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Pyranocoumarin, a novel anti-TB pharmacophore: Synthesis and biological evaluation against *Mycobacterium tuberculosis*

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Abstract—Pyranocoumarin compounds were identified to embody a novel and unique pharmacophore for anti-TB activity. A systematic approach was taken to investigate the structural characteristics. Focused libraries of compounds were synthesized and evaluated for their anti-TB activity in primary screening assays. Compounds shown to be active were further determined for MIC and MBC values. Three of the four bactericidal compounds (**16**, **17c**, and **18f**) were amino derivatives, with MIC values of 16 μg/mL and respective MBC values of 32, 32, and 64 μg/mL.

1. Introduction

Tuberculosis (TB) is one of the leading causes of infectious disease mortality, with 2–3 million deaths annually worldwide.[1,2] One-third (about 2 billion) of the world population is estimated to be infected with *Mycobacterium tuberculosis*. The current treatment for TB recommended by WHO—known as DOTS (Directly Observed Therapy Short-course)—is generally successful in achieving more than 99% efficacy, if patients can adhere to a three- or four-drug regimen comprising isoniazid, rifampin, pyrazinamide, and/or ethambutol for a minimum of 6 months. However, it is very difficult to implement such TB control programs in many regions of the world; patients often fail to complete the therapy due to drug side effects and the complexity of the drug regimen, leading to the emergence of multiple-drug-resistant (MDR) strains of *M. tuberculosis*. Thus, new and effective anti-TB drugs requiring reduced treatment duration or a simplified treatment regimen would be great additions to the anti-TB armamentaria.[3]

In our ongoing efforts to identify novel anti-TB pharmacophores, a class of naturally occurring pyranocoumarin compounds,[4] as exemplified by (+)-calanolide A, was discovered to possess activities against strains of *M. tuberculosis* susceptible or resistant to the standard antitubercular drugs. In order to further understand the structural features of pyranocoumarins necessary for the unique anti-TB activity, we have embarked on the design, synthesis, and evaluation of certain focused libraries of this class of molecules.

Based on the results previously published,[4] our initial analysis of the structure–activity relationships indicated that the hydroxyl group (OH) and the lactone functionality of the coumarin may be essential for the anti-TB activity of pyranocoumarins (Fig. 1). Therefore, our focus has been to systematically modify the chromene and chroman rings (Rings B and C) of the pyranocoumarin (Fig. 1). We have identified 4 different characteristics of analogues of interest, as represented in Table 1. The first three categories of compounds would lead to further clarification of the importance of Rings B and C, and the fourth category is intended to further explore the possibility of replacing the hydroxyl group with other functional groups. Of particular interest for such substitution is the amino group ($X = NH_2$). Similar to an OH group, the NH_2 group can form a hydrogen bond; however, it is less prone to elimination under acidic conditions. Furthermore, an amino compound tends to impart increased water solubility, especially by forming a salt with an acid, which may facilitate the

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Keywords: Pyranocoumarin; Pharmacophore; Mycobacterium tuberculosis.

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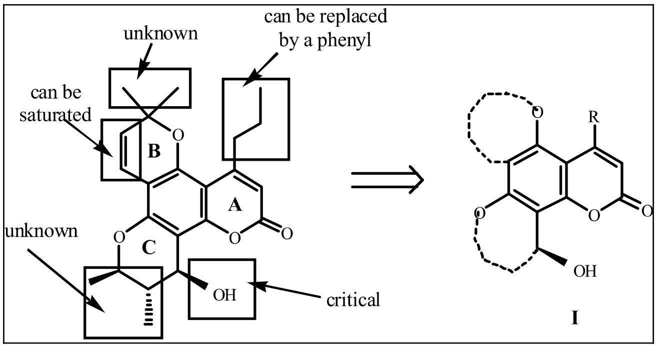
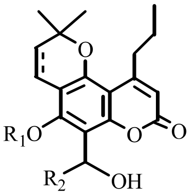
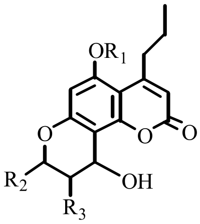
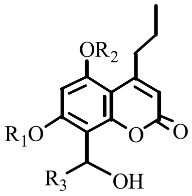
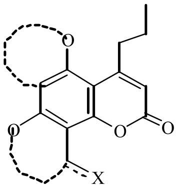


Figure 1. Structure–activity relationships of anti-TB active pyranocoumarins.

Table 1. Analogues proposed for synthesis and evaluation for anti-TB activity

Type I	Type II	Type III	Type IV
			

formulation for future in vivo animal and clinical studies and offer enhanced bioavailability.

2. Results

2.1. Chemistry

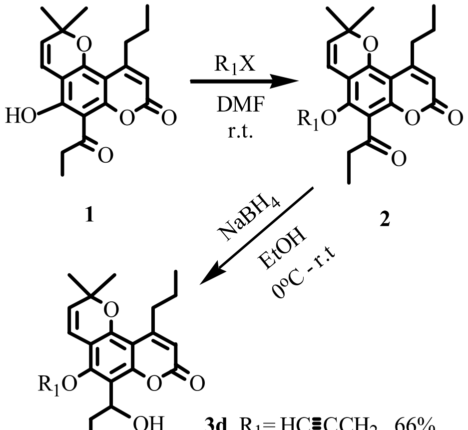
The chemistry program has been carried out with two goals in mind: to obtain as many compounds as possible for biological screening and to set a framework for possible parallel synthesis in the future.

2.2. Synthesis of type I and the corresponding type IV (X = O) compounds

Type I compounds result in the modification on Ring C to determine if the rigidity of the ring system is required for activity. Compound **3c** can be viewed as an acyclic form of calanolide A or B, with the same number of carbon atoms as the latter molecules but with two less chiral centers, leading to more convenient manufacture if it is active and is selected for further development. This compound has been synthesized previously [5] via the corresponding ketone **2** and, therefore, the reported procedures were followed. Thus, compound **1**,[6] prepared according to the published method, was readily alkylated using different alkylating agents in the presence of either Cs_2CO_3 or K_2CO_3 in DMF, leading to the formation of compounds **2** in fair to good yields (Scheme 1). Compound **2e** was synthesized in a one-pot reaction. The crude alkylated acetate intermediate was hydrolyzed directly by NaOH in H_2O/MeOH with an overall yield of 32%. Direct reduction of **2d** and **2e** with $NaBH_4$ proceeded well to afford **3d** and **3e** (Scheme 1). However, the reduction of **2b** and **2c** was somewhat problematic. The reaction was not complete, even though an excess amount of $NaBH_4$ was used, and provided a complicated mixture. After repetitive column chromatography, pure **3b** and **3c** were obtained.

In order to obtain sufficient quantities of **3b** and **3c** for biological testing and for synthesis of other compounds of interest, a selective alkylation of **3a** was developed. Thus, reduction of **1** with $NaBH_4$ afforded **3a** in excellent yield (Scheme 2). Alkylation of **3a** in the presence of Cs_2CO_3 yielded a rather complicated mixture. However, when K_2CO_3 was used instead, the selective alkylation of the phenolic hydroxyl group in **3a** was achieved. Compounds **3b** and **3c** were obtained in 81% and 74% yields, respectively (Scheme 2).

It is worth noting that an attempt to synthesize *t*-butyl derivative **2** (R_1 = *t*-Bu) was unsuccessful. Different *t*-butylating agents and conditions were investigated. For example, reaction of **1** with *O*-*t*-butyl trichloroacetamidate [$CCl_3C(O\text{-}t\text{-}Bu){=}NH$] under neutral or acidic conditions, or with 2-methylpropene in the presence of a catalytic amount of sulfuric acid, resulted in recovery of only starting material. In contrast, the reaction of **1** with *t*-butyl chloride in the presence of K_2CO_3 in DMF led to the formation of a product that was more

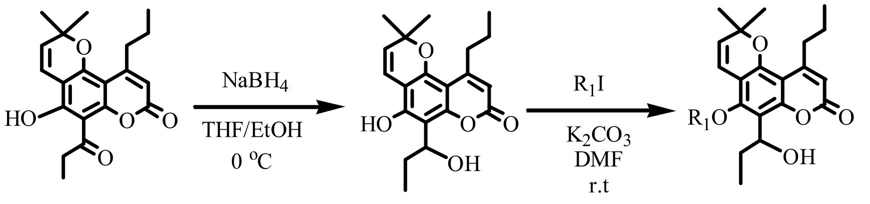


3d, $R_1 = HC\equiv CCH_2$, 66%

3e, $R_1 = HOCH_2CH_2$, 64%

Compound	Conditions	Yield%
2b, R_1=Me	MeI/K_2CO_3	73
2c, R_1=Et	EtI/Cs_2CO_3	84
2d, R_1= $CH\equiv CCH_2$	$CH\equiv CCH_2Cl/Cs_2CO_3$	75
2e, R_1= $HOCH_2CH_2$	1) $AcOCH_2CH_2Br/K_2CO_3$ 2) NaOH in H_2O/MeOH	32
2f, R_1= Ac	Ac_2O/pyridine	71

Scheme 1.



1

3a, 97%

3b, R_1 = Me, 81%
3c, R_1 = Et, 74%

Scheme 2.

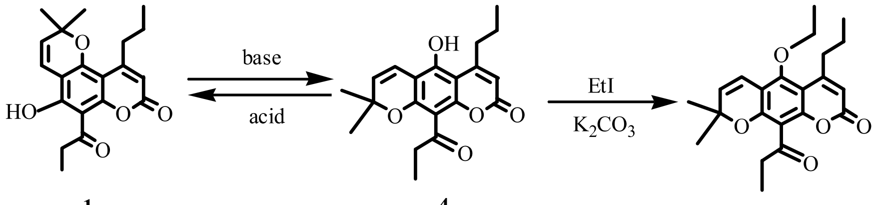
polar than the starting compound **1** as shown by TLC analysis. Spectroscopic data of the isolated product were in agreement with the structure of the chromene ring rearranged isomer **4** (Scheme 3). Under acidic conditions, **4** was partially rearranged back to **1**. Furthermore, treatment of **4** with EtI in the presence of K_2CO_3 afforded compound **5**.

Hydrogenation of **3a**, **b**, **c** with NH_4OH-poisoned PtO_2 or PtS_x on carbon as catalyst furnished the corresponding 7,8-dihydro compounds **6a**, **b**, **c**, respectively (Scheme 4). In addition, both compounds **6d** and **6e** were then prepared by the selective alkylation of the phenolic hydroxyl group in **6a** in the presence of K_2CO_3 as described above (Scheme 4).

In order to further evaluate the flexibility of the OH group in compound **6**, 7,8-dihydroketones **7** were synthesized by either hydrogenation of **1** and **2** or alkylation of **7a** (Scheme 5). It is interesting that hydrogenation of **2e**, when catalyzed with 5% PtS_x on carbon, afforded compound **8** in 59% yield with both double bonds of the chromene and coumarin rings being saturated, along with the isolation of coumarin-hydrolyzed product **9** (Scheme 5).

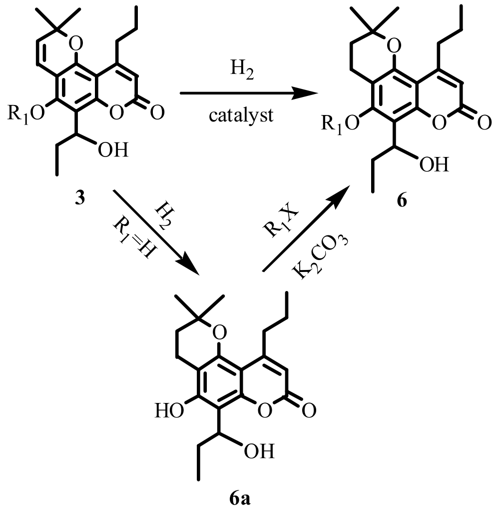
2.3. Synthesis of type II and the corresponding type IV (X = O) compounds

Type II compounds are designed to address the importance of Ring B while maintaining Ring C. We have previously developed a method for the synthesis of *trans*-coumarino-chromanone **10**[7] and demonstrated the ready alkylation of the phenolic hydroxyl group. However, since we have, during this research, developed a new procedure for the selective alkylation of the phenolic hydroxyl group in the presence of an aliphatic hydroxyl group as described in Schemes 3 and 4, this



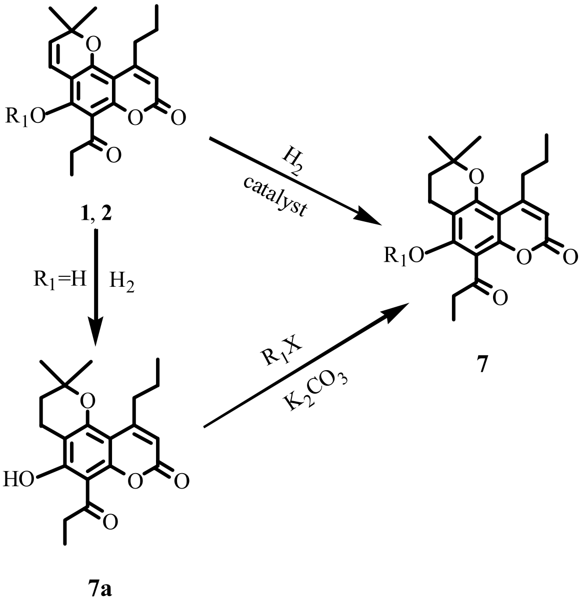
1 **4** **5**

Scheme 3.

