Construction of a Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway

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In this study, a divergent and practical solid-phase parallel diversity-oriented synthesis (DOS) strategy was successfully applied for the construction of five discrete core skeletons embedded with privileged benzopyranyl substructure. The diversity of these core skeletons was expanded through the introduction of various substituents at the R, R^1, and R^2 positions from a single key intermediate in five different pathways. More importantly, we efficiently maximized the molecular diversity through the transformation of the core skeleton itself by using the library-to-library concept and created a distinctively different collection of small molecules with the same building blocks. A 434-member polyheterocyclic benzopyran library was constructed on a scale of about 10 mg with the potential for further diversification. Without further purification, the average purity of the library is 85%.

Introduction

Since the completion of the human genome project in 2003, biomedical communities have been focused on the elucidation of the gene function and the associated control of gene products with small-molecule modulators.[1] The systematic endeavors of scientists in various disciplines led to the birth of a new interdisciplinary research field, chemical biology.[2] The core components of chemical biology are the identification of novel small-molecule modulators as perturbing agents in biological systems and the application of these small bioactive molecules to pinpoint the control of specific gene products.[3] Therefore, there is a great demand for drug-like small molecules with wide bioactivity ranges for the identifying specific small-molecule modulators. To address this issue, the organic chemistry community has investigated diversity-oriented synthesis (DOS)—a new synthesis strategy to efficiently populate the chemical space with skeletally and stereochemically diverse small molecules through complexity-generating reactions.[4] The natural product-like and/or drug-like small-molecule collections constructed using DOS have proved to be effective for identifying bioactive small-molecule modulators and therapeutic agents.[5] Our research group has been working on the development of new DOS pathways and library realization using our new methodology. We are particularly interested in the construction of novel polyheterocyclic core skeletons embedded with privileged substructural motifs, such as benzopyran, pyridine, pyrazole, pyrazolopyrimidine, and pyrimidine.[6] We previously reported a concise and ef-

ficient DOS pathway for the construction of eleven discrete core skeletons embedded with privileged benzopyran substructure via various chemical transformations.[7] Herein, we report the use of our DOS pathway and the solid-phase parallel synthesis to construct a library of natural product-like small molecules that contain benzopyran substructure and have maximum skeletal diversity.

Benzopyran is a well-known privileged substructural motif observed in many biologically active natural products, and it plays a pivotal role in the regulation of various biopolymers.[8] As shown in Figure 1, naturally occurring small benzopyran-containing molecules have huge skeletal diversity through the conjunction of the privileged benzopyran motif in their core skeletons, which allows discrete biological activities associated with their novel polycycles, such as antiproliferative activity against vari-
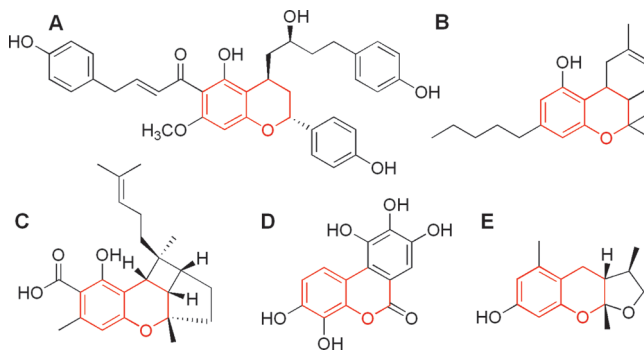

Figure 1. Examples of benzopyran-containing natural products. A, Epicalyxin F that shows antiproliferative activity against carcinoma cells; B, tetrahydrocannabinol that shows agonistic effect on cannabinoid receptors, CB_1 and CB_2; C, rhododaurichromanic acid A that exhibits phytotoxic properties; D, an ellagic acid derivative that shows an inhibitory effect on glucose transport assay; E, (+)-alboatrin that exhibits potent anti-HIV and anti-inflammatory activities.

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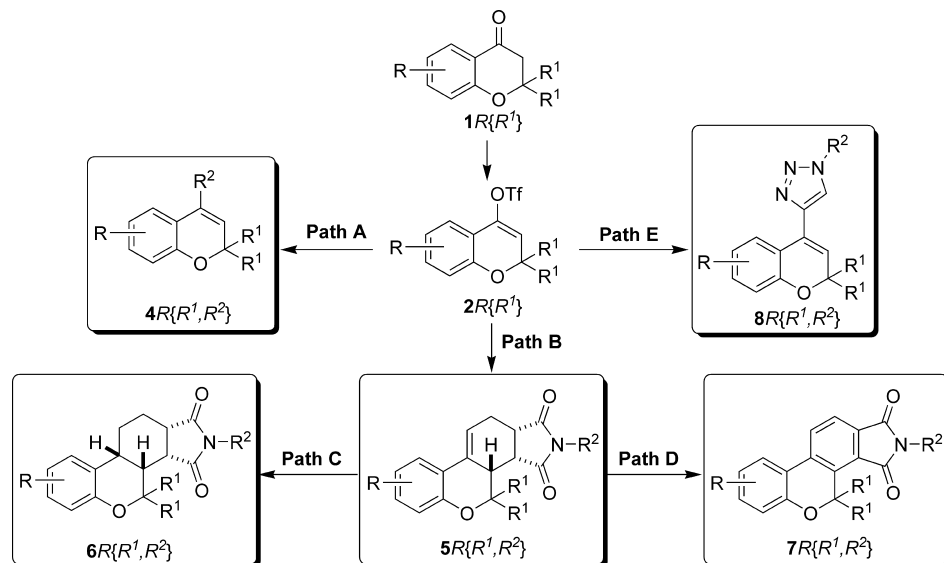‡ Department of Biophysics and Chemical Biology.

Figure 2. Synthetic strategy for the construction of five discrete core skeletons embedded with benzopyran substructure: path A, Suzuki coupling; path B, Stille coupling and subsequent Diels−Alder reaction; path C, asymmetric hydrogenation; path D, aromatization; path E, click chemistry.

ous carcinoma cells;[9] agonistic effect on the cannabinoid receptors, CB_1 and CB_2;[10] inhibitory effect on cellular glucose transport;[11] phytotoxic properties;[12] and potent anti-HIV and anti-inflammatory activities.[13] There have been many studies of the synthesis of benzopyran derivatives, but previous reports focused on limited diversifications of the appendices on the arene region of benzopyrans with a few core structures or simple substituent changes in the pyran region.[14] Therefore, it is worthwhile to construct a collection of drug-like small molecules with diverse benzopyran-containing core skeletons. These efforts will pave the way to demonstrate previously unrevealed advantages of the DOS approach; skeletally diverse core skeletons embedded with privileged substructures aid the search for specific small-molecule modulators for diverse protein receptors in biological systems.

To construct a benzopyran-containing small-molecule library, we selected five discrete core skeletons from our original DOS pathway. These synthetic methods should be applicable for the solid-phase parallel synthesis format without any loss of their molecular diversity. As shown in Figure 2, we planned to access these five discrete core skeletons through various chemical transformations from key intermediate 2, such as palladium-mediated Suzuki coupling (path A), Stille-type vinylation and subsequent Diels−Alder reaction (path B), and Negishi-type alkynylation and subsequent Huisgen 1,3-dipolar [3 + 2] cycloaddition, that is, click chemistry (path E).[15] These synthetic routes were optimized in the solid-phase for the efficient construction of benzopyran-containing small molecules in parallel synthesis format. We also pursued the further diversification of Diels−Alder adducts $5R\{R^1,R^2\}$ from path B transformed into two structurally discrete core skeletons, $6R\{R^1,R^2\}$ and $7R\{R^1,R^2\}$, through a library-to-library approach using substrate-controlled asymmetric hydrogenation (path C) and aromatization (path D) with a high degree of diastereose-

Scheme 1. Synthetic Scheme for Benzopyran Intermediate $3R\{R^1\}$ Loaded on Solid Supports
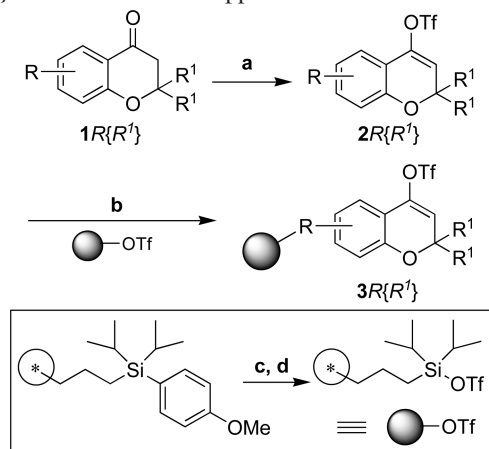
[a] DTBMP, triflic anhydride, CH_2Cl_2, 0 °C, 30 min. [b] 2,6-Lutidine, CH_2Cl_2/THF, room temp. [c] TMSCl, CH_2Cl_2, room temp. [d] TfOH, CH_2Cl_2, room temp.

lectivity in the solution-phase and solid-phase parallel synthesis, respectively.

