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Construction of a 2,6-Difunctionalized 2-Methyl-2*H*-1-benzopyran Library by Using a Solid-Phase Synthesis Protocol

Jong Yeon Hwang,[†,‡] Hyung-Sub Choi,[†,‡] Jin-soo Seo,[†] Hyun Ju La,[†] Dong-Soo Kim,[†] Hyun Suk Jeon,[†] Moon-Kook Jeon,[†] Duck-Hyung Lee,[‡] and Young-Dae Gong*[,†]

Medicinal Science Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusung-gu, Daejeon 305-600, Korea, and Department of Chemistry, Sogang University, Seoul 121-742, Korea

ydgong@krict.re.kr

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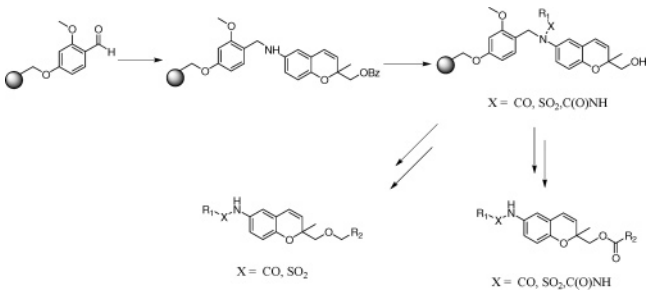
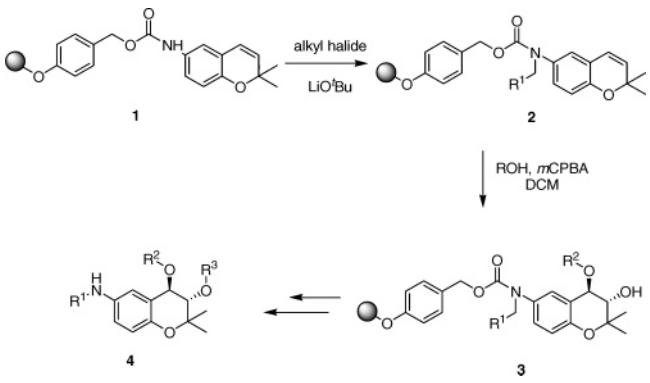


A library containing 1200 analogues of 2,6-difunctionalized 2-methyl-2*H*-1-benzopyran was constructed by using a solid-phase synthesis protocol. Polymer-bound 6-amido-, 6-sulfonamido-, and 6-uredo-functionalized 2-hydroxymethyl-2-methylbenzopyrans **10** were prepared as part of a first-generation diversification step by employing reactions of respective acid halides, sulfonyl chlorides, and isocyanates with the amine precursor **7**. Transformations of the resin-bound intermediates **10** by reactions with alkyl and acid halides were then used to produce a diverse series of 2,6-difunctionalized 2-methyl-2*H*-1-benzopyran analogues **12** and **14**.

Solid-phase synthesis is a powerful technique for the simultaneous generation of a large variety of small organic molecules for use in drug discovery programs.[1] In addition, heterocyclic compounds have found increasing use as scaffolds on which pharmacophores can be placed to yield potent and selective drugs. Importantly, a variety of heterocycles have been synthesized on solid supports.[2] As part of a recent drug discovery effort, we required a facile and rapid solid-phase parallel synthesis protocol that would enable construction of druglike small molecules on a heterocycle scaffold.[3] Our specific interest focused on a substituted benzopyran library because substances in this family show a broad range of biological activities.[4] In this context, we previously described a carbamate linker based solid-phase synthetic pathway to generate a 3,4,6-trisubstituted 6-amino-2,2-dimethyl-2*H*-1-benzopyran library **4** (Scheme 1).[3d] In this approach, polymer-bound hydroxyalkoxychromans **3**, produced by alcohol-promoted ring opening of in situ generated epoxides, served as key intermediates for subsequent diversification. However, broad application of this methodology was severely restricted by the fact that the previously reported method for N-alkylation of carbamate **1** required the use of exceptionally strong bases (e.g., lithium tertiary butoxide or sodium hydride). In addition, various functional groups could not be introduced at the 2-position of the benzopyran system by using this procedure. Consequently, an alternative linker-based synthetic strategy was needed. In the studies described below, we have developed a flexible solid-phase approach for the preparation of a novel 1200 analogue library of 2,6-difunctionalized 2-methyl-2*H*-1-benzopyrans (**9**, **12,** and **14**, Scheme 2) that relies on a methoxybenzaldehyde AMEBA linker. The methodology enables introduction of functional group diversification at both the 2- and 6-positions of the benzopyran ring system.

