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Article

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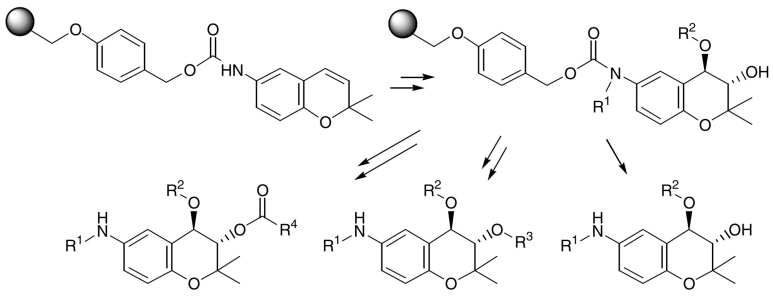

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Construction of 6-Amino-2,2-Dimethyl-3,4,6-Trisubstituted-2*H*-1-Benzopyran Library by Solid Phase Synthesis

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We report the solid-phase library construction of 2000 analogues of 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran. The polymer-bound hydroxyalkoxychromanes **5**, produced by nucleophilic reactions with various alcohols on epoxides generated in situ, served as key intermediates for subsequent diversification. Further reactions on these hydroxyalkoxychromanes **5** with various electrophiles, such as alkyl halides and acid halides, produced the desired 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran analogues **9**, **10**, and **11**. The progress of reactions could be monitored as solid-bound intermediates by ATR-FTIR or HR-MAS-NMR spectroscopy. The final compounds, obtained in good yields and high purity upon cleavage from the resins, were characterized by LC/MS, HRMS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Introduction

Solid-phase organic synthesis has emerged as a powerful technique in generating combinatorial libraries of small organic molecules useful for drug discovery.[1] Heterocyclic compounds provide scaffolds on which pharmacophores can be arranged to yield potent and selective drugs, and a variety of heterocycles have been synthesized on solid support.[2] In our research program for the development of potassium channel activators and antioxidants, we needed to develop a synthetic strategy and chemistry applicable in a combinatorial approach for the preparation of various benzopyran derivatives.[3] Benzopyrans have attracted significant interest in medicinal chemistry because of their broad biological activities in the areas of antioxidants, diabetes, cardiovascular, multidrug resistance, anti-HIV agent, ischemia, etc.[4] Therefore, the solid-phase synthesis of benzopyran containing natural and unnatural products has become one of the active research fields.[5]

Herein, we would like to report the solid-phase library construction of two thousand analogues of 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran. The polymer bound hydroxyalkoxychromane **5**, produced by nucleophilic reactions with various alcohols on epoxides generated in situ, served as key intermediates for subsequent diversification. Further reactions on this hydroxyalkoxychromane **5** with various electrophiles, such as alkyl halides and acid halides, produced the desired 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran analogues **9**, **10**, and **11**.

† Korea Research Institute of Chemical Technology.

Result and Discussion

For the solid-phase parallel synthesis in this report, we selected Wang resin **1** as a polymer support, since the hydroxy group in the Wang resin is suitable for the introduction of a 6-amino-2,2-dimethylchromene building block **12** through the carbamate linker, which would also serve as an efficient protecting group for the amino group against the subsequent oxidation and alkylation reactions.[6] The key intermediates, the carbamate resins **5**, were prepared in a four-step procedure starting from the Wang resin, as shown in Scheme 1. The desired benzopyran products **9**, **10**, and **11** were finally liberated from the resins **5**, **6**, and **7** by trifluoroacetic acid (TFA). The progress of the reactions could be monitored by attenuated total reflection (ATR) FTIR[7] on single beads and high-resolution magic-angle spinning (HR-MAS) NMR[8] (Figures 1 and 2).

As the first step, the *p*-nitrophenyl carbonate resin **2** was prepared from Wang resin **1** and *p*-nitrophenyl chloroformate in CH_2Cl_2.[9] The formation of the carbonate resin **2** was confirmed by the prominent carbonate band at 1765 cm^{-1} by ATR-FTIR (Figure 1B). The reaction of the carbonate resin **2** with 6-amino-2,2-dimethylchromene and *N*,*N*-diisopropylethylamine (DIPEA) in *N*,*N*-dimethylacetamide (DMA) afforded the carbamate resin **3**, which was also confirmed by the appearance of the carbamate band at 1725 cm^{-1} (Figure 1C) and the disappearance of the carbonate stretching frequency at 1765 cm^{-1}.

For the initial variation on the amino group in the chromene system, various alkyl groups on the nitrogen atom in the carbamate moiety were introduced by a nucleophilic

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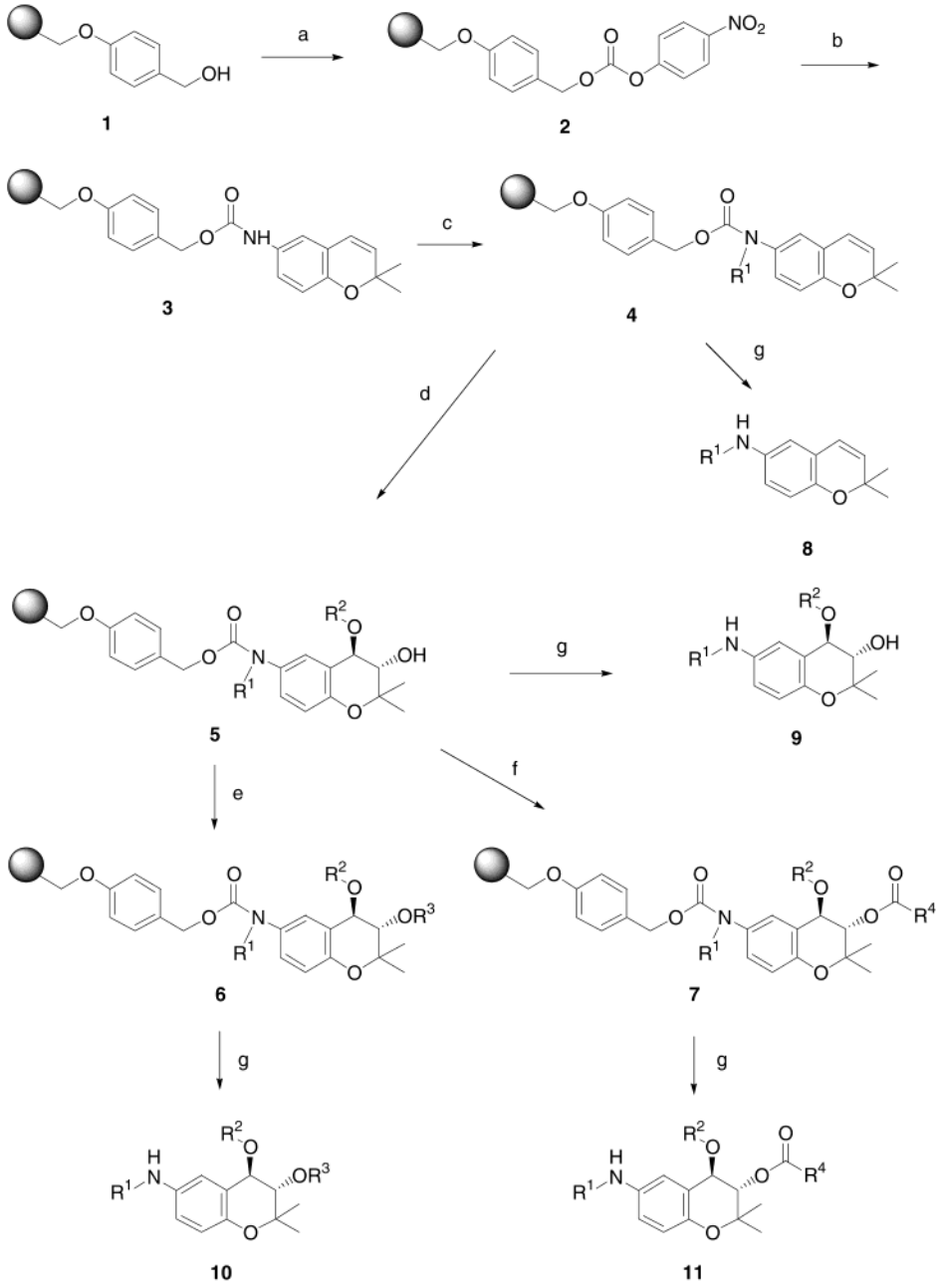
Scheme 1



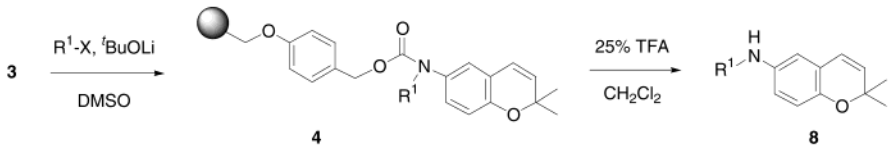
Reagents and conditions: (a) *p*-nitrophenyl chloroformate, pyridine, CH_2Cl_2; (b) 6-amino-2,2-dimethyl chromene **12**, DIPEA, DMA; (c) alkyl or benzyl halide, ^{t}BuOLi, DMSO; (d) *m*-CPBA, alcohol, CH_2Cl_2; (e) alkyl or benzyl halide, ^{t}BuOLi, DMF; (f) acid halide, pyridine, DMAP, CH_2Cl_2; (g) TFA/CH_2Cl_2 (1:3), **5**, **6**, **7**, **9**, **10,** and **11** are racemates.

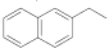
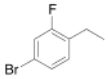
substitution reaction with alkyl halides and lithium *t*-butoxide as a base in dimethyl sulfoxide (DMSO),[10] and the progress of the reaction was monitored by the shift of the carbamate peaks from 1725 cm^{-1} of **3** to 1699 cm^{-1} of **4** in the ATR-FTIR spectrum, as shown in Figure 1D and Table 1.

With the carbamate resins **4** in hand, we examined the epoxidation of **4** under normal oxidation conditions with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane for the second combination. However, under this condition, the *m*-chlorobenzoic acid incorporated adduct resin **14** was obtained predominantly (Scheme 2) as a result of nucleophilic attack of *m*-chlorobenzoic acid on the initially formed epoxide. The *m*-chlorobenzoic acid adduct **15** was identified by ^{1}H, ^{13}C NMR, and HRMS spectroscopies after it was released from the resin **14**.

To solve this problem, we examined various oxidants, such as oxone, dimethyl dioxirane, hydrogen peroxide, *tert*-butyl hydrogen peroxide, and sodium hypochlorite but failed to obtain the desired epoxide resin **13**.[11] We reexamined the oxidation reaction with *m*-CPBA more carefully and particularly scrutinized the solvent systems. After testing various solvent systems, we found that the two-phase solvent system consisting of chloroform and saturated aqueous $NaHCO_3$ was a suitable condition, as we reported earlier,[12] although this new condition was able to produce the desired epoxide on a small scale but was not suitable for a large scale (>1 g resin

Table 1



Compd	R^1	Yield* (%)	Compd	R^1	Yield* (%)
8a	Bn	85	**8i**		77
8b	4-Me-Bn	87	**8j**		82
8c	4-MeO-Bn	77	**8k**		85
8d	2-Me-Bn	78	**8l**		73
8e	3-F-Bn	78	**8m**	Me	81
8f	4-F-Bn	83	**8n**	*n*-pentyl	80
8g	4-^{t}Bu-Bn	80	**8o**	Allyl	77
8h		81	**8p**	Ethyl	71

[a] Two-step overall yield from the carbamate resin **3** (loading capacity of the resin **3** is 0.5 mmol/g).

