil) and heated to 60 °C for 1 h. The mixture was treated portionwise with 2-picolyl chloride hydrochloride (25.1 g, 153.1 mmol) and stirred at 60 °C for 1 h. The mixture was poured into 2 L of 1 N NaOH/ice, and the precipitated solid was filtered and washed with H_2O, MeOH, and Et_2O. The dried material was recrystallized from EtOAc to afford 16 g (62%) of **24**: mp 174–175 °C; ^1H NMR (DMSO-d_6) δ 8.44 (m, 1), 7.71 (m, 1), 7.68 (m, 1), 7.39 (m, 1), 7.20 (m, 1), 6.97 (m, 1), 5.26 (s, 1), 5.16 (s, 2), 3.57 (m, 4), 3.33 (m, 4), 2.15 (s, 3); ^{13}C NMR (DMSO-d_6) δ 177.1, 164.2, 160.6, 157.9, 153.7, 150.9, 138.9, 124.8, 124.7, 123.2, 118.1, 115.0, 111.1, 87.2, 72.7, 67.1, 46.1, 10.1; IR 1651, 1579, 1408, 1296 cm^{-1}. Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

7-[(2-Bromoethyl)oxy]-8-methyl-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (8). A suspension of **7** (6.55 g, 25 mmol) in 60 mL of 50% NaOH was treated successively with n-Bu_4NHSO_4 (1.4 g, 4.1 mmol) and 1,2-dibromoethane (25 mL, 290 mmol), and the reaction mixture was warmed to 65 °C for 1.5 h (mechanical stirrer). The solid was filtered and washed thoroughly with 2 N NaOH, H_2O, and Et_2O. The material was recrystallized from MeOH and chromatographed over 250 g of silica gel (4% MeOH/CH_2Cl_2) to afford 5.5 g (60%) of **8**: mp 211–211.5 °C; ^1H NMR δ 2.30 (s, 3), 3.50 (m, 4), 3.70 (t, J = 6 Hz, 2), 3.85 (m, 4), 4.40 (t, J = 6 Hz, 4), 5.42 (s, 1), 6.85 (d, 1), 7.97 (d, 1); ^{13}C NMR δ 8.5, 24.3, 29.2, 44.7, 66.0, 68.4, 86.7, 108.7, 113.7, 117.1, 123.8, 152.9, 158.9, 162.9, 177.4; IR 1638, 1594, 1414, 1282, 1242 cm^{-1}. Anal. ($C_{16}H_{18}BrNO_4$) C, H, N.

8-Methyl-2-(4-morpholinyl)-7-[2-(1-piperidinyl)ethoxy]-4*H*-1-benzopyran-4-one (34). A suspension of **7** (5.0 g, 19.1 mmol) in 6 mL of DMF was treated with NaH (192 mg, 60% in oil, 4.0 mmol) and stirred for 1 h at 50 °C. The mixture was treated portionwise with *N*-(chloroethyl)piperidine hydrochloride (552 mg, 3.0 mmol) and stirred for 1 h at 60 °C and poured into 75 mL of 1 N NaOH/ice. The precipitate was collected, washed with H_2O, dried, and recrystallized from EtOAc to afford 285 mg (77%) of **34**: mp 154.0–156.0 °C; ^1H NMR δ 1.42–1.65 (m, 6), 2.26 (s, 3), 2.53 (m, 4), 2.83 (t, J = 6.5 Hz, 2), 3.49 (m, 4), 3.85 (m, 4), 4.21 (t, J = 6.5 Hz, 2), 5.42 (s, 1), 6.90 (d, 1), 7.97 (d, 1); ^{13}C NMR δ 8.4, 24.0, 25.9, 44.6, 55.0, 57.7, 65.9, 67.0, 86.5, 100.9, 108.6, 112.9, 116.4, 123.6, 152.8, 159.7, 162.7, 177.5; IR 1627, 1613, 1571, 1419, 1251, 1122 cm^{-1}. Anal. ($C_{21}H_{28}N_2O_4$) C, H, N.