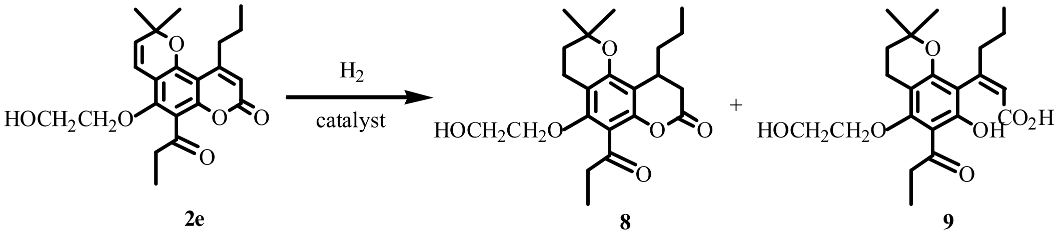


Compound	Catalyst/Reagents	Yield%
6a, R_1=H	$PtO_2(NH_3)$ in toluene	63
6b, R_1=Me	5% PtS_x on C in EtOH	68
6c, R_1= Et	$PtO_2(NH_3)$ in EtOH	61
6d, R_1= CH≡CCH$_2$	CH≡CCH$_2$Cl	63
6e, R_1= $HOCH_2CH_2$	1) $AcOCH_2CH_2Br$ 2) NaOH in H_2O/MeOH	68

Scheme 4.



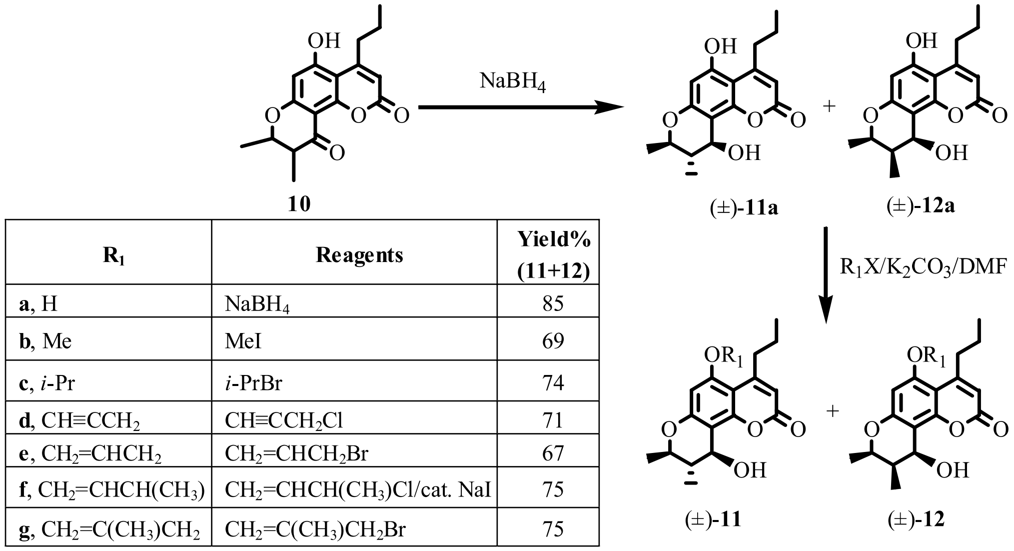
R_1	Catalyst/Reagents	Yield%
a, H	PtO_2 (NH_3) in toluene	
b, Me	5% PtS_x on C in EtOH	68
c, Et	PtO_2 (NH_3) in EtOH	61
d, CH≡CCH$_2$	CH≡CCH$_2$Cl	72
e, CH_2=CHCH$_2$	CH_2=CHCH$_2$Br	93
f, *i*-Pr	*i*-PrBr	89
g, $AcOCH_2CH_2$	$AcOCH_2CH_2Br$	82
h, $HOCH_2CH_2$	Hydrolysis of **7j**	33
i, $MeOCH_2$	$MeOCH_2Br$	92
j, 2-(4-morpholino)-ethyl	2-(4-morpholino)-ethyl Bromide	73
k, EtO_2CCH_2	EtO_2CCH_2Br	81
l, Ac	Ac_2O/pyridine	84
m, *p*-$CH_3C_6H_4SO_2$	*p*-$CH_3C_6H_4SO_2Cl$	85



Scheme 5.

procedure has been employed for the synthesis of type II compounds.

Thus, **10**, prepared according to the reported methods as a *cis*- and *trans*-mixture, was readily reduced by $NaBH_4$ in the presence of $CeCl_3$,[8] resulting in a mixture of **11a** and **12a** with the OH group being predominantly in a β form. Selective alkylation of the phenolic hydroxyl group of **11a** and **12a** in the presence of K_2CO_3 in DMF was generally completed in a few hours, leading to the formation of a mixture of the alkylated **11** and **12** (Scheme 6). Separation of the alkylated **11** and **12** was attempted by using fractional recrystallization, column chromatography, or prepara-



R_1	Reagents	Yield% (11+12)
a, H	NaBH$_4$	85
b, Me	MeI	69
c, *i*-Pr	*i*-PrBr	74
d, CH≡CCH$_2$	CH≡CCH$_2$Cl	71
e, CH$_2$=CHCH$_2$	CH$_2$=CHCH$_2$Br	67
f, CH$_2$=CHCH(CH$_3$)	CH$_2$=CHCH(CH$_3$)Cl/cat. NaI	75
g, CH$_2$=C(CH$_3$)CH$_2$	CH$_2$=C(CH$_3$)CH$_2$Br	75

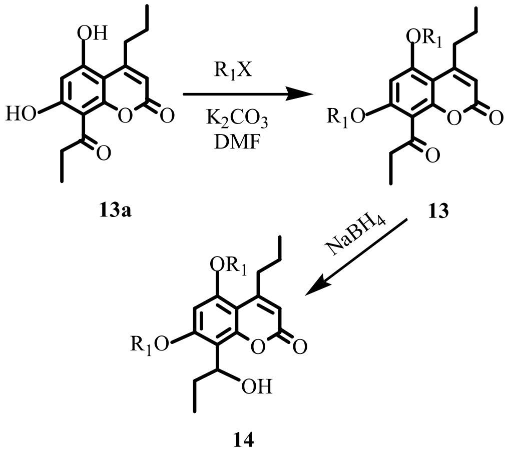
Scheme 6.

tive TLC but each approach proved to be unsuccessful. A preparative HPLC method was then developed and yielded successful separation of **11** and **12**, even though it was somewhat time-consuming. The advantage of using a mixture of *cis*- and *trans*-**10** is that **11** and **12** could be prepared simultaneously. Otherwise, *cis*-**10** would need to be synthesized separately and also isomerization between *cis*- and *trans*-**10** has been reported, resulting in a mixture of **11** and **12** anyway after alkylation.

2.4. Synthesis of type III and the corresponding type IV (X = O) compounds

Type III compounds should be the most intriguing, as they have the least number of rings but may maintain the key structural elements required for anti-TB activity. Furthermore, a significant number of library compounds can be built up by varying the substituents (R_1, R_2, R_3, as well as replacement of the *n*-propyl substituent with other groups). It is our intention to initially synthesize the representative type III and the corresponding type IV (X = O) compounds via conventional medicinal chemistry approaches for anti-TB activity evaluation and to develop synthetic methods which would be applicable to combinatorial chemistry so that a larger library of compounds can be investigated using medium- or high-throughput combinatorial approaches to further optimize the leads discovered.

Coumarin **13a**, prepared according to the literature method,[6] was alkylated directly with different alkylating agents to afford 5,7-bis-*O*-alkylated compounds **13b**, **c**, **d**. Reduction of the alkylated derivatives with NaBH$_4$ proceeded well in general to furnish the corresponding **14** (Scheme 7). However, obtaining pure **14a** from the reduction of **13a** proved to be somewhat problematic. The reduction reaction went relatively smoothly, as other substrates did, forming **14a** predominantly, as shown by ^{1}H NMR, along with some minor impurities. Purification of the crude mixture on column chromatography did not yield purified **14a** in any of the fractions collected. Storing the crude **14a** at rt or in refrigerator led to a decrease in **14a**, as shown by ^{1}H NMR. There-



	13		14
R_1	Reagents	Yield%	Yield%
a, H			N/P
b, Me	MeI	66	48
c, *i*-Pr	*i*-PrBr	56	55
d, CH$_2$=CHCH$_2$	CH$_2$=CHCH$_2$Br	80	36

Scheme 7.

fore, a more straightforward approach from **13a** to **14a** requires further investigation.

2.5. Synthesis of type IV (X = NH_2) Compounds

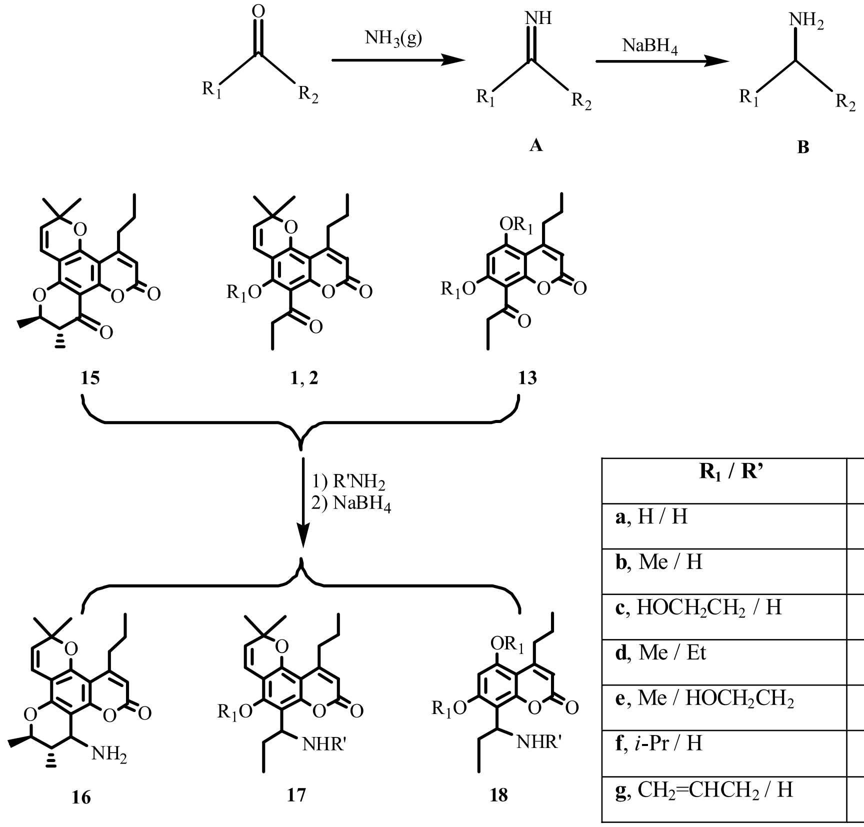
The amino compounds may be of particular interest for a number of reasons. For one, the NH_2 group can form a hydrogen bond in the same way as an OH group. For another, an amino compound tends to have increased solubility in aqueous solutions, especially by forming a salt with an acid, which may offer enhanced bioavailability and facilitate future in vivo and clinical studies.

In general, amino compounds can be derived either via reductive amination from the corresponding carbonyl derivatives[9] or by direct replacement of a hydroxyl group with amines.[10] In attempts to prepare **16** (Scheme 8) under reductive amination conditions (i.e., $NH_4Cl/NaBH_3CN$), no reaction occurred and only starting material was recovered. This may be due to the steric hindrance caused by the α-methyl group and the ring system. Apparently, a more versatile reductive amination protocol is needed.

Indeed, during this research program, we have successfully developed a one-pot stepwise reductive amination which would have a very general application. We have found that the treatment of a ketone with an excessive amount of NH_3(g) in organic solvent led to the formation of a polar spot as shown on TLC, presumably the corresponding imine **A** (Scheme 8). ^{1}H NMR on the isolated product confirmed the structure to be that of imine **A**. Reduction of imine **A** with $NaBH_4$ furnished the corresponding amine **B**. To the best of our knowledge, this is the first time that NH_3(g) is utilized in a stepwise reductive amination. Furthermore, when NH_3(g) is replaced with amine derivatives ($R'NH_2$), the corresponding substituted amino analogues could be prepared. Thus, ketone compounds **1**, **2**, **13**, and **15**[6,8] were treated with NH_3(g) or amine derivatives ($R'NH_2$), followed by $NaBH_4$ reduction, affording the corresponding amino compounds **16**, **17**, and **18** (Scheme 8).

2.6. Evaluation of compounds synthesized for activity against *M. tuberculosis*

In order to determine the structure–activity relationships of the pyranocoumarins, the compounds synthesized were evaluated for activity against *M. tuberculosis* H37Ra using a colorimetric microdilution broth assay that incorporated the REDOX indicator Alamar blue, which indicates growth and viability by the metabolic reduction of the dye from blue to red.[11] The strategy of employing the cultured pathogen to identify compounds that inhibit its growth has several advantages,[12] especially if there are no drug targets known for a novel class of compounds. The inhibitory effect exerted by a compound on the growth of a pathogen would strongly suggest that it targets microbial structures essential for growth. In addition, any active



R_1 / R'	**17** Yield%	**18** Yield%
a, H / H	61	
b, Me / H	98	60
c, $HOCH_2CH_2$ / H	47	
d, Me / Et	27	
e, Me / $HOCH_2CH_2$	22	
f, *i*-Pr / H		23
g, $CH_2{=}CHCH_2$ / H		46

Scheme 8.

compound identified must have the ability to cross the cell wall and bypass potential microbial defenses such as degenerative enzymes and efflux pumps.