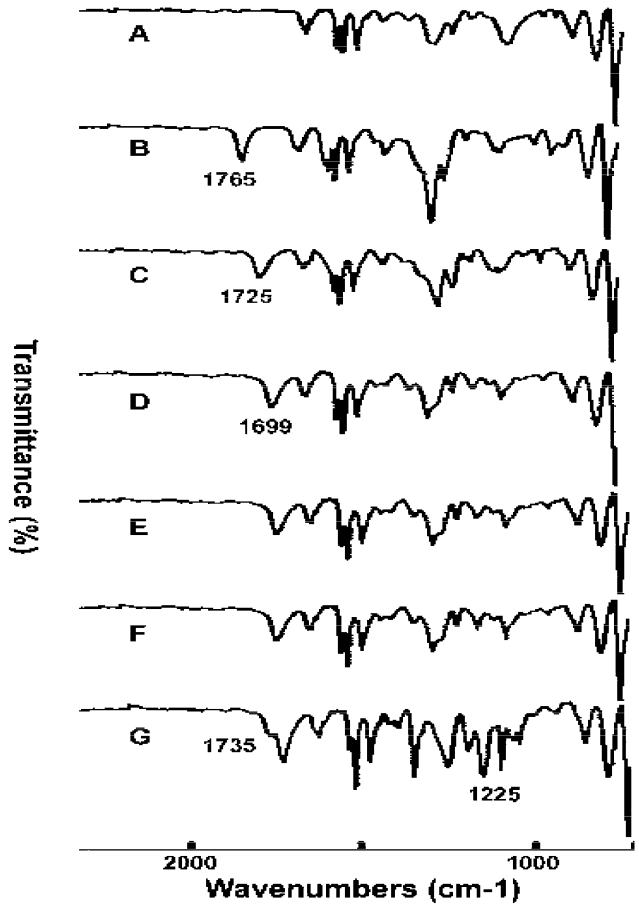


Figure 1. ATR−FTIR spectra on a single bead of resin **1** (A), **2** (B), **3** (C), **4** (D), **5** (E), **6** (F), and **7** (G).

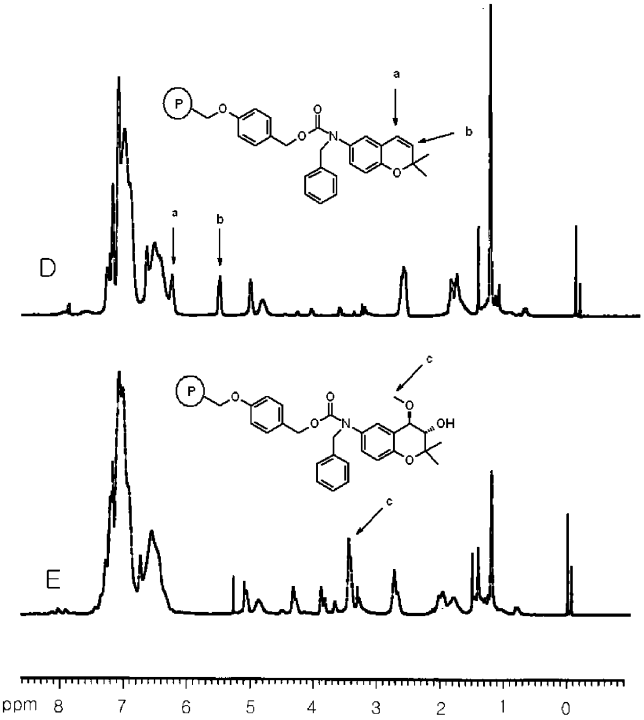
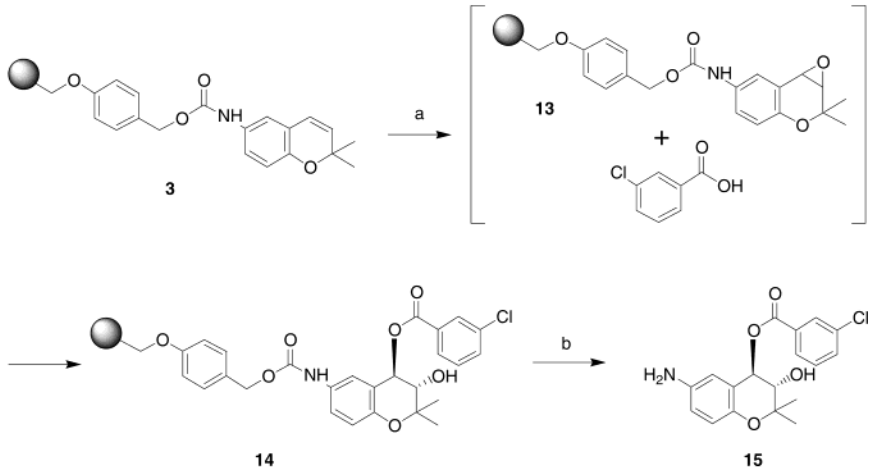


Figure 2. HR-MAS-NMR spectra on single bead of resin **4** (D), and **5** (E).

weight) reaction. When the scale got larger, the formation of *m*-chlorobenzoic acid added product became significan, probably as a result of an inadequate mixing.

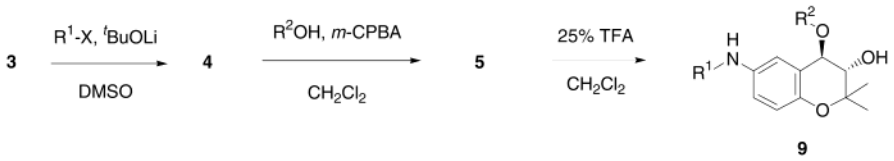
Therefore, we needed to come up with an alternative method, and to this end, we decided to look at the epoxidation reaction in the presence of nucleophiles, in the hope that nucleophiles react with epoxides as soon as they are formed. To our delight, in the case of alcohol-type nucleophiles, such as alkyl alcohols, benzyl alcohol, substituted benzyl alcohols, and primary alcohol attached heterocycles, provided the hydroxyalkoxy resin **5** in high yield without the formation of **14**.[13] For the monitoring of the

Scheme 2



Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2; (b) 25% TFA, CH_2Cl_2.

Table 2



Compd	R^1	R^2	Yield* (%)	Compd	R^1	R^2	Yield* (%)
9a	Bn	Me	62	**9n**	4-CF_3-Bn	Me	65
9b	Bn	^{i}Pr	35	**9o**	4-F-Bn	Me	79
9c	Bn		47	**9p**	4-F-Bn	^{i}Pr	43
9d	Bn	Bn	58	**9q**	4-F-Bn	Bu	74
9e	4-^{t}Bu-Bn	Me	45	**9r**	4-F-Bn		57
9f	4-^{t}Bu-Bn	Et	43	**9s**	4-F-Bn		56
9g	4-Me-Bn	Me	59	**9t**	4-F-Bn	Bn	62
9h	4-MeO-Bn	Me	74	**9u**	3-F-Bn	Me	41
9i	4-MeO-Bn	Et	54	**9v**	Me	Me	63
9j	4-MeO-Bn	^{i}Pr	45	**9w**	Me	Et	57
9k	4-MeO-Bn	Bu	66	**9x**	Me	Bu	47
9l	4-MeO-Bn	Bn	54	**9y**	Me		43
9m	4-MeO-Bn		51	**9z**	H	Me	81

[b] Three-step overall yield from the carbamate resin **3** (loading capacity of the resin **3** is 0.5 mmol/g).

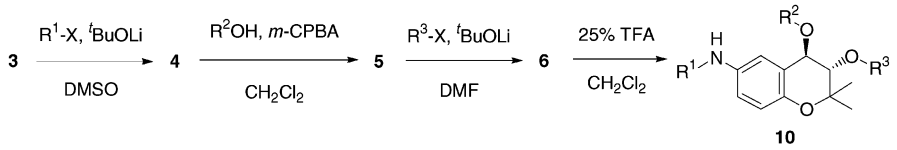
reactions, we found that ATR-FTIR spectroscopy was not adequate, since the spectra from the reactants **4** and the products **5** were indistinguishable, as seen in Figure 1 (D and E). Instead, HR-MAS-NMR spectroscopy was found to be useful so that the hydroxyalkoxylation products were confirmed by the appearance of the alkoxy peak at 3.5 ppm (Figure 2E) and the disappearance of the olefinic peak at 5.6 ppm (Figure 2D).

To conclusively confirm the product formation, we treated the polymer-bound hydroxymethoxide **5a** with 25% TFA in CH_2Cl_2 for 3 h to obtain the desired benzopyran product **9a** in high yield. By using this sequence of reactions, we could obtain various hydroxyalkoxy chromene **9** in relatively good three-step overall yields, as listed in Table 2.

For further combination on the hydroxyl group of the resin **5**, we examined the reactions with alkyl halides and acid halides to generate ethers and esters. To prepare the ether-type resin **6**, resin **5** was treated with various alkyl and benzyl halides in the presence of lithium *t*-butoxide in DMF. The reaction proceeded nicely to provide ether type resins **6**, and subsequent treatment of the resins **6** with 25% TFA in CH_2Cl_2 for 3 h produced the desired 6-alkylamino-2,2-dimethyl-3,4-dialkoxy-substituted-2*H*-1-benzopyran derivatives **10** in good four-step overall yields, as summarized in Table 3.

For the preparation of esters, the resins **5** were treated with various acid halides with pyridine and DMAP as bases in CH_2Cl_2, to produce the ester-type benzopyran resins **9**, which

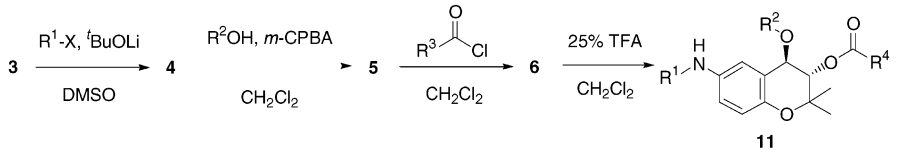
Table 3.



compd	R^1	R^2	R^3	yield[a] (%)	compd	R^1	R^2	R^3	yield[a] (%)
10a	Bn	Me	Me	50	**10n**	4-Me−Bn	Me	4-Br−2-F−Bn	33
10b	Bn	Bn	4-F−Bn	38	**10o**	Me	Bn	Me	33
10c	Bn	Bu	4-Me−Bn	37	**10p**	Me	Bu	Me	34
10d	4-MeO−Bn	Bn	2-Cl−Bn	38	**10q**	Me	Me	Me	45
10e	4-MeO−Bn	Et	Me	41	**10r**	Me	Me	Bn	47
10f	4-MeO−Bn	Et	propargyl	33	**10s**	Me	Me	4-Br−2-F−Bn	35
10g	4-MeO−Bn	Et	2-naphthyl-Me	32	**10t**	Me	Me	3-F−Bn	38
10h	4-MeO−Bn	Bu	2-Cl−Bn	44	**10u**	Me	Me	3,5-CF_3−Bn	34
10i	4-F−Bn	Me	3,5-CF_3−Bn	40	**10v**	Me	Me	propargyl	32
10j	4-F−Bn	^{i}Pr	Me	34	**10w**	Me	Me	2-naphthyl-Me	33
10k	4-F−Bn	^{i}Pr	Pen	24	**10x**	Et	Bn	Bn	31
10l	4-Me−Bn	Me	allyl	34	**10y**	Et	Bu	3-Cl−Bn	29
10m	4-Me−Bn	Me	4-F−Bn	39	**10z**	Et	Bn	propargyl	24

[a] Four-step overall yield from the carbamate resin **3** (loading capacity of the resin **3** is 0.5 mmol/g).