8-Methyl-7-[2-(4-methyl-1-piperazinyl)ethoxy]-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (39). A suspension of **7** (50.8 g, 0.19 mol) in 750 mL of DMF was treated with NaH (7.8 g, 60% in oil, 0.19 mol) and stirred for 30 min at 75 °C. The mixture was treated with 4-methyl-1-(2-chloroethyl)piperazine (94.8 g, 0.58 mol) in 150 mL of DMF, stirred at 70 °C for 1 h, and poured into 1.5 L of 2 N NaOH and 1.5 L of saturated NaCl. The mixture was extracted four times with 500 mL of CH_2Cl_2, and the combined organics were washed two times with 500 mL of half-saturated NaCl, dried (Mg_2SO_4), and evaporated. The slurry was diluted with Et_2O, and the solid was recrystallized from EtOAc to afford 46.2 g (62%) of **39**: mp 159.0–159.5 °C; ^1H NMR δ 2.26 (s, 3), 2.32 (s, 3), 2.52 (bs, 4), 2.68 (bs, 4), 2.88 (m, 2), 3.49 (m, 4), 3.84 (m, 4), 4.22 (m, 2), 5.42 (s, 1), 6.88 (d, 1), 7.96 (d, 1); ^{13}C NMR δ 8.5, 44.7, 45.9, 53.5, 55.1, 57.0, 66.0, 67.1, 86.6, 108.6, 113.1, 116.7, 123.8, 152.9, 159.8, 162.9, 177.6; IR 1629, 1571, 1450, 1276, 1252 cm^{-1}. Anal. ($C_{21}H_{29}N_3O_4$) C, H, N.

8-Methyl-2-(4-morpholinyl)-7-[2-(1-thiomorpholinyl)ethoxy]-4*H*-1-benzopyran-4-one (37). A mixture of **8** (4.0 g, 10.9 mmol) and thiomorpholine (4.5 mL, 43.6 mmol) in 25 mL of $CHCl_3$ was heated at 90 °C for 2 h as the $CHCl_3$ was boiled off. The cooled mixture was taken up in 50 mL of CH_2Cl_2 and washed with 100 mL of 1:1 saturated NaCl/2 N NaOH. The aqueous was back-extracted two times with 25 mL of CH_2Cl_2, and the combined organics were dried ($MgSO_4$) and concentrated. The solid was washed with Et_2O and recrystallized from CH_2Cl_2 and EtOAc to provide 3.75 g (88%) of **37**: mp 207.5 °C; ^1H NMR δ 2.26 (s, 3), 2.69 (m,4), 2.90 (m, 6), 3.50 (m, 4), 3.85 (m, 4), 4.18 (t, J = 6 Hz, 2), 5.42 (s, 1), 6.88 (d, 1), 7.97 (d, 1); ^{13}C NMR δ 8.6, 28.0, 44.7, 55.3, 57.9, 66.0, 66.8, 86.6, 108.6, 113.1, 116.7, 123.8, 152.9, 159.7, 162.9, 177.6; IR 1626, 1614, 1572, 1419, 1252, 1118 cm^{-1}. Anal. ($C_{20}H_{26}N_2O_4S$) C, H, N.

3,8-Dimethyl-7-hydroxy-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (12). A solution of 4'-acetoxy-2'-hydroxy-3'-methylpropiophenone (**10**, 6.2 g, 27.9 mmol) in 60 mL of Et_2O was treated with $BF_3{\cdot}OEt_2$ (6.0 mL, 48.8 mmol) and stirred overnight at room temperature. The precipitate was collected by filtration and was washed with 150 mL of Et_2O to afford 6.8 g (90%) of the BF_2 complex **11**: ^1H NMR δ 1.23 (t, J = 7 Hz, 3), 2.13 (s, 3), 2.37 (s, 3), 3.10 (q, J = 7, 14 Hz, 2), 6.79 (d, 1), 7.70 (d, 1); ^{13}C NMR δ 9.3, 10.2, 20.8, 29.5, 113.4, 116.3, 122.5, 128.4, 160.4, 164.3, 167.7, 205.6. A suspension of the BF_2 complex **11** (3.0 g, 11.1 mmol) was combined with **5** (2.5 g, 12.2 mmol) in 29 mL of $Cl(CH_2)_2Cl$ and heated to 60 °C for 3.5 h. The cooled mixture was evaporated and dissolved in 30 mL of CH_3CN. The solution was warmed to 60 °C, diluted with 25 mL of H_2O, and stirred for 5 min. The mixture was immediately quenched with 30 mL of saturated $NaHCO_3$ and concentrated *in vacuo*. The residue was extracted with 4 × 25 mL of CH_2Cl_2, and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The crude chromone acetate (2.82 g) was dissolved in 30 mL of MeOH and 15 mL of H_2O and treated with LiOH–H_2O (800 mg, 19.1 mmol). The mixture was stirred for 1 h at room temperature, concentrated in vacuo, and treated with 5% HCl to pH 5. The precipitated phenol was collected by filtration and dried to afford 1.2 g (40%) of **12**: mp >300 °C; ^1H NMR (DMSO-d_6) δ 1.79 (s, 3), 2.11 (s, 3), 3.27 (m, 4), 3.65 (m, 4), 6.81 (d, 1), 7.55 (d, 1), 10.31 (bs, 1); ^{13}C NMR (DMSO-d_6) δ 9.8, 12.3, 49.9, 67.9, 101.8, 112.3, 114.7, 116.4, 124.7, 154.8, 160.8, 163.3, 179.0; IR 1627, 1554, 1426, 1286 cm^{-1}; MS calcd for $C_{15}H_{17}NO_4$ 275.1157, found 275.1154.