Table 2. Activity of compounds against *M. tuberculosis* H37Ra from the initial screening

Compound	MIC (μg/mL)
1	>128
2b	>12.8 < 128
2c	>128
2d	>128
2e	>12.8 < 128
2f	>12.8 < 128
3a	>12.8 < 128
3b	>12.8 < 128
3c	>12.8 < 128
3d	>12.8 < 128
4	>12.8 < 128
5	>12.8 < 128
6a	>12.8 < 128
6b	>12.8 < 128
6c	>128
6d	>12.8 < 128
6e	>12.8 < 128
7a	>128
7b	***>1.28 < 12.8***
7c	>128
7d	>128
7e	>128
7f	>128
7g	>12.8 < 128
7h	>12.8 < 128
7i	>128
7j	>128
7k	>128
7l	>128
7m	>128
11b	>12.8 < 128
11c	>12.8 < 128
11d	>128
11e	>128
11f	>12.8 < 128
11g	>128
12b	>128
12c	***>1.28 < 12.8***
12d	>12.8 < 128
12e	>12.8 < 128
12f	***>1.28 < 12.8***
12g	>12.8 < 128
13a	>12.8 < 128
13b	>128
13c	>128
13d	>128
14b	>12.8 < 128
14c	>128
14d	***>1.28 < 12.8***
16	***>1.28 < 12.8***
17a	>12.8 < 128
17b	>12.8 < 128
17c	**>1.28 < 12.8**
17d	>12.8 < 128
17e	>12.8 < 128
18b	>12.8 < 128
18f	***>1.28 < 12.8***
18g	>12.8 < 128
Ethambutol	4

Table 3. MIC and MBC values of compounds against *M. tuberculosis* H37Ra

Compound	MIC	MBC	MBC/MIC
7b	16	>64	>4
12c	16	64	4
12f	16	>64	>4
14d	16	>64	>4
16	16	32	2
17c	16	32	2
18f	16	64	4

MIC and MBC: μg/mL.

The compounds were initially assayed in duplicate at four $\log_{10}$ dilutions, with the highest concentration being 128 μg/mL (therefore, tested concentrations were 0.128, 1.28, 12.8, and 128 μg/mL) using a colorimetric microdilution broth assay.[11] The initial screening results are shown in Table 2.

Compounds exhibiting activity with an MIC range less than 12.8 μg/mL in the initial screening were further assayed within an appropriate concentration range using 2-fold serial dilutions to determine the minimum inhibitory concentration (MIC), which is defined as the lowest concentration of drug that completely inhibits growth of *M. tuberculosis*, and the minimum bactericidal concentration (MBC), defined as the lowest drug concentration that reduced the initial viable count by 99%. The results are shown in Table 3. Four of the compounds (**12c**, **16**, **17c**, and **18f**) were bactericidal in their effect on *M. tuberculosis* since their MBC/MIC ratios were 4 or less. All these compounds had an MIC value of 16 μg/mL.

3. Conclusion

Over 60 compounds, representing four different classes of pyranocoumarin compounds as designed, have been synthesized and evaluated for anti-TB activity. Seven of these compounds exhibited activity with an MIC range less than 12.8 μg/mL in the initial screening and were further assayed to determine the MIC and minimum bactericidal concentration (MBC). Four compounds were found to be bactericidal in their effect on *M. tuberculosis*. It is worth noting that three out of the four bactericidal compounds (**16**, **17c**, and **18f**) are amino derivatives. The detailed SAR study is a subject of an on-going research and will be disclosed in due course.

4. Experimental

All chemical reagents and solvents were purchased from Aldrich and used as received. ^{1}H NMR and ^{13}C NMR were obtained using a Varian INOVA-500 spectrometer. IR spectra were determined with a Nicolet Nexus 470 FT-IR spectrophotometer. MS spectra were recorded on a single quad PE Sciex 150 spectrometer. HPLC was performed on a Hitachi instrument fitted with a L-7100 pump and D-7000 interface, using a normal phase Zorbax SIL column (4.6 mm × 25 cm) and UV diode array detection (Hitachi L-7455). TLC was performed on EMD Silica Gel 60 F254. The plates were visualized under UV light or by staining with phosphomolybdic acid, $KMnO_4$ or I_2. Amines were also visualized by staining with ninhydrin. Elemental analysis was performed by Midwest Microlab, LLC (Indianapolis, IN).

4.1. Preparation of 5-alkyloxy-2,2-dimethyl-6-propionyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (2)

To a mixture of 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (**1**)[6] (1.0 equiv) and K_2CO_3 or Cs_2CO_3 (5–10 equiv) in DMF (10–30 mL/mmol) was added an alkylating reagent (2.0–2.5 equiv). The mixture was stirred at ambient temperature until the reaction was completed (16 to 24 h). The mixture was partitioned between water (10 × volume of DMF used) and ethyl acetate (50 mL/mmol). The organic layer was separated, washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuum. The desired product was isolated using silica gel column chromatography eluted with 10–30% ethyl acetate in hexanes.

4.2. 2,2-Dimethyl-5-methoxy-6-propionyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (2b)

73% yield: ^1H NMR ($CDCl_3$): 1.04 (t, $J = 7.2$ Hz, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.52 (s, 6H), 1.66 (sext, $J = 7.7$ Hz, 2H), 2.91 (apparent q, $J = 7.3$ Hz, 4H), 3.80 (s, 3H), 5.67 (d, $J = 9.5$ Hz, 1H), 6.03 (s, 1H), 6.55 ($J = 10.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): 7.9, 13.9, 23.0, 27.8, 38.4, 38.5, 63.6, 78.2, 106.3, 111.1, 112.7, 116.4, 117.7, 128.7, 151.9, 152.6, 155.2, 157.3, 159.5, 202.9; IR: 1728, 1701, 1637, 1607 cm^{-1}; MS (APCI+) *m*/*z*: 357 (M+1); Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79 Found: C, 70.41; H 6.75.

4.3. 2,2-Dimethyl-5-ethoxy-6-propionyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (2c)

85% yield: ^1H NMR ($CDCl_3$): 1.05 (t, $J = 7.2$ Hz, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.52 (s, 6H), 1.67 (sext, $J = 7.7$ Hz, 2H), 2.90 (m, 4H), 3.96 (q, $J = 7.0$ Hz, 2H), 5.69 (d, $J = 10.0$ Hz, 1H), 6.03 (s, 1H), 6.54 ($J = 10.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): 7.8, 13.8, 15.3, 23.0, 27.7, 38.3, 38.4, 72.3, 78.0, 106.2, 111.4, 112.6, 116.57, 117.9, 128.5, 151.8, 152.4, 154.2, 157.3, 159.5, 203.0; IR: 1734, 1703, 1639, 1607 cm^{-1}; MS (APCI+) *m*/*z*: 371 (M+1).

4.4. 2,2-Dimethyl-6-propionyl-10-propyl-5-(prop-2-ynyloxy)-2*H*-pyrano[2,3-*f*]chromen-8-one (2d)

75% yield: ^1H NMR ($CDCl_3$): 1.05 (t, $J = 7.2$ Hz, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.52 (s, 6H), 1.66 (sext, $J = 7.7$ Hz, 2H), 2.56 (t, $J = 2.5$ Hz, 1H), 2.91 (t, $J = 8.5$ Hz, 2H), 2.93 (q, $J = 7.3$ Hz, 2H), 4.60 (d, $J = 2.5$ Hz, 2H), 5.68 (d, $J = 10.0$ Hz, 2H), 6.05 (s, 1H), 6.66 (d, $J = 10.0$ Hz, 2H); IR: 3064, 2130, 1722, 1697, 1638, 1607, 1564 cm^{-1}; MS (APCI+) *m*/*z*: 381 (M+1).

4.5. 2,2-Dimethyl-5-(2-hydroxy-ethoxy)-6-propionyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (2e)

To a solution of compound **1** (3.40 g, 10 mmol, 1.0 equiv) in DMF (60 mL) was added potassium carbonate (13.8 g 100 mmol, 10.0 equiv) followed by 2-bromoethyl acetate (5 g, 30 mmol, 3.0 equiv). The reaction mixture was stirred for 2 days at ambient temperature and then partitioned between water (600 mL) and ethyl acetate (300 mL). The organic layer was separated, washed with an additional portion of water (600 mL), dried, and concentrated. The solid residue was re-dissolved in methanol (200 mL) followed by addition of 2 N aqueous sodium hydroxide (20 mL). The mixture was stirred for 2 h at rt, pH adjusted to 6.0 with concentrated hydrochloric acid, and the mixture was then concentrated under vacuum. The residue was partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was separated, washed successively with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The solid residue was crystallized from cyclohexane/ethanol 80/20 and re-crystallized from methanol/water 95/5, affording 1.23 g of **2e** (32% yield). ^1H NMR ($CDCl_3$): 1.05 (t, $J = 7.5$ Hz, 3H), 1.21 (t, $J = 7.0$ Hz, 3H), 1.53 (s, 6H), 1.67 (sext, $J = 7.4$ Hz, 2H), 2.91 (t, $J = 8.2$ Hz, 2H), 2.94 (q, $J = 7.2$ Hz, 2H), 3.29 (t, $J = 6.5$ Hz, 2H), 3.84 (m, 2H), 4.11 (t, $J = 4.2$ Hz, 2H), 5.68 (d, $J = 10.0$ Hz, 1H), 6.04 (s, 1H), 6.54 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): 8.0, 13.9, 23.1, 27.6, 38.5, 38.6, 62.0, 78.1, 78.4, 106.2, 110.8, 112.6, 116.9, 117.0, 128.8, 152.3, 153.1, 154.8, 157.4, 159.4, 203.6; IR: 3432, 1708 cm^{-1}; MS (APCI+) *m*/*z*: 387 (M+1), 369 ($M-H_2O$); Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78; Found: C, 68.21; H 6.90.

4.6. 5-Acetoxy-2,2-dimethyl-6-propionyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (2f)

Into a solution of compound **1** (0.5 g, 1.43 mmol) in anhydrous CH_2Cl_2 (10 mL) containing 0.5 mL of dry pyridine and 20 mg of DMAP was added acetic anhydride (183 mg, 1.8 mmol). The resulting mixture was stirred at rt overnight and then quenched with 150 mL of cold 1 N HCl solution, followed by an extraction with AcOEt (2× 25 mL). The organic layers were seperated, combined, and washed with an additional 100 mL of 1 N HCL solution. After being dried over Na_2SO_4, solvents were removed under vacuum and the residue was triturated with 5 mL of hexane to furnish 395 mg of **2f** (71% yield). ^1H NMR ($CDCl_3$): 1.05 (t, $J = 7.2$ Hz, 3H), 1.18 (t, $J = 7.2$ Hz, 3H), 1.53 (s, 6H), 1.67 (sext, $J = 7.5$ Hz, 2H), 2.30 (s, 3H), 2.62 (t, $J = 7.0$ Hz, 2H), 2.92 (t, $J = 7.7$ Hz, 2H), 2.99 (q, $J = 7.2$ Hz, 2H), 5.67 (d, $J = 10.0$ Hz, H), 6.10 (s, 1H), 6.32 (d, $J = 10.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): 8.2, 13.9, 20.5, 23.0, 28.0, 37.6, 38.6, 78.9, 107.7, 111.3, 113.5, 115.7, 116.5, 129.8, 145.6, 152.4, 152.9, 157.2, 159.0, 168.5, 201.4; IR: 1768, 1723, 1697, 1640 cm^{-1}; MS (APCI+) *m*/*z*: 385 (M+1), 343 ($M-C_3H_6$).

4.7. Preparation of 2,2-dimethyl-5-hydroxy-6-(1-hydroxypropyl)-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (3a)

A solution of compound **1** (10.0 g, 29.2 mmol, 1.0 equiv) in a mixture of ethanol (500 mL) and THF (200 mL) was cooled to 0 °C and sodium borohydride (1.7 g, 45.0 mmol, 1.54 equiv) was added portionwise within 1 h. The reaction mixture was allowed to warm up to rt and stirred for 3.5 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (20 mL). The solvents were removed under vacuum and the residue was partitioned between ice-cold 1 N hydrochloric acid (200 mL) and ethyl acetate (500 mL). The organic layer was separated and washed successively with saturated sodium bicarbonate (200 mL) and brine (200 mL). The organic solution was dried over anhydrous sodium sulfate and concentrated under vacuum. The product was purified on a silica gel column eluted with 20–50% ethyl acetate in hexanes, affording 7.1 g of **3a** (71% yield). ^{1}H NMR ($CDCl_3$): 1.00 (t, $J = 7.5$ Hz, 3H), 1.02 (t, $J = 7.5$ Hz, 3H), 1.46 (s, 3H), 1.51 (s, 3H), 1.61 (m, 2H), 1.80-1.94 (m, 2H), 2.75–2.81 (m, 1H), 2.87–2.93 (m, 1H), 4.97 (d, $J = 3.5$ Hz, 1H), 5.55 (d, $J = 10.0$ Hz, 1H), 5.56 (td, $J = 6.5$, 3.5 Hz, 1H), 5.78 (s, 1H), 6.70 (d, $J = 9.5$ Hz, 1H), 10.19 (s, 1H); ^{13}C NMR ($CDCl_3$): 9.6, 14.0, 23.1, 27.5, 28.1, 29.8, 38.6, 70.7, 77.6, 102.9, 107.2, 107.6, 109.1, 116.6, 126.8, 150.9, 151.3, 156.1, 159.7, 162.0; IR: 3300, 3138, 1683, 1574 cm^{-1}; MS (APCI+) *m*/*z*: 327 (M−H_2O+1). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02; Found: C, 69.83; H, 7.04.

4.8. Alkylation of 3a. Preparation of 3b and 3c

To a mixture of 2,2-dimethyl-5-hydroxy-6-(1-hydroxypropyl)-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (**3a**) (1.0 equiv) and K_2CO_3 (10 equiv) in anhydrous DMF (10–15 mL/mmol of starting material) was added alkylating reagent (2.0–2.5 equiv). The reaction mixture was stirred overnight at ambient temperature. The mixture was poured into water (10 volumes of DMF) and extracted with ethyl acetate (50 mL/mmol of starting material). The organic layer was separated, washed with brine, and dried over anhydrous sodium sulfate. Solvent was removed under vacuum and the product purified on a silica gel column eluted with 10–30% ethyl acetate in hexanes.