Results and Discussion

Construction of Small Molecule Library with New Benzopyran-containing Core Skeleton $4R\{R^1,R^2\}$ through Path A. To maximize the molecular diversity of our proposed library, we initiated the synthetic route from eight different chromanone moieties $1R\{R^1\}$, synthesized from four different hydroxyacetophenones through the cyclization with acetone [R^1 = methyl] or cyclopentanone [R^1 = -$(CH_2)_4$-] in the presence of pyrrolidine catalyst. As shown in Scheme 1, the resulting chromanone underwent triflation using triflic anhydride in the presence of the proton sponge 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to yield the key isolable intermediate, vinyl triflate $2R\{R^1\}$. After activation of (4-methoxyphenyl)diisopropylsilylpropyl polystyrene resins by treating TfOH, eight different vinyl triflated intermediates

Table 1. Classification of Loaded Intermediates $3R\{R^1\}$ on Solid Supports

R^1 \ $3R$	**3a**	**3b**	**3c**	**3d**
Methyl	*3a{1}*	*3b{1}*	*3c{1}*	*3d{1}*
-(CH₂)₄-	*3a{2}*	*3b{2}*	*3c{2}*	*3d{2}*

Table 2. Purity and Mass of Representative Compounds $4R\{R^1,R^2\}$ in Path A
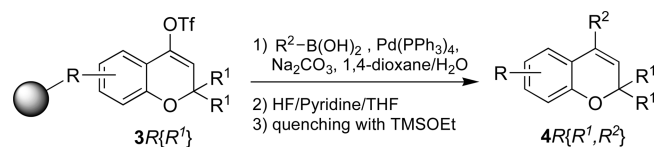
ID	R	R^1	R^2	purity[a](%)	MS(calcd)	MS[b](found)
4a{1,17}	7-hydroxy	methyl	4-chloro-2-methylphenyl	96	299.08	298.86
4b{1,8}	8-hydroxy-7-methoxy	methyl	4-fluorophenyl	99	301.12	300.99
4c{1,8}	6-(3-hydroxyphenyl)	methyl	4-fluorophenyl	99	345.13	345.03
4d{1,8}	6-chloro-8-(3-hydroxyphenyl)	methyl	4-fluorophenyl	99	381.11	380.96

[a] Purities were obtained by LC/MS analysis (PDA data) of final products without further purification.   [b] Mass analysis were performed with electron spray ionization (ESI) method.

$2R\{R^1\}$ were immobilized on these activated resins in the presence of 2,6-lutidine to afford intermediates $3R\{R^1\}$ on solid supports (see Table 1). The average loading level was about 0.9 mmol/g, measured by the weight gain of the loaded resins and cross-checked against the weight of cleaved products from loaded resins.

The common vinyl triflate moiety on intermediate $3R\{R^1\}$ is an excellent substrate for a palladium-mediated C–C cross-coupling reaction; therefore, we first introduced various substituted aryl rings via the Suzuki coupling of aryl boronic acids. Among the many conditions tested in the solid phase, Pd(PPh₃)₄ and Na₂CO₃ in aqueous 1,4-dioxane demonstrated a robust chemical transformation of $3R\{R^1\}$ with various substituted aryl boronic acids, resulting in high yields of the desired product $4R\{R^1,R^2\}$ (see Table 2). Under this reaction condition, we synthesized benzopyran-containing small molecules [$4a\{R^1,R^2\}$–$4d\{R^1,R^2\}$] using 18 different aryl boronic acids in combination with eight vinyl triflate intermediates $3R\{R^1\}$ after cleaving the desired product from the solid support by using HF/pyridine in tetrahydrofuran (THF) and subsequent quenching with TMSOEt. The Suzuki-type diversification at the R^2 position introduced the new privileged heterobiaryl structural motif in the new benzopyran-containing core skeleton $4R\{R^1,R^2\}$, and the resulting

144-member small-molecule collection was synthesized on a scale of 10−20 mg. The identity and purity of the final products were determined using an LC/MS instrument, injected with an aliquot of the crude cleavage product. As shown in Tables 2 and 3, the presence of all the desired compounds was unambiguously confirmed by their molecular mass and their average purity was 87% without any purification steps. The purities of the individual compounds are shown in different colors.

Construction of Small-Molecule Library with Polyheterocyclic Core Skeletons $5R\{R^1,R^2\}$−$7R\{R^1,R^2\}$ through Paths B−D Using Library-to-Library Approach. We previously reported the DOS pathway, which contains palladium-mediated Stille-type vinylation on vinyl triflate intermediate and subsequent *endo*-selective Diels−Alder reaction with substituted maleimides as dienophiles to yield diastereoselective benzopyran-containing heterocyclic compounds $5R\{R^1,R^2\}$. In this study, eight different vinyl triflate intermediates $3R\{R^1\}$ underwent palladium-mediated Stille-type vinylation on the solid support to maximize the molecular diversity of the final products. After extensive washing, the resulting dienes were subjected to an in situ Diels−Alder reaction with various maleimides on the solid support (see Scheme 2). Among the 35 commercially
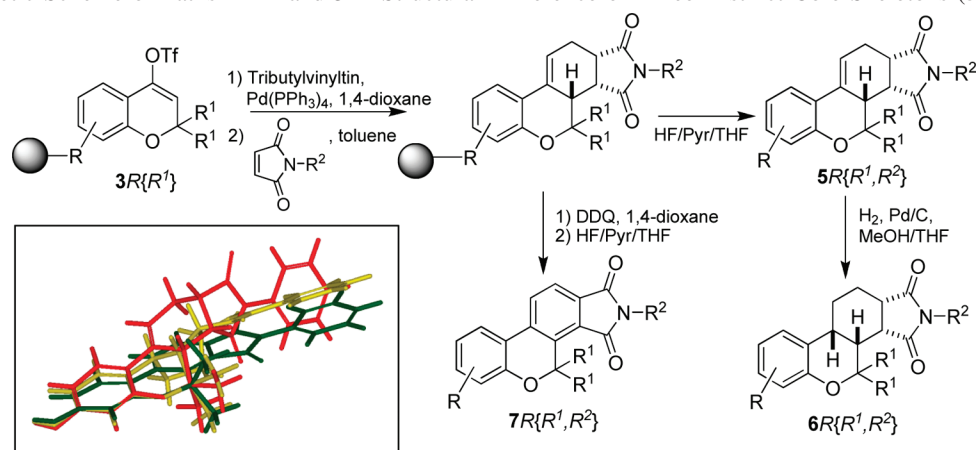
Table 3. Sets of Building Blocks and Purities of Compounds $4R\{R^1,R^2\}$

Scheme 2. Synthetic Scheme of Paths B−D and 3-D Structural Difference of Three Distinct Core Skeletons (**5−7**)[a]

[a] 3-D structure of each molecules, **5a{1,3}** in red, **6a{1,3}** in yellow, and **7a{1,3}** in green, were superimposed with three points of each benzopyran (1O, 2C, and 7C) by using Discovery Studio 1.7 software (Accelrys Software Inc.).