SCHEME 1



In the strategy we have developed, the methoxybenzaldehyde (AMEBA) resin **5** was selected as the polymer support since the secondary amino group, resulting from reductive amination, should be highly reactive with various alkyl halides, acid halides, isocyanates, and sulfonyl chlorides. Moreover, the final products should

* Corresponding author. Tel: +82-42-860-7149. Fax: +82-42-861-1291.
† Korea Research Institute of Chemical Technology.
‡ Sogang University.

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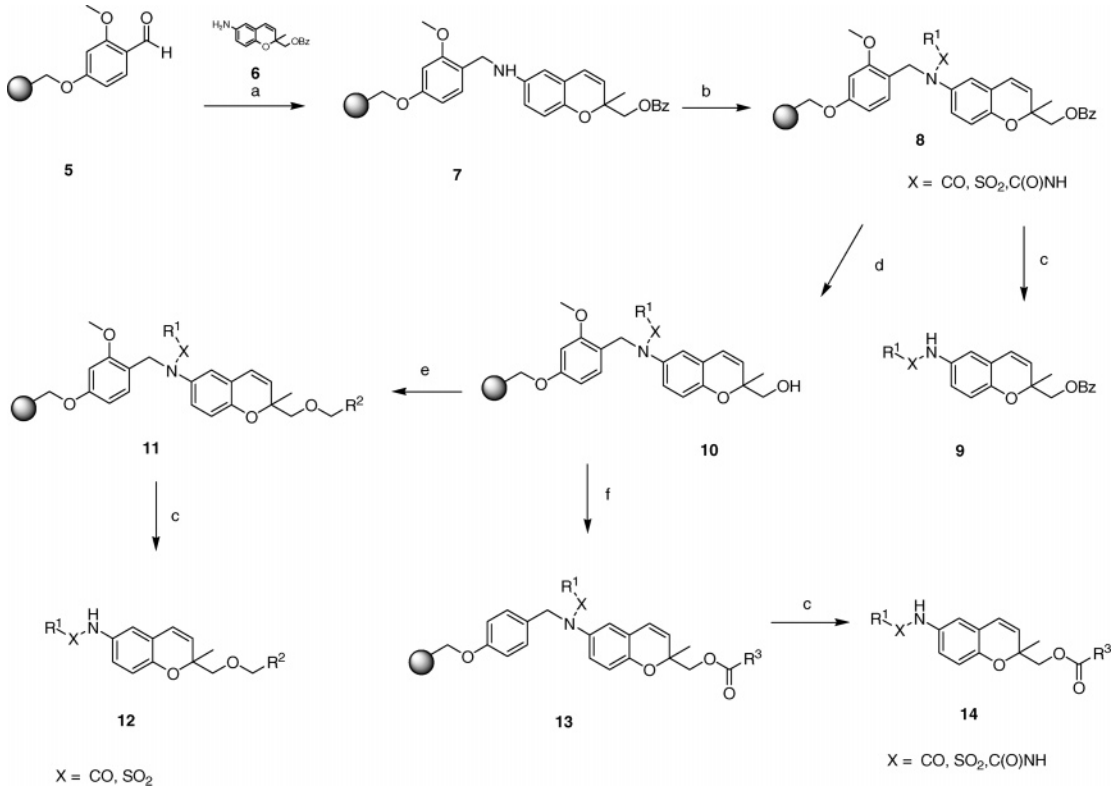
SCHEME 2[a]



[a] Key: (a) $NaBH(OAc)_3$, 1% AcOH/DMF, rt, 24 h; (b) electrophiles, DMF, rt, 24 h; (c) 20% TFA/DCM, rt, 3 h; (d) NaOMe/MeOH, THF, rt, 12 h; (e) alkyl halide, LiO^tBu, DMF, 40 °C, 24 h; (f) acid chloride, DBU, DMAP, DMF, 40 °C, 24 h.

be readily cleaved from the support by using dilute TFA solutions.[6] In the first step of the sequence, 6-aminobenzopyran resin **7** was prepared by reaction of AMEBA[6c] resin **5** with 6-aminobenzopyran **6**[7] under reductive amination conditions ($NaBH(OAc)_3$ in DMF containing 1% acetic acid).[8] The success of this process was confirmed by the disappearance of the aldehyde carbonyl band in the ATR-FTIR spectrum at 1677 cm^{-1} and the appearance of the benzoate ester carbonyl band at 1720 cm^{-1} (Figure 1B).

