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Synthesis and Biological Activity of High-Affinity Retinoic Acid Receptor Antagonists

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Abstract—This article reports the synthesis and biological activity of new high affinity retinioic acid receptor (RAR) antagonists. The effect of introducing heteroatoms in the bicyclic ring system of the potent dihydronaphthalene RAR antagonist **8**, and the variation of the pendant aromatic group on the ability of these compounds to function as RAR antagonists is discussed. The use of binding, transcriptional, and in vivo assays revealed that the 2,2-dimethylthiochromene analogue **59**, and the 2,2-dimethylchromene derivative **85**, were the most effective in blocking retinoid agonist induced activity.

Introduction

Recent advances in retinoid research underscore the importance of these molecules in controlling normal cellular processes.[1] Upon binding to and activating nuclear receptors, retinoids function as modulators of gene transcription and thus play a key role in both embryogenesis and the proper maintenance of various cellular functions such as differentiation and proliferation. Two classes of retinoid receptors are currently known. The retinoic acid receptors (RARα, −β, and −γ)[2a–e] have all-*trans* retinoic acid (ATRA) (**1**) as their natural ligand, and the retinoid X-receptors (RXRα, −β, and −γ)[2f,g] for which 9-*cis*-retinoic acid (**2**) has been proposed as the endogenous ligand[3] (Chart 1). The potential use of retinoid agonists in the treatment of various human diseases, such as psoriasis,[4] acne,[5] cancer,[6] and diabetes,[7] continues to foster the search for new classes of compounds with improved therapeutic ratios.

During the course of this work, a diverse group of compounds **3**–**8** has emerged (Chart 1) that have been shown to be antagonists of retinoid action mediated by the RAR family of receptors.[8] Compounds **3**–**6** are low affinity antagonists which required their use at concentrations in excess of 100- to 1000-fold of the natural hormone ATRA to inhibit retinoid induced biological activity. In contrast, retinoids **7** and **8** have been shown to be potent RAR antagonists with binding affinities comparable to the natural ligand ATRA.

Various studies using these compounds have demonstrated their potential as biological tools in understanding the mechanisms of retinoid action,[9] and as antidotes to retinoid induced toxicity.[10] The present clinical applications of nuclear receptor hormone antagonists such as tamoxifen and RU 486[11] suggests that an RAR antagonist may also be of therapeutic value. In addition, the recent finding that certain RAR antagonists can function as inverse agonists[12] provides further interest in these molecules as it affords an opportunity to explore a new area of RAR biology. In this paper we present our recent findings on the synthesis of heterocyclic analogues of **8** and comment on their ability to function as RAR antagonists in cell based assays and in vivo.

Chemistry

The synthetic strategy used to prepare each series of RAR antagonists of general structure **A** (Scheme 1) follows our previously used route in the synthesis of the dihydronaphthalene based RAR antagonist AGN 193109 (**8**)[8i] (Scheme 1). In each case, a ketone of the general structure **B** served as the key intermediate in the preparation of the final retinoids by allowing the facile addition of various aryl groups via a common enoltriflate. The aryl acid moieties **D**, are connected to the bicyclic ring system **C** via an acetylene group using standard palladium catalyzed coupling chemistry. Thus, our initial focus was directed towards designing an efficient synthesis of thiochromanones **13** (Scheme 2) and **20**–**22** (Scheme 3), and the chromanones **28** and **29** (Scheme 4).

Key words: retinoic acid; receptor; antagonist; cutaneous; toxicity.
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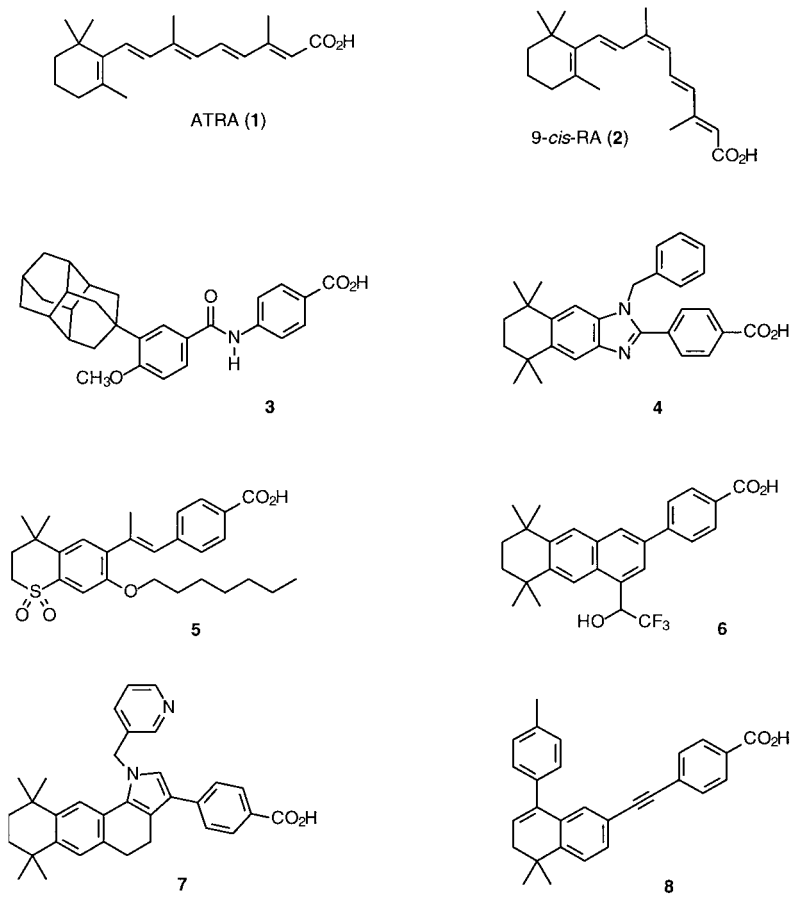
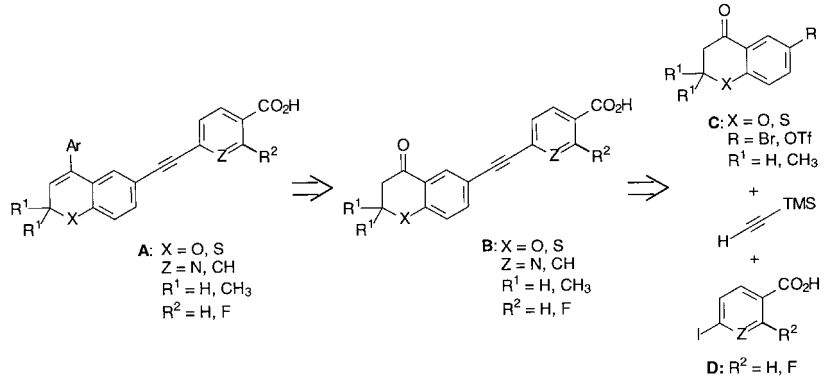


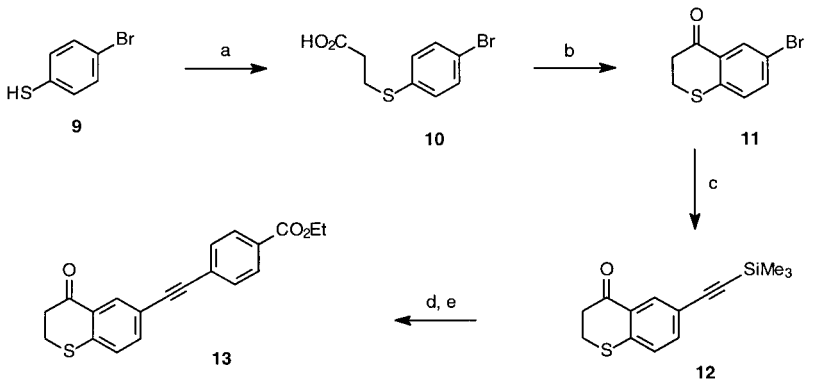
Chart 1.



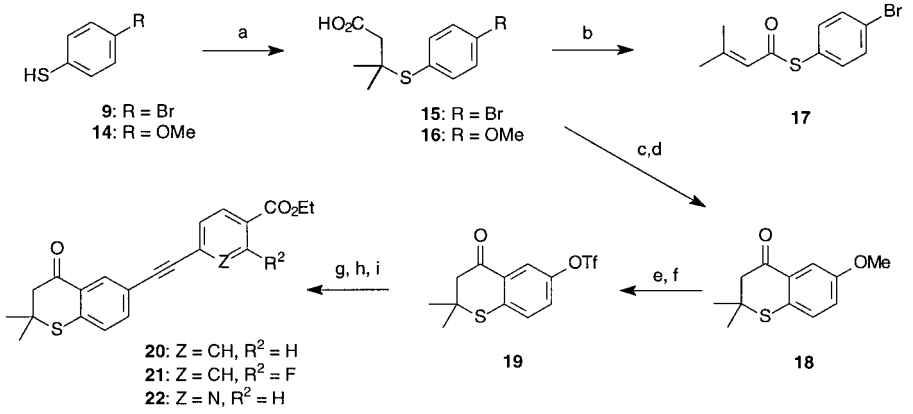
Scheme 1. Retrosynthetic analysis of chromene and thiochromene RAR antagonists.

The synthesis of thiochromanone **13** began with 4-bromothiophenol (**9**) (Scheme 2). Treatment of **9** with aqueous base followed by the addition of the potassium salt of 3-bromopropionic acid afforded **10** as a crystalline solid in 75% yield.[13] An intramolecular Friedel–Crafts acylation reaction carried out in methanesulfonic acid afforded the desired thiochromanone **11** in excellent yield.[14] Coupling of **11** with trimethylsilylacetylene using palladium catalysis at room temperature provided **12** in a modest 65% yield. Exposure of **12** to K_2CO_3 in methanol followed by a second palladium catalyzed coupling reaction of the intermediate terminal acetylene with ethyl 4-iodo-benzoate afforded the target compound **13** in 29% overall yield from **9**.

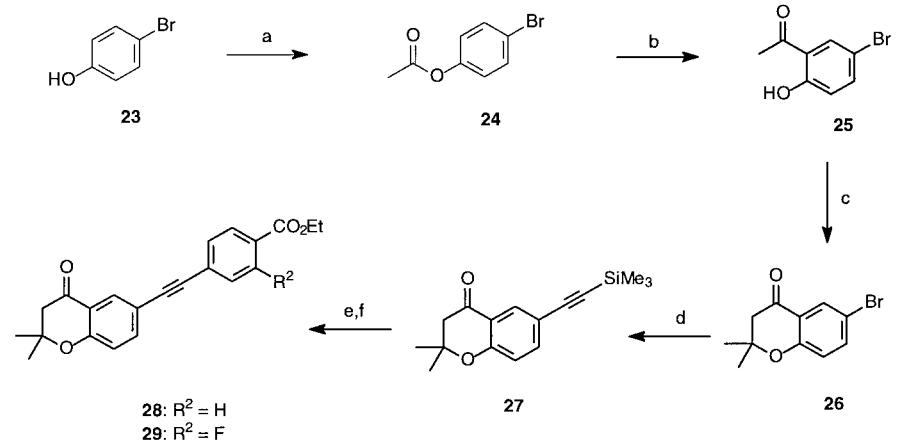
Our initial approach to thiochromanones **20**–**22** also began with thiophenol **9** (Scheme 3). Heating **9** with 3-methyl-2-butenoic acid and a catalytic amount of piperidine afforded **15** in good yield.[15] However, all attempts to ring close this carboxylic acid under standard Freidel–Crafts acylation conditions gave either thioester **17** or a complex mixture of products. As a result, we were forced to consider alternate routes to the intermediate thiochromanone from which the following



Scheme 2. [a](a) NaOH, $BrCH_2CH_2CO_2K$, H_2O, rt (75%); (b) CH_3SO_3H, 75 °C, 1 h (90%); (c) $HCCSiMe_3$, $PdCl_2(PPh_3)$, CuI, DMF, Et_2NH, rt (65%); (d) K_2CO_3, MeOH, rt (96%); (e) 4-I-$C_6H_4CO_2Et$, $PdCl_2(PPh_3)_2$, CuI, THF, Et_3N, 60 °C (69%).



Scheme 3. (a) $(CH_3)_2C{=}CHCO_2H$, piperdine, 105 °C, (**15**, 79%), (**16**, 82%); (b) H^+; (c) $(COCl)_2$, bz, rt; (d) $SnCl_4$, CH_2Cl_2, 0 °C, 2 h (78%); (e) BBr_3, CH_2Cl_2, −23 °C (40%); (f) Tf_2O, pyr 0 °C to rt (47%); (g) TMSC≡CH, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 95 °C (91%); (h) K_2CO_3, MeOH (99%); (i) 4-$IC_6H_4CO_2Et$, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, (**20**, 72%), with 2-F-4-$IC_6H_4CO_2Et$ (**21**, 78%), with 6-I-C_5H_3N-3-CO_2Et (**22**, 78%).



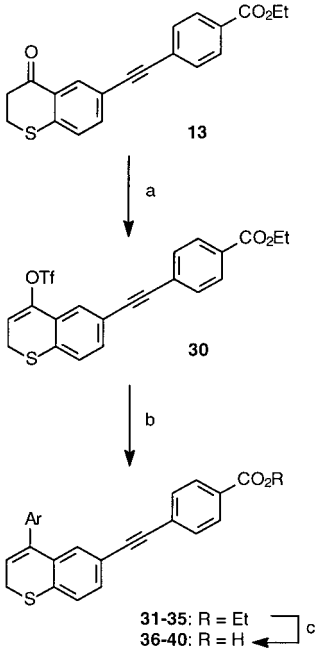
Scheme 4. (a) AcCl, Et_3N, CH_2Cl_2, rt (83%); (b) $AlCl_3$, 155 °C, (72%); (c) acetone, piperidine, piperidinium trifluoroacetate, bz, 90 °C, 44 h, (62%); (d) TMSC≡CH, $Pd(PPH_3)_2Cl_2$, CuI, Et_3N, 70 °C, 24 h, (89%); (e) K_2CO_3, MeOH, (91%); (f) 4-$IC_6H_4CO_2Et$, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, (**28**, 50%), with 2-F-4-$IC_6H_4CO_2Et$ (**29**, 69%).

sequence proved successful. Thus, addition of 4-methoxythiophenol (**14**) to 3-methyl-2-butenoic acid afforded **16** which was then converted to the corresponding acid chloride under standard conditions. Lewis acid mediated cyclization of this intermediate proceeded without incident to give **18** in good overall yield. Conversion of methyl ether **18** to the corresponding phenol using an excess of BBr_3[16] followed by treatment with trifluoromethanesulfonic anhydride in pyridine[17] afforded triflate **19**. Following the same protocol as described in

Scheme 2, thiochromanone **20** was prepared from **19** in good overall yield. In the same manner, the use of ethyl 2-fluoro-4-iodobenzoate or ethyl 6-iodo-nicotinate in place of ethyl 4-iodo-benzoate provided the *o*-fluorobenzoate **21** and nicotinate **22** in good yield.