4.9. 2,2-Dimethyl-6-(1-hydroxypropyl)-5-methoxy-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (3b)

81% yield: ^{1}H NMR ($CDCl_3$): 1.00 (t, $J = 7.5$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H), 1.49 (s, 3H), 1.53 (s, 3H), 1.66 (sext, $J = 7.8$ Hz, 2H), 1.88 (m, 1H), 2.09 (m, 1H), 2.91 (m, 2H), 3.11 (d, $J = 11.0$ Hz, 1H), 3.84 (s, 3H), 5.04 (m, 1H), 5.66 (d, $J = 9.5$ Hz, 1H), 6.04 (s, 1H), 6.54 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): 10.9, 13.9, 23.1, 27.3, 27.8, 30.6, 38.7, 63.1, 69.4, 77.5, 106.9, 111.0, 112.3, 117.1, 117.2, 128.5, 151.2, 153.4, 156.7, 158.1, 156.0; IR: 3442, 1729, 1640, 1605 cm^{-1}; MS (APCI+) *m*/*z*: 359 (M+1), 341 (M+1−H_2O). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.15; H, 7.35.

4.10. 2,2-Dimethyl-6-(1-hydroxypropyl)-5-ethoxy-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (3c)

74% yield: analytical data were identical to those reported in the literature.[5]

4.11. Reduction of 2. Preparation of 3d and 3e

To a solution of 5-alkyloxy-2,2-dimethyl-6-propionyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (**2**) in ethanol (100 mL/mmol) was added portionwise sodium borohydride (3–5 equiv) at 0 °C. The reaction mixture was allowed to reach rt and was stirred until all starting material was consumed (3–4 h). Excess sodium borohydride was quenched with saturated aqueous ammonium chloride and the mixture was concentrated under vacuum. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was chromatographed on a silica gel column to provide the desired compound **3**.

4.12. 2,2-Dimethyl-6-(1-hydroxypropyl)-10-propyl-5-(prop-2-ynyloxy)-2*H*-pyrano[2,3-*f*]chromen-8-one (3d)

40% yield: ^{1}H NMR ($CDCl_3$): 0.99 (t, $J = 7.5$ Hz, 3H), 1.05 (t, $J = 7.5$ Hz, 3H), 1.49 (s, 3H), 1.52 (s, 3H), 1.67 (sext, $J = 7.5$ Hz, 2H), 1.91 (apparent sept, $J = 6.9$ Hz, 1H), 2.14 (apparent sept, $J = 7.4$ Hz, 1H), 2.62 (t, $J = 2.5$ Hz, 1H), 2.92 (td, $J = 7.7$, 3.6 Hz, 2H), 2.96 (s, 1H), 4.60 and 4.64 (d-AB type, $J = 2.5$ Hz, $J_{AB} = 15.5$ Hz, 2H), 5.06-5.11 (m, 1H), 5.67 (d, $J = 10.0$ Hz, 1H), 6.05 (s, 1H), 6.59 (d, $J = 9.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): 10.9, 13.9, 23.1, 27.3, 27.7, 30.3, 38.7, 62.8, 69.4, 76.7, 77. 6, 77.9, 107.5, 111.3, 112.6, 117.2, 117.7, 128.8, 151.2, 153.5, 154.5, 158.0, 159.8; IR: 3594, 3294, 2127, 1714, 1640, 1607 cm^{-1}; MS (APCI+) *m*/*z*: 383 (M+1), 365 (M+1−H_2O). Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.04; H, 7.18.

4.13. 2,2-Dimethyl-5-(2-hydroxyethoxy)-6-(1-hydroxypropyl)-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (3e)

64% yield: ^{1}H NMR ($CDCl_3$): 0.96 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H), 1.49 (s, 3H), 1.52 (s, 3H), 1.66 (m, 2H), 1.94 (apparent sept, $J = 7.0$ Hz, 1H), 2.14 (apparent sept, $J = 7.0$ Hz, 1H), 2.91 (t, $J = 7.7$ Hz, 2H), 3.35-3.39 (br s, 2H), 3.89 and 4.00 (AB type, $J_{AB} = 12.2$ Hz, 2H), 4.05 and 4.15 (dd-AB type, $J_{AB} = 9.4$ Hz, $J = 6.2$, 2.3 Hz, 2H), 5.21 (br s, 1H), 5.64 (d, $J = 10.0$ Hz, 1H), 6.03 (s, 1H), 6.56 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): 10.9, 13.9, 23.1, 27.2, 27.7, 29.9, 38.7, 61.7, 68.7, 77.0, 77.2, 106.6, 111.2, 112.2, 116.9, 117.5, 128.2, 151.3, 153.2, 156.4, 158.2, 160.3; IR: 3392, 1730, 1688, 1604 cm^{-1}; MS (APCI+) *m*/*z*: 371 (M−H_2O+1). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.04; H, 7.21.

4.14. Ring rearrangement of 1. Isolation of 8,8-dimethyl-5-hydroxy-10-propionyl-4-propyl-7,9a-dihydro-8*H*-pyrano[3,2-*g*]chromen-2-one (4)

A mixture of compound **1** (300 mg, 0.87 mmol), K_2CO_3 (1.21 g, 8.76 mmol), and $(n\text{-Bu})_4NCl$ (25 mg, 0.90 mmol) in DMF (20 mL) was stirred at 45 °C for 4 days. TLC analysis revealed the formation of a single product with the R_f value lower than that of the starting compound **1**. The mixture was poured into 200 mL of water and then extracted with ethyl acetate (2× 25 mL). The organic layer was separated, washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was chromatographed on a silica gel column, eluting with 10-30% ethyl acetate in hexanes, to afford 80 mg (27% yield) of compound **4**. ^{1}H NMR ($CDCl_3$): 0.99 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 1.39 (s, 6H), 1.62 (sext, J = 7.3 Hz, 2H), 2.85 (q, J = 7.3 Hz, 2H), 2.89 (apparent t, J = 7.5 Hz, 2H), 5.62 (d, J = 10.0 Hz, 1H), 5.92 (s, 1H), 6.55 (J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): 7.8, 13.9, 22.4, 27.6, 38.2, 38.3, 77.6, 104.7, 107.6, 110.7, 112.4, 115.3, 129.5, 151.0, 151.7, 152.5, 158.9, 160.3, 205.3; IR: 3368, 1711, 1691, 1636 cm^{-1}; MS (APCI+) m/z: 343 (M+1).

4.15. In situ Alkylation of 4. Isolation of 8,8-dimethyl-5-ethoxy-10-propionyl-4-propyl-7,9a-dihydro-8*H*-pyrano[3,2-*g*]chromen-2-one (5)

A mixture of compound **1** (4.4 g, 12.85 mmol) and K_2CO_3 (10.0 g, 72.40 mmol) in DMF (100 mL) was stirred at 55 °C for 27 h. The mixture was then cooled to rt, into which was added 2 mL of EtI. The resulting mixture was continued to stir at rt for 5 h and concentrated under vacuum. The residue was partitioned between water (250 mL) and ethyl acetate (250 mL). The organic layer was separated, washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was chromatographed on a silica gel column, eluting with 10–25% ethyl acetate in hexanes, to afford 1.25 g (26% yield) of compound **5**. ^{1}H NMR ($CDCl_3$): 1.02 (t, J = 7.5 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H), 1.45 (s, 6H), 1.47 (t, J = 7.5 Hz, 3H),1.65 (sext, J = 7.3 Hz, 2H), 2.84 (m, 4H), 3.88 (q, J = 7.0 Hz, 2H), 5.72 (d, J = 10.0 Hz, 1H), 6.04 (s, 1H), 6.51 (J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): 7.7, 13.9, 15.1, 22.5, 27.9, 37.2, 38.2, 72.3, 77.8, 107.5, 112.1, 112.3, 115.9, 116.2, 130.6, 151.7, 152.9, 153.4, 156.8, 159.7, 202.2; MS (APCI+) m/z: 371 (M+1).

4.16. Hydrogenation of 3. Preparation of 6a–6c

A solution of 5-alkyloxy-6-(1-hydroxy-propyl)-2,2-dimethyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (**3**) in ethanol (50 mL/mmol) was flushed with nitrogen for 15 min. Catalyst (100–150 mg per 1 mmol) was added to the solution and the mixture was stirred overnight at ambient temperature under atmospheric pressure of hydrogen. The mixture was filtered through a pad of Celite and the filtrate was concentrated under vacuum. The product was purified on a silica gel column eluted with 15–30% ethyl acetate in hexanes. The representative compounds are shown below.

4.17. 2,2-Dimethyl-5-hydroxy-6-(1-hydroxypropyl)-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (6a)

63% yield: ^{1}H NMR ($CDCl_3$): 0.99 (t, J = 7.5 Hz, 3H), 1.00 (t, J = 7.5 Hz, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 1.60 (sext, J = 7.7 Hz, 2H), 1.74–1.94 (m, 4H), 2.62–2.74 (m, 2H), 2.80–2.90 (m, 2H), 5.12 (d, J = 4.0 Hz, 1H), 5.65 (m, 1H), 5.81 (s, 1H), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$): 9.6, 14.0, 16.8, 23.4, 26.4, 26.9, 30.0, 31.5, 39.2, 70.7, 75.6, 102.8, 106.1, 106.4, 108.9, 150.7, 151.7, 158.6, 160.3, 162.3; IR: 3151, 1684, 1618, 1591 cm^{-1}; MS (APCI+) m/z: 347 (M+1), 329 (M−H_2O+1). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 68.53; H, 7.59.

4.18. 2,2-Dimethyl-5-methoxy-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (6b)

68% yield: ^{1}H NMR ($CDCl_3$): 1.03 (t, J = 7.5 Hz, 3H), 1.22 (t, J = 7.3 Hz, 3H), 1.41 (s, 6H), 1.63 (sext, J = 7.5 Hz, 2H), 1.82 (t, J = 6.7 Hz, 2H), 2.75 (t, J = 6.7 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 2.92 (q, J = 7.3 Hz, 2H), 3.79 (s, 3H), 6.01 (s, 1H); ^{13}C NMR ($CDCl_3$): 8.0, 13.9, 17.2, 23.2, 26.7, 31.3, 38.5, 39.0, 62.1, 76.4, 106.2, 110.7, 112.5, 116.6, 151.3, 153.5, 157.5, 157.9, 159.9, 203.4; IR: 1724, 1704, 1607 cm^{-1}; MS (APCI+) m/z: 359 (M+1). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.15; H, 7.28.

4.19. 2,2-Dimethyl-5-ethoxy-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (6c)

61% yield: ^{1}H NMR ($CDCl_3$): 1.03 (t, J = 7.5 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H), 1.35 (t, J = 7.0 Hz, 3H), 1.41 (s, 6H), 1.63 (sext, J = 7.5 Hz, 2H), 1.82 (t, J = 6.7 Hz, 2H), 2.75 (t, J = 6.7 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 2.91 (q, J = 7.3 Hz, 2H), 3.94 (q, J = 7.0 Hz, 2H), 6.00 (s, 1H); ^{13}C NMR ($CDCl_3$): 8.0, 13.9, 15.6, 17.4, 23.2, 26.7, 31.4, 38.5, 39.0, 70.8, 76.3, 106.1, 110.9, 112.5, 116.9, 151.2, 153.4, 156.7, 157.9, 160.0, 203.5; IR: 1711, 1607 cm^{-1}; MS (APCI+) m/z: 373 (M+1). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.12; H, 7.49.

4.20. Hydrogenation of 1 or 2

A solution of 5-alkyloxy-2,2-dimethyl-6-propionyl-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (**1** or **2**) in ethanol (30–100 mL/mmol) was hydrogenated under atmospheric pressure of hydrogen in the presence of sulfided platinum (5% on carbon, 100 mg/mmol). The reaction was carried out overnight at ambient temperature. The mixture was filtered through a pad of Celite and the filtrate was concentrated under vacuum. The residue was chromatographed on a silica gel column eluted with 15–30% ethyl acetate in hexanes.

4.21. 2,2-Dimethyl-5-hydroxy-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7a)

A mixture of compound **1** (5 g, 14.60 mmol) and sulfided platinum (5% on carbon, 1 g) in toluene/isopropyl alcohol (200/50 mL) was hydrogenated for 16 h at rt under atmospheric pressure of hydrogen. The catalyst was filtered off and the filtrate was concentrated under vacuum. The solid residue was crystallized from ethanol and re-crystallized from acetone to provide 2.66 g of **7a** (53% yield). ^{1}H NMR (CDCl$_3$): 1.03 (t, J = 7.5 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H), 1.42 (s, 6H), 1.64 (m, 2H), 1.84 (t, J = 6.5 Hz, 2H), 2.70 (t, J = 6.5 Hz, 2H), 2.90 (m, 2H), 3.34 (q, J = 7.0 Hz, 2H), 5.98 (s, 1H), 14.61 (s, 1H); ^{13}C NMR (CDCl$_3$): 8.5, 13.9, 16.4, 23.4, 26.6, 31.2, 38.1, 39.4, 77.6, 102.8, 103.4, 105.3, 110.2, 156.4, 157.3, 158.9, 159.8, 165.8, 206.7; IR: 1730 cm^{-1}; MS (APCI+) *m*/*z*: 345 (M+1). Anal. Calcd for C$_{20}$H$_{24}$O$_5$: C, 69.75; H, 7.02. Found: C, 70.03; H, 7.18.

4.22. 2,2-Dimethyl-5-methoxy-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7b)

68% yield: ^{1}H NMR (CDCl$_3$): 1.02 (t, J = 7.5 Hz, 3H), 1.22 (t, J = 7.5 Hz, 3H), 1.41 (s, 6H), 1.62 (m, 2H), 1.82 (t, J = 6.5 Hz, 2H), 2.75 (t, J = 6.5 Hz, 2H), 2.91 (m, 4H), 3.78 (s, 3H), 6.01 (s, 1H); ^{13}C NMR (CDCl$_3$): 8.0, 13.8, 17.2, 23.2, 26.7, 31.3, 38.5, 39.0, 62.1, 76.4, 106.1, 110.7, 112.5, 116.6, 151.2, 153.5, 157.5, 157.9, 159.9, 203.4; IR: 1724, 1704 cm^{-1}; MS (APCI+) *m*/*z*: 359 (M+1). Anal. Calcd for C$_{21}$H$_{26}$O$_5$: C, 70.37; H, 7.31. Found: C, 70.15; H, 7.28.