In the first-generation diversification step, the secondary amine group in **7** was transformed into the amide, sulfonamide, or urea groups in resin **8** by respective room-temperature reactions with acid chlorides, sulfonyl chlorides, and isocyanates in the presence of TEA in DMF. The progress of each of these reactions was assessed by the appearance of characteristic bands (amide **8a**: 1650 cm^{-1}, sulfonamide **8m**: 1380 cm^{-1}, urea **8q**: 1672 cm^{-1}) in the ATR-FTIR spectrum (Figure 1C–E). To confirm product formation, resin **8a** was treated with 20% TFA in CH_2Cl_2 for 3 h to obtain the *N*-

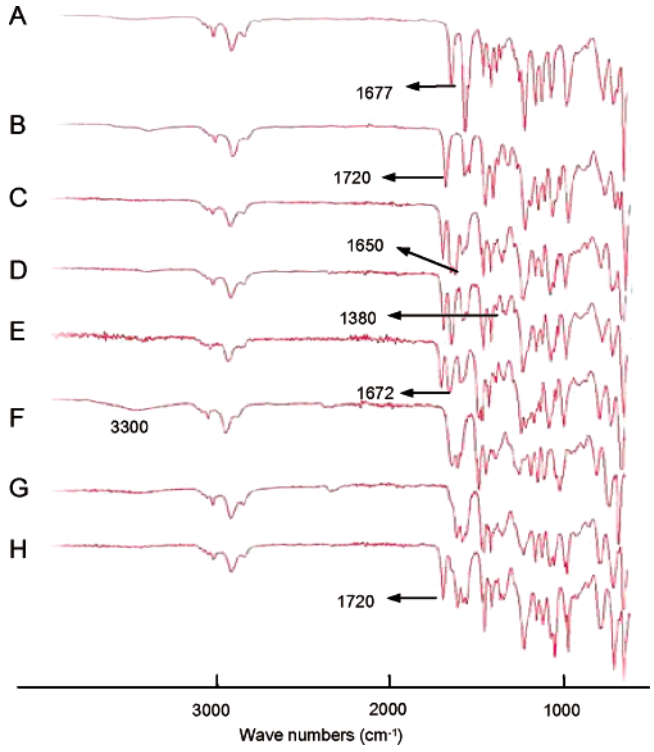


FIGURE 1. ATR-FTIR spectra on single beads of resins **5** (A), **7** (B), **8a** (C), **8m** (D), **8q** (E), **10a** (F), **11a** (G), and **13a** (H).

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TABLE 1. Preparation of Bezopyrans 9

Product	X	R^1	Yield (%)[a]	Purity(%)[b]	$(M+H)^+$
9a	CO	*tert*-$BuCH_2$	85	95	394
9b	CO	2-ClPh	77	87	434
9c	CO	4-ClPh	81	91	434
9d	CO	*c*-Hex	65	90	406
9e	CO	*c*-Pr	79	98	364
9f	CO		82	95	378
9g	CO	4-MeOPh	71	96	430
9h	CO	2-F Ph	89	95	418
9i	CO	*n*-Bu	76	100	380
9j	CO	3,4-Di-MeOPh	69	96	460
9k	CO		65	100	406
9l	SO_2	4-*tert*-BuPh	71	95	492
9m	SO_2	4-ClPh	66	88	470
9n	SO_2	2-Naph	74	72	486
9o	SO_2		68	77	442
9p	C(O)NH	*n*-Bu	70	90	395
9q	C(O)NH		73	85	453
9r	C(O)NH	2-ClPh	80	93	449
9s	C(O)NH	*c*-Hex	76	85	421
9t	C(O)NH	2,6-Di-MePh	59	91	443
9u	C(O)NH	2-EtOPh	69	91	459
9v	C(O)NH	2-EtPh	78	95	443
9w	C(O)NH	4-FPh	85	91	433
9x	C(O)NH	4-MeOPh	82	94	445
9y	C(O)NH	4-O_2NPh	75	85	460

[a] Three-step overall yield from the resin **7** (loading capacity of the resin **7** is 1.1 mmol/g). [b] Purity of the final products were established by using LC/MS.

substituted 6-aminobenzopyran **9a** in high yield and purity (Table 1).