Table 4. Purity and Mass of Representative Compounds in Paths B−D

ID	R	R^1	R^2	purity[a] (%)	MS(calcd)	MS[b](found)
5a{1,3}	7-hydroxy	methyl	phenyl	96	376.15	376.08
5b{2,3}	8-hydroxy-7-methoxy	-(CH$_2$)$_4$-	phenyl	92	432.18	432.07
5c{2,3}	6-(3-hydroxyphenyl)	-(CH$_2$)$_4$-	phenyl	99	478.20	478.06
5d{1,3}	6-chloro-8-(3-hydroxyphenyl)	methyl	phenyl	97	486.15	486.01
6a{2,3}	7-hydroxy	-(CH$_2$)$_4$-	phenyl	80	404.19	404.05
6b{2,3}	8-hydroxy-7-methoxy	-(CH$_2$)$_4$-	phenyl	92	434.20	434.00
6c{2,3}	6-(3-hydroxyphenyl)	-(CH$_2$)$_4$-	phenyl	99	480.22	480.10
7a{2,3}	7-hydroxy	-(CH$_2$)$_4$-	phenyl	99	396.12	395.91
7b{1,3}	8-hydroxy-7-methoxy	methyl	phenyl	87	400.12	400.23

[a] Purities were obtained by LC/MS analysis (PDA data) of final products without further purification. [b] Mass analyses were performed with the electron spray ionization (ESI) method.

available maleimides tested for this reaction, we selected 17 substituted maleimides for the actual library synthesis to ensure high yield and purity without any loss of molecular diversity. After HF/pyridine cleavage and subsequent quenching with TMSOEt, we obtained a 136-member diastereomerically enriched small-molecule collection [**5a{R^1,R^2}**−**5d{R^1,R^2}**] with a novel polyheterocyclic core skeleton containing privileged benzopyran substructure on a scale of 10 mg each. Their average purity (see Table 4 and 5), measured by LC/MS analysis of the crude products, was around 85%.

To expand the molecular diversity of the small-molecule collection, we applied the library-to-library approach to transform the polyheterocyclic core skeleton **5R{R^1,R^2}** into two discrete core skeletons, **6R{R^1,R^2}** and **7R{R^1,R^2}**, using robust chemical transformations such as Pd/C-based hydrogenation (path C) and DDQ-mediated aromatization (path D), respectively. We previously confirmed that this substrate-controlled asymmetric hydrogenation of polyheterocyclic monoene **5R{R^1,R^2}** under mild reaction conditions using heterogeneous catalyst Pd/C can yield diastereochemically

Table 5. Sets of Building Blocks and Purities of Compounds $5R\{R^1,R^2\}-7R\{R^1,R^2\}$

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
5a{1,R²}	5a{1,1}	5a{1,2}	5a{1,3}	5a{1,4}	5a{1,5}	5a{1,6}	5a{1,7}	5a{1,8}	5a{1,9}	5a{1,10}	5a{1,11}	5a{1,12}	5a{1,13}	5a{1,14}	5a{1,15}	5a{1,16}	5a{1,17}
5a{2,R²}	5a{2,1}	5a{2,2}	5a{2,3}	5a{2,4}	5a{2,5}	5a{2,6}	5a{2,7}	5a{2,8}	5a{2,9}	5a{2,10}	5a{2,11}	5a{2,12}	5a{2,13}	5a{2,14}	5a{2,15}	5a{2,16}	5a{2,17}
5b{1,R²}	5b{1,1}	5b{1,2}	5b{1,3}	5b{1,4}	5b{1,5}	5b{1,6}	5b{1,7}	5b{1,8}	5b{1,9}	5b{1,10}	5b{1,11}	5b{1,12}	5b{1,13}	5b{1,14}	5b{1,15}	5b{1,16}	5b{1,17}
5b{2,R²}	5b{2,1}	5b{2,2}	5b{2,3}	5b{2,4}	5b{2,5}	5b{2,6}	5b{2,7}	5b{2,8}	5b{2,9}	5b{2,10}	5b{2,11}	5b{2,12}	5b{2,13}	5b{2,14}	5b{2,15}	5b{2,16}	5b{2,17}
5c{1,R²}	5c{1,1}	5c{1,2}	5c{1,3}	5c{1,4}	5c{1,5}	5c{1,6}	5c{1,7}	5c{1,8}	5c{1,9}	5c{1,10}	5c{1,11}	5c{1,12}	5c{1,13}	5c{1,14}	5c{1,15}	5c{1,16}	5c{1,17}
5c{2,R²}	5c{2,1}	5c{2,2}	5c{2,3}	5c{2,4}	5c{2,5}	5c{2,6}	5c{2,7}	5c{2,8}	5c{2,9}	5c{2,10}	5c{2,11}	5c{2,12}	5c{2,13}	5c{2,14}	5c{2,15}	5c{2,16}	5c{2,17}
5d{1,R²}	5d{1,1}	5d{1,2}	5d{1,3}	5d{1,4}	5d{1,5}	5d{1,6}	5d{1,7}	5d{1,8}	5d{1,9}	5d{1,10}	5d{1,11}	5d{1,12}	5d{1,13}	5d{1,14}	5d{1,15}	5d{1,16}	5d{1,17}
5d{2,R²}	5d{2,1}	5d{2,2}	5d{2,3}	5d{2,4}	5d{2,5}	5d{2,6}	5d{2,7}	5d{2,8}	5d{2,9}	5d{2,10}	5d{2,11}	5d{2,12}	5d{2,13}	5d{2,14}	5d{2,15}	5d{2,16}	5d{2,17}

R^2: 1 ($-H$), 2 ($-CH_3$), 3 (phenyl), 4 (4-bromophenyl), 5 (2-phenylbenzoxazole), 6 (3-chloro-4-methylphenyl), 7 (thiophene), 8 (cyclohexyl), 9 (4-chlorophenyl), 10 (4-morpholinophenyl), 11 (4-acetylphenyl), 12 (phenylazophenyl), 13 (benzylpiperidine), 14 (2,6-dinitro-N,N-dimethylaniline), 15 (pyrene), 16 (benzyl), 17 (hydroxy-ketone chain)

Purity: >90%, 80-90%, 70-80%, <70%

	1	2	3	4	5	6	7	8	9
6a{1,R²}	6a{1,1}	6a{1,2}	6a{1,3}	6a{1,4}	6a{1,5}	6a{1,6}	6a{1,7}	6a{1,8}	6a{1,9}
6a{2,R²}	6a{2,1}	6a{2,2}	6a{2,3}	6a{2,4}	6a{2,5}	6a{2,6}	6a{2,7}	6a{2,8}	6a{2,9}
6b{1,R²}	6b{1,1}	6b{1,2}	6b{1,3}	6b{1,4}	6b{1,5}	6b{1,6}	6b{1,7}	6b{1,8}	6b{1,9}
6b{2,R²}	6b{2,1}	6b{2,2}	6b{2,3}	6b{2,4}	6b{2,5}	6b{2,6}	6b{2,7}	6b{2,8}	6b{2,9}
6c{1,R²}	6c{1,1}	6c{1,2}	6c{1,3}	6c{1,4}	6c{1,5}	6c{1,6}	6c{1,7}	6c{1,8}	6c{1,9}
6c{2,R²}	6c{2,1}	6c{2,2}	6c{2,3}	6c{2,4}	6c{2,5}	6c{2,6}	6c{2,7}	6c{2,8}	6c{2,9}

R^2: 1 ($-H$), 2 ($-CH_3$), 3 (phenyl), 4 (4-bromophenyl), 5 (2-phenylbenzoxazole), 6 (3-chloro-4-methylphenyl), 7 (thiophene), 8 (pyrene), 9 (4-acetylphenyl)

	1	2	3	4	5	6	7	8	9
7a{1,R²}	7a{1,1}	7a{1,2}	7a{1,3}	7a{1,4}	7a{1,5}	7a{1,6}	7a{1,7}	7a{1,8}	7a{1,9}
7a{2,R²}	7a{2,1}	7a{2,2}	7a{2,3}	7a{2,4}	7a{2,5}	7a{2,6}	7a{2,7}	7a{2,8}	7a{2,9}
7b{1,R²}	7b{1,1}	7b{1,2}	7b{1,3}	7b{1,4}	7b{1,5}	7b{1,6}	7b{1,7}	7b{1,8}	7b{1,9}
7b{2,R²}	7b{2,1}	7b{2,2}	7b{2,3}	7b{2,4}	7b{2,5}	7b{2,6}	7b{2,7}	7b{2,8}	7b{2,9}