Table 4.



compd	R^1	R^2	R^4	yield[a] (%)	compd	R^1	R^2	R^4	yield[a] (%)
11a	Bn	Me	Me	53	**11n**	4-MeO−Bn	*n*-Bu	^{c}Hex	42
11b	4-F−Bn	Me	Me	56	**11o**	4-MeO−Bn	*n*-Bu	acryl	40
11c	4-F−Bn	Me	^{t}BuMe	47	**11p**	4-MeO−Bn	*n*-Bu	4-F−Ph	43
11d	4-CF_3−Bn	*n*-Bu	4-F−Ph	46	**11q**	Me	Me	^{t}BuMe	38
11e	4-CF_3−Bn	*n*-Bu	2-Furan	53	**11r**	Me	Me	^{c}Hex	40
11f	4-CF_3−Bn	^{c}HexEt	Me	42	**11s**	Me	Et	Me	43
11g	4-CF_3−Bn	^{c}HexEt	4-Me-Ph	37	**11t**	Me	Et	^{t}BuMe	36
11h	4-MeO−Bn	Me	Me	54	**11u**	Et	Me	acryl	38
11i	4-MeO−Bn	Me	^{t}BuMe	44	**11v**	Et	Me	Ph	39
11j	4-MeO−Bn	Me	^{c}Hex	47	**11w**	Et	Me	4-Me-Ph	37
11k	4-MeO−Bn	Me	acryl	43	**11x**	Et	Bn	Me	41
11l	4-MeO−Bn	Me	4-F−Ph	49	**11y**	Et	Bn	2-thiophen	45
11m	4-MeO−Bn	*n*-Bu	Me	53	**11z**	Et	Bn	2-furane	44

[a] Four-step overall yield from the carbamate resin **3** (loading capacity of the resin **3** is 0.5 mmol/g).

were again treated with 25% TFA in CH_2Cl_2 for 3 h to give the desired ester compounds, as listed in Table 4.

In conclusion, we succeeded in the construction of a library of 2000 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran analogues by using 26 hydroxyalkoxylated polymer-bound chromenes **5** as the key intermediates. The hydroxyalkoxide **5** served as key intermediates for subsequent diversification with various alkyl halides and acid halides to provide the desired 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran libraries **9**, **10**, and **11**.

Experimental Section

Materials and Methods. The polystyrene Wang resin (1.0 mmol/g, 1% cross-linking, 100−200 mesh) was obtained from NovaBiochem. Quaternary ammonium styrene divinylbenzene scavenger resin was obtained from Alltech (particle size ~45 to 150 μm, exchange capacity 1.2 meq/mL). Solvents were purchased from Merck and were anhydrous and HPLC grade. Reactions, filtration, and washings were carried out on a Quest210 synthesizer (Agronaut Technology) and a MiniBlock (Bohdan). Solvent evaporation was performed on a GeneVac Atlas HT-4 centrifugal evaporator. Crude products were purified by parallel chromatography using QuadFlash silica-cartridge (Biotage Catalog no. QK0-1107-1504L). All of the solid bound intermediate resins were monitored by ATR-FTIR (SensIR Technology) or HR-MAS NMR (Bruker Advance 500FT-NMR) spectroscopy. The structures of the final products were confirmed by ^{1}H NMR (Bruker DPX-300FT-NMR, Varian GEMINI-200FT-NMR) and HRMS (Micromass Auto Spec MS), MS (Hewlett-Packard 5971A, Shimadzu QP5050) spectroscopy.

General Procedure. Representative Procedure for the Synthesis of *p*-Nitrophenyl Carbonate Wang Resin (2).

Wang resin **1** (10.00 g, 10.00 mmol) was swollen in dry CH_2Cl_2 under Ar gas for 30 min. After filtration of the solvent, a solution of *p*-nitrophenyl chloroformate (10.08 g, 50.00 mmol) was added in dry CH_2Cl_2 (40 mL), followed by slow addition of a solution of dry pyridine (7.91 g, 100.00 mmol) in dry CH_2Cl_2 (40 mL). The suspension was shaken for 48 h at room temperature under Ar. Carbonate resin **2** was filtered and washed with DMF (2 × 100 mL), MeOH (2 × 100 mL), MeOH/CH_2Cl_2 (1:1; 2 × 100 mL), CH_2Cl_2 (2 × 100 mL), MeOH/CH_2Cl_2 (1:1; 2 × 100 mL), and MeOH (2 × 100 mL) and dried under high vacuum. FTIR (cm^{-1}): 1765, 1595, 1349, 1214.

Representative Procedure for the Synthesis of 6-Amino-2,2-dimethyl-2*H*-1-benzopyran Carbamate Wang Resin (3). Carbonate resin **2** (8.00 g, 8.00 mmol) was suspended in dry DMA (50 mL), and 6-amino-2,2-dimethyl-2*H*-1-benzopyran (2.80 g, 16.00 mmol) and DIPEA (5.17 mg, 40.0 mmol) were successively added. The mixture was shaken for 10 h at room temperature. Carbamate resin **3** was filtered and washed with DMF (2 × 80 mL), MeOH (2 × 80 mL), MeOH/CH_2Cl_2 (1:1; 2 × 80 mL), CH_2Cl_2 (2 × 80 mL), MeOH/CH_2Cl_2 (1:1; 2 × 80 mL), and MeOH (2 × 80 mL) and dried under high vacuum. FTIR (cm^{-1}): 1725, 1374, 1055.

Representative Procedure for the First Generation Step by N-Alkylation Reaction (See Table 1); 6-(Benzylamino)-2,2-dimethyl-2*H*-1-benzopyran Resin (4a). The 6-amino-2,2-dimethyl-2*H*-1-benzopyran resin **3** (6.00 g, 3.00 mmol) was suspended in dry DMSO (40 mL), and benzyl bromide (1.54 g, 9.00 mmol) and ^{t}BuOLi (1.20 g, 15.00 mmol) were successively added. The mixture was shaken for 12 h at room temperature. The desired resin **4a** was filtered and washed with DMF (2 × 50 mL), MeOH (2 × 50 mL), MeOH/CH_2Cl_2 (1:1; 2 × 50 mL), CH_2Cl_2 (2 × 50 mL), MeOH/CH_2Cl_2 (1:1; 2 × 50 mL), and MeOH (2 × 50 mL) and dried under high vacuum. FTIR (cm^{-1}): 1699, 1251, 1134.

Representative Procedure for the Cleavage Step from the First Generated Resin (4); 6-(Benzylamine)-2,2-dimethyl-2*H*-1-benzopyran (8a). The N-alkylated resin **4a** (200 mg, 0.10 mmol) was treated with 4 mL of cleavage cocktail (TFA/CH_2Cl_2; 1:3). After the mixture was shaken at room temperature for 3 h, the resin was filtered off and washed with CH_2Cl_2 (3 × 1 mL), followed by MeOH (1 mL). The combined filtrates were evaporated and purified by SAX resin and silica gel column chromatography (15% ethyl acetate in hexane; using Quad3$^+$) to yield (22.6 mg, 85%) 6-(Benzylamino)-2,2-dimethyl-2*H*-1-benzopyran **8a** (93% purity, determined by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.26 (m, 5H), 6.64 (d, 1H, J = 8.5 Hz), 6.45 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.33 (d, 1H, J = 2.8 Hz), 6.24 (d, 1H, J = 9.7 Hz), 5.60 (d, 1H, J = 9.7 Hz), 4.27 (s, 2H), 1.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.17, 142.19, 139.52, 131.59, 128.55, 127.62, 127.17, 122.58, 121.90, 116.80, 113.88, 111.00, 75.46, 49.34, 27.5; HRMS (EI$^+$) *m*/*z* 265.1464 found, 265.1467 calcd for $C_{18}H_{19}N_1O_1$.

2,2-Dimethyl-6-(4-methylbenzylamino)-2*H*-1-benzopyran (8b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, 2H, J = 8.0 Hz), 7.14 (d, 1H, J = 8.0 Hz), 6.64 (d, 1H, J = 8.4 Hz), 6.47 (dd, 1H, J = 8.4 Hz, J = 2.7 Hz), 6.36 (d, 1H, J = 2.7 Hz), 6.24 (d, 1H, J = 9.7 Hz), 5.60 (d, 1H, J = 9.7 Hz), 4.21 (s, 2H), 2.34 (s, 3H), 1.40 (s, 6H); HRMS (EI$^+$) *m*/*z* 279.1625 found, 279.1623 calcd for $C_{19}H_{21}N_1O_1$.

2,2-Dimethyl-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (8c). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.6 Hz), 6.64 (d, 1H, J = 8.5 Hz), 6.45 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.34 (d, 1H, J = 2.8 Hz), 6.24 (d, 1H, J = 9.7 Hz), 5.60 (d, 1H, J = 9.7 Hz), 4.18 (s, 2H), 3.80 (s, 3H), 1.39 (s, 6H); MS (EI$^+$) *m*/*z* 295.

2,2-Dimethyl-6-(2-methylbenzylamino)-2*H*-1-benzopyran (8d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (s, 1H), 7.21−7.17 (m, 3H), 6.66 (d, 1H, J = 8.5 Hz), 6.46 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.34 (d, 1H, J = 2.8 Hz), 6.25 (d, 1H, J = 9.7 Hz), 5.61 (d, 1H, J = 9.7 Hz), 4.21 (s, 2H), 2.37 (s, 3H), 1.40 (s, 6H); HRMS (EI$^+$) *m*/*z* 279.1620 found, 279.1623 calcd for $C_{19}H_{21}N_1O_1$.

2,2-Dimethyl-6-(3-fluorobenzylamino)-2*H*-1-benzopyran (8e). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.64 (d, 1H, J = 8.5 Hz), 6.43 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.31 (d, 1H, J = 2.8 Hz), 6.26 (d, 1H, J = 9.7 Hz), 5.61 (d, 1H, J = 9.7 Hz), 3.04 (t, 2H, J = 7.1 Hz), 1.60 (m, 2H), 1.39−1.34 (m, 10H), 0.91 (t, 3H, J = 6.7 Hz); HRMS (EI$^+$) *m*/*z* 283.1377 found, 283.1372 calcd for $C_{18}H_{18}N_1O_1F_1$.

2,2-Dimethyl-6-(4-fluorobenzylamino)-2*H*-1-benzopyran (8f). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.30 (m, 2H), 7.02−6.99 (m, 2H), 6.64 (d, 1H, J = 8.5 Hz), 6.45 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.34 (d, 1H, J = 2.8 Hz), 6.23 (d, 1H, J = 9.7 Hz), 5.61 (d, 1H, J = 9.7 Hz), 4.22 (s, 2H), 1.39 (s, 6H); HRMS (EI$^+$) *m*/*z* 283.1375 found, 283.1372 calcd for $C_{18}H_{18}N_1O_1F_1$.

6-(4-*tert*-Butyl-benzylamino)-2,2-dimethyl-2*H*-1-benzopyran (8g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.29 (m, 4H), 6.65 (d, 1H, J = 8.5 Hz), 6.47 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.47 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.36 (d, 1H, J = 2.8 Hz), 6.25 (d, 1H, J = 9.7 Hz), 5.61 (d, 1H, J = 9.7 Hz), 4.22 (s, 2H), 1.40 (s, 6H), 1.32 (s, 9H); HRMS (EI$^+$) *m*/*z* 321.2093 found, 321.2093 calcd for $C_{22}H_{27}N_1O_1$.

6-(4-Bromo-2-fluorobenzylamino)-2,2-dimethyl-2*H*-1-benzopyran (8h). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28−7.21 (m, 3H), 6.63 (d, 1H, J = 8.6 Hz), 6.45 (dd, 1H, J = 8.6 Hz, J = 3.1 Hz), 6.34 (d, 1H, J = 3.1 Hz), 6.22 (d, 1H, J = 9.9 Hz), 5.61 (d, 1H, J = 9.9 Hz), 4.29 (s, 2H), 1.39 (s, 6H); HRMS (EI$^+$) *m*/*z* 361.0478 found, 361.0478 calcd for $C_{18}H_{17}N_1O_1F_1Br_1$.

2,2-Dimethyl-6-(2,5-dimethylbenzylamino)-2*H*-1-benzopyran (8i). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 1H), 6.97 (s, 2H), 6.86 (dd, 1H, J = 8.6 Hz, J = 2.5 Hz), 6.79 (d, 1H, J = 2.5 Hz), 6.67 (d, 1H, J = 8.6 Hz), 6.22 (d, 1H, J = 9.8 Hz), 5.64 (d, 1H, J = 9.8 Hz), 4.21 (s, 2H), 2.22 (s, 3H), 2.11 (s, 3H), 1.40 (s, 6H); HRMS (EI$^+$) *m*/*z* 293.1789 found, 293.1780 calcd for $C_{20}H_{23}N_1O_1$.