For the purpose of second-generation diversity, resins **10** containing free primary hydroxyl group were prepared by reaction of resins **8** with NaOMe in MeOH/THF at room temperature.[9] The progress of these processes was monitored by the disappearance of the benzyoxy ester carbonyl band at 1720 cm^{-1} and the appearance of the broad hydroxyl band at 3300 cm^{-1}. Functionalization of the hydroxyl groups in resins **10** was promoted by reactions with alkyl halides and acid halides to generate respective ethers **11** and esters **13**. Alkylation reactions of **10** were carried out in the presence of lithium *tert*-butoxide in DMF and took place smoothly to yield the corresponding ethers. Exceptions to this trend were found with the ureidobenzopyran resins **10q**−**z** which have two acidic protons (−NH and −OH). In these cases, undesired doublly alkylated products **15** were obtained (Scheme 3). Subsequent treatment of the resins **11** with 20% TFA in CH_2Cl_2 for 3 h produced the desired 2,6-difuctionalized 2-methyl-2*H*-1-benzopyran derivatives **12** in high four-step overall yields from resin **7** (Table 2). The ester-containing resins **13** were prepared by treatment of **10** with various acid halides in the presence of DBU and DMAP in DMF. The progress of these processes was

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SCHEME 3

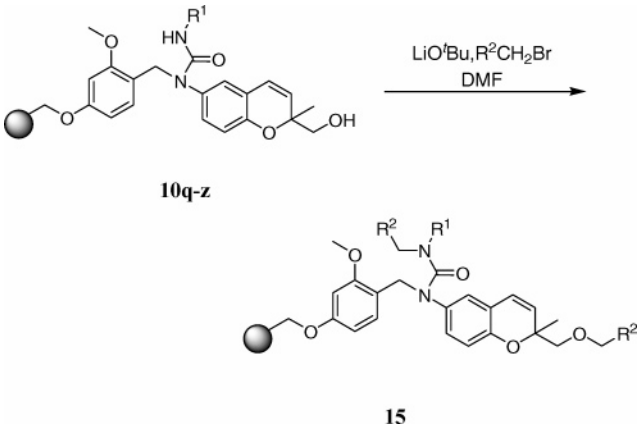

TABLE 2. Preparation of Benzopyrans 12

Product	X	R^1	R^2	Yield (%)[a]	Purity(%)[b]	$(M+H)^+$
12a	CO	2-ClPh	2-ClBn	59	97	454
12b	CO	2-ClPh	Allyl	61	95	370
12c	CO		3-ClBn	52	100	398
12d	CO		3-FBn	67	93	382
12e	CO		Bn	58	99	392
12f	CO		3-FBn	49	97	410
12g	CO		Allyl	56	97	342
12h	CO	4-MeOPh	4-*tert*-BuBn	61	83	472
12i	CO	4-MeOPh	3-FBn	55	98	434
12j	CO	4-MeOPh	4-MeBn	48	96	430
12k	SO_2	4-*tert*-BuPh	3-FBn	84	84	496
12l	SO_2	4-*tert*-BuPh	4-CF_3Bn	64	94	546
12m	SO_2	4-*tert*-BuPh		58	100	442
12n	SO_2	4-*tert*-BuPh	Allyl	56	91	428
12o	SO_2	2-ClPh	4-*tert*-BuBn	37	97	512
12p	SO_2	2-ClPh	3-ClBn	70	95	490
12q	SO_2	2-ClPh	3-FBn	73	93	474
12r	SO_2	2-ClPh	Allyl	65	99	405
12s	SO_2			59	98	391
12t	SO_2	4-MeOPh	4-*tert*-BuBn	26	91	508
12u	SO_2	4-MeOPh	3-ClBn	55	96	486
12v	SO_2	4-MeOPh	4-NCBn	58	99	477

[a] Four-step overall yield from the resin **7** (loading capacity of the resin **7** is 1.1 mmol/g). [b] Purity of final product was checked by LC/MS.

monitored by the appearance of the ester carbonyl band at 1720 cm^{-1}. To confirm product formation, the resins **13** were treated with 20% TFA in CH_2Cl_2 for 3 h to yield the desired ester benzopyrans **14** (Table 3).