R^2: 1 ($-H$), 2 ($-CH_3$), 3 (phenyl), 4 (4-bromophenyl), 5 (2-phenylbenzoxazole), 6 (3-chloro-4-methylphenyl), 7 (thiophene), 8 (cyclohexyl), 9 (benzophenone)
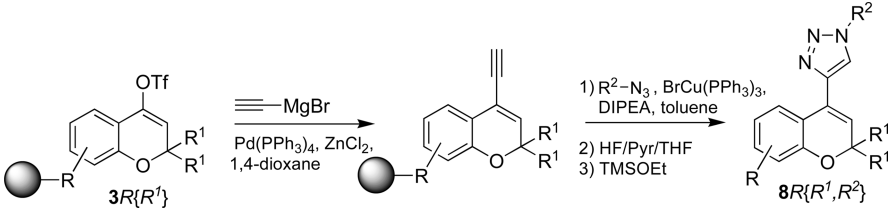
enriched polyheterocycles $6R\{R^1,R^2\}$ in excellent yields (see Scheme 2). The shape of the resulting core skeleton $6R\{R^1,R^2\}$ is structurally discrete and more concave than that of its precursor $5R\{R^1,R^2\}$ because of the conversion at the monoene site of sp^2 carbon to sp^3 carbon through asymmetric hydrogenation. We initially tried to carry out the hydrogenation reaction on solid supports using homogeneous catalysts in organic solvents such as hydrazine[16] and RhCl(PPh₃)₃,[17] but we failed to obtain the desired hydrogenated compounds. We then decided to carry out the hydrogenation reaction using Pd/C and a hydrogen balloon in solution-phase parallel synthesis after the cleavage of the monoene products $5R\{R^1,R^2\}$ from the solid support. Unfortunately, the outcome of the asymmetric hydrogenation was substrate-dependent. Therefore, we proceeded with solution-phase heterogeneous hydrogenation with monoene precursors $5R\{R^1,R^2\}$ generated with only nine maleimides to yield a 54-member collection of small molecules [$6a\{R^1,R^2\}-6c\{R^1,R^2\}$] with a new core skeleton through the transformation of the core skeleton without any changes in the substituents. The average purity of $6R\{R^1,R^2\}$ in path C was about 81% from $3R\{R^1\}$ without further purification, and the purities of the individual compounds are shown in different colors in Table 5.

The additional transformation of the polyheterocyclic core skeleton $5R\{R^1,R^2\}$ was pursued via a DDQ-mediated aromatization reaction using the library-to-library approach. Compared to heterogeneous hydrogenation, which introduces the sp^3 carbon center in an asymmetric fashion, the aromatization using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) can remove the existing stereogenic carbon centers of the monoene precursor $5R\{R^1,R^2\}$ and provide a new flatter core skeleton $7R\{R^1,R^2\}$ with the same substituents (see Scheme 2). Unfortunately, this transformation failed in the case of compounds containing the biphenyl group, $5c$ and $5d$, and gave a complex mixture of products. Therefore, we proceeded the DDQ-mediated aromatization with $5a\{R^1,R^2\}$ and $5b\{R^1,R^2\}$ with nine substituted maleimides as building blocks and obtained a 36-member collection of small molecules [$7a\{R^1,R^2\}$ and $7b\{R^1,R^2\}$] with a new rigid and flat core skeleton. The purities of the individual final compounds are shown in Table 5 in different colors; the average purity, measured by LC/MS analysis of the crude products, was 84%.

Construction of Small-Molecule Library with New Benzopyran-containing Core Skeleton $8R\{R^1,R^2\}$ through Path E. For our synthetic path E, we introduced terminal alkyne to the vinyl triflate intermediates $3R\{R^1\}$ on the solid support through a palladium-mediated Negishi-type cross-coupling reaction. It was not easy to perform this reaction in the parallel block synthesis format because it required anhydrous conditions, so we pursued this transformation using resin-loaded vinyl triflate intermediates $3R\{R^1\}$ in each separate reaction vessel. After Negishi-type alkynylation, the resulting terminal alkynyl moiety on the benzopyran core skeletons was subjected to Huisgen 1,3-dipolar [3 + 2] cycloaddition, namely, Click chemistry, in the presence of BrCu(PPh₃)₃,[18] a Cu-catalyst soluble in organic solvent, and DIPEA to yield a new triazole-containing core skeleton $8R\{R^1,R^2\}$ using solid-phase parallel synthesis (see Table 6). We utilized 8 different azide compounds for the Click
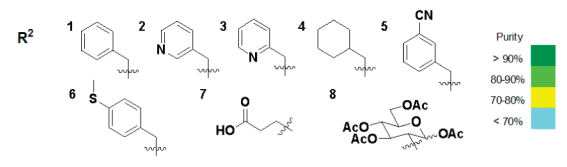
Table 6. Purity and Mass of Representative Compounds $8R\{R^1,R^2\}$ in Path E

ID	R	R^1	R^2	purity[a] (%)	MS(calcd)	MS[b](found)
$8a\{1,1\}$	7-hydroxy	methyl	benzyl	87	334.15	334.42
$8a\{2,1\}$	8-hydroxy-7-methoxy	-(CH$_2$)$_4$-	benzyl	91	360.16	360.30
$8c\{1,1\}$	6-(3-hydroxyphenyl)	methyl	benzyl	79	410.19	410.11
$8d\{2,1\}$	6-chloro-8-(3-hydroxyphenyl)	-(CH$_2$)$_4$-	benzyl	92	470.16	470.08

[a] Purities were obtained by LC/MS analysis (PDA data) of final products without further purification. [b] Mass analyses were performed with the electron spray ionization (ESI) method.

Table 7. Sets of Building Blocks and Purities of Compounds $8R\{R^1,R^2\}$

chemistry and produced a 64-member collection of triazole-containing benzopyranyl compounds $8R\{R^1,R^2\}$ after HF/pyridine cleavage from the solid support and subsequent quenching with TMSOEt. The purities of the individual final compounds are shown in Table 7 in different colors; the average purity, measured by LC/MS analysis of crude products, was 85%.

Conclusion

In this study, we successfully demonstrated the practical construction of a small-molecule library with five discrete core skeletons embedded with privileged benzopyranyl substructure through creative recombination. In particular, we focused on the expansion of the molecular diversity in solid-phase parallel synthesis using the library-to-library approach. Skeletal diversity was efficiently achieved through the application of various chemical transformations on the key intermediates, vinyl triflates $3R\{R^1\}$, such as palladium-mediated Suzuki-type arylation, Stille-type vinylation and subsequent diastereoselective Diels–Alder reaction, and Negishi-type alkynylation and subsequent Huisgen 1,3-dipolar [3 + 2] cycloaddition, to yield three discrete core skeletons, $4R\{R^1,R^2\}$, $5R\{R^1,R^2\}$, and $8R\{R^1,R^2\}$, respectively. The excellent *endo*-selectivity of dienophiles in the Diels–Alder reaction yielded a diastereochemically enriched polyheterocycle, $5R\{R^1,R^2\}$, which was transformed into two

discrete core skeletons, $6R\{R^1,R^2\}$ and $7R\{R^1,R^2\}$, using substrate-controlled heterogeneous catalytic hydrogenation and DDQ-mediated aromatization, respectively. This library-to-library strategy allows the construction of a novel small-molecule collection with three discrete benzopyran-containing core skeletons using the same building blocks. We successfully applied our DOS pathway for the construction of a full-scale benzopyran library with five discrete core skeletons using solid-phase parallel synthesis, and we generated a 434-member drug-like small-molecule library with 85% average purity. Extensive biological evaluation of this benzopyran library will lead to a valuable research tool in the search for small-molecule modulators and potential therapeutic agents. The corresponding biological results will be reported in due course.

Experimental Section

General Information. All reagents in this synthetic procedure were purchase from Sigma-Aldrich [MO, U.S.A.] and TCI [Japan] and were used without further purification unless noted otherwise. The progress of reaction was monitored using thin-layer chromatography (TLC) (silica gel 60 F$_{254}$ 0.25 mm), and components were visualized by observation under UV light (254 nm) or by treating the TLC plates with anisaldehyde staining solution followed by heating. Silica gel 60 (0.040−0.063 mm) used in flash column chromatography was purchased from Merck [Germany]. All reactions were conducted in oven-dried glassware under dry argon atmosphere, unless otherwise specified. CH$_2$Cl$_2$ was distilled from CaH$_2$ immediately prior to use. THF and toluene were distilled in the presence of sodium metal. Other solvents and organic reagents were purchased from commercial vendors and used without further purification unless otherwise mentioned. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-500 [Palo Alto, U.S.A.] or Bruker Avance DPX-300 [Germany], and chemical shifts were measured in parts per million (ppm) relative to internal tetramethylsilane (TMS) standard or specific solvent signal. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); dt (doublet of triplet); td (triplet of doublet); bs (broad singlet), and so forth. Coupling constants were reported in hertz (Hz). Routine mass analysis were performed on a LC/MS system equipped with a reverse phase column (C-18,

50 × 2.1 mm, 5 μm) and electron spray ionization (ESI). The HRMS analyses were conducted at the Mass Spectrometry Laboratory of Seoul National University by direct injection on a JEOL JMS AX505WA spectrometer using the fast atom bombardment (FAB) method.