2,2-Dimethyl-6-(2-naphthalenylmethylamino)-2*H*-1-benzopyran (8j). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82−7.79 (m, 4H), 7.48−7.45 (m, 3H), 6.66 (d, 1H, J = 8.6 Hz), 6.54 (dd, 1H, J = 8.6 Hz, J = 2.8 Hz), 6.46 (d, 1H, J = 2.8 Hz), 6.23 (d, 1H, J = 9.8 Hz), 5.61 (d, 1H, J = 9.8 Hz), 4.41 (s,

2H), 1.41 (s, 6H); HRMS (EI$^+$) *m*/*z* 315.1619 found, 315.1623 calcd for $C_{22}H_{21}N_1O_1$.

2,2-Dimethyl-6-(phenethylamino)-2*H*-1-benzopyran (8k). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.21 (m, 5H), 6.65 (d, 1H, J = 8.5 Hz), 6.45 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.32 (d, 1H, J = 2.7 Hz), 6.25 (d, 1H, J = 9.7 Hz), 5.61 (d, 1H, J = 9.7 Hz), 3.35 (t, 2H, J = 7.0 Hz), 2.90 (t, 1H, J = 7.0 Hz), 1.40 (s, 6H); HRMS (EI$^+$) *m*/*z* 279.1620 found, 279.1623 calcd for $C_{19}H_{21}N_1O_1$.

2,2-Dimethyl-6-(3-phenylallylamino)-2*H*-1-benzopyran (8l). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.22 (m, 5H), 6.66 (d, 1H, J = 8.5 Hz), 6.61 (d, 1H, J = 15.9 Hz), 6.50 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.38 (d, 1H, J = 2.8 Hz), 6.33 (dd, 1H, J = 15.9 Hz, J = 5.9 Hz), 6.26 (d, 1H, J = 9.8 Hz), 5.61 (d, 1H, J = 9.8 Hz), 3.87 (dd, 1H, J = 5.9 Hz, J = 1.5 Hz), 1.40 (s, 6H); HRMS (EI$^+$) *m*/*z* 291.1627 found, 291.1623 calcd for $C_{20}H_{21}N_1O_1$.

2,2-Dimethyl-6-(methylamino)-2*H*-1-benzopyran (8m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (d, 1H, J = 8.5 Hz), 6.45 (dd, 1H, J = 8.5 Hz, J = 2.7 Hz), 6.33 (d, 1H, J = 2.7 Hz), 6.27 (d, 1H, J = 9.7 Hz), 5.62 (d, 1H, J = 9.7 Hz), 2.80 (s, 3H), 1.40 (s, 6H); HRMS(EI$^+$) *m*/*z* 189.1157 found, 189.1154 calcd for $C_{12}H_{15}N_1O_1$.

2,2-Dimethyl-6-(pentylamino)-2*H*-1-benzopyran (8n). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.64 (d, 1H, J = 8.5 Hz), 6.43 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 6.31 (d, 1H, J = 2.8 Hz), 6.26 (d, 1H, J = 9.7 Hz), 5.61 (d, 1H, J = 9.7 Hz), 3.04 (t, 2H, J = 7.1 Hz), 1.60 (m, 2H), 1.39−1.34 (m, 10H), 0.91(t, 3H, J = 6.7 Hz); HRMS (EI$^+$) *m*/*z* 245.1776 found, 245.1780 calcd for $C_{16}H_{23}N_1O_1$.

6-(Allylamino)-2,2-dimethyl-2*H*-1-benzopyran (8o). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (d, 1H, J = 8.6 Hz), 6.51 (dd, 1H, J = 8.6 Hz, J = 2.8 Hz), 6.40 (d, 1H, J = 2.8 Hz), 6.25 (d, 1H, J = 9.8 Hz), 5.95 (m, 1H), 5.61 (d, 1H, J = 9.8 Hz), 5.28 (dd, 1H, J = 17.2 Hz, J = 1.5 Hz), 5.16 (dd, 1H, J = 10.1 Hz, J = 1.5 Hz), 3.72 (d, 2H, J = 4.0 Hz), 1.40 (s, 6H); HRMS (EI$^+$) *m*/*z* 215.1319 found, 215.1310 calcd for $C_{14}H_{17}N_1O_1$.

2,2-Dimethyl-6-(ethylamino)-2*H*-1-benzopyran (8p). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.62 (d, 1H, J = 8.5 Hz), 6.39 (dd, 1H, J = 8.55 Hz, J = 2.6 Hz), 6.28 (d, 1H, J = 2.6 Hz), 6.23 (d, 1H, J = 9.8 Hz), 5.58 (d, 1H, J = 9.8 Hz), 3.07 (q, 2H, J = 7.1 Hz), 2.68 (br, 1H), 1.37 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz); MS (EI$^+$) *m*/*z* 203.

Representative Procedure for the Second Generation Step by Hydroxyalkoxylation Reaction (See Table 2); 6-(Benzyl)amino-2,2-dimethyl-3-hydroxy-4-methoxy-2*H*-1-benzopyran Resin (5a). The 6-(benzylamino)-2,2-dimethyl-2*H*-1-benzopyran Resin **4a** (5.00 g, 2.50 mmol) was suspended in dry CH_2Cl_2 (30 mL), and MeOH (30 mL) and *m*-CPBA (2.16 g, 12.50 mmol) were successively added. After the mixture was shaken for 24 h at room temperature, the solvent was filtered off and washed with DMF (2 × 30 mL), MeOH (2 × 30 mL), MeOH/CH_2Cl_2 (1:1; 2 × 30 mL), CH_2Cl_2 (2 × 30 mL), MeOH/CH_2Cl_2 (1:1; 2 × 30 mL), and MeOH (2 × 30 mL) and dried under high vacuum.

Representative Procedure for the Cleavage Step from the Second Generated Resin (5); 6-(Benzylamino)-2,2-dimethyl-3-hydroxy-4-methoxy-2*H*-1-benzopyran (9a). The hydroxyalkoxylated resin **5a** (200 mg, 0.10 mmol) was treated with 4 mL of cleavage cocktail (TFA/CH_2Cl_2; 1:3). After the mixtures were shaken at room temperature for 3 h, the resin was filtered off and washed with CH_2Cl_2 (3 × 1 mL), followed by MeOH (1 mL). The combined filtrates were evaporated and purified by SAX resin and silica gel column chromatography (25% ethyl acetate in hexane; using Quad3$^+$) to yield (19.4 mg, 62%) 6-(benzylamino)-2,2-dimethyl-3-hydroxy-4-methoxyxy-2*H*-1-benzopyran **9a** (97% purity, determined by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 6.69−6.61 (m, 3H), 4.29 (d, 1H, J = 7.5 Hz), 4.27 (s, 2H), 3.81 (d, 1H, J = 7.5 Hz), 3.40 (s, 3H), 1.42 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.95, 141.11, 138.59, 128.59, 127.92, 127.39, 121.35, 116.25, 112.82, 78.01, 77.53, 71.91, 55.67, 49389, 25.73, 19.96; HRMS (EI$^+$) *m*/*z* 313.1663 found, 313.1678 calcd for $C_{19}H_{23}N_1O_3$.

6-(Benzylamino)-2,2-dimethyl-3-hydroxy-4-isopropoxy-2*H*-1-benzopyran (9b). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40−7.24 (m, 5H), 6.67−6.50 (m, 3H), 4.70 (s, 2H), 6.27 (d, 1H, J = 6.6 Hz), 4.01−3.95 (m, 1H), 3.67 (d, 1H, J = 6.6 Hz), 1.40 (s, 2H), 1.29−1.22 (m, 10H); MS (EI$^+$) *m*/*z* 341.

6-(Benzylamino)-4-(2-cyclohexylethoxy)-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran (9c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.23 (m, 5H), 6.68−6.51 (m, 3H), 4.31 (d, 1H, J = 7.4 Hz), 4.27 (s, 2H), 3.78 (d, 1H, J = 7.4 Hz), 3.66 (t, 2H, J = 6.4 Hz), 1.72−1.63 (m, 5H), 1.50 (t, 2H, J = 6.4 Hz), 1.41 (s, 3H), 1.25 (s, 3H), 1.21−1.17 (m, 4H), 0.92 (m, 2H); MS (EI$^+$) *m*/*z* 409.

6-(Benzylamino)-4-benzyloxy-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran (9d). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37−7.25 (m, 10H), 6.65−6.56 (m, 3H), 4.68 (s, 2H), 4.48 (d, 1H, J = 7.4 Hz), 4.23 (s, 2H), 3.86 (d, 1H, J = 7.4 Hz), 1.43 (s, 3H), 1.25 (s, 3H); MS (EI$^+$) *m*/*z* 389.

6-(4-*tert*-Butyl-benzylamino)-4-methoxy-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran (9e). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, 2H, J = 8.3 Hz), 7.31 (d, 2H, J = 8.3 Hz), 6.67 (d, 1H, J = 8.7 Hz), 6.65 (d, 1H, J = 2.7 Hz), 6.58 (dd, 1H, J = 8.7 Hz, J = 2.7 Hz), 4.31 (d, 1H, J = 7.5 Hz), 4.24 (s, 2H), 3.82 (d, 1H, J = 7.5 Hz), 3.41 (s, 3H), 1.43 (s, 3H), 1.32 (s, 9H), 1.25 (s, 3H); HRMS (EI$^+$) *m*/*z* 369.2311 found, 369.2304 calcd for $C_{23}H_{31}N_1O_3$.

6-(4-*tert*-Butyl-benzylamino)-2,2-dimethyl-4-ethoxy-3-hydroxy-2*H*-1-benzopyran (9f). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, 2H, J = 8.2 Hz), 7.31 (d, 2H, J = 8.2 Hz), 6.66 (d, 1H, J = 8.7 Hz), 6.65 (d, 1H, J = 2.5 Hz), 6.57 (dd, 1H, J = 8.7 Hz, J = 2.5 Hz), 4.33 (d, 1H, J = 7.5 Hz), 4.23 (s, 2H), 3.78 (d, 1H, J = 7.5 Hz), 3.65 (q, 2H, J = 7.0 Hz), 1.43 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz); MS (EI$^+$) *m*/*z* 383.

2,2-Dimethyl-3-hydroxy-4-methoxy-6-(4-methylbenzylamino)-2*H*-1-benzopyran (9g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, 2H, J = 8.0 Hz), 7.14 (d, 2H, J = 8.0 Hz), 6.67 (d, 1H, J = 8.8 Hz), 6.65 (d, 1H, J = 2.9 Hz), 6.56 (dd, 1H, J = 8.8 Hz, J = 2.9 Hz), 4.31 (d, 1H, J = 7.4 Hz), 4.23 (s, 2H), 3.82 (d, 1H, J = 7.4 Hz), 3.43 (s, 3H), 2.34 (s, 3H), 1.43 (s, 9H), 1.25 (s, 3H); HRMS (EI$^+$) *m*/*z* 327.1829 found, 327.1834 calcd for $C_{20}H_{25}N_1O_3$.

2,2-Dimethyl-3-hydroxy-4-methoxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (9h). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.6 Hz), 6.67 (d, 1H, J = 8.7 Hz), 6.64 (d, 1H, J = 2.8 Hz), 6.53 (dd, 1H, J = 8.7 Hz, J = 2.8 Hz), 4.31 (d, 1H, J = 7.3 Hz), 3.81 (d, 1H, J = 7.3 Hz), 3.80 (s, 3H), 3.43 (s, 3H), 1.43 (s, 3H), 1.24 (s, 3H); MS (EI$^+$) *m*/*z* 343.

4-Ethoxy-2,2-dimethyl-3-hydroxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (9i). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.6 Hz), 6.69−6.54 (m, 3H), 4.33 (d, 1H, J = 7.2 Hz), 3.80 (s, 3H), 3.78 (d, 1H, J = 7.2 Hz), 3.67 (q, 2H, J = 6.8 Hz), 1.43 (s, 3H), 1.24 (s, 3H), 1.35−1.20 (m, 3H); MS (EI$^+$) *m*/*z* 357.