4.23. 2,2-Dimethyl-5-(2-hydroxyethoxy)-6-propionyl-10-propyl-3,4,9,10-tetrahydro-2*H*-pyrano[2,3-*f*]chromen-8-one (8)

59% yield: ^{1}H NMR (CDCl$_3$): 0.92 (t, J = 7.0 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H), 1.23–1.39 (m, 2H), 1.34 (s, 3H), 1.40 (s, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 2.73 (m, 2H), 2.74 and 2.84 (d-AB type, J_{AB} = 15.9 Hz, J = 6.5, 1.7 Hz, 2H), 2.86 (q, J = 7.2 Hz, 2H), 3.07 (t, J = 6.2 Hz, 1H), 3.33 (q, J = 6.5 Hz, 1H), 3.83 (dd, J = 8.7, 5.7 Hz, 2H), 4.03 (dd, J = 4.2, 3.7 Hz, 2H); ^{13}C NMR (CDCl$_3$): 8.1, 13.9, 17.7, 19.8, 26.3, 27.2, 28.4, 31.8, 34.1, 36.3, 38.7, 62.1, 75.3, 76.3, 110.7, 111.1, 116.2, 147.2, 152.6, 153.6, 167.6, 204.9; IR: 3258, 1775, 1700 cm^{-1}; MS (APCI+) *m*/*z*: 391 (M+1), 373 (M+1-H$_2$O). Anal. Calcd for C$_{22}$H$_{30}$O$_6$: C, 67.67; H, 7.74. Found: C, 67.30; H, 7.62.

4.24. 2,2-Dimethyl-5-(2-hydroxyethoxy)-8-oxo-10-propyl-3,4-dihydro-2*H*,8*H*-pyrano[2,3-*f*]chromen-6-carboxylic acid methyl ester (9)

^{1}H NMR (CDCl$_3$): 0.91 (t, J = 7.2, 3H), 1.17 (t, J = 7.2, 3H), 1.18 (s, 3H), 1.25 (s, 3H), 1.37 (sext, J = 7.2 Hz, 1H), 1.45 (sext, J = 7.2 Hz, 1H), 1.69 (t, J = 6.5 Hz, 2H), 2.32 and 2.51 (t-AB Type, J_{AB} = 15.0, J_t = 7.5 Hz, 2H), 2.64 (m, 2H), 3.12 (q, J = 7.3 Hz, 1H), 3.92 (m, 2H), 3.96 (m, 2H), 5.94 (s, 1H); ^{13}C NMR (CDCl$_3$): 8.8, 13.8, 17.2, 20.5, 26.5, 26.8, 32.0, 35.8, 40.4, 61.9, 75.5, 75.7, 106.4, 108.6, 112.6, 119.3, 155.1, 157.2, 158.5, 170.6, 206.5; IR: 3250, 1694, 1648, 1612 cm^{-1}; MS (APCI−) *m*/*z*: 405 (M−1), 361 (M−CO$_2$). Anal. Calcd for C$_{22}$H$_{30}$O$_7$: C, 65.01; H, 7.44. Found: C, 64.69; H, 7.45.

4.25. Alkylation of 7a

To a mixture of compound **7a** and potassium carbonate (10 equiv) in DMF (15 mL/mmol) was added alkyl halide (2–5 equiv) and the reaction was carried out for 16 h at ambient temperature. The mixture was partitioned between water (10 volumes of DMF) and ethyl acetate (50 mL/mmol). The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuum. The product was purified by column chromatography. The representative compounds are shown below.

4.26. 2,2-Dimethyl-6-propionyl-10-propyl-5-(prop-2-ynyloxy)-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7d)

72% yield: ^{1}H NMR (CDCl$_3$): 1.03 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.5 Hz, 3H), 1.42 (s, 6H), 1.64 (sext, J = 7.5 Hz, 2H), 1.83 (t, J = 7.0 Hz, 2H), 2.54 (t, J = 2.7, 1H), 2.85 (t, J = 6.7 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.93 (q, J = 7.2 Hz, 2H), 4.62 (d, J = 2.5 Hz, 2H), 6.03 (s, 1H); ^{13}C NMR (CDCl$_3$): 8.0, 13.9, 17.7, 23.2, 26.7, 31.4, 38.4, 39.0, 62.6, 75.1, 76.5, 78.2, 106.8, 111.7, 112.9, 117.2, 151.2, 153.6, 155.4, 157.8, 159.7, 203.3; IR: 3231, 2113, 1710, 1607, 1580 cm^{-1}; MS (APCI+) *m*/*z*: 383 (M+1).

4.27. 5-Allyloxy-2,2-dimethyl-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7e)

93% yield: ^{1}H NMR (CDCl$_3$): 1.03 (t, J = 7.5 Hz, 3H), 1.21 (t, J = 7.5 Hz, 3H), 1.41 (s, 6H), 1.63 (sext, J = 7.5 Hz, 2H), 1.82 (t, J = 6.7 Hz, 2H), 2.76 (t, J = 6.7 Hz, 2H), 2.89–2.94 (m, 4H), 4.40 (dm, J = 6.0 Hz, 2H), 5.25 (dm, J = 6.0 Hz, 1H), 5.38 (dm, J = 17.5 Hz, 1H), 5.96–6.04 (m, 1H), 6.01 (s, 1H); ^{13}C NMR (CDCl$_3$): 7.9, 13.8, 17.5, 23.2, 26.7, 31.4, 38.5, 39.0, 75,6, 76.3, 106.3, 111.0, 112.6, 117.0, 118.1, 132.9, 151.1, 153.4, 156.3, 157.9, 159.9, 203.4; IR: 1710, 1605, 1577 cm^{-1}; MS (APCI+) *m*/*z*: 385 (M+1).

4.28. 2,2-Dimethyl-5-isopropoxy-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7f)

89% yield: ^{1}H NMR (CDCl$_3$): 1.03 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.25 (d, J = 6.0 Hz, 6H), 1.41 (s, 6H), 1.63 (sext, J = 7.6 Hz, 2H), 1.80 (t, J = 6.7 Hz, 2H), 2.74 (t, J = 6.7 Hz, 2H), 2.90 (q, J = 7.2 Hz, 4H), 4.27 (sept, J = 6.0 Hz, 1H), 6.00 (s, 1H); ^{13}C NMR (CDCl$_3$): 7.9, 13.9, 18.2, 22.4, 23.2, 26.7, 31.6, 38.4, 39.0, 76.2, 77.5, 105.9, 111.4, 112.4, 116.9, 151.1, 153.3, 155.5, 157.9, 160.1, 203.5; IR: 1711 cm^{-1}; MS (APCI+) *m*/*z*: 387 (M+1). Anal. Calcd for C$_{23}$H$_{30}$O$_5$: C, 71.48; H, 7.82. Found: C, 71.61; H, 7.89.

4.29. 5-(2-Acetoxyethoxy)-2,2-dimethyl-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7g)

82% yield: ^{1}H NMR (CDCl$_3$): 1.03 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.42 (s, 6H), 1.63 (sext, J = 7.5 Hz, 2H), 1.83 (t, J = 6.7 Hz, 2H), 2.12 (s, 3H), 2.77 (t, J = 7.0 Hz, 2H), 2.92 (apparent qui, J = 7.5 Hz, 4H), 4.09 (t, J = 4.5 Hz, 2H), 4.34 (t, J = 4.7 Hz, 2H), 6.02 (s, 1H); ^{13}C NMR (CDCl$_3$): 7.9, 13.8, 17.2, 20.8, 23.2, 26.7, 31.3, 38.5, 39.0, 63.1, 76.5, 76.4, 106.5, 110.8, 112.7, 116.9, 151.2, 153.5, 155.8, 157.8, 159.8, 170.7, 203.3; IR: 1727, 1692, 1607 cm^{-1};

MS (APCI+) *m*/*z*: 431 (M+1). Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.82; H, 7.00.

4.30. 2,2-Dimethyl-5-(2-hydroxyethoxy)-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7h)

33% yield: ^{1}H NMR ($CDCl_3$): 1.03 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.5 Hz, 3H), 1.43 (s, 6H), 1.63 (sext, J = 7.5 Hz, 2H), 1.82 (t, J = 6.7 Hz, 2H), 2.79 (t, J = 6.7 Hz, 2H), 2.91 and 2.94 (t-AB type, $J = J_{AB}$ = 7.4 Hz, 4H), 3.05 (t, J = 6.5 Hz, 1H), 3.85 (m, 2H), 4.07 (t, J = 4.5 Hz, 2H), 6.02 (s, 1H); ^{13}C NMR ($CDCl_3$): 8.1, 13.9, 17.9, 23.2, 26.7, 31.4, 38.6, 39.0, 62.1, 76.5, 76.5, 106.2, 110.5, 112.6, 116.4, 151.5, 153.9, 156.7, 157.9, 159.8, 204.7; IR: 3349, 1720, 1694 cm^{-1}; MS (APCI+) *m*/*z*: 388 (M+1). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 68.03; H, 7.30.

4.31. 2,2-Dimethyl-5-methoxymethoxy-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7i)

92% yield: ^{1}H NMR ($CDCl_3$): 1.03 (t, J = 7.5 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.41 (s, 6H), 1.63 (sext, J = 7.5 Hz, 2H), 1.82 (t, J = 6.7 Hz, 2H), 2.81 (t, J = 6.7 Hz, 2H), 2.91 (t, J = 7.7 Hz, 2H), 2.93 (q, J = 7.2 Hz, 2H), 3.52 (s, 3H), 5.00 (s, 2H), 6.02 (s, 1H); ^{13}C NMR ($CDCl_3$): 7.9, 13.8, 17.9, 23.2, 26.7, 31.5, 38.4, 39.0, 57.5, 76.4, 100.7, 106.5, 111.3, 112.7, 117.2, 151.3, 153.5, 155.2, 157.9, 159.8, 203.1; IR: 1707 cm^{-1}; MS (APCI+) *m*/*z*: 389 (M+1).

4.32. 2,2-Dimethyl-5-(2-morpholin-4-yl-ethoxy)-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7j)

73% yield: ^{1}H NMR ($CDCl_3$): 1.03 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 1.41 (s, 6H), 1.63 (sext, J = 7.5 Hz, 2H), 1.82 (t, J = 6.7 Hz, 2H), 2.53 (m, 4H), 2.71 (t, J = 5.5 Hz, 2H), 2.78 (t, J = 6.7 Hz, 2H), 2.91 (qui, J = 7.2 Hz, 4H), 3.74 (t, J = 4.7 Hz, 4H), 4.01 (t, J = 5.5 Hz, 2H), 6.01 (s, 1H); ^{13}C NMR ($CDCl_3$): 7.9, 13.9, 17.4, 23.2, 26.7, 31.4, 38.5, 39.0, 53.9, 58.3, 66.9, 71.8, 76.3, 106.3, 110.9, 112.6, 117.0, 151.2, 153.5, 156.4, 157.9, 159.9, 203.5; IR: 1713 cm^{-1}; MS (APCI+) *m*/*z*: 458 (M+1). Anal. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 68.14; H, 7.77; N 3.04.

4.33. 2-(2,2-Dimethyl-8-oxo-6-propionyl-10-propyl-3,4-dihydro-2*H*,8*H*-pyrano[2,3-*f*]chromen-5-yloxy)-acetic acid ethyl ester (7k)

81% yield: ^{1}H NMR ($CDCl_3$): 1.03 (t, J = 7.5 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.41 (s, 6H), 1.63 (sext, J = 7.5 Hz, 2H), 1.82 (t, J = 6.7 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H), 2.90 (apparent t, J = 7.7 Hz, 2H), 2.95 (q, J = 7.0 Hz, 2H), 4.27 (q, J = 7.0 Hz, 2H), 4.52 (s, 2H), 6.03 (s, 1H); ^{13}C NMR ($CDCl_3$): 7.9, 13.8, 14.1, 17.3, 23.2, 26.7, 31.3, 38.5, 39.0, 61.3, 71.2, 76.6, 106.7, 111.0, 112.9, 116.8, 151.3, 153.7, 155.5, 157.8, 159.7, 168.2, 203.4; IR: 1758, 171 cm^{-1}; MS (APCI+) *m*/*z*: 431 (M+1). Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02; Found: C, 66.76; H, 7.02.

4.34. 5-Acetoxy-2,2-Dimethyl-6-propionyl-10-propyl-3,4-dihydro-2*H*-pyrano[2,3-*f*]chromen-8-one (7l)

84% yield by following the procedures described for **2f**. ^{1}H NMR ($CDCl_3$): 1.04 (t, J = 7.5 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 1.42 (s, 6H), 1.65 (sext, J = 8.0 Hz, 2H), 1.83 (t, J = 6.7 Hz, 2H), 2.29 (s, 3H), 2.62 (t, J = 7.0 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 2.99 (q, J = 7.3 Hz, 2H), 6.09 (s, 1H); ^{13}C NMR ($CDCl_3$): 8.2, 13.8, 17.4, 20.5, 23.1, 26.6, 31.0, 37.7, 39.0, 107.8, 111.0, 113.4, 115.7, 148.5, 151.7, 154.0, 157.8, 159.4, 168.4, 201.6; IR: 1762, 1726, 1716, 1695, 1610 cm^{-1}; MS (APCI+) *m*/*z*: 387 (M+1).

4.35. Toluene-4-sulfonic acid 2,2-dimethyl-8-oxo-6-propionyl-10-propyl-3,4-dihydro-2*H*,8*H*-pyrano[2,3-*f*]chromen-5-yl ester (7m)

85% yield: ^{1}H NMR ($CDCl_3$): 1.04 (t, J = 7.5 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H), 1.41 (s, 6H), 1.64 (sext, J = 8.0 Hz, 2H), 1.78 (t, J = 6.7 Hz, 2H), 2.48 (s, 3H), 2.84 (t, J = 6.7 Hz, 2H), 2.92 (t, J = 7.7 Hz, 2H), 2.99 (q, J = 7.0 Hz, 2H), 6.10 (s, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): 7.8, 13.8, 18.3, 21.7, 23.1, 26.6, 31.2, 38.0, 39.0, 77.2, 108.6, 112.9, 114.0, 118.0, 128.3, 129.9, 132.7, 145.4, 145.9, 151.1, 153.8, 157.5, 159.2, 200.8; IR: 1733, 1699, 1610 cm^{-1}; MS (APCI+) *m*/*z*: 499 (M+1).