The synthesis of the chromanone analogues **28** and **29** (Scheme 4) was based in part on a procedure to the known 6-bromochromanone **26**.[18] Thus, acylation of phenol **23** with acetyl chloride followed by Fries rearrangement of ester **24** afforded the disubstituted acetophenone **25** in 62% yield. Following the published report, **25** was refluxed with an excess of acetone in the presence of piperidine. To our surprise ketone **25** was recovered unchanged. In an effort to facilitate this aldol process[19] a catalytic amount of piperidinium trifluoroacetate was added to the reaction mixture. This change produced the desired chromanone **26** in 60% yield. The use of weaker acids such as NH_4OAc or piperidinium acetate also gave the desired product but in lower yields. One explanation for the observed discrepancy with the published procedure is that in our case ketone **25** was purified by recrystallization prior to the condensation step. The use of **25** directly from the Fries rearrangement step may have retained some HCl and thus the production of **26** was a result of catalysis by piperidinium hydrochloride. Having secured a route to bromochromane **26**, the standard sequence of palladium catalyzed coupling reactions described above afforded chromanones **28** and **29** in good overall yield.

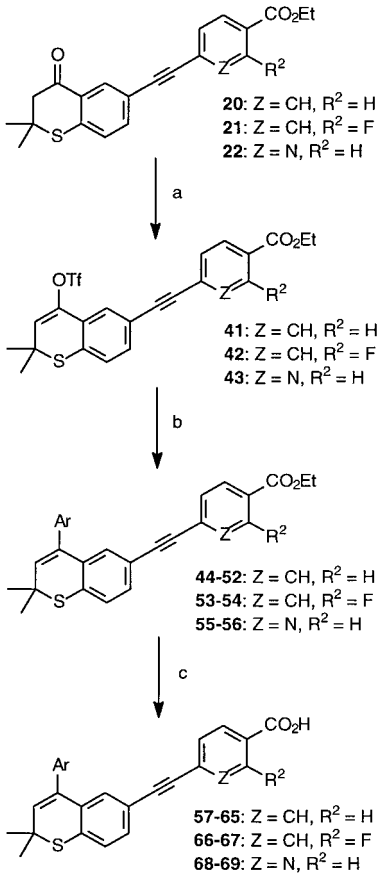
Preparation of the 4-aryl substituted thiochromene antagonists was carried out using the synthetic sequence outlined in Scheme 5. Conversion of ketone **13** to vinyl triflate **30** was readily accomplished by quenching the sodium enolate of **13** with the bis-triflimide reagent first reported by Comins.[20] Palladium catalyzed coupling of triflate **30** with the organozinc reagent[21] prepared from the appropriate aryl halides afforded thiochromenes **31**–**35** in 40 to 94% yield. The required free carboxylic acids **36**–**40** were then prepared in good yield using standard base hydrolysis conditions. Following the same synthetic sequence, the 2,2-dimethylthiochromene derivatives **57**–**69**, and the 2,2-dimethylchomene analogues **79**–**85**, were prepared as shown in Schemes 6 and 7.



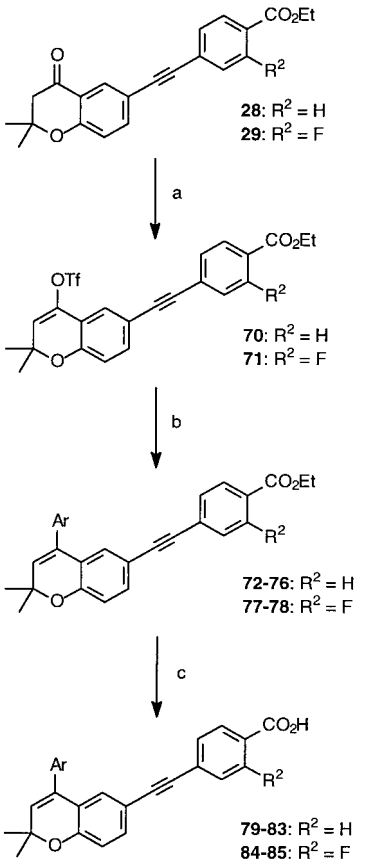
Scheme 5. (a) $NaN(TMS)_2$, THF, 5-Cl-2-NTf_2-pyr, −78 °C to 0°C (69%); (b) ArZnCl, $Pd(PPh_3)_4$, THF, 50 °C, (**31**–**35**, 40–94%); (c) NaOH, THF, EtOH, H_2O, (**36**–**40**, 78–85%).

Results and Discussion

The carboxylic acids prepared above were analyzed for retinoid activity by testing in RAR and RXR binding and transactivation assays. None of the compounds had any detectable binding affinity for the RXRs and were also transcriptionally inactive at all three RXR subtypes. All of the compounds tested lacked transcriptional activity but displayed high affinity for the RARs. In general, the data in Table 1 indicate that all of the retinoids bind to RARβ with affinities similar to the natural ligand ATRA. In addition, these data also indicate that the analogues bearing a 4-methyl- or 4-ethylphenyl group have the highest affinities for the three RAR subtypes.



Scheme 6. (a) $NaN(TMS)_2$, THF, 5-Cl-2-NTf_2-pyr, −78 °C to 0 °C, (**41**, 61%), (**42**, 71%),(**43**, 87%); (b) ArZnCl, $Pd(PPh_3)_4$ THF, 50 °C (**44**–**52**, 16–96%), (**53**, 79%), (**54**, 86%), (**55**, 76%), (**56**, 83%); (c) NaOH, THF, EtOH, H_2O (**57**–**65**, 54–93%), (**66**, 83%), (**67**, 86%), **68** (81%), **69** (96%).



Scheme 7. (a) $NaN(TMS)_2$, THF, 5-Cl-2-NTf_2-pyr, −78 °C to 0 °C, (**70**, 64%), (**71**, 58%); (b) ArZnCl, $Pd(PPh_3)_4$, THF, 50 °C (**72**–**76**, 59–92%), (**77**, 62%), (**78**, 79%), (c) NaOH, THF, EtOH, H_2O, (**79**–**83**, 74–85%), (**84**, 94%), (**85**, 91%).

The thiochromene analogues **36**–**40** display the lowest affinity of the present set of compounds for RARγ, having K_d values 15- to 38-fold lower than the value for AGN 193109 (**8**). In this same group of compounds, the affinity for RARα increases upon going from the phenyl analogue **36**, to the 4-methyl and 4-ethyl derivatives **37** and **38**, but then decreases with an increase in size of the 4-alkyl groups as observed with **39** and **40**.

The effect of introducing a *gem*-dimethyl group at C-2 of the thiochromene ring system was also explored. The resulting 2,2-dimethylthiochromene analogues **57**–**61**, were found to bind with high affinity to all three RARs, displaying an 8 to 18-fold increase in affinity at RARα and an 8 to 30-fold increase at RARγ relative to the *des*-methyl analogues **36**–**40**. The affinity to RARβ was also increased although to a lesser extent. In this same series, the use of heteroaromatic substituents such as pyridyl and thienyl in place of a phenyl group at C-4 **62**–**65**, showed little or no change in binding affinity relative to the 4-phenyl analogues. In contrast, replacement of the benzoic acid moiety with the nicotinic acid group to give **68** and **69** proved detrimental to binding at RARα resulting in an 11- to 23-fold drop in affinity at this RAR subtype while affinity to RARβ and RARγ was retained.

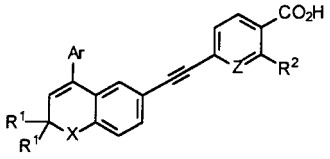
The binding data for the 2,2-dimethylchromene analogues **79**–**83**, appears closer in profile to the corresponding thiochromenes **36**–**40** as compared to the 2,2-dimethylthiochromenes **57**–**61**. Although the same trends in the affinity of the ligand for RARα and RARγ are observed with a change in alkyl substitution, they appear less pronounced in this series. Thus, the difference in C–O versus C–S bond lengths (1.4 A versus 1.8 A) appears to have placed the *gem*-dimethyl groups of the chromenes in a slightly less favorable position for interaction with the binding pocket of RARα and RARγ relative to the thiochromene analogues.

Previous work from these laboratories[22] indicated that the presence of a fluorine atom *ortho*- to the carboxyl group can increase ligand binding to all three receptor subtypes. However, this modification when applied to the present series of compounds resulted in no significant change in K_d values relative to the parent antagonists (compare **66** versus **58**, **67** versus **59**, **84** versus **80**, and **85** versus **81**).

To determine if the compounds listed in Table 1 would function as antagonists in vitro, they were tested for their ability to inhibit the transcriptional activity of the potent RAR agonist TTNPB. Using a constant dose of TTNPB, an increasing concentration of test antagonist was used to determine an IC_{50} value at each RAR subtype. The potency of each antagonist relative to AGN 193109 (**8**) was then determined from the observed IC_{50} values of the test compound at each RAR subtype and the IC_{50} for **8** in the same experiment. The results of these experiments indicate that all of the compounds tested can function as RAR antagonists in vitro as initially suggested from their ability to bind to the RARs in the absence of transcriptional activity. Table 2 contains data for a subset of the antagonists listed in Table 1. The lack of a correlation between the observed potencies and K_d values is attributed to the different experimental conditions used in the binding and transactivation assays.[23] In general, we observed that only when the difference in K_d values between **8** and the test compound was greater than 10-fold would the relative potency of the antagonist under study fall below a value of one. This is exemplified by retinoid **38** where a 16-fold difference in K_d values at RARγ results in a relative potency of 0.3 (Table 2). Although the resolution of this assay is low, these data do show that each of these compounds can compete with an RAR agonist in binding and activation of the RARs.

In a recent publication we presented in vivo evidence for the potential of using RAR antagonists in the prevention and treatment of retinoid induced toxicity.[10] Following the same protocol, compounds from the present set of RAR antagonists were tested for their ability to inhibit topical toxicity induced by TTNPB. The data in Table 3 shows the results of these experiments for a subset of the compounds discussed above, along with data for compound **8**. At one half the concentration of the RAR agonist, two of the antagonists, **59** and **85**, along with the reference compound **8**, display very significant inhibition of retinoid induced toxicity. At these

Table 1. Binding affinities for chromene and thiochromene RAR antagonists and reference compounds[a]



Compound	X	Z	Ar	R^1	R^2	RAR[a] α	β	γ
ATRA (**1**)						15 ± 25	13 ± 3	18 ± 1
TTNPB[b]						72 ± 37	5 ± 2	26 ± 20
8	CMe_2	CH	4-Me-C_6H_5-	H	H	17 ± 5	7 ± 3	7 ± 1
36	S	CH	C_6H_5-	H	H	143 ± 46	25 ± 10	380 ± 199
37	S	CH	4-Me-C_6H_5-	H	H	27 ± 9	4 ± 1	116 ± 33
38	S	CH	4-Et-C_6H_5-	H	H	28 ± 8	3 ± 1	115 ± 33
39	S	CH	4-iPr-C_6H_5-	H	H	124 ± 8	9 ± 1	297 ± 31
40	S	CH	4-tBu-C_6H_5-	H	H	130 ± 42	7 ± 3	155 ± 26
57	S	CH	C_6H_5-	CH_3-	H	8 ± 3	5 ± 1	13 ± 2
58	S	CH	4-Me-C_6H_5-	CH_3-	H	4 ± 2	2 ± 1	10 ± 3
59	S	CH	4-Et-C_6H_5-	CH_3-	H	3 ± 2	2 ± 1	5 ± 1
60	S	CH	4-iPr-C_6H_5-	CH_3-	H	7 ± 3	2 ± 1	10 ± 3
61	S	CH	4-tBu-C_6H_5-	CH_3-	H	13 ± 4	4 ± 2	20 ± 3
62	S	CH	6-Me-3-C_5H_3N-	CH_3-	H	4 ± 1	2 ± 0	17 ± 4
63	S	CH	5-Me-2-C_4H_2S-	CH_3-	H	12 ± 3	6 ± 3	18 ± 1
64	S	CH	5-ET-2-C_4H_2S-	CH_3-	H	6 ± 2	2 ± 0	17 ± 7
65	S	CH	5-tBu-2-C_4H_2S-	CH_3-	H	19 ± 2	5 ± 1	57 ± 28
66	S	CH	4-Me-C_6H_5-	CH_3-	F	2 ± 0	2 ± 1	3 ± 1
67	S	CH	4-Et-C_6H_5-	CH_3-	F	4 ± 1	10 ± 7	4 ± 1
68	S	N	4-Me-C_6H_5-	CH_3-	H	45 ± 5	6 ± 4	5 ± 1
69	S	N	4-Et-C_6H_5-	CH_3-	H	70 ± 1	4 ± 1	9 ± 1
79	O	CH	C_6H_5-	CH_3-	H	36 ± 1	11 ± 3	49 ± 2
80	O	CH	4-Me-C_6H_5-	CH_3-	H	14 ± 1	5 ± 1	14 ± 0
81	O	CH	4-Et-C_6H_5-	CH_3-	H	12 ± 3	3 ± 0	24 ± 4
82	O	CH	4-iPr-C_6H_5-	CH_3-	H	16 ± 3	8 ± 3	39 ± 1
83	O	CH	4-tBu-C_6H_5-	CH_3-	H	72 ± 4	9 ± 4	108 ± 13
84	O	CH	4-Me-C_6H_5-	CH_3-	F	14 ± 6	6 ± 3	28 ± 8
85	O	CH	4-Et-C_6H_5-	CH_3-	F	5 ± 1	2 ± 0	16 ± 4

[a]K_d + SEM (nM).
[b]TTNPB = (Ro 13-7410), (E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)propen-1-yl]benzoic acid.