2,2-Dimethyl-3-hydroxy-4-isopropoxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (9j). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 6.65 (br, 2H), 6.75 (s, 1H), 4.26 (d, 1H, J = 6.6 Hz), 4.19 (s, 2H), 3.98 (m, 1H), 3.78 (s, 3H), 3.66 (d, 1H, J = 6.6 Hz), 1.40−1.23 (m, 12H); MS (EI$^+$) *m*/*z* 371.

4-Butoxy-2,2-dimethyl-3-hydroxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (9k). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, 2H, J = 8.6 Hz), 6.83 (d, 2H, J = 8.6 Hz), 6.70 (m, 3H), 4.28 (d, 1H, J = 7.1 Hz), 4.20 (s, 2H), 3.77 (s, 3H), 3.76 (d, 1H, J = 7.1 Hz), 3.61 (t, 2H, J = 6.6 Hz), 1.58 (m, 2H), 1.38 (m, 2H), 1.42 (s, 3H), 1.25 (s, 3H), 0.93 (d, 3H, J = 7.3 Hz); MS (EI$^+$) *m*/*z* 385.

4-Benzyloxy-2,2-dimethyl-3-hydroxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (9l). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.24 (m, 7H), 6.83 (d, 2H, J = 8.7 Hz), 6.72−6.64 (m, 3H), 4.68 (s, 2H), 4.45 (d, 1H, J = 7.1 Hz), 4.15 (s, 2H), 3.85 (d, 1H, J = 7.1 Hz), 3.76 (s, 2H), 1.43 (s, 3H), 1.25 (s, 3H); MS (EI$^+$) *m*/*z* 419.

2,2-Dimethyl-3-hydroxy-6-(4-methoxybenzylamino)-4-phenethyloxy-2*H*-1-benzopyran (9m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (m, 6H), 7.17 (t, 1H, J = 7.2 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.52 (dd, 1H, J = 8.7 Hz, J = 2.8 Hz), 6.38 (d, 1H, J = 2.8 Hz), 4.30 (d, 1H, J = 7.8 Hz), 4.12 (s, 2H), 3.83 (m, 2H), 3.79 (s, 3H), 3.67 (d, 1H, J = 7.8 Hz), 2.89 (t, 2H, J = 6.5 Hz), 1.36 (s, 3H), 1.17 (s, 3H); MS (EI$^+$) *m*/*z* 433.

2,2-Dimethyl-3-hydroxy-4-methoxy-6-(4-trifluoromethylbenzylamino)-2*H*-1-benzopyran (9n). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59 (d, 2H, J = 8.1 Hz), 7.48 (d, 2H, J = 8.1 Hz), 6.67 (d, 1H, J = 8.5 Hz), 6.61 (d, 1H, J = 2.8 Hz), 6.53 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 4.36 (s, 2H), 4.29 (d, 1H, J = 7.4 Hz), 3.81 (d, 1H, J = 7.4 Hz), 3.40 (s, 3H), 2.69 (br, 2H), 1.43 (s, 3H), 1.24 (s, 3H)

2,2-Dimethyl-6-(4-fluorobenzylamino)-3-hydroxy-4-methoxy-2*H*-1-benzopyran (9o). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (m, 2H), 7.01 (m, 2H), 6.67 (d, 1H, J = 8.7 Hz), 6.63 (d, 1H, J = 2.7 Hz), 6.55 (dd, 1H, J = 8.7 Hz, J = 2.7 Hz), 4.30 (d, 1H, J = 7.5 Hz), 4.25 (s, 2H), 3.81 (d, 1H, J = 7.5 Hz), 3.42 (s, 3H), 1.43 (s, 3H), 1.24 (s, 3H); HRMS (EI$^+$) *m*/*z* 331.1581 found, 331.1584 calcd for $C_{19}H_{22}N_1O_3F_1$.

2,2-Dimethyl-6-(4-fluorobenzylamino)-3-hydroxy-4-isopropoxy-2*H*-1-benzopyran (9p). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, 2H, J = 8.3 Hz, J = 5.7 Hz), 7.01 (t, 2H, J = 8.6 Hz), 6.65 (m, 2H), 6.60 (d, 1H, J = 8.6 Hz), 4.26 (d, 1H, J = 6.8 Hz), 4.24 (s, 2H), 3.97 (m, 1H), 3.66 (d, 1H, J = 6.8 Hz), 1.40 (s, 3H), 1.28 (s, 3H), 1.27−1.23 (m, 6H); HRMS (EI$^+$) *m*/*z* 359.1891 found, 359.1897 calcd for $C_{21}H_{26}N_1O_3F_1$.

4-Butoxy-2,2-dimethyl-6-(4-fluorobenzylamino)-3-hydroxy-2*H*-1-benzopyran (9q). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30−7.28 (m, 2H), 6.98−6.94 (m, 2H), 6.90 (s, 1H), 6.81 (d, 1H, J = 9.0 Hz), 6.69 (d, 1H, J = 9.0 Hz), 4.25(d, 1H, J = 7.0 Hz), 4.23 (s, 2H), 3.76 (d, 1H, J = 7.0 Hz), 3.62 (t, 2H, J = 5.3 Hz), 1.58 (m, 2H), 1.44−1.35 (m, 5H), 1.26 (s, 3H), 0.94 (t, 3H, J = 7.3 Hz); HRMS (EI$^+$) *m*/*z* 373.2052 found, 373.2053 calcd for $C_{22}H_{28}N_1O_3F_1$.

4-(2-Cyclohexylethoxy)-2,2-dimethyl-6-(4-fluorobenzylamino)-3-hydroxy-2*H*-1-benzopyran (9r). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, 2H, J = 8.6 Hz, J = 2.1 Hz), 7.01 (dd, 2H, J = 8.6 Hz, J = 2.1 Hz), 6.66 (d, 1H, J = 8.7 Hz), 6.64 (d, 1H, J = 2.8 Hz), 6.56 (dd, 1H, J = 8.7 Hz, J = 2.8 Hz), 4.29 (d, 1H, J = 7.4 Hz), 4.24 (s, 2H), 3.84 (d, 1H, J = 7.4 Hz), 3.63 (t, 2H, J = 6.7 Hz), 1.71−1.67 (m, 4H), 1.52−1.18 (m, 8H), 1.42 (s, 3H), 1.24 (s, 3H), 0.92 (m, 1H); HRMS (EI$^+$) *m*/*z* 427.2520 found, 427.2523 calcd for $C_{26}H_{34}N_1O_3F_1$.

2,2-Dimethyl-6-(4-fluorobenzylamino)-3-hydroxy-4-phenethyloxy-2*H*-1-benzopyran (9s). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.17 (m, 7H), 7.00 (t, 2H, J = 8.7 Hz), 6.62 (d, 1H, J = 8.7 Hz), 6.54 (dd, 1H, J = 8.7 Hz, J = 2.7 Hz), 6.31 (d, 1H, J = 2.7 Hz), 4.27 (d, 1H, J = 7.8 Hz), 4.15 (s, 2H), 3.89−3.76 (m, 2H), 3.65 (d, 1H, J = 7.8 Hz), 2.88 (dd, 2H, J = 6.6 Hz), 1.35 (s, 3H), 1.16 (s, 3H); HRMS (EI$^+$) *m*/*z* 4211.2058 found, 421.2053 calcd for $C_{26}H_{28}N_1O_3F_1$

4-Benzyloxy-2,2-dimethyl-6-(4-fluorobenzylamino)-3-hydroxy-2*H*-1-benzopyran (9t). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.15 (m, 8H), 7.01 (d, 1H, J = 8.8 Hz), 6.89 (t, 2H, J = 8.6 Hz), 6.68 (d, 1H, J = 8.8 Hz), 4.16 (s, 2H), 3.99−3.95 (m, 1H), 3.82−3.78 (m, 1H), 3.55 (d, 1H, J = 7.7 Hz), 2.91−2.87 (m, 2H), 1.25 (s, 3H), 1.17 (s, 3H); MS (EI$^+$) *m*/*z* 407.

2,2-Dimethyl-6-(3-fluorobenzylamino)-3-hydroxy-4-methoxy-2*H*-1-benzopyran (9u). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (m, 1H), 7.15 (d, 1H, J = 7.5 Hz), 7.09 (m, 1H), 6.95 (dd, 1H, J = 8.2 Hz, J = 2.5 Hz), 6.67 (d, 1H, J = 8.7 Hz), 6.65 (d, 1H, J = 2.8 Hz), 6.57 (dd, 1H, J = 8.7 Hz, J = 2.8 Hz), 4.30 (d, 1H, J = 7.5 Hz), 4.29 (s, 2H), 3.81 (d, 1H, J = 7.5 Hz), 3.41 (s, 3H), 1.43 (s, 3H), 1.25 (s, 3H); HRMS (EI$^+$) *m*/*z* 331.1581 found, 331.1584 calcd for $C_{19}H_{22}N_1O_3F_1$.

2,2-Dimethyl-3-hydroxy-4-methoxy-6-(methylamino)-2*H*-1-benzopyran (9v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (d, 1H, J = 8.7 Hz), 6.65 (d, 1H, J = 2.7 Hz), 6.58 (dd, 1H, J = 8.7 Hz, J = 2.7 Hz), 4.34 (d, 1H, J = 7.4 Hz), 3.84 (d, 1H, J = 7.4 Hz), 3.49 (s, 3H), 2.82 (s, 3H), 1.43 (s, 3H), 1.26 (s, 3H); HRMS (EI$^+$) *m*/*z* 237.1367 found, 237.1365 calcd for $C_{13}H_{19}N_1O_3$.

2,2-Dimethyl-4-ethoxy-3-hydroxy-6-(methylamino)-2*H*-1-benzopyran (9w). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.70−6.50 (m, 3H), 4.36 (d, 1H, J = 7.4 Hz), 3.82−3.67 (m, 3H), 2.81 (s, 3H), 1.43 (s, 3H), 1.32−1.25 (m, 6H); MS (EI$^+$) *m*/*z* 251.

4-Butoxy-2,2-dimethyl-3-hydroxy-6-(methylamino)-2*H*-

1-benzopyran (9x). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.70−6.50 (m, 3H), 4.35 (d, 1H, J = 7.2 Hz), 3.80 (d, 1H, J = 7.2 Hz), 3.67 (t, 2H, J = 6.2 Hz), 2.81 (s, 3H), 1.67−1.53 (m, 2H), 1.49−1.30 (m, 2H), 1.42 (s, 3H), 1.25 (s, 3H), 0.94 (t, 3H, J = 7.2 Hz); MS(EI$^+$) *m*/*z* 279.

4-(2-Cyclohexylethoxy)-2,2-dimethyl-3-hydroxy-6-(methylamino)-2*H*-1-benzopyran (9y). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.70−6.52 (m, 3H), 4.34 (d, 1H, J = 7.0 Hz), 3.80 (d, 1H, J = 7.0 Hz), 3.70 (t, 2H, J = 6.6 Hz), 2.81 (s, 3H), 1.75−0.94 (m, 19H); MS (EI$^+$) *m*/*z* 333.

6-Amino-2,2-dimethyl-3-hydroxy-4-methoxy-2*H*-1-benzopyran (9z). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (d, 1H, J = 2.4 Hz), 6.66−6.57 (m, 2H), 4.29 (d, 1H, J = 7.3 Hz), 3.81 (d, 1H, J = 7.3 Hz), 3.49 (s, 3H), 3.01−2.87 (br, 3H), 1.43 (s, 3H), 1.25 (s, 3H); MS (EI$^+$) *m*/*z* 223.

Representative Procedure for the Third Generation Step by 3-Etherfication Reaction (See Table 3); 6-(Benzylamino)-3-benzyloxy-2,2-dimethyl-4-methoxy-2*H*-1-benzopyran Resin (6a). The 6-(benzylamino)-2,2-dimethyl-3-hydroxy-4-methoxy-2*H*-1-benzopyran resin **5a** (0.20 g, 0.10 mmol) was suspended in dry DMF (5 mL), and ^{t}BuOLi (0.08 mg, 1.00 mmol) was added, and the mixture was shaken for 30 min. Iodomethane (0.14 g, 1.00 mmol) was added, the mixture shaken for 12 h at room temperature, and the solvent was filtered off and washed with DMF (2 × 10 mL), MeOH (2 × 10 mL), MeOH/CH_2Cl_2 (1:1; 2 × 10 mL), CH_2Cl_2 (2 × 10 mL), MeOH/CH_2Cl_2 (1:1; 2 × 10 mL), and MeOH (2 × 10 mL) and dried under high vacuum.