4.36. 5,10-Dihydroxy-8,9-dimethyl-4-propyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (11a and 12a)

A solution of 5-hydroxy-8,9-dimethyl-4-propyl-8,9-dihydro-pyrano[2,3-*f*]chromene-2,10-dione (**10**)[7] (2 g, 6.61 mmol, 1.00 equiv) and cerium(III) chloride septahydrate (2.5 g, 6.71 mol, 1.02 equiv) in methanol (300 mL) was cooled to 0 °C. Sodium borohydride (0.62 g, 16.39 mmol, 2.48 equiv) was added portionwise to the stirred solution within 1 h while the temperature was maintained at 0-5 °C. The reaction mixture was allowed to warm up to rt and stirring was continued for 2 h. Solvent was removed under vacuum and the residue was partitioned between dichloromethane (200 mL) and ice-cold 1 N hydrochloric acid (100 mL). The organic layer was separated, washed successively with saturated solution of sodium bicarbonate (200 mL) and brine (200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum yielding 1.97 g (98%) of a mixture of **11a** and **12a**. The crude product was used for the next step without further purification.

4.37. Alkylation of 11a and 12a

To a stirred mixture of a crude 10-hydroxy-5-methoxy-8,9-dimethyl-4-propyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]-chromen-2-one (**11a** and **12a**) (0.5 g, 1.64 mmol, 1.00 equiv) and potassium carbonate (4.18 g, 30.24 mmol, 18.44 equiv) in anhydrous DMF (50 mL) was added alkylating reagent (4.00–5.00 equiv). The reaction mixture was stirred overnight at rt. The mixture was then poured into water (200 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated and washed successively with water (2× 100 mL) and brine. The organic solution was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a short silica gel column (15–30% ethyl acetate in hexanes) to provide a mixture of isomers. Two major isomers were separated on preparative HPLC (Alltech Econosil 10 μm, 250 × 22 mm column, 15–30% ethyl acetate in hexanes) in a ratio of 65:45. The representative compounds are shown below.

4.38. 8,9-Dimethyl-10-hydroxy-5-methoxy-4-propyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (11b and 12b)

69% combined yield. **11b**: ^{1}H NMR (CDCl$_3$) δ 1.01 (3H, t, J = 7.5 Hz), 1.15 (3H, d, J = 7.0 Hz), 1.42 (3H, d, J = 6.5 Hz), 1.61 (2H, sext, J = 7.0 Hz), 2.29 (1H, qdd, J = 7.5, 4.5, 3.5 Hz), 2.80–2.92 (2H, m), 3.17 (1H, d, J = 3.5 Hz), 3.86 (3H, s), 4.37 (1H, qd, J = 6.6, 3.3 Hz), 5.10 (1H, dd, J = 5.0, 3.5 Hz), 5.96 (1H, s), 6.25 (1H, s); ^{13}C NMR (CDCl$_3$) δ 9.5, 14.0, 16.1, 22.8, 35.7, 38.7, 55.7, 75.7, 96.0, 104.1, 106.0, 109.9, 155.6, 156.9, 158.1, 159.0, 160.7; IR (film) 3471, 2998, 2963, 2937, 2891, 2873, 1702, 1614, 1584, 1486, 1455, 1378, 1346, 1300, 1280, 1204, 1158, 1115, 1063, 1031, 965, 820 cm^{-1}; MS (APCI+) *m*/*z*: 319 (M+1), 301 (M−OH). Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.65; H, 7.08. **12b**: ^{1}H NMR (CDCl$_3$) δ 1.01 (3H, t, J = 7.5 Hz), 1.14 (3H, d, J = 7.0 Hz), 1.45 (3H, d, J = 6.0 Hz), 1.61 (2H, sext, J = 7.3 Hz), 1.94 (1H, sext, J = 7.2 Hz), 2.80–2.92 (2H, m), 3.60 (1H, d, J = 2.5 Hz), 3.85 (3H, s), 3.95 (1H, dq, J = 8.7, 6.2 Hz), 4.73 (1H, dd, J = 7.5, 2.5 Hz), 5.96 (1H, s), 6.26 (1H, s); ^{13}C NMR (CDCl$_3$) δ 14.0, 15.1, 18.9, 22.9, 38.7, 40.4, 55.8, 66.9, 77.1, 95.9, 104.4, 106.5, 109.9, 155.5, 157.9, 158.0, 159.0, 160.5; IR (film) 3480, 3403, 2965, 2934, 2898, 2872, 1695, 1615, 1585, 1465, 1374, 1346, 1327, 1297, 1233, 1200, 1166, 1129, 1116, 1109, 1060, 1031, 819 cm^{-1}; MS (APCI+) *m*/*z*: 319 (M+1), 301 (M−OH). Anal. Calcd for $C_{18}H_{22}O_5 \cdot 1/4H_2O$: C, 66.96; H, 7.02. Found: C, 66.92; H, 7.13.

4.39. 8,9-Dimethyl-10-hydroxy-4-propyl-5-(*i*-propyloxy)-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (11c and 12c)

74% combined yield. **11c**: ^{1}H NMR (CDCl$_3$) δ 1.01 (3H, t, J = 7.2 Hz), 1.14 (3H, d, J = 7.5 Hz), 1.40 (6H, d, J = 6.0 Hz), 1.41 (3H, d, J = 6.5 Hz), 1.63 (2H, sext-d, J = 7.9, 2.2 Hz), 2.24–2.32 (1H, m), 2.82-2.95 (2H, m), 3.31 (1H, br s), 4.35 (1H, qd, J = 6.7, 3.1 Hz), 4.64 (1H, sept, J = 6.0 Hz), 5.09 (1H, d, J = 5.0 Hz), 5.94 (1H, s), 6.22 (1H, s); ^{13}C NMR (CDCl$_3$) δ 9.5, 13.9, 16.1, 21.7, 23.2, 35.8, 39.0, 62.9, 70.7, 75.7, 97.0, 104.5, 105.5, 109.9, 155.8, 156.2, 156.9, 159.3, 160.8; IR (film) 3433, 2975, 2934, 2874, 1723, 1701, 1615, 1584, 1480, 1451, 1381, 1349, 1331, 1298, 1231, 1202, 1161, 1130, 1108, 1062, 1034, 967, 830 cm^{-1}; MS (APCI+) *m*/*z*: 347 (M+1). Anal. Calcd for $C_{20}H_{26}O_5 \cdot 2/3\ H_2O$: C, 67.02; H, 7.69. Found: C, 67.08; H, 7.68. **12c**: ^{1}H NMR (CDCl$_3$) δ 1.01 (3H, t, J = 7.5 Hz), 1.14 (3H, d, J = 7.0 Hz), 1.39 (3H, d, J = 6.5 Hz), 1.41 (3H, d, J = 6.0 Hz), 1.44 (3H, d, J = 6.5 Hz), 1.62 (2H, sext, J = 7.3 Hz), 1.91–1.97 (1H, m), 2.83–2.94 (2H, m), 3.61 (1H, br s), 3.90–3.98 (1H, m), 4.63 (1H, sept, J = 6.0 Hz), 4.72 (1H, d, J = .0 Hz), 5.94 (1H, s), 6.23 (1H, s); ^{13}C NMR (CDCl$_3$) δ 13.9, 15.1, 18.9, 21.6, 21.8, 23.2, 39.0, 40.5, 67.0, 70.7, 76.7, 96.9, 104.8, 106.1, 109.9, 155.7, 156.1, 157.9, 159.3, 160.6; IR (film) 3357, 2969, 2934, 2873, 1722, 1696, 1615, 1585, 1480, 1453, 1377, 1350, 1295, 1232, 1199, 1169, 1110, 1063, 1029 cm^{-1}; MS (APCI+) *m*/*z*: 347 (M+1), 329 (M−OH). Anal. Calcd for $C_{20}H_{26}O_5 \cdot H_2O$: C, 65.92; H, 7.74. Found: C, 65.46; H, 7.48.

4.40. 8,9-Dimethyl-10-hydroxy-4-propyl-5-(prop-2-ynyloxy)-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (11d and 12d)

71% combined yield. **11d**: ^{1}H NMR (CDCl$_3$) δ 1.03 (3H, t, J = 7.2 Hz), 1.15 (3H, d, J = 7.0 Hz), 1.42 (3H, d, J = 7.0 Hz), 1.63 (2H, sext, J = 7.1 Hz), 2.28 (1H, qdd, J = 7.0, 5.0, 3.0 Hz), 2.58 (1H, t, J = 2.5 Hz), 2.82–2.94 (2H, m), 3.21 (1H, d, J = 3.0 Hz), 4.37 (1H, qd, J = 6.7, 3.0 Hz), 4.72 and 4.73 (2H, d-AB type, J_{AB} = 15.4 Hz, J = 2.5 Hz), 5.10 (1H, dd, J = 5.0, 2.0 Hz), 5.98 (1H, s), 6.32 (1H, s); ^{13}C NMR (CDCl$_3$) δ 9.5, 13.9, 16.1, 23.0, 35.7, 38.8, 56.4, 62.9, 75.8, 76.4, 97.2, 104.3, 106.7, 107.9, 110.4, 155.6, 155.9, 156.7, 158.7, 160.5; IR (film) 3431, 3288, 2962, 2936, 2874, 2125, 1706, 1616, 1588, 1483, 1454, 1384, 1349, 1297, 1231, 1202, 1161, 1130, 1107, 1064, 1035, 1000, 968 cm^{-1}; MS (APCI+) *m*/*z*: 343 (M+1), 325 (M−OH). Anal. Calcd for $C_{20}H_{22}O_5 \cdot 1/2H_2O$: C, 68.36; H, 6.60. Found: C, 68.26; H, 6.57. **12d**: ^{1}H NMR (CDCl$_3$) δ 1.03 (3H, t, J = 7.2 Hz), 1.15 (3H, d, J = 7.0 Hz), 1.45 (3H, d, J = 6.5 Hz), 1.63 (2H, sext, J = 7.2 Hz), 1.94 (1H, sext, J = 7.8 Hz), 2.58 (1H, t, J = 2.5 Hz), 2.82-2.94 (2H, m), 3.70 (1H, d, J = 3.0 Hz), 3.95 (1H, dq, J = 8.7, 6.7 Hz), 4.72 (3H, m), 5.99 (1H, s), 6.32 (1H, s); ^{13}C NMR (CDCl$_3$) δ 13.9, 15.1, 18.9, 23.0, 38.8, 40.4, 56.4, 66.9, 76.4, 76.8, 97.0, 104.6, 107.4, 107.9, 110.3, 155.5, 155.7, 157.8, 158.9, 160.5; IR (film) 3467, 3380, 3212, 2964, 2933, 2899, 2872, 2117, 1699, 1613, 1589, 1458, 1384, 1344, 1326, 1292, 1259, 1235, 1170, 1127, 1110, 1065, 1034, 997, 813 cm^{-1}; MS (APCI+) *m*/*z*: 343 (M+1), 325 (M−OH). Anal. Calcd for $C_{20}H_{22}O_5 \cdot 1/2H_2O$: C, 68.36; H, 6.60. Found: C, 68.37; H, 6.91.

4.41. 5-(Allyloxy)-8,9-dimethyl-10-hydroxy-4-propyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (11e and 12e)

69% combined yield. **11e**: ^{1}H NMR (CDCl$_3$) δ 0.99 (3H, t, J = 7.2 Hz), 1.14 (3H, d, J = 7.0 Hz), 1.41 (3H, d, J = 6.5 Hz), 1.61 (2H, sext, J = 7.5 Hz), 2.24–2.31 (1H, m), 2.82–2.94 (2H, m), 3.29 (1H, br s), 4.36 (1H, qd, J = 6.7, 3.5 Hz), 4.56 (2H, d, J = 6.0 Hz), 5.09 (1H, d, J = 5.0 Hz), 5.36 (1H, dd, J = 9.5, 2.0 Hz), 5.43 (1H, dd, J = 17.0, 1.5 Hz), 5.96 (1H, s), 6.03–6.11 (1H, m), 6.24 (1H, s); ^{13}C NMR (CDCl$_3$) δ 9.7, 13.9, 16.1, 23.0, 35.7, 38.8, 62.9, 70.0, 75.7, 96.9, 104.2, 106.1, 110.0, 119.2, 132.0, 155.6, 156.8, 157.1, 159.0, 160.7; IR (film) 3436, 3083, 2964, 2934, 2874, 1723, 1617, 1587, 1483, 1456, 1423, 1382, 1350, 1299, 1231, 1195, 1162, 1108, 1064, 1034, 991, 967, 924, 819 cm^{-1}; MS (APCI+) *m*/*z*: 345 (M+1). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.17; H, 7.09. **12e**: ^{1}H NMR (CDCl$_3$) δ 0.99 (3H, t, J = 7.2 Hz), 1.14 (3H, d, J = 7.0 Hz), 1.45 (3H, d, $J = 6.0$ Hz), 1.61 (2H, sext, $J = 7.3$ Hz), 1.94 (1H, sext, $J = 7.0$ Hz), 2.82–2.94 (2H, m), 3.67 (1H, d $J = 3.0$ Hz), 3.94 (1H, dq, $J = 8.5$, 6.2 Hz), 4.56 (2H, d, $J = 5.5$ Hz), 4.72 (1H, dd, $J = 8.0$, 2.5 Hz), 5.36 (1H, dd, $J = 10.5$, 1.0 Hz), 5.42 (1H, dd, $J = 17.0$, 1.0 Hz), 5.96 (1H, s), 6.03–6.11 (1H, m), 6.25 (1H, s); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.1, 18.9, 23.0, 38.9, 40.4, 66.9, 70.0, 76.7, 96.8, 104.5, 106.7, 110.0, 119.2, 132.0, 155.5, 156.9, 157.8, 159.1, 160.5; IR (film) 3448, 2970, 2936, 2891, 2870, 1690, 1615, 1583, 1485, 1455, 1377, 1359, 1347, 1289, 1229, 1200, 1175, 1106, 1065, 1054, 1036, 819 cm^{-1}; MS (APCI+) *m/z*: 345 (M+1), 327 (M−OH). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 68.94; H, 7.16.