4'-(Acetyloxy)-2'-hydroxy-3'-iodoacetophenone. A solution of 2',4'-dihydroxy-3'-iodoacetophenone (**14a**, 15.0 g, 53.9 mmol) and Et_3N (7.5 mL, 53.9 mmol) in 90 mL of CH_2Cl_2 at 0 °C was treated dropwise with AcCl (4.4 mL, 62.0 mmol). The reaction was stirred for 1 h at 0 °C and for 2.5 h at room temperature. The mixture was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated to give 17.58 g. Recrystallization from EtOH afforded 13.31 g (77%) of the acetate: mp 101–102 °C; ^1H NMR δ 2.40 (s, 3), 2.66 (s, 3), 6,74 (d, J = 8.5 Hz, 1), 7.78 (d, J = 8.5 Hz, 1), 13.48 (s, 1); IR 1770, 1762, 1635, 1369, 1249 cm^{-1}; MS calcd for $C_{10}H_9O_4I$ 319.9547, found 319.9561.

7-(Acetyloxy)-8-iodo-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (15a). A suspension of 4'-(acetyloxy)-2'-hydroxy-3'-iodoacetophenone (13.0 g, 40.6 mmol) in 225 mL of Et_2O was treated with $BF_3{\cdot}OEt_2$ (7.49 mL, 60.9 mmol) and stirred for 16 h at room temperature. The solid was filtered and washed well with Et_2O to afford 11.95 g (80%) of the BF_2 complex (86% pure by ^1H NMR): ^1H NMR δ 2.43 (s, 3), 2.91 (s, 3), 6.90 (d, J = 8.8 Hz, 1), 7.82 (d, J = 8.8 Hz, 1). A suspension of the BF_2 complex (11.95 g, 32.5 mmol) and **5** (7.64 g, 37.3 mmol) in 100 mL of $Cl(CH_2)_2Cl$ was heated at 70 °C for 5 h. The cooled mixture (0 °C) was filtered, and the solid (13.46 g) was washed well with Et_2O and suspended in 100 mL of CH_3CN and 10 mL of H_2O. The mixture was stirred at room temperature overnight, at 40 °C for 30 min, at 45 °C for 30 min, and at 50 °C for 1.5 h. The mixture was evaporated, taken up in saturated $NaHCO_3$, and extracted two times with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and evaporated to give 8.93 g of material. Recrystallization from MeOH afforded 6.37 g (47%) of **15a**: mp 201.5–202.5 °C; ^1H NMR δ 2.42 (s, 3), 3.61 (m, 4), 3.86 (m, 4), 5.49 (s, 1), 7.12 (d, J = 8.5 Hz, 1), 8.16 (d, J = 8.5 Hz, 1); ^{13}C NMR δ 21.1, 45.0, 65.8, 81.3, 86.5, 119.7, 121.5, 126.8, 153.8, 154.7, 162.7, 167.9, 175.8; IR 1764, 1650, 1614, 1594, 1407, 1203 cm^{-1}. Anal. ($C_{15}H_{14}O_5NI$) C, H, N.