The effort described above has led to the development of a novel solid-phase synthetic strategy for the preparation of a broad 2,6-difuctionalized 2*H*-benzopyran library. In the sequences, the key polymer-bound 6-amino-functionalized 2-hydroxymethyl-2-methyl-2*H*-benzopyrans **10** are produced by a first generation diversification step involving reaction of the amine containing resin **7** with acid halides, sulfonyl chlorides, or isocyanates. Ensuing reactions of resins **10** with various alkyl and acid halides followed by TFA-promoted benzylamine cleavage leads

TABLE 3. Preparation of Benzopyrans 14

Product	X	R^1	R^3	Yield (%)[a]	Purity(%)[b]	$(M+H)^+$
14a	CO	2-ClPh	4-ClPh	57	100	468
14b	CO		2-ClPh	64	94	412
14c	CO		2- FPh	61	98	396
14d	CO			73	98	368
14e	CO			67	94	384
14f	CO		Me	52	99	344
14g	CO		4-ClPh	55	92	424
14h	CO	4-MeOPh	2- FPh	64	98	448
14i	SO_2	4-*tert*-BuPh	Me	48	98	430
14j	SO_2	4-*tert*-BuPh		57	100	470
14k	SO_2	4-*tert*-BuPh		68	92	482
14l	SO_2	4-*tert*-BuPh	2- F_3CPh	60	100	560
14m	SO_2		Me	61	100	380
14n	SO_2	4-MeOPh	4-FPh	72	88	484
14o	C(O)NH	4-FPh	2-ClPh	63	91	467
14p	C(O)NH	4-FPh		68	97	411
14q	C(O)NH	4-FPh		73	93	423
14r	C(O)NH	2-EtOPh	Me	29	77	397
14s	C(O)NH	2-EtPh	2-ClPh	50	81	477
14t	C(O)NH	2-EtPh	2-FPh	58	88	461
14u	C(O)NH	Ph	Me	56	82	353

[a] Four-step overall yield from the resin **7** (loading capacity of the resin **7** is 1.1 mmol/g). [b] Purity of the final product was determined by LC/MS.

to the desired 2,6-difunctionalized 2-methyl-2*H*-1-benzopyrans **12** and **14**.

Experimental Section

Preparation of Polymer-Bound 6-Aminobenzopyran 7. To a suspension of AMEBA resin **5** (1.0 g, 1.6 mmol, loading capacity 1.6 mmol/g) in DMF (30 mL) containing 1% acetic acid were added successively 6-aminobenzopyran **6** (0.94 mg, 3.2 mmol) and $NaBH(OAc)_3$ (0.67 g, 3.2 mmol). The suspension was shaken for 24 h at room temperature under N_2. The suspension was filtered, and the precipitate containing the 6-aminobenzopyran resin **7** was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}): 1720, 1612, 1492, 1269, 1025.

Representative Procedure for the First-Generation Diversification Step. Formation of 8a. To a suspension of resin **7** (1.0 g, 1.1 mmol, loading capacity 1.1 mmol/g) in DMF were added *tert*-butylacetyl chloride (1.5 mL, 11.0 mmol) and TEA (1.5 mL, 11.0 mmol). The suspension was shaken for 24 h at room temperature under N_2. The suspension was filtered, and the precipitate containing resin **8a** was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}): 1720, 1675, 1489, 1268, 1112, 1025.

Representative Procedure for Cleavage of Resins 8. Preparation of 2-Benzoyloxymethyl-6-(3,3-dimethylbutyrylamino)-2-methyl-2*H*-1-benzopyran (9a). *N*-Acylated resin **8a** (100 mg, 0.11 mmol) was treated with 3 mL of 1:4 TFA/DCM. After being shaken at room temperature for 3 h, the mixture was filtered and the precipitate containing resin washed with DCM (3 mL × 2). The combined filtrates were concentrated in vacuo to yield 2-benzoyloxymethyl-6-(3,3-dimethylbutyrylamino)-2-methyl-2*H*-1-benzopyran **9a** (43 mg, 85%) as an oil. ^1H NMR (200 MHz, $CDCl_3$): δ 7.83 (d, 2H, J = 8.4 Hz), 7.53−7.48 (m, 1H), 7.39−7.34 (m, 2H), 7.14 (s, 1H), 7.06 (dd, 1H, J = 8.7, 2.4 Hz), 6.75 (d, 1H, J = 8.7 Hz), 6.44 (d, 1H, J = 9.6 Hz), 5.62 (d, 1H, J = 9.6 Hz), 4.44 (d, 1H, J = 11.4 Hz), 4.29 (d, 1H, J = 11.4 Hz), 2.23 (s, 2H), 1.52 (s, 3H), 1.10 (s, 9H). LC/MS (ESI): *m/z* 394 $(M + H)^+$.