Representative Procedure for the Cleavage Step from the Third Generated Resin (6); 6-(Benzylamino)-3,4-dimethoxy-2,2-dimethyl-2*H*-1-benzopyran (10a). The resin **6a** (200 mg, 0.10 mmol) was treated with 4 mL of cleavage cocktail (TFA/CH_2Cl; 1:3). After the mixtures were shaken at room temperature for 3 h, the resin was filtered off and washed with CH_2Cl_2 (3 × 1 mL), followed by MeOH (1 mL). The combined filtrates were evaporated to and purified by SAX resin and silica gel column chromatography (15% ethyl acetate in hexane using Quad3$^+$) to yield (16.3 mg, 50%) 6-(benzylamino)-2,2-dimethyl-2*H*-1-benzopyran **10a** (92% purity, determined by HPLC). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26−7.37 (m, 5H), 6.63−6.65 (m, 3H), 4.28 (d, 1H, J = 7.3 Hz), 4.27 (s, 2H), 3.61 (s, 3H), 3.50 (s, 3H), 3.33 (d, 1H, J = 7.3 Hz), 1.41 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.57, 141.36, 138.98, 128.55, 127.29, 122.44, 117.64, 115.80, 112.52, 82.60, 77.79, 77.69, 60.32, 57.06, 49.76, 26.07, 20.24; HRMS (EI$^+$) *m*/*z* 327.184319 found, 327.183444 calcd for $C_{20}H_{25}N_1O_3$.

6-(Benzylamino)-4-butoxy-2,2-dimethyl-3-(4-fluorobenzyloxy)-2*H*-1-benzopyran (10b). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35−7.24 (m, 10H), 7.06−6.97 (m, 4H), 6.98−6.57 (m, 3H), 4.85 (d, 1H, J = 11.5 Hz), 4.70 (m, 4H), 4.21 (s, 2H), 3.68 (d, 1H, J = 7.0 Hz), 1.43 (s, 3H), 1.26 (s, 3H); MS (EI$^+$) *m*/*z* 497.

6-(Benzylamino)-4-butoxy-2,2-dimethyl-3-(4-methylbenzyloxy)-2*H*-1-benzopyran (10c). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40−7.18 (m, 9H), 6.68−6.59 (m, 3H), 4.91 (d, 1H, J = 11.6 Hz), 4.68 (d, 1H, J = 11.6 Hz), 4.42 (d, 1H, J = 7.1 Hz), 4.28 (s, 2H), 3.63−3.57 (m, 3H), 2.35 (s, 3H), 1.56−1.26 (m, 4H), 1.37 (s, 3H), 1.23 (s, 3H), 0.90 (t, 3H, J = 7.3 Hz); MS (EI$^+$) *m*/*z* 459.

4-Benzyloxy-3-(2-chlorobenzyloxy)-2,2-dimethyl-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (10d). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84 (m, 2H), 7.26 (m, 2H), 6.88 (d, 2H, J = 8.5 Hz), 6.70−6.59 (m, 3H), 5.06 (d, 1H, J = 12.5 Hz), 4.84 (d, 1H, J = 12.5 Hz), 4.50 (d, 1H, J = 7.7 Hz), 4.22 (s, 2H), 3.81 (s, 3H), 3.65 (d, 1H, J = 7.7 Hz), 3.43 (s, 3H), 1.46 (s, 3H), 1.26 (s, 3H); MS (EI$^+$) *m*/*z* 543.

2,2-Dimethyl-4-ethoxy-3-methoxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (10e). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, 2H, J = 8.4 Hz), 6.87 (d, 2H, J = 8.4 Hz), 6.66−6.49 (m, 3H), 4.33 (d, 1H), 4.20 (s, 2H), 3.80 (s, 3H), 3.76 (m, 2H), 3.60 (s, 3H), 3.31 (d, 1H, J = 7.3 Hz), 1.41 (s, 3H), 1.25 (t, 3H, J = 7.0 Hz), 1.20 (s, 3H); MS (EI$^+$) *m*/*z* 371.

2,2-Dimethyl-4-ethoxy-6-(4-methoxybenzylamino)-3-(prop-2-ynyloxy)-2*H*-1-benzopyran (10f). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, 2H, J = 8.7 Hz), 6.86 (d, 2H, J = 8.7 Hz), 6.67−6.57 (m, 3H), 4.45 (d, 2H, J = 2.2 Hz), 4.19 (s, 2H), 3.80 (s, 3H), 3.70 (m, 2H), 2.45 (t, 1H, J = 2.3 Hz), 1.44 (s, 3H), 1.24 (m, 3H), 1.22 (s, 3H)); MS (EI$^+$) *m*/*z* 395.

4-Ethoxy-2,2-dimethyl-6-(4-methoxybenzylamino)-3-(naphthalene-2-ylmethoxy)-2*H*-1-benzopyran (10g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (m, 4H), 7.53−7.46 (m, 3H), 7.30 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.68−6.52 (m, 3H), 5.07 (d, 1H, J = 11.4 Hz), 4.88 (d, 1H, J = 11.4 Hz), 4.48 (d, 1H, J = 7.4 Hz), 4.21 (s, 2H), 3.80 (s, 3H), 3.74 (m, 2H), 3.66 (d, 1H, J = 7.4 Hz), 1.42 (s, 3H), 1.26 (m, 3H), 1.23 (s, 3H); MS (EI$^+$) *m*/*z* 497.

4-Butoxy-3-(2-chlorobenzyloxy)-2,2-dimethyl-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (10h). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90−7.73 (m, 4H), 7.29 (d, 2H, J = 8.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 5.04 (d, 1H, J = 12.3 Hz), 4.84 (d, 1H, J = 12.3 Hz), 4.49 (d, 1H, J = 7.7 Hz), 4.21 (s, 2H), 3.80 (s, 3H), 3.70−3.58 (m, 3H), 1.62−1.20 (m, 4H), 1.44 (s, 3H), 1.25 (s, 3H), 0.89 (t, 3H, J = 7.1 Hz).

3-(3,5-Bis-trifluoromethylbenzyloxy)-2,2-dimethyl-6-(4-fluorobenzylamino)-4-methoxy-2*H*-1-benzopyran (10i). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83 (s, 3H), 7.29−7.36 (m, 2H), 6.96−7.05 (m, 2H), 6.63−6.73 (m, 3H), 5.05 (d, 1H, J = 12.6 Hz), 4.83 (d, 1H, J = 12.6 Hz), 4.46 (d, 1H, J = 7.5 Hz), 4.25 (s, 2H), 3.63 (d, 1H, J = 7.5 Hz), 3.42 (s, 3H), 1.45 (s, 3H), 1.25 (s, 3H); MS (EI$^+$) *m*/*z* 557.

2,2-Dimethyl-6-(4-fluorobenzylamino)-4-isopropoxy-3-methoxy-2*H*-1-benzopyran (10j). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26−7.38 (m, 2H), 6.97−7.05 (m, 2H), 6.48−6.64 (m, 3H), 4.28 (d, 1H, J = 7.1 Hz), 4.24 (s, 2H), 3.98−4.10 (m, 1H), 3.58 (s, 3H), 3.22 (d, 1H, J = 7.1 Hz), 1.40 (s, 3H), 1.28 (s, 3H), 1.26 (d, 3H, J = 2.2 Hz), 1.23 (d, 3H, J = 2.2 Hz); MS (EI$^+$) *m*/*z* 373.

2,2-Dimethyl-6-(4-fluorobenzylamino)-4-isopropoxy-3-pentyloxy-2*H*-1-benzopyran (10k). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31−7.38 (m, 2H), 6.96−7.07 (m, 2H), 6.49−6.64 (m, 3H), 4.28 (d, 1H, J = 7.1 Hz), 4.24 (s, 2H), 3.99−4.11 (m, 1H), 3.78−3.86 (m, 1H), 3.58−3.76 (m, 1H), 3.52−3.56 (m, 1H), 3.31 (d, 1H, J = 7.1 Hz), 1.44−1.62 (m, 2H),

1.39 (s, 3H), 1.30−1.35 (m, 4H), 1.25−1.26 (m, 6H), 1.23 (s, 3H); MS (EI^+) *m*/*z* 429.

3-Allyloxy-2,2-dimethyl-4-methoxy-6-(4-methylbenzylamino)-2*H*-1-benzopyran (10l). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25−7.29 (m, 2H), 7.12−7.16 (m, 2H), 6.02−6.67 (m, 3H), 5.88−5.99 (m, 1H), 5.37 (dd, 1H, J = 17.3 Hz, J = 1.6 Hz), 5.19 (dd, 1H, J = 10.4 Hz, J = 1.4 Hz), 4.35 (d, 1H, J = 7.5 Hz), 4.23 (s, 2H), 4.18−4.36 (m, 2H), 3.51 (d, 1H, J = 7.5 Hz), 3.49 (s, 3H), 2.34 (s, 3H), 1.42 (s, 3H), 1.22 (s, 3H); MS (EI^+) *m*/*z* 367.

2,2-Dimethyl-3-(4-fluorobenzyloxy)-4-methoxy-6-(4-methylbenzylamino)-2*H*-1-benzopyran (10m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26−7.40 (m, 4H), 7.00−7.25 (m, 4H), 6.54−6.68 (m, 3H), 4.87 (d, 1H, J = 11.4 Hz), 4.67 (d, 1H, J = 11.6 Hz), 4.42 (d, 1H, J = 7.5 Hz), 4.23 (s, 2H), 3.60 (d, 1H, J = 7.5 Hz), 3.45 (s, 3H), 2.34 (s, 3H), 1.41 (s, 3H), 1.23 (s, 3H); MS (EI^+) *m*/*z* 435.

3-(4-Bromo-2-fluorobenzyloxy)-2,2-dimethyl-4-methoxy-6-(4-methylbenzylamino)-2*H*-1-benzopyran (10n). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.17−7.39 (m, 7H), 6.51−6.68 (m, 3H), 4.90 (d, 1H, J = 12.0 Hz), 4.73 (d, 1H, J = 12.0 Hz), 4.41 (d, 1H, J = 7.3 Hz), 4.23 (s, 2H), 3.61 (d, 1H, J = 7.3 Hz), 3.46 (s, 3H), 2.35 (s, 3H), 1.40 (s, 3H), 1.21 (s, 3H); MS (EI^+) *m*/*z* 513.

4-Benzyloxy-2,2-dimethyl-3-methoxy-6-(methylamino)-2*H*-1-benzopyran (10o). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48−7.30 (m, 5H), 6.70−6.60 (m, 3H), 4.87 (d, 1H, J = 11.6 Hz), 4.77 (d, 1H, J = 11.6 Hz), 4.53 (d, 1H, J = 6.9 Hz), 3.61 (s, 3H), 3.42 (d, 1H, J = 6.9 Hz), 2.75 (s, 3H), 1.45 (s, 3H), 1.24 (s, 3H); MS (EI^+) *m*/*z* 327.

4-Butoxy-2,2-dimethyl-3-methoxy-6-(methylamino)-2*H*-1-benzopyran (10p). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.68−6.42 (m, 3H), 4.33 (d, 1H, J = 7.3 Hz), 3.62 (s, 3H), 3.55 (s, 3H), 3.34 (d, 1H, J = 7.3 Hz), 2.80 (s, 3H), 1.42 (s, 3H), 1.20 (s, 3H); MS (EI^+) *m*/*z* 293.