7-Hydroxy-8-vinyl-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (16, Y = Vinyl). A mixture of **15a** (415 mg, 1.0 mmol), LiCl (127 mg, 3.0 mmol), tetravinyltin (191 μL, 1.05 mmol), and $(Ph_3P)_2PdCl_2$ (14 mg, 0.02 mmol) in 4 mL of DMF was heated at 100 °C for 15 min. The cooled mixture was treated with 5 mL of 2 N NaOH for 30 min, poured into H_2O, and extracted three times with EtOAc. The aqueous layer was treated with carbon black, filtered through Celite, and acidified to pH 5.8 with 10% HCl. The solid was filtered, washed with H_2O and Et_2O, and dried to afford 0.24 g (89%) of **16** (Y = vinyl): ^1H NMR (DMSO-d_6) δ 3.59 (t, 4), 3.86 (t, 4), 5.54 (s, 1), 5.71 (m, 1), 6.26 (m, 1), 7.06 (m, 2), 7.82 (d, 1); ^{13}C NMR (DMSO-d_6) δ 44.74, 65.51, 85.81, 111.59, 113.52, 115.27, 120.46, 124.65, 126.34, 152.20, 159.71, 162.59, 175.51; MS calcd for $C_{15}H_{15}NO_4$ 272.1001, found 273.0995.

2'-Hydroxy-3'-allyl-4'-(acetyloxy)acetophenone. A suspension of 3'-allyl-2',4'-dihydroxyacetophenone (**14b**, 139.4 g, 0.72 mol) in 2.2 L of CH_2Cl_2 was treated with Et_3N (100.8 mL, 0.72 mol) and cooled to 0 °C. Acetyl chloride (59.5 mL, 0.837 mol) was added dropwise, and the mixture was stirred for 1 h at 0 °C and at 10 °C for 30 min. The reaction was quenched with 690 mL of 5% HCl, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The oil was crystallized from absolute EtOH to afford 105.8 g (62%) of the acetate: mp 56–57 °C; ^1H NMR δ 2.32 (s, 3), 2.61 (s, 3), 3.37 (m, 2), 5.01 (m, 2), 5.87 (m, 1), 6.66 (d, 1), 7.66 (d, 1), 12.84 (s, 1); ^{13}C NMR δ 21.0, 26.7, 27.6, 113.4, 115.4, 117.4, 121.2, 129.4, 134.8, 154.8, 162.2, 168.6, 203.9; IR 1760, 1639, 1417, 1369, 1249 cm^{-1}. Anal. ($C_{13}H_{14}O_4$) C, H.

7-(Acetyloxy)-8-allyl-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (15b). A solution of 3'-allyl-4'-(acetyloxy)-2'-hydroxyacetophenone (111.9 g, 0.48 mol) in 2.4 L of Et_2O was treated with $BF_3{\cdot}OEt_2$ (89.5 mL, 0.73 mol) and stirred overnight at room temperature. The solid was filtered and washed with Et_2O to afford 101.7 g (76%) of the BF_2 complex: ^1H NMR δ 2.35 (s, 3), 2.85 (s, 3), 3.42 (m, 2), 5.02 (m, 2), 5.83 (m, 1), 6.84 (d, 1), 7.72 (d, 1). A suspension of the BF_2 complex (1.37 g, 4.85 mmol) and **5** (1.20 g, 5.87 mmol) in 15.2 mL of ethylene dichloride was heated at 65 °C overnight. The cooled mixture was filtered and washed with Et_2O. The solid was suspended in 16.4 mL of CH_3CN and 1.6 mL of H_2O and stirred at 50 °C for 90 min. The mixture was evaporated, taken up in CH_2Cl_2, and washed with saturated $NaHCO_3$ and brine. The aqueous layer was extracted with CH_2Cl_2, and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The solid was recrystallized from EtOAc to afford 0.59 g (37%) of **15b**: mp 183–184.5 °C; ^1H NMR δ 2.35 (s, 3), 3.51 (m, 6), 3.84 (m, 4), 5.03 (m, 2), 5.58 (s, 1), 5.87 (m, 1), 7.09 (d, 1), 8.08 (d, 1); ^{13}C NMR δ 20.9, 28.3, 44.8, 65.9, 87.2, 116.1, 119.5, 120.0, 121.0, 124.4, 134.1, 151.9, 152.5, 162.7, 168.8, 176.8; IR 1760, 1627, 1413, 1215 cm^{-1}. Anal. ($C_{18}H_{19}O_5N$) C, H, N.