Table 2. Relative potency[a] and K_d *values*[b] of selected RAR antagonists in the inhibition of transcriptional activity by the RAR agonist TTNPB

Entry	RAR α	β	γ
38	1.1	4.4	0.3
	28 ± 8	*3 ± 1*	*115 ± 33*
59	7.5	6.5	4.0
	3 ± 2	*2 ± 1*	*5 ± 1*
62	9.3	19.0	3.3
	4 ± 1	*2 ± 0*	*17 ± 4*
64	2.5	5.5	2.2
	6 ± 2	*2 ± 0*	*17 ± 7*
81	4.4	11.8	2.4
	12 ± 3	*3 ± 0*	*24 ± 4*
85	2.4	12.2	2.2
	5 ± 1	*2 ± 0*	*16 ± 4*

[a]Relative Potency = IC_{50} (test compound)/IC_{50}(**8**).
[b]K_d *values* (nM) from Table 1.

same concentrations, the heterocyclic analogues **62** and **64** appear less efficient although they are still able to block agonist activity. Using a twofold excess of the antagonist relative to TTNPB results in ≥75% reduction in the observed toxicity with all the analogues, while at an eightfold higher concentration these compounds appear to offer complete protection from retinoid agonist induced toxicity.

Conclusions

The present series of compounds have been shown to function as potent RAR antagonists in vitro and in vivo. The introduction of heteroatoms into the basic framework of AGN 193109 (**8**) has afforded RAR antagonists with similar or improved activity. The 4-methyl- and 4-ethylphenyl analogues in the 2,2-dimethylchromene and dimethylthiochromene series were found to be the most potent of the compounds prepared. In addition, the 2,2-dimethylthiochromene framework appears to be optimum for *pan*-RAR antagonist activity showing no sensitivity to the size of the 4-alkyl group of the aryl substituent located at C-4 of the heterocyclic ring system. The potential use of these compounds as inhibitors of retinoid induced toxicity in vivo has also been clearly demonstrated by their ability to block the activity of the potent RAR agonist TTNPB. As a result, compound **59** (AGN 194310) is

Table 3. Percent inhibition[a] of TTNPB induced cutaneous toxicity at various antagonist–agonist ratios[b]

Entry	Ratio 0.5	2.0	8.0
8	72	85	98
59	79	84	94
62	32	76	90
64	44	78	84
85	71	86	92

[a]Determined using the cutaneous toxicity scores[10a] for TTNPB with vehicle control and in combination with the RAR antagonist.
[b]Ratio = [antagonist]/[TTNPB].

currently in pre-clinical development as a topical agent for the treatment and prevention of the mucocutaneous toxicity produced by systemic retinoids such as Accutane™.

Experimental

General methods

^{1}H NMR spectra were recorded using a Varian Gemini 300 spectrometer (300 MHz) and ^{13}C NMR spectra using a Varian XL 300 spectrometer (75.5 MHz) in the solvent indicated. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison NJ. All final retinoids were characterized by IR, low-resolution MS, ^{1}H and ^{13}C NMR.

Thin-layer chromatography (TLC) was carried out using Whattman silica gel 60 A plates (0.25 mm). Flash chromatography was performed using E. Merck silica gel 60 (230–400 mesh). All reactions were carried out under a positive pressure of argon using reagent grade or anhydrous solvents as received.

3-(4-Bromothiophenoxy)propionic acid (10). To a solution of 1.44 g (35.7 mmol) of NaOH on 20.0 mL degassed H_2O (sparged with argon) was added 6.79 g (35.7 mmol) of 4-bromothiophenol. The resulting mixture was stirred at room temperature for 30 min. A second flask was charged with 2.26 g (16.3 mmol) of K_2CO_3 and 15.0 mL degassed H_2O. To this solution was added in small portions 5.00 g (32.7 mmol) of 3-bromopropionic acid. The resulting potassium carboxylate solution was added to the sodium thiolate solution and the resulting mixture stirred at room temperature for 48 h. The mixture was filtered and the aqueous extracted with benzene and the organic layers discarded. The aqueous layer was acidified with 10% aqueous HCl and extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residual solid was recrystallized from ether/hexanes to give 6.18 g (72%) of the title compound as off-white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (2H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.4 Hz), 3.15 (2H, t, J = 7.3 Hz), 2.68 (2H, t, J = 7.3 Hz).

6-Bromo-thiochroman-4-one (11). A solution of 3.63 g (13.9 mmol) of **10** in 60 mL of methanesulfonic acid was heated to 75 °C for 1.5 h. After cooling to room temperature the solution was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with 2 N aqueous NaOH, H_2O, and saturated aqueous NaCl before being dried over $MgSO_4$. The title compound 2.26 g (67%), was isolated by column chromatography (3% EtOAc/hexanes) as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (1H, d, J = 2.1 Hz), 7.48 (1H, dd, J = 2.1, 8.3 Hz), 7.17 (1H, d, J = 8.5 Hz), 3.24 (2H, t, J = 6.4 Hz), 2.98 (2H, t, J = 6.7 Hz).

6-(2-Trimethylsilylethynyl)-thiochroman-4-one (12). A solution of **11** 1.00 g (4.11 mmol) and 78.3 mg (0.41 mmol) CuI in 15.0 mL THF and 6.0 mL Et_2NH was sparged with argon for 5 min. To the resulting solution was added 2.0 mL (1.39 g, 14.2 mmol) of (trimethylsilyl)-acetylene and 288.5 mg (0.41 mmol) of $Pd(PPh_3)_2Cl_2$. After stirring for 3 days at room temperature the mixture was filtered through a pad of Celite and solids washed with EtOAc. The filtrate was washed with H_2O and saturated aqueous NaCl before being dried over $MgSO_4$ and concentrated under reduced pressure. The title compound 600.0 mg (55%), was isolated by column chromatography (4% EtOAc/hexanes) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (1H, d, J = 1.9 Hz), 7.36 (1H, dd, J = 2.1, 8.2 Hz), 7.14 (1H, d, J = 8.2 Hz), 3.19 (2H, d, J = 6.3 Hz), 2.91 (2H, d, J = 6.3 Hz), 0.21 (9H, s).

Ethyl 4-[2-(4-oxo-thichroman-6-yl)ethynyl]benzoate (13). A solution of **12** (600.0 mg, 2.25 mmol) and K_2CO_3 (100.0 mg, 0.72 mmol) in 15 mL of MeOH was stirred overnight at room temperature. The solution was diluted with H_2O and extracted with Et_2O. The combined organic layers were washed with H_2O and saturated aqueous NaCl before being dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded 405.0 mg (96%) of 6-ethynyl-thiochroman-4-one as an orange solid which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (1H, d, J = 1.8 Hz), 7.40 (1H, dd, J = 1.8, 8.2 Hz), 7.19 (1H, d, J = 8.2 Hz), 3.22 (2H, t, J = 6.3 Hz), 3.08 (1H, s), 2.94 (2H, t, J = 6.3 Hz).

A solution 6-ethynyl-thiochroman-4-one (405.0 mg, 2.15 mmol) and ethyl 4-iodobenzoate (594.0 mg, 2.15 mmol) in 15 mL Et_3N and 3 mL THF was sparged with argon for 15 min. To this solution was added $Pd(PPh_3)_2Cl_2$ (503.0 mg, 0.72 mmol), and CuI (137.0 mg, 0.72 mmol). After stirring at room temperature for 20 h the mixture was filtered through a pad of Celite using an EtOAc wash. The combined organic layers were washed with H_2O and saturated aqueous NaCl before being dried over $MgSO_4$. Column chromatography (3% EtOAc/hexanes) afforded 500.0 mg (69%) of the title compound as a pale-orange solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.15 (1H, d, J = 2.0 Hz), 8.02 (2H, d, J = 8.5 Hz), 7.69 (2H, d, J = 8.5 Hz), 7.61 (1H, dd, J = 2.1, 8.3 Hz), 7.40 (1H, d, J = 8.2 Hz), 4.35 (2H, q, J = 7.1 Hz), 3.40 (2H, t, J = 6.3 Hz), 2.96 (2H, t, J = 6.3 Hz), 1.37 (3H, t, J = 7.1 Hz).

Ethyl 4-[(4-trifuoromethylsulfonyloxy-(2*H*)-thiochromen-6-yl)ethynyl] benzoate (30). To a solution of sodium bis(trimethylsilyl)amide (221.9 mg, 1.21 mmol) in 3.0 mL

THF at −78 °C was added **13** (370.0 mg, 1.10 mmol) in 4.0 mL THF. After 30 min a solution of 2[*N*,*N*-bis(trifluormethylsulfonyl)amino]-5-chloropyridine (475.4 mg, 1.21 mmol) in 4.0 mL THF was added and the resulting solution allowed to slowly warm to room temperature. After 5 h the reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and the combined organic layers washed with 5% aqueous NaOH, H_2O, and saturated aqueous NaCl before being dried over $MgSO_4$. Removal of the solvents under reduced pressure followed by column chromatography (4% EtOAc/hexanes) of the residual oil afforded 81.0 mg (69%) of the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.12 (2H, d, J = 8.5 Hz), 7.66 (2H, d, J = 8.5 Hz), 7.56 (1H, d, J = 1.7 Hz), 7.49 (1H, dd, J = 1.7, 8.1 Hz), 7.40 (1H, d, J = 8.1 Hz), 6.33 (1H, t, J = 5.7 Hz), 4.35 (2H, q, J = 7.1 Hz), 3.82 (2H, d, J = 5.7 Hz), 1.37 (3H, t, J = 7.1 Hz).

General procedure A: ethyl 4-[(4-phenyl-(2*H*)-thiochroman-6-yl)ethynyl] benzoate (31). To a solution of bromobenzene (101.0 mg, 0.63 mmol) in 2.0 mL THF at −78 °C was added *t*-BuLi (0.74 mL of a 1.7 M solution in pentane, 1.25 mmol). After stirring for 30 min a solution of $ZnCl_2$ (119.0 mg, 0.88 mmol) in 2.0 mL THF was added and the resulting pale-yellow solution warmed to room temperature. Stirring for 40 min was followed by the transfer of this solution to a second flask containing **30** (120.0 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (24.0 mg, mmol) in 2.0 mL of THF. The resulting solution was heated to 50 °C for 2 h, cooled to room temperature and quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and the combined organic layers washed with H_2O and saturated aqueous NaCl before being dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (3 to 5% EtOAc/hexanes) afforded 40.0 mg (40%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.98 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.54–7.37 (5H, m), 7.32–7.29 (2H, m), 7.12 (1H, d, J = 1.7 Hz), 6.17 (1H, t, J = 5.7 Hz), 4.34 (2H, q, J = 7.1 Hz), 3.56 (2H, d, J = 5.7 Hz), 1.35 (3H, t, J = 7.1 Hz). Anal. calcd for $C_{26}H_{20}O_2S$: C, 78.76; H, 5.08. Found: C, 78.66; H, 4.79.

Ethyl 4-[(4-(4-methylphenyl)-(2*H*)-thiochromen-6-yl)ethynyl] benzoate (32). Following general procedure A; 4-bromotoluene (120.8 mg, 0.70 mmol), *t*-BuLi (0.81 mL, 1.38 mmol), $ZnCl_2$ (131.6 mg, 0.97 mmol), **30** (129.2 mg, 0.28 mmol) $Pd(PPh_3)_4$ (14.0 mg, 0.012 mmol) afforded 45.0 mg (40%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.98 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 7.44–7.38 (2H, m), 7.26–7.15 (5H, m), 6.14 (1H, t, J = 5.8 Hz), 4.34 (2H, q, J = 7.1 Hz), 3.53 (2H, d, J = 5.8 Hz), 2.37 (2H, s), 1.35 (3H, t, J = 7.1 Hz). Anal. calcd for $C_{27}H_{22}O_2S$: C, 78.9; H, 5.40. Found: C, 78.75; H, 5.23.

Ethyl 4-[(4-ethylphenyl)-(2*H*)-thiochromen-6-yl)ethynyl] benzoate (33). Following general procedure A; 4-ethylbromobenzene (128.0 mg, 0.69 mmol), *t*-BuLi (0.81 mL, 1.38 mmol), $ZnCl_2$ (131.6 mg, 0.97 mmol), **30** (129.2 mg, 0.28 mmol) and $Pd(PPh_3)_4$ (14.0 mg, 0.012 mmol) afforded 110.0 mg (93%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.98 (2H, d, J = 8.14 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.45–7.36 (2H, m), 7.29–7.16 (5H, m), 6.15 (1H, t, J = 5.7 Hz), 4.31 (2H, q, J = 7.1 Hz), 3.50 (2H, d, J = 5.7 Hz), 2.68 (2H, q, J = 7.5 Hz), 1.35 (3H, t, J = 7.1 Hz),1.24 (3H, t, J = 7.5 Hz), Anal. calcd for $C_{28}H_{24}O_2S$: C, 79.21; H, 5.70. Found: C, 79.06; H, 5.48.

Ethyl 4-[(4-(4-(1-methylethyl)phenyl)-(2*H*)-thiochromen-6-yl)ethynyl] benzoate (34). Following general procedure A; 4-*iso*-propylbromobenzene (159.0 mg, 0.80 mmol), *t*-BuLi (0.94 mL, 1.60 mmol), $ZnCl_2$ (153.0 mg, 1.12 mmol), **30** (150.0 mg, 0.32 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.021 mmol) afforded 63.0 mg (45%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (2H, d, J = 8.4 Hz), 7.39–7.20 (7H, m), 6.07 (1H, t, J = 5.7 Hz), 4.36 (2H, q, J = 6.8 Hz), 3.48 (2H, d, J = 5.7 Hz), 2.97 (1H, hept, J = 6.8Hz), 1.57 (3H, t, J = 7.1 Hz), 1.32 (6H, d, J = 6.8 Hz). Anal. calcd for $C_{29}H_{26}O_2S$: C, 79.42; H, 5.98. Found: C, 79.25; H, 6.07.