3,4-Dimethoxy-2,2-dimethyl-6-(methylamino)-2*H*-1-benzopyran (10q). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42−7.29 (m, 5H), 6.70−6.50 (m, 3H), 4.93 (d, 1H, J = 11.6 Hz), 4.73 (1H, d, J = 11.6 Hz), 4.45 (d, 1H, J = 7.3 Hz), 3.63 (d, 1H, J = 7.3 Hz), 3.51 (s, 3H), 3.63 (s, 3H), 1.42 (s, 3H), 1.24 (s, 3H); MS (EI^+) *m*/*z* 251.

3-Benzyloxy-2,2-dimethyl-4-methoxy-6-(methylamino)-2*H*-1-benzopyran (10r). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40−7.22 (m, 3H), 6.69−6.50 (m, 3H), 4.90 (d, 1H, J = 11.8 Hz), 4.73 (d, 1H, J = 11.8 Hz), 4.42 (d, 1H, J = 7.5 Hz), 3.61 (d, 1H, J = 7.5 Hz), 3.51 (s, 3H), 2.81 (s, 3H), 1.40 (s, 3H), 1.21 (s, 3H); MS (EI^+) *m*/*z* 327.

3-(4-Bromo-2-fluorobenzyloxy)-2,2-dimethyl-4-methoxy-6-(methylamino)-2*H*-1-benzopyran (10s). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31 (m, 1H), 7.16−7.0 (m, 2H), 6.99 (m, 1H), 6.70−6.50 (m, 3H), 4.93 (d, 1H, J = 11.9 Hz), 4.72 (d, 1H, J = 11.8 Hz), 4.46 (d, 1H, J = 7.4 Hz), 3.62 (d, 1H, J = 7.5 Hz), 3.50 (s, 3H), 2.81 (s, 3H), 1.43 (s, 3H), 1.24 (s, 3H); MS (EI^+) *m*/*z* 423.

2,2-Dimethyl-3-(3-fluorobenzyloxy)-4-methoxy-6-(methylamino)-2*H*-1-benzopyran (10t). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83 (s, 3H), 6.71−6.51 (m, 3H), 5.07 (d, 1H, J = 12.6 Hz), 4.85 (d, 1H, J = 12.6 Hz), 4.53 (d, 1H, J = 7.7 Hz), 3.66 (d, 1H, J = 7.7 Hz), 3.47 (s, 3H), 2.82 (s, 3H), 1.45 (s, 3H), 1.25 (s, 3H); MS (EI^+) *m*/*z* 345.

3-(3,5-Bis-trifluoromethylbenzyloxy)-2,2-dimethyl-4-methoxy-6-(methylamino)-2*H*-1-benzopyran (10u). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95−6.70 (m, 3H), 4.44 (s, 2H), 4.39 (d, 1H, J = 6.9 Hz), 3.72 (d, 1H, J = 6.9 Hz), 3.56 (s, 3H), 2.86 (s, 3H), 2.47 (t, 1H, J = 2.2 Hz), 1.44 (s, 3H), 1.25 (s, 3H); MS (EI^+) *m*/*z* 463.

2,2-Dimethyl-4-methoxy-6-(methylamino)-3-(prop-2-ynyloxy)-2*H*-1-benzopyran (10v). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (m, 4H), 7.50 (m, 3H), 6.71−6.51 (m, 3H), 5.08 (d, 1H, J = 11.6 Hz), 4.89 (d, 1H, J = 11.6 Hz), 4.49 (d, 1H, J = 7.2 Hz), 3.69 (d, 1H, J = 7.2 Hz), 3.51 (s, 3H), 2.82 (s, 3H), 1.43 (s. 3H), 1.27 (s, 3H); MS (EI^+) *m*/*z* 275.

2,2-Dimethyl-4-methoxy-6-(methylamino)-3-(naphthalene-2-ylmethoxy)-2*H*-1-benzopyran (10w). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.75−6.63 (m, 3H), 4.34 (d, 1H, J = 7.1 Hz), 3.80−3.71 (m, 2H), 1.41 (s, 3H), 1.21 (s, 3H), 0.96 (t, 3H, J = 7.1 Hz); MS (EI^+) *m*/*z* 377.

3,4-Dibenzyloxy-2,2-dimethyl-6-(ethylamino)-2*H*-1-benzopyran (10x). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42−7.23 (m, 10H), 6.69−6.52 (m, 3H), 4.94−4.62 (m, 5H), 3.71 (d, 1H, J = 7.1 Hz), 3.05 (dd, 2H, J = 14.2 Hz, J = 7.1 Hz), 1.44 (s, 3H), 1.27 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz); MS (EI^+) *m*/*z* 417.

4-Butoxy-3-(3-chlorobenzyloxy)-2,2-dimethyl-6-(ethylamino)-2*H*-1-benzopyran (10y). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39−7.24 (m, 4H), 6.67−6.49 (m, 3H), 4.87 (d, 1H, J = 12.0 Hz), 4.69 (d, 1H, J = 12.0 Hz), 4.46 (d, 1H, J = 7.5 Hz), 3.68 (t, 2H, J = 6.5 Hz), 3.59 (d, 1H, J = 7.5 Hz), 3.11 (dd, 2H, J = 14.2 Hz, J = 7.1 Hz), 1.67−1.37 (m, 4H), 1.41 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz), 1.24 (s, 3H), 0.93 (t, 3H, J = 7.3 Hz); MS (EI^+) *m*/*z* 417.

4-Benzyloxy-2,2-dimethyl-6-(ethylamino)-3-(prop-2-ynyloxy)-2*H*-1-benzopyran (10z). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47−7.27 (m, 5H), 6.69−6.52 (m, 3H), 4.78 (s, 2H), 4.60 (d, 1H, J = 6.9 Hz), 4.44 (d, 2H, J = 2.6 Hz), 3.82 (d, 1H, J = 6.9 Hz), 3.05 (dd, 2H, J = 14.2 Hz, J = 7.10 Hz), 2.47 (t, 1H, J = 2.2 Hz), 1.47 (s, 3H), 1.26 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz); MS (EI^+) *m*/*z* 365.

Representative Procedure for the Third Generation Step by 3-Etherfication Reaction (See Table 4); 3-Acetoxy-6-(benzylamino)-2,2-dimethyl-4-methoxy-2*H*-1-benzopyran Resin (7a). The 6-(benzylamino)-2,2-dimethyl-3-hydroxy-4-methoxy-2*H*-1-benzopyran resin **5a** (0.20 g, 0.10 mmol) was suspended in dry CH_2Cl_2 (5 mL), pyridine (0.12 g, 1.50 mmol) was added, and the mixture was shaken for 30 min. Acetyl chloride (0.12 g, 1.50 mmol) and DMAP (0.01 g, 0.10 mmol) were successively added. After the mixture was shaken for 6 h at room temperature, the solvent was filtered off and washed with DMF (2 × 10 mL), MeOH (2 × 10 mL), MeOH/CH_2Cl_2 (1:1; 2 × 10 mL), CH_2Cl_2 (2 × 10 mL), MeOH/CH_2Cl_2 (1:1; 2 × 10 mL), and MeOH (2 × 10 mL) and dried under high vacuum. FTIR (cm^{-1}): 1735, 1324, 1120, 1066.

Representative Procedure for the Cleavage Step from the Third Generated Resin (7); 3-Acetoxy-6-(benzylamino)-2,2-dimethyl-4-methoxy-2*H*-1-benzopyran (11a). The resin **7a** (200 mg, 0.10 mmol) was treated with 4 mL

of cleavage cocktail (TFA/CH_2Cl_2; 1:3). After the mixtures were shaken at room temperature for 3 h, the resin was filtered off and washed with CH_2Cl_2 (3 × 1 mL), followed by MeOH (1 mL). The combined filtrates were evaporated and purified by SAX resin and silica gel column chromatography (15% ethyl acetate in hexane; using Quad3$^+$) to yield (18.8 mg, 53%) 3-acetoxy-6-(benzylamino)-2,2-dimethyl-4-methoxy-2*H*-1-benzopyran **11a** (93% purity, determined by HPLC). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37−7.25 (m, 5H), 6.72−6.55 (m, 3H), 5.22 (d, 1H, J = 5.7 Hz), 4.28 (m, 3H), 3.39 (s, 3H), 2.11 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.23, 145.76, 141.12, 138.56, 128.56, 127.91, 127.27, 120.50, 118.05, 116.51, 113.49, 75.64, 75.41, 71.36, 55.45, 49.88, 24.44, 22.23, 21.03; HRMS (EI$^+$) *m*/*z* 355.176 948 found, 355.178 359 calcd for $C_{21}H_{25}N_1O_4$.

3-Acetoxy-6-(4-fluorobenzylamino)-2,2-dimethyl-4-methoxy-2*H*-1-benzopyran (11b). ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.37−7.26 (m, 2H), 7.06−6.97 (m, 2H), 6.68−6.53 (m, 3H), 5.22 (d, 1H, J = 5.70 Hz), 4.28 (d, 1H, J = 5.70 Hz), 4.24 (s, 2H), 3.40 (s, 3H), 2.11 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H); MS (EI$^+$) *m*/*z* 373.

3-(*tert*-Butyl acetoxy)-2,2-dimethyl-6-(4-fluorobenzylamino)-4-methoxy-2*H*-1-benzopyran (11c). ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.36−7.26 (m, 2H), 7.05−6.97 (m, 2H), 6.72−6.55 (m, 3H), 5.23 (d, 1H, J = 6.10 Hz), 5.32 (d, 1H, J = 6.10), 4.24 (s, 2H), 3.35 (s, 3H), 2.26 (s, 2H), 1.36 (s, 3H), 1.28 (s, 3H), 1.04 (s, 9H); MS (EI$^+$) *m*/*z* 471.

4-Butoxy-2,2-dimethyl-3-(4-fluorobenzoyloxy)-6-(4-trifluoromethylbenzylamino)-2*H*-1-benzopyran (11d). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08−8.01 (m, 2H), 7.58 (d, 2H, J = 8.3 Hz), 7.48 (d, 2H, J = 8.3 Hz), 7.14−7.06 (m, 2H), 6.77−6.71 (m, 1H), 6.61−6.55 (m, 2H), 5.39 (d, 1H, J = 5.1 Hz), 4.39 (d, 1H, J = 5.1 Hz), 4.35 (s, 2H), 3.67−3.59 (m, 2H), 1.53−1.18 (m, 4H), 1.39 (s, 3H), 1.37 (s, 3H), 0.85 (t, 3H, J = 7.1 Hz); MS (EI$^+$) *m*/*z* 545.

4-Butoxy-2,2-dimethyl-3-(2-furoyloxy)-6-(4-trifluoromethylbenzylamino)-2*H*-1-benzopyran (11e). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.61−7.46 (m, 5H), 7.19 (d, 1H, J = 3.6 Hz), 6.74−6.69 (m, 1H), 6.59−6.48 (m, 3H), 5.36 (d, 1H, J = 5.5 Hz), 4.41 (d, 1H, J = 5.5 Hz), 4.35 (s, 2H), 3.62 (t, 2H, J = 6.6 Hz), 1.53−1.18 (m, 4H), 1.38 (s, 3H), 1.35 (s, 3H), 0.85 (t, 3H, J = 7.2 Hz); MS (EI$^+$) *m*/*z* 517.

3-Acetyloxy-4-(2-cyclohexylethoxy)-2,2-dimethyl-6-(4-trifluoromethylbenzylamino)-2*H*-1-benzopyran (11f). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (d, 2H, J = 8.2 Hz), 7.47 (d, 2H, J = 8.2 Hz), 6.74−6.61 (m, 3H), 5.17 (d, 1H, J = 4.9 Hz), 4.35 (s, 2H), 4.25 (d, 1H, J = 4.9 Hz), 3.68−3.53 (m, 2H), 2.10 (s, 3H), 1.80−1.15 (br, 11H), 1.34 (s, 3H), 1.30 (s, 3H), 0.92 (br, 2H); MS (EI$^+$) *m*/*z* 519.