General Procedure for the Synthesis of Compound 1. Hydroxyacetophenone derivative (1.0 equiv) was dissolved in EtOH. Pyrrolidine (3.0 equiv) was added to the solution, followed by the addition of either acetone (10 equiv) or cyclopentanone (3.0 equiv). The reaction mixture was then heated to reflux for about 24 h. After the completion of reaction monitored by TLC, the reaction mixture was concentrated *in vacuo*. The residue was redissolved in ethyl acetate and washed several times with 1N HCl aqueous solution. After washing with brine, the combined organic layer was dried over anhydrous MgSO$_4$, filtrated, and evaporated in vacuo. The resulting mixture was purified with silica gel flash column chromatography to provide desired products [**1a{1}**−**1d{2}**]. Among these compounds, **1ãb{1−2}** were previously reported.[7]

6-(3-Hydroxyphenyl)-2,2-dimethylchroman-4-one (1c{1}). Colorless crystal (86%); ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.06 (d, J = 2.3 Hz, 1H), 7.66 (dd, J = 8.6 and 2.3 Hz, 1H), 7.26−7.21 (m, 1H), 7.09−7.05 (m, 2H), 6.93 (d, J = 8.6 Hz, 1H), 6.77 (dd, J = 7.7 and 1.4 Hz, 1H), 2.73 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 193.3, 159.7, 156.3, 141.2, 135.0, 133.4, 130.1, 124.6, 120.0, 118.9, 118.8, 114.3, 113.6, 79.5, 48.8, 26.6; MS (ESI-) m/z calculated for C$_{17}$H$_{15}$O$_3$ [M − H]$^-$: 267.10; Found: 267.02.

6-(3-Hydroxyphenyl)spiro(chroman-2,1′-cyclopentan)-4-one (1c{2}). Colorless crystal (82%); ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.13 (d, J = 2.3 Hz, 1H), 7.71 (dd, J = 8.6 and 2.3 Hz, 1H), 7.32−7.26 (m, 1H), 7.14−7.12 (m, 2H), 6.99 (d, J = 8.6 Hz, 1H), 6.83 (dd, J = 8.1 and 1.8 Hz, 1H), 5.94 (bs, 1H), 2.89 (s, 2H), 2.14−2.06 (m, 2H), 1.95−1.87 (m, 2H), 1.77−1.63 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 193.7, 160.1, 156.3, 141.2, 134.9, 133.4, 130.1, 124.8, 120.8, 119.1, 118.9, 114.3, 113.6, 90.2, 47.0, 37.5, 23.9; MS (ESI-) m/z calculated for C$_{19}$H$_{17}$O$_3$ [M − H]$^-$: 293.12; Found: 292.86.

6-Chloro-8-(3-hydroxyphenyl)-2,2-dimethylchroman-4-one (1d{1}). Colorless crystal (84%); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.84 (d, J = 2.6 Hz, 1H), 7.49 (d, J = 2.6 Hz, 1H), 7.31−7.28 (m, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.01 (s, 1H), 6.87 (dd, J = 8.0 and 2.1 Hz, 1H), 5.23 (s, 1H), 2.75 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 192.2, 155.6, 137.7, 136.8, 133.2, 129.6, 126.4, 125.5, 122.0, 121.8, 116.5, 115.1, 80.1, 48.7, 26.7; MS (ESI-) m/z calculated for C$_{17}$H$_{14}$ClO$_3$ [M − H]$^-$: 301.06; Found: 300.85.

6-Chloro-8-(3-hydroxyphenyl)spiro(chroman-2,1′-cyclopentan)-4-one (1d{2}). Colorless crystal (81%); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.84 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.31−7.26 (m, 1H), 7.04 (d, J = 7.7 Hz, 1H), 6.98 (s, 1H), 6.84 (dd, J = 8.0 and 2.1 Hz, 1H), 2.85 (s, 2H), 2.10−2.05 (m, 2H), 1.74−1.61 (m, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 192.5, 156.1, 137.9, 137.4, 133.5, 130.6, 126.5, 126.0, 122.3, 122.1, 118.1, 114.2, 90.6, 46.8, 36.9, 24.0; MS (ESI-) m/z calculated for C$_{19}$H$_{16}$ClO$_3$ [M − H]$^-$: 327.08; Found: 327.86.

General Procedure for the Synthesis of Compound 2. After silyl protection of hydroxyl group in compound **1**, each compound (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 1.3 equiv) were dissolved in anhydrous CH$_2$Cl$_2$. To this solution, triflic anhydride (Tf$_2$O, 1.2 equiv) was added at 0 °C with ice-bath under N$_2$ atmosphere. After the reaction mixture was stirred for 10 min at the same temperature, the resulting solid was filtered off and the filtrate was concentrated in vacuo. The remaining residue was redissolved in ethyl acetate and washed with sat. NaHCO$_3$ solution and brine. The combined organic layer was dried over anhydrous MgSO$_4$, filtrated, and evaporated in vacuo. The resulting mixture was purified with silica gel flash column chromatography to provide product. After the deprotection of silyl group, compound **2ãd{1−2}** were obtained in good yields.

7-Hydroxy-2,2-dimethyl-2H-chromen-4-yltrifluoromethanesulfonate (2a{1}). Colorless liquid (88%); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.11 (d, J = 8.4 Hz, 1H), 6.41 (dd, J = 8.4 and 2.3 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 5.47 (s, 1H), 5.13 (s, 1H), 1.50 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 158.4, 155.2, 142.5, 122.9, 115.4, 109.6, 108.4, 104.1, 78.3, 27.9; MS (ESI-) m/z calculated for C$_{12}$H$_{10}$F$_3$O$_5$S [M − H]$^-$: 323.02; Found: 322.87.

7-Hydroxyspiro(chromene-2,1′-cyclopentane)-4-yl trifluoromethanesulfonate (2a{2}). Colorless liquid (84%); ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.87 (d, J = 8.4 Hz, 1H), 6.27 (dd, J = 8.4 and 2.3 Hz, 1H), 6.15 (d, J = 2.3 Hz, 1H), 5.35 (s, 1H), 2.16−2.12 (m, 2H), 1.86−1.83 (m, 2H), 1.66−1.60 (m, 4H), 1.25−1.17 (m, 3H), 1.06 (d, J = 6.8 Hz, 18H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 158.9, 154.9, 142.7, 122.2, 114.5, 112.9, 110.4, 108.7, 88.4, 39.1, 23.3, 17.9, 12.6; MS (ESI+) m/z calculated for C$_{23}$H$_{34}$F$_3$O$_5$SSi [M + H]$^+$: 507.18; Found: 507.46 (It was identified as a TIPS protected form).

8-Hydroxy-7-methoxy-2,2-dimethyl-2H-chromen-4-yl trifluoromethanesulfonate (2b{1}). Colorless liquid (90%); ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.81 (d, J = 8.6 Hz, 1H), 6.53 (d, J = 8.6 Hz, 1H), 5.55 (s, 1H), 4.67 (bs, 1H), 3.93 (s, 3H), 1.58 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 149.6, 142.7, 140.9, 134.3, 120.0, 117.5, 116.6, 112.8, 110.8, 104.0, 79.0, 56.4, 28.1; MS (ESI-) m/z calculated for C$_{13}$H$_{12}$F$_3$O$_6$S [M − H]$^-$: 353.03; Found: 352.94.

8-Hydroxy-7-methoxyspiro(chromene-2,1′-cyclopentane)-4-yl trifluoromethanesulfonate (2b{2}). Colorless liquid (84%); ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.76 (d, J = 8.6 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 5.56 (s, 1H), 4.68 (bs, 1H), 3.88 (s, 3H), 2.26−2.22 (m, 2H), 1.98−1.92 (m, 2H), 1.78−1.64 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 149.6, 142.8, 140.9, 134.5, 115.9, 112.7, 111.5, 104.1, 89.4, 56.4, 39.4, 23.7; MS (ESI-) m/z calculated for C$_{15}$H$_{14}$F$_3$O$_6$S [M − H]$^-$: 379.05; Found: 378.81.