Ethyl 4-[(4-(4-(1,1-dimethylethyl)phenyl)-(2*H*)-thiochromen-6-yl)ethynyl] benzoate (35). Following general procedure A; 4-*tert*-butylbromobenzene (148.0 mg, 0.69 mmol), *t*-BuLi (0.81 mL, 1.39 mmol), $ZnCl_2$ (132.0 mg, 0.97 mmol), **30** (130.0 mg, 0.28 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.021 mmol) afforded 75.0 mg (65%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.98 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.49–7.39 (4H, m), 7.25–7.22 (2H, m), 7.17 (1H, d, J = 1.7 hz), 6.16 (1H, t, J = 5.7 Hz), 4.33 (2H, q, J = 7.1 Hz), 3.53 (2H, d, J = 5.7 Hz), 1.34 (9H, s), 1.34 (3H, t, J = 7.1 Hz). Anal. calcd for $C_{30}H_{28}O_2S$: C, 79.43; H, 6.05. Found: C, 79.61; H, 6.24.

General procedure B 4-[2-(4-phenyl-(2*H*)-thiochromen-6-yl)-ethynyl]-benzoic acid (36). To a solution of **31** (27.7 mg, 0.07 mmol) in 2.0 mL THF and 2.0 mL EtOH was added NaOH (80.0 mg, 2.0 mmol, 2.0 mL of a 1 M aqueous solution). The resulting solution was heated to 40 °C and stirred overnight. Upon cooling to room temperature the reaction was acidified with 10% aqueous HCl and extracted with EtOAc. The combined organic layers were washed with H_2O, saturated aqueous NaCl, and dried (Na_2SO_4) before removing the solvent under reduced pressure. The residual solid was recrystallized from CH_3CN to give 20.0 mg (78%) of the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.90 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.45–7.37 (5H, m), 7.28–7.25 (2H, m), 7.01 (1H, d, J = 1.7 Hz), 6.15 (1H, t, J = 5.7 Hz), 3.57 (2H, d, J = 5.7 Hz). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 166.6, 139.7, 139.6, 135.4, 133.9, 131.4, 130.6, 130.5, 129.7, 129.4, 128.6, 128.1, 127.9, 126.3, 123.1, 118.5, 91.6, 88.6, 24.3.

4-[2-(4-(4-Methylphenyl)-(2*H*)-thiochromen-6-yl)-ethynyl]-benzoic acid (37). Following general procedure B, **32** (29.0 mg, 0.07 mmol) in 2.0 mL THF and 2.0 mL EtOH and NaOH (160.0 mg, 4.0 mmol, 2.0 mL of a 2 M aqueous solution afforded 22.0 mg (82%) of the title compound

as a pale-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.90 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.46–7.40 (4H, m), 7.25–7.13 (4H, m), 7.02 (1H, d, J = 1.7 Hz), 6.11 (1H, t, J = 5.7 Hz), 3.54 (2H, d, J = 5.7 Hz), 2.34 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 166.7, 139.5, 137.2, 136.8, 135.5, 134.5, 130.6, 130.5, 129.8, 129.5, 129.2, 128.5, 128.1, 126.4, 122.5, 118.5, 91.6, 88.6, 24.4, 20.8.

4-[2-(4-(4-Ethylphenyl)-(2*H*)-thiochromen-6-yl]-ethynyl)-benzoic acid (38). Following general procedure B, **33** (90.0 mg, 0.21 mmol) in 3.0 mL THF and 3.0 mL EtOH and NaOH (240.0 mg, 6.0 mmol, 3.0 mL of a 2 M aqueous solution) afforded 66.0 mg (79%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.89 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 7.46–7.37 2H, m)m 7.28–7.16 (4H, m), 7.03 (1H, d, J = 1.6 Hz), 6.13 (1H t, J = 5.6 Hz), 3.54 (2H, d, J = 5.6 Hz), 2.64 (2H, q, J = 7.5 Hz), 1.21 (3H, t, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 166.6, 143.5, 139.5, 137.1, 135.5, 134.0, 131.5, 130.6, 130.4, 129.7, 129.4, 128.5, 128.1, 128.0, 126.4, 122.6, 118.5, 91.6, 88.6, 27.8, 24.3, 15.3.

4-[2-(4-(4-(1-Methylethyl)phenyl)-(2*H*)-thiochromen-6-yl)-ethynyl]-benzoic acid (39). Following general procedure B, **34** (44.0 mg, 0.10 mmol) in 3.0 mL THF and 3.0 mL EtOH and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution) afforded 35.0 mg (85%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.90 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 7.47–7.17 (6H, m), 7.04 1H, d, J = 1.7 Hz), 6.13 (1H, t, J = 5.7 Hz), 3.54 (2H, d, J = 5.7 Hz), 2.92 (1H, hept., J = 6.8 Hz), 1.23 (6H, d, J = 6.8 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 166.5, 148.0, 139.4, 137.1, 135.5, 133.9, 131.4, 130.6, 130.4, 129.6, 129.4, 128.5, 128.0, 126.5, 126.3, 122.6, 118.4, 91.5, 88.5, 33.0, 24.3, 23.7.

4-[2-(4-(4-(1,1-Dimethylethyl)phenyl)-(2*H*)-thiochromen-6-yl)-ethynyl]-benzoic acid (40). Following general procedure B, **35** (50.0 mg, 0.11 mmol) in 2.0 mL THF and 2.0 mL EtOH and NaOH (160.0 mg, 4.0 mmol, 2.0 mL of a 2 M aqueous solution) afforded 38.0 mg (81%) of the title compound as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.90 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.47–7.38 (4H, m), 7.21–7.18 (2H, m), 7.05 (1H, s), 6.13 (1H, t, J = 5.7 Hz), 3.54 (2H, d, J = 5.7 Hz), 1.31 (9H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 166.7, 150.3, 139.4, 136.8, 135.5, 134.0, 131.4, 130.7, 129.6, 129.4, 128.3, 128.1, 126.3, 125.4, 122.7, 118.5, 91.6, 88.6, 34.3, 31.1, 24.3.

3-(4-Methoxy-phenylsulfanyl)-3-methyl-butyric acid (16). A heavy-walled screw cap tube was charged with 3-methyl-2-butenoic acid (13.86 g, 138.4 mmol), 4-methoxy thiophenol (20.0 g, 138.4 mmol), and piperidine (3.45 g, 41.6 mmol). This mixture was heated to 105 °C for 32 h, cooled to room temperature and dissolved in EtOAc (700 mL). The resulting solution was washed with 1 M aqueous HCl, H_2O, and saturated aqueous NaCl before being dried over Nac_2SO_4. Concentration of the dry solution under reduced pressure afforded an oil which upon standing in the freezer provided a crystalline solid. The title compound was isolated using a pentane wash as pale-yellow crystals (27.33 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (2H, d, J = 9.0 Hz), 6.89 (2H, d, J = 8.9 Hz), 3.83 (3H, s), 2.54 (2H, s), 1.40 (6H, s).

6-Methoxy-2,2-dimethyl-thiochroman-4-one (18). To a solution of 3-(4-methoxy-phenylsulfanyl)-3-methyl-butyric acid (20.0 g, 83.2 mmol) in 250 mL of benzene at room temperature was added a solution of oxalyl chloride (15.84 g, 124.8 mmol) in 10 mL of benzene over 30 min. After 4 h, the solution was washed with ice cold 5% aqueous NaOH (CAUTION: a large volume of gas is released during this procedure), followed by ice cold H_2O, and finally saturated aqueous NaCl. The solution was dried (Na_2SO_4) and concentrated under reduced pressure to give the acyl chloride as a clear yellow oil. This material was used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 (2H, d, J = 8.8 Hz), 6.90 (2H, d, J = 8.8 Hz), 3.84 (3H, s), 3.12 (2H, s), 1.41 (6H, s).

To a solution of the acyl chloride (21.5 g, 83.2 mmol) in 250 mL of CH_2Cl_2 at 0 °C was added dropwise a solution of $SnCl_4$ (21.7 g, 83.2 mmol) in 30 mL of CH_2Cl_2. After 2 h the reaction was quenched by the slow addition of 150 mL H_2O. The organic layer was washed with 1 M aqueous HCl, 5% aqueous NaOH, H_2O, and finally saturated aqueous NaCl before being dried over $MgSO_4$. Concentration under reduced pressure and vacuum distillation of the residual oil (bulb-to-bulb, 125–135 °C, 5 mm/Hg) afforded 14.48 g (78%) of the title compound as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (1H, d, J = 2.9 Hz), 7.14 (1H, d, J = 8.6 Hz), 7.03 (1H, dd, J = 2.8, 8.3 Hz), 3.83 (3H, s), 2.87 (2H, s), 1.46 (6H, s).

2,2-Dimethyl-4-oxo-thiochroman-6-yl trifluoromethanesulfonate (19). To a solution of 6-methoxy-2,2-dimethyl-thiochroman-4-one (6.0 g, 27 mmol) in 50 mL CH_2Cl_2 cooled to −23 °C was added BBr_3 (20.0 g, 80.0 mmol; 80.0 mL of a 1 M solution in CH_2Cl_2) over a 20 min period. After stirring for 5 h at −23 °C the solution was cooled to −78 °C and quenched by the slow addition of 50 mL of H_2O. Upon warming to room temperature the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl before being dried over $MgSO_4$. Removal of the solvents under reduced pressure gave a green-brown solid which upon recrystalization (Et_2O/hexanes) afforded 2.25 g (40%) of the intermediate phenol as a light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (1H, d, J = 2.8 Hz), 7.15 (1H, d, J = 8.5 Hz), 7.01 (1H, dd, J = 2.8, 8.5 Hz), 2.87 (2H, s), 1.46 (6H, s).

To a solution of the phenol (165.0 mg, 0.79 mmol) in 5.0 mL of anhydrous pyridine at 0 °C was added trifluoromethanesulfonic anhydride (245.0 mg, 0.87 mmol). After 4 h at 0 °C the solution was concentrated and the residual oil dissolved in Et_2O, washed with H_2O followed by saturated aqueous NaCl, and dried over

$MgSO_4$. Removal of the solvents under reduced pressure and column chromatography (5% EtOAc/hexanes) afforded 126.0 mg (47%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (1H, s), 7.32 (2H, s), 2.90 (2H, s), 1.49 (6H, s).

Ethyl 4-[(2,2-dimethyl-4-oxo-thiochroman-6-yl)ethynyl]-benzoate (20). A solution of **19** (2.88 g, 8.50 mmol) in 10 mL Et_3N and 20.0 mL DMF was sparged with argon for 10 min. To this solution was added trimethylsilylacetylene (4.15 g, 42.0 mmol) and bis(triphenylphosphine)-palladium(II) chloride (298.0 mg, 0.425 mmol). The solution was heated to 95 °C for 5 h, cooled to room temperature, and diluted with H_2O. Extraction with EtOAc was followed by washing the combined organic layers with H_2O and saturated aqueous NaCl and drying over $MgSO_4$. Concentration of the dry solution under reduced pressure and isolation of the product by column chromatography (3% EtOAc/hexanes) afforded 2.23 g (91%) of 2,2-dimethyl-6-trimethylsilanylethynyl-thiochroman-4-one as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (1H, d, J = 1.9 Hz), 7.34 (1H, dd, J = 1.9, 8.1 Hz), 7.15 (1H, d, J = 8.1 Hz), 2.85 (2H, s), 1.45 (6H, s), 0.23 (9H, s).

A solution of 2,2-dimethyl-6-trimethylsilanylethynyl-thiochroman-4-one (110.0 mg, 0.38 mmol) and K_2CO_3 (40.0 mg, 0.29 mmol) in 10.0 mL MeOH was stirred overnight at room temperature. The solution was diluted with H_2O and extracted with Et_2O. The combined organic layers were washed with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded 81 mg (99%) of 6-ethynyl-2,2-dimethylthiochroman-4-one as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 (1H, d, J = 1.9 Hz), 7.46 (1H, dd, J = 1.9, 8.1 Hz), 7.18 (1H, d, J = 8.1 Hz), 3.08 (1H, s), 2.86 (2H, s), 1.46 (6H, s)

A solution of 6-ethynyl-2,2-dimethylthiochroman-4-one (82.0 mg, 0.38 mmol) and ethyl 4-iodobenzoate (104.9 mg, 0.38 mmol) in 5.0 mL Et_3N was purged with argon for 10 min. To this solution was added $Pd(PPh_3)_2Cl_2$ (88.0 mg, 0.12 mmol) and copper(I) iodide (22.9 mg, 0.12 mmol). After sparging for an additional 5 min with argon the solution was stirred overnight at room temperature. The reaction mixture was filtered through a pad of Celite using an Et_2O wash. Concentration of the filtrate under reduced pressure, followed by column chromatography of the residual solid afforded 100 mg (72%) of the title compound as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (1H, d, J = 1.8 Hz), 8.00 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.4 Hz), 7.53 (1H, dd, J = 1.8, 8.2 Hz), 7.21 (1H, d, J = 8.2 Hz), 4.37 (2H, q, J = 7.1 Hz), 2.88 (2H, s), 1.47 (6H, s), 1.39 (3H, t, J = 7.1 Hz).