4-(2-Cyclohexylethoxy)-2,2-dimethyl-3-(4-methylbenzoyloxy)-6-(4-trifluoromethylbenzylamino)-2*H*-1-benzopyran (11 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, 2H, J = 8.3 Hz), 7.57 (d, 2H, J = 8.5 Hz), 7.47 (d, 2H, J = 8.5 Hz), 7.23 (d, 2H, J = 8.3 Hz), 6.80−6.61 (m, 3H), 5.40 (d, 1H, J = 5.2 Hz), 4.40 (d, 1H, J = 5.2 Hz), 4.35 (s, 2H), 3.71−3.64 (m, 2H), 2.41 (s, 3H), 1.70−1.10 (br, 11H), 1.39 (s, 3H), 1.37 (s, 3H), 0.86 (br, 2H); MS (EI$^+$) *m*/*z* 593.

3-Acetyloxy-2,2-dimethyl-4-methoxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11h). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, 2H, J = 8.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 6.72−6.55 (m, 3H), 5.22 (d, 1H, J = 5.7 Hz), 4.29 (d, 1H, J = 5.7 Hz), 4.19 (s, 2H), 3.79 (s, 3H), 3.40 (s, 3H), 2.11 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H); MS (EI$^+$) *m*/*z* 385.

3-(*tert*-Butyl-acetoxy)-2,2-dimethyl-4-methoxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11i). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27 (m, 2H), 6.87 (d, 2H, J = 8.7 Hz), 6.70 (d, 1H, J = 8.5 Hz), 6.62−6.50 (m, 2H), 5.24 (d, 1H, J = 6.0 Hz), 4.34 (d, 1H, J = 6.0 Hz), 4.20 (s, 2H), 3.80 (s, 3H), 3.37 (s, 3H), 2.27 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.05 (s, 9H); MS (EI$^+$) *m*/*z* 427.

3-Cyclohexanecarbonyloxy-2,2-dimethyl-4-methoxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11j). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, 2H, J = 9.0 Hz), 6.86 (d, 2H, J = 9.0 Hz), 6.84−6.60 (m, 3H), 5.22 (d, 1H, J = 5.7 Hz), 4.30 (d, 1H, J = 5.7 Hz), 4.19 (s, 3H), 3.79 (s, 3H), 3.38 (s, 3H), 2.36 (m, 1H), 2.05−1.20 (m, 10H), 1.33 (s, 3H), 1.28 (s, 3H); MS (EI$^+$) *m*/*z*.453.

3-Acryloyloxy-2,2-dimethyl-4-methoxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11k). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, 2H, J = 9.0 Hz), 6.86 (d, 2H, J = 9.0 Hz), 6.72−6.56 (m, 3H), 5.71 (d, 1H, J = 1.2 Hz), 5.25 (d, 1H, J = 5.3 Hz), 4.29 (d, 1H, J = 5.3 Hz), 4.19 (s, 2H), 3.79 (s, 3H), 3.44 (s, 3H), 2.18 (s, 3H), 1.89 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H); MS (EI$^+$) *m*/*z* 425.

3-(4-Fluorobenzoyloxy)-2,2-dimethyl-4-methoxy-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11l). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10−8.03 (m, 2H), 7.31−7.25 (m, 2H), 7.15−7.07 (m, 2H), 6.87 (d, 2H, J = 8.8 Hz), 6.75 (d, 1H, 8.5 Hz), 5.45 (d, 1H, J = 5.4 Hz), 4.44 (d, 1H, J = 5.4 Hz), 4.20 (s, 2H), 3.80 (s, 3H), 3.46 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H); MS (EI$^+$) *m*/*z* 465.

3-Acetoxy-4-butoxy-2,2-dimethyl-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.83−6.55 (m, 3H), 5.18 (d, 1H, J = 5.2 Hz), 4.28 (d, 1H, J = 5.2 Hz), 4.19 (s, 2H), 3.80 (s, 3H), 3.75−3.56 (m, 2H), 2.10 (s, 3H), 1.58−1.51 (m, 2H), 1.48−1.38 (m, 2H), 1.35 (s, 3H), 1.29 (s, 3H), 0.91 (t, 3H); MS (EI$^+$) *m*/*z* 427.

4-Butoxy-3-cyclohexanecarbonyloxy-2,2-dimethyl-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11n). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 6.72−6.60 (m, 3H), 5.18 (d, 1H, J = 5.5 Hz), 4.28 (d, 1H, J = 5.5 Hz), 4.19 (s, 2H), 3.79 (s, 3H), 3.58−3.57 (m, 2H), 2.30 (m, 1H), 2.0−1.20 (m, 14H), 1.33 (s, 3H), 1.28 (s, 3H), 0.90 (t, 3H, J = 7.2 Hz); MS (EI$^+$) *m*/*z* 495.

3-Acryloyloxy-4-butoxy-2,2-dimethyl-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11o). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, 2H, J = 8.7 Hz), 6.86 (d, 2H, J = 8.7 Hz), 6.72−6.60 (m, 3H), 5.70 (d, 1H, J = 1.2 Hz), 5.20 (d, 1H, J = 5.0 Hz), 4.28 (d, 1H, J = 5.0 Hz), 4.19 (s, 2H), 3.79 (s, 3H), 3.68−3.55 (m, 2H), 2.17 (s, 3H), 1.89 (s, 3H), 1.62−1.45 (m, 2H), 1.42−1.26 (m, 2H), 1.35 (s, 3H), 1.29 (s, 3H), 0.90 (t, 3H, J = 7.2 Hz); MS (EI$^+$) *m*/*z* 467.

4-Butoxy-2,2-dimethyl-3-(4-fluorobenzoyloxy)-6-(4-methoxybenzylamino)-2*H*-1-benzopyran (11p). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08−8.01 (m, 2H), 7.30−7.14 (m, 2H),

7.10−7.05 (m, 2H), 6.87−6.73 (m, 5H), 5.39 (d, 1H, J = 5.1 Hz), 4.40 (d, 1H, J = 5.1 Hz), 4.19 (s, 2H), 3.78 (s, 3H), 3.66 (m, 2H), 1.57−1.25 (m, 4H), 1.40 (s, 3H), 1.37 (s, 3H), 0.87 (t, 3H, J = 7.2 Hz); MS (EI^+) *m*/*z* 507.

3-(*tert*-Butyl-acetoxy)-2,2-dimethyl-4-methoxy-6-(methylamino)-2*H*-1-benzopyran (11q). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.74−6.55 (m, 3H), 5.24 (d, 1H, J = 6.0 Hz), 4.35 (d, 1H, J = 6.0 Hz), 3.41 (s, 3H), 2.80 (s, 3H), 2.27 (s, 2H), 1.36 (s, 3H), 1.29 (s, 3H), 1.05 (s, 9H); MS (EI^+) *m*/*z* 335.

3-Cyclohexanecarbonyloxy-2,2-dimethyl-4-methoxy-6-(methylamino)-2*H*-1-benzopyran (11r). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.74 (m, 3H), 5.23 (d, 1H, J = 5.8 Hz), 4.29 (d, 1H, J = 5.8 Hz), 3.44 (s, 3H), 2.81 (s, 3H), 2.35 (m, 1H), 1.93−1.26 (m, 10H), 1.34 (s, 3H), 1.29 (s, 3H); MS (EI^+) *m*/*z* 347.

3-Acetoxy-2,2-dimethyl-4-ethoxy-6-(methylamino)-2*H*-1-benzopyran (11s). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.73−6.53 (m, 3H), 5.19 (d, 1H, J = 5.2 Hz), 4.33 (d, 1H, J = 5.2 Hz), 3.70 (q, 2H, J = 7.0 Hz), 2.81 (s, 3H), 2.11 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H), 1.23 (t, 3H, J = 6.9 Hz); MS (EI^+) *m*/*z* 293.

3-(*tert*-Butyl-acetoxy)-2,2-dimethyl-4-ethoxy-6-(methylamino)-2*H*-1-benzopyran (11t). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.73−6.52 (m, 3H), 5.21 (d, 1H, J = 5.7 Hz), 4.38 (d, 1H, J = 5.7 Hz), 3.66 (q, 2H, J = 6.9 Hz), 2.80 (s, 3H), 2.26 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.21 (t, 3H, J = 6.9 Hz), 1.04 (s, 9H); MS (EI^+) *m*/*z* 349.

3-Acryloyloxy-2,2-dimethyl-6-(ethylamino)-4-methoxy-2*H*-1-benzopyran (11u). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.97−6.74 (m, 3H), 5.71 (d, 1H, J = 1.5 Hz), 5.24 (d, 1H, J = 5.0 Hz), 4.26 (d, 1H, J = 5.0 Hz), 3.49 (s, 3H), 3.18 (q, 2H, J = 7.1 Hz), 2.18 (s, 3H), 1.89 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.25 (m, 3H); MS (EI^+) *m*/*z* 333.

3-Benzoyloxy-2,2-dimethyl-6-(ethylamino)-4-methoxy-2*H*-1-benzopyran (11v). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08−8.03 (m, 2H), 7.58−7.53 (m, 1H), 7.48−7.26 (m, 2H), 6.82−6.75 (m, 3H), 5.47 (d, 1H, J = 5.5 Hz), 4.44 (d, 1H, J = 5.5 Hz), 3.51 (s, 3H), 3.15 (q, 2H, J = 7.2 Hz), 1.41 (s, 3H), 1.39 (s, 3H), 1.25 (t, 3H, J = 7.2 Hz); MS (EI^+) *m*/*z* 355.

2,2-Dimethyl-6-(ethylamino)-3-(4-methyl-benzoyloxy)-4-methoxy-2*H*-1-benzopyran (11w). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.03 (d, 2H, J = 7.6 Hz), 7.23 (d, 2H, J = 7.6 Hz), 6.82−6.75 (m, 3H), 5.46 (d, 1H, J = 5.5 Hz), 4.43 (d, 1H, J = 5.5 Hz), 3.51 (s, 3H), 3.15 (q, 2H, J = 7.2 Hz), 2.41 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz); MS (EI^+) *m*/*z* 369.

3-Acetoxy-4-benzyloxy-2,2-dimethyl-6-(ethylamino)-2*H*-1-benzopyran (11x). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42−7.24 (m, 5H), 6.73−6.47 (m, 3H), 5.27 (d, 1H, J = 4.7 Hz), 4.72 (s, 2H), 4.42 (d, 1H, J = 4.7 Hz), 3.05 (q, 2H, J = 7.1 Hz), 2.10 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz); MS (EI^+) *m*/*z* 369.

4-Benzyloxy-2,2-dimethyl-6-(ethylamino)-3-(2-thiopencarbonyloxy)-2*H*-1-benzopyran (11y). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84−7.82 (m, 1H), 7.60 (m, 1H), 7.40−7.26 (m, 5H), 6.73 (d,1H, J = 8.3 Hz), 6.59−6.51 (m, 2H), 5.47 (d, 1H, J = 5.3 Hz), 4.77 (s, 2H), 4.62 (d, 1H, J = 5.3 Hz), 3.03 (q, 2H, J = 7.1 Hz), 1.44 (s, 3H), 1.39 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz); MS (EI^+) *m*/*z* 437.

4-Benzyloxy-2,2-dimethyl-6-(ethylamino)-3-(2-furoyloxy)-2*H*-1-benzopyran (11z). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60−7.59 (m, 1H), 7.41−7.18 (m, 6H), 6.73 (d, 1H, J = 8.5 Hz), 6.59−6.45 (m, 3H), 5.47 (d, 1H, J = 5.1 Hz), 4.77 (s, 2H), 4.58 (d, 1H, J = 5.0 Hz), 3.10−3.02 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 1.21 (m, 3H); MS (EI^+) *m*/*z* 421.

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Supporting Information Available. ATR-FTIR spectra of the solid-phase synthesis for resins **1**−**3**, **4a**, **5a**, **6a**, **7a**; analytical data (^{1}H NMR, ^{13}C NMR, HRMS, and HPLC) of the representative procedure for compounds **8a**, **9a**, **10a**, and **11a** and for the major side product **15**; and ^{1}H NMR spectra for the final products **8b**−**8p**, **9b**−**9z**, **10b**−**10z**, and **11b**−**11z**. This material is available free of charge via the Internet at http://pubs.acs.org.

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