6-(3-Hydroxyphenyl)-2,2-dimethyl-2H-chromen-4-yl trifluoromethanesulfonate (2c{1}). Colorless liquid (81%); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.44−7.41 (m, 2H), 7.28 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.99 (t, J = 2.5 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.81 (dd, J = 8.0 and 2.5 Hz, 1H), 5.68 (s, 1H), 5.36 (s, 1H), 1.54 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 156.1, 153.3, 142.5, 141.9, 134.2, 130.4, 130.3, 120.1, 119.4, 119.0, 117.4, 116.5, 114.4, 113.8,

78.2, 28.1; MS (ESI-) *m/z* calculated for $C_{18}H_{14}F_3O_5S$ [M − H]$^-$: 399.05; Found: 399.19.

6-(3-Hydroxyphenyl)spiro(chromene-2,1′-cyclopentane)-4-yl trifluoromethanesulfonate (2c{2}). Colorless liquid (83%); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.42−7.39 (m, 2H), 7.29−7.24 (m, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.80 (dd, *J* = 7.8 and 1.7 Hz, 1H), 5.71 (s, 1H), 4.98 (bs, 1H), 2.28−2.23 (m, 2H), 1.98−1.92 (m, 2H), 1.79−1.66 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 156.0, 153.2, 142.3, 141.8, 134.0, 130.1, 129.9, 120.7, 119.9, 119.2, 117.9, 117.2, 117.0, 114.1, 113.6, 88.4, 39.4, 23.5; MS (ESI-) *m/z* calculated for $C_{20}H_{16}F_3O_5S$ [M − H]$^-$: 425.07; Found: 425.09.

6-Chloro-8-(3-hydroxyphenyl)-2,2-dimethyl-2*H*-chromen-4-yl trifluoromethanesulfonate (2d{1}). Colorless crystal (81%); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28 (d, *J* = 2.5 Hz, 1H), 7.26 (s, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.0 and 2.0 Hz, 1H), 5.71 (s, 1H), 1.51 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 155.6, 149.1, 141.7, 137.7, 132.4, 131.7, 129.6, 126.5, 122.0, 120.8, 119.7, 118.2, 116.4, 115.0, 78.4, 27.9; MS (ESI-) *m/z* calculated for $C_{18}H_{13}ClF_3O_5S$ [M − H]$^-$: 433.01; Found: 432.89.

6-Chloro-8-(3-hydroxyphenyl)spiro(chromene-2,1′-cyclopentane)-4-yl trifluoromethanesulfonate (2d{2}). Colorless crystal (76%); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28 (d, *J* = 3.0 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 7.01 (dd, *J* = 7.5 and 1.5 Hz, 1H), 6.95 (dd, *J* = 2.5 and 1.5 Hz, 1H), 6.82 (dd, *J* = 8.5 and 2.5 Hz, 1H), 5.75 (s, 1H), 2.21−2.01 (m, 2H), 1.76−1.59 (m, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 155.5, 149.0, 141.7, 137.7, 132.0, 131.8, 129.5, 126.5, 121.9, 120.7, 118.9, 118.7, 116.4, 114.9, 88.8, 39.3, 23.5; MS (ESI-) *m/z* calculated for $C_{20}H_{15}ClF_3O_5S$ [M − H]$^-$: 459.03; Found: 458.91.

General Procedure for the Loading Step of Solid-Phase, Compound 3. (4-Methoxyphenyl)-diisopropylsilylpropyl polystyrene resins (1.5 mmol/g, 1.0 equiv) were swelled in CH$_2$Cl$_2$ with TMSCl (4.0 equiv) for 15 min to remove residual water in solid supports. After filtration and then washing with CH$_2$Cl$_2$, the resins were treated with 3% (v/v) trifluoromethanesulfonic acid (6.0 equiv) in CH$_2$Cl$_2$ for 15 min. Then the resins were filtered, washed three times with CH$_2$Cl$_2$, and then suspended in CH$_2$Cl$_2$. 2,6-Lutidine (8.0 equiv) and each compound **2** (3.5 equiv) were added sequentially, and then the reactor was shaken for 12 h. After filtration, the resulting resins were washed with CH$_2$Cl$_2$ and THF (three times each) and then dried in vacuo to provide benzopyran intermediates **3ãd{1−2}**.

General Procedure of Suzuki Coupling for Compound 4 (Path A). Benzopyran-loaded resins **3** (1.0 equiv) were separated into each well of a 96-deep-well filtration block, and solutions of 18 different boronic acids (3.0 equiv) in 1,4-dioxane were dispensed into the designated wells of the reaction block. Then, the solution of Pd(PPh$_3$)$_4$ (0.1 equiv) in 1,4-dioxane and 10% aqueous Na$_2$CO$_3$ solution were added to the reaction block. The reaction mixture was shaken at 70 °C in a rotating oven for 24 h, followed by washing with THF, CH$_2$Cl$_2$, DMF, and MeOH (three times each). After drying in vacuo, the resins in the reaction blocks were

treated with HF/Pyridine/THF (5/5/90) for 4 h at room temperature, and then ethoxytrimethylsilane was added and allowed to react for 1 h to quench excessive HF (HF/pyridine protocol). After removing resins by filtration, the filtrate was condensed in vacuo using a GeneVac EZ-2 Plus to obtain the desired product **4**.

Compound 4a{1,17}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.22 (d, *J* = 2.2 Hz, 1H), 7.19−7.16 (m, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.45−6.35 (m, 2H), 6.23 (dd, *J* = 8.3 and 2.5 Hz, 1H), 5.32 (s, 1H), 5.28 (s, 1H), 2.13 (s, 3H), 1.49 (d, *J* = 16.4 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 156.9, 154.3, 138.8, 136.7, 133.4, 133.2, 131.2, 130.1, 127.0, 126.4, 126.1, 115.9, 107.9, 104.2, 76.7, 28.2, 27.8, 19.8; HRMS (FAB+) *m/z* calculated for $C_{18}H_{17}ClO_2$ [M]$^+$: 300.0917; Found: 300.0914.

Compound 4b{1,8}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.31−7.28 (m, 2H), 7.08−7.04 (m, 2H), 6.43 (dd, *J* = 33.3 and 8.5 Hz, 2H), 5.49 (s, 1H), 5.48 (s, 1H), 3.87 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 163.6, 161.6, 147.9, 140.7, 134.6, 134.5, 134.1, 130.5, 130.4, 127.3, 116.7, 116.3, 115.4, 115.3, 115.2, 103.6, 103.5, 56.3, 56.2, 27.7; HRMS (FAB+) *m/z* calculated for $C_{18}H_{17}FO_3$ [M]$^+$: 300.1162; Found: 300.1166.

Compound 4c{1,8}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36 (dd, *J* = 8.3 and 2.2 Hz, 1H), 7.33 (dd, *J* = 8.8 and 5.4 Hz, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.08 (t, *J* = 8.8 Hz, 2H), 7.02−6.98 (m, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.89−6.87 (m, 1H), 6.74−6.70 (m, 1H), 5.62 (s, 1H), 4.97 (bs, 1H), 1.51 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 163.7, 161.7, 156.0, 153.3, 142.8, 134.4, 134.1, 133.5, 130.6, 130.1, 129.8, 128.2, 124.2, 122.6, 119.5, 117.5, 115.6, 113.8, 76.3, 27.8; HRMS (FAB+) *m/z* calculated for $C_{23}H_{20}FO_2$ [M + H]$^+$: 347.1447; Found: 347.1447.

Compound 4d{1,8}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.33−7.23 (m, 3H), 7.19 (d, *J* = 2.7 Hz, 1H), 7.14−7.07 (m, 3H), 7.04 (dd, *J* = 2.5 and 1.5 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.84−6.80 (m, 1H), 5.65 (s, 1H), 5.00 (bs, 1H), 1.46 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 163.8, 161.8, 155.4, 149.0, 138.8, 134.1, 133.7, 131.5, 130.6, 130.2, 129.4, 125.6, 124.6, 122.2, 116.6, 115.7, 114.5, 76.5, 27.5; HRMS (FAB+) *m/z* calculated for $C_{23}H_{19}ClFO_2$ [M + H]$^+$: 381.1058; Found: 381.1057.