Ethyl 4-[(2,2-dimethyl-4-oxo-thiochroman-6-yl)ethynyl]-2-fluorobenzoate (21). A solution of 6-ethynyl-2,2-dimethylthiochroman-4-one (1.37 g, 6.34 mmol) and ethyl 2-fluro-4-iodobenzoate (1.86 g, 6.34 mmol) in 40.0 mL Et_3N was purged with argon for 20 min. To this solution was added $Pd(PPh_3)_2Cl_2$ (1.05 g, 1.5 mmol) and copper(I) iodide (286.0 mg, 1.5 mmol). After sparging for an additional 10 min with argon, the solution was stirred overnight at room temperature. The reaction mixture was filtered through a pad of Celite using an Et_2O wash. Concentration of the filtrate under reduced pressure followed by column chromatography (5% EtOAc/hexanes) of the residual solid afforded 1.8 g (78%) the title compound as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (1H, d, J = 1.9 Hz), 7.92 (1H, d, J = 7.8 Hz), 7.52 (1H, dd, J = 1.9, 8.2 Hz), 7.36–7.24 (3H, m), 4.41 (2H, q, J = 7.1 Hz), 2.90 (2H, s), 1.50 (6H, s), 1.41 (3H, t, J = 7.1 Hz).

Ethyl 6-[(2,2-dimethyl-4-oxo-thiochroman-6-yl)ethynyl]-nicotinate (22). A solution of 6-ethynyl-2,2-dimethylthiochroman-4-one (510.0 mg, 2.36 mmol) and ethyl 6-iodonicotinate (654.0 mg, 2.36 mmol) in 20.0 mL Et_3N was purged with argon for 20 min. To this solution was added $Pd(PPh_3)_2Cl_2$ (425.0 mg, 0.60 mmol) and copper(I) iodide (115.0 mg, 0.60 mmol). After sparging for an additional 10 min with argon, the solution was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (20 mL) and filtered through a pad of Celite using an Et_2O wash. Concentration of the filtrate under reduced pressure, followed by column chromatography (10 to 20% EtOAc/hexanes) of the residual solid afforded 675.0 mg (78%) of the title compound as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.20 (1H, d, J = 1.0 Hz), 8.34 (1H, d, J = 1.8 Hz), 8.29 (1H, dd, J = 2.2, 8.2 Hz), 7.60 (2H, m), 7.25 (1H, d, J = 8.4 Hz), 4.43 (2H, q, J = 7.1 Hz), 2.90 (2H, s), 1.49 (6H, s), 1.43 (3H, t, J = 7.1 Hz).

Ethyl 4-((2,2-dimethyl-4-trifluoromethanesulfonyloxy-(2*H*)-thiochromen-6-yl)ethynyl)-benzoate (41). A solution of sodium bis(trimethylsilyl)amide (1.12 g, 6.13 mmol) in 16.2 mL of THF was cooled to −78 °C and a solution of **20** (1.86 g, 5.10 mmol) in 15.0 mL of THF slowly added. After 30 min a solution of 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-pyridine (2.40 g, 6.13 mmol) in 10 mL of THF. After 5 min the solution was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with 5% aqueous NaOH and H_2O before being dried ($MgSO_4$) and concentrated under reduced pressure. The title compound, 1.53 g (61%), was isolated by column chromatography (2% EtOAc/hexanes) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (2H, d, J = 8.4 Hz), 7.61 (1H, d, J = 1.8 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.41 (1H, dd, J = 1.8, 8.1Hz), 7.29 (1H, d, J = 8.1 Hz), 5.91 (1H, s), 4.39 (2H, q, J = 7.1 Hz), 1.53 (6H, s), 1.41 (3H, t, J = 7.1 Hz).

Ethyl 4-(2,2-dimethyl-4-trifluoromethanesulfonyloxy-(2*H*)-thiochromen-6-ylethynyl)-2-fluorobenzoate (42). A solution of sodium bis(trimethylsilyl)amide (0.82 g, 5.90 mmol) in 16.2 mL of THF was cooled to −78 °C and a solution of **21** (1.88 g, 4.91 mmol) in 15.0 mL slowly added. After 30 min a solution of 2-[*N*,*N*-bis-(trifluoromethanesulfonyl)amino]-5-pyridine (2.32 g, 5.90 mmol) in 10 mL of THF was added. After 5 min the solution was warmed to room temperature and stirred overnight. The reaction was quenched by the addition

of saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with 5% aqueous NaOH and H_2O before being dried ($MgSO_4$) and concentrated under reduced pressure. The title compound, 1.80 g (71%), was isolated by column chromatography (5% EtOAc/hexanes) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.93 (1H, d, $J=7.8$ Hz), 7.61 (1H, d, $J=1.6$ Hz), 7.43–7.27 (4H, m), 5.92 (1H, s), 4.41 (2H, q, $J=7.1$ Hz), 1.53 (6H, s), 1.42 (3H, t, $J=7.1$ Hz).

Ethyl 6-(2,2-dimethyl-4-trifluoromethanesulfonyloxy-(2*H*)-thiochromen-6-ylethynyl)-nicotinate (43). A solution of sodium bis(trimethylsilyl)amide (284.2 mg, 1.55 mmol) in 3.6 mL of THF was cooled to −78 °C and a solution of **22** (480.0 mg, 1.31 mmol) in 3.0 mL THF slowly added. After 30 min a solution of 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-pyridine (608.0 mg, 1.55 mmol) in 3.0 mL of THF. After 5 min the solution was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with 5% aqueous NaOH and H_2O before being dried ($MgSO_4$) and concentrated under reduced pressure. The title compound was isolated by column chromatography (20% EtOAc/hexanes) as a yellow solid, 566.0 mg (87%). ^1H NMR (300 MHz, $CDCl_3$) δ: 9.21 (1H, d, $J=2.0$ Hz), 8.30 (1H, dd, $J=2.0$, 8.1 Hz), 7.68 (1H, d, $J=1.5$ Hz), 7.61 (1H, d, $J=8.2$ Hz), 7.49 (1H, dd, $J=1.7$, 8.1 Hz), 7.31 (1H, d, $J=8.2$ Hz), 5.92 (1H, s), 4.41 (2H, q, $J=7.1$ Hz), 1.53 (6H, s), 1.43 (3H, t, $J=7.1$ Hz).

Ethyl 4-[[4-phenyl-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (44). Following general procedure A, bromobenzene (190.0 mg, 1.18 mmol), *tert*-butyllithium (151.2 mg, 2.36 mmol, 1.4 mL of a 1.7 M solution in pentane), $ZnCl_2$ (225.0 mg, 1.4 mmol) **41** (200.0 mg, 0.40 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol). The title compound, 155.0 mg (91%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (2H, d, $J=8.4$ Hz), 7.52 (2H, d, $J=8.4$ Hz), 7.42–7.24 (8H, m), 5.78 (1H, s), 4.38 (2H, q, $J=7.1$ Hz), 1.50 (6H, s), 1.40 (3H, t, $J=7.1$ Hz).

Ethyl 4-[[4-(4-methylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (45). Following general procedure A and using 4-methylbromobenzene (203.0 mg, 1.15 mmol) in 2.0 mL of THF, *tert*-butyllithium (147.4 mg, 2.30 mmol, 1.4 mL of a 1.7 M solution in pentane), $ZnCl_2$ (219.4 mg, 1.4 mmol) in 4.0 mL THF, **41** (230.0 mg, 0.46 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF, afforded 165.0 mg (82%) of the title compound as a colorless solid after column chromatography (5% EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.98 (2H, d, $J=8.4$ Hz), 7.51 (2H, d, $J=8.4$ Hz), 7.35–7.21 (7H, m), 5.84 (1H, s), 4.38 (2H, q, $J=7.1$ Hz), 2.42 (3H, s), 1.48 (6H, s), 1.40 (3H, s).

Ethyl 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (46). Following general procedure A and 4-ethylbromobenzene (670.9 mg, 3.63 mmol) in 4.0 mL of THF, *tert*-butyllithium (464.5 mg, 7.25 mmol, 4.26 mL of a 1.7 M solution in pentane), $ZnCl_2$ (658.7 mg, 4.83 mmol) in 8.0 mL THF, **41** (1.20 g, 2.42 mmol) and $Pd(PPh_3)_4$ (111.7 mg, 0.097 mmol) in 8.0 mL THF. The title compound, 943.5 mg (87%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (2H, d, $J=8.2$ Hz), 7.52 (2H, d, $J=8.4$ Hz), 7.40 (5H, m), 7.35 (2H, m), 5.85 (1H, s), 4.38 (2H, q, $J=7.1$ Hz), 2.72 (2H, q, $J=7.6$ Hz), 1.48 (6H, s), 1.40 (3H, t, $J=7.1$ Hz), 1.30 (3H, t, $J=7.6$ Hz).

Ethyl 4-[[4-(4-isopropylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (47). Following general procedure A and 4-isopropylbromobenzene (161.0 mg, 0.81 mmol) in 2.0 mL of THF, *tert*-butyllithium (103.8 mg, 1.62 mmol, 0.95 mL of a 1.7 M solution in pentane), $ZnCl_2$ (175.5 mg, 1.3 mmol) in 4.0 mL THF, **41** (160.0 mg, 0.32 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 128.0 mg (85%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (2H, d, $J=8.4$ Hz), 7.53 (2H, d, $J=8.1$ Hz), 7.38–7.22 (7H, m), 5.86 (1H, s), 4.38 (2H, q, $J=7.1$ Hz), 2.98 (1H, hept, 7.0 Hz), 1.49 (6H, s), 1.43 (3H, t, $J=7.1$ Hz), 1.32 (6H, d, $J=7.0$ Hz).

Ethyl 4-[[4-(4-*tert*-butylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (48). Following general procedure A and 4-*tert*-butylbromobenzene (149.0 mg, 0.70 mmol) in 2.0 mL of THF, *tert*-butyllithium (92.6 mg, 1.44 mmol, 0.85 mL of a 1.7 M solution in pentane), $ZnCl_2$ (133.0 mg, 0.98 mmol) in 4.0 mL THF, **41** (140.0 mg, 0.28 mmol) $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 94.0 mg (70%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.98 (2H, d, $J=8.3$ Hz), 7.52 (2H, d, $J=8.3$ Hz), 7.43–7.22 (7H, m), 5.86 (1H, s), 4.38 (2H, q, $J=7.1$ Hz), 1.47 (6H, s), 1.40 (3H, t, $J=7.1$ Hz), 1.38 (9H, s).

Ethyl 4-[[4-(6-methyl-pyridin-3-yl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (49). Following general procedure A and 5-bromo-2-methylpyridine[30] (220.0 mg, 1.28 mmol) in 2.0 mL of THF, *tert*-butyllithium (164.0 mg, 2.56 mmol, 1.5 mL of a 1.7 M solution in pentane), $ZnCl_2$ (348.0 mg, 2.56 mmol) in 4.0 mL THF, **41** (172.0 mg, 0.35 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 109.0 mg (72%) was isolated by column chromatography (5% EtOAc/hexanes) as a pale-yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.45 (1H, d, $J=2.0$ Hz), 8.00 (2H, d, $J=8.5$ Hz), 7.52 (2H, d, $J=8.5$ Hz), 7.49 (1H, dd, $J=2.3$, 8.1 Hz), 7.36 (2H, m), 7.20 (1H, d, $J=8.1$ Hz), 7.16 (1H, d, $J=1.5$ Hz), 5.86 (1H, s), 4.38 (2H, q, $J=7.1$ Hz), 2.63 (3H, s), 1.50 (6H, s), 1.40 (3H, t, $J=7.1$ Hz).

Ethyl 4-[[4-(5-methyl-thiophen-2-yl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (50). Following general procedure A and 2-methylthiophene (100.0 mg, 1.00 mmol) in 2.0 mL of THF, *n*-butyllithium (64.0 mg,

1.00 mmol, 0.63 mL of a 1.6 M solution in hexanes), $ZnCl_2$ (218.0 mg, 1.60 mmol) in 3.0 mL THF, **41** (200.0 mg, 0.40 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 170.0 mg (96%), was isolated by column chromatography (5% EtOAc/hexanes) as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (2H, d, J = 8.3 Hz), 7.63 (1H, s), 7.55 (2H, d, J = 8.3 Hz), 7.35 (2H, s), 6.82 (1H, d, J = 3.5 Hz), 6.72 (1H, m), 6.00 (1H, s), 4.38 (2H, q, J = 7.1 Hz), 2.52 (3H, s), 1.46 (6H, s), 1.40 (2H, t, J = 7.1 Hz).

Ethyl 4-[[4-(5-ethyl-thiophen-2-yl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (51). Following general procedure A and 2-ethylthiophene (112.0 mg, 1.00 mmol) in 2.0 mL of THF, *n*-butyllithium (64.0 mg, 1.00 mmol, 0.63 mL of a 1.6 M solution in hexanes), $ZnCl_2$ (218.0 mg, 1.60 mmol) in 3.0 mL THF, **41** (200.0 mg, 0.40 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 29.0 mg (16%), was isolated by HPLC (1.25% EtOAc/hexanes) as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (2H, d, J = 8.4 Hz), 7.65 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.35 (2H, s), 6.84 (1H, d, J = 3.5 Hz), 6.77 (1H, m), 6.02 (1H, s), 4.39 (2H, q, J = 7.1 Hz), 2.88 (2H, q, J = 7.6 Hz), 1.46 (6H, s), 1.41 (2H, t, J = 7.1 Hz), 1.35 (2H, t, J = 7.6 Hz).

Ethyl 4-[[4-(5-*tert*-butyl-thiophen-2-yl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoate (52). Following general procedure A and 2-*tert*-butylthiophene[31] (105.0 mg, 0.75 mmol) in 2.0 mL of THF, *n*-butyllithium (48.1 mg, 0.75 mmol, 0.47 mL of a 1.6 M solution in hexanes), $ZnCl_2$ (163.2 mg, 1.20 mmol) in 3.0 mL THF, **41** (200.0 mg, 0.40 mmol) and $Pd(PPh_3)_4$ (20.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 110.0 mg (76%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (2H, d, J = 8.3 Hz), 7.68 (1H, s), 7.56 (2H, d, J = 8.3 Hz), 7.36 (2H, m), 6.82 (2H, m), 6.04 (1H, s), 4.39 (2H, q, J = 7.1 Hz), 1.46 (6H, s), 1.43 (9H, s), 1.41 (2H, t, J = 7.1 Hz).