Representative Procedure for the Debenzoylation of Resin 8. A suspension of resin **8a** (1.0 g, 1.1 mmol) in MeOH/THF (5 mL) at room temperature was treated with NaOMe (11.0 mmol) for 12 h and filtered. The filtrate was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum to give resin **10a**. FTIR (cm^{-1}): 3500, 1643, 1611, 1263, 1032.

Representative Procedure for the Second-Generation, *O*-Akylation Diversification Step. Formation of 6-(2-Chlorobenzoylamino)-2-(2-chlorobenzyloxymethyl)-2-methyl-2*H*-1-benzopyran Resin (11a). To a suspension of resin **10** (1.0 g, 1.1 mmol) in DMF were added 2-chlorobenzyl bromide (0.71 mL, 5.5 mmol) and 1 M LiO^tBu in THF (5.5 mL, 5.5 mmol). The suspension was shaken for 24 h at 40 °C and filtered. The filtrate containing resin **11a** was washed with DMF (×2), DCM (×2), and MeOH (×2) and dried under high vacuum. FTIR (cm^{-1}): 1638, 1489, 1250, 1029, 819.

Representative Procedure for the Cleavage of Resins 11. Formation of 6-(2-Chlorobenzoylamino)-2-(2-chlorobenzyloxymethyl)-2-methyl-2*H*-1-benzopyran (12a). A suspension of resin **11a** (100 mg, 0.11 mmol) in 3 mL of 1:4 TFA/DCM was shaken at room temperature for 3 h and filtered and the filtrate was washed with DCM (3 mL × 2). The combined filtrates were concentrated in vacuo to yield 6-(2-chlorobenzoylamino)-2-(2-chlorobenzyloxymethyl)-2-methyl-2*H*-1-benzopyran (**12a**) (29 mg, 59%) as an oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, 2H, J = 8.5 Hz), 7.70 (s, 1H), 7.44−7.39 (m, 4H), 7.31 (s, 1H), 7.26−7.18 (m, 4H), 6.80 (d, 1H, J = 8.5 Hz), 6.42 (d, 1H, J = 9.8 Hz), 5.69 (d, 1H, J = 9.8 Hz), 4.72 (d, 1H, J = 13.3 Hz), 4.64 (d, 1H, J = 13.4 Hz), 3.64 (d, 1H, J = 10.1 Hz), 3.61 (d, 1H, J = 10.1 Hz), 1.5 (s, 3H); LC/MS (ESI) *m/z* 454 $(M + H)^+$.

Representative Procedure for the Cleavage of Resins 11. Formation of 6-(2-Chlorobenzoylamino)-2-(4-chlorobenzyloxymethyl)-2*H*-1-benzopyran (14a). A suspension of resin **13a** (100 mg, 0.11 mmol) in 3 mL of 1:4 TFA/DCM was shaken at room temperature for 3 h and filtered, and the filtrate was washed with DCM (3 mL × 2). The combined filtrates were concentrated in vacuo to yield 6-(2-chlorobenzoylamino)-2-(4-chlorobenzyloxymethyl)-2*H*-1-benzopyran **14a** (29 mg, 57%) as a foam. ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.79−7.76 (m, 2H), 7.69−7.61 (m, 1H), 7.27−7.16 (m, 2H), 6.73 (d, 1H, J = 8.5 Hz), 6.42 (d, 1H, J = 9.8 Hz), 5.66 (d, 1H, J = 9.8 Hz), 4.42 (d, 1H, J = 11.6 Hz), 4.33 (d, 1H, J = 11.6 Hz), 1.44 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 165.2, 164.5, 149.8, 138.0, 133.9, 133.2, 132.7, 131.7, 131.1, 131.0, 129.4, 129.0, 128.4, 126.6, 126.5, 124.8, 121.9, 120.9, 119.3, 116.4, 69.3, 23.8. LC/MS (ESI): *m/z* 468 $(M + H)^+$. HRMS (EI): $[M]^+$ calcd for $C_{25}H_{19}Cl_2NO_4$ 467.0691, found 467.0701.

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Supporting Information Available: General experimental procedures and analytical spectra (^1H NMR, ^{13}C NMR, and LC/MS) are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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