General Procedure of Diels−Alder Reaction for Compound 5 (Path B). Benzopyran-loaded resins **3** (1.0 equiv) were separated into each well of a 96-deep-well filtration block, and a solution of tributyl(vinyl)tin (3.0 equiv) and Pd(PPh$_3$)$_4$ (0.1 equiv) in 1,4-dioxane was dispensed into each well of the reaction block. The reaction mixture was shaken at 70 °C in a rotating oven for 36 h. Then, the resulting resins were washed with THF, CH$_2$Cl$_2$, hexane, and MeOH (three times each), and treated with 0.2 M solution of diethyldithiocarbamate in THF twice to remove the residual palladium catalyst on solid supports. Seventeen different maleimides (3.0 equiv) in toluene were dispensed into the designated wells of the reaction block, and the reaction mixture was shaken at 40 °C in a rotating oven for 48 h. After washing with toluene, CH$_2$Cl$_2$, THF, and DMF sequentially (three times each), the resulting resins were dried

in vacuo, and the desired product **5** was cleaved from solid supports by using HF/pyridine cleavage protocol.

Compound 5a{1,3}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.46 (s, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.38−7.28 (m, 3H), 6.86−6.82 (m, 2H), 6.30 (dd, J = 8.6 and 2.5 Hz, 1H), 6.27−6.22 (m, 1H), 6.11 (d, J = 2.5 Hz, 1H), 3.68 (dd, J = 8.3 and 4.9 Hz, 1H), 3.38 (d, J = 6.9 Hz, 1H), 2.71 (ddd, J = 14.7, 7.5, and 1.3 Hz, 1H), 2.65 (d, J = 3.4 Hz, 1H), 2.35−2.27 (m, 1H), 1.73 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 179.3, 176.6, 158.9, 153.7, 133.3, 133.1, 129.5, 128.8, 127.3, 124.2, 115.5, 113.0, 109.8, 104.8, 104.7, 75.8, 44.6, 43.0, 42.4, 29.3, 26.4, 25.8; MS (ESI+) m/z calculated for $C_{23}H_{22}NO_4$ [M + H]$^{+}$: 376.15; Found: 376.08.

Compound 5b{2,3}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.35−7.25 (m, 3H), 7.02−6.95 (m, 3H), 6.53 (d, J = 8.8 Hz, 1H), 6.34−6.27 (m, 1H), 5.55 (s, 1H), 3.88 (s, 3H), 3.58 (dd, J = 8.7 and 5.3 Hz, 1H), 3.38 (dt, J = 8.4, 6.6, and 1.6 Hz, 1H), 3.06 (ddd, J = 14.9, 7.5, and 1.6 Hz, 1H), 2.91−2.82 (m, 1H), 2.62 (d, J = 4.4 Hz, 1H), 2.34−2.26 (m, 1H), 2.11−1.74 (m, 5H), 1.73−1.62 (m, 1H), 1.44−1.34 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 178.4, 175.6, 147.3, 140.4, 135.6, 133.3, 132.0, 129.0, 128.5, 126.5, 117.5, 116.0, 113.2, 105.8, 88.7, 56.3, 44.9, 42.8, 42.2, 39.9, 36.0, 25.4, 23.9, 23.5; HRMS (FAB+) m/z calculated for $C_{26}H_{25}NO_5$ [M]$^{+}$: 431.1733; Found: 431.1731.

Compound 5c{2,3}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.67 (d, J = 2.2 Hz, 1H), 7.32 (dd, J = 8.3 and 2.2 Hz, 1H), 7.28−7.19 (m, 4H), 7.09 (d, J = 7.6 Hz, 1H), 7.01−6.98 (m, 1H), 6.95−6.90 (m, 3H), 6.75 (dd, J = 8.0 and 1.6 Hz, 1H), 6.50−6.45 (m, 1H), 5.47−5.20 (bs, 1H), 3.59 (dd, J = 8.6 and 5.4 Hz, 1H), 3.45−3.33 (m, 1H), 3.10 (ddd, J = 14.9, 7.5, and 1.6 Hz, 1H), 2.88−2.78 (m, 1H), 2.67 (d, J = 5.4 Hz, 1H), 2.38−2.29 (m, 1H), 2.15−2.06 (m, 1H), 2.02−1.92 (m, 2H), 1.90−1.76 (m, 2H), 1.73−1.60 (m, 1H), 1.48−1.39 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 178.5, 175.7, 156.3, 152.5, 142.7, 134.2, 133.9, 132.0, 130.1, 129.0, 128.5, 128.2, 126.5, 122.1, 121.3, 119.6, 119.4, 119.3, 114.0, 113.9, 87.4, 45.1, 42.9, 42.3, 39.9, 36.2, 25.7, 23.8, 23.5; HRMS (FAB+) m/z calculated for $C_{31}H_{27}NO_4$ [M]$^{+}$: 477.1940; Found: 477.1946.

Compound 5d{1,3}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.43 (d, J = 2.5 Hz, 1H), 7.34−7.27 (m, 3H), 7.25−7.21 (m, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.06−7.02 (m, 2H), 6.95−6.91 (m, 2H), 6.80−6.76 (m, 1H), 6.48−6.42 (m, 1H), 6.30 (bs, 1H), 3.62 (dd, J = 8.6 and 5.1 Hz, 1H), 3.39−3.31 (m, 1H), 3.09 (ddd, J = 15.0, 7.5, and 1.7 Hz, 1H), 2.55 (d, J = 3.9 Hz, 1H), 2.37−2.27 (m, 1H), 1.78 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 178.2, 176.0, 155.6, 148.0, 138.2, 133.2, 131.9, 130.0, 129.4, 129.3, 128.9, 126.6, 126.1, 123.0, 121.4, 121.2, 120.8, 116.9, 114.7, 75.7, 45.7, 42.3, 42.0, 28.6, 26.0; HRMS (FAB+) m/z calculated for $C_{29}H_{24}ClNO_4$ [M]$^{+}$: 485.1394; Found: 485.1391.

General Procedure of Hydrogenation Reaction for Compound 6 (Path C). Solution of each compound **5** (1.0 equiv) and 10% Pd/C (10 mol %) in MeOH/THF (1:1) was purged with hydrogen. Then, the reaction mixture was stirred under this hydrogen atmosphere for 3 h at room temperature.

After the reaction completion, the reaction mixture was filtrated and then evaporated in vacuo to provide the desired product **6**.

Compound 6a{2,3}. ^{1}H NMR (500 MHz, acetone-d_6): δ 8.05 (s, 1H), 7.33−7.21 (m, 3H), 6.93 (d, J = 8.6 Hz, 1H), 6.69−6.57 (m, 2H), 6.35 (dd, J = 8.3 and 2.5 Hz, 1H), 6.14 (d, J = 2.5 Hz, 1H), 3.47 (dd, J = 9.5 and 5.6 Hz, 1H), 3.41−3.33 (m, 1H), 3.33−3.25 (m, 1H), 2.57−2.51 (m, 1H), 2.45 (dd, J = 14.1 and 10.6 Hz, 1H), 2.40 (t, J = 6.7 Hz, 1H), 2.03−1.91 (m, 3H), 1.90−1.67 (m, 5H), 1.67−1.58 (m, 1H), 1.55−1.44 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6): δ 178.5, 175.8, 157.1, 154.5, 133.4, 128.5, 127.8, 127.0, 116.0, 107.9, 103.3, 86.9, 41.6, 40.1, 39.3, 38.1, 37.0, 28.7, 25.5, 23.9, 23.7, 21.1; HRMS (FAB+) m/z calculated for $C_{25}H_{25}NO_4$ [M]$^{+}$: 403.1784; Found: 403.1784.

Compound 6b{2,3}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.30−7.21 (m, 3H), 6.61 (dd, J = 7.5 and 1.8 Hz, 2H), 6.57 (d, J = 8.6 Hz, 1H), 6.52−6.45 (m, 1H), 5.44 (s, 1H), 3.86 (s, 3H), 3.45−3.31 (m, 2H), 3.27−3.14 (m, 1H), 2.74−2.62 (m, 1H), 2.42 (dd, J = 14.1 and 10.6 Hz, 1H), 2.24−2.16 (m, 2H), 2.15−2.08 (m, 1H), 2.07−1.99 (m, 1H), 1.99−1.70 (m, 5H), 1.69−1.58 (m, 1H), 1.56−1.49 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 178.5, 175.6, 146.1, 141.1, 134.2, 132.1, 128.9, 128.4, 126.4, 117.4, 116.8, 105.0, 87.9, 56.6, 41.4, 40.1, 39.6, 39.0, 37.4, 28.9, 25.1, 24.1, 23.9, 21.3; HRMS (FAB+) m/z calculated for $C_{26}H_{27}NO_5$ [M]$^{+}$: 433.1889; Found: 433.1887.