4.42. 8,9-Dimethyl-10-hydroxy-5-(1-methylallyloxy)-4-propyl-9,10-dihydro-8H-pyrano[2,3-*f*]chromen-2-one (11f and 12f)

75% combined yield. **11f**: ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, t, $J = 7.2$ Hz) [0.98 (t, $J = 7.2$ Hz)], 1.14 (3H, d, $J = 7.0$ Hz) [1.13 (d, $J = 7.0$ Hz)], 1.40 (3H, d, $J = 6.5$ Hz), 1.50 (3H, d, $J = 6.5$ Hz) [1.51 (d, $J = 6.0$ Hz)], 1.64 (2H, sext, $J = 7.2$ Hz) [1.61 (sext, $J = 7.1$ Hz)], 2.27 (1H, qdd, $J = 7.0$, 4.5, 1.0 Hz), 2.82-2.96 (2H, m), 3.18 (1H, br s), 4.34 (1H, qd, $J = 7.0$, 3.0 Hz), 4.89 (1H, sext, $J = 4.0$ Hz), 5.10 (1H, dd, $J = 4.5$, 2.5 Hz), 5.25 (1H, d, $J = 10.5$ Hz), 5.30 (1H, dd, $J = 16.5$, 1.0 Hz), 5.86–5.95 (1H, m), 5.95 (1H, s), 6.23 (1H, s) [6.24 (1H, s)]; ^{13}C NMR ($CDCl_3$) δ 9.5, 13.9, 16.1, 21.0 (21.2), 23.2 (23.1), 35.7, 39.0 (38.9), 63.0, 69.7, 75.7 (75.6), 98.0 (96.8), 104.4 (104.2), 105.8 (105.7), 110.1 (110.0), 116.7 (116.6), 137.8, 155.7, 156.3, 156.7 (157.2), 159.1, 160.7; IR (film) 3438, 3086, 2963, 2934, 2874, 1721, 1616, 1586, 1480, 1448, 1380, 1349, 1296, 1231, 1199, 1162, 1130, 1104, 1064, 1035, 967 cm^{-1}; MS (APCI+) *m/z*: 359 (M+1), 341 (M−OH), 287 (M−OH−C_4H_6). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 69.99; H, 7.21. **12f**: ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, t, $J = 7.2$ Hz) [0.98 (t, $J = 7.2$ Hz)], 1.14 (3H, d, $J = 6.5$ Hz) [1.13 (d, $J = 7.0$ Hz)], 1.43 (3H, d, $J = 6.5$ Hz), 1.50 (3H, d, $J = 6.5$ Hz) [1.51 (d, $J = 6.0$ Hz)], 1.64 (2H, sext, $J = 7.5$ Hz) [1.61 (sext, $J = 7.2$ Hz)], 1.92 (1H, sext, $J = 7.2$ Hz), 2.82–2.96 (2H, m), 3.58 (1H, br s), 3.92 (1H, m), 4.71 (1H, dd, $J = 7.5$, 2.0 Hz), 4.88 (1H, sext, $J = 6.0$ Hz), 5.23–5.32 (2H, m), 5.85–5.95 (1H, m), 5.96 (1H, s), 6.24 (1H, s) [6.23 (1H, s)]; ^{13}C NMR ($CDCl_3$) δ 13.8, 15.1, 18.9, 21.1, 23.2 (23.1), 39.0 (38.9), 40.4, 67.0, 69.7, 75.6 (75.5), 97.8 (96.6), 104.6 (104.5), 106.4, 110.0, 116.7 (116.6), 137.8 (137.6), 155.5, 156.1, 157.8 (157.1), 159.1, 160.5; IR (film) 3427, 2966, 2933, 2873, 1723, 1617, 1587, 1480, 1448, 1376, 1293, 1232, 1195, 1172, 1104, 1064, 1028, 992, 895, 830 cm^{-1}; MS (APCI+) *m/z*: 359 (M+1), 341 (M−OH), 287 (M−OH−C_4H_6). Anal. Calcd for $C_{21}H_{26}O_5 \cdot 1/2H_2O$: C, 68.65; H, 7.27. Found: C, 68.89; H, 7.39.

4.43. 8,9-Dimethyl-10-hydroxy-5-(2-methylallyloxy)-4-propyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (11g and 12g)

75% combined yield. **11g**: ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, t, $J = 7.2$ Hz), 1.14 (3H, d, $J = 7.0$ Hz), 1.41 (3H, d, $J = 7.0$ Hz), 1.62 (2H, sext, $J = 7.2$ Hz), 1.87 (3H, s), 2.24–2.31 (1H, m), 2.82–2.94 (2H, m), 3.23 (1H, d, $J = 3.0$ Hz), 4.36 (1H, qd, $J = 6.7$, 3.2 Hz), 4.47 (2H, s), 5.06 (1H, s), 5.09 (2H, s), 5.97 (1H, s), 6.25 (1H, s); ^{13}C NMR ($CDCl_3$) δ 9.5, 13.8, 16.1, 22.8, 35.7, 38.7, 62.9, 73.2, 75.7, 97.0, 104.2, 106.1, 109.9, 114.5, 139.6, 155.6, 155.8, 157.4, 159.0, 160.6; IR (film) 3513, 3083, 2957, 2932, 2911, 2874, 1707, 1616, 1587, 1487, 1460, 1438, 1382, 1368, 1261, 1202, 1159, 1132, 1110, 1063, 1033, 970, 923, 843, 823 cm^{-1}; MS (APCI+) *m/z*: 359 (M+1), 341 (M−OH). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.08; H, 7.32. **12g**: ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, t, $J = 7.2$ Hz), 1.14 (3H, d, $J = 6.5$ Hz), 1.44 (3H, d, $J = 6.0$ Hz), 1.62 (2H, sext, $J = 7.3$ Hz), 1.86 (3H, s), 1.94 (1H, sext, $J = 7.2$ Hz), 2.82–2.94 (2H, m), 3.71 (1H, br s), 3.94 (1H, dq, $J = 8.7$, 6.2 Hz), 4.47 (2H, s), 4.72 (1H, d, $J = 7.5$ Hz), 5.06 (1H, s), 5.09 (1H, s), 5.97 (1H, s), 6.25 (1H, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 15.1, 18.9, 19.7, 22.8, 38.8, 40.4, 66.9, 73.2, 76.7, 96.9, 104.5, 106.7, 109.8, 114.5, 139.6, 155.5, 157.2, 157.8, 159.1, 160.6; IR (film) 3441, 3203, 2938, 2900, 2874, 1698, 1618, 1586, 1486, 1384, 1355, 1325, 1297, 1275, 1229, 1210, 1174, 1127, 1109, 1068, 1029, 882 cm^{-1}; MS (APCI+) *m/z*: 359 (M+1), 341 (M−OH). Anal. Calcd for $C_{21}H_{26}O_5 \cdot 1/4H_2O$: C, 69.50; H, 7.36. Found: C, 69.47; H, 7.38.

4.44. Alkylation of 13a

The same procedure as used in the preparation of **2**.

4.45. 5,7-Dimethoxy-8-propionyl-4-propyl-chromen-2-one (13b)

^{1}H NMR ($CDCl_3$): 1.01 (t, $J = 7.5$ Hz, 3H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.61 (sext, $J = 7.5$ Hz, 2H), 2.85 (m, 4H), 3.89 (s, 3H), 3.95 (s, 3H), 5.96 (s, 1H), 6.33 (s, 1H). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.21; H, 6.66.

4.46. 5,7-Bis(isopropyloxy)-8-propionyl-4-propyl-chromen-2-one (13c)

^{1}H NMR ($CDCl_3$): 1.00 (t, $J = 7.5$ Hz, 3H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.34 (d, $J = 6.0$ Hz, 3H), 1.43 (d, $J = 6.0$ Hz, 3H), 1.61 (sext, $J = 7.5$ Hz, 2H), 2.81 (q, $J = 7.3$ Hz, 2H), 2.86 (apparent t, $J = 7.5$ Hz, 2H), 4.57 (m, 1H), 4.68 (m, 1H), 5.93 (s, 1H), 6.28 (s, 1H). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.41; H, 7.84.

4.47. 5,7-Bis(allyloxy)-8-propionyl-4-propyl-chromen-2-one (13d)

^{1}H NMR ($CDCl_3$): 1.00 (t, $J = 7.2$ Hz, 3H), 1.19 (t, $J = 7.5$ Hz, 3H), 1.61 (sext, $J = 7.5$ Hz, 2H), 2.85 (q, $J = 7.3$ Hz, 2H), 2.87 (apparent t, $J = 7.5$ Hz, 2H), 4.61 (m, 4H), 5.31 (dq, $J = 10.2$, 1.2 Hz, 1H), 5.38 (dq, $J = 17.5$, 1.5 Hz, 1H), 5.39 (dq, $J = 9.7$, 1.0 Hz, 1H), 5.45 (dq, $J = 17.0$, 1.5 Hz, 1H), 5.97 (s, 1H), 5.98 (m, 1H), 6.06 (ddt, $J = 17.5$, 10.5, 7.0 Hz, 1H), 6.32 (s, 1H). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.51; H, 6.78.

4.48. Reduction of 13

The same procedure as used in the preparation of **3e**.

4.49. 5,7-Dimethoxy-8-(1-hydroxy-propyl)-4-propyl-chromen-2-one (14b)

^{1}H NMR (CDCl$_3$): 0.95 (t, $J = 7.5$ Hz, 3H), 1.01 (t, $J = 7.2$ Hz, 3H), 1.61 (sext, $J = 7.5$ Hz, 2H), 1.82 (m, 1H), 2.01 (m, 1H), 2.86 (t, $J = 7.7$ Hz, 2H), 3.93 (s, 3H), 3.95 (s, 3H), 5.97 (s, 1H), 6.35 (s, 1H); ^{13}C NMR (CDCl$_3$): 10.6, 14.0, 22.8, 30.2, 38.8, 55.8, 55.9, 68.7, 91.3, 104.2, 110.9, 112.4, 153.8, 157.8, 158.2, 159.9, 160.4; IR: 3480, 1718 cm^{-1}; MS (APCI+) m/z: 307 (M+1), 289 (M−H$_2$O+1).

4.50. 5,7-Bis(isopropyloxy)-8-(1-hydroxy-propyl)-4-propyl-chromen-2-one (14c)

^{1}H NMR (CDCl$_3$): 0.95 (t, $J = 7.2$ Hz, 3H), 1.01 (t, $J = 7.2$ Hz, 3H), 1.42 (s, 12H), 1.63 (sext, $J = 7.3$ Hz, 2H), 1.83 (m, 1H), 2.00 (apparent sept, $J = 7.2$ Hz, 1H), 2.89 (t, $J = 7.5$ Hz, 2H), 3.37 (d, $J = 12.0$ Hz, 1H), 4.67 (sept, $J = 5.9$ Hz, 2H), 5.19 (dm, $J = 11.5$ Hz, 1H), 5.95 (s, 1H), 6.32 (s, 1H); ^{13}C NMR (CDCl$_3$): 10.6, 13.9, 21.8, 21.77, 22.0, 22.1, 23.1, 30.3, 39.0, 68.8, 70.7, 70.9, 94.1, 104.4, 110.8, 112.6, 154.1, 155.6, 158.1, 158.5, 160.5; IR: 1714 cm^{-1}; MS (APCI+) m/z: 364 (M+1), 363 (M), 345 (M−H$_2$O+1).

4.51. 5,7-Bis(allyloxy)-8-(1-hydroxy-propyl)-4-propyl-chromen-2-one (14d)

^{1}H NMR (CDCl$_3$): 0.96 (t, $J = 7.5$ Hz, 3H), 1.00 (t, $J = 7.2$ Hz, 3H), 1.62 (sext, $J = 7.5$ Hz, 2H), 1.86 (apparent sept, $J = 7.1$ Hz, 1H), 2.00 (apparent sept, $J = 7.2$ Hz, 1H), 2.89 (t, $J = 7.5$ Hz, 2H), 3.27 (d, $J = 11.5$ Hz, 1H), 4.62 (d, $J = 6.0$ Hz, 2H), 4.66 (d, $J = 5.0$ Hz, 2H), 5.23 (m, 1H), 5.38 (t, $J = 9.9$ Hz, 2H), 5.45 (d, $J = 16.5$ Hz, 2H), 5.99 (s, 1H), 6.08 (m, 2H), 6.37 (s, 1H); ^{13}C NMR (CDCl$_3$): 10.6, 13.9, 22.9, 30.2, 38.8, 68.8, 69.5, 70.1, 93.6, 104.4, 111.1, 112.8, 118.6, 119.2, 132.1, 153.8, 156.5, 158.2, 158.7, 160.3; IR: 1708 cm^{-1}; MS (APCI+) m/z: 359 (M+1), 341 (M−H$_2$O+1).

4.52. Reductive amination

Ketone compound (e.g., **1**, **2**, **13** or **15**[6,8]) was dissolved in 7 N methanolic ammonia (5–10 mL/mmol). The reaction mixture was stirred at ambient temperature overnight or until the starting material was completely consumed. Volatiles were removed under vacuum and the residue was re-dissolved in methanol (5–10 mL/mmol) and the solution was cooled to 0 °C. Sodium borohydride (5 equiv) was added and the mixture was stirred for 2 h, quenched with water, and partitioned with ethyl acetate (50 mL/mmol). The ethyl acetate layer was separated, washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The desired product was separated on a silica gel column eluted with 2–10% methanol in dichloromethane. In some cases, the hydrochloride of the amine compound was prepared (from HCl/ether or HCl/dioxane).