Ethyl 4-[[4-(4-methylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-2-fluorobenzoate (53). Following general procedure A and 4-methylbromobenzene (280.0 mg, 1.64 mmol) in 2.0 mL of THF, *tert*-butyllithium (209.5 mg, 3.27 mmol, 1.9 mL of a 1.7 M solution in pentane), $ZnCl_2$ (680.0 mg, 5.0 mmol) in 4.0 mL THF, **42** (200.0 mg, 0.39 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 177.0 mg (79%), was isolated by column chromatography (5% EtOAc/hexanes) as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (1H, d, J = 7.8 Hz), 7.28–7.18 (9H, m), 5.84 (1H, s), 4.39 (2H, q, J = 7.1 Hz), 2.42 (3H, s), 1.48 (6H, s), 1.40 (3H, t, J = 7.1 Hz).

Ethyl 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-2-fluorobenzoate (54). Following general procedure A and 4-ethylbromobenzene (185.0 mg, 1.00 mmol) in 2.0 mL of THF, *tert*-butyllithium (128.5 mg, 2.0 mmol, 1.2 mL of a 1.7 M solution in pentane), $ZnCl_2$ (204.5 mg, 1.5 mmol) in 4.0 mL THF, **42** (200.0 mg, 0.39 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 158.0 mg (86%), was isolated by column chromatography (5% EtOAc/hexanes) as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (1H, d, J = 7.8 Hz), 7.39–7.20 (9H,m), 5.86 (1H, s), 4.40 (2H, q, J = 7.1 Hz), 2.72 (2H, q, J = 7.6 Hz), 1.49 (6H, s), 1.40 (3H, t, J = 7.1 Hz), 1.30 (3H, t, J = 7.6 Hz).

Ethyl 6-[[4-(4-methylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-nicotinate (55). Following general procedure A and 4-methylbromobenzene (280.0 mg, 1.64 mmol) in 2.0 mL of THF, *tert*-butyllithium (209.5 mg, 3.27 mmol, 1.9 mL of a 1.7 M solution in pentane), $ZnCl_2$ (680.0 mg, 5.0 mmol) in 4.0 mL THF, **43** (120.0 mg, 0.24 mmol) and $Pd(PPh_3)_4$ (20.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 80.0 mg (76%), was isolated by column chromatography (10 to 15% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.15 (1H, d, J = 2.2 Hz), 8.23 (1H, dd, J = 2.1, 8.0 Hz), 7.51 (1H, d, J = 8.1 Hz), 7.40–7.32 (3H, m), 7.18 (4H, m), 5.83 (1H, s), 4.40 (2H, q, J = 7.1 Hz), 2.40 (3H, s), 1.47 (6H, s), 1.40 (3H, t, J = 7.1 Hz).

Ethyl 6-[[4-(4-ethylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-nicotinate (56). Following general procedure A and 4-ethylbromobenzene (300.0 mg, 1.62 mmol) in 2.0 mL of THF, *tert*-butyllithium (207.6 mg, 3.24 mmol, 1.9 mL of a 1.7 M solution in pentane), $ZnCl_2$ (408.0 mg, 3.0 mmol) in 4.0 mL THF, **43** (178.0 mg, 0.36 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.02 mmol) in 2.0 mL THF. The title compound was isolated by column chromatography (10 to 15% EtOAc/hexanes) and recrystalization from CH_3CN to give 136.0 mg (83%) of pale yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.15 (1H, s), 8.23 (1H, dd, J = 2.2, 8.2 Hz), 7.51 (1H, d, J = 8.1 Hz), 7.49–7.34 (3H, m), 7.24–7.17 (4H, m), 5.83 (1H, s), 4.40 (2H, q, J = 7.1 Hz), 2.70 (2H, q, J = 7.6 Hz), 1.47 (6H, s), 1.40 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz).

4-[[4-Phenyl-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (57). Following general procedure B, **44** (105.0 mg, 0.247 mmol) in 3.0 mL THF and 3.0 mL EtOH was added NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.00 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.48–7.29 (7H, m), 7.18 (1H, d, J = 1.3 Hz), 5.96 (1H, s), 1.48 (6H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 141.3, 138.8, 135.9, 135.5, 133.9, 132.2, 131.5, 131.0, 130.9, 130.5, 129.9, 129.4, 128.9, 128.7, 128.3, 119.9, 92.5, 89.2, 41.7. Anal. calcd for $C_{26}H_{20}O_2S$: C, 78.76; H, 5.08. Found: C, 78.44; H, 4.99.

4-[[4-(4-Methylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (58). Following general procedure B, **45** (126.0 mg, 0.287 mmol) in 3.0 mL THF and 3.0 mL EtOH, NaOH (160.0 mg, 4.0 mmol, 2.0 mL of a 2 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 85.0 mg (72%) the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz,

acetone-d_6) δ: 8.00 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 7.45–7.38 (2H, m), 7.28–7.17 (5H, m), 5.92 (1H, s), 2.37 (3H, s), 1.47 (6H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 138.7, 138.4, 138.3, 135.9, 135.1, 134.1, 132.2, 131.4, 131.1, 130.9, 130.5, 130.0, 129.8, 128.9, 128.4, 119.8, 92.6, 89.1, 41.7, 21.1. Anal. calcd for $C_{27}H_{22}O_2S$: C, 78.99; H, 5.40. Found: C, 78.66; H, 5.21.

4-[[4-(4-Ethylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (59). Following general procedure B and **46** (940.0 mg, 2.08 mmol) in 10.0 mL THF and 5.0 mL EtOH, and NaOH (416.0 mg, 10.4 mmol, 5.2 mL of a 2 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 786.0 mg (89%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.01 (2H, d, J = 8.3 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.42 (2H, m), 7.29 (2H, m), 7.22 (3H, m), 5.94 (1H, s), 2.69 (2H, q, J = 7.7 Hz), 1.47 (6H, s), 1.25 (3H, t, J = 7.7 Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 144.8, 138.7, 138.6, 135.9, 135.1, 134.1, 132.2, 131.4, 131.0, 130.9, 130.5, 129.9, 128.9, 128.8, 128.4, 119.8, 92.6, 89.1, 41.7, 30.1, 29.0, 15.9.

4-[[4-(4-Isopropylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (60). Following general procedure B and **47** (89.0 mg, 0.19 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (80.0 mg, 2.0 mmol, 2.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 78.0 mg (93%) of the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.00 (2H, d, J = 8.4 Hz), 7.58 (2H, d, J = 8.4 Hz), 7.45–7.21 (7H, m), 5.93 (1H, s), 2.95 (1H, hept, J = 7.0 Hz), 1.47 (6H, s), 1.25 (6H, d, J = 7.0 Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 149.4, 138.7, 135.9, 135.2, 134.0, 132.2, 131.5, 131.0, 130.9, 130.5, 129.8, 128.9, 128.4, 127.3, 119.8, 92.6, 89.1, 41.7, 34.5, 24.2. Anal. calcd for $C_{29}H_{26}O_2S$: C, 79.42; H, 5.98. Found: C, 79.15; H, 5.80.

4-[[4-(4-*tert*-Butylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (61). Following general procedure B and **48** (65.0 mg, 0.135 mmol) in 2.0 mL THF and 2.0 mL EtOH, and NaOH (80.0 mg, 2.0 mmol, 2.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 33.0 mg (54%) of the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.01 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.45 (4H, m), 7.24 (3H, m), 5.93 (1H, s), 1.47 (6H, s), 1.34 (9H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 151.6, 138.6, 138.3, 135.9, 135.3, 134.0, 132.2, 131.5, 131.0, 130.5, 129.6, 129.0, 128.4, 126.2, 119.8, 92.6, 89.2, 41.7, 35.1, 31.6. Anal. calcd for $C_{30}H_{28}O_2S$: C, 79.61; H, 6.24. Found: C, 79.25; H, 5.92.

4-[[4-(6-Methylpyridin-3-yl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (62). Following general procedure B and **49** (70.0 mg, 0.159 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from acetone to give 60.0 mg (92%) of the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.36 (1H, d, J = 2.1 Hz), 7.91 (2H, d, J = 8.3 Hz), 7.60 (2H, d, J = 8.3 Hz), 7.56 (1H, dd, J = 2.1 8.0 Hz), 7.45 (2H, m), 7.31 (1H, d, J = 8.0 Hz), 7.06 (1H, s), 6.06 (1H, s), 2.51 (3H, s), 1.44 (6H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 166.6, 157.5, 148.5, 136.6, 135.6, 134.4, 133.9, 132.4, 132.1, 131.5, 130.9, 130.5, 129.4, 129.3, 128.3, 126.4, 122.8, 118.5, 91.5, 88.6, 41.0, 28.4, 23.8. Anal. calcd for $C_{26}H_{21}NO_2S$: C, 75.89; H, 5.14. Found: C, 75.68; H, 4.92.

4-[[4-(5-Methyl-thiopen-2-yl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (63). Following general procedure B and **50** (143.0 mg, 0.322 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (160.0 mg, 4.0 mmol, 4.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 110.0 mg (82%) of the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.03 (2H, d, J = 8.4 Hz), 7.63 (2H, d, J = 8.3 Hz), 7.60 (1H, s), 7.44 (2H, s), 6.87 (1H, d, J = 3.5 Hz), 6.79 (1H, m), 6.10 (1H, s), 2.49 (3H, s), 1.45 (6H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 140.7, 140.3, 135.9, 135.4, 133.4, 132.3, 132.2, 131.7, 131.1, 131.0, 130.5, 129.0, 128.4, 127.8, 126.5, 120.0, 92.5, 89.3, 41.7, 28.7, 15.2. Anal. calcd for $C_{25}H_{20}O_2S_2$: C, 72.08; H, 4.84. Found: C, 71.80; H, 4.84.

4-[[4-(5-Ethyl-thiophen-2-yl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (64). Following general procedure B and **51** (23.0 mg, 0.05 mmol) in 1.0 mL THF and 1.0 mL EtOH, and NaOH (40.0 mg, 1.0 mmol, 1.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 15.5 mg (72%) of the title compound as an orange solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.03 (2H, d, J = 8.3 Hz), 7.63 (2H, d, J = 8.3 Hz), 7.61 (1H, s), 7.44 (2H, s), 6.90 (1H, d, J = 3.5 Hz), 6.83 (1H, d, J = 3.5 Hz), 6.10 (1H, s), 2.86 (2H, q, J = 7.6 Hz), 1.45 (6H, s), 1.30 (3H, t, J = 7.6 Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 148.3, 140.0, 136.0, 135.5, 133.4, 132.3, 132.2, 131.7, 131.1, 130.0, 130.6, 129.1, 128.4, 127.6, 124.8, 120.0, 92.6, 89.3, 41.7, 28.7, 23.9, 16.2.

4-[[4-(5-*tert*-Butylthiopen-2-yl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-benzoic acid (65). Following general procedure B and **52** (88.0 mg, 0.181 mmol) in 2.0 mL THF and 2.0 mL EtOH, and NaOH (160.0 mg, 4.0 mmol, 4.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 68.0 mg (82%) of the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.03 (2H, d, J = 8.3 Hz), 7.63 (2H, d, J = 8.3 Hz), 7.62 (1H, s), 7.44 (2H, d, J = 1.2 Hz), 6.87 (2H, s), 6.11 (1H, s), 1.45 (6H, s), 1.39 (9H, s). ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 157.9, 139.5, 136.0, 135.4, 133.3, 132.3, 132.2, 131.7, 131.1, 131.0, 130.6, 129.1, 128.4, 127.3, 122.8, 120.0, 92.6, 89.3, 41.7, 35.2, 32.7, 32.6, 28.7. Anal. calcd for $C_{28}H_{26}O_2S_2$: C, 73.32; H, 5.71. Found: C, 72.97; H, 5.62.

4-[[4-(4-Methylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-2-fluorobenzoic acid (66). Following general procedure B and **53** (100.0 mg, 0.219 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (80.0 mg, 2.0 mmol,

2.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 78.0 mg (83%) of the title compound as a pale-yellow solid. ^1H NMR (300 MHz, acetone-d_6) δ: 7.94 (1H, d, $J=7.8$ Hz), 7.43–7.17 (9H, m), 5.93 (1H, s), 2.38 (3H, s), 1.47 (6H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 164.6 (d, $J=1.5$ Hz), 162.4 (d, $J=259.1$ Hz), 138.6, 138.3 (d, $J=8.8$ Hz), 136.3, 135.1, 134.1, 133.4, 133.3, 131.5, 131.1, 130.1 (d, $J=10.4$ Hz), 130.0, 129.8, 129.0, 128.0 (d, $J=3.7$ Hz), 120.2 (d, $J=24.4$ Hz), 119.6 (d, $J=10.7$ Hz), 119.4, 93.5, 87.9 (d, $J=2.8$ Hz), 41.8, 21.2. Anal. calcd for $C_{27}H_{21}FO_2S$: C, 75.68; H, 4.94. Found: C, 75.77; H, 4.87.

4-[[4-(4-Ethylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-2-fluorobenzoic acid (67). Following general procedure B and **54** (125.0 mg, 0.266 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 100.0 mg (86%) of the title compound as a pale-yellow solid. ^1H NMR (300 MHz, acetone-d_6) δ: 7.94 (1H, d $J=7.8$ Hz), 7.43–7.20 (9H, m), 5.93 (1H, s), 2.68 (2H, q, $J=7.6$ Hz), 1.47 (6H, s), 1.24 (3H, t, $J=7.6$ Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 164.6 (d, $J=3.2$ Hz), 162.4 (d, $J=259.3$ Hz), 144.8, 138.6 (d, $J=11.0$ Hz), 136.4, 135.2, 134.1, 133.3, 131.5, 131.1, 130.1 (d, $J=10.7$ Hz), 129.8, 129.0, 128.8, 128.0 (d, $J=3.5$ Hz), 120.2 (d, $J=24.4$ Hz), 119.5 (d, $J=10.1$ Hz), 119.4, 93.5, 87.9 (d, $J=3.1$ Hz), 41.8, 41.6, 30.6, 15.9.