7-(Acetyloxy)-8-propyl-2-(4-morpholinyl)-4*H*-1-benzopyran-4-one (15c). A solution of **15b** (5.0 g, 15.2 mmol) in 150 mL of 1:1 THF/EtOH containing 0.55 g of 10% Pd/C was shaken under 45 psi of H_2 for 1.3 h. The mixture was filtered through Celite and washed well with CH_2Cl_2. The filtrate was concentrated to afford 5.12 g (100%) of **15c**: mp 183.5–184.5 °C; ^1H NMR δ 0.96 (t, 3), 1.62 (m, 2), 2.37 (s, 3), 2.69 (t, 2), 3.49 (m, 4), 3.85 (m, 4), 5.48 (s, 1), 7.06 (d, 1), 8.03 (d, 1); ^{13}C NMR δ 14.2, 20.9, 22.4, 26.2, 44.7, 65.9, 87.2, 119.4, 120.9, 122.6, 123.8, 151.8, 152.6, 162.7, 169.0, 176.9; IR 1759, 1629, 1415, 1251 cm^{-1}. Anal. ($C_{18}H_{21}O_5N$) C, H, N.

Assessment of Platelet Aggregation *in vitro*. Venous blood from drug-free donors was drawn by venipuncture into 1/10 volume of 3.8% sodium citrate. Platelet-rich plasma (PRP) was prepared by centifuging the blood at 300*g* for 10 min at room temperature. Platelets were allowed to recover for 30 min before the initiation of the experiment. The test compounds were initially dissolved in DMSO at a concentration of 10 mg/mL. In a Payton dual-channel aggregometer, the test compound was added to 1 mL of PRP and warmed at 37 °C for 2 min under constant stirring. ADP (8 μM) was added to the warmed PRP, and aggregation was recorded. Control aggregation was performed with an equivalent amount of DMSO. The effect of a test compound on platelet aggregation was expressed as a percent of control aggregation. The concentration of a compound at which the aggregation was inhibited by 50% of the control was derived graphically (IC_{50}).

Platelet Aggregation in the Dog Coronary Artery. Adult mongrel dogs (10–15 kg) of either sex were anesthetized with sodium pentobarbital (30 mg/kg, iv). Respiration was maintained with a positive pressure pump (Harvard Apparatus) at a rate of 12 inflations/min with a tidal volume of 20 mL/kg (room air) for each inflation. Previous studies have shown that this respiratory rate maintains normal physiological pH and blood gas profile. The heart was exposed through a left thoracotomy at the fifth intercostal space and suspended in a pericardial cradle. The circumflex coronary artery was then dissected free from the surrounding myocardium for a distance of 20 mm, tying side branches when necessary. Blood flow in the circumflex coronary artery was measured by placing an electromagnetic flow probe (Carolina Medical Electronics) on the proximal portion of the vessel. A snare ligature was placed on the distal end of the exposed

artery to determine zero flow and to produce reactive hyperemic responses by occluding the vessel for 15 s. Phasic and mean aortic blood pressure were monitored via a catheter placed in the right femoral artery and attached to a pressure transducer (Gould-Statham P23P6). The right femoral vein and left cephalic vein were cannulated for administration of drugs or supplemental anesthetic, respectively. All parameters were recorded on a polygraph with curvilinear writing pens (Grass Model 7D). To monitor platelet aggregation in vivo, a technique which was originally described by Folts and colleagues[25] was utilized with some modifications.[8,19] The circumflex coronary artery was partially obstructed so that intravascular platelet aggregation could be monitored as a gradual reduction in blood flow as platelets occluded the narrowed lumen at the obstructed site. A plastic (Lexan) cylinder with a hole drilled lengthwise down the center (i.d. 1.0–1.5 mm) and a radial slit that opened the center hole to the lateral surface was placed around the artery to partially obstruct it so that the reactive hyperemic response was abolished. Abolition of the reactive hyperemic response occurs when the cross-sectional area of the vessel is reduced 90–95%. Under these conditions, any further reduction in lumen size at the site of the obstructive cylinder can be recorded as a reduction in blood flow. Thus, as blood platelets aggregate in the narrowed lumen, blood flow progresses to zero. These so called cylical declines in blood flow (CFRs) are amenable to drug intervention such that thrombus formation is interrupted and coronary blood flow is maintained. A somewhat subjective rating system has been devised for this model such that a zero rating indicates no effect of a given drug, 1 indicates a change in the slope of the declining blood flow curve such that it takes longer to achieve zero blood flow, 2 indicates spontaneous restoration of blood flow without the need for mechanical dislodgement, and 3 indicates cessation of coronary thrombus formation with complete maintenance of blood flow.