Compound 6c{2,3}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29−7.24 (m, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.17−7.13 (m, 3H), 7.01 (d, J = 8.3 Hz, 1H), 6.94−6.91 (m, 1H), 6.81−6.76 (m, 1H), 6.70 (dd, J = 7.7 and 2.1 Hz, 1H), 6.54−6.48 (m, 2H), 5.92 (bs, 1H), 3.50−3.41 (m, 1H), 3.36 (dd, J = 9.5 and 5.4 Hz, 1H), 3.24−3.15 (m, 1H), 2.66−2.56 (m, 1H), 2.53−2.43 (m, 1H), 2.24−2.16 (m, 2H), 2.16−2.08 (m, 1H), 2.08−2.00 (m, 1H), 1.99−1.86 (m, 2H), 1.86−1.69 (m, 3H), 1.68−1.58 (m, 1H), 1.57−1.45 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 179.1, 176.2, 156.5, 153.2, 143.0, 133.2, 132.0, 130.0, 129.0, 128.6, 126.9, 126.5, 125.9, 124.3, 119.1, 117.8, 113.9, 113.8, 87.0, 41.5, 40.3, 39.8, 38.7, 37.6, 29.4, 25.3, 24.1, 23.9, 21.5; HRMS (FAB+) m/z calculated for $C_{31}H_{29}NO_4$ [M]$^{+}$: 479.2097; Found: 479.2093.

General Procedure of Aromatization Reaction for Compound 7 (Path D). Before the cleavage step of compound **5** synthesized by Diels−Alder reaction, a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 5.0 equiv) in 1,4-dioxane was added to each well, and then the reaction mixture was shaken at 75 °C in a rotating oven for 24 h. After washing with THF, CH$_2$Cl$_2$, DMF, and MeOH (three times each), the resulting resins were dried in vacuo, and the desired product **7** was cleaved from solid supports by using HF/pyridine cleavage protocol.

Compound 7a{2,3}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.99 (bs, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.50 (t, J = 7.1 Hz, 2H), 7.42 (t, J = 6.5 Hz, 3H), 6.51 (d, J = 8.6 Hz, 1H), 6.31 (s, 1H), 2.55−2.36 (m, 2H), 2.13−2.00 (m, 2H), 1.99−1.85 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.3, 171.8, 166.0, 158.8, 142.4, 142.3, 137.4, 136.0, 134.2, 133.5, 133.1, 133.0, 132.2, 131.3, 131.2, 117.6, 115.8, 109.6, 94.8, 44.6, 29.9;

HRMS (FAB+) *m/z* calculated for $C_{25}H_{19}NO_4$ [M]$^+$: 397.1314; Found: 397.1306.

Compound 7b{1,3}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.53−7.50 (m, 2H), 7.44−7.40 (m, 3H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.66 (d, *J* = 9.0 Hz, 1H), 5.59 (bs, 1H), 3.95 (s, 3H), 1.99 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.2, 166.8, 149.3, 140.6, 139.8, 136.9, 135.1, 131.9, 131.6, 129.3, 128.5, 127.7, 127.2, 127.0, 123.5, 115.0, 114.9, 105.8, 80.4, 56.5, 27.3; HRMS (FAB+) *m/z* calculated for $C_{24}H_{19}NO_5$ [M]$^+$: 401.1263; Found: 401.1269.

General Procedure of Click Chemistry for Compound 8 (Path E). Ethynyl magnesium bromide (8.0 equiv) in THF (0.5 M) was added to anhydrous ZnCl$_2$ (10 equiv), and then this reaction mixture was stirred vigorously at 0 °C for 30 min under anhydrous condition. Benzopyran-loaded resins **3** (1.0 equiv) were separated into each well of a 96-deep-well filtration block, and the prepared zinc reagent solution and Pd(PPh$_3$)$_4$ (0.1 equiv) in 1,4-dioxane solution were sequentially added into each well charged with resins. After vigorous shaking for 12 h, the resulting resins were filtrated and sequentially washed with CH$_2$Cl$_2$, THF, acetone, and EtOH (three times each). Then, resultants were treated with 0.2 M solution of diethyldithiocarbamate in THF twice and dried in vacuo. After this reaction, each alkynylated benzopyran-loaded resin was separated into each well of a 96-deep-well filtration block, and 8 different azides (3.0 equiv) in toluene were dispensed into the designated wells of the reaction block. After the addition of BrCu(PPh$_3$)$_3$ (0.2 equiv) in toluene and DIPEA (6.0 equiv) into the reaction block, the reaction mixture was shaken at room temperature in a rotating oven for 36 h. The resulting resins were sequentially washed with toluene, THF, CH$_2$Cl$_2$, DMF, and MeOH (three times each), dried in vacuo, and the desired product **8** was cleaved from solid supports by using HF/pyridine cleavage protocol.

Compound 8a{1,1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.50 (s, 1H), 7.39−7.37 (m, 3H), 7.31−7.26 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 1H), 6.37 (dd, *J* = 8.3 and 2.2 Hz, 1H), 5.93 (s, 1H), 5.57 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 157.2, 154.8, 145.2, 134.5, 129.2, 128.8, 128.1, 127.5, 125.7, 123.6, 121.6, 114.1, 107.9, 104.4, 76.0, 54.3, 27.3; MS (ESI+) *m/z* calculated for $C_{20}H_{20}N_3O_2$ [M + H]$^+$: 334.16; Found: 334.42.

Compound 8a{2,1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.51 (s, 1H), 7.39−7.37 (m, 3H), 7.31−7.26 (m, 2H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.38 (d, *J* = 2.2 Hz, 1H), 6.33 (dd, *J* = 8.3 and 2.2 Hz, 1H), 6.00 (s, 1H), 5.57 (s, 2H), 2.15−2.05 (m, 2H), 1.88−1.86 (m, 2H), 1.70−1.60 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 157.2, 154.8, 145.2, 134.5, 129.2, 128.9, 128.1, 126.7, 125.5, 124.3, 121.6, 108.0, 104.6, 86.9, 54.3, 38.5, 23.4; MS (ESI+) *m/z* calculated for $C_{22}H_{22}N_3O_2$ [M + H]$^+$: 360.17; Found: 360.30.

Compound 8c{1,1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.53 (s, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.35−7.27 (m, 4H), 7.26−7.21 (m, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.00−6.97 (m, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.80 (dd, *J* = 8.1 and 2.5 Hz, 1H), 6.09 (s, 1H), 5.50 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 156.8,

153.1, 144.8, 142.5, 134.5, 133.9, 131.2, 130.0, 129.4, 129.2, 129.1, 128.4, 128.3, 128.1, 123.8, 123.2, 122.3, 121.0, 118.8, 117.6, 114.2, 114.0, 76.1, 54.6, 27.4; HRMS (FAB+) *m/z* calculated for $C_{26}H_{24}N_3O_2$ [M + H]$^+$: 410.1869; Found: 410.1871.

Compound 8d{2,1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.56 (s, 1H), 7.41−7.33 (m, 3H), 7.33−7.29 (m, 2H), 7.24 (d, *J* = 2.7 Hz, 1H), 7.21 (t, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 2.7 Hz, 1H), 7.03−6.97 (m, 2H), 6.86−6.82 (m, 1H), 6.18 (s, 1H), 5.59 (s, 2H), 2.18−1.98 (m, 2H), 1.70−1.63 (m, 2H), 1.63−1.49 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 156.0, 148.9, 144.7, 138.4, 134.5, 132.0, 131.1, 130.0, 129.4, 129.3, 129.1, 128.4, 128.3, 125.7, 124.2, 123.7, 123.6, 122.0, 121.5, 116.6, 114.7, 87.2, 77.4, 54.6, 38.4, 23.6, 23.5; HRMS (FAB+) *m/z* calculated for $C_{28}H_{25}ClN_3O_2$ [M + H]$^+$: 470.1635; Found: 470.1630.

Supporting Information Available. Experimental procedures and spectral data correspond to representative compounds (^{1}H, ^{13}C NMR, and LC/MS). This material is available free of charge via the Internet at http://pubs.acs.org.

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