6-[[4-(4-Methylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-nicotinic acid (68). Following general procedure B and **55** (66.0 mg, 0.15 mmol) in 2.0 mL THF and 2.0 mL EtOH, and NaOH (80.0 mg, 2.0 mmol, 2.0 mL of a 1 M aqueous solution). The solvent was removed under reduced pressure to give the title compound as a yellow solid, 50.0 mg (81%). ^1H NMR (300 MHz, acetone-d_6) δ: 9.09 (1H, d, $J=1.4$ Hz), 8.30 (1H, dd, $J=2.0$, 8.1 Hz), 7.65 (1H, d, $J=8.1$ Hz), 7.46 (2H, s), 7.24 (5H, m), 5.94 (1H, s), 2.37 (3H, s), 1.48 (6H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.0, 151.8, 147.5, 138.6, 138.4, 138.2, 138.1, 136.8, 135.1, 134.1, 131.6, 131.5, 130.0, 129.8, 129.0, 127.5, 125.9, 118.9, 91.7, 89.3, 21.1.

6-[[4-(4-Ethylphenyl)-2,2-dimethyl-(2*H*)-thiochromen-6-yl]-ethynyl]-nicotinic acid (69). Following general procedure B and **56** (110.0 mg, 0.24 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The solvent was removed under reduced pressure to give 100 mg (96%) of the title compound as a colorless solid. ^1H NMR (300 MHz, acetone-d_6) δ: 9.08 (1H, d, $J=2.0$ Hz), 8.30 (1H, dd, $J=2.2$, 8.2 Hz), 7.66 (1H, d, $J=8.2$ Hz), 7.46 (2H, s), 7.31–7.21 (5H, m), 5.95 (1H, s), 2.69 (2H, q, $J=7.6$ Hz), 1.48 (6H, s), 1.25 (3H, t, $J=7.6$ Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 165.9, 151.8, 147.5, 144.8, 138.6, 138.5, 138.1, 136.8, 135.2, 134.1, 131.7, 131.5, 129.9, 129.0, 128.8, 127.6, 125.8, 118.9, 91.8, 89.3, 41.8, 29.1, 15.9.

4-Bromophenylacetate (24). To a solution of 4-bromophenol (20.0 g, 0.121 mol) in 200 mL CH_2Cl_2 was added triethylamine (14.0 g, 0.139 mol) followed by acetyl chloride (9.53 g, 0.121 mol) in small portions at room temperature. After stirring for 21 h the mixture was poured into 200 mL H_2O. The organic layer was washed with 5% aqueous NaOH, H_2O, and dried over $MgSO_4$. Removal of the solvent under reduced pressure and distillation of the residue afforded 20.6 g (83%) of the product as a colorless oil, bp 93–95 °C/2 mm.

2-Hydroxy-5-bromo-acetophenone (25). A mixture of $AlCl_3$ (6.20 g, 46.50 mmol) **24** (10.0 g, 46.50 mmol) was heated to 150 °C for 30 min while a stream of argon was passed over the molten solid. Upon cooling to room temperature the orange solid was carefully treated with 100 mL of H_2O and 100 mL of 10% aqueous HCl. The resulting mixture was extracted with EtOAc and the combined organic layers washed with H_2O and saturated aqueous NaCl before being dried over Na_2SO_4. Concentration of the solution under reduced pressure afforded a tan solid which after recrystallization from *i*-PrOH provided 7.18 g (72%) of the title compound as an off-white crystalline solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 12.17 (1H, s), 7.84 (1H, d, $J=2.6$ Hz), 7.55 (1H, dd, $J=2.5$, 9.0 Hz), 6.90 (1H, d, $J=8.9$ Hz), 2.64 (3H, s).

2,2-Dimethyl-6-bromo-chroman-4-one (26). To a solution of piperidine (2.83 g, 33.25 mmol) in 45 mL benzene was added trifluoroacetic acid (344.6 mg, 3.02 mmol) as a solution in 4.0 mL of benzene. Acetone (8.78 g, 151.3 mmol) was added followed by **25** (6.50 g, 30.23 mmol). The resulting solution was heated to reflux in a flask fitted with a Dean–Stark trap. After 24 h, an additional 2.5 equiv of acetone and 0.1 equiv of trifluoroacetic acid were added. After a total of 43 h the reaction was cooled to room temperature and diluted with EtOAc. The solution was washed with 1 M aqueous HCl, H_2O, and saturated aqueous NaCl before being dried ($MgSO_4$) and concentrated under reduced pressure. Distillation of the residual oil (bulb-to-bulb) afforded 4.80 g (62%) of the title compound as a clear yellow oil, bp 105–115 °C/5 mm. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.97 (1H, d, $J=2.6$ Hz), 7.54 (1H, dd, $J=2.6$, 8.7 Hz), 6.84 (1H, d, $J=8.8$ Hz), 2.72 (2H, s), 1.46 (6H, s).

2,2-Dimethyl-6-trimethylsilanylethynyl-chroman-4-one (27). A solution of **26** (4.30 g, 16.85 mmol) and copper (I) iodide (321 mg, 0.17 mmol) in 55.0 mL Et_3N was sparged with argon for 30 min. To this solution was added trimethylsilylacetylene (4.66 g, 50.56 mmol) and bis(triphenylphosphine)palladium(II) chloride (1.18 g, 0.17 mmol). The mixture was heated to 70 °C for 26 h, cooled to room temperature, and diluted with Et_2O (100 mL). The resulting mixture was filtered through a pad of Celite using an Et_2O wash and the filtrate washed with H_2O, a solution of NH_4OH saturated aqueous NH_4Cl (9/1), H_2O, 1 M aqueous HCl, H_2O and saturated aqueous NaCl before being dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (5% EtOAc/hexanes) of the residual oil afforded 4.09 g (89%) of the product as a yellow waxy solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (1H, d, $J=2.1$ Hz), 7.53 (1H, dd, $J=2.2$, 8.6 Hz), 6.86 (1H, d, $J=8.6$ Hz), 2.72 (2H, s), 1.45 (6H, s), 0.24 (9H, s).

Ethyl 4-[(2,2-dimethyl-4-oxo-chroman-6-yl)ethynyl]-benzoate (28). To a solution of **27** (4.05 g, 14.87 mmol) in 60.0 mL of MeOH was added K_2CO_3 (410.9 mg, 2.97 mmol) The resulting mixture stirred at room temperature for 24 h, diluted with EtOAc (100 mL) and washed with H_2O and saturated aqueous NaCl, and dried over Na_2SO_4. Concentration of this solution under reduced pressure afforded 2.71 g (91%) of 2,2-dimethyl-6-ethynyl-chroman-4-one as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (1H, d, J = 2.2 Hz), 7.56 (1H, dd, J = 2.2, 8.6 Hz), 6.90 (1H, d, J = 8.6 Hz), 3.02 (1H, s), 2.74 (2H, s), 1.47 (6H, s).

A solution of the alkyne (2.60 g, 13.0 mmol) and ethyl 4-iodobenzoate (3.6 g, 13.0 mmol) in 50.0 mL Et_3N was purged with argon for 15 min. To this solution was added $Pd(PPh_3)_2Cl_2$ (1.82 g, 2.6 mmol) and copper(I) iodide (496 mg, 2.6 mmol). After sparging for an additional 10 min with argon, the solution was stirred overnight at room temperature. The reaction mixture was filtered through a pad of Celite using an Et_2O wash. Concentration of the filtrate under reduced pressure followed by column chromatography (2–5% EtOAc/hexanes) of the residual solid afforded 2.28 g (50%) the title compound as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (1H, d, J = 2.2 Hz), 8.02 (2H, d, J = 8.5 Hz), 2.61 (1H, dd, J = 2.2, 8.6 Hz), 7.55 (2H, d, J = 8.5 Hz), 6.93 (1H, d, J = 8.6 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.75 (3H, s), 1.48 (6H, s), 1.41 (t, J = 7.1 Hz).

Ethyl 2-fluoro-4-[(2,2-dimethyl-4-oxo-chroman-6-yl)-ethynyl]-benzoate (29). A solution of 6-ethynyl-2,2-dimethylchroman-4-one (314.0 mg, 1.57 mmol) and ethyl 2-fluoro-4-iodobenzoate (440.0 mg, 1.50 mmol) in 10.0 mL Et_3N was purged with argon for 15 min. To this solution was added $Pd(PPh_3)_2Cl_2$ (275.0 mg, 0.39 mmol) and copper(I) iodide (75.0 mg, 0.39 mmol). After sparging for an additional 10 min with argon, the solution was stirred overnight at room temperature. The reaction mixture was filtered through a pad of Celite using an Et_2O wash. Concentration of the filtrate under reduced pressure, followed by column chromatography (3–5% EtOAc/hexanes) of the residual solid afforded 400.0 mg (69%) the title compound as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (1H, d, J = 2.1 Hz), 7.90 (1H, d, J = 7.8 Hz), 7.60 (1H, dd, J = 2.2 8.5 Hz), 7.29 (1H, dd, J = 1.5, 8.2 Hz), 7.25 (1H, d, J = 11.4 Hz), 6.93 (1H, d, J = 8.5 Hz), 4.39 (2H, q, J = 7.1 Hz), 2.75 (2H, s), 1.48 (6H, s), 1.40 (3H, t, J = 7.1 Hz).

Ethyl 4-(2,2-dimethyl-4-trifluoromethanesulfonyloxy-(2*H*)-chromen-6-ylethynyl)-benzoate (70). A solution of sodium bis(trimethylsilyl)amide (1.56 g, 8.5 mmol) in 18.0 mL of THF was cooled to −78 °C and a solution of **28** (2.26 g, 6.49 mmol) in 15.0 mL slowly added. After 30 min a solution of 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-pyridine (3.10 g, 7.79 mmol) in 10 mL of THF. After 5 min the solution was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with 5% aqueous NaOH and H_2O before being dried ($MgSO_4$) and concentrated under reduced pressure. The title compound, 2.0 g (64%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (2H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.3 Hz), 7.45–7.21 (2H, m), 6.85 (1H, d, J = 8.4 Hz), 5.69 (1H, s), 4.40 (2H, q, J = 7.1 Hz), 1.55 (6H, s), 1.4 (3H, t, J = 7.1 Hz).

Ethyl 2-fluoro-4-((2,2-dimethyl-4-trifluoromethanesulfonyloxy-(2*H*)-chromen-6-yl)ethynyl)-benzoate (71). A solution of sodium bis(trimethylsilyl)amide (238.0 mg, 1.30 mmol) in 3.0 mL of THF was cooled to −78 °C and a solution of ethyl 4-((2,2-dimethyl-4-oxo-chroman-6-yl)ethynyl)-benzoate (400.0 mg, 1.09 mmol) in 2.0 mL slowly added. After 30 min a solution of 2-[*N*,*N*-bis(trifluoromethanesulfonyl)-amino]-5-pyridine (510.0 mg, 1.30 mmol) in 1.0 mL of THF was added. After 5 min the solution was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with 5% aqueous NaOH and H_2O before being dried ($MgSO_4$) and concentrated under reduced pressure. The title compound, 315.0 mg (58%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (1H, d, J = 7.8 Hz), 7.44–7.26 (4H, m), 6.85 (1H, d, J = 8.7 Hz), 5.70 (1H, s), 4.31 (2H, q, J = 7.1 Hz), 1.55 (6H, s), 1.41 (3H, t, J = 7.1 Hz).

Ethyl 4-[[4-phenyl-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoate (72). Following general procedure A and bromobenzene (250.0 mg, 1.59 mmol) in 3.0 mL of THF, *tert*-butyllithium (203.7 mg, 3.18 mmol, 1.9 mL of a 1.7 M solution in pentane), $ZnCl_2$ (440.0 mg, 3.18 mmol) in 5.0 mL THF, **70** (150.0 mg, 0.31 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 110.0 mg (87%), was isolated by column chromatography (2.5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (2H, d, J = 8.3 Hz), 7.51 (2H, d, J = 8.3 Hz), 7.47–7.35 (6H, m), 7.21 (1H, d, J = 2.0 Hz), 6.88 (1H, d, J = 8.4 Hz), 5.66 (1H, s), 4.38 (2H, q, J = 7.1 Hz), 1.52 (6H, s), 1.40 (3H, t, J = 7.1 Hz).

Ethyl 4-[[4-(4-methylphenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoate (73). Following general procedure A and 4-methylbromobenzene (237.0 mg, 1.38 mmol) in 3.0 mL of THF, *tert*-butyllithium (177.5 mg, 2.77 mmol, 1.6 mL of a 1.7 M solution in pentane), $ZnCl_2$ (377.0 mg, 2.77 mmol) in 5.0 mL THF, **70** (150.0 mg, 0.31 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 120.0 mg (92%), was isolated by column chromatography (2.5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (2H, d, J = 8.5 Hz), 7.50 (2H, d, J = 8.5 Hz), 7.34 (1H, dd, J = 2.1, 8.3 Hz), 7.25–7.21 (5H, m), 6.85 (1H, d, J = 8.3 Hz), 5.62 (1H, s), 4.36 (2H, q, J = 7.1 Hz), 2.41 (3H, s), 1.49 (6H, s), 1.39 (3H, t, J = 7.1 Hz).

Ethyl 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoate (74). Following general procedure A and 4-ethylbromobenzene (280.0 mg, 1.51 mmol) in

3.0 mL of THF, *tert*-butyllithium (198.6 mg, 3.10 mmol, 1.9 mL of a 1.7 M solution in pentane), $ZnCl_2$ (408.0 mg, 3.10 mmol) in 5.0 mL THF, **70** (150.0 mg, 0.31 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 123.0 mg (91%), was isolated by column chromatography (2.5% EtOAc/hexanes) as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (2H, d, J = 8.4 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.36 (1H, dd, J = 2.0, 8.3 Hz), 7.31–7.25 (5H, m), 6.88 (1H, d, J = 8.3 Hz), 5.65 (1H, s), 4.38 (2H, q, J = 7.1 Hz), 2.73 (2H, q, J = 7.6 Hz), 1.52 (6H, s), 1.41 (3H, t, J = 7.1 Hz), 1.31 (2H, t, J = 7.6 Hz).