References

(1) Shebuski, R. J. Emerging Drug Discovery Targets in Thrombosis and Coagulation. *Annu. Rep. Med. Chem.* **1991**, *26*, 93–101.

(2) Stein, B.; Fuster, V.; Israel, D. H.; Cohen, M.; Badimon, L.; Badimon, J. J.; Cheseboro, J. H. Platelet Inhibitor Agents in Cardiovascular Disease: An Update. *J. Am. Coll. Cardiol.* **1989**, *14*, 813–836.

(3) Hamberg, J.; Svensson, J.; Samuelsson, B. Thromboxanes: A New Group of Biologically Active Compounds Derived from Prostaglandin Endoperoxides. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994–2998.

(4) Baumgartner, H. R.; Born, G. V. R. Effects of Hydroxytryptamine on Platelet Aggregation. *Nature* **1968**, *218*, 137–141.

(5) Chignard, M.; Le Couedic, J. P.; Tence, M.; Vargaftig, B. B.; Benveniste, J. The Role of Platelet-Activating Factor in Platelet Aggregation. *Nature* **1979**, *279*, 799–800.

(6) Gorman, R. R.; Bunting, S.; Miller, O. V. Modulation of Human Platelet Adenylate Cyclase by Prostacyclin (PGX). *Prostaglandins* **1977**, *13*, 377–388.

(7) Peerschke, E. I.; Zucker, M. B.; Grant, R. A.; Egan, J. J.; Johnson, M. M. Correlation Between Fibrinogen Binding to Human Platelets and Platelet Aggregability. *Blood* **1980**, *55*, 841–847.

(8) Aiken, J. W.; Gorman, R. R.; Shebuski, R. J. Prevention of Blockage of Partially Obstructed Coronary Arteries with Prostacyclin Correlates with Inhibition of Platelet Aggregation. *Prostaglandins* **1979**, *17*, 483–494.

(9) Gammill, R. B.; Judge, T. M.; Morris, J. Antiatherosclerotic and Antithrombotic 1-Benzopyran-4-ones and 2-Amino-1,3-benzoxazine-4-ones. WO 90/06921.

(10) (a) Mazzei, M.; Balbi, A.; Roma, G.; Di Braccio, M.; Leoncini, G.; Buzzi, E.; Maresca, M. Synthesis and Antiplatelet Activity of Some 2-(Dialkylamino)chromones. *Eur. J. Med. Chem.* **1988**, *23*, 237–242. (b) Mazzei, M.; Sottofattori, E.; Di Braccio, M.; Balbi, A.; Leoncini, G.; Buzzi, E.; Maresca, M. Synthesis and Antiplatelet Activity of 2-(Diethylamino)-7-ethoxychromone and Related Compounds. *Eur. J. Med. Chem.* **1990**, *25*, 617–622. (c) Leoncini, G.; Maresca, M.; Colao, C.; Buzzi, E.; Mazzei, M. Mode of Action of 2-(Diethylamino)-7-Ethoxychromone on Human Platelets. *Cell Biochem. Function* **1991**, *9*, 79–85. (d) Leoncini, G.; Maresca, M.; Colao, C.; Buzzi, E.; Mazzei, M.; Balbi, A. Antiplatelet Effect of 2-(Diethylamino)-7-Hydroxychromone. *Pharm. Res.* **1991**, *23*, 139–148.

(11) Nash, S. A.; Gammill, R. B. The Addition of Amines to 3-Bromochromone and 6-Bromofurochromone. An Unexpected Ring Contraction of the Pyrone Ring. *Tetrahedron Lett.* **1983**, 3435–3438.