4.53. 12-Amino-4-propyl-6,6,10,11-tetramethyl-11,12dihyro-6*H*,10*H*-dipyrano[2,3-*f*; 2′,3′-*h*]chromen-8-one (16)

53% yield: ^{1}H NMR (DMSO-d_6): 0.99 (t, $J = 7.4$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 1.35 (d, $J = 6.3$ Hz, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 1.63 (m, 3H), 1.85 (br s, 2H), 2.85 (m, 2H), 4.00 (t, $J = 3.6$ Hz, 1H), 4.29 (dq, $J = 10.5$, 6.3 Hz, 1H), 5.68 (d, $J = 10.2$ Hz, 1H), 5.97 (s, 1H), 6.54 (d, $J = 10.2$ Hz, 1H); IR: 3390, 3316, 1706, 1584, 1570 cm^{-1}; MS (APCI+) m/z: 371 (M+1), 353 (M+1−NH$_3$). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.51; H, 7.42; N, 3.88.

4.54. 6-(1-Aminopropyl)-2,2-dimethyl-5-hydroxy-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (17a)

61% yield: ^{1}H NMR (CDCl$_3$): 0.97 (t, $J = 7.5$ Hz, 3H), 1.03 (t, $J = 7.5$ Hz, 3H), 1.48 (s, 3H), 1.49 (s, 3H), 1.66 (sext, $J = 7.5$ Hz, 2H), 1.78 (m, 2H), 2.89 (apparent oct, $J = 7.5$ Hz, 2H), 4.85 (t, $J = 6.7$ Hz, 1H), 5.53 (d, $J = 10.0$ Hz, 1H), 5.88 (s, 1H), 6.68 (d, $J = 10.5$ Hz, 1H); ^{13}C NMR (DMSO-d_6): 10.2, 14.0, 23.6, 26.2, 27.2, 27.3, 38.0, 49.8, 76.4, 96.6, 102.9, 104.0, 107.8, 118.3, 123.6, 150.9, 153.8, 158.7, 160.3, 167.8; IR: 3081, 1683, 1641, 1585, 1556 cm^{-1}; MS (APCI+) m/z: 344 (M+1), 327 (M+1−NH$_3$). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.97; H, 7.30; N, 4.08.

4.55. 6-(1-Aminopropyl)-2,2-dimethyl-5-methoxy-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one, hydrochloride (17b)

98% yield: ^{1}H NMR (DMSO-d_6): 0.83 (t, $J = 7.2$ Hz, 3H), 1.01 (t, $J = 7.2$ Hz, 3H), 1.49 (s, 3H), 1.51 (s, 3H), 1.61 (sext, $J = 7.5$ Hz, 2H), 1.99 (sept, $J = 7.5$ Hz, 2H), 2.11 (sept, $J = 6.9$ Hz, 1H), 2.91 (t, $J = 7.7$ Hz, 2H), 3.88 (s, 3H), 4.56 (m, 1H), 5.90 (d, $J = 9.5$ Hz, 1H), 6.19 (s, 1H), 6.58 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (DMSO-d_6): 11.3, 14.5, 26.32, 27.6, 27.9, 38.4, 47.8, 64.1, 67.6, 78.6, 106.4, 110.5, 111.2, 113.0, 117.1, 130.0, 152.5, 158.0, 159.1; IR: 3071, 3030, 1743, 1640, 1608, 1571, 1522 cm^{-1}; MS (APCI+) m/z: 358 (M+1), 341 (M+1−NH$_3$). Anal. Calcd for $C_{21}H_{27}NO_4 \cdot HCl \cdot 1/4H_2O$: C, 63.31; H, 7.21; N, 3.53. Found: C, 63.4; H, 7.34; N, 3.41.

4.56. 6-(1-Aminopropyl)-2,2-dimethyl-5-(2-hydroxyethoxy)-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one (17c)

47% yield: ^{1}H NMR (CDCl$_3$): 0.87 (t, $J = 7.5$ Hz, 3H), 1.05 (t, $J = 7.5$ Hz, 3H), 1.50 (s, 3H), 1.52 (s, 3H), 1.67 (sext, $J = 7.5$ Hz, 2H), 2.00 (dq, $J = 13.5$, 7.5 Hz, 1H), 2.12 (dq, $J = 13.5$, 7.7 Hz, 1H), 2.92 (qui–d, $J = 9.0$, 3.2 Hz, 2H), 3.80 (t, $J = 3.7$ Hz, 2H), 4.14 (m, 1H), 4.21 (m, 1H), 4.63 (t, $J = 7.5$ Hz, 1H), 5.64 (d, $J = 10.0$ Hz, 1H), 6.02 (s, 1H), 6.51 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (CDCl$_3$): 11.5, 14.0, 23.2, 27.3, 27.6, 29.3, 38.7, 49.2, 61.7, 78.6, 106.4, 110.7, 112.0, 118.0, 127.8, 151.4, 153.8, 158.3, 160.4; IR: 3348–3185, 1721, 1638, 1604, 1575 cm^{-1}; MS (APCI+) m/z: 388 (M+1), 371 (M+1−NH$_3$). Anal. Calcd for $C_{22}H_{29}NO_5 \cdot 0.\ 5H_2O$: C, 66.65; H, 7.63; N, 3.53. Found: C, 66.61; H, 7.31; N, 3.29.

4.57. 2,2-Dimethyl-6-(1-ethylaminopropyl)-5-methoxy-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one, hydrochloride (17d)

27% yield: ^{1}H NMR (DMSO-d_6): 0.77 (t, *J* = 7.5 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.50 (s, 3H), 1.53 (s, 3H), 1.62 (sext, *J* = 7.5 Hz, 2H), 2.25 (m, 1H), 2.80 (s, 2H), 2.91 (apparent t, *J* = 6.5 Hz, 2H), 3.90 (s, 3H), 4.54 (s, 1H), 5.90 (d, *J* = 10.0 Hz, 1H), 6.19 (s, 1H), 6.59 (d, *J* = 10.0 Hz, 1H), 8.42 (s, 1H); ^{13}C NMR (DMSO-d_6): 10.76, 13.74, 22.92, 27.23, 37.68, 63.46, 66.31, 77.94, 110.33, 112.33, 116.5, 152.3, 157.2, 157.8, 158.3; IR: 3073, 1733, 1636, 1608 cm^{-1}; MS (APCI+) *m*/*z*: 386 (M+1), 341 (M-$C_2H_5NH_2$+1). Anal. Calcd for $C_{23}H_{31}NO_4\cdot HCl$: C, 65.47; H, 7.64; N, 3.32. Found: C, 65.15; H, 7.76; N, 3.32.

4.58. 2,2-Dimethyl-6-[1-(2-hydroxyethylamino)propyl]-5-methoxy-10-propyl-2*H*-pyrano[2,3-*f*]chromen-8-one, hydrochloride (17e)

22% yield: ^{1}H NMR (CD_3OD): 0.89 (t, *J* = 7.5 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.55 (s, 3H), 1.59 (s, 3H), 1.70 (sext, *J* = 7.8 Hz, 2H), 2.22 (qui, *J* = 7.4 Hz, 2H), 2.94–3.11 (m, 4H), 3.74–3.79 (m, 3H), 3.96 (s, 3H), 5.88 (d, *J* = 10.0 Hz, 1H), 6.16 (s, 1H), 6.62 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (CD_3OD): 11.1, 14.4, 24.7, 28.2, 39.8, 43.0, 57.0, 57.8, 59.0, 64.4, 80.0, 107.9, 112.8, 113.4, 117.9, 130.8, 155.0, 159.8, 160.6, 161.7; IR: 3333, 3137, 1723, 1636, 1608 cm^{-1}; MS (APCI+) *m*/*z*: 402 (M+1), 341 (M-C_2H_6NO).

4.59. 8-(1-Aminopropyl)-5,7-dimethoxy-4-propyl-chromen-2-one, hydrochloride (18b)

60% yield. Hygroscopic. ^{1}H NMR (DMSO-d_6): 0.77 (t, *J* = 7.5 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H), 1.55 (sext, *J* = 7.5 Hz, 2H), 1.95 (apparent sept, *J* = 7.0 Hz, 1H), 2.04 (apparent sept, *J* = 6.8 Hz, 1H), 2.86 (apparent oct, *J* = 7.5 Hz, 2H), 3.98 (s, 3H), 4.00 (s, 3H), 4.62 (br s, 1H), 6.06(s, 1H), 6.71 (s, 1H), 8.37 (br s, 3H); ^{13}C NMR (DMSO-d_6): 10.3, 13.8, 22.6, 24.8, 37.9, 46.8, 56.4, 56.5, 66.3, 92.8, 102.8, 104.1, 110.2, 153.5, 158.0, 158.9, 160.8; IR: 3401, 1719, 1615, 1588 cm^{-1}; MS (APCI+) *m*/*z*: 306 (M+1), 289 (M−NH_3+1). Anal. Calcd for $C_{17}H_{23}NO_4\cdot HCl\cdot H_2O$: C, 56.74; H, 7.28; N, 3.89. Found: C, 56.19; H, 6.88; N, 3.80.

4.60. 8-(1-Aminopropyl)-5,7-diisopropoxy-4-propyl-chromen-2-one, hydrochloride (18f)

23% yield. hygroscopic. ^{1}H NMR (DMSO-d_6): 0.77 (t, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), 1.36 (d, *J* = 6.0 Hz, 12H), 1.57 (m, 2H), 2.05 (m, 2H), 2.87 (m, 2H), 4.62 (br s, 1H), 4.99 (m, 2H), 6.04 (s, 1H), 6.67 (s, 1H), 8.22 (br s, 3H); ^{13}C NMR (DMSO-d_6): 10.4, 13.7, 21.3, 22.9, 38.1, 46.7, 70.7, 71.2, 94.7, 103.1, 104.1, 110.3, 154.3, 156.7, 158.2, 158.8, 158.9; IR: 1720 cm^{-1}; MS (APCI+) *m*/*z*: 362 (M+1), 345 (M−NH_3+1). Anal. Calcd for $C_{21}H_{31}NO_4\cdot HCl\cdot 1/2H_2O$: C, 61.98; H, 8.17, N, 3.44. Found: C, 61.85; H, 8.04; N, 3.56.

4.61. 8-(1-Aminopropyl)-5,7-bis(allyloxy)-4-propyl-chromen-2-one, hydrochloride (18g)

46% yield. Hygroscopic. ^{1}H NMR (DMSO-d_6): 0.77 (t, *J* = 7.5 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H), 1.55 (sext, *J* = 7.3 Hz, 2H), 2.04 (m, 2H), 2.87 (m, 2H), 4.65 (br s, 1H), 4.77 (d, *J* = 5.5 Hz, 2H), 4.87 (d, *J* = 5.0 Hz, 2H), 5.36 (dd, *J* = 27.0, 10.5 Hz, 2H), 5.45 (dd, *J* = 25.1, 17.0 Hz, 2H), 6.08 (s, 1H), 6.11 (m, 2H), 6.71 (s, 1H), 8.37 (br s, 3H); ^{13}C NMR (DMSO-d_6): 10.4, 13.7, 22.7, 24.8, 37.9, 46.7, 69.4, 70.2, 94.7, 103.0, 104.4, 110.5, 118.3, 119.4, 132.5, 133.0, 157.4, 158.0, 158.8, 159.3; IR: 3402, 1712, 1611, 1586 cm^{-1}; MS (APCI+) *m*/*z*: 358 (M+1), 341 (M−NH_3+1). Anal. Calcd for $C_{21}H_{27}NO_4\cdot HCl\cdot 1/2H_2O$: C, 62.60; H, 7.25; N 3.48. Found: C, 62.70; H, 7.23; N, 3.54.

5. Biological evaluation against *M. tuberculosis* by microdilution Alamar blue assay

The anti-TB activity of the synthesized compounds was determined using a microdilution broth assay that incorporates the REDOX indicator Alamar blue and *M. tuberculosis* H37Ra (ATCC 25177).[11] Briefly, the assay involved serially diluting each stock solution of drug in broth medium (Middlebrook 7H9 + ADC enrichment + 0.2% glycerol) at twice the desired concentration and then adding 0.05 mL to each well in duplicate. The inoculum for each well consisted of 0.05 mL of culture standardized to about 1×10^5 CFU/mL. Each plate also contained uninoculated drug controls, a viability control, and an uninoculated medium control. The plates were covered with a lid, placed in polyethylene bags, and incubated at 37 °C for 6 days. The REDOX dye Alamar blue (Trek Diagnostic Systems), diluted in Tween 80, was then added to each well, the plates incubated for an additional 16–20 h and read in an optical microtiter plate reader programmed to subtract the absorbance at 600 nm from that at 570 nm to blank out turbidity and absorbance due to oxidized dye. The MIC was reported as the lowest concentration of drug yielding a differential absorbance of zero or less. This approximated the color change of blue to red that was observed visually after metabolic reduction of dye and represented the concentration at which no visible growth occurred. Each drug was tested initially in duplicate at 0.128, 1.28, 12.8, and 128 μg/mL to determine the range of concentrations within which the MIC fell. The assay was then repeated using 2-fold serial dilutions of drug. Ethambutol, which was used as a positive drug control, had an MIC of 4 μg/mL. The diluent, DMSO, was diluted in the same manner as the tested compounds and assayed as a negative control. Bactericidal activity was assessed by direct plating from those wells in the microtiter plate that showed no visible growth prior to the addition of dye.[13] Each well was mixed by carefully drawing liquid in and out of a microliter pipette and plated (10 μL) on to 7H11 agar in duplicate. The plates were incubated for 14 days in polyethylene bags and the colonies then counted with the aid of a dissecting microscope. The counts were compared with those of the initial inoculum to calculate the percent reduction in survivors. The MBC was defined as the lowest drug concentration that reduced the viable count by 99%.

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