Ethyl 4-[[4-(4-(1-methylethyl)phenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoate (75). Following general procedure A and 4-*iso*-propylbromobenzene (250.0 mg, 1.25 mmol) in 3.0 mL of THF, *tert*-butyllithium (160.8 mg, 2.51 mmol, 1.5 mL of a 1.7 M solution in pentane), $ZnCl_2$ (345.0 mg, 2.53 mmol) in 5.0 mL THF, **70** (150.0 mg, 0.31 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 100.0 mg (72%), was isolated by column chromatography (2.5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (2H, d, J = 8.3 Hz), 7.52 (2H, d, J = 8.3 Hz), 7.36 (1H, dd, J = 2.1, 8.3 Hz), 7.30–7.26 (5H, m), 6.88 (1H, d, J = 8.3 Hz), 5.64 (1H, s), 4.38 (2H, q, J = 7.1 Hz), 2.98 (1H, hept, J = 7.0 Hz), 1.51 (6H, s), 1.40 (3H, t, J = 7.1 Hz), 1.31 (6H, d, J = 7.0 Hz).

Ethyl 4-[[4-(4-(1,1-dimethylethyl)phenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoate (76). Following general procedure A and 4-*tert*-butylbromobenzene (280.0 mg, 1.61 mmol) in 3.0 mL of THF, *tert*-butyllithium (206.3 mg, 3.22 mmol, 1.7 mL of a 1.7 M solution in pentane), $ZnCl_2$ (380.0 mg, 3.22 mmol) in 5.0 mL THF, **70** (150.0 mg, 0.31 mmol) $Pd(PPh_3)_4$ (24.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 85.0 mg (59%), was isolated by column chromatography (2.5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (2H, d, J = 8.3 Hz), 7.53 (2H, d, J = 8.3 Hz), 7.45 (1H, d, J = 8.4 Hz), 7.37 (1H, dd, J = 2.0, 8.3 Hz), 7.32–7.28 (3H, m), 6.89 (1H, d, J = 8.3 Hz), 5.66 (1H, s), 4.39 (2H, q, J = 7.1 Hz), 1.52 (6H, s), 1.40 (3H, t, J = 7.1 Hz), 1.39 (9H, s).

Ethyl 2-fluoro-4-[[4-(4-methylphenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoate (77). Following general procedure A and 4-methylbromobenzene (140.0 mg, 0.80 mmol) in 3.0 mL of THF, *tert*-butyllithium (102.5 mg, 1.60 mmol, 0.94 mL of a 1.7 M solution in pentane), $ZnCl_2$ (174.0 mg, 1.28 mmol) in 5.0 mL THF, **71** (150.0 mg, 0.31 mmol) and $Pd(PPh_3)_4$ (20.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 86.0 mg (62%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (1H, d, J = 7.8 Hz), 7.35 (1H, d, J = 7.8 Hz), 7.35 (1H, dd, J = 2.0, 8.4 Hz), 7.28–7.19 (7H, m), 6.88 (1H, d, J = 8.3 Hz), 5.64 (1H, s), 4.40 (2H, q, J = 7.1 Hz), 2.43 (3H, s), 1.51 (6H, s), 1.41 (3H, t, J = 7.1 Hz).

Ethyl 2-fluoro-4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoate (78). Following general procedure A and 4-ethylbromobenzene (150.0 mg, 0.80 mmol) in 3.0 mL of THF, *tert*-butyllithium (102.5 mg, 1.60 mmol, 0.94 mL of a 1.7 M solution in pentane), $ZnCl_2$ (218.0 mg, 1.60 mmol) in 5.0 mL THF, **71** (160.0 mg, 0.32 mmol) and $Pd(PPh_3)_4$) (20.0 mg, 0.02 mmol) in 2.0 mL THF. The title compound, 115.0 mg (79%), was isolated by column chromatography (5% EtOAc/hexanes) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (1H, d, J = 7.8 Hz), 7.35 (1H, dd, J = 2.0, 8.3 Hz), 7.28–7.20 (7H, m), 6.88 (1H, d, J = 8.3 Hz), 5.65 (1H, s), 4.39 (2H, q, J = 7.1 Hz), 2.73 (2H, q, J = 7.6 Hz), 1.52 (6H, s), 1.40 (3H, t, J = 7.1 Hz), 1.31 (3H, t, J = 7.6 Hz).

4-[[4-Phenyl-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoic acid (79). Following general procedure B and **72** (70.0 mg, 0.171 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 48.0 mg (74%) the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.00 (2H, d, J = 8.2 Hz), 7.57 (2H, d, J = 8.2 Hz), 7.51–7.37 (6H, d), 7.14 (1H, d, J = 2.0 Hz), 6.91 (1H, d, J = 8.3 Hz), 5.80 (1H, s), 1.50 (6H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 167.0, 155.2, 138.6, 134.6, 133.8, 132.1, 131.0, 130.7, 130.5, 129.5, 129.4, 129.3, 128.9, 128.7, 123.4, 118.2, 115.4, 93.0, 87.9, 77.4, 27.8. Anal. calcd for $C_{26}H_{20}O_3$: C, 82.08; H, 5.30. Found: C, 81.85; H, 5.02.

4-[[4-(4-Methylphenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoic acid (80). Following general procedure B and **73** (90.0 mg, 0.213 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 70.0 mg (83%) the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.01 (2H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.3 Hz), 7.40 (1H, dd, J = 2.1, 8.3 Hz), 7.30–7.20 (4H, m), 7.16 (1H, d, J = 2.0 Hz), 6.90 (1H, d, J = 8.3 Hz), 5.67 (1H, s), 2.38 (3H, s), 1.49 (6H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 166.9, 155.2, 138.6, 135.7, 134.5, 133.7, 132.1, 130.6, 130.5, 130.1, 129.3, 128.8, 123.5, 118.2, 115.3, 93.1, 87.9, 77.4, 27.9, 21.2.

4-[[4-(4-Ethylphenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoic acid (81). Following general procedure B and **74** (82.0 mg, 0.188 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 65.0 mg (85%) the title compound as a colorless solid. ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.01 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.40 (1H, dd, J = 2.0, 8.3 Hz), 7.35–$d_6$7.25 (4H, m), 7.17 (1H, d, J = 2.0 Hz), 6.90 (1H, d, J = 8.3 Hz), 5.77 (1H, s), 2.69 (2H, q, J = 7.6 Hz), 1.49 (6H, s), 1.24 (2H, t, J = 7.6 Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 167.0, 155.2, 145.0, 135.9, 134.5, 133.7, 132.1, 130.7, 130.5, 129.4, 129.3, 128.9, 128.8, 123.5, 118.2, 115.3, 93.1, 87.9, 77.4, 29.1, 27.9, 15.9.

4-[[4-(4-(1-Methylethyl)phenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoic acid (82). Following general

procedure and **75** (95.0 mg, 0.210 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 75.0 mg (84%) the title compound as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.05 (2H, d, $J=8.4$ Hz), 7.55 (2H, d, $J=8.4$ Hz), 7.36 (1H, dd, $J=2.0$, 8.3 Hz), 7.30–7.26 (5H, m), 6.88 (1H, d, $J=8.3$ Hz), 5.64 (1H, s), 2.98 (1H, hept, $J=6.9$ Hz), 1.51 (6H, s), 1.31 (6H, d, $J=6.9$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 171.3, 154.2, 148.7, 135.2, 134.0, 133.0, 131.4, 130.1, 129.5, 129.3, 129.0, 128.6, 128.1, 126.6, 122.6, 117.2, 114.2, 93.5, 87.1, 33.9, 27.8, 24.0. Anal. calcd for $C_{29}H_{26}O_3$: C, 82.44; H, 6.20. Found: C, 82.25; H, 6.28.

4-[[4-(4-(1,1-Dimethylethyl)phenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoic acid (83). Following general procedure and **76** (72.0 mg, 0.155 mmol) in 3.0 mL THF and 3.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 50.0 mg (74%) the title compound as a colorless solid. ^1H NMR (300 MHz, acetone-d_6) δ: 8.00 (2H, d, $J=8.3$ Hz), 7.57 (2H, d, $J=8.3$ Hz), 7.51 (2H, d, $J=8.3$ Hz), 7.41 (1H, dd, $J=2.0$, 8.3 Hz), 7.31 (2H, d, $J=8.3$ Hz), 7.19 (1H, d, $J=2.0$ Hz), 6.91 (1H, d, $J=8.3$ Hz), 5.78 (1H, s), 1.49 (6H, s), 1.35 (9H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 167.0, 155.2, 151.8, 135.7, 134.4, 133.8, 132.1, 130.8, 130.7, 130.5, 129.3, 129.1, 128.8, 126.3, 123.4, 118.2, 115.3, 93.1, 87.9, 77.4, 35.2, 31.6, 29.0, 27.9. Anal. calcd for $C_{30}H_{28}O_3$: C, 82.54; H, 6.46. Found: C, 82.29; H, 6.59.

2-Fluoro-4-[[4-(4-methylphenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoic acid (84). Following general procedure and **77** (60.0 mg, 0.136 mmol) in 2.0 mL THF and 1.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 53.0 mg (94%) the title compound as a colorless solid. ^1H NMR (300 MHz, acetone-d_6) δ: 7.93 (1H, d, $J=7.8$ Hz), 7.43–7.16 (8H, m), 6.91 (1H, d, $J=8.3$ Hz), 5.77 (1H, s), 2.38 (3H, s), 1.49 (6H, s); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 164.6 (d, $J=3.3$ Hz), 162.5 (d, $J=259.4$ Hz), 155.5, 138.6, 135.6, 134.4, 133.9, 133.3, 130.7, 130.6 (d, $J=8.1$ Hz), 130.1, 129.5, 129.3, 127.8 (d, $J=3.5$ Hz), 123.5, 120.0 (d, $J=14.6$ Hz), 119.2 (d, $J=10.5$ Hz), 118.2, 114.8, 94.1, 86.7 (d, $J=2.7$ Hz), 77.5, 27.9, 21.2. Anal. calcd for $C_{27}H_{21}FO_3$: C, 78.63; H, 5.13. Found: C, 78.49; H, 5.13.

2-Fluoro-4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2*H*)-chromen-6-yl]-ethynyl]-benzoic acid (85). Following general procedure B and **78** (82.0 mg, 0.180 mmol) in 2.0 mL THF and 2.0 mL EtOH, and NaOH (120.0 mg, 3.0 mmol, 3.0 mL of a 1 M aqueous solution). The residual solid was recrystallized from CH_3CN to give 70.0 mg (91%) the title compound as a pale-yellow solid. ^1H NMR (300 MHz, acetone-d_6) δ: 7.93 (1H, d, $J=7.8$ Hz), 7.41 (1H, dd, $J=2.1$, 8.3 Hz), 7.37–7.25 (6H, m), 7.18 (1H, d, $J=2.0$ Hz), 6.91 (1H, d, $J=8.3$ Hz), 5.77 (1H, s), 2.69 (2H, q, $J=7.6$ Hz), 1.49 (6H, s), 1.24 (3H, t, $J=7.6$ Hz); ^{13}C NMR (75.5 MHz, acetone-d_6) δ: 164.6, 162.4 (d, $J=258.9$ Hz), 155.5, 145.0, 135.9, 134.4, 133.9, 133.3, 130.7, 130.6 (d, $J=11.7$ Hz), 129.4, 129.3, 128.9, 127.8 (d, $J=3.8$ Hz), 123.5, 120.0 (d, $J=24.2$ Hz), 118.2, 114.8, 94.1, 86.7 (d, $J=2.3$ Hz), 77.5, 29.1, 27.9, 15.9. Anal. calcd for $C_{28}H_{23}FO_3$: C, 78.86; H, 5.44. Found: C, 78.58; H, 5.35.

Biological assays

RAR binding assay. Each receptor subtype was expressed in Baculovirus. Stock solutions of all compounds were prepared as 10 mM ethanol solutions and serial dilutions carried out into 1/1 DMSO/glycerol, 120 mM KCl, 8 mM Tris, 5 mM CHAPS, 4 mM DTT, and 0.24 mM PMSF, at PH 7.4 at room temperature. The final assay volume was 250 μL and contained 10–40 μg of protein extract along with 5 nM of [^3H] all-*trans* retinoic acid and varying concentrations of competing ligand that ranged from 10^{-10}–10^{-5} M. The assays were run using a Biomek formatted for a 96-well minitube system. Incubations were carried out at 4 °C until equilibrium was achieved. Nonspecific binding was defined as that binding remaining in the presence of 1000 nM of unlabeled RA. At the end of the incubation period, 50 μL of 6.25% hydroxyapitite was added in a wash buffer which consisted of 100 nM KCl, 10 mM Tris, and 0.5% Triton X-100. The mixture was vortexed and incubated for 10 min at 4 °C, centrifuged and the supernatant removed. The hydroxyapitite was washed three more times with the buffer and the amount of receptor–ligand complex determined by liquid scintillation counting of the pellet.

After correcting for nonspecific binding, IC_{50} values were determined graphically from a log-logit plot of the data. The K_d values were determined by application of the Cheng–Prussof equation[24] to the IC_{50} values, the labeled ligand concentration, and the K_d of the labeled ligand.

Cotransfection transactivation assay. Eukaryotic expression vectors pRShRARα,[25] pRShRARβ,[26] pRSh RARγ,[26] were cotransfected with the D-MTV-Luc reporter plasmid containing two copies of the TRE-palindromic response element[27] into green monkey CV-1 cells using calcium phosphate precipitation.[28] After 18 h of retinoid treatment the cells were harvested in 0.1 M KPO_4 (pH 7.8), 1.0% Triton X-100, 1.0 mM DTT, and 2 mM EDTA, and analyzed for luciferase activity as previously described.[29]

Antagonist assay. To test the ability of the compounds to function as RAR antagonists in vitro, the transactivation assays were repeated in the presence of a constant dose of the RAR agonist TTNPB = (Ro 13-7410), (E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)propen-1-yl] benzoic acid. The concentration used at RARα = 3.2×10^{-8} M, RARβ = 1.0×10^{-8} M, and RARγ = 3.2×10^{-9} M. In each experiment the reference compound AGN 193109 (**8**) was included in order to determine the relative potency of the test compound where Relative Potency = IC_{50}(test compound)/IC_{50} (**8**).

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