(12) Bush, L. R.; Shebuski, R. J. In Vivo Models of Arterial Thrombosis and Thrombolysis. *FASEB* **1990**, *4*, 3087–3098.

(13) Morris, J.; Wishka, D. G.; Fang, Y. A Novel Synthesis of 2-Aminochromones via Phosgeniminium Salts. *J. Org. Chem.* **1992**, *57*, 6502–6508.

(14) The tetrazole-containing alkyl chlorides were prepared by treatment of the appropriate amine with chloroacetyl chloride followed by sequential reaction of the resultant chloroamide with PCl_5 and hydrazoic acid; see: (a) Harvill, E. K.; Herbst, R. M.; Schreiner, E. C.; Roberts, C. W. The Synthesis of 1,5-Bis Tetrazoles. *J. Org. Chem.* **1950**, *15*, 662–669. (b) Nishi, T.; Tabusa, F.; Tanaka, T.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. Studies on 2-Oxoquinoline Derivatives as Blood Platelet Aggregation Inhibitors. II. 6-[3-(1-Cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline and Related Compounds. *Chem. Pharm. Bull.* **1983**, *31*, 1151–1157.

(15) Burke, J. M.; Scannell, R. T.; Stevenson, R. Synthesis of Isoeuparin, A Benzofuran Extractive of *Tagetes Patula*. *Phytochemistry* **1986**, 1248–1249.

(16) Echavarren, A. M.; Stille, J. K. Palladium-Catalyzed Coupling of Aryl Triflates with Organostannanes. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486.

(17) Grenette, R.; Gauthier, J. Y.; Young, R. N.; Zamboni, R.; Kakushima, M.; Verhoeven, T. R. Stereoselective Synthesis of Leukotriene Antagonists. U.S. Patent 4,857,659, 1989.

(18) Compound **58** was prepared via Pd(II)-catalyzed coupling of Me_4Sn with the corresponding 6-I chromone derived from 2,4-dihydroxy-5-iodo-3-methylacetophenone via the phosgeniminium salt chemistry.

(19) Aiken, J. W.; Shebuski, R. J.; Miller, O. V.; Gorman, R. R. Endogenous Prostacyclin Contributes to the Efficacy of a Thromboxane Synthetase Inhibitor for Preventing Coronary Artery Thrombosis. *J. Pharmacol. Exp. Ther.* **1981**, *219*, 299–308.

(20) Shebuski, R. J.; Berry, D. E.; Bennett, D. B.; Romoff, T.; Storer, B. L.; Ali, F.; Samanen, J. Demonstration of Ac-Arg-Gly-Asp-Ser-NH_2 as an Antiaggregatory Agent in the Dog by Intracoronary Administration. *Thromb. Haemostasis* **1989**, *61*, 183–188.

(21) Shebuski, R. J.; Ramjit, D. R.; Bencen, G. H.; Polokoff, M. A. Characterization and Platelet Inhibitory Activity of Bitistatin, a Potent Arginine-Glycine-Aspartic Acid-containing Peptide from the Venom of the Viper *Bitis arietans*. *J. Biol. Chem.* **1989**, *264*, 21550–21556.

(22) Shebuski, R. J. Effect of a Thromboxane A_2 (TXA) Receptor Antagonist (TRA) Alone and in Combination with a Thromboxane Synthase Inhibitor (TSI) on Cyclic Flow Reductions (CFRs) in Stenosed Coronary Arteries. *Circulation* **1987**, *76*, IV-101.

(23) Benjamin, C. W.; Lin, A. H.; Morris, J.; Wishka, D. G.; Gorman, R. R. 2-Aminochromones Block Human Platelet Aggregation by Inhibiting cAMP-Dependent Phosphodiesterase Leading to Reduced Platelet Phospholipase C Activity. *J. Pharm. Exp. Ther.* **1993**, *265*, 457–462.

(24) Meanwell, N. A. Inhibitors of Platelet Phosphodiesterase: Potential Antithrombotic Agents. *DN&P* **1991**, *4*, 400–413.

(25) Folts, J. D.; Crowell, E. D.; Rowe, G. G. Platelet Aggregation in Partially Obstructed Vessels and its Elimination with Aspirin. *Circulation* **1976**, 54, 365–370.